The Neurophysiologic Function of Magnesium: An Update

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Zusammenfassung

Es wird ein Überblick gegeben über die im Zeitraum von 1976 bis 1980 publizierten Befunde, die die physiologische und biochemische Bedeutung von Mg im zentralen und peripheren Nervensystem betreffen. Unberücksichtigt bleiben die biologischen Wirkungen, die Mg auch in anderen Geweben entfaltet. — Seit dem 2. Internationalen Symposium sind hierzu generell nur wenig neue grundlegende Erkenntnisse hinzugewonnen worden.
Orte der chemischen Neurotransmission sind, ob sie zentral oder peripher lokalisiert sind, funktionell am leichtesten verwundbar gegenüber akuten Veränderungen der Konzentration an extrazellulärem Mg, eine Tatsache, die die Interaktion zwischen Mg und Ca bei der präsynaptischen Freisetzung der bekannten Neurotransmitter und der entsprechenden post-synaptischen Antwort widerspiegelt. Die zugrunde liegenden Mechanismen sind für das periphere Nervensystem im größten Detail herausgearbeitet worden; bezüglich des ZNS bleibt noch viel zu tun.
Das ZNS ist von Schwankungen der Mg-Konzentration in peripheren Flüssigkeitsräumen durch die Blut-Hirn- und die Blut-Liquor-Schranke geschützt. Unterschiede, wie diese zwei Makromembranen das Gleichgewicht des Mg-Influx regulieren, sind jetzt klarer definiert.
Tubulin, axonaler Transport, Plastizität und Regeneration im ZNS stehen jetzt im Brennpunkt eines beachtlichen Forschungsinteresses. Man kann voraussehen, daß die Bedeutung von Mg und Ca auf diesen Gebieten in den nächsten Jahren zunehmend offenkundig wird.

Summary

Data on the physiologic and biochemical importance of Mg in the central and peripheral nervous systems published from 1976 through 1980 were reviewed. Those biologic actions of Mg shared in common with other soft tissues were not included. In general, little new basic information has appeared since the last report on this topic was delivered at the Second International Symposium.
Sites of chemical neurotransmission, whether located centrally or peripherally, are most vulnerable functionally to the adverse effects of acute changes in the concentration of extracellular Mg, reflecting the interaction between Mg and Ca in the presynaptic release of and post-synaptic responses to the established neurotransmitters. The underlying mechanisms have been worked out in greatest detail for the peripheral nervous system. Much is yet to be learned about those involved in the CNS.
The CNS is well-protected form fluctuations in the concentration of Mg in the systemic interstitial fluids by the blood-brain and blood-CSF barriers. The differences in the way these two macromembranes function in the homeostatic regulation of the influx of Mg are now more clearly defined.
Tubulin, axonal transport, plasticity and regeneration in the nervous system are topics of considerable investigative interest. One would anticipate that the importance of Mg and Ca in these areas will become increasingly apparent in the next few years.

Résumé

Nous avons passé en revue les données sur l'importance physiologique et biochimique du magnésium dans les systèmes nerveux central et périphérique publiées depuis 1976 jusqu'à 1980 inclusivement. Les actions biologiques du magnésium qui sont partagées par d'autres tissus mous n'ont pas été comprises dans cette revue. En règle générale, il est apparu peu d'information nouvelle fondamentale depuis le dernier rapport sur ce sujet présenté au 2ème Symposium International.
Les sites de la neurotransmission chimique, qu'ils soient de localisation centrale ou périphérique, sont les plus vulnérables fonctionnellement à des effets défavorables de modifications aiguës dans la concentration du magnésium extracellulaire, en reflètant l'interaction entre le magnésium et le calcium, dans la libération présynaptique et les réponses postsynaptiques aux neurotransmetteurs de rôle établi. Les mécanismes sous-jacents ont été élucidés dans le plus grand détail pour le système nerveux périphérique. Nous avons encore beaucoup à apprendre en ce qui concerne les mécanismes impliqués dans le S.N.C.
Le S.N.C. est bien protégé des fluctuations de la concentration du magnésium dans les liquides interstitiels systémiques par les barrières hémato-encéphalique et sang-LCR. Les différences dans le processus selon lequel fonctionnent ces deux macromembranes sont maintenant plus clairement définies.
La tubuline, le transport axonal, la plasticité et la régénération dans le système nerveux sont des sujets d'un intérêt considérable pour la recherche. On pourraît anticiper que l'importance du calcium et du magnésium dans ces domaines deviendra de plus en plus manifeste dans les toutes prochaines années.

