Headquarters Office

The Headquarters Office is located in the Helix Room in the Town & Country Hotel. Telephone number: (619) 291-7131 (ask for Helix Room).

On-Site Registration

The registration fee includes the Opening Reception, banquet, entrance to scientific sessions, and receipt of the Program/Abstract Volume.

The guest registration fee includes the opening reception and banquet. Guest registrants are nonscientist family members of registrants and may not attend scientific sessions.

Location: Mission Foyer

Hours:	
Saturday, October 2	2:00 pm–8:00 pm
Sunday, October 3	7:30 am–4:30 pm
Monday, October 4	8:00 am–4:30 pm
Tuesday, October 5	8:00 am–Noon

Fees:	
APS Member	$230.00
Retired Member	$ 70.00
Nonmember	$275.00
Student	$ 70.00
Guest	$ 40.00

Press

Press badges will be issued in the Headquarters Office only to members of the working press and freelance writers bearing a letter of assignment from an editor. Representatives of allied fields (public relations, public information, public affairs, etc.) may register as nonmembers in the registration area.

CME Credit

The Conference has been certified as a continuing medical education activity for credit on an hour-for-hour basis in Category 1 of the Physician's Recognition Award of the American Medical Association. Application's may be picked up in the Headquarters Office, Helix Room. There is a $25 CME application fee, payable upon submission of the form.

Program/Abstract Volume

The August issue of *The Physiologist* contains the contributed abstracts and program for the conference. Advance registrants were sent a pick-up card which may be exchanged at the Registration Desk for their copy of the Program/Abstracts Volume. Replacement copies may be purchased for $20.00.

Message Center

The message board will be located in the Mission Foyer by the Registration Desk. Registrants should check for message daily. Please suggest that callers who wish to reach you during the day leave a message with the Headquarters Office during registration hours at (619) 291-7131 (ask for Helix Room).

Airline Reservations

Arrangements have been made with United and Delta Airlines to offer registrants special discounts off supersaver and unrestricted fares. Reservations may be made by calling the airlines directly or by using your choice of travel agent. To take advantage of the United discounts, you must call 1-800-521-4041 and refer to file #536AP. To take advantage of the Delta discounts, you must call 1-800-241-6760 and refer to file #NO826.

Car Rental

Alamo Car Rental has been appointed the official car rental company for the meeting. Special discounted rates have been extended to any participant. Reservations may be made by calling toll-free 1-800-732-3232. Be sure to identify yourself as an APS Conference attendee and give the meeting dates, I.D. #68970 and Plan Code GR to guarantee the special rate.

Airport Transportation

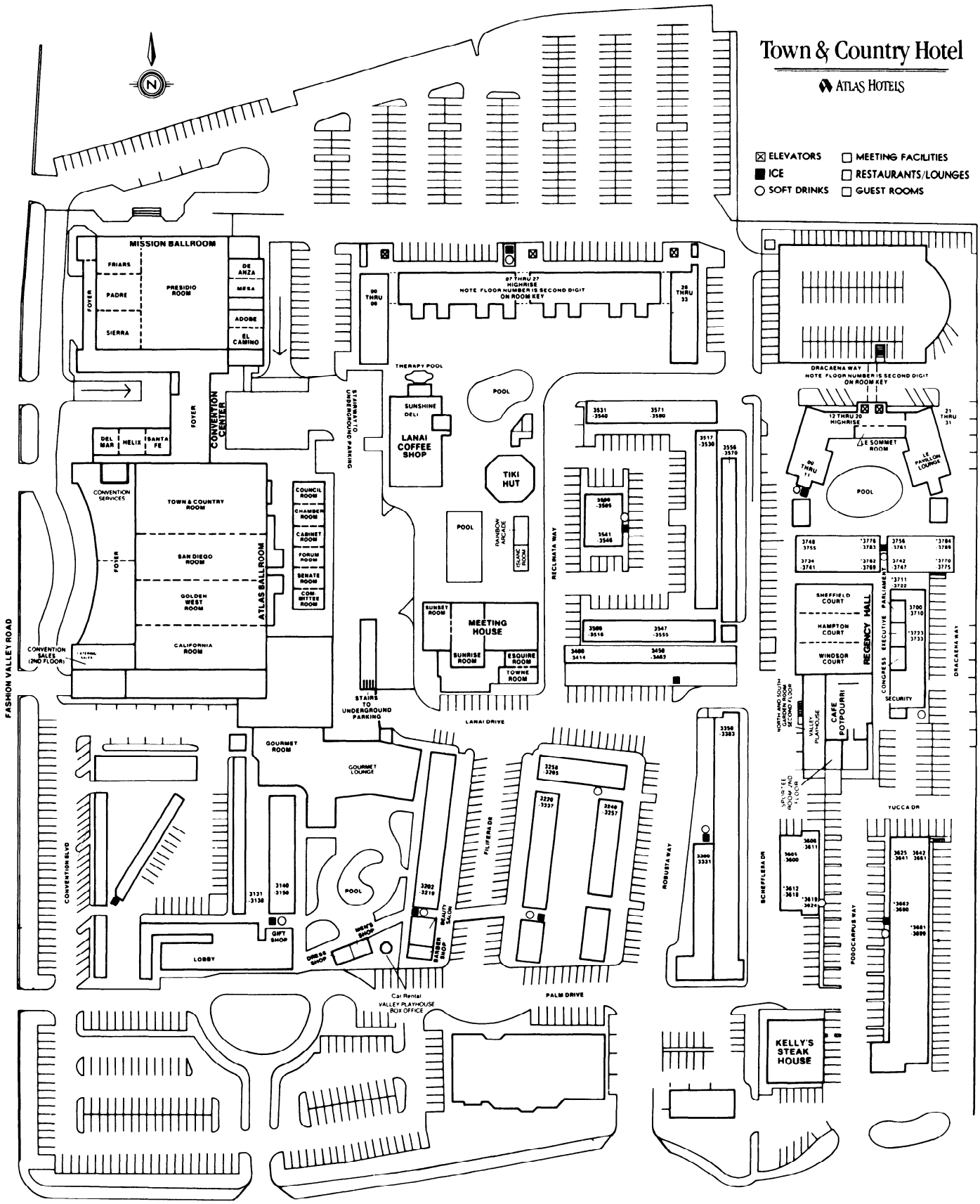
The "Super Shuttle" provides shuttle service from the airport to the Town & Country Hotel. The cost is $8.00 one way. Taxi fares are approximately $12.00–$16.00.

Social Program

Opening Reception. The Opening reception will be held in the Tiki Hut at the Town & Country Hotel on Saturday, October 2, 5:00–6:45 pm.

Banquet Lecture and Student Awards Presentation. All registrants are invited to attend the banquet on Monday evening in the California Room. A cash bar reception is scheduled at 6:30 pm in the Atlas Ballroom foyer followed by dinner at 7:30 pm. The lecture will be presented after dinner at 9:00 pm by Gerald Edelman of the Research Institute of Scripps Clinic. Tickets are required for admittance. Each registrant will receive a coupon in the registration packet which must be exchanged for a dinner ticket before 10:00 am on Sunday, October 3.

HOTEL FLOOR PLAN



Physiology and Pharmacology of Motor Control

October 2–5, 1993
San Diego, California

Saturday, October 2	Sunday, October 3	Monday, October 4	Tuesday, October 5
5:00–6:45 pm Tiki Hut Opening Reception	8:30 am–12:30 pm Sierra Room Neurotransmitter and Receptors Chair: Floyd Bloom	8:30 am–12:30 pm Sierra Room Neurophysiology of Control of Movement in Mammals Chair: James C. Houk	8:30–10:30 am Sierra Room Diseases of Movement Chair: Joseph B. Martin
7:00–7:30 pm Sierra Room Overview Floyd E. Bloom	1:00–3:00 pm Presidio Room Free Time for Poster Sessions	1:00–3:00 pm Presidio Room Free Time for Poster Sessions	10:30–11:30 am Sierra Room Summation Joseph B. Martin
7:30–9:30 pm Sierra Room Anatomy of Neurotransmitter Systems Chair: Tomas Hökfelt	3:00–6:00 pm Sierra Room Neuropharmacology of Movement Control Chair: Sten Grillner	3:00–6:00 pm Sierra Room Neuropharmacology of Motoneurons Chair: Jack L. Feldman	
		6:30 pm Atlas Ballroom Foyer Banquet Reception 7:30 pm Atlas Ballroom Banquet Lecture and Student Awards Presentation Speaker: Gerald Edelman	

APS Conference

Physiology and Pharmacology of Motor Control

Daily Schedule

Saturday

1. Overview

F. Bloom, Scripps Clinic

SAT. 7:00 PM—Town & Country, Sierra Room

Symposium

2. Anatomy of Neurotransmitter Systems

Chaired: **T. Hökfelt**, Karolinska Inst., Stockholm

SAT. PM—Town & Country, Sierra Room

7:30 Anatomy of fast neurotransmitters in relation to motorcontrol. **J. Storm-Mathisen**. Univ. of Oslo, Norway.
8:00 Spinal motoneuron afferents: ultrastructure, transmitters and origin. **J.C. Holstege**. Erasmus Univ., The Netherlands.
8:30 Peptides and coexisting transmitters in bulbospinal systems. **T. Hökfelt**. Karolinska Inst.
9:00 Neuropeptides in and on the spinal motoneuron. **S. Cullheim**. Karolinska Inst., Stockholm, Sweden.

Sunday

Symposium

3. Neurotransmitters and Receptors

Chaired: **F. Bloom**, Scripps Clinic

SUN. PM—Town & Country, Sierra Room

8:30 Molecular biology of glutamate receptors. **S. Heinemann**. The Salk Inst.
9:00 Physiological characterization of glutamate receptor function. **M.L. Mayer**. NICHD, NIH.
9:30 Molecular biology of GABA production and action. **A.J. Tobin**. UCLA.
10:00 Physiological characterization of GABA receptor function. **R.A. Nicoll**. UCSF.
10:30 Electrophysiological actions of serotonin (5-HT) on facial motoneurons. **G.K. Aghajanian**. Yale Sch. of Med.
11:00 Peptides and Endorphins. **G.R. Siggins**. Scripps Res. Inst.

Symposium

4. Neuropharmacology of Movement Control

Chaired: **S. Grillner**, Karolinska Inst., Stockholm

SUN. PM—Town & Country, Sierra Room

3:00 Modulation of oscillatory neural networks. **E. Marder** Brandeis Univ.
3:30 Transmission in the network underlying neurons in lamprey. **S. Grillner**. Karolinska Inst., Stockholm, Sweden.
4:00 Studies of presynaptic mechanisms in reticulospinal glutamate neurons. **L. Brodin**. Karolinska Inst., Stockholm, Sweden.
4:30 Dynamic regulation of gne expression in neurocircuits the basal ganglia. **A.M. Graybiel.** MIT.
5:00 Neurotransmitter control of cortical and thalamic actic **D.A. McCormick**. Yale Univ. Med. Sch.

Posters

5. Anatomy of Neurotransmitter Systems

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time

Board #

1 11:00 **5.1** Synaptic vesicle proteins in the mon (*Macaca fascicularis*) spinal cord with emphasis on 5-HT and GABA system in motor nuclei. **U. Arvidss F. Piehl, B. Meister, O. Shupliakov, L. Brodin Hökfelt, and S. Cullheim**. Karolinska Inst., Stockhol

2 12:00 **5.2** Glutamatergic system in pontomedul reticular formation participating in movement i gration. **Y.Y. Lai and J.M. Siegel**. UCLA and VA M Ctr., Sepulveda, CA.

3 11:00 **5.3** Modulation of motoneuron activity: tribution of glycine receptors and serotonergic input motoneuron dendrites. **R.E.W. Fyffe, F.J. Alvarez, , Pearson, D. Harrington, and D.E. Dewey**. Wright S Univ.

4 12:00 **5.4** Immunohistochemical analysis serotonin, dopamine and GABA in dorsal and ver striatum. **C.F. Phelix, T. Jackson, P.A. Broderick, M.J. Wayner**. Univ. of Texas, San Antonio and CU Med. Sch.

5 11:00 **5.5** Effects of L-dihydroxyphenylalnine on nigrostriatal dopamine immunoreactivity in 6-hydroxydopamine-lesioned rats. **D. Jackson, A. Mura, M.S. Manley, S.J. Young, and P.M. Groves**. UCSD.

Posters

6. Neurotransmitters and Receptors

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

6 12:00 **6.1** C-DNA/PCR cloning, characterization and distribution of inward rectifier K^+ channels in neonatal rat brainstem. **J.S. Lai, G.D. Funk, S.M. Johnson, J.C. Smith, and J.L. Feldman.** UCLA.

7 11:00 **6.2** Respiratory rhythm modulation by $GABA_B$, $5HT_{1A}$, and α_2-adrenergic receptors: mediation via an inward rectifying K^+ conductance? **S.M. Johnson, J.C. Smith, and J.L. Feldman**. UCLA.

8 12:00 **6.3** $5\text{-}HT_{1B}$ receptor "knock-out": pharmacological and behavioral consequences. **F. Saudou, U. Boschert, M. Lemeur, A. Dierich, D. Ait Amara, M.C. Buhot, L. Segu, R. Misslin, and R. Hen.** CNRS, INSERM, Strasbourg and CNRS, Marseille, France.

9 11:00 **6.4** Neuromodulatory actions of dopamine are dependent upon the excitatory amino acid receptor subtypes activated in neostriatal slices. **M.S. Levine, C. Cepeda, and N.A. Buchwald**. UCLA.

10 12:00 **6.5** The metabotropic glutamate receptor agonist 1-amino-cyclopentane-1,3-dicarboxylic acid inhibits both post-synaptic potentials and *N*-methyl-D-aspartate-evoked responses in neostriatum. **C.S. Colwell and M.S. Levine**. UCLA.

11 11:00 **6.6** Intracellular redistribution of β-adrenergic receptors in rat liver during different phases of sepsis. **M-S. Liu, C. Tang, and L-W. Guo**. St. Louis Univ.

2 12:00 **6.7** Striatal and limbic dopamine overflow in the rat is frequency and pulse-dependent: *in vivo* fast cyclic voltammetric data. **C.D. Earl, J.X. Xie, S.J. Trout, Z.L. Kruk, A. Kupsch, W.H. Oertel, and G. ten Bruggencate**. Univ. of Munich, Germany and Queen Mary & Westfield Col., London, UK.

Posters

7. Neuropharmacology of Movement Control

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

13 11:00 **7.1** Respiratory rhythm generation and drive transmission *in vitro*; role of excitatory amino acid receptors. **G.D. Funk, J.C. Smith, and J.L. Feldman.** UCLA.

14 12:00 **7.2** $GABA_B$ receptor-mediated long-term depression of the nVIII-evoked EPSP in rat medial vestibular nucleus neurons patch-clamped *in vitro*. **G.A. Kinney, B.W. Peterson, and N.T. Slater.** Northwestern Univ.

15 11:00 **7.3** Intravenous haloperidol administration effects on movement time and reaction time in young and old healthy subjects. **A. Berardi, J.F. Kelly, K.C. Raffaele, T.T. Soncrant, and J.V. Haxby**. NIH.

16 12:00 **7.4** Serotonergic drugs markedly affect locomotion in chronic spinal cats but not normal cats. **J.A. Hodgson, R. deLeon, R.R. Roy, D. Chin, and V.R. Edgerton**. UCLA.

17 11:00 **7.5** Neuronal activity in the guinea pig medial vestibular nucleus following chronic diazepam administration. **C.L. Darlington and P.F. Smith**. Univ. of Otago, Dunedin, New Zealand.

18 12:00 **7.6** Rapid tolerance to the effects of diazepam on guinea pig motor control using divided doses. **P.F. Smith and C.L. Darlington**. Univ. of Otago, Dunedin, New Zealand.

19 11:00 **7.7** Opposite effects of short and long-term haloperidol treatment on levels of mRNA encoding glutamic acid decarboxylase in rat globus pallidus. **J.M. Delfs, G.D. Ellison, and M-F. Chesselet**. Univ. of Pennsylvania and UCLA.

20 12:00 **7.8** Influence of flupirtine on lower limb reflexes in humans. **D. Timmann, C. Plummer, M. Schwarz, and H-C. Diener.** Univ. of Essen, Germany.

21 11:00 **7.9** Role of excitatory and inhibitory amino acids in transmission of masticatory drive signals in the guinea pig. **T. Inoue and S.H. Chandler**. UCLA.

22 12:00 **7.10** Stimulation of locomotion in neonate rat pups by thyroliberin analogue CG3703. **K.A. Clarke and K.J. Kirby**. Univ. of Sheffield, UK.

23 11:00 **7.11** Low-dose chronic ethanol improves tilt-plane performance in pontine-damaged but not normal rats. **R.M. Chesire and B.E. Digman**. Univ. of Hawaii, Honolulu.

24 12:00 **7.12** The organization of pacemaker control in weakly electric fish. **J.E. Spiro, C.J.H. Wong, and W. Heiligenberg**. UCSD.

25 11:00 **7.13** Influence of acute and chronic administration of neuroleptics on leg EMG responses in dynamic posturography. **A. Banaski, D. Timmann, M. Jüptner, M. Schwarz, J. Rimpel, and H-C. Diener.** Univ. of Essen, Germany.

26 12:00 **7.14** Cocaine and citalopram effects on locomotion in maturing mice. **C. Goodrich.** Cleveland State Univ.

27 11:00 **7.15** *N*-methyl-D-aspartate receptor-mediated voltage oscillations in rat central spinal neurons. **S. Hochman, L.M. Jordan, and J.F. MacDonald**. Univ. of Toronto and Univ. of Manitoba.

28 12:00 **7.16** Brain serotonergic neurons in cats discharge in relation to tonic and rhythmic motor function. **C.A. Fornal, S.C. Veasey, and B.L. Jacobs**. Princeton Univ.

29 11:00 **7.17** Purkinje cell GAD mRNA in rats with olivo-cerebellar dysfunction. **G.A. Oltmans, S.M. Drengler, and J.F. Lorden**. Chicago Med. Sch. and Univ. of Alabama, Birmingham.

30 12:00 **7.18** Increased muscle tone following nigral dopamine receptor inactivation. **A.D. Crocker and K.L. Double**. Flinders Univ., South Australia.

31 11:00 **7.19** Immunohistochemical study of the distribution of corticotropin releasing factor and serotonin in the cerebellar nuclei of monkeys. **C.I. Cha and E.Y. Lee**. Seoul Natl. Univ. and Chungbuk Natl. Univ., Seoul, Rep. of Korea.

32 12:00 **7.20** Dorsal and ventral striatal cholinergic systems: the regulation of different forms of motor behavior. **K.B. Shapovalova and E.V. Pominova**. I.P. Pavlov Inst. of Physiol. and Russian Acad. of Sci., St. Petersburg, Russia.

Posters

8. Diseases of Movement

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at t indicated time.

Board #

33 11:00 **8.1** Impairment of rhythmic voluntary mo ment in Huntington's disease. **J.S. Freeman and F.W Cody**. Univ. of Manchester, UK.

34 12:00 **8.2** The masseteric silent periods, evoked chin taps during maximal clenches, are shorter alcoholics than in non-alcoholics. **B. Bishop, C. Vern J.A. Hirsch, and J.L. York**. SUNY, Buffalo and R Inst. on Alcoholism, Buffalo.

35 11:00 **8.3** Rhythmic leg and jaw movements dur sleep: epidemiologic and polysomnographic obs vations. **G. Lavigne and J. Montplaisir**. Univ. Montreal and Sacré-Couer Hosp.

36 12:00 **8.4** A nonlinear model of levodopa-indu tremor and dyskinesia in Parkinson's disease. M **Caligiuri and J.B. Lohr**. UCSD.

37 11:00 **8.5** Changes in movement kinematics discrete arm movements in Parkinson's disease. **P. W and G.E. Stelmach**. Arizona State Univ.

38 12:00 **8.6** Cue utilization in prehensile moveme in Parkinson's disease. **A. Chaiken, P. Weiss, and G Stelmach.** Arizona State Univ.

39 11:00 **8.7** Myoblast strengthen dystrophic musc **P. Law, T. Goodwin, Q. Fang, M. Deering, Duggirala, C. Larkin, A. Florendo, D. Kirby, L. Li Shirzad, T. Quinley, T. Yoo, and R. Holcomb.** (Therapy Res. Fndn., Memphis, TN.

40 12:00 **8.8** Pharmacological evidence for a decr in tonic descending inhibition mediated via adrenoceptors in the spinal cord-injured ketami anesthetized cat. **J.S. Taylor, C.J. Vierck, Jr., Radisavljevic, and J.B. Munson**. Univ. of Florida.

41 11:00 **8.9** Zonal purkinje cell loss revealed by bindin expression in the leaner mutant mouse. **I Abbott and J.A. Heckroth**. Univ. of Illinois and Indi State Univ.

42 12:00 **8.10** Short vs. long term antipsychotic drug effects on striatal function: implications for drug-induced extrapyramidal syndromes. **R.E. See**. Washington State Univ.

43 11:00 **8.11** Quantifying comparable movement disorders in humans and rats using videotracking techniques: application to studies of tardive dyskinesia. **G. Ellison, A. Keys, and W. Wirsching**. UCLA and VA Movement Disorders Clin., Brentwood, CA.

44 12:00 **8.12** Efficacy and safety of tizanidine for reduction of spasticity in multiple sclerosis. **K. Shellenberger, A. Stazio, T. Vollmer, and US Tizanidine MS Study Group.** Athena Neurosciences, Inc., Tulane Med. Ctr., and Yale Sch. of Med.

Poster

9. Trace Elements—Mineral Interactions

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

45 11:00 **9.1** Trace element-mineral interactions in man: zinc-magnesium. **H. Spencer**. VA Hosp., Hines, IL.

Poster

10. Aging Effects on Motor Control

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

46 12:00 **10.1** Decreasing muscle mass in the elderly: a possible confounding variable in motor control. **R.P. Spencer**. Univ. of Connecticut Hlth. Ctr.

Poster

11. Education

SUN. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

47 11:00 **11.1** Moral expectation or miraculous robots: statistics in medicine and physiology. **R. Jevning, R. Anand, and M. Biedebach**. California State Univ., Long Beach and US Internatl. Univ., San Diego.

Monday

Symposium

12. Neurophysiology of Control of Movement in Mammals

Chaired: **J.C. Houk**, Northwestern Univ.

MON. AM—Town & Country, Sierra Room

8:30 Functional organization of motoneurons and motor units. **R.E. Burke**. NINDS, NIH.
9:00 Spinal cord interneurons. **E. Jankowska**. Univ. of Göteborg, Sweden.
9:30 Olivocerebellar system and motor coordination. **R. Llinás**. New York Univ.
10:00 Inhibitory control of saccadic eye movement by the basal ganglia. **O. Hikosaka**. Natl. Inst. Physiol. Sci., Okazaki, Japan.
10:30 The superior colliculus as a model of sensorimotor control. **R.H. Wurtz**. Natl. Eye Inst., NIH.
11:00 Motor cortex. **A.P. Georgopolous.** VA Med. Ctr., Minneapolis, MN.
11:30 Representation of motor programs in the cerebellum and premotor network. **J.C. Houk**. Northwestern Univ.

Symposium

13. Neuropharmacology of Motoneurons

Chaired: **J.L. Feldman**, UCLA

MON. PM—Town & Country, Sierra Room

3:00 Control of phrenic motoneuronal excitability. **J. Feldman.** UCLA.
3:30 Transmitter controlled intrinsic properties of spinal motoneurons. **H. Hultborn**. Copenhagen Univ., Denmark.
4:00 Monoamines, peptides and motoneurons. **S.R. White**. Washington State Univ.
4:30 Neurophysiology and pharmacology of respiratory rhythm generation in mammals. **J.C. Smith**. UCLA.
5:00 Descending control of locomotion. **L.M. Jordan.** Univ. of Manitoba.

Posters

14. Neurophysiology of Movement Control

MON. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

1 11:00 **14.1** The relationship between sensory input and motor output during swallowing. **K.M. Mosier, J.**

Spiro, J. Rendell, A.G. Lurie, and T. Gay. Univ. of Connecticut Hlth. Ctr.

2 12:00 **14.2** Excitotoxin lesions of the neostriatum in the cat produce apraxia and changes in pallidal neuronal activity related to movement. **J.W. Aldridge, J.F. Thompson, R.C. Meyer, and S. Gilman.** Univ. of Michigan.

3 11:00 **14.3** Rapid learning of a motor task in the cat lumbar spinal cord. **V.R. Edgerton, J. Hodgson, R.R. Roy, R. deLeon, and K. Nakata.** UCLA.

4 12:00 **14.4** Imaging whole cell recording of proprio-spinal activity in the embryonic chick spinal cord. **A.M. Ritter and M.J. O'Donovan.** NIH.

5 11:00 **14.5** Comparison of vestibulospinal and Ia afferent synaptic inputs in cat triceps surae motoneurons. **S.L. Wescott, R.K. Powers, F.R. Robinson, M.A. Konodi, and M.D. Binder.** Univ. of Washington.

6 12:00 **14.6** Locomotor-like movement depression of H reflex transmission can be induced at the spinal level in the human. **J.D. Brooke, W.E. McIlroy, D.F. Collins, and J.E. Misiaszek.** Univ. of Guelph.

7 11:00 **14.7** Stimulation of group II muscle afferents in hindlimb flexor nerves resets the step cycle during MLR evoked fictive locomotion. **M-C. Perreault, M.J. Angel, P. Guertin, P.A. Carr, and D.A. McCrea.** Univ. of Manitoba.

8 12:00 **14.8** The generators of human movement-related cortical potentials. **I.M. Tarkka.** Baylor Col. of Med.

9 11:00 **14.9** Characterization of motor control from surface EMG. **A.M. Sherwood.** Baylor Col. of Med.

10 12:00 **14.10** The influence of muscle strain on stimulus duration of slow muscles performing simulated locomotory activity. **V.J. Caiozzo, M.J. Baker, and K.M. Baldwin.** Univ. of California, Irvine.

11 11:00 **14.11** Tremor and synchronous EMG bursting is accentuated during eccentric muscle action. **J.N. Howell, D. Karapondo, G. Chleboun, and R. Conaster.** Ohio Univ.

12 12:00 **14.12** Locomotion stimulates group III muscle afferents. **J.G. Pickar, J.M. Hill, and M.P. Kaufman.** Univ. of California, Davis.

13 11:00 **14.13** In situ power production from rat soleus and plantaris. **S.J. Swoap, V.J. Caiozzo, and K.M. Baldwin.** Univ. of California, Irvine.

14 12:00 **14.14** Posture/respiration interaction in hum intercostal muscles. **W.A. Whitelaw, G.T. Ford, a K.P. Rimmer.** Univ. of Calgary.

15 11:00 **14.15** Electromyographic activity of hum knee extensors during "dry" slope skiing. **E. Gardn and H.C. Richardson.** Univ. of Manchester, UK.

16 12:00 **14.16** Multifunctional CPG for the control different forms of cat locomotion. **J.L. Smith, J. Buford, C. Chen, T.V. Trank, O.T. Wang, and H Wijesinghe.** UCLA.

17 11:00 **14.17** Toe joint kinetics during forward a backward walking. **T.V. Trank, K.L. Perell, R. Gregor, and J.L. Smith.** UCLA.

18 12:00 **14.18** Ankle extensor group I afferents exc extensors throughout the hindlimb during MLR-evok fictive locomotion in the cat. **P. Guertin, M.J. Ang M-C. Perreault, P.A. Carr, and D.A. McCrea.** Univ. Manitoba.

19 11:00 **14.19** The effect of ankle joint angle on t ankle torque profile in the cat. **J.H. Lawrence, III a T.R. Nichols.** Emory Univ.

20 12:00 **14.20** Mechanical-reflex oscillations of t human finger are not augmented during acute exposu to hypoxia. **W.L. Krause, J.C. Leiter, J. Daubenspeck, and S.M. Tenney.** Dartmouth Med. Sch

21 11:00 **14.21** Input-output relations of real and moc motoneurons. **R.K. Powers and M.D. Binder.** Univ. Washington.

22 12:00 **14.22** Nucleus retroambiguus projections hindlimb motoneurons in the cat: involvement of t emotional motor system. **V.G.J.M. VanderHorst and Holstege.** Univ. of Groningen, The Netherlands.

23 11:00 **14.23** Vibrissal receptive fields in lobule IXa the adult rat cerebellum align with zebrin-negati purkinje cell compartments. **V. Chockkan and Hawkes.** Univ. of Calgary.

24 12:00 **14.24** Primate spinal motoneuron physiolo and synaptic covering after H-reflex opera conditioning. **J.S. Carp, X.Y. Chen, K.A. Starr, a J.R. Wolpaw.** New York State Dept. of Hlth. and SUN Albany.

25 11:00 **14.25** Reduction of the AHP with Mn^{2} decreases the initial adaptation, but increases the la adaptation in rat hypoglossal motoneuron discharge. **Sawczuk and M.D. Binder.** Univ. of Washington.

26 12:00 **14.26** Subthalamic nucleus and globus pallidus lesions alter activity in nigrothalamic neurons in rats. **L.J. Ryan and D.J. Sanders.** Oregon State Univ.

27 11:00 **14.27** Prefrontal "fixation" neurons active during periods of memory-guided eye fixation. **R.G. Erickson**. NIMH.

28 12:00 **14.28** $GABA_A$ and $GABA_B$ receptors are involved in the control of locomotor networks in newborn rats. **F. Clarac, Y. Sqalli-Houssaini, and J.R. Cazalets**. CNRS-NBM, Marseille, France.

29 11:00 **14.29** To swim or not to swim: control of swimming by neurons in the head ganglion of the medicinal leech. **P.D. Brodfuehrer and A. Burns**. Bryn Mawr Col.

30 12:00 **14.30** Activation of D1 dopamine receptors facilitates premotor and motor cortical functions for reaching movements in monkeys. **K. Kubota, T. Sawaguchi, and I. Yamane**. Kyoto Univ., Aichi, Japan.

31 11:00 **14.31** Adaptive mechanisms in the motor control of swallowing. **T. Gay, J. Rendell, J. Spiro, K.M. Mosier, and A.G. Lurie**. Univ. of Connecticut Htlh. Ctr.

32 12:00 **14.32** Effects of interruption of nervous circuitry between gastric corpus and antrum on gastric motility. **G.E. Holle and E. Steinbach**. Walther Straub Inst., L.M. Univ., Munich, Germany.

33 11:00 **14.33** Evidence for heartbeat excited 8-12 Hz reflex oscillations in the low innervated muscle. **E. Gallasch and T. Kenner.** Univ. of Graz, Austria.

34 12:00 **14.34** Dose response dependence of ciliary neurotrophic factor on electromechanical parameters following peroneal nerve crush. **K.A. Williams and F.L. Strand**. New York Univ.

35 11:00 **14.35** Ciliary neurotrophic factor increases endplate internal branching. **T.S. Lee and F.L. Strand**. New York Univ.

36 12:00 **14.36** The role of caudate nucleus in the instrumental behavior of monkeys: unit activity and effects of microinjections. **B.F. Tolkunov, A.A. Orlov, and S.V. Afanas'ev**. Sechenov Inst. of Evol. Physiol. and Biochem., St. Petersburg, Russia.

Poster

15. Neuropharmacology and Neurophysiology of Motoneurons

MON. PM—Town & Country, Presidio Room

Authors will be in attendance for one hour beginning at the indicated time.

Board #

37 11:00 **15.1** Functional locomotor recovery after spinal cord hemisection in the chick. **G.D. Muir and J.D. Steeves.** Univ. of British Columbia.

38 12:00 **15.2** Crossed phrenic responses to spinal stimulation in rats: effects of old age or chronic spinal hemisection. **L. Ling, K.B. Bach, and G.S. Mitchell.** Univ. of Wisconsin.

39 11:00 **15.3** Modulation of excitatory synaptic transmission to phrenic motoneurons by adenosine receptors. **X-W. Dong, G. Liu, and J.L. Feldman**. UCLA.

40 12:00 **15.4** Effects of $GABA_A$ and $GABA_B$ agonists on respiratory related activity in the isolated brainstem of the frog. **H. Kawasaki, N. Kimura, S.F. Perry, and J.E. Remmers**. Univ. of Calgary.

41 11:00 **15.5** Substance P and physalaemin elicit glutamate-like modulation of respiratory related activity in the *in vitro* brainstem of the frog, *Rana pipiens*. **S.F. Perry, M. Sakurai, N. Kimura, and J.E. Remmers**. Univ. of Calgary.

42 12:00 **15.6** Mu-receptors mediate respiratory depressant action of opioids in the frog, *Rana pipiens*. **N. Kimura, S.F. Perry, and J.E. Remmers**. Univ. of Calgary and Jikei Univ., Tokyo, Japan.

43 11:00 **15.7** Role of excitatory amino acids in the production of spontaneous and reflexly evoked activity in expiratory bulbospinal neurons. **Z. Dogas, E. Stuth, M. Tonkovic, J. Bajic, F. Hopp, D. McCrimmon, and E. Zuperku**. Zablocki VA Med. Ctr., Miklwaukee, Med. Col. of Wisconsin, and Northwestern Univ.

44 12:00 **15.8** Electrical properties and transmitter responses of crayfish swimmeret motor neurons. **C.M. Sherff and B. Mulloney**. Univ. of California, Davis.

45 11:00 **15.9** Neural mechanisms of hypoglossal (XII) motoneuron depression during REM sleep-like atonia. **L. Kubin, A.I. Pack, and R.O. Davies**. Univ. of Pennsylvania.

46 12:00 **15.10** Absence of a biomechanical or metabolic significance to neuromuscular compartments. **L.L. Glenn**. East Tennessee State Univ.

47 11:00 **15.11** Experimental mononeuropathy increases GAP-43 mRNA levels in spinal motoneurons bilaterally. **C.E. Blanco, T. Mosconi, P.E. Micevych, and L. Kruger**. UCLA.

48 12:00; **15.12** A transient decrease in specific resistance during postnatal development of mammalian motoneurons. **W.E. Cameron, P.A. Nunez-Abades, J.M. Spielmann, and G. Barrionuevo**. Univ. of Pittsburgh.

49 11:00 **15.13** Independent recruitment to tonic firing among rat soleus motoneurons during spontaneous activity. **T. Eken and T. Lømo**. Univ. of Oslo, Norway.

50 12:00 **15.14** Effects of serotonin on repetitive firing and AHP in lumbar motoneurons of the neonatal rat. **M.K. Floeter**. NIH.

51 11:00 **15.15** Interaction of antispastic drugs and thyrotropin-releasing hormone in neonatal rat spinal cord *in vitro*. **S.B. Deshpande and J.E. Warnick**. Univ. of Maryland, Baltimore.

Tuesday

Symposium

16. Diseases of Movement

Chaired: **J.B. Martin**, UCSF

TUES. AM—Town & Country, Sierra Room

8:30 Pharmacology of locomotion after spinal cord injury. **Rossignol.** Univ. of Montreal and McGill Univ.
9:00 Parkinson's disease. **Y. Agid**. INSERM, Hosp. Salpêtrière, Paris, France.
9:30 Motor dysfunction in huntington's disease. **A.B. You** Mass. Gen. Hosp.
10:00 Neurophysiology of Pakinson's disease. **M.R. DeLo** Emory Univ.

17. Summation

J.B. Martin, UCSF.

TUES. AM—Town & Country, Sierra Room

Sessions with Contributed Abstracts

Invited Speaker Abstracts with Annotated Bibliographies

Poster Session Abstracts

Future APS Conferences and Meetings

1994

Intersociety Meeting

Regulation, Integration, Adaptation: A Species Approach — October 29–November 2
Organizers: E. J. Braun, J. R. Hazel, and S. H. Wright — San Diego, CA

APS Conferences

Physiology of the Release and Activity of Cytokines — June 25–28
Organizers: J. T. Stitt, J. G. Cannon, G. W. Duff, M. J. Kluger, A. J. Lewis, and I. G. Otterness — Yale University, New Haven, CT

Mechanotransduction and the Regulation of Growth and Differentiation — October 5–8
Organizers: H. E. Morgan, P. A. Watson, D. E. Rannels, F. Sachs, M. Schwartz, and H. Vandenburgh — Sarasota, FL

1995

Understanding the Biological Clock: From Genetics to Physiology
Organizers: Jay C. Dunlap and Jennifer J. Loros

New Discoveries Within the Pancreatic Polypeptide Family: Molecules to Medicine
Organizers: William Zipf, Ian Taylor, Claes R. Wahlestedt, Richard Rogers, and Helen J. Cooke

2.1

Anatomy of fast neurotransmitters in relation to motor control.

Jon Storm-Mathisen and Ole P. Ottersen, Anatomical Institute, University of Oslo, POB 1105 Blindern, N-0317 Oslo, Norway.

The main fast transmitters, glutamate, GABA and glycine, govern excitation and inhibition in all parts of the CNS. Examples of their localization in neuron systems implicated in motor control will be given. When cross-linked to tissue macromolecules by suitable fixative, free amino acids can be studied immunocytochemically.[1] Postembedding immunogold detection combined with the use of test sections (containing known concentrations of protein-fixed amino acids) allows quantification and verification of specificity. It permits two amino acids to be studied in the same ultrathin section. Glutamate is concentrated in nerve terminals, synapsing by asymmetric contacts on spines, including those of corticofugal fibers to striatum and pons, and those of cerebellar parallel, mossy and climbing fibers. Within the terminals, glutamate is concentrated in synaptic vesicles, from which it is depleted Ca^{2+}-dependently upon prolonged depolarization in tissue slices. The synapses are surrounded by astrocytic processes normally poor in glutamate, but rich in glutamine and in glutamate transporter.[2] Glutamate receptors have been detected immunocytochemically adjacent to the terminals, in postsynaptic dendritic spines or in astrocytic processes.[3] GABA is concentrated in terminals and usually in the parent perikarya of neurons with locally ramifying axons in all regions, and in addition in some projection neurons, including the Purkinje cells and striatonigral neurons. Glycine is in local neurons in the brain stem and spinal cord and in cerebellar Golgi cells. It is partly colocallized with GABA. -Supported by NAVF.

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2.2

SPINAL MOTONEURON AFFERENTS: ULTRASTRUCTURE, TRANSMITTERS AND ORIGIN

J.C. Holstege, Dept. of Anatomy, Erasmus University Rotterdam, The Netherlands.

The ultrastructure and transmitter content of the direct projections to spinal motoneurons may be summarized as follows:

1. The peripheral projection to motoneurons is derived from muscle spindles. These terminals are large, contain spherical vesicles (S-type) and probably use glutamate as a transmitter. They are often contacted presynaptically by other terminals (P-types), which contain GABA. This synaptic arrangement is the morphological substrate of presynaptic inhibition.

2. Many propriospinal projections to motoneurons originate from nearby interneurons (e.g. from Renshaw cells) and give rise to both S-type and F-type (with many fattened vesicles) terminals. GABA and glycine (1) are the (inhibitory) transmitters, often coexisting, of the F-type terminals. The excitatory interneuronal projections are probably of the S-type and contain glutamate as a transmitter, but aspartate and acetyl-choline may also be present. Terminals from motor-axon recurrent collaterals are also S-type and contain acetyl-choline.

3. In primates, like chimpanzee and man, a major supraspinal projection to motoneurons is derived from the motor cortex. The terminals of these projections are S-type and may contain glutamate. Brain stem projections to spinal motoneurons were recently identified to give rise to F-, S-, G(granular) and C(subsynaptic cistern)-type terminals. The G-type terminals are derived mainly from the caudal raphe nuclei and contain serotonin, sometimes in co-existence with substance P or other peptides. The F- and S-type terminals are derived mainly from the reticular formation of the ventro-medial lower brain stem and from the vestibular nuclei. The S-type terminals may contain glutamate (2), while the F-type terminals contain GABA and/or glycine (3). In addition there exists a noradrenergic projection from the locus coeruleus and a dopaminergic projection from the posterior hypothalamus to spinal motoneurons.

It is concluded A) that differences in terminal morphology are correlated with differences in transmitter content rather than differences in origin and B) that several brain stem projections, with various transmitters, terminate directly on spinal motoneurons.

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Glycine-like immunoreactivity in synaptic boutons of identified inhibitory interneurons in the mammalian spinal cord. *Brain Res. 547 (1991) 175-179.* In this paper a combination of intracellular staining with HRP and the immunogold technique with a glycine antibody is used at the ultrastructural level to show that physiologically identified Renshaw cells and Ia inhibitory interneurons give rise to terminals with flattened vesicles, containing glycine.

2. Nicholas A. P., Pieribone V. A., Arvidsson U. and Hökfelt T.
Serotonin-, substance P- and glutamate/aspartate-like immunoreactivities in medullo-spinal pathways of rat and primate. *Neuroscience 48 (1992) 545-559.* Light microscopic retrograde and anterograde tracing combined with immunocytochemistry showed glutamate and aspartate co-existing with serotonin and/or substance P in spinal projecting cells and their terminals around motoneurons, suggesting that excitatory amino acids may be the "main" transmitter in the descending serotonergic fibers.

3. Holstege J. C.
Ultrastructural evidence for GABAergic brain stem projections to spinal motoneurons in the rat. *J. Neurosci. 11 (1991) 159-167.*
A combination of anterograde tracing with GABA immunocytochemistry shows that 40% of projections descending from the ventro-medial reticular formation contain GABA. Some of these terminals may also contain serotonin or glycine (Holstege JC & Bongers, Brain Res. 566 (1991) 308-315).

2.4

NEUROPEPTIDES IN AND ON THE SPINAL MOTONEURON. Staffan Cullheim, Ulf Arvidsson, Fredrik Piehl, Brun Ulfhake and Tomas Hökfelt, Dept. of Neuroscience and Anatomy, Karolinska Institutet, Stockholm, Sweden.

Acetylcholine is the classical transmitter in the spinal motoneuron. Recently, also a number of peptides have been observed in motoneurons of several species, especially during development and after lesion. The most extensively studied peptide in motoneurons is calcitonin gene-related peptide (CGRP). CGRP has several effects at the neuromuscular junction including regulation of nicotinic acetylcholine receptor synthesis in the muscle cells. No clear correlation between motoneuron type and CGRP content is at hand, except for the consistently low levels or absence of CGRP in gamma motoneurons. Motoneuron injury and manipulation of afferent inputs to these cells alter the levels of CGRP peptide and CGRP mRNA, suggesting a role for survival and/or regeneration of motoneurons.

A selective chemical lesion of the descending serotoninergic (5-HT) pathway leads to an upregulation of CGRP in motoneurons. The mechanism for this is unknown, but it is of interest that 5-HT fibers in the spinal motor nuclei co-contain a number of peptides (substance P, thyrotropin-releasing hormone, CGRP in the monkey) and growth-related substances (GAP-43 and trkC in the monkey), possibly reflecting a role for these fibers in the plasticity of the motor system.

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3.1

MOLECULAR BIOLOGY OF GLUTAMATE RECEPTORS

Bettler, B., Boulter, J., Brose, N., Dingledine, R., Edgebjerge, J., Gasic, G., Hollmann, M., Hume, R.I., Okado, H., Puchalski, R., Vetter, D., and **Heinemann, S.** Molecular Neurobiology Laboratory, The Salk Institute, P.O. Box 85800, San Diego, California 92138

The glutamate receptor system is thought to be involved in the first steps of learning and memory acquisition and has also been implicated in a number of degenerative brain diseases involving neuronal cell death. In order to study the glutamate receptor system at the molecular and physiological level, we have used an expression cloning approach to identify and clone a family of glutamate receptor genes. The first gene that we identified, GluR1, codes for a functional glutamate receptor. There are at least fourteen additional genes related to the GluR1 gene which have been cloned and code for glutamate receptor subunits. By assembling the subunits in different combinations we have demonstrated that it is possible to make glutamate receptors with different biophysical and pharmacological properties. The relationship of this diverse set of possible glutamate receptor subtypes to glutamate receptor function in the brain will be discussed.

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1.

2.

3.

3.2

PHYSIOLOGICAL CHARACTERIZATION OF GLUTAMATE RECEPTOR FUNCTION. Mark L. Mayer, Lab. Cellular and Molecular Neurophysiology, NICHD, NIH.

Glutamate is believed to be the principle excitatory transmitter in the mammalian CNS because, with few exceptions, selective glutamate receptor antagonist block synaptic transmission at pathways in the brain, spinal cord and retina blocked. At virtually every synapse examined, excitatory synaptic currents have fast and slow components mediated by AMPA/kainate- and NMDA-preferring subtypes of glutamate receptor. The identification of multiple gene families for glutamate receptors has now revealed that, within these broad categories, there potentially exists multiple receptor subtypes. Analysis of the functional properties of glutamate receptor subunits expressed from individual cDNAs reveals differences in affinity for glutamate and, for NMDA receptors, glycine, plus subtype specific alterations in relative permeability for Ca over Na. Currently, little is known concerning the diversity of glutamate receptor properties in different areas of the CNS, and the subunit composition of native glutamate receptors remains poorly understood. To address these issues we have identified agonists and modulators which differentiate glutamate receptor subtypes in neurons and glia, as well as following expression in oocytes and HEK-293 cells.

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Cyclothiazide selectively modulates AMPA- but not kainate-preferring glutamate receptors.
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3.3

MOLECULAR BIOLOGY OF GABA PRODUCTION AND ACTION. A.J. Tobin. Department of Biology, Brain Research Institute, & Molecular Biology Institute, UCLA, Los Angeles, CA 90024.

Inhibitory interactions in the nervous system are critical to a wide variety of neural networks, including those that control movements. To understand the production and action of GABA, the most prominent inhibitory neurotransmitter, we have used molecular techniques to study the structure, function, and regulation of the two GABA-synthesizing enzymes and $GABA_A$ receptors. The two GADs, which derive from a two-member multigene family, differ in sequence, regulatory responses, and intracellular location. Similarly, $GABA_A$ receptor polypeptides derive from related multigene families. Individual GAD and $GABA_A$ receptor polypeptides appear to be under different selection pressures, suggesting that each polypeptide could either play a distinctive functional role, or that each gene could have a distinctive response to developmental cues or neuronal activity. Molecular biological approaches allow the dissection of the differing functional and regulatory properties of GAD and $GABA_A$ receptor polypeptides. In addition, the genetic engineering of somatic cells permits examination of the mechanisms for the cellular regulation of GABA production and release. (Supported by NIH NS22256.)

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Rat-1 fibroblasts engineered with GAD_{65} and GAD_{67} cDNAs in retroviral vectors produce and release GABA.
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3.4

PHYSIOLOGICAL CHARACTERIZATION OF GABA RECEPTOR FUNCTION. Roger A. Nicoll*. Depts. of Pharmacology and Physiology, University of California, San Francisco, CA 94143-0450

Virtually all neurons in the CNS receive GABAergic synaptic inhibition. The action of GABA is mediated by two types of receptor: $GABA_A$ and $GABA_B$ receptors. Most attention has been given to $GABA_A$ receptors which form channels that are selective for Cl^- ions and mediate a fast IPSP. Synapses mediating $GABA_A$ IPSPs are concentrated on the soma and initial segment, but are also present at lower density throughout the dendritic tree of pyramidal cells. $GABA_B$ receptors are G-protein-coupled receptors that activate a slow K^+ -dependent IPSP. In the hippocampus these IPSPs are localized to the dendrites and are mediated by interneurons distinct from those mediating $GABA_A$ IPSPs. $GABA_B$ receptors are also present on the terminals of excitatory as well as inhibitory synapses. Synaptically released GABA acts on autoreceptors to inhibit the release of GABA and also diffuses to neighboring excitatory synapses to inhibit the release of glutamate. The differential localization of $GABA_A$ and $GABA_B$ receptors as well as their activation by distinct classes of interneurons provides enormous flexibility for selective control of excitability not only at the somatic and dendritic level, but also at the presynaptic level.

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This paper shows a functional role for presynaptic $GABA_B$ receptors and that GABA can "spill-over" to neighboring synapses.

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Similarities in circuitry between Ammon's horn and dentate gyrus: local interactions and parallel processing.
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The article reviews the various types of interneurons present in the hippocampus and their roles in information processing.

3.5

ELECTROPHYSIOLOGICAL ACTIONS OF SEROTONIN (5-HT) ON FACIAL MOTORNEURONS (FMNs). G.K. Aghajanian, Departments of Psychiatry and Pharmacology, Yale School of Medicine, New Haven, CT 06508

In FMNs, both *in vivo* and *in vitro* in brain slices, 5-HT induces a subthreshold depolarization associated with an increase in input resistance and an increase in electrical excitability. These effects are mediated by G proteins as they are rendered irreversible by intracellular GTPγS, a non-hydrolyzable analog of GTP (Aghajanian, 1990). Recent data show that 5-HT has a dual effect on FMNs (Garratt et al., 1993; Larkman and Kelly, 1992): 1) a decrease in a resting potassium current ($I_{K(r)}$) and 2) an enhancement of a hyperpolarization-activated cationic current (I_h). When I_h is blocked by CsCl, the remaining component of the 5-HT-inward current reverses near the expected reversal potential for potassium (Garratt et al., 1993). Although both $I_{K(r)}$ and I_h are mediated by 5-HT_2-type receptors, they display different agonist efficacies. For example, LSD has low efficacy relative to 5-HT in decreasing $I_{K(r)}$ (and acts as a potent partial agonist in relation to the depolarizing effect of 5-HT) but has high efficacy relative to 5-HT in enhancing I_h. The difference in efficacy between 5-HT and LSD on these two currents could be due to either: 1) the presence of two subtypes of 5-HT_2 receptors having differential efficacy with respect to different agonists or 2) a single type of 5-HT_2 receptor whose agonist efficacy is altered by its coupling to different G proteins.

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3.6

Peptides and Endorphins. George Robert Siggins, Dept. of Neuropharm., The Scripps Res. Inst., La Jolla, California 92037.

Although the neuropeptides share many actions, or electrophysiologic messages, with the monoamine neurotransmitters, in many neuron types there are emerging differences. As a group, the peptides have been generally characterized as exerting actions 1) with slow onset and long duration, 2) involving second messengers or G-protein mediation (rather than directly activating receptor-ionophore complexes), 3) on voltage-dependent or ion-dependent channels, or 4) of a modulatory nature, especially in regulating release of other transmitters. Four types of peptides–LHRH, CRF, somatostatin and the opioid peptides–illustrate the spectrum of electrophysiological actions of peptides on central and peripheral neurons. LHRH and CRF tend to be predominantly excitatory, and the other two, predominantly inhibitory. For a given neuron, each of these peptides may act on at least one (and often more) of four major ion conductance types: 1) the M-current (a voltage-dependent K^+ conductance); 2) the afterhyperpolarization current (a Ca^{++}-dependent K^+ conductance), 3) inward rectifier currents (voltage-dependent K^+ currents), and 4) voltage-dependent Ca^{++} currents. A case can be made that peptide regulation of these four conductances (using only two, opposing, ion species, Ca^{++} and K^+) will allow precise, reciprocal coordination of Ca^{++} influx and therefore of transmitter and hormone release. Furthermore, our group has found that in the same cell type, somatostatin and some opioid peptides can activate the same K^+ conductance (the M-current) that is inactivated by non-peptide transmitters like acetylcholine and glutamate, providing two examples of reciprocal regulation of excitability. The recently reported close homology between the structure of the opiate delta receptor and somatostatin receptors may explain one element of these findings. Finally, two different members (dynorphin and enkephalin) of the same peptide family (opioids), acting on different receptor subtypes, can reciprocally regulate the same channel species (the M-channel) in a single neuron type (CA3 pyramidal neurons). These and other new data verify the importance of the identity of peptide receptor subtypes (perhaps with unique subunit arrangements), and suggest that peptides can provide a sensitive and long-lasting bias of excitability, synaptic strength and hormone release.

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4.1

MODULATION OF OSCILLATORY NEURAL NETWORKS.
Eve Marder, Biology Department and Center for Complex Systems, Brandeis University, Waltham, MA 02254.

The rhythmic neural circuits within the stomatogastric nervous system are reconfigured by numerous neuromodulatory substances. We now view these systems as multiple task processors (Marder and Weimann, 1992), and find that modulatory substances "construct" different functional circuits as appropriate for the behavioral state of the animal, by modifying intrinsic membrane properties of individual neurons and the strengths of synaptic connections. Specifically, we find that some neurons switch between different central pattern generating circuits, and become integral components of different networks as the modulatory environment is modified (Weimann et al., 1991). I will discuss the use of the new dynamic clamp technique (Sharp et al., 1993) to study how the actions of neuromodulatory substances on specific target neurons and synaptic connections can lead to changes in network function. This method allows us to add voltage and time dependent conductances to neurons, as well as to create artificial chemical and electrical synapses among neurons.
Supported by NS17813.

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4.2

TRANSMISSION IN THE NETWORK UNDERLYING NEURONES IN LAMPREY. S. Grillner. Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden.

The lamprey brainstem-spinal cord can be maintained in vitro for periods of 103 days, and the motor patterns underlying for instance locomotion and respiration can be elicited in the isolated nervous system. This condition has allowed a detailed analysis of the different types of synaptic transmission and membrane properties which are important. The basic circuitry in the network utilizes excitatory glutamate transmission via AMPA/kainate and NMDA receptors and glycinergic inhibition. However, presynaptic modulation occurs via both $GABA_A$ and inhibition. However, presynaptic modulation occurs via both $GABA_A$ and $_B$ receptors on the axonal terminals of both inhibitory and excitatory premotor interneurones. In the soma-dendritic membrane an activation of $GABA_B$ receptors causes a depression of both high and low voltage activated Ca^{2+} currents in network interneurones. 5-HT acts on K_{Ca} and control the frequency regulation of network interneurones.

The different synaptic mechanisms used, and their specific role for the pattern generation will be addressed.

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4.3

Studies of presynaptic mechanisms in reticulospinal glutamate neurons
Lennart Brodin, The Nobel Institute for Neurophysiology, Karolinska Institutet Box 60400, S-104 01 Stockholm, Sweden

The giant reticulospinal neurons in lamprey offer an attractive model for studies of vertebrate presynaptic mechanisms, as their large axons permit direct recording with microelectrodes[1,2]. The clusters of synaptic vesicles within the axons show a strong accumulation of glutamate immunogold labelling, which indicates an intravesicular glutamate concentration of 60 mM or more[3]. Immunoreactivity to other excitatory amino acids[2], does not accumulate over synaptic vesicles. The synapses, which activate AMPA and NMDA receptors[1], appear to operate at a low level, as a spike broadening induced by current pulses causes a marked increase of the EPSP amplitude, but individual EPSPs along the same axon exhibit different degrees of use-dependent modulation (facilitation and depression). The latter can be altered by intraaxonal current pulses indicating a dependence on presynaptic mechanisms. Intraaxonal injection of antiserum to synapsin (I and II) produces a selective labeling of the active zone areas and, like in squid, injection of dephosphosynapsin I reduces the amplitude of the EPSP. The axoplasmic matrix surrounding the synaptic vesicle clusters contain a very low concentration of fixed glutamate (⟨0.5 mM of fixed glu). The low extravesicular glutamate level may relate to the synaptic properties, as these neurons normally fire in brief bursts, and the transmission fatigues during long-term stimulation. Other glutamate synapses, with a predominantly tonic firing pattern, show more than 4 times higher glutamate levels in axoplasmic matrix[3], and the ratio between glutamate and glutamine labelling in synaptic mitochondria is significantly higher, indicating that the glutamate synthesis is more efficient than in the reticulospinal synapses.

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4.4

DYNAMIC REGULATION OF GENE EXPRESSION IN NEUROCIRCUITS OF THE BASAL GANGLIA. A.M. Graybiel. Massachusetts Institute of Technology, Cambridge, MA.

The basal ganglia participate in motor control and probably also in processing related to cognition and affect. The basal ganglia have the interesting feature of "releasing" their target structures from inhibition. Many of the neuropeptide neuromodulators identified in the forebrain have high levels in the basal ganglia. These intrinsic modulators are especially concentrated in the striatum, the main input side of the basal ganglia. Extrinsic modulators such as dopamine also affect the basal ganglia, and strongly target the striatum. The striatum is thus a potential focal point for plasticity in basal ganglia function. This lecture will focus on new evidence suggesting that striatal neuromodulators are part of a control system whereby the levels of neuromodulators in the basal ganglia can be regulated by gene expression. Both therapeutic drugs and drugs of abuse induce marked changes in levels of gene expression in striatal neurons. These drug-induced changes provide a clinically interesting tool for studying the dynamic control of gene expression in the mammalian forebrain.

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4.5

NEUROTRANSMITTER CONTROL OF CORTICAL AND THALAMIC ACTION. David A. McCormick, Thierry Bal, Marcus von Krosigk, and Zhong Wang Section of Neurobiology, Yale University Medical School, 333 Cedar St. New Haven, CT

Awakening from sleep and increases in arousal are associated with abolition of slow oscillations in thalamic and cortical networks and preparation for processing sensory information and production of motor output. These changes are brought about through the actions of a variety of neurotransmitters including acetylcholine, norepinephrine, serotonin, histamine, and glutamate released from brainstem/hypothalamic/basal forebrain and local circuits (McCormick, 1992).

Increased release of these neurotransmitters during arousal results in an increase in neuronal excitability throughout the nervous system, often, but not always, through membrane depolarization mediated by reduction of specialized K^+ conductances. Transmitter-induced depolarizations in thalamic networks abolish intrinsic slow rhythms in both relay cells and the GABAergic neurons of the nucleus reticularis (see McCormick, 1992) and consequently abolish intra-thalamic network slow oscillations (von Krosigk et al., 1993) and replace these with activity that is more conducive to the performance of sensory/motor tasks. Similarly in cortical networks, release of a wide variety of neurotransmitters alters the cellular and network properties from one of slow, rhythmic burst discharge in sub-cortically projecting layer V cells (Wang and McCormick, 1993) to more tonic activity. Under certain conditions, higher frequency (20-60 Hz) rhythmic burst activity in multiple cell types in the cerebral cortex can also be generated. The synchronization of this rhythmic activity may be useful for the processing of sensory information and the temporary formation of functionally related pools of neurons. We propose that these alterations in cellular activities prepare forebrain networks for the motoric interaction with the sensory world. Supported by NIH and the Klingenstein Fund.

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12.1

Functional Organization of Motoneurons and Motor Units R. E. Burke, Lab. of Neural Control, NINDS, NIH, Bethesda, MD 20892

The neural control of movement inevitably involves the output elements of the motor system - motoneurons and their muscle units (collectively motor units). A half century of systematic study has produced a wealth of information about the properties of motoneurons and their relation to the mechanical and biochemical characteristics of their muscle units, all subsumed under the rubric of "motor unit types". There has also been some progress in defining the organization of synaptic input to the three basic unit types that make up heterogeneous muscles. The systematic interrelations evident among these domains can be related in turn to the functional usage of the various identified types during motor unit recruitment, which is one of the two major mechanisms of output control. The other control mechanism involves regulation of motoneuron firing rate (often referred to as "rate coding"). The mechanisms of rate modulation are well studied but its highly non-linear effects on muscle units during actual movements are less fully understood. Two important and unsettled issues are: 1) the definition of functional motor unit "pools" within which recruitment sequences operate during motor performance in intact animals; and 2) the existence and functional importance of alternative recruitment sequences that may occur under different conditions. All of these topics will be reviewed briefly.

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12.2

SPINAL CORD INTERNEURONS

Jankowska, E.
Dept. of Physiology, University of Göteborg,
S-413 90 Göteborg, Sweden

The properties of spinal interneurons are highly differentiated, even for those populations of interneurons which mediate responses evoked from the same type of receptor. E.g. individual interneurones in pathways from muscle spindles of one muscle may have different target cells and may be activated under different circumstances. They may also have different membrane properties. They may therefore react in different ways to similar stimuli and be under the control of different neuronal systems, e.g. either noradrenergic or serotonergic. These features allow the selection of different subpopulations of spinal interneurons to subserve various movements. These general statements will be illustrated with observations on recently investigated populations of interneurones in pathways from group II muscle afferents.

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12.3

OLIVOCEREBELLAR SYSTEM AND MOTOR COORDINATION

R. Llinás, J. Welsh, E.J. Lang and I. Sugihara, NYU Medical Center, Dept. of Physiology /Biophysics, 550 First Avenue, New York, New York 10016

Recent multiple-electrode recording experiments in the rat cerebellar cortex indicate that climbing-fiber-activated Purkinje-cell complex spikes occur synchronously (within 1 msec) in rostrocaudal bands which extend down the folial walls to the deeper folds of the cerebellar cortex.

Studies of the olivocerebellar system demonstrate that the conduction time for these afferents is uniform and therefore independent of pathway length. This indicates that conduction velocity in this system is organized so as to produce synchronous complex spikes in Purkinje cells through the cerebellar cortex (i.e. while the cerebellar cortex is folded anatomically, it is actually an isochronic surface functionally). Multiple-electrode recordings from awake rats also demonstrate that a close correlation exists between Purkinje cell complex spikes and the time of generation of certain mouth and tongue movements. Moreover, it was found that the degree and distribution of simultaneity of Purkinje-cell complex spikes in the cerebellar cortex, could be modulated by inhibitory systems arising from cerebellar nuclei and terminating in the vicinity of the electrical junction in the inferior olive cells. Thus, the climbing-fiber system presents a rhythmic oscillating network dynamically controlled by the shunting of electrical transmission and temporally related to the execution of movement.

Supported by: NS13742

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12.4

Inhibitory Control of Saccadic Eye Movement by the Basal Ganglia

O. Hikosaka, Laboratory of Neural Control, National Institute for Physiological Sciences, Myodaijicho, Okazaki 444, Japan

The oculomotor function of the basal ganglia is mediated by an inhibitory connection from the substantia nigra pars reticulata (SNr) to the superior colliculus (SC). The caudate nucleus inhibits SNr, leading to a disinhibition of SC. In addition, the caudate has indirect access to SNr through the external segment of globus pallidus (GPe) and the subthalamic nucleus (STN). The indirect pathway, Cd-GPe-STN-SNr, is thought to be antagonistic to the direct mechanism, Cd-SNr-SC, because GPe neurons are inhibitory while STN neurons are excitatory. Indeed, our recent study has suggested that STN participates in suppression of saccades by maintaining excitation of SNr neurons. In the dorsal part of GPe also were found neurons showing visuo-oculomotor activities. In GPe different responses (e.g., visual, saccadic, reward-related) tended to be combined in single neurons; the visual/saccadic responses were often spatially non-selective. These signals, conveyed to SNr directly or via STN, would exert surrounding effects (facilitatory or inhibitory), not yielding specific motor outputs.