This review covers the period 1976 through 1980. It supplements similar reports presented at the First and Second International Symposia on Magnesium in 1971 and 1976 [14, 15]. When necessary, previous data are summarized. The interested reader should turn to the earlier reports for references. As before, those actions of magnesium (Mg) which are neurophysiologically unique will be discussed.

The extradural (peripheral) efferent and afferent nervous system

The axon

Magnesium (and potassium) may be essential for the growth and survival of embryonic sensory neurites in the presence of growth factor [63].
No new information is available on the concentration of cellular Mg in peripheral nerve in higher vertebrates or on the effect of acute and chronic changes in extracellular Mg (Mg_e) on the chemical composition of the axoplasm. Studies on the giant acon of the squid support earlier reports that Mg efflux across the axolemma is an energy-dependent process carried out against a large electrochemical gradient; is coupled with sodium (Na) influx, perhaps in a 2 Na for 1 Mg exchange. The carrier system requires ATP. Whether

ATP acts as a substrate to drive the system or as a catalyst to increase the affinity of one or the other cations for the carrier is not known. Sodium could energize the system as it moves along its electrochemical gradient. The Na-Mg exchange ist probably distinct from the Na-calcium (Ca) "pump" [2, 12, 15, 20, 48]. Magnesium influx is in the direction of its electrochemical gradient, is not affected either by the concentration of extracellular potassium (K) or inhibition of the Na-K "Pump" and increases with electrical depolarization of the axoplasmalemma. Influx is maximal in the presence of intracellular Na and ATP, suggesting the presence of a transport mechanism [2, 12, 47]. The giant axon of the squid is normally bathed by fluids containing 50 to 60 mM of Mg. Therefore, the findings may not apply to mammals. A separate ionic channel for MG has been postulated from observations on the generation of action potentials in molluscan neurons [38].

Very large concentrations of extracellular Mg "stabilize" axons and isolated nodes of Ranvier *in vitro*, preventing depolarization. The underlying mechanisms are still not known [15]. A report attempting to correlate prolonged nerve conduction with two-to-three fold increases in plasma Mg in chronic uremics is interesting but unconvincing [25]. Electromyogams and nerve conduction velocities were normal in markedly hypomagnesemic sheep [59].

Somatic neuromuscular motor endplate

Earlier, now classic studies showed that: Ca regulates the probability of quantal release of acetylcholine (ACh) and, therefore, is essential for neuromuscular transmission [5]; Mg antagonizes this action of Ca by blocking Ca influx into the nerve terminal, both at rest and particularly following an action potential; and Mg initially activates and, at increasing concentrations, progressively depresses subsynaptic cholinergic receptors [15]. Thus, neuromuscular transmission is inversely related to the concentration of interstitial Mg.

Most of the recent work is confirmatory. Mg-ATP in the presence of bicarbonate inhances the uptake of ACh into synaptic vesicles isolated from the electric organ of *Torpedo* [36]. The concentration of Mg increases temporarily in the vesicles after depolarization. The excess may bind to negative charges vacated by the decrease in ATP and ACh [58]. Magnesium reportedly decreases the quantal content of the excitatory endplate potential (a presynaptic effect), the frequency of the miniature endplate potentials (mepp) and the amplitude of the mepp (a postsynaptic effect) [10, 60]. It also decreases the frequency of mepps in the cockroach, an animal in which the neurotransmitter is believed to be L-glutamate [69]. In the lobster and crayfish, Mg increases the threshold to depolarization and decreases nonspecific conductance in response to ACh in the endplate [3]. The spider crab has developed pre- and postsynaptic mechanisms to minimize the blocking effect of Mg to transmitter release [42].

The myoneural junction is the major site in the peripheral somatic motor system for harmful effects of changes in the systemic extracellular concentration of Mg. Acute hypermagnesemia produces a transmission block and flaccid paralysis. Hypomagnesemia should cause increased transmitter release and neuromuscular hyperirritability. Critical studies on the latter problem have not yet been done *in vivo*.