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12.5

THE SUPERIOR COLLICULUS AS A MODEL OF SENSORIMOTOR CONTROL. Robert H. Wurtz, Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, MD 20892 USA.

Vision consists of periods of fixation on objects of interest interrupted by rapid or saccadic eye movements from one object of interest to another. Both fixation and saccadic eye movements are essential to normal vision. Recent experiments on the superior colliculus (SC) of awake behaving old world monkeys (macaca mulatta) have revealed neural mechanisms underlying both of these critical functions.

Cells related to saccades are located in the intermediate layers of the SC, and activity develops before a saccade at a locus on the SC motor map coding the amplitude and direction of an impending saccade. One type of cell gives a burst of activity before a saccade. The burst frequently terminates with the end of the saccade, and this observation has led to the hypothesis that the superior colliculus lies inside a feedback loop that controls the amplitude of the saccade. A second type of cell has a slow buildup of discharge rate in addition to saccade related bursts. Once the saccade begins, cells of this type located progressively more rostral to the initially active zone are activated sequentially starting at progressively later times. This spread of activity might also contribute to the feedback related to terminating the saccade or to the control of combined eye and head movements. A third type of cell, located in the rostral pole of the SC intermediate layers, increases its discharge rate during active visual fixation. These cells are related to the act of fixation not the visual fixation target, and the cells pause during saccades with a duration proportional to the duration of the saccade.

There is thus a reciprocal relationship between cells in the rostral colliculus, which increase their discharge during fixation and pause during saccades, and those burst cells in the caudal colliculus, which are silent during fixation and burst during saccades. These experimental results have been incorporated into a revised model of the saccadic system that includes visual fixation and places the SC in the feedback loop controlling saccadic amplitude.

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12.7

REPRESENTATION OF MOTOR PROGRAMS IN THE CEREBELLUM AND PREMOTOR NETWORK. James C. Houk, Department of Physiology, Northwestern University Medical School, 303 E. Chicago Ave., Chicago, IL 60611-3008

Neuroanatomical studies have demonstrated a network of interconnections between the motor cortex, red nucleus and cerebellum, forming a premotor network for controlling limb movement. Single unit studies indicate that command signals for limb movements are distributed broadly throughout this network. Cellular studies have demonstrated multiple recurrent loops in this network, and the presence of excitatory and inhibitory amino acid neurotransmitters. A recent model suggests that movement commands are initiated by sensory inputs to these loops, and that positive feedback, regulated by inhibition from cerebellar Purkinje cells, distributes commands throughout the limb premotor network. This model offers a new framework for exploring relationships between basic neural mechanisms and motor program concepts that derive from experimental psychology.

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NEUROPHARMACOLOGY OF MOTONEURONS

13.1

Control of phrenic motoneuronal excitability. JL Feldman & G Liu. Systems Neurobiology Lab., Department of Physiological Science, UCLA, Los Angeles, CA, 90024-1527

Phrenic motoneurons have a straightforward task: control the diaphragm. Regulation of their excitability is critical for the precise control of breathing. Transmission of excitatory inspiratory drive to phrenic motoneurons is mediated by the release of glutamate acting on postsynaptic AMPA, kainate and NMDA receptors; the postsynaptic action appears quantized. Intrinsic and synaptic properties lead to a marked voltage-dependent response to inspiratory drive currents. Presynaptic modulation of the drive is mediated by receptors for $GABA_B$, adenosine, 5-HT and AP4. We propose that high levels of inspiratory drive will elevate glutamate in the synaptic cleft to activate AP4 autoreceptors to reduce further release. This may act as a governor on phrenic motoneuronal activity to reduce the likelihood of diaphragmatic fatigue during sustained epochs of high ventilatory demands. We have evidence for pre- and/or postsynaptic receptors for glutamate, GABA, 5-HT, NE, and many peptides. We propose several hypotheses as to the role of these multiple transmitters: i) They operate over markedly different time scales. ii) They provide mechanisms for cascade control of output. iii) They permit differential control of excitability. We propose a simple schema for the differential control of excitability by 5-HT which may underlie its effects on motoneuronal activity during the sleep-wake cycle. Supported by NS 24742.

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13.2

TRANSMITTER CONTROLLED INTRINSIC PROPERTIES OF SPINAL MOTONEURONS H. Hultborn, Dept. of Medical Physiology, Copenhagen University, Copenhagen, Denmark.

The classical view of the mammalian spinal motoneuron emerged from the laboratories of Eccles and Granit during the 1950s and 1960s. They held the view that the cell membrane in areas of synaptic contact was essentially passive, allowing a linear summation of synaptic inputs at the spike-initiating region. It is now known that there are several active membrane properties that contribute to the electro-responsiveness of motoneurons. In addition a great number of reports have appeared during the past 5 years showing that such properties are often strongly transmitter modulated. Taken together this implies that not only do motoneurons actively take part in information processing, but also that the input-output relation of individual motoneurons seems to be a flexible variable that may be adapted according to the external requirements. This presentation will focus on the recent analysis of the monoaminergic control of motoneuronal behavior in the cat, rat and turtle. In this analysis we have shown that a brief synaptic depolarization may evoke large and longlasting plateau potentials, which can be terminated by short-lasting synaptic hyperpolarisation. These plateau-potentials are contingent upon a noradrenergic or serotonergic innervation of the motoneurons.

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13.3

MONOAMINES, PEPTIDES AND MOTONEURONS. S. R. White, Dept. of VCAPP, Washington State Univ., Pullman, WA 99164.

Spinal motoneurons are richly innervated by norepinephrine (NE)- and serotonin (5HT)-containing terminals, many of which contain colocalized glutamate, substance P (SP) and/or thyrotropin releasing hormone (TRH). Intracellular and extracellular recording combined with microiontophoresis in anesthetized rats and decerebrate cats *in situ* revealed that 5HT, NE, SP and TRH produced small-amplitude, long-lasting depolarizations of both extensor and flexor motoneurons and facilitated motoneuron responses to intracellular depolarizing pulses and extracellular application of excitatory amino acids. The excitatory effects of 5HT on glutamate-evoked responses appeared to be mediated by 5HT2/5HT1C receptors and those of NE were mediated by alpha1-adrenergic receptors.

Concurrent application of SP enhanced the excitatory effects of 5HT on spinal motoneurons but concurrent application of TRH diminished the excitatory effects of 5HT. Moreover, marked tachyphylaxis developed to the facilitatory effects of TRH alone on glutamate-evoked firing, often reversing facilitation to inhibition in these adult animals. These results indicate that whereas 5HT and NE both enhance spinal motoneuron excitability when applied alone, colocalized peptides may interact with these monoamines to enhance or inhibit motoneuron excitability depending upon which peptides are released and the time which has elapsed since previous exposure to the peptides.

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13.4

NEUROPHYSIOLOGY AND PHARMACOLOGY OF RESPIRATORY RHYTHM GENERATION IN MAMMALS. JC Smith, GD Funk, SM Johnson, and JL Feldman. Department of Physiological Science, UCLA, Los Angeles, CA 90024.

The brainstem networks generating respiratory rhythm represent an important model system for analysis of neurochemical and physiological mechanisms underlying rhythmic motor behavior in mammals. *In vitro* brainstem-spinal cord and medullary slice preparations from neonatal rat that retain respiratory network activity have been developed which allow mechanisms of rhythmogenesis to be studied concurrently at the cellular, synaptic, and network levels. With these preparations, we have identified the main locus for respiratory rhythm generation in the medulla. We have also obtained evidence that the kernel of the respiratory oscillator may consist of pacemaker-like neurons embedded in a network where rhythm generation is regulated by interactions of synaptic inputs and intrinsic membrane currents within the pacemaker cell population. Synaptic interactions mediated by excitatory amino acids acting at non-NMDA receptors are critical for generation and transmission of the rhythm. Rhythm can be modulated by a variety of neurochemicals including serotonin, norepinephrine, GABA, and substance P. Receptor subtypes for these transmitters that are linked to inward rectifying potassium conductances may be particularly important in modulation of rhythm. We have developed computational models of oscillatory neurons and networks that demonstrate the plausibility of rhythm generation via the synaptic and intrinsic membrane conductance mechanisms suggested by experimental data. (Supported by NIH Grants HL40959 & HL02204).

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13.5

DESCENDING CONTROL OF LOCOMOTION. Larry M. Jordan. Univ. of Manitoba, Winnipeg, MB, Canada R3N 0W4

The descending pathways which influence the control of locomotion serve several functions, including initiation and termination of activity in spinal locomotor circuits, modulation of stepping frequency, control of gait pattern, and control of firing rate, plateau potentials and after-hyperpolarizations in motoneurons. The descending pathway responsible for the initiation of locomotion originates in the medial reticular formation and terminates on segmental interneurons. This pathway appears to produce rhythmic activity through the release of an excitatory amino acid acting at NMDA receptors. Other descending pathways implicated in the initiation of locomotion include those originating in brainstem noradrenaline- and serotonin-containing neurons. The release of an excitatory amino acid at the segmental level appears to be required, because brainstem evoked locomotor activity is reversibly blocked by NMDA antagonists. Resetting and/or entrainment of the locomotor rhythm can be achieved through the vestibulospinal and reticulospinal pathways, and together with the corticospinal and rubrospinal systems, these pathways appear to control the amplitude of motoneuron output during locomotion. The corticospinal pathway is especially important for the control of the distal musculature during stepping, and for voluntary modification of gait.

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Intrathecal infusions of NMDA agonists and EAA uptake inhibitors induce treadmill locomotion in decerebrate cats, while NMDA and non-NMDA antagonists block brainstem evoked locomotor.

16.1

PHARMACOLOGY OF LOCOMOTION AFTER SPINAL CORD INJURY. S. Rossignol, H. Barbeau, C. Chau and K. E. Norman. Center for Research in Neurological Sciences, U. de Montréal and School of Physical and Occupational Therapy, McGill U., Montréal.

In the first week after a complete spinalisation at T13, cats can walk with their hindlimbs on a treadmill after an injection of norepinephrine (NE), L-DOPA or α-2 NE agonists (clonidine or oxymetazoline). After a few weeks, cats gradually recuperate their ability to walk spontaneously on the moving belt. α-2 NE agonists, given i.p. or intrathecally, can significantly increase the cycle duration and the amplitude of the locomotor movements. This is often accompanied by a foot drag in swing and a reduction in cutaneous reflex excitability. These effects are reversed by noradrenergic blockers. The α-1 agonist Methoxamine, on the contrary, has only small effects on locomotion while reflex excitability appears to be increased. Serotonergic agonists also significantly increase the locomotor movements and cutaneous excitability, effects which are blocked by cyproheptadine, a serotonergic blocker. These observations served as a basis for trials in spinal cord injured patients, using oral clonidine and cyproheptadine and locomotor training with a weight support system over a treadmill. Cyproheptadine markedly reduced clonus and spasms during walking while clonidine improved the regularity of stepping on the treadmill. Combined clonidine and cyproheptadine and locomotor training further improved the walking pattern so that at least two patients were capable of walking with aids whereas they were mainly wheelchair-bound previously. (Supported by the MRC and the Network of Centers of Excellence on Neural Regeneration and Functional Recovery).

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16.2

PARKINSON'S DISEASE Yves Agid. Hôpital de la Salpêtrière, Paris, France

Parkinson's disease is the only neurodegenerative disorder in which symptoms can be successfully treated long-term. Despite treatment, motor and cognitive symptoms may worsen as a result of increasingly complex combinations of dopaminergic and non-dopaminergic brain lesions. Levadopa-responsive patients have a continued response to treatment, suggesting that they have a severe but selective degeneration of the nigrostriatal dopaminergic system sparing the striatal outputs. In other patients (progressive supranuclear palsy), response to levodopa is prevented by lesions of non-dopaminergic efference neurones located downstream from the striatum. Most cases of patients with Parkinson's disease lie between these extremes: levodopa still improves parkinsonian disability but drug-resistant axial symptoms (gait disorder, postural instability, dementia) develop as a result from additional lesions which are located in parallel with dopaminergic lesions. The loss of dopaminergic neurones projecting towards the cerebral cortex, limbic areas and the various parts of the striatum, very likely contributes to psychic, cognitive and motor symptoms. For instance, neurons originating in the mesencephalic A8 area seems to play a critical role in the occurrence of tremor. The respecitve role of genetic and environmental factors in dopaminergic nerve cell death is not clear. The hypothesis of a genetically determined vulnerability of dopaminergic neurons to an exogenous agent that results in subacute toxic cell death is attractive. Within the cascade of biochemical events leading to nerve cell death, the most popular are: oxidative stress, defective mitochondrial respiration, lack of specific trophic factors, vulnerability to calcium, defect in the membrane dopamine transporter, etc., all hypotheses which are not exculsive.

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3.

16.3

MOTOR DYSFUNCTION IN HUNTINGTON'S DISEASE

Anne B. Young. Massachusetts General Hospital.

In adult onset Huntington's disease (HD) the motor disorder begins incidiously with a combination of decreased fine motor coordination, abnormal saccades and brief involuntary movements of the limbs, trunk and face (chorea). These progress gradually until the patient has prominent involuntary movements, dystonia, rigidity, and dysarthria. In some adult onset patients and most juvenile onset patients, the motor disorder begins as bradykinesia, rigidity or dystonia and chorea is a minor or nonexistent component.

The pathology of mildly to moderately affected adult onset HD cases shows the most prominent pathology in the striatal projections to lateral pallidum (LGP) and substantia nigra pars reticulata (SNr) with relative sparing of the striatal projections to medial pallidum (MGP). In juvenile cases and adult onset rigid cases, severe pathology is seen in the striatal projections to all three regions, LGP, MGP, and SNr. Thus, in early adult HD, the indirect pathway is underactive as is the direct pathway to the SNr. In juvenile and rigid adult cases, both direct and indirect pathways are devastated.

The relationship of pathology severity to the number of triplet repeats in the HD gene is still unknown as is the reason why the gene selectively affects only subpopulations of striatal neurons. The pathophysiology of the dystonia observed in HD is also a mystery.

Supported by USPHS grant NS19613.

REFERENCES:

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5.1

SYNAPTIC VESICLE PROTEINS IN THE MONKEY (Macaca fascicularis) SPINAL CORD WITH EMPHASIS ON THE 5-HT AND GABA SYSTEM IN THE MOTOR NUCLEI

U Arvidsson*, F Piehl, B Meister, O Shupliakov, L Brodin, T Hökfelt and S Cullheim. Department of Neuroscience and Anatomy, Karolinska Institutet, Stockholm, Sweden.

Spinal cord motoneurons receive information from a large number of different sources and calculations indicate that one single alpha-motoneuron is contacted by at least 50.000-100.000 nerve terminals. So far, only few inputs to motoneurons have been identified with respect to their content of transmitter substances. One such system, however, the descending 5-HT raphe-spinal system seems to constitute one of the largest inputs to the spinal motor nuclei. 5-HT-immunoreactive nerve terminals in this part of the cord harbor also to a variable degree other neuroactive compounds such as several peptides. In contrast to the 5-HT system the GABAergic innervation of motoneurons seems to have its origin mainly from neurons at spinal cord levels. No coexistence between GABA and other neuroactive compounds including 5-HT has been described. Thus, the serotoninergic and GABAergic systems represent inputs to spinal cord motoneurons which differ with respect to both origin and degree of coexistence with other neuroactive compounds. In order to study possible molecular differences between different types of terminals/synapses on motoneurons we have here analyzed with immunohistochemistry 5-HT- and GABA-containing (analyzed with GAD) nerve terminals in the ventral horn of the grey monkey with regard to their contents of the synaptic vesicle proteins: synapsin, synaptophysin, rab3, synaptobrevin and synaptotagmin. A large number of varicosities contained synapsin-, synaptophysin-, rab3, synaptobrevin- and synaptotagmin-LI in the motor nuclei. In general, immunolabeling of all synaptic vesicle proteins outlined unstained somata and dendrites and crossectioned processes in the neuropil. The distribution pattern and density for each compound was not identical, however. Instead a specific staining pattern and also a variation in density for each compound was seen. Double labeled sections, analyzed with a confocal microscope, indicate that none of the synaptic vesicle protein-LIs could be found in 5-HT-IR terminals, whereas GAD-IR terminals exhibit all synaptic vesicle protein-LIs with the exception of synaptotagmin-LI. The results of this study suggest that 5-HT terminals differ from GABA terminals in the monkey motor nuclei with respect to their content of synaptic vesicle proteins. This could reflect that the exocytotic machinery in 5-HT terminals differs from that of GABA terminals.

5.2

GLUTAMATERGIC SYSTEM IN PONTOMEDULLARY RETICULAR FORMATION PARTICIPATING IN MOVEMENT INTEGRATION. Y.Y. Lai and J.M. Siegel. Dept Psychiat, Sch Med, UCLA and Neurobiol Res, VAMC, Sepulveda, CA 91343.

The pontomedullary reticular formation has been found to mediate locomotor excitation and inhibition in the decerebrate cat. Single train electrical stimulation in either pons or nucleus magnocellularis (NMC) of the medulla produced muscle inhibition, while repetitive train stimulation induced locomotion. Chemical microinjection into both areas demonstrated that N-methyl-D-aspartate (NMDA) induced locomotion while non-NMDA agonists induced muscle inhibition.

Fifty nanoliters of WGA-HRP was injected into NMC. After 2 days, the cat was perfused and its brainstem was processed with TMB and glutamate immunohistochemistry. Some WGA-HRP projection neurons could be seen throughout the brainstem. However, very intense projections from the pontine reticular formation (PRF) were found. Double-labeled WGA-HRP and glutamate neurons made up 50% of the PRF projection. We conclude that the activation of NMDA and non-NMDA receptors in NMC by glutamatergic neurons in PRF is important in the integration of muscle tone and movement.

Supported by the Medical Service Veteran Administration and HL41370.

5.3

MODULATION OF MOTONEURON ACTIVITY: DISTRIBUTION OF GLYCINE RECEPTORS AND SEROTONERGIC INPUTS ON MOTONEURON DENDRITES. Robert E.W. Fyffe*, Franciso J. Alvarez*, John C.Pearson*, Deborah Harrington* and Dianne E. Dewey*. Dept. of Anatomy, Wright State Univ. Dayton, Ohio 45435

Physiologically identified α- and γ-motoneurons (MNs) were labeled by intracellular injection of neurobiotin (NB) or horseradish peroxidase (HRP). NB-labeled cells were revealed using 7-amino-4-methyl-coumarin-3-acetic acid and glycine receptors (Gly-Rs) on these cells were detected by immunofluorescence with an antibody against the 93 kDa Gly-R-associated protein, and fluorescein-labeled secondary antibodies. α-MNs display Gly-Rs throughout their dendritic tree including dendrites in the white matter and in some dendritic spines. On soma and proximal dendrites, Gly-R labeling appeared in small clusters, whereas on distal dendrites the clusters were larger. In contrast, γ-MNs had few Gly-R clusters, and they were usually found only on the distal dendrites. Standard HRP histochemistry combined with serotonin immunocytochemistry, using diaminobenzidine as chromogen, revealed that α-MNs receive contacts from 1-2 x 10^3 serotonergic boutons. The contacts were distributed over soma and dendrites but were more frequent within 400 μm of the soma. We conclude that both inhibitory and "gain setting" synaptic inputs are widely distributed on MN dendrites. Supported by NIH grant NS25547.

5.4

IMMUNOHISTOCHEMICAL ANALYSIS OF SEROTONIN, DOPAMINE AND GABA IN DORSAL AND VENTRAL STRIATUM. C.F. Phelix*[1], T. Jackson*[1], P.A. Broderick*[2], M.J. Wayner[1]. Div. Life Sci., Univ. Texas, San Antonio, TX 78249[1]; Dept. Pharmacol., CUNY Med. Sch., NY 10031[2]

Our studies of ethanol and cocaine effects on limbic and extrapyramidal motor circuits has suggested regional variability of biogenic amines. These observations have been confirmed by our anatomical mapping studies of serotonin (5HT), dopamine (tyrosine hydroxylase - containing, TH) and GABA (glutamic acid decarboxylase - containing, GAD) axons. In this report we examined the dorsal striatum (DStr), ventral striatum (nucleus accumbens, NAcc) and pallidum in rat and mouse (*Pyromiscus lupus*). An immunocytochemical technique including silver intensification was used to detect 5HT, TH, or GAD in coronal sections of formaldehyde-fixed tissue. In rostral levels, 5HT axons were more dense in the lateral than medial DStr; this heterogeneity was not apparent in the caudal levels. The greater density in the lateral DStr was due to the presence of smaller diameter 5HT axons. In NAcc, 5HT axons had a greater density in medial versus lateral subdivisions; the relative contribution of small and large diameter axons was more uniform than in DStr. The pallidum had a substantial density of 5HT axons. In contrast, TH axons were sparse in the pallidum where GAD axon density was similar to 5HT. In DStr, TH axons had a density greater in the medial than lateral portions; GAD was uniformly dense. The core of NAcc had greater density of TH axons than the shell and within the core the medial component had the greatest mosaic patterning of terminals.

5.5

EFFECTS OF L-DIHYDROXYPHENYLALANINE ON NIGROSTRIATAL DOPAMINE IMMUNOREACTIVITY IN 6-HYDROXYDOPAMINE-LESIONED RATS. Denise Jackson*, Anna Mura*, Michael S. Manley*, Steven J. Young*, and Philip M. Groves* Dept. of Psychiatry, Univ. of California at San Diego, La Jolla, CA, 92093.

The dopamine (DA) precursor, L-dihydroxyphenylalanine (L-DOPA), alleviates symptoms of Parkinson's disease despite major degeneration of nigrostriatal DA afferents. Though these afferents contain the vast majority of aromatic amino acid decarboxylase (AADC) which converts L-DOPA to DA, AADC has also been detected in a small number of striatal neurons. A greater number of such neurons is unmasked by destruction of nigrostriatal afferents. Disclosure of AADC in striatal neurons leaves open the possibility that exogenous L-DOPA may be converted to DA in these cells. We have examined striatal DA-like immunoreactivity in DA-depleted rats treated with exogenous L-DOPA. Male Sprague Dawley rats (150-200 g) received unilateral medial forebrain bundle injections of 6-hydroxydopamine (8 μg). Five days after surgery, some animals were given the peripheral decarboxylase inhibitor, benserazide hydrochloride (50 mg/kg, i.p.) followed two hours later by L-DOPA (100 mg/kg, i.p.). Rats exhibiting at least 20 contralateral rotations per min, indicative of large DA lesions (>90%), were perfused with a 5% glutaraldehyde fixative two hours after L-DOPA injections. Untreated lesioned rats were also perfused. Brains were removed, cryoprotected, then cut with a freezing microtome (40 μm). Tissue was processed for DA immunoreactivity with a rabbit anti-DA polyclonal followed by avidin-biotin peroxidase staining methods. DA staining in the substantia nigra contralateral to the lesion was significantly increased by L-DOPA treatment ($P<.05$, n=4-7). DA-like immunoreactivity in striatum ipsilateral to the lesion was notably less than that observed in the contralateral striatum. L-DOPA increased immunoreactivity in striatum ipsilateral to the lesion and we observed DA-like immunoreactivity in some dorsomedial striatal cells. These cells contained labeled processes and soma (area; 45-55 μm^2). They were infrequently encountered in lesioned striatum in the absence of L-DOPA or in striatum contralateral to the lesion. Our results demonstrate the formation of DA in striatal cells, a process which may have consequences related to the therapeutic as well as possible neurotoxic effects of L-DOPA. Supported by grants NIDA DA 02854 and NSF BNS 9006155

6.1

C-DNA/PCR CLONING, CHARACTERIZATION AND DISTRIBUTION OF INWARD RECTIFIER K^+ CHANNELS IN NEONATAL RAT BRAINSTEM. J.S. Lai*, G.D. Funk, S.M. Johnson, J.C. Smith, & J.L. Feldman, Systems Neurobiology Laboratory, Dept. of Physiological Science, UCLA, Los Angeles, CA, 90024-1527.

We have postulated that an inward rectifier K^+ channel (IRKC) may play an important role in the neural control of breathing (Johnson et al., Soc. Neurosci. Abstr. 18: 488, '92). C-DNA of ATP-regulated IRKC from rat kidney–ROMK1 (Ho et al., Nature 362: 31, '93) and C-DNA of IRKC from mouse macrophage cell line–IRK1 (Kubo et al., Nature 362: 127, '93) have been cloned and characterized. To investigate the existence of these IRKC in rat brainstem, we used the polymerase chain reaction (PCR) technique to amplify the C-DNA generated from the medulla of the neonatal rat.

Two sets of PCR primer were used: i) ROMK1 primers - oligonucleotides identical to the C-DNA sequence of the M0 & M2 region of ROMK1. ii) IRK1 primers - oligonucleotides identical to the C-DNA sequence of the M1 & M2 region of IRK1.

Two PCR DNA fragments assigned as rat brainstem K1 (RBSK1) and rat brainstem K2 (RBSK2) were generated. By subsequently cloning and DNA sequencing we found: i) The DNA sequence of RBSK1 was identical to ROMK1. This result is in contrast to Ho et al., who did not identify ROMK1 in RNA in the rat brainstem region. ii) The DNA sequence of RBSK2 had a high degree of similarity to IRK1.

We are using the C-RNA probe generated from RBSK1 & RBSK2 to do *in situ* hybridization in the rat brainstem region to reveal the distribution of the two types of IRKC. Supported by NIH Grants HL37941, NS24742 and HL40959.

6.2

RESPIRATORY RHYTHM MODULATION BY $GABA_B$, $5HT_{1A}$, AND α_2-ADRENERGIC RECEPTORS: MEDIATION VIA AN INWARD RECTIFYING K^+ CONDUCTANCE? Stephen M. Johnson*, Jeffrey C. Smith, & Jack L. Feldman, Systems Neurobiology Lab, Dept. of Physiological Science, UCLA, Los Angeles, CA, 90024-1527

The *in vitro* brainstem-spinal cord of neonatal rat generates a respiratory rhythm whose frequency is decreased by the application of agonists that activate $GABA_B$, $5HT_{1A}$, and α_2 adrenergic receptors [receptors that are G-protein coupled to an inward rectifying K^+ conductance ($K_{in\ rec}$)]. Respiratory neurons that express these receptors, however, have not been located. To address this question, we used medullary slices (650 μm thick) from neonatal rats (0-4 days old) that generate rhythmic respiratory oscillations (Smith *et al., Science* 254:726, '91). Application of natural ligands/agonists [GABA/baclofen, 5HT/8-OH-DPAT (8-Hydroxydipropylaminotetralin hydrobromide), norepinephrine/clonidine] to the perfusate caused a dose-dependent decrease in the frequency of rhythmic hypoglossal nerve discharge, ultimately abolishing the rhythm (10-100 μM). To determine whether neurons with pacemaker-like properties that may be involved in rhythm generation express $GABA_B$ receptors, slices were bathed in low Ca^{++}/high Mg^{++} solution (to block synaptic transmission) and neurons in the ventrolateral medulla that continued to generate oscillatory bursts of action potentials were located by extracellular recordings. In four of five of these cells, 10-100 μM baclofen abolished bursting. All five bursting cells were identified as inspiratory neurons in control solution.

These data show that: (i) activation of $GABA_B$, $5HT_{1A}$, and α_2 adrenergic receptors decreases the frequency of respiratory motor discharge in medullary slices, (ii) $GABA_B$ receptor activation can modulate (decrease) bursting frequency of respiratory neurons with pacemaker-like properties. Computer simulations of neurons with this type of intrinsic oscillatory behavior show that $K_{in\ rec}$ can play a fundamental role in regulation of oscillatory bursting. We hypothesize that $K_{in\ rec}$ linked to $GABA_B$, $5HT_{1A}$, and α_2 receptors plays an important role in modulating respiratory rhythm. Supported by NIH HL02204, HL40959, and HL08524.

6.3

5-HT1B RECEPTOR "KNOCK OUT": PHARMACOLOGICAL AND BEHAVIORAL CONSEQUENCES. [1]E. Saudou, [1]U. Boschert, [1]M. Lemeur, [1]A. Dierich, [3]D. Ait Amara, [3]M.C. Buhot, [3]L. Segu, [2]R. Misslin and [1]R. Hen. [1]CNRS, INSERM, Faculté de Médecine, 11 rue Humann; [2]Laboratoire de Psychophysiologie, 7 rue de l' Université, 67000 Strasbourg - [3]CNRS, Laboratoire de Neurobiologie, BP 71, 13402 Marseille 09 - France.

The 5-HT1B receptor, which is the rodent homologue of the human 5-HT1Dβ receptor has been suggested to be involved in a number of physiological states such as appetite, locomotor activity and agressivity, as well as in certain pathological states such as migraines. In order to study the functions of the 5-HT1B receptor in the mouse, we have generated by homologous recombination, mutant mice lacking the gene encoding the 5-HT1B receptor. Such mice develop and live apparently normally and do not display any gross abnormality. Using a 5-HT1B specific ligand, [^{125}I]-cyanopindolol, we have shown that the 5-HT1B sites are totally absent in the homozygous mutant mice. Interestingly, the 5-HT1B/5-HT1D specific ligand, SCMG[^{125}I]TNH2 (serotonin-O-carboxy-methyl-glycyl-[^{125}I]-tyrosinamide) (Immunotech), labels in the mutant animals, a population of sites which correspond most likely to 5-HT1Dα receptors, since they are not displaced by the 5-HT1B specific ligand cyanopindolol (100 nM)), but they are displaced by the 5-HT1D preferring ligand PAPP (1[2-(4-aminophenyl)ethyl]-4-(3trifluoro methylphenyl) piperazine) (100 nM). These 5-HT1D sites are apparently not upregulated in the mutant mice.

Preliminary experiments performed on 10 homozygous mutant mice reveal a lower level of locomotor activity (measured in a 90 min. activity test), compared to wild type animals. The hyperlocomotor effect of the 5-HT1A/5-HT1B agonist, RU 24969 (5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole,butane dioate(2/1)) (4mg/kg, ip), was completely absent in mutant mice, indicating that this effect is entirely mediated by the 5-HT1B receptor. When analyzed in a free exploratory test and in a light/dark choice test, the mutant mice behaved like the wild type animals. However, the anxiogenic effect of RU 24969 was not observed in mutant mice indicating that this effect is mediated by 5-HT1B receptors. These preliminary results reveal the considerable potential of the "gene knock out" approach to sort out the contributions of individual receptor subtypes to physiology and behavior.

6.4

NEUROMODULATORY ACTIONS OF DOPAMINE ARE DEPENDENT UPON THE EXCITATORY AMINO ACID RECEPTOR SUBTYPES ACTIVATED IN NEOSTRIATAL SLICES. M.S. Levine*, C. Cepeda* and N.A. Buchwald, Mental Retardation Research Center, UCLA School of Medicine, Los Angeles, CA 90024.

These experiments examined the electrophysiological interactions among responses evoked by activation of specific subtypes of excitatory amino acid (EAA) and dopamine (DA) receptors in neostriatal slices. When EAAs and DA were applied iontophoretically, DA enhanced response evoked by activation of N-methyl-d-aspartate (NMDA) receptors and attenuated response evoked by glutamate or activation of non-NMDA receptors. The enhancement of NMDA receptor mediated responses was mimicked by bath application of the D_1 receptor agonist SKF 38393. The D_2 receptor agonist quinpirole attenuated responses evoked by both NMDA and non-NMDA receptor agonists. When depolarizing synaptic potentials (DPSPs) were evoked by local electrical stimulation, bath application of DA attenuated the amplitude and duration of this response. This DPSP is mediated primarily by activation of non-NMDA receptors, since it is blocked by the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). DPSPs mediated by activation of NMDA receptors can be unmasked if slices are bathed in Mg^{2+}-free Ringer's to abolish the voltage-dependent Mg^{2+} blockade of the NMDA receptor. In Mg^{2+}-free Ringer's, DA potentiated DPSPs in 44% of the cells and attenuated responses in 30%. If neurons were bathed in Mg^{2+}-free Ringer's and CNQX, to activate only NMDA receptors, it potentiated responses in 75% of the cells and did not attenuate responses. In contrast, when bathed in Mg^{2+}-free Ringer's and the NMDA receptor antagonist 2-amino-5-phosphonovalerate to activate only non-NMDA receptors, DA attenuated 60% of the responses and did not potentiate responses. These results indicate that the complex modulatory actions of DA in the neostriatum are a function of the EAA and DA receptor subtype activated. Supported by USPHS HD05958 and AG 10252.

6.5

THE METABOTROPIC GLUTAMATE RECEPTOR AGONIST 1-AMINO-CYCLOPENTANE-1,3-DICARBOXYLIC ACID INHIBITS BOTH POST-SYNAPTIC POTENTIALS AND N-METHYL-D-ASPARTATE-EVOKED RESPONSES IN NEOSTRIATUM. C.S. Colwell* and M.S. Levine*. Mental Retardation Res. Ctr., UCLA, Los Angeles, CA 90024.

The role of metabotropic glutamate receptors (mGluR) in the neostriatum was investigated by examining the effects of the mGluR agonist 1-amino-cyclopentane-1,3-dicarboxylic acid (t-ACPD) on neurons in vitro. Bath application of t-ACPD inhibited the evoked depolarizing post-synaptic potentials recorded in neostriatal cells. This effect was insensitive to the mGluR antagonist 2-amino-3-phosphono-propionic acid (AP-3). The application of phorbol 12-myristate 13-acetate (PMA), but not 4-α-PMA, mimicked the inhibitory actions of t-ACPD. The t-ACPD was also found to markedly attenuate excitatory responses induced by the iontophoretic application of N-methyl-D-aspartate (NMDA). This inhibitory effect was stereo-selective, long lasting and sensitive to AP-3. In contrast, t-ACPD had no consistent action on responses evoked by non-NMDA glutamate agonists. Thus, mGluRs may play an important role in regulating glutamatergic transmission in the neostriatum. Supported by HD 05958.

6.6

INTRACELLULAR REDISTRIBUTION OF β-ADRENERGIC RECEPTORS IN RAT LIVER DURING DIFFERENT PHASES OF SEPSIS. Maw-Shung Liu, Chaoshu Tang* and Li-Wu Guo*. Saint Louis Univ. Sch. of Med., St. Louis, MO 63104.

Changes in the distribution of β-adrenergic receptors (βAR) in two subcellular fractions, the plasma membrane and the light vesicle, of rat liver were studied using ^{3}H-dihydroalprenolol (^{3}H-DHA) binding and photoaffinity labeling with ^{125}I-iodocyanopindolol diazirine in combination with SDS-PAGE. Sepsis was induced by cecal ligation and puncture (CLP). ^{3}H-DHA binding studies show that in the plasma membrane fraction, the Bmax was decreased by 30% ($p<0.01$) and 33% ($p<0.01$) during the early (9 hr post CLP) and late (18 hr post CLP) phases of sepsis, respectively, with no change in the Kd values. In the light vesicle fraction, the Bmax was increased by 48% ($p<0.01$) and 58% ($p<0.01$) during the early and the late sepsis, respectively, without significant change in the Kd values. The photoaffinity labeling studies revealed one major binding peptide with M_r of 64,000. The binding of the labeled peptide in the plasma membranes was decreased by 29% ($p<0.01$) and 46% ($p<0.01$) during the early and late sepsis, respectively. In the light vesicle fraction, the binding of 64 kD peptide was increased by 46% ($p<0.01$) and 84% ($p<0.01$) during the early and late sepsis, respectively. These data indicate that βAR was internalized from the plasma membrane fraction to the intracellular vesicles during CLP sepsis. Since hepatic glucose metabolism is controlled by catecholamines through βAR mediation, an internalization of βAR in the liver may contribute to the development of glucose dyshomeostasis during septic shock. (Supported by NIH grants GM-31664 and HL-30080).

6.7

STRIATAL AND LIMBIC DOPAMINE OVERFLOW IN THE RAT IS FREQUENCY AND PULSE-DEPENDENT: *IN VIVO* FAST CYCLIC VOLTAMMETRIC DATA. C.D. Earl[1], J.X. Xie[1], S.J. Trout[3], Z.L. Kruk[3], A. Kupsch[2], W.H. Oertel[2] & G. ten Bruggencate[1]. [1]Institute of Physiology, Pettenkoferstraße 12, 8000 Munich 2, FRG; [2]Dept. of Neurology, Marchioninistraße 15, 8000 Munich 70, FRG; [3]Dept. of Pharmacology, Queen Mary & Westfield College, Mile End Road, London, E1 4NS, UK.

Dopamine (DA) overflow in the rat caudate nucleus (CPu) is known to be frequency dependent following sine-wave (< 10 s) electrical stimulation of the median forebrain bundle (MFB) (Stamford *et al.*, 1987). The present study characterises DA overflow in the CPu and nucleus accumbens (ACb) following shorter train stimulations which consist of varying numbers of pulses applied at varying frequencies.

Fast cyclic voltammetry was used *in vivo* in the anaesthetised rat to measure DA overflow in the CPu and ACb following square-wave stimulation of the rat MFB. 20, 60, 100 or 150 square-wave pulses were applied at 20–180 Hz.

Using 20–150 pulses significant differences in stimulated DA overflow were observed between the frequencies used in the ACb ($P < 0.0005$; ANOVA). However, in the CPu significant differences were observed only when the trains consisted of 60–150 pulses ($P = 0.001$; ANOVA). Frequency dependence of DA overflow showed a similar pattern in the CPu and ACb and resulted in similar 'bell-shaped' curves. Comparing the number of applied pulses revealed significant differences in DA overflow in the CPu when they were applied at 40–140 Hz ($P < 0.05$; ANOVA) and 20–140 Hz in the ACb ($P < 0.05$; ANOVA). Maximum overflow followed 150 pulses, 60 Hz (ACb: 308 ± 54% of control (60 pulses, 60 Hz) or 150 pulses, 100 Hz (CPu: 291 ± 52% of control).

We conclude that DA overflow following square-wave stimulation is frequency-dependent in both the CPu and ACb. Reasons for this frequency dependence maybe related to increases in the relative refractory period of the unmylinated fibres in the MFB. The results also show DA overflow within the CPu and ACb occurs in a pulse dependent manner up to 150 pulses but differences are seen between the regions.

NEUROPHARMACOLOGY OF MOVEMENT CONTROL

7.1

RESPIRATORY RHYTHM GENERATION AND DRIVE TRANSMISSION *IN VITRO*; ROLE OF EXCITATORY AMINO ACID (EAA) RECEPTORS. G.D. Funk*, J.C. Smith, & J.L. Feldman. Systems Neurobiology Lab, Dept. Physiological Science, UCLA, Los Angeles, CA, 90024-1527.

Medullary slices from neonatal rat containing the pre-Bötzinger Complex (pre-BötC) generate inspiratory (I) oscillations in cranial nerves IX and XII (Smith *et al., Science*, 254,'91). To determine the role of EAAs in rhythmogenesis and drive transmission, antagonists of NMDA (MK-801;(+)-5-methyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-iminemaleate, 100μM) and non-NMDA receptors (CNQX; 6-cyano-7-nitroquinoxaline-2,3-dione, 20 μM) were injected into the pre-BötC and rostral ventral respiratory group (rVRG). MK-801 had no effect. Injections of CNQX produced dose-dependent decreases in: i) I amplitude (Amp); ii) I frequency (f) and Amp. Amp reductions were produced following injections in rVRG and pre-BötC. Perturbations in f only occurred following injections into a limited region of pre-BötC. We tested the effects of CNQX, MK-801 and AP-4 (D,L-2-amino-4-phosphonobutyric acid) on I-modulated synaptic inputs to XII motoneurons (XII MNs). CNQX (50 μM) reduced synaptic currents by >95%, MK-801 (1.0 mM) had little effect, and AP-4 (1.0 mM) produced a 25% reduction. Local application of NMDA and non-NMDA (Quisqualate, Kainate, AMPA; [(R,S)-a-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid hydrobromide]) agonists to synaptically isolated XII MNs (1.0 μM TTX) induced large inward currents. We also examined the role of EAA receptor desensitization in I drive transmission to XII MNs. Desensitization was blocked by local application of 50-250μM cyclothiazide. I currents increased 10-15%. Results indicate that: i) rhythm generation *in vitro* is dependent on endogenously released EAAs acting at non-NMDA receptors within a specific region of the pre-BötC; ii) EAA transmission within rVRG is involved in transmission of I drive to motor or premotoneurons; iii) XII MNs possess NMDA and non-NMDA receptors, however, non-NMDA receptors primarily mediate transmission of I drive to XII MNs; iv) minimal desensitization of glutamate receptors occurs during I-mediated glutamate release at the XII MN. Supported by NIH Grants HL40959 & HL02204 (JCS) and Parker B. Francis Foundation (GDF).

7.2

GABA$_B$ RECEPTOR-MEDIATED LONG-TERM DEPRESSION OF THE nVIII-EVOKED EPSP IN RAT MEDIAL VESTIBULAR NUCLEUS NEURONS PATCH-CLAMPED *IN VITRO*. G.A. Kinney, B.W. Peterson and N.T. Slater Dept. of Physiology, Northwestern Univ. Med. School, 303 E. Chicago Ave., Chicago, IL 60611.

The brainstem vestibular nuclear complex is believed to be a critical site for the long-term adaptive change in vestibulo-ocular reflex gain. While little information is available regarding potential cellular substrates of synaptic plasticity in this brain region, *in vivo* studies suggest that cerebellar projections to vestibular nuclei play an important role in this phenomenon. Neurons in the rat medial vestibular nucleus were recorded using whole-cell patch-clamp methods in 400 μm thick transverse slices cut at the level of nVIII, and stimulating electrodes were placed in the nVIII and m.l.f. to evoke monosynaptic EPSPs. EPSPs evoked by stimulation of either site were not affected by the NMDA receptor antagonist D-2-amino-5-phosphonovalerate (AP5; 20 μM), but were blocked by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 μM). An AP5-sensitive component of both EPSPs was revealed in Mg^{2+}-free, bicuculline-containing medium. Tetanic stimulation of the nVIII or m.l.f. failed to produce consistent long-term changes in the AMPA receptor-mediated EPSP amplitude. Bath application of the GABA$_B$ receptor agonist baclofen (1-10 μM) produced a blockade of both EPSPs. However, following the washout of baclofen, the amplitude of the nVIII-evoked EPSP exhibited a long-term depression. A stable reduction of 40% was observed after the washout of baclofen, whereas the m.l.f.-evoked EPSP was not significantly affected. The results provide evidence for a GABA$_B$ receptor-mediated form of long-term synaptic depression of the nVIII-evoked EPSP. This might be physiologically produced by descending cerebellar inputs to mediate long-lasting changes in the gain of the vestibulo-ocular reflex. Supported by USPHS Grants EY 06485 and NS 17489.

7.3

INTRAVENOUS HALOPERIDOL ADMINISTRATION EFFECTS ON MOVEMENT TIME AND REACTION TIME IN YOUNG AND OLD HEALTHY SUBJECTS. A. Berardi*, J.F Kelly*, K.C. Raffaele*, T.T. Soncrant* J.V. Haxby*. Lab. of Neurosciences, NIA, NIH, Bethesda, MD 20892.

The purpose of this study was to investigate the effects of intravenous haloperidol administration on motor function in healthy aging. Six young (age: 29 ± 4 years; range: 25-34) and 9 old subjects (age: 72 ± 4 years; range: 66-77) were administered .014 mg/kg intravenous haloperidol in a double-blind (DB) placebo-controlled crossover design. Motor function was assessed by measuring reaction time (RT) and movement time (MVT). Two computer-controlled boxes with one response key on each were set 50 cm apart in front of the subject. At random times, one of the response keys lit up, requiring the subject to move his hand to press the lit response key on the other box. RT was measured as the time needed to release a button, after the button on the other box lit up. MVT was measured as the time needed after release of a button to press the button on the other box. Motor function was assessed at times -2 (1-3 days before DB infusion), and at -1, 1, 2, 3, 4, 6, 23 and 47 hours after infusion during each phase of the DB. Because no significant differences were found among baseline sessions (-2 and -1) in both young and old subjects (all p's > .05), baselines were combined for each DB phase, and change scores from baseline in each phase calculated. Repeated measures ANOVA's on median RT and MVT times separately, indicated that young and old healthy subjects did not differ on RT and MVT times (both $F < 1$). For all subjects combined, movement times were slowed on haloperidol (DB main effect; haloperidol: 71.3 ± 63.7 msec; placebo: 31.0 ± 58.5 msec, $p < .005$). For all subjects, movement time on haloperidol was slowed compared to both baseline and placebo sessions (all $p < .05$). No other main effects or interactions were significant (all $p > .05$). Haloperidol had a nonsignificant effect on RT (main DB effect; haloperidol: 16.4 ± 31 msec; placebo: 1.11 ± 31 msec, $p < .13$). A significant session effect was found on RT ($p < .005$) indicating possible fatigue effects or long-term drug action. No other main effects or interactions were significant. These results indicate that intravenous haloperidol infusion does not differentially affect MVT and RT in young and old subjects, as no interaction involving group was significant.

7.4

SEROTONERGIC DRUGS MARKEDLY AFFECT LOCOMOTION IN CHRONIC SPINAL CATS BUT NOT NORMAL CATS. J.A. Hodgson, R. deLeon, R.R. Roy, D. Chin, V.R. Edgerton. Brain Research Institute and Department of Physiological Science, UCLA, Los Angeles, CA 90024

EMG and video recordings were made from six cats during bipedal treadmill locomotion (0.1 to 1.0 $m \cdot s^{-1}$) before and after complete transection of the spinal cord (T12-T13). Cats trained (30min/day) to walk on a treadmill exhibited full weight-bearing stepping one month after transection and continued to step for several months thereafter. Quipazine (2-3mg/kg), a 5-HT agonist and cyproheptadine (0.25-3mg/kg), a 5-HT antagonist had no appreciable effect on locomotion before transection. In spinal cats that were able to take full weight-bearing steps, quipazine (0.3-1.5mg/kg) enhanced dorsiflexion so that the foot was lifted higher and the occurrence of stepping on the dorsum of the foot was reduced. In two spinal cats which were unable to take full weight-bearing steps but exhibited alternating activity in the hindlimbs, quipazine treatment resulted in full weight-bearing steps. Quipazine was unable to elicit stepping in cats which did not exhibit alternating activity before drug administration. After quipazine the step cycle period and the EMG burst durations of flexor and extensor muscles were prolonged, but mean EMG amplitudes were unchanged. Cyproheptadine alone (0.3-3mg/kg) produced the opposite effects on locomotion: flexor deficits in many cases resulting in failure of locomotion, and shorter cycle periods and EMG burst durations. These results indicate that the 5-HT system in the spinal cord plays a significant role in the swing phase of locomotion. Furthermore, the disruption of spinal locomotion by cyproheptadine indicates that at least portion of the spinal 5-HT system is still functional several months after transection.

7.5

NEURONAL ACTIVITY IN THE GUINEA PIG MEDIAL VESTIBULAR NUCLEUS FOLLOWING CHRONIC DIAZEPAM ADMINISTRATION. Cynthia L. Darlington* and Paul F. Smith. University of Otago, Department of Psychology and the Neuroscience Research Centre, Dunedin, New Zealand.

Diazepam is known to disrupt vestibular reflex function through its actions on benzodiazepine binding sites on $GABA_A$ receptors in the medial vestibular nucleus (MVN). The aim of this study was to examine the effects of chronic diazepam administration on MVN neuron function. Guinea pigs received: once daily, single i.p. injections of 5 mg/kg diazepam (Valium 10, Roche; n = 8 animals) or equivalent volume of vehicle (n = 4) for 3-4 weeks (short-term/high-dose group); or once daily, single i.p. injections of 2 mg/kg diazepam (n = 4) or equivalent volume of vehicle for 6-9 weeks (n = 4) (long-term/high-dose group). Daily righting reflex latency (RRL) measurements were made using an electronic measurement system. Animals were then anesthetised and brainstem slices were prepared for extracellular single neuron recording using standard in vitro methods. Animals in the short-term/high-dose group showed large increases in the RRL ($p \leq 0.05$) and there was no significant reduction in RRL over time. Recordings from MVN neurons from diazepam-treated animals indicated no significant difference in average resting activity (n = 23 neurons) compared to neurons from untreated animals (n = 41). There were also no significant differences in the responses of MVN neurons to superfused GABA or glycine (both 10 nM). Two/four animals in the long-term/low-dose group showed significant tolerance to the depressive effects of diazepam on the RRL ($p \leq 0.05$). MVN neurons in slices from these animals had an average resting activity which was significantly higher than MVN neurons from untreated animals (29.7 spikes/s (n = 18 neurons) compared to 13.0 spikes/s (n = 15); $p < 0.005$). These results suggest that long-term, low-dose diazepam therapy may produce changes in MVN neuronal activity which short-term, high-dose therapy does not. This research was supported by the Otago Medical Research Foundation and the Health Research Council of New Zealand.

7.6

RAPID TOLERANCE TO THE EFFECTS OF DIAZEPAM ON GUINEA PIG MOTOR CONTROL USING DIVIDED DOSES. Paul F. Smith* and Cynthia L. Darlington*. University of Otago, Dept. of Psychology and the Neuroscience Research Centre, Dunedin, New Zealand.

Tolerance and dependence to the depressive effects of benzodiazepine (BDZ) tranquilizers has been correlated with a functional subsensitivity of some CNS neurons to GABA. Although some studies have found that tolerance develops with once daily, single i.p. injections of diazepam, in most cases the process takes several weeks. Many of the lower mammalian species used in such studies metabolise diazepam rapidly; therefore, one possibility is that the rapid development of tolerance requires more continuous occupation of CNS BDZ binding sites. We sought to test this hypothesis by comparing the chronic effects of the following diazepam injection schedules on the guinea pig righting reflex latency (RRL): i) once daily, single 6 mg/kg i.p. injections of diazepam (Valium 10, Roche) for 5 days (n = 4 guinea pigs); ii) 3 times daily, single 6 mg/kg i.p. injections of diazepam for 5 days (n = 4); and iii) once daily, single 20 mg/kg i.p. injections of diazepam for 14 days (n = 4). The RRL was measured daily using a computerised measurement device consisting of a 2 kg load cell connected to a strain gauge amplifier and one channel of a MacLab data acquisition system; righting reflex traces were displayed on a MacLab computer using the Chart program. In all cases, single diazepam injections significantly increased the RRL ($p \leq 0.005$). There was no significant decrease in the RRL over 5 days for either the 6 mg/kg/day or the 20 mg/kg/day group; however, over 14 days the latter group showed a small, but significant, degree of tolerance ($p \leq 0.02$). By contrast, animals which received 6 mg/kg, 3 times a day (i.e., 'divided doses'), showed complete tolerance in 3 days ($p \leq 0.05$). Since the animals which received diazepam in divided doses received less diazepam per day than those animals in the 20 mg/kg/day group, these results are consistent with the hypothesis that the duration of occupation of CNS BDZ binding sites is a critical factor in the development of BDZ tolerance and dependence. This research was supported by the Otago Medical Research Foundation and the Health Research Council of New Zealand.

7.7

OPPOSITE EFFECTS OF SHORT AND LONG-TERM HALOPERIDOL TREATMENT ON LEVELS OF mRNA ENCODING GLUTAMIC ACID DECARBOXYLASE (GAD 67) IN RAT GLOBUS PALLIDUS. Jill M. Delfs*, Gaylord D. Ellison* and Marie-Françoise Chesselet*
Dept. of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104 and Dept. of Psychology, UCLA, Los Angeles, CA 90024.

Movement disorders, as seen in Parkinson's and Huntington's disease, are often classified as either hypokinetic or hyperkinetic, although both types of symptoms can occur as a function of the disease progression. This range of symptoms is also observed clinically following treatment with neuroleptic drugs, such as haloperidol (HAL). Acute administration of HAL causes akinesia and rigidity whereas long-term therapy results in tardive dyskinesia (TD), a hyperkinetic disorder characterized by orofacial dyskinesias and motor tics. It has been hypothesized that alterations in the activity of neurons within the basal ganglia underlie these motor dysfunctions. Little is known, however, about the effects of HAL on GABAergic neurons of the pallidum, an essential part of basal ganglia circuitry. Levels of GAD mRNA were measured by in situ hybridization in pallidal neurons of rats treated with HAL for 7 days (1 mg/kg, s.c.), when animals exhibit moderate catalepsy, or 8 months (1 mg/kg, depot followed by oral) when rats show a TD-like syndrome. Single cell analysis of GAD mRNA levels in the globus pallidus (GP) revealed opposite effects of 7-day and 8-month HAL treatment. A marked increase in the levels of GAD mRNA was observed in the GP after 7-day treatment with HAL. In contrast, the levels of GAD mRNA were decreased in the GP of rats receiving HAL for 8 months. Levels of GAD mRNA were significantly increased in the entopeduncular nucleus (EP) of rats treated with HAL for 8 months, but were unchanged in the EP of 7-day treated animals. These data suggest that the ability of haloperidol to induce both hypokinetic and hyperkinetic side effects may be due to differential effects of the drug on GP and EP neurons over time. This work was supported by MH 44896, MH17168 and MH12841.

7.8

INFLUENCE OF FLUPIRTINE ON LOWER LIMB REFLEXES IN HUMANS. Dagmar Timmann*, Chris Plummer, Michael Schwarz and Hans-Christoph Diener. Department of Neurology, University of Essen, Essen 1, FRG

Recent animal experiments have shown muscle relaxant properties of Flupirtine. The effect of a single 400mg dose on postural EMG responses in (I) dynamic posturography, (II) H-reflexes and (III) flexor reflexes in normal human subjects were investigated. (I) Dynamic posturography: 16 subjects stood on a moveable forceplate which was tilted upwards around the ankle joint. Short-, medium- and long latency-responses (= SL, ML, LL) were recorded half-hourly for 3 hours after intake of the drug and placebo. Flupirtine significantly decreased the size of the ML-response (ANOVA-test $p < 0.0001$) without affecting SL and LL. (II) H-reflex: In 6 subjects the H-reflex was elicted by electrical stimuli of the posterior tibial nerve in the popliteal fossa. Measurements were done hourly for 3 hours after the intake of the drug and placebo. There was no significant change of the Hmax/Mmax ratio. (III) Flexor reflexes: 7 subjects were investigated. Flexor reflexes of the anterior tibial muscle were elicted by electrical stimulation (stimulus train of 5 pulses at 200 Hz, pulse width 0.2ms) of the posterior tibial nerve behind the medial malleolus at 25% maximum voluntary contraction, measurments as in (II). Flupirtine significantly decreased the size of the flexor reflex (ANOVA-test $p < 0.05$). Flexor reflexes are increased in spasticity. Their reduction with Flupirtine shows a possible muscle relaxant property of the drug.

7.9

ROLE OF EXCITATORY AND INHIBITORY AMINO ACIDS IN TRANSMISSION OF MASTICATORY DRIVE SIGNALS IN THE GUINEA PIG. Tomio Inoue* and Scott H. Chandler, Department of Physiological Science, UCLA, Los Angeles, CA 90024

In order to elucidate the pharmacological properties of transmission of the masticatory drive signal from the masticatory central pattern generator to rhythmically active (RA) brainstem neurons, we have examined the effects of iontophoretic application of antagonists to excitatory and inhibitory amino acid receptors on RA neurons during cortically induced masticatory activity (RMA) in the anesthetized guinea pig. RA neurons were divided into closer (CRA) and opener type (ORA) neurons according to the phase of activation during RMA. Neuronal discharge of CRA neurons were suppressed by iontophoretic application of both CNQX, a non-NMDA receptor antagonist, and CPP, an NMDA receptor antagonist. Discharge of ORA neurons were also reduced by CNQX, but were not affected by CPP. The results indicate that both non-NMDA and NMDA receptors are concerned with transmission of the excitatory masticatory drive from the CPG to CRA neurons, whereas NMDA receptors do not seem to be crucial for rhythmic activation of ORA neurons during mastication. Furthermore, in CRA neurons glycine inhibition occurs to suppress activity during the interburst phase of RMA. Supported by NIH grant DE 06193.

7.10

STIMULATION OF LOCOMOTION IN NEONATE RAT PUPS BY THYROLIBERIN ANALOGUE CG3703. Kenneth A. Clarke* and Kris J. Kirby*. Dept. Biomedical Science, University of Sheffield, S10 2TN, U.K.

Thyroliberin and its analogues induce rhythmic activity in respiratory neurons[1], locomotion in adult rats[2] and depolarise motoneurons in isolated neonate spinal cord[3]. In the light of such evidence, the present experiments were performed to determine whether analogue CG3703 (6-methyl-5-oxo-thiomorpholinyl-3-carbonyl-His-Pro-NH_2) activated locomotion in neonates which were not yet walking spontaneously. Ten, four day old rat pups were each injected with CG3703 (5 mg kg^{-1} in 0.9% saline, i.p.), and placed in chambers to allow recording of total activity and detailed locomotor analysis. Two to five minutes following injection, each pup started to produce co-ordinated locomotion. Total activity (mean $\pm$ 1 SEM) over the following 5 minutes was almost 6 times greater than in the 5 minutes preceding injection (346 $\pm$ 45.5 and 60.9 $\pm$ 11.7 motor events). Mean velocity of locomotion was 1.9 $\pm$ 16 cm/sec^{-1}, Stride length 2.4 $\pm$ 14 cm, Stride time 1310 $\pm$ 70 ms, Stance time 900 $\pm$ 50 ms and Swing time 410 $\pm$ 40 ms. It is concluded that this analogue does stimulate locomotion in the neonate rat.

1 Dekin, M.S. et al. (1985) Science 229, 67-69.
2 Clarke, K.A. and Steadman, P. (1989) Neuropeptides 14 (1), 65-70.
3 Takahashi, T. (1985) Proc. R. Soc. Lond. B 225, 391-398.

Experiments performed under Home Office Licence PIL 50/01202

7.11

LOW-DOSE CHRONIC ETHANOL IMPROVES TILT-PLANE PERFORMANCE IN PONTINE-DAMAGED BUT NOT NORMAL RATS. Rebecca M. Chesire* & Barbara E. Digman.* Psychology Dept., Univ. Hawaii, Honolulu, HI 96822.

Electrolytic lesions (1mA anodal, 20 sec.) or chemical impairment (focally applied gamma-amino-butyric acid or morphine) of the nucleus reticularis tegmenti pontis (NRTP) can produce a dramatically rapid, straightforward form of locomotion that is not inhibited by large doses of acutely administered haloperidol, morphine or ethanol (Chesire, et al., Physiol. Behav. 30: 1983; Chesire, R.M. Neurosci. Abs. 12: 1986). Thus, the intact NRTP is a critical mediator of the motor inhibitory effects of some substances of abuse. In this report, we describe a marked improvement (approx. gain of 4-6°) in tilt-plane performance in NRTP-damaged rats (n=7) that were permitted chronic, no-choice self-administration of 0-8% ethanol in a 25% sucrose and/or tap water solution. At the same doses, unoperated rats (n=7) were impaired (approx. loss of 2-3°). The results suggest that (1) low-dose chronic ethanol intake in the presence of NRTP damage or dysregulation can improve at least one form of motor performance, thereby creating an appetitive window for continued use and (2) the potential appetitive aspect of ethanol use in the presence of pontine dysregulation is related to vestibular integrity.

7.12

THE ORGANIZATION OF PACEMAKER CONTROL IN WEAKLY ELECTRIC FISH J.E. Spiro*, C.J.H. Wong* and W. Heiligenberg* Department of Biology and Group in Neurosciences, UCSD, La Jolla, CA 92093-0202

Weakly electric fish discharge an electric organ in their tail which is driven by a signal from an endogenous neural oscillator, the medullary pacemaker nucleus. The nucleus consists of only 2 identified neuronal cell types: pacemaker cells, which synapse within the nucleus and are spontaneously active, and relay cells which project down the spinal cord and synapse on the motoneurons that drive the electric organ. The fish monitor the electric field that is produced with receptors in their skin and, in different behavioral contexts, modulate the electric organ discharge (EOD) to produce a number of outputs with distinct temporal dynamics. We are studying the control of this oscillator from inputs originating in the diencephalon and midbrain. Previous studies in curarized preparations have shown that different blockers of the subtypes of the glutamate receptor block different types of modulations of the EOD. These modulations can be elicited behaviorally or via local stimulation of presynaptic areas. In addition, some species exhibit GABAergic afferents to the pacemaker. We are extending these studies to a more detailed cellular level by using an *in vitro* preparation of the pacemaker nucleus which survives for many hours and is spontaneously active. We can record intracellularly from the pacemaker and relay cells and also stimulate presynaptic afferents which induce changes of the rhythm, mimicking modulations seen during natural behaviors. Additionally, we are using immunohistochemistry to localize neurotransmitters and the receptors that are involved in the different forms of the modulations, with the goal of constructing a detailed model of how a seemingly simple oscillator can produce multiple distinct outputs.

7.13

INFLUENCE OF ACUTE AND CHRONIC ADMINISTRATION OF NEUROLEPTICS ON LEG EMG RESPONSES IN DYNAMIC POSTUROGRAPHY Andrea Banaski*, Dagmar Timmann, Markus Jüptner, Michael Schwarz, Jürgen Rimpel+, Hans-Christoph Diener. Department of Neuroloy, +Department of Psychiatry, University of Essen, Essen, FRG

The effects of haloperidol (2 and 4 mg, p.o.) in normals (n= 5, mean age 31 years, range 24-53) and of long-term neuroleptic treatment in schizophrenic patients (n=17, mean age 37 years, range 26-62) on leg EMG responses were examined. Normals were tested before, 2 hours after and hourly for six hours after intake of haloperidol or placebo. Patients were tested once. Short, medium and long latency reflexes of the anterior tibial and triceps surae muscles were recorded after toe-up, toe-down, backwards and forwards pertubations of a moveable platform. Compared to age- and sex-matched controls (n=16) the EMG integral was reduced in patients in the triceps surae muscle after backwards movement (24%, $p<0.05$), in the anterior tibial muscle after toe-up pertubations (50%, $p<0.01$). Preliminary data on 5 normals taking haloperidol showed no significant changes in any of the leg muscles recorded. The results show a decrease of stabilizing EMG-responses under long term neuroleptic treatment.