Skeletal muscle

Quantitative considerations. Several methods have been used to calculate the chemical state of intracellular Mg (Mg_i) in muscle [11, 15, 29]. Based on recent estimates in amphibian satorius and gastrocnemius, free Mg_i is about 5% of the total cellular Mg; ATP-Mg_i, 93%; phosphocreatine-Mg_i, 3% and myosin-Mg_i, less than 1% [29]. Neither an increase in Mg_e nor insulin increases free Mg_i. A postulated extrusion of free Mg_i against an electrochemical gradient has not been proved experimentally [29]. While severe Mg deficiency can produce an isolated decrease in the concentration of Mg_i in predominantly red an white muscle *in vivo*, the precise role of Mg_e in the regulation of Mg_i is still not clear [15].

The sarcolemma. Concentrations of extracellular Mg large enough to block neuromuscular transmission also reversibly decrease mechanical contraction without depressing the excitability of the sarcolemma. At very high levels of Mg_e but still less than those which alter axonal excitability, the sarcolemmal threshold to activation increases without a significant change in the resting membrane potential [15]. In chronically denervated muscle, Mg_e impairs the effects of acetylcholine (ACh) by "stabilizing" the sarcolemma, decreases the severity of contracture following ACh-induced depolarization and has no effect on subsequent relaxation [28]. When added in high concentrations to a K-rich, Ca-deficient perfusate, Mg restores the excitability, overshoot and propogated action potential in mammalian cardiac muscle. These data supply additional support for a transmembranous carrier system or "pore" for Mg which may be distinct from those for Na and Ca [62]. This channel might activate as part of the ACh-stimulated, nonspecific increase in sarcolemmal permeability at the motor endplate. Sarcoplasmic Mg promotes Ca uptake into the sarcoplasmic reticulum, perhaps by accelerating the reaction in which the terminal phosphate of ATP is transferred to the membrane-bound "Ca pump" [21, 26, 49, 61, 64, 65]. Depolarization of the sarcoplasmic reticulum releases Ca. The resulting increase in myoplasmic Ca excites muscle contraction. Influx of magnesium into the sarcoplasm would be expected to produce the inhibition of muscle contraction noted in the denervation studies.

Mechanical contraction. Magnesium and MgATP are

important for the concentration and relaxation of muscle because of their effects on the interaction between actin and myosin. This topic will not be reviewed further here because the literature dealing with this complex area of biochemical research is too extensive.

Sensory receptors

Little has appeared recently on the role of Mg in physiologic or biochemical mechanisms of sensory transducers. The concentration of Mg was measured in retinas from rodents at various ages; the level of Mg_i in photoreceptors, calculated; and the effect of retinal degeneration, studied [24]. Decreasing Mg_e in solutions bathing the ventral nerve photoreceptor of *Limulus* causes an increase in receptor potential and membrane current in response to light and an increase in membrane dark conductance (in the presence of low Ca_e). The authors propose that a decrease in Mg_e causes opening of Ca-dependent ion channels in the photoreceptor membranes in the dark — channels which normally open in response to light [66].
The sensitivity of isolated, perfused carotid baroreceptors is inversely related to the concentration of Mg in the perfusate. It is not clear at what site Mg is acting physiologically [41]. Increasing the concentration of Mg in artificial endolymph in the scala tympani reportedly decreases spontaneous firing and sound-induced discharges of the acoustic nerve. These responses are presumably the result of direct action on the hair cells [53].

The extradural autonomic system

Autonomic ganglia. Mg inhibits the release of ACh from presynaptic terminals by blocking Ca influx and decreases postsynaptic sensitivity to ACh. As is the case at the neuromuscular junction, Ca and repetitive stimuli reverse the presynaptic effects, at least in sympathetic ganglia [15]. No new reports were found which provided additional information concerning mechanisms.
Neuroeffector junctions. That selected beta-adrenergic agonists inhibit influx of Mg into cultured S49 lymphoma cells is of tangential interest. While the inhibition appears to be mediated by receptors identical in properties to those linked to adenylate cyclase, cyclic AMP may not be the mediator [45]. Ca and Mg are antagonists at inhibitory neuro-effector junctions of gut smooth muscle, perhaps by competing for receptor sites which initiate Ca influx following depolarization of the cell membrane [43]. The physiological and chemical actions of Mg on smooth muscle are the subject of another review in this symposium.

The adrenal medulla. Magnesium depresses ACh-mediated release of catecholamines from the medulla. Mg-ATP stimulates the uptake of catecholamines into the chromaffin granules and forms ternary complexes with monoamines [15]. Recent reports corroborate these earlier findings [25, 36, 50, 67]. Ca uptake into the chromaffin cells via a "slow channel" precedes the release of the monoamines. Mg may block Ca uptake or act at a different intracellular site. The chromaffin cells contain a Ca-Mg ATPase which may be involved in the uptake of catecholamines [67].