7.14

COCAINE AND CITALOPRAM EFFECTS ON LOCOMOTION IN MATURING MICE. Cecilie Goodrich. Cleveland State University, Cleveland, OH 44115

Several monoamines are known to have transient effects on neuronal circuits during maturation. The catecholamines norepinephrine and dopamine and 5-hydroxytryptamine (5-HT, serotonin) are released in mature brain regulatory regions for locomotion, and 5-HT is released in the ventral horn of the spinal cord. They mature at varying times. This pilot study examines relationships between the locomotory effects of two drugs that act on monoamines and the established patterns of monoamine system maturation. Digital video images were used to establish a baseline for changes in whole body velocity, forelimb stride length, and forelimb cycle time in mice aged from 1 to 21 days *postpartum* (weaning). A temperature gradient (18°-37° C) encouraged movement. Maturation increases velocity through a combination of increasing stride length and decreasing cycle time. Citalopram, a specific reuptake inhibitor for 5-HT, was compared with cocaine, which inhibits reuptake of monoamines generally (among a variety of other effects). Four different litters were studied at ages 3, 5, 7, 10 or 14 days (total 21-26 animals for each age and treatment). Treated animals were injected with 20 mg/kg citalopram or 30 mg/kg cocaine in saline, while control littermates were injected with saline only. After 24 hr, animals were videotaped in the temperature gradient and later scored for body velocity, forelimb stride length and forelimb cycle time -- all double blind. Drug effects were analyzed by a mixed model ANOVA (SAS "Mixed" procedure). Citalopram effects appeared and diminished with maximal significant increases in velocity and stride length, and decreased cycle time at 5 days; a highly variable decrease in velocity with increased cycle time were seen at 14 days. Cocaine effects were weaker, but generally opposite to citalopram, suggesting a mechanism on locomotion other than 5-HT reuptake.

7.15

N-METHYL-D-ASPARTATE (NMDA) RECEPTOR-MEDIATED VOLTAGE OSCILLATIONS IN RAT CENTRAL SPINAL NEURONS. S. Hochman*, L.M. Jordan, and J.F. MacDonald*. *Dept. of Physiology, Univ. of Toronto, Toronto, ON. M5S 1A8; Dept. of Physiology, Univ. of Manitoba, Winnipeg, MB. R3E 0W3

Neurons near the central canal have recently been associated with locomotor activity (Dai et al., *Soc. Neurosci. Abstr.*, 1990; Jordan and Noga, *Soc. Neurosci Abstr.*, 1991). The present study was undertaken to determine whether similarly located neurons are capable of rhythmic voltage oscillations in response to perfusion with neuroactive substances implicated in the genesis of rhythmic motor activity. Visually-identified neurons surrounding the central canal were recorded with the whole-cell patch clamp technique in transverse slices (300 µm) of 7-14 day old rat lumbosacral spinal cord. In several neurons (18/42) perfusion of NMDA (in 1 µM tetrodotoxin) elicited either rhythmic or unpatterned voltage oscillations. Rhythmical oscillations were localized to neurons in a region ventrolateral to the central canal, approximating the intermediomedial nucleus. Oscillations evoked by NMDA (20 - 100 µM) were dose-dependent and ranged from 0.09 to 1.45 Hz (n = 5). These doses and resulting frequencies are comparable to those observed during NMDA-evoked locomotion in the *in vitro* newborn rat spinal cord (Kudo and Yamada, *Neurosci. Lett.*, 1987; Smith et al., *FASEB J.*, 1988; Cazalets et al., *J. Physiol.*, 1992). Oscillations arose from a mean resting potential of -67 mV with plateau voltages of -39 mV. While L-glutamate (100 - 1000 µM), the putative excitatory amino acid neurotransmitter, also evoked voltage oscillations, kainate (10 - 100), serotonin (10 - 200), and nor-adrenaline (50 - 100) did not. Thus central spinal neurons can elicit voltage oscillations by NMDA receptor activation at frequencies that would support a role in the central pattern generation of locomotion. (Supported by the Canadian Network of Centres of Excellence for Neural Regeneration and Functional Recovery).

7.16

BRAIN SEROTONERGIC NEURONS IN CATS DISCHARGE IN RELATION TO TONIC AND RHYTHMIC MOTOR FUNCTION. C.A. Fornal*, S.C. Veasey*, and B.L. Jacobs*. Dept. of Psychol., Prog. Neurosci., Princeton Univ., Princeton, NJ 08544.

Serotonergic neurons project heavily to brainstem and spinal motoneurons and have been implicated in motor function. Previous studies in our laboratory have shown that the activity of brain serotonergic neurons varies primarily in association with behavioral state or postural EMG activity. The present study shows that a substantial number of serotonergic neurons also display changes in activity in relation to specific motor behaviors. Cats were implanted with chronic microelectrodes for recording single unit activity in the mesencephalic nuclei raphe dorsalis (DRN) and centralis superior (NCS), and in the medullary nucleus raphe pallidus (NRP). A subgroup of DRN and NCS serotonergic neurons was found to display dramatic increases (up to 400%) in activity in association with rhythmic tongue and jaw movements during feeding, licking, or grooming behavior. Most cells were tonically activated during these behaviors, while some discharged in phase with the rhythmic behaviors. The increase in neuronal activity often preceded movement onset by several seconds and terminated with the offset of the behavior. Some of these neurons were also activated by somatosensory stimulation of the head and neck area. In addition, we observed a subgroup of NRP serotonergic neurons that showed increases (up to 100%) in activity in association with treadmill locomotion. A strong positive correlation was observed between neuronal activity and speed of locomotion. These NRP cells were unresponsive to somatosensory stimuli. These data will be discussed within the context of a general theory that the primary role of 5-HT neurons is to facilitate motor output, while simultaneously suppressing sensory information processing, and also coordinating autonomic activity in relation to the level of motor output. Supported by grants from AFOSR (90-0294), NIMH (MH-23433) and NIH (HL-07713).

7.17

PURKINJE CELL GAD mRNA IN RATS WITH OLIVO-CEREBELLAR DYSFUNCTION. Gary A. Oltmans*, Susan M. Drengler*, and Joan F. Lorden*
UHS/CMS, North Chicago, IL 60064 and UAB, Birmingham, AL 35294

In the genetically dystonic (dt) rat, glutamic acid decarboxylase (GAD) activity is selectively increased in the deep cerebellar nuclei (DCN). A similar effect is obtained in normal rats by making lesions of the inferior olive with 3-acetylpyridine (3AP). To explore the basis for this effect, in situ hybridization histochemistry was used to examine the transcription of GAD_{67} mRNA in the Purkinje cells of the cerebellar cortex. In dt rats at 25 days of age, approximately 2 wk after the appearance of the dt movement disorder, GAD_{67} mRNA was significantly increased (+26%) in comparison with normal controls as measured by grain density. In 3AP-treated rats, a 2-4 fold increase in message was seen 8 h after toxin injection (75 mg/kg). In 3AP-treated rats, this is a time at which the simple spike activity of Purkinje cells is greatly increased. The message declined to normal control levels after 15 days, when simple spike activity is also known to decline. Harmaline, a drug that decreases DCN GAD activity and suppresses the simple spike activity of Purkinje cells by activation of the olivo-cerebellar system, did not alter GAD_{67} mRNA when administered for 16 h. Because cerebellar norepinephrine can also have inhibitory effects on Purkinje cell activity, animals were pretreated with either clenbuterol (10 mg/kg), a β_2 adrenergic agonist, or amphetamine (2 mg/kg) prior to 3AP. Pretreatment blocked the increase in message seen with 3AP alone. The effects of clenbuterol and amphetamine in 3AP-treated rats were reversed by propranolol (9 mg/kg). These results suggest that the message for GAD can be rapidly changed by conditions that increase cellular demand for transmitter and that NE systems may modify GAD message levels. (Supported the Dystonia Med. Res. Fdn.)

7.18

INCREASED MUSCLE TONE FOLLOWING NIGRAL DOPAMINE RECEPTOR INACTIVATION *A.D. Crocker and K.L. Double, Department of Clinical Pharmacology and Centre for Neuroscience, Flinders University, Bedford Park, South Australia, 5042, Australia*

Recent results from our laboratory challenge the belief that the therapeutic basis for dopamine agonist treatment in Parkinson's Disease is the stimulation of striatal dopamine receptors. In these studies we measured tonic EMG activity in the antagonistic muscles of the rat hindlimb as an index of muscle tone. We reported previously that this measure was increased following 6-hydroxydopamine lesions of the ascending nigrostriatal neurons (Double and Crocker, 1993). In the present study EMG activity was not increased in experiments in which large areas of striatal dopamine receptors were inactivated following injection of the irreversible dopamine receptor antagonist, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). However, eight hours following inactivation of dopamine receptors in the substantia nigra, by stereotaxic injection of EEDQ, there was a significant increase in EMG activity in the tibialis (241%, $P<0.002$) and gastrocnemius (239%, $P<0.01$) muscles, compared with controls). This was associated with significant reductions in nigral D_1 (72%, $P<0.01$) and D_2 (52%, $P<0.01$) dopamine receptors compared with control injected animals. The increased EMG activity was attenuated by subcutaneous injection of $1\mu mol.kg^{-1}$ apomorphine, but not reduced further by $10\mu mol.kg^{-1}$ apomorphine. These results suggest maintenance of dopaminergic activity in the substantia nigra is critical for the control of normal muscle tone and therefore, in agonist treatment of movement disorders.

Double, K.L. & Crocker, A.D. (1993) Brain Research, **604**, 342-334.

7.19

Immunohistochemical Study of the Distribution of Corticotropin Releasing Factor and Serotonin in the Cerebellar Nuclei of Monkeys. C.I. Cha and E.Y. Lee. Dept. Anat., Col. Med., Seoul Natl. Univ. and Chungbuk Natl. Univ., Korea

CRF-IR labeled fibers were observed in all deep cerebellar nuclei of the squirrel monkey. All these fibers were varicose. The fibers of the dentate and interposed nucleus were denser than those of the fastigial nucleus. There was no difference in the density of fibers between the interposed and the dentate nucleus, but finer fibers were observed in the dentate nucleus.

Immunoreactive fibers in the molecular layer of the cerebellar cortex exhibited a higher density than those of the cerebellar nuclei.

The distribution of serotonin-IR fibers was similar to the point that these fibers were observed in all deep cerebellar nuclei. But the distribution of the serotonin-IR fibers was denser than that of CRF-IR fibers. These labeled fibers were varicose and also, some exhibited a long running appearance. There was no evidence of greater density in any given area of the three deep cerebellar nuclei. The caliber of fibers in the fastigial and the interposed nuclei was generally constant. But fine and thick fibers were mixed together in the dentate nucleus.

Immunoreactive fibers were observed, with varying densities, throughout all of the major regions of the cerebellar cortex. These were especially prominent in the granule cell layer. A lower density of immunoreactive fibers was observed in the molecular layer and occasional long fibers were seen in the white matter. A network of immunoreactive fibers was also observed in the cerebellar commissure which connects the right and left cerebellar nuclei.

7.20

Dorsal and Ventral Striatal Cholinergic Systems: The Regulation of Different Forms of Motor Behavior. K.B. Shapovalova and E.V. Pominova. I.P. Palov Institute of Physiology, Russian Academy of Science, St. Petersburg, Russia.

We perform comparative analysis of the involvement of dorsal (Neostriatum, NS) and ventral (Nucleus Accumbens, NAC) striatal cholinergic systems in the regulation of two different forms of defensive behavior: instrumental response (IR), connected with the maintenance of certain flexor posture (in dogs) and active avoidance (AA) in T-mase, connected with locomotor activity (in rats). It was shown that neither carbachol (0,03 mkg), no scopolamine (0,3 mkg) microinjections into NS affect the aquisition of AA. At the same time carbachol microinjections (0,05 mkg) into the contralateral NS significantly improved IR due to increasing of a tonic movement component and inhibition of interstimulus and phasic leg raising. It was shown that the cholinergic system of NS was of great importance for the regulation of the main component of postural adjustment: the unloading of the working limb. The same micro/injections into NAC significantly improved (ipsi- and contralaterally) both the IR in dogs due to prolonged increasing of a phasic component of movement and its amplitude as well as the aquisition of AA in rats. It can be suggested that the NS cholinergic system is structurally included into the motor components realization of IR, connected with a certain posture maintance and not involved in the regulation of AA, connected with locomotor activity. The activity of cholinergic system of NAC affects both forms of motor behavior in an excitatory way, being of nonspecific and prolonged character.

DISEASES OF MOVEMENT

8.1

IMPAIRMENT OF RHYTHMIC VOLUNTARY MOVEMENT IN HUNTINGTON'S DISEASE. J.S. Freeman* and F.W.J. Cody*. Department of Physiological Sciences, University of Manchester, Manchester M13 9PT, UK.

The ability of Huntington's disease (HD) patients and healthy subjects to produce rhythmic finger tapping movements at target rates (1-5Hz) signalled by auditory cues and to sustain tapping tempo following sudden withdrawal of cues was investigated. Healthy subjects were able accurately to duplicate the mean rates of cue signals over the 1-5Hz range. HD patients, however, had significantly reduced mean tapping rates at 3 ($p<0.05$, Mann-Whitney and Bonferroni correction), 4 ($p<0.01$) and 5Hz ($p<0.01$) target frequencies which for 3 ($p<0.01$, Wilcoxon and Bonferroni correction) and 4Hz ($p<0.05$) targets were significantly less than their maximal tapping frequencies. In neither patient nor control group did auditory cue suppression elicit significant changes in mean tapping rates. No correlation was found between mean tapping performance (an index of actual versus signal frequency using linear regression) and clinical scores of chorea, bradykinesia or tremor in the patient group. Overall, HD patients demonstrated a deficit of finger tapping performance (a depression of mean tapping rates at higher target frequencies) which could not be simply attributed to an impairment of movement speed, and was insensitive to cue removal. These results are as indicative of a disturbance of programming of rhythmic voluntary movements in HD.

8.2

THE MASSETERIC SILENT PERIODS, EVOKED BY CHIN TAPS DURING MAXIMAL CLENCHES, ARE SHORTER IN ALCOHLICS THAN IN NON-ALCOHOLICS. B. Bishop, C. Vernon*, J.A. Hirsch, and J.L. York*. Dept. of Physiology, SUNY/B and Research Institute on Alcoholism. Buffalo, NY 14214.

Since inhibitory deficits may contribute to the motor incoordination of alcoholism, we hypothesized that the duration of masseteric silent period (SP), an inhibitory reflex, would be shorter in alcoholics (AL) than in non-alcoholics (NA). To test this hypothesis we have measured the SP in 11 AL and in 11 NA matched for age (from 31 to 49 years), race, gender, and life style. All subjects were normotensive and had full dentition. The AL, participants in an in-patient treatment program, were screened to eliminate individuals with major medical problems. Sensory and motor conduction velocities (SNCV and MNCV, respectively) of the ulnar and medial nerves were determined for each subject. Surface EMGs were detected bilaterally from the masseter muscles. The chin was manually tapped with a rubber hammer containing a circuit to trigger the CRO on which the EMGs were displayed. Just prior to each tap the subject was instructed to clench maximally and hold. The latency and duration of the SP of 15 responses, measured from the CRO trace, were averaged. The Group means for the SNCV, the MNCV, and the SP latencies were not different between the two groups The SP duration of the right masseter was not different from that of the left masseter. The AL's mean SP duration was 10.9 ± 0.8 ms and that of the NA's was 26.4 ± 0.9, significantly different from that of the AL's. Double SPs occurred far more commonly in AL than in NA. We conclude that the results support the hypothesis that chronic alcoholism may interfere with inhibitory mechanisms in the CNS and contribute to the motor incoordination seen in alcoholics. Funded in part by NIAA Abuse Grant, R01-AA-06867)

8.3

RHYTHMIC LEG AND JAW MOVEMENTS DURING SLEEP: EPIDEMIOLOGIC AND POLYSOMNOGRAPHIC OBSERVATIONS. Gilles Lavigne and Jacques Montplaisir. Hôpital du Sacré-Coeur and Université de Montréal, Montréal, Canada, H3C 3J7.

Several types of rhythmic motor activity occur during sleep, such as periodic leg movements in sleep (PLMS) and rhythmic masticatory muscle activity (RMMA). In the present study, we investigated the association between these two conditions in an epidemiological study conducted on 2019 subjects representing the various regions of Canada. Overall, 12% of the subjects reported an history of PLMS and 8% were aware of frequent tooth grinding, an extreme form of RMMA. The two conditions were concomittent, respectively, in 10.3 and 15.9% of the persons interviewed. Regional differences were found for PLMS but not for sleep bruxism. PLMS occurred significantly more often in eastern Canada, especially among French speaking Canadians. This condition is known to run in families, and a large number of familial cases have already been reported in the province of Québec. Polysomnographic sleep recordings were also obtained for nine patients with both PLMS and RMMA. A strong relationship was found between these conditions and both were closely associated with the presence of micro-arousals in stage 2 sleep, characterized by the presence of a K-complex followed by a short burst of alpha activity on the EEG. These micro-arousals were frequently associated with motor events. These results suggest that periodic arousals may play a major role in the physiopathology of both PLMS and RMMA. Supported by the MRC, FRSQ and Dupont Merck Pharma Canada.

8.4

A NONLINEAR MODEL OF LEVODOPA-INDUCED TREMOR AND DYSKINESIA IN PARKINSON'S DISEASE. Michael P. Caligiuri* and James B. Lohr*. Dept Psychiatry, UCSD San Diego, CA 92053

It has been observed that levodopa may induce a worsening of resting tremor along with the emergence of dyskinesia in Parkinson's disease patients. The dyskinetogenic properties of levodopa are well recognized, however its tremogenic capability remains unclear. We examined a simplified nonlinear model in an attempt to explain the relationship between dyskinesia and tremor. Modeling was performed using the Runge-Kutta method for numerical approximations and parameters were entered based on basal ganglia circuitry. Data generated from the model were compared with spectral measurements of tremor and dyskinesia from patients with levodopa-induced dyskinesia. The computer model yielded periodic and irregular waveforms that resembled tremor and dyskinesia, respectively. The model was consistent with patient data which revealed an increase in tremor amplitude prior to the development of dyskinesia. Our results indicate that chaotic behavior appears to occur in the model under circumstances which may relate to the appearance of levodopa-induced hyperkinesia.

Supported by NIMH R29-MH45959 and R29-MH45142

8.5

CHANGES IN MOVEMENT KINEMATICS IN DISCRETE ARM MOVEMENTS IN PARKINSON'S DISEASE. P. Weiss*, G.E. Stelmach* Motor Control Lab., Arizona State Univ., Tempe, AZ 85287 -0404

A group of young adults performed discrete arm movements with a lever device, without vision of their arm. Their task was to displace a cursor associated with the lever into a target displayed on a computer screen. Using this feedback they had to move as quickly and as accurately as possible in one step into targets of three different sizes covering two different distances. The angular position of the lever was recorded at 100 Hz. After filtering, the kinematics of the movements were analyzed, using reaction time (RT), movement time (MT), time to peak velocity (TPV), deceleration time (DT), time to peak acceleration (TPA) and time to peak deceleration (TPD) variables.

The lengthening of the movement distance led to an increase in all time parameters. Similarly, the measured times decreased, when the target size was enlarged. These results are in line with the predicted kinematics according to Fitts' law. However, the examination of the Parkinsonian patients revealed a different movement pattern with disproportional lengthening of the deceleration phase, especially in the long distance condition.

These results suggests that Parkinsonian patients are more impaired by changes of the movement constraints than normal controls. An explanation of this finding could be that Parkinsonian patients require more visual processing during the homing phase of the movement.

8.6

CUE UTILIZATION IN PREHENSILE MOVEMENTS IN PARKINSON'S DISEASE. A. Chaiken*,P. Weiss*, G.E. Stelmach* Motor Control Lab., Arizona State Univ., Tempe, AZ 85287 -0404

A group of 9 patients with Parkinson's disease, a age-matched elderly control group and a young control group performed a prehension task to two different object sizes under valid or invalid precue-conditions. Three infrared emitting diodes (IREDs) were placed on the subject's index finger, thumb and wrist. These IREDs recorded by an Optotrak®-3D-System at 100 Hz described the kinematics of the reach and grasp phase. The following variables were used in the analysis: reaction time (RT), transport time (TT), manipulation time (MAT), time to maximum grip aperture (TMGA), time to peak velocity (TPV), time to peak acceleration (TPA) and time to peak deceleration (TPD) and deceleration time (DT).

A valid precue reduced the RT significantly for all groups (valid precue: 373 ms, invalid: 398 ms). The interaction of group by validity just failed to reach level of significance ($p = 0.7$). The group main effects showed that the Parkinsonian patients are slower than controls, concerning MAT, TT, TPV, TPA, TPD and DT. When the subjects grasped the large object, they reached their maximum grip aperture, peak velocity, peak acceleration and peak deceleration later than when they reached for the small object. Similarly, the TPA, TPV, TPD were longer under the invalid precue condition. But DT was prolonged under the valid-precue condition. Finally, there were group by validity-interactions for TPV and TPA. The validity had almost no influence on the variables in both control groups, but both times were lengthened in Parkinsonian patients.

The results showed that the kinematics were affected by the different object sizes and the precue conditions. But besides a general slowing, the Parkinsonian patients were more disturbed by an invalid precue, showing problems in timing their peak velocity and peak acceleration. These results suggest that Parkinsonian patients have difficulty restructuring a prepared prehensile movement.

8.7

MYOBLAST STRENGTHEN DYSTROPHIC MUSCLES P. Law, T. Goodwin*, Q. Fang*, M. Deering*, V. Duggirala*, C. Larkin*, A. Florendo*, D. Kirby*, L. Li*, A. Shirzad*, T. Quinley*, T. Yoo*, and R. Holcomb*, Cell Therapy Research Foundation, Memphis, TN 38117. The feasibility, safety, and efficacy of myoblast transfer therapy (MTT) were assessed in an experimental lower body treatment involving 32 Duchenne muscular dystrophy (DMD) boys aged 6-14 yr, half of whom were non-ambulatory. Through 48 injections, five billion (55.6×10^6 / mL) normal myoblasts were transferred into 22 major muscles in both lower limbs, in 10 minutes with the subject under general anesthesia. Myoblasts were cultured from 1-g fresh muscle biopsies of normal males aged 9-21 yr or from reserves frozen 1 mo to 1.5 yr ago. All subjects took oral cyclosporine (Cy) for 6 mo. There was no evidence of an adverse reaction to MTT or Cy. Objective functional tests using the KinCom Robotic Dynamometer measured the maximum isometric contractile forces of the ankle plantar flexors (AF), knee flexors (KF), and knee extensors (KE) before MTT and at 3, 6, and 9 mo after MTT. The AF showed progressive increases in force at 6 and 9 mo after MTT. At 9 mo after MTT, 60% of the 60 AF examined showed a mean increase of 50% in force ; 28% showed no change; and only 12% showed a mean decrease in force of 29% when compared to the function of the same muscles before MTT. The KF and the KE, being proximal and more degenerative before MTT, showed less improvement at 9 mo after MTT according to Wilcoxon signed rank test. Ambulatory subjects improved more than non-ambulatory ones. Progressive increase in force in the AF and arrest of weakening in the KF and KE were observed in the ambulatory subjects as early as 3 months and continued up to 9 months after MTT. The results indicate that 1) MTT is safe; 2) MTT improves muscle function in DMD : 88% of the AF, 49% of the KF, and 45% of the KE showed either increase in strength or no loss of strength 9 mo after MTT; 3) the myoblast dosage used is more effective in the AF than in the KF, and is least effective in the KE. The more degenerated proximal muscles will need more myoblasts per unit muscle volume than the distal muscles for MTT to be effective; 4) more than 5 billion myoblasts are necessary to strengthen both lower limbs of a DMD boy between 6 to 14 yr of age; 5) MTT is more effective in the younger, ambulatory subjects than in the older, non-ambulatory subjects; 6) Cy is not responsible for the functional improvement, since muscle function continues to improve 9 mo after MTT despite Cy withdrawal at 6 mo after MTT; 7) Cy immunosuppression permits donor cell survival and development without overt rejection symptoms; 8) myoblasts from frozen reserves are as effective as those from fresh muscle biopsies; 9) fifteen billion myoblasts can be cultured from a 1-g muscle biopsy; 10) billions of cultured myoblasts can be injected into subjects without tumor formation. (Supported by public donations to Cell Therapy Research Foundation.)

8.8

PHARMACOLOGICAL EVIDENCE FOR A DECREASE IN TONIC DESCENDING INHIBITION MEDIATED VIA α_2-ADRENOCEPTORS IN THE SPINAL CORD-INJURED KETAMINE-ANESTHETIZED CAT. **J.S. Taylor*, C.J. Vierck, Jr*, B. Radisavljevic*, J.B. Munson. Dept. of Neuroscience, Univ. of Florida, Gainesville, FL 32610.**

As an animal model of spinal spasticity we have identified an increase in ipsilateral triceps surae stretch-evoked reflex activity and muscle tone following a unilateral T12-L2 dorsal quadrant (DQ) spinal cord injury (SCI). The aim of this work was to examine the role of the tonic noradrenergic descending inhibitory systems mediated through α_2-adrenoceptors before and after SCI. The major quantitative effects of SCI in the behaviorally conditioned cat were increases in the ipsilateral length-tension curve, in the ratio (lesion/intact) of electromyographic (EMG) and torque measures and in the ipsilateral tonic baseline EMG activity. These lesion-induced stretch reflex deficits were also present in the Ketamine-anesthetized (10-13 mg/kg/hr) cat. Increases in ipsilateral muscle tone were observed with the Ashworth test during ankle or knee joint flexion. A disruption in the descending control of spinal reflex function following DQ injury was suggested by significant ipsilateral increases in both the tonic and evoked Babinski sign, in addition to an ipsilateral hypermetria, evoked during air suspension or during the positive support test. Systemic administration of the α_2 noradrenergic agonist Clonidine (0.01-10.00 µg/kg) produced a dose-dependent inhibition of stretch-evoked EMG activity in the uninjured ketamine-anesthetized animal. However following the DQ lesion ipsilateral clonidine-induced reflex inhibition was significantly attenuated. These data suggest that a unilateral dorsal quadrant spinal lesion in the ketamine-anesthetized cat produces an ipsilateral stretch-evoked hyperreflexia which is in part due to an attenuation in tonic descending inhibitory systems mediated via α_2-adrenoceptors. Supported by Grant NS27511 and the Florida IDSTF.

8.9

ZONAL PURKINJE CELL LOSS REVEALED BY CALBINDIN (CB) EXPRESSION IN THE LEANER MUTANT MOUSE. Louise C. Abbott* & John A. Heckroth*, Dept. Veterinary Biosci., Univ. of Ill., Urbana, IL 61801 and Indiana State Univ., Terre Haute Center for Medical Ed., Terre Haute, IN 47809.

Homozygous leaner mice exhibit severe ataxia beginning at P10. Purkinje cell (PC) and granule cell (GC) loss is known to occur in these mice, with GC loss starting at P10 and PC loss starting around P40. Standard CB immunohistochemistry, was performed on coronal frozen sections of cerebella and brainstems from 20 day old and 6 month old leaner and wild-type, C57BL/6J mice. In adult leaner mice, CB+ PCs formed rostrocaudal stripes with intervening empty zones. The pattern of CB+ PCs resembled the pattern of zones revealed by Zebrin stripes in wild-type mice. The zonal loss of PCs also resulted in a patterned loss of CB+ terminals in the cerebellar nuclei and a patterned loss of inferior olivary neurons. All PCs appeared to be present in young leaners (P20). CB+ PCs were present throughout the PC layer but a striped pattern of staining was evident, with rostrocaudal stripes of light-staining CB+ PCs alternating with darker staining CB+ PCs. We propose that the light-staining PCs are the cells that will be lost as leaner mice age. In both young and old leaner mice, axonal swellings (torpedoes) were observed on PC axons. We postulate that the leaner mutation results in a functional deficit producing ataxia and secondary PC loss. Support: Grant 5S07RR5371 to JAH, BRSG prog., NIH.

8.10

SHORT VS LONG TERM ANTIPSYCHOTIC DRUG EFFECTS ON STRIATAL FUNCTION: IMPLICATIONS FOR DRUG-INDUCED EXTRAPYRAMIDAL SYNDROMES. Ronald E. See. Department of Psychology, Washington State University, Pullman, WA 99164-4820

Repeated administration of antipsychotic drugs (APDs) during the treatment of schizophrenia often results in severe extrapyramidal side effects. Animal models have been established in order to examine the effects of prolonged APDs on neural function, particularly in the nuclei of the basal ganglia. A crucial issue in assessing the effects of APDs on motor function is the duration of drug exposure, since different motor syndromes exhibit unique times of onset during the course of treatment (eg. acute dystonia vs. tardive dyskinesia). Intracranial microdialysis was utilized in a rat model of long-term APD administration in order to measure changes in striatal extracellular neurotransmitter activity. Data from several studies will be presented demonstrating that changes in striatal dopamine function are uniquely different following short term (weeks) vs. long term (months) APD administration. Additional findings drawn from neurochemical, electrophysiological and behavioral studies are incorporated into a suggested model of APD effects on striatal function and the possible implications for understanding the pathophysiology of time dependent APD-induced motor side effects.

8.11

QUANTIFYING COMPARABLE MOVEMENT DISORDERS IN HUMANS AND RATS USING VIDEOTRACKING TECHNIQUES: APPLICATION TO STUDIES OF TARDIVE DYSKINESIA. G. ELLISON*, A. KEYS*, and W. WIRSCHING*. Department of Psychology, UCLA, 405 Hilgard Ave., Los Angeles, CA 90024; Movement Disorders Clinic, Veterans Administration, Brentwood, CA 90024.

The form of the altered Oral Movements (OMs) in rats administered chronic neuroleptics have been measured using computerized spot-detection circuitry involving fluorescent dyes placed on the rat's muzzle. Using these techniques we have found progressive alterations in the form of spontaneous OMs in rats administered chronic neuroleptics and obtained evidence of an altered pattern generator.

These procedures have now been applied to humans using a new rapid color-detection circuit. Small colored spots were placed on the upper and lower lips of humans with tardive dyskinesia, the video records analyzed by computer using fast-fourier and other methods and the results compared with those of normal controls. This method permits the study of both vertical and lateral components of the altered oral movements without any attached device with minimal disturbance to the patient. Two video cameras can be used to record simultaneously OMs and movements of the hands or feet so that the temporal relationship between different body movements can be quantified. This system is applicable to a wide range of behaviors in humans and animals. (USPHS MH12841).

8.12

EFFICACY AND SAFETY OF TIZANIDINE FOR REDUCTION OF SPASTICITY IN MULTIPLE SCLEROSIS. Shellenberger, K.*1, Stazio, A.*2, Vollmer, T.*3, and The U.S. Tizanidine MS Study Group. [1]Athena Neurosciences, Inc., South San Francisco, CA 94080, Tulane Medical Center, New Orleans, LA 70112, and Yale School of Medicine, New Haven, CT 06510.

Tizanidine (TIZ) is an imidazoline which has full agonist activity at α_2-adrenergic receptors and also binds to I (imidazoline) receptor sites. Animal and human neurophysiologic studies indicate that TIZ acts in the spinal cord to reduce hyperreflexia and elevated or enhanced muscle tone associated with spasticity. Clinical studies have evaluated the efficacy of TIZ in treatment of spasticity. This multicentered (14 sites), double-blind study compared TIZ to placebo to confirm efficacy in the treatment of spasticity associated with multiple sclerosis. The study in 258 patients was conducted in accordance with Good Clinical Practices and the Helsinki Accord. All study sites obtained IRB approval and informed consent was obtained from all patients enrolled. The primary efficacy parameter, change in muscle tone, was assessed by the Ashworth scale. Patients were titrated to an optimal, tolerated dose not to exceed 36 mg/day. Most patients achieved dosages in the 24-36 mg/day range. Statistical analysis (ANOVA) was performed on data from the evaluable (204 patients) and intent-to-treat (258 patients) populations. TIZ was found to produce a significant reduction in muscle tone relative to placebo in both populations. Evaluation of muscle strength, using the BMRC scale, found no significant changes. The most common study associated adverse events were drowsiness and dry mouth and were reported most frequently in the TIZ treated patients. Additionally, mean blood pressure was slightly lower in the TIZ treated patients although there were no changes in pulse rate. TIZ was judged to be safe and effective in treatment of spasticity from MS.

TRACE ELEMENTS—MINERAL INTERACTIONS

9.1

TRACE ELEMENT-MINERAL INTERACTIONS IN MAN: ZINC-MAGNESIUM. Herta Spencer, Metabolic Research, VA Hospital, Hines, IL 60141

Large doses of zinc (140 mg/day) decrease the intestinal absorption of calcium during a low calcium intake of 230 mg/day but not during a normal calcium intake of 800 mg/day (J. Am. Coll. Nutr. 6:47-51, 1987 and 11:561-566, 1992). In order to determine whether the effect of zinc also applies to the absorption of magnesium, the net absorption of magnesium was determined by performing metabolic balances of zinc under strictly controlled study conditions in adult males in control studies and during the high zinc intake. The zinc intake was increased by 55, 100, and 140 mg elemental zinc as $ZnSO_4$. These studies were carried out during different calcium intakes of 230, 500, 800 and 1400 mg/day. The 140 mg dose of zinc decreased the absorption of magnesium and the magnesium balance significantly during the low calcium intake of 230 mg/day and during the 500 mg calcium intake, while this dose of zinc had no effect on magnesium net absorption during the 800 mg or higher calcium intakes. The doses of 55 and 100 mg zinc had no effect on the magnesium balance nor on the net absorption of magnesium during any of the calcium intakes. The effect of the large dose zinc, 140 mg/day, on magnesium absorption is similar to its effect on calcium absorption during a low (230 mg) calcium intake but also during a 500 mg calcium intake.

10.1

DECREASING MUSCLE MASS IN THE ELDERLY: A POSSIBLE CONFOUNDING VARIABLE IN MOTOR CONTROL. Richard P. Spencer. University of Connecticut Health Center, Farmington, CT 06030.

One part of the regulation of both voluntary & involuntary body activity depends upon the muscle mass. This mass however is not constant, and begins to decline in the elderly. To gain some understanding of the magnitude of change and age at onset in males/females, we began by analyzing values culled from the literature; several analytical techniques were employed. For cardiac muscle, Fig. 5 of Kitzman et al (Mayo Clin. Proc. 63: 137, 1988) shows a decline in weight (W) after an age (A) of 65. Least squares equations for data collected by decades were W = 444 - 2.30 A for males and W = 393 - 1.58 A for females. From ages 65 to 95 years, there was a 19.5% cardiac weight loss in males and 17.4% in females. There are too few data as yet, to attempt an allometric description of declining heart weight versus declining body weight. For voluntary muscle, an analysis was made of mid-upper arm mass. Crude data on New Zealand women over age 70 (Campbell, Borrie, Human Biol. 60: 57, 1988) revealed a 13.6% loss in the next 15 years, and a value of 14.9% when corrected for the humerus. These values are not too discrepant as compared with overall body weight loss in the aging process. Studies on motor control in the elderly, and on the functioning of nonstriated muscle, have to factor in the declining muscle mass with age.

EDUCATION

11.1

MORAL EXPECTATION OR MIRACULOUS ROBOTS: STATISTICS IN MEDICINE AND PHYSIOLOGY. R. Jevning*, R. Anand, and M Biedebach*. California State University, Long Beach, CA 90840; and United States International University, San Diego, CA 92345.

A vast literature on "methods" in statistics and the existence of such terms as "rejection" or "acceptance" has shrouded the proper use of probability as a means of expressing "moral expectation," that is, considered opinion (educated guessing). Most likely deriving from probability's use in physics, the vigorous program to make probability objective has had deleterious consequences for physiology and medicine by the program's creation of miraculous robots that convert uncertainty into certainty in any laboratory. From these robots consumers (and scientists!) expect (and receive!) verified conclusions about drugs, diet, exercise, etc. only to be "surprised" shortly that such conclusions are not in fact such. Central to the robot's uncertainty conversion mechanism is some form of probameter, a device from physics that measures the amount of chance in an experiment. For molecules distributed between 2 sides of a container, for example, measured chance content is $(1/2)^N$, where N is number of molecules. The same chance content is found in coin tossing and drug testing, where now N is the number of tosses or patients. For drug testing, most probameters then also convert chance content into drug effectiveness. While confirmed only for molecules, the precision, and easy applicability, of the probameter has led to its widespread use. Only more remarkable than the robots themselves is their uncritical purchase by physiologists.

14.1

THE RELATIONSHIP BETWEEN SENSORY INPUT AND MOTOR OUTPUT DURING SWALLOWING. Kristine M. Mosier,* Jeffrey Spiro,* Jill Rendell,* Alan G. Lurie,* and Thomas Gay.* University of Connecticut Health Center, Farmington, CT 06030.

The motor control of swallowing movements is generally believed to rely on input from various sensory receptors of the upper airway. This study sought to determine the effects of sensory deprivation on oral cavity and laryngeal movements during swallowing. Movements of oral cavity and laryngeal structures were tracked using quantitative videofluoroscopy. Lead pellets were attached to the upper and lower lips, mandibular central incisor, anterior, middle, and posterior aspects of the surface of the tongue, and the superior surface of the soft palate. A reference pellet was attached to the an upper central incisor. Six subjects were visualized swallowing a 10 ml bolus of water both under natural conditions and local anesthesia applied to the lingual nerve and the greater palatine nerve bilaterally, and to the surfaces of the oral cavity and posterior pharyngeal wall by topical spray. The videotaped images were input to a microcomputer where changes in the x and y positions of the pellets were measured in relation to the position of the reference pellet, frame-by-frame. Results showed that anesthesia had different effects depending on the individual subject: most showed changes in coordination patterns during the first few swallows; only one showed virtually no effect. All anesthesia effects subsided after the first two or three swallows suggesting that subjects learned to overcome the effects of desensitization. Results suggest that swallowing is a more plastic and adaptive behavior than previously believed.

14.2

EXCITOTOXIN LESIONS OF THE NEOSTRIATUM IN THE CAT PRODUCE APRAXIA AND CHANGES IN PALLIDAL NEURONAL ACTIVITY RELATED TO MOVEMENT. J.W. Aldridge*, J.F. Thompson*, R.C. Meyer* and S. Gilman*. Dept. of Neurology, Univ. of Michigan, 1103 E. Huron, Ann Arbor, MI 48104.

We studied the effects of a unilateral excitotoxic lesion of the neostriatum on motor behavior and neuronal activity in the pallidum (globus pallidus and entopeduncular nucleus). Cats were trained in a GO/NO-GO motor task that required a forelimb reaching movement. After training, they were prepared for chronic recording of neuronal activity. Control data were collected prior to lesioning the caudate nucleus and putamen with multiple (15-17) injections (.25-1.25 μl) of 200 nM quinolinic acid. Short term lesion effects (disturbed locomotion, circling and sensory inattention) subsided within 1-3 days. Free range behavior recovered completely. The only overt long term deficit occurred in the context of the GO/NO-GO task. The animals were unable to complete the reaching movement sequence in GO trials even though the initial postural movements were triggered and they could perform similar reaching movements in contexts outside of the task. The animals recovered partially over a period of weeks, however, an inability to withhold movements in NO-GO trials became more prominent. Both reaction time and movement time increased significantly after the lesion and neither returned to baseline. Neuronal activity correlated to the motor task was observed in the pallidum both before and after the lesion. Indeed, the proportion of neurons exhibiting increases in activity rose from 31% to 61%. The proportion of neurons with decreases of discharge fell from 13% to 4%. There was little or no change in the firing rate. These findings suggest that interruption of basal ganglia function interferes with skilled movements producing an apraxia in which the animal has the capabilities to make a movement but fails in specific behavioral contexts. This disturbance may be related to the loss of GABAergic afferents to the pallidum, which appears to unmask excitatory inputs that may arise in the subthalamic nucleus. Support: NIH grant NS19613 and United Cerebral Palsy Foundation.

14.3

RAPID LEARNING OF A MOTOR TASK IN THE CAT LUMBAR SPINAL CORD. V.R. Edgerton, J. Hodgson, R.R. Roy, R. deLeon and K. Nakata, Department of Physiological Science and Brain Research Institute, UCLA, Los Angeles, CA, 90024.

Previous studies have shown that adult cats spinalized at T12-T13 can regain the capacity to execute full weight-supporting steps by the hindlimbs and that recovery is improved if they undergo 30 minutes of locomotor training per day. These studies also demonstrated that if the cats are trained to stand rather than walk, they largely lose the ability to step. Both findings suggest that the spinal cord can undergo functional changes in response to prolonged training. It has also been shown that walking spinal cats respond when obstructions are placed in the path of the hindlimb during the swing phase by lifting the paw higher after contact with the obstacle. The present data demonstrate that after making contact with an obstacle, adult spinalized cats can modify the kinematics of the hindlimb in the succeeding step. Once the obstacle had been presented a change in trajectory of the swing phase was evident as soon as the paw left the ground. In some instances the obstacle was completely avoided. Both of these observations suggest anticipation of the obstacle in the step following its initial presentation. Further evidence for the anticipatory response was the observation that in each subsequent step with the obstacle placed to impede the swing, the force of the contact by the paw on the object remains substantially lower than occurs in steps not preceded by the obstacle's presence. After removal of the obstacle, the limb kinematics returns to normal within two steps. Thus the spinal cord appears to 'learn' of the presence or absence of an obstacle and modify the limb kinematics of subsequent steps to suit the prevailing condition.

14.4

IMAGING AND WHOLE CELL RECORDING OF PROPRIOSPINAL ACTIVITY IN THE EMBRYONIC CHICK SPINAL CORD. Amy M. Ritter* and Michael J. O'Donovan*, Lab of Neural Control, NINDS, NIH, Bethesda MD 20892

Early in development the spinal cord of the chick embryo generates spontaneous episodes of patterned motor activity. Lesion studies have shown that propriospinal neurons which send axons through the ventrolateral white matter tracts (VLT cells) synchronize activity between segments, and provide excitatory drive to motoneurons (Ho and O'Donovan 1993 J Neurosci 13:1354). Optical recordings were made from VLT cells during rhythmic motor activity which had been backfilled with calcium indicator dyes from the tract. Many cells were active at the same time and in phase with motoneurons, as measured from the ventral root discharge. However, other cells which had been filled with dye did not produce optical signals. The population of filled cells included some located contralateral to the injection site, which were visible as a discrete column when viewed through the ventral surface of the cord. Again, this population included a mix of active and inactive cells. Whole cell patch recordings from interneurons located in the same regions as the VLT cells, and from antidromically identified VLT cells, confirm the optical experiments. Many cells were activated synchronously with motoneurons during rhythmic motor activity. The activity of the identified VLT cells was heterogeneous, and indistinguishable from that of the population of unidentified cells. The synaptic drive potentials in these cells was highly variable, ranging from a few millivolts to as much as 30 mV. It is unlikely that the extremely small modulation seen in some cells would have generated optical signals.

We also examined the projection of the tract onto other interneurons. It was found that every interneuron which was rhythmically active received short latency synaptic input from the VLT. This would provide a potential substrate for the synchronous activation of the network. These results then support a role for at least a subset of VLT cells as transmission elements during this rhythm. Experiments are under way to examine other possible functions for this anatomically defined group of cells.

14.5

COMPARISON OF VESTIBULOSPINAL AND IA AFFERENT SYNAPTIC INPUTS IN CAT TRICEPS SURAE MOTONEURONS. Sarah L. Wescott*, Randall K. Powers*, Farrel R. Robinson*, Mark A. Konodi* and Marc D. Binder*. Univ. of Washington, Sch. of Medicine, Seattle, WA 98195.

We compared the steady-state effective synaptic currents (I_N) produced by stimulating Deiter's nucleus (DN) and Ia afferent fibers in triceps surae motoneurons of the cat. The motoneurons received considerably less synaptic input from DN (2.5 nA ± 2.6 SD; n=34) than from the Ia afferents (4.2 nA ± 2.1 SD; n=19). The magnitudes of the two inputs were not correlated in the same cells and their distributions were different. The Deiter's input was larger in the high-threshold motoneurons than in the low-threshold cells, whereas the opposite trend appeared for the Ia input. We also measured the changes in motoneuron firing rate produced by activating these synaptic inputs. The Ia input increased the discharge rate of each motoneuron tested (range +1 to +10 impulses/s; mean +7.5 ips; n=5). The Deiter's input, however, exerted much less of an effect on motoneuron discharge and in 4 of 11 cells, caused a decrease in motoneuron firing rate (range -2.7 to +1.1 impulses/s; mean -0.2 ips) (Supported by NIH grant NS 26840)

14.6

LOCOMOTOR-LIKE MOVEMENT DEPRESSION OF H REFLEX TRANSMISSION CAN BE INDUCED AT THE SPINAL LEVEL IN THE HUMAN. **John D. Brooke*, William E. McIlroy*, David F. Collins* and John E. Misiaszek*. Biophysics Interdepartmental Group and School of Human Biology, University of Guelph, Ontario Canada N1G 2W1.**

H reflex depression during gait can arise through somatosensory discharge from passive movement of lower limb segments. Is this a spinal effect? It was hypothesized that, if the movement-induced discharge works through rapid oligosegmental circuits, H reflex depression could start within 60 ms of movement onset. In four volunteers, the right foot was strapped to a pedal on an ergometer crank which, from 90° past top-dead-centre, could rotate without warning to the subject. Soleus and tibialis anterior EMGs were recorded from movement onset. Approx. 20 stimuli were presented over the tibial nerve, for each 10 ms interval, in random order over the first 200 ms of movement. Controls with the limb stationary were interdigitated between movement samples. Stimulus constancy was inferred from M wave stability. Tonic EMGs were quiet throughout. Calculation of soleus H reflex magnitudes supported the research hypothesis in all four subjects. Significant reflex depression ($p<.05$) appeared by 40 ms and increased over the collection period. By 200 ms, the mean H reflex was 44% of control. We conclude that this aspect of locomotor control has a base in the human spinal cord. **Supported by NSERC CANADA and U.G. Fellowships.**

14.7

STIMULATION OF GROUP II MUSCLE AFFERENTS IN HINDLIMB FLEXOR NERVES RESETS THE STEP CYCLE DURING MLR EVOKED FICTIVE LOCOMOTION. M-C. Perreault*, M.J. Angel*, P. Guertin*, P.A. Carr* and D.A. McCrea*, Dept. Physiology, U. Manitoba, Winnipeg, R3E0W3 CANADA.

Conway et al. (Exp Brain Res 68:643-656, 1987) demonstrated that stimulation of extensor but not flexor group I afferents can reset the fictive locomotor cycle. The present study examines the effects of higher strength flexor nerve stimulation during MLR evoked fictive locomotion in paralysed, decerebrate cats while recording activity in peripheral nerves. Sartorius (Sart), tibialis anterior (TA), and posterior biceps-semitendinosus (PBSt) nerves were stimulated (100 or 200Hz, 20-50 shocks) during flexion or extension. During flexion Sart stimulation at 5T but not 2T (i.e. with group II afferent recruitment) caused resetting. Flexor activity was terminated and a burst of large-amplitude, long-duration activity was initiated in hip and knee extensors. Compared to the hip and knee, much of the ankle extensor activity during resetting was delayed. The threshold for TA-evoked resetting was 1.8T allowing the possibility that higher threshold group I afferents in the TA nerve contribute to resetting. PBSt stimulation during flexion did not reset locomotion. During extension 5T TA stimulation but not 2T produced inhibition of medial gastrocnemius and excitation of quadriceps and PBSt. Preliminary results suggest that effects of 5T Sart and TA stimulation during extension are similar. PBSt stimulation during extension produced a different pattern of excitation.

In conclusion stimulation of both flexor and extensor hindlimb afferents can reset the locomotor step cycle. Compared to extensors, however, the effects from flexor nerve stimulation occur at higher strengths. The result of either flexor or extensor afferent stimulation is to promote the onset or increase the duration of ipsilateral extension. Supported by the MRC of Canada and Human Frontiers.

14.8

THE GENERATORS OF HUMAN MOVEMENT-RELATED CORTICAL POTENTIALS. I.M. Tarkka* Division of Restorative Neurology, Baylor College of Medicine, Houston, Tx 77030.

Scalp topographic, electrical and magnetic source localization techniques were utilized to localize cortical generators of human movement-related cortical potentials (MRCP). The EEG topography of MRCP was studied with 29 recording channels. Ten healthy subjects performed self-paced voluntary unilateral index finger and toe movements. Cortical potentials were backaveraged according to the onset of rectified electromyogram (EMG), which indicated the onset of voluntary movement. A window of 450 ms was collected and 150 sweeps were averaged for each recording. Topographic analysis and electrical multiple source localization were performed on grand average data of all subjects. Source localization using single dipole model was performed also on 7-channel magnetoencephalographic (MEG) data of individual subjects. Topographic mapping revealed a large, parietal, slightly contralateral negativity prior to the onset of EMG, a contralateral focal negativity at the onset of EMG and a frontal midline negativity after the movement. A model of 3 equivalent temporally overlapping electrical dipoles was developed to explain electrical MRCP. This model was able to explain the 450 ms left hand data 96.4 %, right hand data 94.2 % and toe movement data 93.1 %. MEG results showed dipoles in the supplementary motor area and sensorimotor cortex verifying the spatio-temporal 3-dipole of electrical data.

14.9

CHARACTERIZATION OF MOTOR CONTROL FROM SURFACE EMG
Arthur M. Sherwood, P.E., Ph.D*., Baylor College of Medicine, Houston, TX 77030

Following an insult to the central nervous system, the loss of motor control may not correlate to the anatomical extent of damage as defined by existing imaging techniques. As a basis for a therapeutic intervention, it is necessary to define changes in motor control functionally. Motor control of the limbs exists as a tangible entity initially at the spinal segmental level where afferent and efferent activity converge. We propose that the pattern of activity of the spinal motor centers expressed as the mean firing rate of the motor pool should be considered as the "gold standard" for studies of motor control in individuals with impaired voluntary movement secondary to upper motor neuron dysfunction. Surface EMG recordings during a standardized protocol provides a means of estimation of that conceptual ideal. Traditionally, interpretation of EMG data has been based on an implied relationship of EMG activity to force of the muscle, which is tenuous at best. We chose rather to interpret the data in terms of activity of the spinal motor neuron pools as expressed in the EMG. Transformation of that surface EMG can thus provide a representation of the motor control. As a first approximation, we assumed a linear, constant transformation of motor pool firing rate to the envelope of the EMG activity. Ultimately, it will be necessary to define the limits of accuracy imposed by individual variations in the transformation of motor neuron firings to surface EMG signals. Nevertheless, the results obtained to date suggest that a great deal of useful information can be obtained by linear combinations of the EMG data which should not be obscured by undue data reduction through, e.g., thresholding or normalization. Examples of motor control profiles in healthy subjects and those with upper motor neuron dysfunction will be presented.

14.10

THE INFLUENCE OF MUSCLE STRAIN ON STIMULUS DURATION OF SLOW MUSCLES PERFORMING SIMULATED LOCOMOTORY ACTIVITY. Vincent J. Caiozzo, Michael J. Baker, and Kenneth M. Baldwin. Departments of Orthopaedics and Physiology, University of California, Irvine, Ca 92717.

The work loop technique represents a powerful approach for exploring important issues related to locomotion. Using this method, muscles are required to perform sinusoidal length changes that consist of repetitive shortening and lengthening phases. During the shortening phase, positive mechanical work is produced by the muscle, whereas work is done on the muscle during the lengthening phase. In part, the amount of mechanical work produced by the muscle during the shortening phase is dependent upon the duration of activation. Since muscles cannot instantaneously relax, part of the shortening phase must be devoted to relaxation. Consequently, any factor that influences the rate of relaxation, will influence the duration of activation and hence the mechanical work produced by a muscle. The objective of this study was to examine the influence of strain (amplitude of shortening) upon stimulus duration. Soleus muscles (n=6) performed sinusoidal length changes at a frequency of 2 Hz and at strains of 1, 2, 3, 4, 5, 6, and 7 mm. The duration of the shortening phase was 250 ms. At a strain of 1 mm, the mean ($\pm$ SD) stimulus duration was 40 $\pm$ 0 ms. Therefore, at this strain, the muscles were stimulated for only 16% of the shortening phase. As the strain was increased, the duration of stimulation increased substantially ($P < 0.001$). For instance, at a strain of 7 mm, the mean stimulus duration was 150 $\pm$ 9 ms, or 60% of the shortening phase. The results of this study demonstrate that the amplitude of strain plays a key role in dictating the rate at which a muscle can relax. When the strain is large, muscles can relax at a faster rate, hence they can be activated for longer periods of time and produce more mechanical work. An important question for future consideration is whether the central nervous system takes advantage of this form of shortening inactivation when muscles perform locomotory tasks.

Supported in part by grants from OREF and NIH AR30346

14.11

TREMOR AND SYNCHRONOUS EMG BURSTING IS ACCENTUATED DURING ECCENTRIC MUSCLE ACTION.
John N. Howell, D. Karapondo, G. Chleboun and R. Conatser. Somatic Dysfunction Res. Inst., Ohio Univ., Athens, OH 45701

Recent reports suggest that the pattern of motor unit recruitment in the human triceps surae during eccentric, or lengthening, contractions may be quite different from that during isometric or concentric activity (Nardone et al., J. Physiol. 409:451, 1989). Using both surface and intramuscular EMG electrodes with the flexors and extensors of the elbow as well as the triceps surae during lifting and lowering of loads, we observed shifts in the EMG pattern during eccentric activity from the typical interference pattern to one characterized by a flat baseline interrupted by bursts of activity, which often occurred synchronously in synergistic muscles, e.g., soleus and gastroc. The bursting exhibited a frequency of 7.5-11 Hz and showed no systematic dependence on load, but it did increase with increasing rates of movement as the lifting-lowering cycle was increased in frequency from 0.5 to 1.0 to 1.5 Hz. The bursting pattern and the associated tremor was much more pronounced in some subjects than in others. Our observations are consistent with the idea that recruitment patterns differ according to the type of contraction for which the muscle is being recruited. (Supported by AOA Grant #08-259)

14.12

LOCOMOTION STIMULATES GROUP III MUSCLE AFFERENTS. Joel G. Pickar, Janeen M. Hill and Marc P. Kaufman. Univ. of California, Div. Cardiovascular Med., Davis, CA 95616.

Muscular contraction stimulates group III afferents whose activation, in turn, reflexly affects both the autonomic and somatic nervous systems. Our knowledge of the discharge properties of group III afferents responding to muscle contraction has been obtained using electrical stimulation of α-motoneurons in ventral roots or muscle nerves. This method of exciting axons recruits α-motoneurons in an order opposite to that occurring during physiological activation. We, therefore, determined the responses of group III muscle afferents to locomotion. Locomotion was induced by electrical stimulation of the mesencephalic locomotor region in decerebrate cats. We recorded single unit activity in fine dorsal root filaments innervating the triceps surae muscles while the cats walked on a moving treadmill. We found that 13 of 15 group III afferents (c.v. >2.5 and <30m/s) whose receptive fields were in the triceps surae muscles were stimulated by locomotion. Moreover, many group III muscle afferent endings discharged in response to very low muscle tension (60 grams). We also examined the responses of six group III muscle afferents to locomotion and to static muscle contraction induced by electrical stimulation of the sciatic nerve. The tension generated by the triceps surae muscles was similar during the two protocols. Afferents that responded mildly to locomotion responded weakly to static contraction. Our data suggest that muscular contraction induced by an α-motoneuron discharge pattern causing locomotion can effectively distort the receptive fields of group III muscle afferents. In addition, both direct electrical stimulation and physiological activation of α-motoneurons can activate the same population of group III muscle afferents.
Supported b NIH grant HL-08144 (to JGP) and HL-30710 (to MPK).

14.13

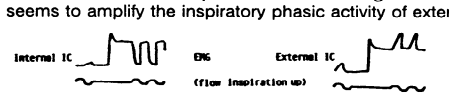
IN SITU POWER PRODUCTION FROM RAT SOLEUS AND PLANTARIS Steven J. Swoap, Vincent J. Caiozzo, and Kenneth M. Baldwin. Univ. of Cal., Irvine, CA 92717.

Two synergistic muscles, soleus and plantaris, have distinct functional properties, yet they are required to perform the same ankle-extensor function during locomotion. Further, these muscles are of different length, and thus over the same range of ankle motion, they produce force at different regions of their force-velocity (F-V) curves. To date, very few investigations have compared the ability of synergistic muscles to produce mechanical work. The 3 primary objectives of this study were 1) To compare the work capacity of the soleus and plantaris using the work-loop technique (WL), a powerful approach for simulating muscle function during locomotion; 2) To identify the velocity ($V_{opt\text{-}wl}$) derived from frequency and strain (distance of shortening) that produces maximal power in WL (see below); 3) To compare $V_{opt\text{-}wl}$ with the velocity that corresponds to maximal power derived from F-V curves ($V_{opt\text{-}fv}$). F-V measure-ments were made on the soleus (n=7) and plantaris (n=4), to determine $V_{opt\text{-}fv}$. Then, sinusoidal length changes (strain) were imposed upon the muscle, stimulating the muscle to produce tension only during the shortening phase. To generate a family of velocities of shortening, both strain and cycle frequency were altered. To determine the $V_{opt\text{-}wl}$, work was measured at mutliple cycle frequencies (soleus = 1.5-4Hz - steps of 0.5 Hz: plantaris = 4-8Hz - steps of 1 Hz) and multiple strains (1-8 mm - steps of 1 mm for both muscles). Results were as follows: 1) At 4 Hz and any given strain, power produced by the plantaris was about 9-fold greater than soleus power; 2) maximal power attained for the soleus was 26 W/kg and occured at 1.5Hz and a strain of 5 mm ($V_{opt\text{-}wl}$ = 15 mm/s), while the plantaris produced a maximal power of 141 W/kg at 6 Hz and 4 mm strain ($V_{opt\text{-}wl}$= 48 mm/s) and 3) These $V_{opts\text{-}wl}$ were identical to $V_{opt\text{-}fv}$. Thus, both slow and fast skeletal muscles have inherent optimal velocities of shortening that produce maximal power for locomotion: a combination of ankle extensor cycle frequency and range of motion (strain). *Supported in part by OREF and NIH AR-30346*

14.14

POSTURE/RESPIRATION INTERACTION IN HUMAN INTERCOSTAL MUSCLES. UNIVERSITY OF CALGARY, ALBERTA, T2N 1H9
William A. Whitelaw, G. T. Ford and K.P. Rimmer*

Intercostal muscles (IC) of the lateral chest wall in humans are used for respiration (external IC in inspiration, internal IC in expiration) mainly when ventilation is above the resting level. They are also used for twisting the thorax. To study interaction between postural and respiratory control, these muscles were monitored with bipolar fine wire EMG electrodes in seated subjects who breathed at rest or with CO_2 stimulation and from time to time induced steady tone in IC's by twisting their thorax to left or right and holding the position. Internal (IC) muscles had no activity or very low grade phasic expiratory activity before the twist. During a R twist, they showed expiratory tone, which was strongly inhibited during inspiration. External IC had low grade phasic inspiratory activity. During a L twist they showed a steady discharge which was not inhibited in expiration; phasic inspiratory activity was increased compared to before the twist. The results suggest that internal IC receive phasic inhibitory influence from the respiratory centre even when they are inactive. The time course of the inhibition can bè seen in the pattern of EMG during twists. The postural tone seems to amplify the inspiratory phasic activity of external IC.



Supported by M.R.C. of Canada

14.15

ELECTROMYOGRAPHIC ACTIVITY OF HUMAN KNEE EXTENSORS DURING 'DRY' SLOPE SKIING. Ed Gardner* and Helen C. Richardson*, Dept. Biological Sciences, University of Manchester, Manchester M13 9PT.

As part of a study of human movement coordination when skiing on an artificial 'dry' ski slope, we have compared the relative amplitude and timing of electromyographic activity (EMG) generated by two muscles of the quadriceps group - rectus femoris (RF) and vastus medialis (VM), during parallel (P) and snowplough (SP) skiing. Subjects classed as 'intermediate' skiers repeatedly ski, self-paced, a prescribed course comprising 8-10 turns. EMG from each muscle is telemetered by a miniature FM transmitter to a receiver at the top of the slope, amplified and stored on FM magnetic tape for subsequent analysis. The analogue data is captured at 5 kHz per channel and digitised using a CED 1401 Signal Processor and CED Spike II software running on a 486 PC. The consecutive bursts of EMG associated with turning are rectified and measurements are made using CED Sigavg software by positioning interactive cursors on the computer screen. Discrete EMG bursts from VM and RF coincide with the onset of turns in both snowplough (SP) and parallel (P) turns, with little activity during traverses. Comparison of mean values for SP turns with P turns of the same subject showed the following differences (Wilcoxon matched-pairs signed-ranks test, $n=6$, $p<0.05$): (i) SP turns were made at a lower frequency than P, (ii) both burst duration and interburst (traverse) interval were approximately twice as long in SP than in P turning, (iii) time of onset to peak EMG was longer for SP than for P turns, (iv) the mean amplitude of EMG in each burst was less for SP than for P turns. These differences in EMG profiles are consistent with the generally predicted useage of these muscles during skiing - SP turns are associated with lower levels but prolonged bursts of EMG activity, while P turns are associated with shorter, sharper EMG bursts.

Supported by The Royal Society, and the Samuel Gratrix Scholarship fund. Sponsored by Ski Rossendale.

14.16

MULTIFUNCTIONAL CPG FOR THE CONTROL OF DIFFERENT FORMS OF CAT LOCOMOTION. J. L. Smith*, J. A. Buford*, C. Chen*, T. V. Trank*, O. T. Wang*, H. S. Wijesinghe*. Dept. Physiological Science, UCLA, Los Angeles, CA 90024-1568.

The details of muscle activity during locomotion depend on the limb dynamics (for methods see Smith & Zernicke, *TINS* 10: 1987). Fictive patterns recorded from decerebrate and spinalized cats reveal different motor output depending on the neuropharmacological agent used to evoke the pattern and the static position of the limb (e.g., Pearson & Rossignol, *J. Neurophysiol.* 66: 1991). Some of the fictive patterns are typical of forward walking, others of backward (Buford & Smith, *J. Neurophysiol.* 64: 1990). Taken together, these data are consistent with the hypothesis that a multifunctional CPG controls different forms of walking. We have studied several forms of locomotion in normal cats to determine how muscle patterns change to match the demands of the limb kinetics. Here we focus on the joint dynamics when the knee is flexing at the onset of swing, as well as changes in EMG patterns of the semitendinosus (ST), a bifunctional posterior thigh muscle. During the walk and trot, a flexor muscle (MUS) torque at the knee countered an extensor gravitational torque at the onset of swing. During galloping, however, an extensor MUS torque countered a flexor inertial torque due to leg angular accerleration (LAA); thus, the flexor ST burst—typical of the walk and trot—was absent during the gallop swing, especially at high speeds. In contrast, the flexor ST burst was prolonged during swing of backward walking to counterbalance an extensor inertial torque due to LAA. During the crouch, knee flexion persisted through midswing, similar to backward swing, as the limb flexed to clear the floor; the same was true for uphill walking but not for downhill walking (33% grade). We hypothesize that details of the pattern, such as the duration of the ST flexor burst at the onset of swing, arise via interactions among afferent feedback and supraspinal input—unique to different forms of walking—that adapt a generalized output from a single CPG. Research supported by NIH NS 19684.

14.17

TOE JOINT KINETICS DURING FORWARD AND BACKWARD WALKING. Tamara V. Trank*, Karen L. Perell*, Robert J. Gregor*, and Judith L. Smith*, Laboratories of Biomechanics and Neuromotor Control, Dept. of Physiological Science, UCLA, Los Angeles, CA, 90024-1568.

We have previously described the kinematics and related EMG of the metatarsophalangeal (MTP) joint during forward (FWD) and backward (BWD) walking in the cat (*Soc. Neurosci. Abstr.* 1992). As both kinematics and EMG may be poor predictors of joint kinetics and muscle function, it is necessary to determine the joint kinetics. MTP joint kinetics were calculated using methods described by Fowler et al. (*J. Biomech* 26: 465-483, 1993). Briefly, hindlimb segments were modelled as a linked system of rigid bodies, and a generalized muscle (MUS) torque (sum of active and passive forces) for the MTP joint was calculated for stance using techniques of inverse dynamics. Data were obtained from two cats trained to walk through a plexiglas enclosed walkway containing two miniature force plates capable of measuring normal and tangential ground reaction forces (GRF). Previously we reported MUS torques for the hip, knee, and ankle joints (Perell et al. *Soc. Neurosci. Abstr.*, 1991) for BWD and FWD walking. The MUS torque at the toe was flexor (plantarflexor) for both walking directions, resulting from the anteriorly oriented GRF in relation to the estimated joint center. The average peak flexor MUS torque was similar for FWD and BWD stance at 49.5±16 N•cm and 51.8±16 N•cm, respectively; but the torque profiles were different. For FWD stance, the MUS torque showed a ramp-like increase that peaked about midstance and declined thereafter. For BWD stance, the MUS torque peaked early in stance (25%), tended to plateau, and declined rapidly at about 75% of stance. The MTP joint absorbed power (Watts = jt. ang. vel. x MUS torque) during most of FWD stance as extension occurred with a flexor MUS torque. Conversely, the MTP joint generated power during BWD stance as flexion occurred with a flexor MUS torque. The only other joint to generate power during BWD stance was the ankle. The EMG profile of the FHL, a toe flexor active during stance, was consistent with the MUS torque profiles, peaking early for BWD stance and by midstance for FWD stance. Research supported by NIH NS 19864.

14.18

ANKLE EXTENSOR GROUP I AFFERENTS EXCITE EXTENSORS THROUGHOUT THE HINDLIMB DURING MLR-EVOKED FICTIVE LOCOMOTION IN THE CAT P. Guertin*, M.J. Angel*, M-C. Perreault*, P.A. Carr* and D.A. McCrea*, Dept. Physiology, U. Manitoba, Winnipeg, R3E 0W3, CANADA.

Plantaris (PL) stimulation during pharmacologically-induced locomotion in the spinal cat resets locomotion by terminating flexion (Conway et al Exp Brain Res 68:643-656, 1987) or prolonging extension (Pearson & Collins in press). These effects have been attributed to the activation of group Ib afferents. In the present study trains of stimuli (200Hz, 20-50 shocks) were delivered to ankle extensor nerves (PL; MG, medial gastroc.; LGS, lateral gastroc-soleus) during flexion or extension. Stimulation of PL during flexion, as in the spinal cat, terminates flexion and initiates extension. Furthermore, stimulation of the MG and LGS nerves also produce resetting and at similar (1.5T) stimulation strengths. During extension stimulation of PL, MG or LGS increased extensor amplitude and duration. Ankle extensor-evoked excitation was distributed throughout the hindlimb to other extensors; semimembranosus, anterior biceps, quadriceps, flexor digitorum longus as well as ankle extensors. The threshold for these effects was as low as 1.15T suggesting a contribution from group Ia afferents. Stimulation at 1.4T of the distal portion of the posterior tibial nerve (predominantly cutaneous) also produced resetting and extension prolongation similar to that evoked from ankle extensors. Thus during extension in fictive locomotion, group I ankle extensor and low threshold tibial afferents produce short-latency excitation of extensor motoneurons throughout the limb. Activity in afferents signalling foot contact and ankle extensor muscle length and force may thus act as a positive feedback system regulating extension during normal locomotion. Supported by MRC Canada and Human Frontiers.

14.19

THE EFFECT OF ANKLE JOINT ANGLE ON THE ANKLE TORQUE PROFILE IN THE CAT. J. H. Lawrence, III* and T. R. Nichols. Department of Physiology, Emory University Atlanta, GA 30322.

We have previously shown that the triceps surae group, as well as other muscles that cross the ankle joint, exert substantial extra-sagittal torques at cat ankle control orientations of 90,0,0° (extension, adduction, and eversion, respectively; Lawrence et al., *J. Neurophysiol.*, vol. 69, no. 1, 282-285, 1993) and 110,0,0° (Bonasera et al., *Soc. Neurosci. Abs.*, Vol. 18, 646.16, 1992). Recently, Young et al. (*Neurosci. Lett.*, 145(2): 137-140, 1992) have predicted through individual muscle moment arm measurement that the adduction torque for tibialis anterior (TA) is zero at a cat ankle orientation of 90,0,0°. At different ankle orientations, we measured the resulting isometric torques from electrically stimulated muscles crossing the ankle joint in cats deeply anesthetized with pentobarbitol using a multiaxis force-moment transducer. We found that the adduction torque exerted by TA is maintained throughout a range of from 20° abduction to 10° adduction. However, the abduction torques of medial and lateral gastrocnemius (MG and LG) switch to adduction when the cat ankle is abducted by 5 to 10° (110,-10,0°) from control. Furthermore, the relationship between adduction and inversion (and abduction and eversion) appears to be constant for ankle angle changes of ±30° extension, ±20° adduction, and ±20° eversion from the control orientation, with varying combinations of directional excursions.

(Supported by NIH grant NS20855)

14.20

MECHANICAL-REFLEX OSCILLATIONS OF THE HUMAN FINGER ARE NOT AUGMENTED DURING ACUTE EXPOSURE TO HYPOXIA. W. L. Krause, J. C. Leiter, J. A. Daubenspeck, and S. M. Tenney. Dartmouth Medical School, Department of Physiology, Lebanon, NH 03756-0001.

BACKGROUND: During inertial loading of a limb, the predominant tremor oscillations are of mechanical-reflex origin. Mechanical-reflex oscillations arise from the interaction between the passive mechanical properties of the limb and the dynamics of the stretch reflex. Recently, we have shown that acute hypoxia augments the 6-15 Hz components of physiological tremor during *elastic* loading in humans. Given that segmental reflex mechanisms can alter motoneuron drive, we hypothesized that hypoxia augmented tremor through increased stretch reflex drive. To test this hypothesis, we studied tremor during hypoxia using a loading condition which favored stretch reflex drive.

METHODS: We studied twelve male volunteers during hypoxia (inspired oxygen=10%). The right index finger was loaded with a 50 gram mass. We measured tremor from an accelerometer (Entran Devices EGAX-10) taped on the fingernail. Tremor was quantified by computing the power spectrum and summing the total power between 6 and 15 Hz.

RESULTS: No difference in the total power between 6 and 15 Hz was observed during hypoxia and room air controls.

CONCLUSION: Since hypoxia did not augment tremor during inertial loading, we conclude that hypoxic augmentation of tremor during elastic loading does not result from alteration of motoneuron drive by segmental reflex mechanisms. Furthermore, we conclude that hypoxic augmentation of tremor represents increased entrainment of motoneuron discharge descending from the central nervous system. (This work supported by NIH HL07449.)

14.21

INPUT-OUTPUT RELATIONS OF REAL AND MODEL MOTONEURONS. Randall K. Powers* and Marc D. Binder*.Univ. of Washington, Sch. of Medicine, Seattle, WA 98195.

We are studying the quantitative relation between the discharge rates of pre- and postsynaptic neurons. Two different quantitative expressions have been proposed: (1) that the change in discharge rate (ΔF) of the postsynaptic cell is the product of the mean synaptic current reaching the soma (I_N) and the slope of its frequency-current relation (Powers et al. *J. Neurophysiol.* 68: 964, 1992), and (2) that ΔF is equal to the firing rate of the presynaptic cell times the relationship between synaptic potential amplitude and the change in firing probability (Fetz et al. *Prog. Brain Res.* 80: 437, 1989). We compared the predicted outcomes of these two expressions in cat spinal motoneurons by using 1 sec depolarizing current steps to elicit repetitive discharge, and superimposing trains of short (0.5 to 5 ms) current pulses at frequencies of 20 - 600 Hz in alternate trials. We calculated ΔF as the mean difference in discharge rate measured in trials with and without the superimposed short pulses. We measured I_N as the mean current added by the pulses and we measured the amplitudes of the voltage deflections produced by the pulses. The first expression, based on I_N, consistently underestimated the observed ΔF, while the second expression, based on voltage, was consistently too high. Neither expression could account for the effects of mixtures of hyperpolarizing and depolarizing pulses, which could often increase discharge rate even though the net current and mean voltage were negative. We were able to simulate some of these experimental results with a threshold-crossing motoneuron model, in which spike threshold showed a delayed dependence on membrane voltage. (Supported by NIH grant NS 26840)

14.22

NUCLEUS RETROAMBIGUUS PROJECTIONS TO HINDLIMB MOTONEURONS IN THE CAT; INVOLVEMENT OF THE EMOTIONAL MOTOR SYSTEM. Veronique G.J.M. VanderHorst* and Gert Holstege*. Dept. Anatomy, University of Groningen, The Netherlands.

The nucleus retroambiguus (NRA), a group of interneurons in the caudal medulla oblongata extending from the obex to the rostral part of C1, is known to project to groups of motoneurons which play a role in expiration related activities. Examples are motoneurons innervating the pharynx, larynx, abdominal muscles and muscles of the pelvic floor. These motoneurons are located in the medulla and spinal cord. The NRA in turn receives bilateral projections from the caudal and intermediate periaqueductal gray (PAG). These projections form the final common pathway for the sound production in vocalization, an example of specific emotional behavior (Holstege, G. 1992). Apart from the projections related to sound production, the NRA also appeared to project to a specific group of L4-L7 motoneurons, which projections cannot be related to expiration.

In order to study these NRA projections, a combined retro- and anterograde study was done. For identification of the motoneuronal cell groups receiving projections from the NRA, injections of HRP were made in different hindlimb muscles. To localize and quantify the retrogradely labeled NRA neurons projecting to the lumbar enlargement, hemi-injections of WGA-HRP were made at levels L5-L6 and L7-S1. Injections of 3H-leucine and WGA-HRP were made in the NRA to anterogradely label the fibers terminating in the lumbar ventral horn. The results show that numerous neurons located in the caudal part of the NRA project predominantly contralaterally to lumbar motoneuronal cell groups. The anterograde study reveals that only certain groups of motoneurons receive projections from the NRA, most consistently motoneurons innervating the hamstrings. Rostrocaudally, the projections involve the segments L4-S2, but are densest at the transition L6-L7. These NRA projections to the lumbar enlargement suggest that the NRA is not only involved in expiration and sound production, but also in other activities that can be elicited by stimulating in the PAG, such as jumping.

14.23

VIBRISSAL RECEPTIVE FIELDS IN LOBULE IXa OF THE ADULT RAT CEREBELLUM ALIGN WITH ZEBRIN-NEGATIVE PURKINJE CELL COMPARTMENTS. V. Chockkan* and R. Hawkes*
Dept. Anatomy and Neuroscience Research Group, U. Calgary, Calgary, Alberta T2N 4N1, Canada.

Electrophysiological micromapping has identified prominent vibrissal receptive fields in the dorsal surface of lobule IXa of the rat. In the same region, immunocytochemical staining for zebrin II, a 35 kDa Purkinje cell antigen, reveals an array of parasagittal compartments. Zebrin II immunocytochemistry was combined with RF mapping to compare the molecular and functional maps. Nine adult rats were mapped electrophysiologically, then perfused, sectioned and immunostained by using *anti-zebrin II*. After 3-D reconstruction, the antigenic and functional maps were superimposed. Anti-zebrin II immunostaining reveals 4 zebrin$^+$ bands on each side of the midline (P1$^+$ - P4$^+$), interposed by 3 zebrin$^-$ zones (P1$^-$ - P3$^-$). Electrophysiological micromapping revealed 3 discrete vibrissal receptive fields each side of the midline. These align reliably with the zebrin compartmentation with one centered on each zebrin$^-$ band. The alignment is not precise, as the RFs consistently overlap the zebrin$^{+/-}$ borders at each side. A reproducible relationship between the sensory and motor maps suggests that Purkinje cell compartmentation, which is present very early in cerebellar development, may serve as a substrate to organize cerebellar function into discrete modules.
Supported by grants from the MRC (Canada) and the AHFMR.

14.24

PRIMATE SPINAL MOTONEURON PHYSIOLOGY AND SYNAPTIC COVERING AFTER H-REFLEX OPERANT CONDITIONING. J.S. Carp*, X.Y. Chen*, K.A. Starr* and J.R. Wolpaw*. Wadsworth Center for Laboratories and Research, New York State Department of Health and State University of New York, Albany, NY 12201.

Operant conditioning of monkeys (*Macaca nemestrina*) can gradually increase (HR$\uparrow$ mode) or decrease (HR$\downarrow$ mode) the triceps surae H-reflex (HR), the electrical analog of the monosynaptic stretch reflex. This conditioning changes the spinal cord (TINS 13:137-42, 1990). We are investigating the role of spinal plasticity in this behavioral change through intracellular study of motoneuron (MN) physiological properties and electron microscopic (EM) analysis of MN synaptic covering. MNs from the trained side of successful HR$\downarrow$ animals had more positive firing thresholds, greater differences between resting potential and firing threshold, and slower axonal conduction velocities. No other differences were noted. MNs from the trained side of unsuccessful HR$\downarrow$ animals showed no differences from MNs of naive animals. These data are consistent with the hypothesis that operantly conditioned decrease in HR size is due to a positive shift in MN firing threshold and a consequent increase in the depolarization needed to reach that threshold. The threshold shift could also underlie the observed decrease in conduction velocity. Analysis of initial EM data suggests that MNs from the trained side of HR$\downarrow$ animals have a higher fraction of F-type and a lower fraction of C-type synaptic contacts on cell bodies and proximal dendrites than do MNs from naive animals. These preliminary results suggest that HR$\downarrow$ conditioning is associated with type-specific changes in MN synaptic covering. (Supported by NIH NS22189 & Paralyzed Veterans of America Spinal Cord Research Foundation.)

14.25

REDUCTION OF THE AHP WITH Mn^{++} DECREASES THE INITIAL ADAPTATION, BUT INCREASES THE LATE ADAPTATION IN RAT HYPOGLOSSAL MOTONEURON DISCHARGE. A. Sawczuk* and M.D. Binder*. Dept. of Physiology & Biophysics, Univ. of Washington, Seattle, WA 98195.

In response to a constant-current stimulus, motoneurons display a pronounced reduction in firing rate during the first few (2-10) interspike intervals (initial adaptation). This is followed by a late phase of adaptation, during which firing frequency follows an exponential decline for the duration of the stimulus (up to 5 minutes). It has been proposed that adaptation is related to an increase in the K^+ conductances associated with the AHP. It has also been proposed that changes in the spike-generating conductances during repetitive firing contribute to adaptation. To examine the contributions that these different conductances make to adaptation, we injected long (30-60s), supra-threshold depolarizing current pulses into hypoglossal motoneurons in brainstem slices of young (3-7 weeks) rats before and after adding Mn^{++} (2 mM) to the bathing solution. The Mn^{++} produced a reversible reduction in the AHP following single action potentials, and resulted in about a 25% reduction in the early phase of adaptation. However, the late adaptation approximately doubled in the presence of Mn^{++}. Significant changes in spike and AHP shape were observed with Mn^{++}, but these were not correlated with late adaptation. (Supported by NIDR grant DE00161 and NIH grant NS26840)

14.26

SUBTHALAMIC NUCLEUS AND GLOBUS PALLIDUS LESIONS ALTER ACTIVITY IN NIGROTHALAMIC NEURONS IN RATS. Lawrence J. Ryan* and David J. Sanders*, Dept. Psychology, Oregon State Univ., Corvallis, OR 97331-5303.

Lesions of the subthalamic nucleus or the globus pallidus altered the response of substantia nigra pars reticulata neurons (antidromically identified as projecting to the thalamus) to electrical stimulation of the frontal agranular cortex (Area FRII). In intact animals, cortical stimulation evokes three independent responses (excitation-inhibition-excitation) that may occur singly or in various combinations. Subthalamic lesions increased total response duration (from 28.4 to 39.7 ms), increased the duration of inhibition (from 18 to 30 ms), decreased the occurrence of excitatory responses and decreased the intensity of the second excitation (from 1.1 to 0.6 spikes/second). Lesion of the globus pallidus also increased total response duration (up to 38 ms), but by increasing the duration of the second excitation (from 15.1 up to 23.8 ms), the intensity of the second excitation (from 1.1 to 1.5 spikes/stimulus) and the number of cells showing the first and second excitations. The incidence, but not the duration, of the inhibition also increased. The mean firing rate increased after subthalamic nucleus lesion (34.2 spikes/sec) as compared to intact (27.0) or globus pallidus lesion (25.6). These changes may reflect the relative loss of the four different pathways transmitting information from the cortex to the substantia nigra. In all cases the "direct" cortico-striato-nigral pathway is intact. In subthalamic lesioned rats the cortico-subthalamo-nigral path and the "indirect" cortico-striato-pallidal-subthalamo-nigral path are destroyed. This lesion shifts the balance towards increased transmission of evoked inhibitory responses. In contrast, globus pallidus lesion eliminates the "indirect" cortico-striato-pallidal-subthalamo-nigral path and the "indirect" cortico-striato-pallido-nigral path. The net effect of this lesion is to shift the balance of these pathways to transmitting excitation mediated by the cortico-subthalamic path. Both of these lesions alter the timing and pattern of the cortically-evoked basal ganglia output destined to influence the cortex.

This research was supported in part by grant MH45341 (to LJR) from the National Institute for Mental Health and by NIH Biomedical Research Support Grant RR 07079.

14.27

Prefrontal 'Fixation' Neurons Active During Periods of Memory-Guided Eye Fixation. R.G. Erickson. LNP, NIMH.

Neurons tonically active during periods of attentive Visual Fixation (VF neurons) have been found in several parts of both the cortex and brainstem. The fixation-related activity of VF neurons in the parietal cortex was shown to also be modulated by eye position (Sakata et al., J. Neurophysiol. 43:1654-1672), prompting the hypothesis that parietal VF neurons may specify the spatial coordinates of fixated visual targets as well as help maintain the direction of gaze. To determine how primates maintain memory-guided as opposed to visually-guided fixation I hypothesized that parts of the prefrontal cortices serve as a selective relay allowing stored rather than current extero-ceptive information to be sent to motor areas. Rhesus monkeys were trained to make delayed, memory-guided eye movements to targets flashed 3-5 sec previously, and then to fixate (in total darkness) the remembered spatial location for 1-3 sec. Randomly interleaved trials were used to either briefly show cues at one of 9 positions (8 eccentric and 1 adjacent to the initial fixation point) or to show continuously visible cues allowing visually-guided as opposed to memory-guided eye movements and fixation. Of 201 neurons analysed to date, 10 showed modulation of activity only during the delay-period prior to a memory-guided saccade. Another 13 were either inhibited or became tonically active during maintenance of memory-guided eye fixation at specific eye positions after the initial saccade and not during the delay period prior to a memory guided saccade or during the saccade. Initial tests showed that at least some of these 'Memory Fixation' (MF) neurons are not modulated during fixation of visible cues at the same locations.

These data suggest that, for some prefrontal MF neurons, remembered information is only accessed when it is actually being used to effect memory-guided as opposed to sensory-guided ocular fixation.

14.28

GABA$_A$ AND GABA$_B$ RECEPTORS ARE INVOLVED IN THE CONTROL OF LOCOMOTOR NETWORKS IN NEWBORN RATS. F. Clarac, Y. Sqalli-Houssaini and J.R. Cazalets, CNRS, NBM, BP 71 13402 marseille CEDEX 09

This study was undertaken to investigate the possibility that, in addition to the activating inputs which are able to initiate the CPG activity in mammals, an "inactivatory" pathway exists, that could strongly control the CPG for locomotion, and which when it is active, can either completely stop all locomotor activity or modify the ongoing period of the CPG. We present evidence that GABA is a transmitter involved in this mode of control, and that it can directly modulate the oscillatory behaviour of the CPG for locomotion in newborn rats. Experiments were performed using an isolated brain stem/spinal cord preparation taken from new born rats (0-3 days). Locomotor-like activities were recorded in the ventral roots, and the various neurochemical compounds were added to the superfusion saline. The bath-application of g-amino-butyric acid (GABA) decreased or completely suppressed in a dose-dependent manner, the motor activity induced by excitatory amino acids. The GABA$_A$ agonist muscimol and the GABA$_B$ agonist baclofen mimicked the effects of GABA, by slowing down or stopping the rhythmic activity. The GABA uptake inhibitor nipecotic acid suppressed the rhythmic motor pattern induced by EAAs in a dose dependent manner. This suppression of locomotor-like activity induced by nipecotic acid was reversed by bicuculline or phaclofen. It was shown that the motor pattern depended on the balance between activatory and inactivatory influences, and we concluded that the central pattern generators which organize locomotor activities in mammals are strongly controlled by GABAergic inputs which set he locomotor period.

14.29

TO SWIM OR NOT TO SWIM: CONTROL OF SWIMMING BY NEURONS IN THE HEAD GANGLION OF THE MEDICINAL LEECH. P.D. Brodfuehrer* and A. Burns* Dept. of Biology, Bryn Mawr College, Bryn Mawr, PA 19010.

It is known that a competent neuronal oscillator for swimming is located in the segmental ganglia, and that the head ganglion is not necessary for the generation of swimming activity. However, lesion studies have shown that the head ganglion substantially decreases the likelihood of initiating and maintaining swimming activity in response to a given stimulus. How the head ganglion alters the swim generating system in the segmental nerve cord is presently unknown.

Recently, we have identified two bilaterally symmetrical pairs of descending interneurons (cells SIN1 and Tr4) in the head ganglion that demonstrate two opposing mechanisms for controlling swimming. First, spiking activity in cell SIN1 decreases the probability that swimming will be initiated by a given stimulus. In fact, SIN1 spiking activity must be suppressed for swimming to be initiated, and depolarization of cell SIN1 during swimming quickly terminates an ongoing swim bout. Termination is most likely due to the indirect inhibition of segmental swim gating interneurons. Second, spiking activity in cell Tr4 increases the probability that swimming will be initiated. Tr4's swim facilitatory effect is most likely mediated by a direct, excitatory connection to segmental swim gating interneurons. Thus whether a leech swims in response to a given stimulus may depend on the relative levels of excitation in cells Tr4 and SIN1. (Supported by NIH grant NS29509-01 and the Whitehall Foundation)

14.30

ACTIVATION OF D1 DOPAMINE RECEPTORS FACILITATES PREMOTOR AND MOTOR CORTICAL FUNCTIONS FOR REACHING MOVEMENTS IN MONKEYS. K. Kubota*, T. Sawaguchi*, and I. Yamane*, Dept. of Behavioral and Brain Sciences, Primate Res. Inst., Kyoto Univ., Inuyama, Aichi 484, Japan.

To reveal the roles of dopamine receptors in motor cortical functions, we have done two series of experiments in the premotor and motor cortex of rhesus monkeys: 1) iontophoretic experiments in which dopamine antagonists (SCH23390 for D1 receptors and sulpiride for D2 receptors) were applied iontophoretically to neurons whose activity was related to a visual reaching task with a delay; and 2) local injection experiments in which the dopamine antagonists were locally injected into the cortex to examine their effects on performance of the task. The task was initiated when the monkeys pressed a central lever. After receiving a visual go signal, they then released the lever and reached out to one of three target locations (left, upper, or right) that had been indicated by a visual cue prior to a delay period (2-5 s). Iontophoretically-applied SCH23390 (usually applied with 50 nA) suppressed the delay- and/or movement-related activity of most neurons in the premotor/motor cortex, whereas neither sulpiride nor an inactive analogue of SCH23390, SCH23388, had a significant effect. Local injections of SCH23390 (20-50 µg) into the premotor/motor cortex increased significantly reaction time (from the go signal to movement onset) and/or reaching time (from movement onset to offset). By contrast, injections of sulpiride (50 µg) or SCH23388 (50 µg) had no clear effects on task performance. Similar effects by SCH23390 on behaviors were obtained in freely moving infant monkeys that performed also a visual reaching task with a delay to pick up a small piece of apple: i.e., local injections of this drug into the premotor/motor cortex increased reaction time and/or reaching time in reaching movements for picking up the food. Taken together, these data suggest that the activation of D1 dopamine receptors plays a role to facilitate premotor and motor cortical functions for controlling reaching movements.

14.31

ADAPTIVE MECHANISMS IN THE MOTOR CONTROL OF SWALLOWING. Thomas Gay,* Jill Rendell,* Jeffrey Spiro,* Kristine M. Mosier,* and Alan G. Lurie.* University of Connecticut Health Center, Farmington, CT 06030.

Swallowing is an important biological function generally presumed to rely on basic invariant reflex mechanisms of motor activity. Recent research, however, has suggested the existence of both intra- and inter-subject variability in swallowing behavior. In order to determine if presumed individual variability reflects the operation of adaptive motor control mechanisms, we compared the coordination patterns of oral cavity and laryngeal muscles for swallowing produced under both normal and mechanically perturbed conditions. The mechanical perturbation was in the form of a 12mm bite block placed between each subject's molars. Intramuscular electromyography was used to study the coordination of lip, tongue, soft palate, suprahyoid, and laryngeal muscle activity. Ten adults served as subjects, each swallowing 12ml of water 15-20 times under both the normal and bite block conditions. The results of the analyses showed that swallowing function is highly variable from individual-to-individual in terms of the specific muscles used and how their actions are coordinated with other muscles, and that different subjects use individual motor strategies to compensate for the bite block: some maintain temporal stability but increase overall muscle activity; others reorganize temporal relationships either with or without corresponding muscle activity adjustments. These results suggest that swallowing function is characterized by motor plasticity and involves the operation of adaptive control mechanisms.

14.32

EFFECTS OF INTERRUPTION OF NERVOUS CIRCUITRY BETWEEN GASTRIC CORPUS AND ANTRUM ON GASTRIC MOTILITY G.E.Holle, E.Steinbach. Gastroenterol.Research Labs. Walther Straub Inst.L.M.University Munich, F.R.G.

Myoelectric(8 bipolar electrodes) and mechanical(7strain gauges) activity was studied in digest. (300g solid meat meal)and interdigestive state in gastric corpus, antrum, pylorus and duodenum before and after circumferential myotomy(cM) in the dog. Motility index(MI), contraction frequency(CA), slow wave frequency(BER)and amplitude were evaluated. By X-ray examination gastric emptying was studied after the meal was mixed with barium.

Myotomy destabilized the BER distal to cM (33% tachyarrhythmia, 17% bradyarrhythmia and combination, 78-126%increased slow wave amplitudes, 106 and 68% increased MI in the first postprandial 30 min). The uncoupled BER caused a completely spatial and sequential disorganization of contractions resulting in a 30% gastric emptying delay (50 min total). This indicates that myotomy eliminates an inhibitory progressive corpro-antro-pyloric nervous influence, which normally stabilizes BER and contractile coordination and favours gastric emptying. Despite the disturbances, the interdigestive rhythm was not altered after myotomy; MMC 107 min pre and post cM. Supported by the German Research Council DFG/Ho936.

14.33

EVIDENCE FOR HEATBEAT EXCITED 8-12 HZ REFLEX OSCILLATIONS IN THE LOW INNERVATED MUSCLE.

Eugen Gallasch* and Thomas Kenner
Dept. Physiology Univ Graz, A-8010 Graz, Austria

High resolution accelerometric recordings on the relaxed trunk and at low level innervated limbs show the existence of decaying 8-12 Hz mechanical oscillations that are strongly correlated to the heartbeat. Recent findings (exposure of man to 0g, REM/NREM sleep studies, optokinetic stimulation) indicate that these oscillations strongly depend on resting muscle tone. As passive resonance models based on impulse excitation by the impact of heartbeat fail to explain the gobal existence of these oscillations, an active motor control model based on the tonic stretch servo is proposed.
Heartbeat generates pressure waves that progagate in the muscular body. For low innervated muscles (Matthews, animal experiments, 1969) it was shown that the Ia afferents have an increased sensitivity for small elongations up to 100 μm (nonlinear mechanotranduction). It is therefore conceivable that the intermittent pressure waves are captured by the spindles and the Ia afferents will modulate motor outflow in low innervated muscles. Normal action of the stretch servo is to maintain muscle stiffnes (tonic activity) and to resist against motor disturbances (phasic activity). As for very small motor disturbances the gain in the reflex loop is increased due to the nonlinear spindle transducer characteristics (marginal stability in the control loop), amplitude limited, decaying reflex oscillations are generated after each heartbeat. Frequency of the oscillation is determined by the latencies of the nerves in the monosynaptic reflex arc.
In this sense heartbeat can be considered as an "intrinsic motor disturbance" on the tonic stretch servo.

14.34

DOSE RESPONSE DEPENDENCE OF CILIARY NEUROTROPHIC FACTOR (CNTF) ON ELECTROMECHANICAL PARAMETERS FOLLOWING PERONEAL NERVE CRUSH K.A. Williams* and F.L. Strand, New York University, Department of Biology and Center for Neural Science, New York, N.Y. 10003.

Ciliary Neurotrophic Factor (CNTF) was isolated from concentrated extracts of intraocular tissue by Manthorpe et al. in 1980. Since then the literature has been flooded with articles pertaining to CNTF's trophic characteristics particularly on motoneurons. In this study Sprague-Dawley rats (200-275g) were subjected to crush denervation under ketamine (80mg/kg) and xylazine (5mg/kg) anesthesia. A 1 mm lesion was made on the deep peroneal nerve with #5 watchmaker forceps. Immediately after surgery and every 48h until day 8 post crush, the animals were injected i.p. with either 10µg/kg, 100µg/kg of CNTF, or physiological saline. On day 9 the animals were subjected to electromechanical tests in which twitch response, motor unit size, tetanic tension at fusion frequency and fatigue at 400Hz of the extensor digitorum longus muscle were obtained. The data obtained from trials thus far indicate that the 10µg/kg dosage was more effective than the 100µg/kg dose but neither was significantly different from saline treated animals. With regard to twitch parameters significance from saline was not evident in terms of contraction amplitude, rate of rise or half relaxation time. However, the overall effect of both dosages of CNTF on these parameters was better than that seen in saline treated animals. The smaller CNTF dosage was significantly better than the larger amount in terms of tetanic peak amplitude. Once again this dose difference clearly illustrates the deleterious nature of peptides if not administered optimally. The paradigm used to test these peptides has been employed in our lab for several years and it is possible that this mode of testing CNTF may be too stringent to illustrate CNTF's possible role in peripheral nerve regeneration.

14.35

CNTF INCREASES ENDPLATE INTERNAL BRANCHING. Tommy S. Lee and Fleur L. Strand. Department of Biology and the Center for Neural Science, New York University, Washington Square East, New York, N.Y. 10003.

Ciliary neurotrophic factor (CNTF) was first isolated in the chick ocular tissue.[1] It is an acidic protein with 200 amino acids and its gene sequence has been cloned from rat, rabbit, and human sources.[2] Its name CNTF was coined after its first biological activity which supported the survival of ciliary ganglions of chick's parasympathetic system *in vitro*. Later studies have shown that CNTF supports the survival or maturation of both sensory and motor[5] spinal neurons, cranial ganglia, sympathetic neurons,[3] and neurons of the cerebellum[4].

Interestingly, Arakawa and his colleagues (1990) have shown that CNTF actually promotes the survival of motor neurons during development *in vivo*. Although, the understanding of the mechanism of action of CNTF is still in its infancy, studies of nerve regeneration have shown that CNTF is released by the degenerating nerve as well as the Schwann cells in response to nerve injury. While CNTF has been detected throughout the brain and the spinal cord, skeletal muscle is the only non-neuronal tissue which contains CNTF-Immunoreactivity. Thus the effects of CNTF on the neuromuscular system are of special interest.

Sprague Dawley animals (175-200g) are subjected to peroneal nerve crush under Ketaset/Xylazine combination anesthesia. Immediately following surgery, the animals received either CNTF or 0.9% physiological saline. Control animals included both saline-sham and saline-crush. Seven days after the nerve lesion, CNTF treated animals exhibited significant increase in endplate morphology, specifically internal branching when compared to saline-crush animals. This internal complexity is often associated with the mature neuromuscular junction seen during development and regeneration. This neurotrophic property of CNTF warrants further investigation. [1]Alder, *et al.*, Science **204**, 1434 (1979) [2]Stöckli, *et al.*, Nature **342** 920 (1989) [3]Barbin, *et al.*, J. Neurochem **43** 1468 (1984) [4]Larkfors, *et al.*, in press [5]Arakawa, *et al.*, J. Neurosci **10** 3507 (1990).

14.36

The Role of Caudate Nucleus in the Instrumental Behavior of Monkeys: Unit Activity and Effects of Microinjections. B.F. Tolkunov, A.A. Orlov, and S.V. Afanas'ev. Sechenov Inst. of Evolut. Physiol. Biochem., St. Petersburg, Russia.

This study was aimed to examine the participation of n.Cd in the motor and cognitive mechanisms. the pig-tailed monkeys were trained to perform the bimanual instrumental task. Monkey delivered the conditioned signal, when it held both hands in the symmetrical start position. After the cognitive problem was solved, animal took off either left or right hand (in depend on the meaning of the signal) for the motor response. In the first group of experiments unilateral microinjections of carbacholine and scopolamine into the head of n.Cd were made. These microinjections significantly influenced on the time of solving the sensory task and taking the decision about the active hand. In the second group of experiments monkey were recorded simultaneously. The activities of related to the analysis of the conditioned signals and reward were obtained in 57% and 74% neurons, related to the two-hand movements--22%, related to the one-hand movement- 39%. Unit activities during the same form of movements changed if they followed of another conditioned signal, more difficult for monkey. The common pattern activities of all six simultaneously recorded neurons was more sensitive to the changes of the kind of conditioned signal than the changes of working hand. The obtained data evidence that to the participance of the n.Cd in the organization of motor behavior consists in the processing of the sensory information about the conditions in which the movement is performing.

NEUROPHARMACOLOGY AND NEUROPHYSIOLOGY OF MOTONEURONS

15.1

FUNCTIONAL LOCOMOTOR RECOVERY AFTER SPINAL CORD HEMISECTION IN THE CHICK. G.D.Muir* and J.D.Steeves. Depts of Zoology and Anatomy, University of British Columbia, Vancouver, B.C. V6T 1Z4.

To characterize the locomotor deficits resulting from an incomplete spinal cord injury in a bipedal animal, lateral hemisections of the lower thoracic cord were performed on hatchling chicks. Twenty-four hours after the injury, all chicks were able to walk, though with visible abnormalities. The locomotor characteristics of each animal were examined at intervals over a two week recovery period. Three sets of data (kinematic and kinetic measurements of limb motion, as well as electromyographic (EMG) records from four identified hindlimb muscles) were collected simultaneously during each recording session, as the animal walked and ran along a straight path. Ground reaction forces in three orthogonal directions were measured using a force platform embedded within the substrate. Kinematic and EMG analyses revealed lack of normal flexion at the hip, knee and ankle of the limb ipsilateral to the lesion during the swing phase. The amplitude of the vertical ground reaction force was reduced in the ipsilateral limb. Fore-aft ground reaction forces showed that all deceleration was accomplished by the limb contralateral to the lesion, while all forward propulsion was accomplished by the ipsilateral limb. The amplitude of the medial-lateral force was generally greater in the limb ipsilateral to the lesion when compared to that of the contralateral limb and to that in sham-operated animals. Two weeks after the hemisection, the locomotor characteristics of all experimental animals approached those of sham-operated animals, with some experimental animals being indistinguishable from controls. (Supported by NSERC and a fellowship to G.D.M. from the MRC).

15.2

CROSSED PHRENIC RESPONSES TO SPINAL STIMULATION IN RATS: EFFECTS OF OLD AGE OR CHRONIC SPINAL HEMISECTION L. Ling*, K.B. Bach* and G.S. Mitchell, Dept. Comp. Biosciences and Center for Neuroscience, University of Wisconsin, Madison, WI 53706

Serotonin reveals ineffective spinal pathways from the C_2 lateral funiculus to contralateral phrenic motoneurons in adult rats with acute spinal hemisection (Ling *et al.* FASEB, **7**: A401, 1993). We tested the hypothesis that old age or chronic hemisection strengthens these pre-existing crossed spinal pathways. Sprague-Dawley rats were anesthetized (urethane), paralyzed, vagotomized and ventilated. A tungsten stimulating electrode was positioned at the C_2 dorsal root entry zone and lowered to the dorsolateral (1.0 - 1.1 mm) or ventrolateral (2.2 - 2.4 mm) funiculus. Hemisection (C_1 - C_2) contralateral to the electrode was performed acutely in old rats (n = 4; ~22 mo; 950 - 1200g), and 3-5 days prior to study in younger adult rats (n = 5; ~6 mo; 350 - 600g). In control, no contralateral (hemisected side) phrenic responses were elicited by stimulation (100 - 500 μA, 0.1 - 0.5 ms, 2 Hz). Administration (i.v.) of pargyline (25 mg/kg), a monoamine oxidase inhibitor, and 5-hydroxytryptophan (5-HTP; 5-10 mg/kg), a serotonin precursor: 1) induced spontaneous, tonic phrenic activity; 2) revealed two contralateral evoked excitations (latencies: ~0.9 and 2.0 ms) in both groups; and 3) revealed a long-latency (~7.3 ms) excitation in young adults with chronic hemisection, but not in the old rats. The latency, amplitude and threshold of these excitations were similar to data on young adults with acute hemisection. The results indicate that neither chronic hemisection nor old age alone strengthens crossed spinal pathways to phrenic motoneurons. Furthermore, old age eliminated a long-latency, serotonin dependent crossed spinal pathway that is typically observed in young adult rats. (Supported by NIH HL36780).

15.3

MODULATION OF EXCITATORY SYNAPTIC TRANSMISSION TO PHRENIC MOTONEURONS BY ADENOSINE RECEPTORS.

X-W. Dong*, G. Liu*, & J. L. Feldman. Systems Neurobiology Lab., Dept. of Physiological Science, UCLA, Los Angeles, CA 90024-1527.

Multiple mechanisms are involved in the regulation of the phrenic motoneuron (PMN) excitability. In turn, the activity of PMNs determines the pattern and efficiency of the activity of the diaphragm (major inspiratory muscle). We examined the role of adenosine receptors in transmission of endogenous inspiratory drive to PMNs in the brainstem-spinal cord preparation from neonatal rats. PMN activity was recorded under whole cell patch-clamp conditions. Drugs were applied via pressure ejection from micropipettes positioned over the PMN pool. The adenosine analogue N^6-cyclopentyl-adenosine (CPA; 25 μM) reversibly reduced peak inspiratory-modulated synaptic current (I_{insp}) to 74±6% (n=6) of control. To examine the role of endogenous adenosine, we applied the adenosine receptor antagonist, 3-isobutyl-1-methylxanthine (IBMX, 0.5-1 mM), which increased I_{insp} ≈15% above control; similar effects were produced by the selective A_1 receptor antagonist 8-cyclopentyltheophylline (CPT; 50 μM). This indicates a tonic endogenous release of adenosine. To elucidate underlying mechanisms, we performed analysis during the expiatory period. None of these drugs produced significant changes in steady-state membrane current, but the frequency and peak amplitude of spontaneous excitatory postsynaptic currents (EPSCs) were reduced by CPA and increased by IBMX and CPT. Moreover, following 1μM TTX perfusion, bath application of CPA reduced the frequency of miniature EPSCs to below half of the pre-CPA value. This reduction was reversed with bath application of IBMX. We suggest that adenosine receptors are involved in the presynaptic modulation of endogenous inspiratory transmission to PMNs. Supported by NIH Grant NS 24742.

15.4

EFFECTS OF GABAA AND GABAB AGONISTS ON RESPIRATORY RELATED ACTIVITY IN THE ISOLATED BRAINSTEM OF THE FROG.

Hiroshi Kawasaki*, Naofumi Kimura*, Steven F. Perry* and John E. Remmers. Dept. of Medical Physiology, Univ. of Calgary, Calgary, AB, Canada T2N 4N1

In mammalian in vivo preparations, the effect of GABAA and GABAB agonists on respiratory activity is controversial. GABAA agonists appears to decrease tidal volume while the GABAB agonist, baclofen, increases respiratory frequency in the rat but decreases frequency in the cat. GABA has been shown to be a powerful inhibitor of spontaneous respiratory related motor activity in the in vitro frog brainstem (McLean et al., Soc. Neurosci, 17:198, 1991). We therefore tested the effect of specific GABAA and GABAB agonists, muscimol and baclofen on this preparation. Whole nerve recordings which exhibited spontaneous respiratory related activity were obtained from the trigeminal (V), the vagal (X) and the hypoglossal (H) nerve rootlets. Superfusion of muscimol (100-520nM) and baclofen (100-800nM) reduced the frequency of the respiratory related burst in dose dependent manner: the highest dose completely abolished burst discharge. Concentrations of either agonist which had little effect on the amplitude of V, X, or second component of H completely eliminated the first component of H. These results suggest that modulatory action on amplitude of H and frequency are mediated by both GABA receptor subtypes in the frog. (Medical Research Council of Canadian Grant MA-9719)

15.5

SUBSTANCE P AND PHYSALAEMIN ELICIT GLUTAMATE-LIKE MODULATION OF RESPIRATORY RELATED ACTIVITY IN THE *IN VITRO* BRAINSTEM OF THE FROG, *RANA PIPIENS*.

Steven F. Perry*, Makoto Sakurai*, Naofumi Kimura* and John E. Remmers. Respiratory Research Group, Univ. of Calgary, Calgary, AB, Canada T2N 4N1

Substance P (SP) has a stimulatory effect on mammalian *in vitro* or decerebrated *in situ* preparations. In the frog *in vitro* brainstem preparation, however, SP was reported to elicit a biphasic response in spontaneous, respiratory-related discharge recorded from the trigeminal and vagal nerve rootlets (Perry *et al.*, Soc. Neurosci., *18*:489, 1992). In order to resolve this apparent discrepancy between the mammalian and amphibian data, we compared in the isolated brainstem preparation of *Rana pipiens* the effects of the potent tachykinin neuropeptide physalaemin (PHY) with those of glutamate (GLU). GLU has been shown to stimulate respiratory-related activity in the *in vitro* frog brainstem. The time course of PHY action was very similar to that of SP. Beginning at 3 nM, PHY elicited a dose-dependent transient increase in frequency followed by a decrease to below control level. A marked increase in amplitude accompanied both phases of the reaction but was more pronounced (approximately twice the control value) in the late phase. The time courses of the PHY (30 Nm) and GLU (100μM) reactions were similar except that the frequency during GLU application tended to remain above the control level. Spontaneous motor activity and the responses induced by PHY or GLU were completely abolished by kynurenate (200-400 μM). The data are consistent with a model in which neurons containing tachykinin receptors have powerful modulatory effects on excitatory amino acid pathways, which are intimately associated with the respiratory central pattern generator. (MRC Grant MA-9719 to JER).

15.6

MU-RECEPTORS MEDIATE RESPIRATORY DEPRESSANT ACTION OF OPIOIDS IN THE FROG, *RANA PIPIENS*.

Naofumi Kimura*§, Steven F. Perry* and John E. Remmers. Respiratory Research Group, University of Calgary, Calgary, AB, Canada T2N 4N1. § Department of Pharmacology (II), Jikei University School of Medicine, Tokyo 105, Japan

Depressant action of opioids on breathing is known in mammals, but little is known about their effect on breathing in other classes. We have shown that breathing in amphibians is also sensitive to morphine (Kimura *et al.*, Soc. Neurosci. 18: 489, 1992). In order to identify the receptor subtype mediating the respiratory depressant action of opioids, we recorded spontaneous lung ventilatory activity from the trigeminal, vagal and hypoglossal nerve roots of the *in vitro* frog brainstem superfused with oxygenated HEPES buffer (pH7.9, 20-22°C) and applied selective opioid agonists for μ-, δ- and κ-receptors into the bath. The selective μ-agonists, DAGO and dermorphin, exerted a potent dose-dependent depressant action on the frequency of respiratory bursts [IC50: 10 nM (N = 18) and 5.0 nM (N = 7), respectively]. The selective δ-opioid agonists, DPDPE and [D-Ala^2]-deltorphin I, and the κ-opioid agonist, spiradoline (U-62066) required more than 100 times higher concentrations to depress respiratory frequency. The estimated IC50 values for DPDPE, [D-Ala^2]-deltorphin I, and spiradoline were >1000 nM (N = 6), >2000 nM (n = 9), and 1140 nM (N = 7), respectively. The depressant effect on frequency induced by both μ-opioid agonists tested was antagonized by naloxone. Pretreatments with 1 μM naloxone or with 0.1 to 1 μM naloxonazine shifted the concentration-response curve of DAGO to the right. These results indicate that in frogs, opioids selectively depress the generation of respiratory rhythm by acting on the μ-receptor subtype. (Supported by MRC Grant MA-9719 to JER)

15.7

ROLE OF EXCITATORY AMINO ACIDS (EEAs) IN THE PRODUCTION OF SPONTANEOUS AND REFLEXLY EVOKED ACTIVITY IN EXPIRATORY BULBOSPINAL (EBS) NEURONS.

Z. Dogas, E. Stuth, M. Tonkovic, J. Bajic, F. Hopp, D. McCrimmon, and E. Zuperku. Zablocki VA Med. Ctr., Med. Col. of WI, Milwaukee, WI 53295 and Northwestern U., Chicago, IL.

The discharge frequency, F_n, of EBS neurons in the caudal VRG is highly dependent on the level of chemodrive and transpulmonary pressure, P_t, acting via pulmonary stretch receptors. The involvement of NMDA and nonNMDA receptors was evaluated via dose-response plots of peak spontaneous F_n and inflation response *sensitivity* during steady-state conditions due to continuous pressure ejection of antagonists: (±)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonate (CPP), and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). Multibarrel micropipettes were used to record unit activity and deliver agents in anesthetized dogs. Ejected volumes/time were measured via meniscus. During the expiratory phase (per phrenic neurogram) slow test ramp inflations were used to obtain data for plots of F_n vs. P_t and non-inflation cycles for spontaneous F_n. Cycle-triggered histograms and regression analysis were used to quantify changes in F_n-P_t slopes. F_n-P_t slopes were *unchanged* by both types of antagonists and agonists. CPP produced marked dose-dependent reductions in peak F_n and antagonized exogenous NMDA but *not* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). CNQX also produced marked reductions of F_n, but antagonized reponses to NMDA and AMPA. Neuronal EC_{50} values (@ electrode tip) for each agent were remarkably consistent. EBS neurons appear to derive *most* of their spontaneous excitation via endogenously released EAAs acting at NMDA receptors. Neither NMDA or AMPA receptors appear to be involved in the inhibitory pulmonary reflex. *Funded by VA Medical Research.*

15.8

ELECTRICAL PROPERTIES AND TRANSMITTER RESPONSES OF CRAYFISH SWIMMERET MOTOR NEURONS.

C.M. Sherff* and B. Mulloney. Division of Biological Sciences, University of California, Davis, CA 95616.

The crayfish swimmeret motor pattern is characterized by alternating bursts of action potentials in power-stroke (PS) and return-stroke (RS) motor axons. These two groups can be further divided into two functional types: excitors and inhibitors. Excitors release glutamate at their neuromuscular junctions, while inhibitors release γ-aminobutyric acid (GABA). We studied the electrical properties (resting membrane potential, input resistance and time constant) of these four types of swimmeret motor neurons and found no significant differences between them. Swimmeret motor neurons had low input resistances. The median membrane time constant was 9 ms. (25^{th}, 75^{th} percentiles = 7, 14). In addition to their peripheral functions, these motor neurons also make important central synapses. These can be either electrical (excitatory) or chemical (inhibitory). If these neurons release the same transmitters centrally as they do at the muscle, the postsynaptic cells at these two sites must have different responses to these transmitters. We pressure-ejected GABA and glutamate independently from a mutibarreled micropipet into the neuropil of single abdominal ganglia and recorded changes in the swimmeret motor pattern and changes in membrane potentials and input resistances of individual swimmeret neurons. Both GABA and glutamate disrupted the motor pattern and inhibited swimmeret neurons. Input resistances were reduced and the neurons were hyperpolarized even in the presence of elevated Mg^{2+}, indicating that these effects were direct. Research was supported by a grant from NSF.

15.9

NEURAL MECHANISMS OF HYPOGLOSSAL (XII) MOTONEURON DEPRESSION DURING REM SLEEP-LIKE ATONIA. L. Kubin*, A.I. Pack and R.O. Davies. University of Pennsylvania, Philadelphia, PA 19104.

To study the hypotonia of upper airway muscles that occurs during REM sleep, we adapted a decerebrate cat model whereby both upper airway and postural muscle atonia can be induced pharmacologically by microinjections of carbachol into the dorsal pontine tegmentum. We showed that microinjections of antagonists of fast synaptic inhibition into the XII motor nucleus do not prevent the carbachol-induced depression of XII nerve activity. Intracellular recordings from XII motoneurons during the induced depression had characteristics that were consonant with disfacilitation rather than Cl^--mediated inhibition. Microinjections of serotonin (5HT) excited XII motoneurons whereas microinjections of methysergide (5HT antagonist) reduced the spontaneous activity of XII motoneurons. Serotonergic excitation markedly reduced the depression induced by pontine carbachol. Finally, the 5HT level in the region of the XII nucleus, as assessed by microdialysis, decreases during the carbachol-induced atonia during which, as during REM sleep, there is a decrease in the firing of 5HT-containing raphe neurons. These findings suggest that disfacilitation from the excitatory effects of 5HT plays a prominent role in REM sleep decrements of hypoglossal (and other upper airway) motoneurons. (H. Kimura, H. Tojima, C. Reignier, O. Taguchi and G. Woch collaborated with the authors in individual projects summarized in this abstract. Supported by HL42236 and HL47600.)

15.10

ABSENCE OF A BIOMECHANICAL OR METABOLIC SIGNIFICANCE TO NEUROMUSCULAR COMPARTMENTS.

Loyd Lee Glenn*. E Tenn St Univ, Johnson City, TN 37614.

Previous glycogen-depletion studies in the feline quadriceps femoris muscle determined that the muscle could be divided into at least ten compartments that had discrete intramuscular boundaries. Ninety-one percent of the boundaries were non-overlapping, as defined by a boundary width of less than 3 muscle fiber diameters. Driven by the assumption that the compartments would have some functional significance, we measured the difference in fiber type composition and the difference in origin-to-insertion force vectors in compartments.

The proportions and ratios of the three main fiber types (fast glycolitic, fast oxidative glycolytic, slow oxidative) were plotted on section planes perpendicular to the long axis of the muscle. Mathematical models of compartment mechanics were formulated based on the assumption of constant muscle fiber volume.

The fiber composition varied between, as well as within, all adjacent compartments. The composition gradient was smooth and did not show any significant discontinuities at boundaries. The models showed that there were no force vector differences between compartments. Thus, no evidence was found to support the assumption of a functional significance for compartments. (NIH NS 25992)

15.11

EXPERIMENTAL MONONEUROPATHY INCREASES GAP-43 mRNA LEVELS IN SPINAL MOTONEURONS BILATERALLY. C.E. Blanco*, T.Mosconi*, P.E Micevych* and L. Kruger. UCLA School of Medicine, Los Angeles, CA 90024.

Mononeuropathy induced by enveloping the sciatic nerve with polyethylene tubing of fixed diameter results in degeneration of a large proportion of heavily myelinated axons distal to the cuff. This suggests that the motor component of the sciatic nerve is damaged, and the procedure may result in muscle denervation. Two weeks after the nerve was cuffed the motor function of the affected hindlimb was maximally impaired during locomotor behaviors and weight-bearing had been shifted to the contralateral hindlimb. The purpose of this study was to determine whether motoneuronal mRNA levels of a protein implicated in axonal outgrowth subsequent to denervation, GAP-43 (growth associated protein 43kD), were altered by acutely-induced mononeuropathy. Two weeks after slit polyethylene rings were placed on one sciatic nerve, or after unilateral sciatic nerve axotomy, animals were transcardially perfused under pentobarbital anesthesia. The lumbosacral spinal cords were removed and subsequently processed for GAP-43 mRNA *in situ* hybridization histochemistry using an ^{35}S-labelled ribonucleic acid probe. In sham operated animals, motoneuron expression of GAP-43 mRNA was very low. Unilateral axotomy of the sciatic nerve increased motoneuronal GAP-43 mRNA levels in the retrodorsal lateral nucleus (RDLN; sciatic nerve motoneuron pool) ipsilateral to nerve section. Nerve cuff increased GAP-43 mRNA levels in two lumbosacral motor pools: RDLN motoneurons ipsilateral to the nerve cuff and in cell bodies located rostral to the sciatic nerve motor pools and contralateral to nerve cuff placement. These data suggest that in this experimental mononeuropathy the gene expression of a molecule associated with axonal growth is upregulated in motoneurons by direct axonal insult and, we hypothesize, by mechanisms underlying the compensatory alterations in the motor activity of the uninjured hindlimb.

Supported by HD 7228, NS 9176 and NS 5685.

15.12

A TRANSIENT DECREASE IN SPECIFIC RESISTANCE DURING POSTNATAL DEVELOPMENT OF MAMMALIAN MOTONEURONS. William E. Cameron, Pedro A. Núñez-Abades*, John M. Spielmann* and German Barrionuevo*. Depts. of Behavioral Neuroscience and Psychiatry, Univ. of Pittsburgh, PA 15260

At birth, mammalian motoneurons have a relatively tight membrane. Within the first few weeks of postnatal life, there is a dramatic decrease in the input resistance while the cell shows no increase in total membrane surface area. Using intracellular recording from *in vitro* slice preparations of rat brainstem and spinal cord, we have measured input resistance and membrane time constants of hypoglossal and phrenic motoneurons at four postnatal ages. Following the recordings, the cells were labeled by intracellular injection of neurobiotin and their cell morphology quantified using a computer-assisted, three-dimensional neuronal reconstruction system (*Eutectic*). Anatomical analysis revealed that there was no net increase in total membrane surface area in the first two weeks while there was a significant decrease in the number of dendritic terminals. Assuming that the motoneuron geometry can be approximated by an equivalent cylinder, the specific membrane resistance (R_m) of these cells was calculated (Rall, '77). This analysis revealed that there was a transient decrease in R_m at approximately two weeks of age for both of these motor pools. Based on the density of GAD-positive (GABA) terminals in these nuclei at various postnatal ages, we propose that the drop in R_m results, in part, from the arrival of new descending inhibitory synapses. Supported by a grant from NIH (HD 22703).

15.13

INDEPENDENT RECRUITMENT TO TONIC FIRING AMONG RAT *SOLEUS* MOTONEURONES DURING SPONTANEOUS ACTIVITY. Torsten Eken* and Terje Lømo*. Dept. of Neurophysiology, University of Oslo, 0317 Oslo, Norway

Single-motor-unit activity and gross EMG were recorded from chronically implanted electrodes. Integrated rectified gross EMG consistently showed tonic segments at different amplitudes lasting for up to several minutes while the animal was standing still or lying down. They were typically initiated and terminated by high-amplitude phasic episodes caused by gross limb movements. The underlying phenomenon was a prolonged firing at stable high frequencies (typically 20–25 Hz) by one or a few motor units while the rest of the units were silent. Different units were active in different tonic segments. A single unit could also abruptly shift from low-frequency firing (typically 10 Hz) to sustained firing at a high frequency. Similar jumps can be induced by short synaptic excitation (Eken & Kiehn, *Acta Physiol. Scand.* 135:383–394, 1989). The tonic firing matures after 3 weeks postnatally (Eken, Elder & Lømo; *Soc. Neurosci. Abstr.* 16:331, 1990), and disappears after selective depletion of descending monoaminergic fibres (Kiehn, Erdal, Eken & Bruhn; *Acta Physiol. Scand.* 146 Suppl. 608:77, 1992). It appears that descending monoaminergic systems may be important in maintaining tonic motoneurone activity, possibly through activation of plateau potentials.

15.14

EFFECTS OF SEROTONIN ON REPETITIVE FIRING AND AHP IN LUMBAR MOTONEURONS OF THE NEONATAL RAT. M.K. Floeter. Lab. Neural Control, NINDS, NIH, Bethesda, MD. 20892.

The regulation of postspike afterhyperpolarization (AHP) by neurotransmitters such as serotonin (5HT) plays a key role in some models of locomotor networks. In an in vitro preparation of the isolated cord of the neonatal rat, 5HT has been shown by several groups to promote rhythmic alternating activity in lumbar ventral roots. In this study, the direct effects of low concentrations of 5HT (0.1-1 uM, subthreshold for inducing alternating rhythms) on the AHP following antidromically activated action potentials and on the repetitive firing properties of lumbar motoneurons from neonatal rats, 0-5 days old, in the isolated spinal cord preparation were observed, using KCl-filled micropipettes. In normal extracellular solution, the majority of motoneurons (MNs) studied to date exhibit a single linear relationship between steady state repetitive firing frequency and the amount of intracellular current injection, using 1 sec current pulses. The mean slope of this line (F-I slope) in 14 MNs was 15 spikes/sec/nA, and the maximum firing frequency was around 12 Hz. Secondary ranges of firing were not observed. Spike frequency adaptation typically occurred. Measurements of AHP peak amplitude, duration at half maximal amplitude, and time to peak amplitude all exhibited a very modest correlation with F-I slope. When the [Ca++] in the bath solution was reduced and 5mM magnesium added, evoked synaptic activity was blocked and repetitive firing was enhanced, mean F-I slope=25 spikes/s/nA. The increase in firing rates was not well correlated with changes in measures of the AHP. Addition of 5HT to low Ca++, high Mg++ bath solution led to further increases in the rate of steady state repetitive firing in 5 of 7 MNs, mean F-I slope=35, without corresponding changes in measurements of AHP, MN depolarization, or evident postsynaptic potentials. In all cases, repetitive firing did not outlast the duration of the injected current pulse. These results suggest that 5HT may alter repetitive firing through a direct effect on motoneurons which is not necessarily reflected in measures of the AHP following antidromically activated action potentials. Further experiments will examine blockade of conductances underlying the AHP and effects of 5HT receptor-subtype specific agonists and antagonists.

15.15

INTERACTION OF ANTISPASTIC DRUGS AND THYROTROPIN-RELEASING HORMONE IN NEONATAL RAT SPINAL CORD IN VITRO. Shripad B Deshpande* and Jordan E Warnick*. Dept. Pharmacol. Expt. Therap., Univ. of Maryland, School of Medicine, Baltimore MD 21201. USA.

Thyrotropin-releasing hormone (TRH) by exerting excitatory actions on spinal motoneurons has been reported to reverse the phencyclidine-, organophosphates- and methysergide-induced depression of the spinal monosynaptic reflex (MSR). TRH has been implicated in the aetiopathogenesis of spastic conditions. The present study therefore, has been undertaken to investigate the TRH interactions with antispastic drugs (diazepam and baclofen), in rat spinal cord in vitro. Stimulation of dorsal root evoked a MSR in the ventral root, and superfusion of TRH (0.01-1.0 uM) potentiated the reflex. Diazepam (1-30 uM) antagonized the TRH-induced potentiation in dose dependent manner and half maximal potentiation occuring at 8 uM of diazepam. Diazepam (30 uM) either by itself or on presynaptic inhibition produced to MSR had no effect. Baclofen, (0.3 uM) depressed the MSR by 90% and TRH reversed this depression upto 65-70% of control in a dose dependent manner (0.03-0.3 uM). Results indicate that the antispastic drugs act probably by antagonizing the excitatory actions of TRH on motoneurons. (Supported by NIH grant # 21312)