The intradural (central) nervous systems

Magnesium homeostasis

General: The intradural fluid compartments are buffered from deleterious fluctuations in the concentrations of inorganic and organic substances in the systemic extracellular environment by the "blood-cerebrospinal fluid-barrier" (B—CSF—B) and "blood-brain-barrier" (BBB). The former consists of the ephithelial cells of the choroid plexi; the latter, the endothelial cells of the cerebral microvasculature. An ionized substance normally penetrates these proteolipid membranes slowly by diffusion, unless its transmembranous flux is increased by some type of carrier mechanism. Magnesium is no exception. Magnesium in the vetriculo-subarachnoid and parenchymal interstitial fluids is presumably in diffusional equilibrium across the ependymal and pia-glial "membranes". However, an acute change in the concentration of a cation in either physiologic compartement may take some time to equilibrate, because of the anatomically large distances which must be traversed and the large numbers of acidophilic groups slowing diffusion through the neuropil.
The blood-cerebrospinal fluid-barrier and the concentration of Mg in the CSF (CSF-Mg) and CNS interstitial fluid (IF-Mg). The CSF-Mg exceeds plasma ultrafilterable Mg in most mammalian species studied, indicating transport from plasma to CSF against an electrochemical gradient. Combining the results of several earlier and recent reports, the following can be said about regulation of Mg homeostasis: CSF-Mg is maintained within very narrow limits by an active transport system which moves Mg from plasma into the CSF. Whether or not this carrier is coupled in any way with Na is not yet known. The carrier acts as if it is fully saturated at normal and, probably, well below normal levels of Mg in plasma. It is possible that the choroid plexi "monitor" the CSF-Mg and adjust influx accordingly. Sustained hypermagnesemia produces a small increase in CSF-Mg. This is most likely due to diffusion through the slightly permeable B—CSF—B and into those areas of the brain adjacent to the CSF which lack a BBB. There is no longer any doubt that the CSF-Mg (and IF-Mg) decrease during severe, prolonged hypomagnesemia, presumably because the carrier desaturates and can no longer replenish losses resulting, at a minimum, from bulk flow of CSF [9, 15, 16, 52]. Many of the details characterizing the transport remain to be worked out.
The blood-brain barrier and regulation of parenchymal

interstitial and cellular concentrations of Mg. Experimentally, al low CSF-Mg is accompanied by a small but physiologically important decrease in cellular Mg in the brain. This indicates the existence of a labile interstitial-intracellular pool of Mg which may be as large as 12 to 15% of the total parenchymal Mg. While the CSF-Mg is corrected very rapidly after parenteral administration of Mg, cellular Mg increases very slowly [4, 15]. This discrepancy is explained by the fact that the BBB has no demonstrable carrier system for Mg, at least in rats and inferentially in rabbits [15, 16]. It follows that the CSF must be the principle source of Mg to be used to restore depleted Mg stores in the brain and spinal cord promptly. Additional Mg must diffuse slowly across the BBB also. The quantitative importance of these two routes is not known. More data are also needed about the exchange of Mg across the CNS-systemic barriers and across cellular membranes in the CNS in other animals before the above conclusions can be generalized with confidence.

Derangements in Mg homeostasis in the CNS. Dietary-induced Mg deficiency remains the most potent way to deplete labile Mg stores in the CNS. Recently, phenobarbital and ethanol were reported to decrease Mg significantly in the brains of mice. The CSF was not analyzed [5, 6]. In a second report, withdrawal of mice from pentobarbital after acute and chronic administration had no effect on the subcellular distribution of Mg in the brain. Withdrawal from ethanol after acute exposure was associated with a slight increase in synaptosomal Mg; after chronic exposure, with a slight decrease in Mg in myelin fractions [34]. On the other hand, CSF-Mg did not change in rats acutely or chronically intoxicated with and then withdrawn from alcohol, despite clinical symptoms of withdrawal and a decrease in plasma Mg in chronically exposed animals [33]. While not strictly germane, CSF-Mg is slightly increased in chronic epileptics on dilantin, phenobarbital and other anticonvulsants (no correlation was made with the drugs used) [32] and is normal in chronic alcoholics suffering from delirium tremens [37]. Therefore, the results in mice need to be confirmed; and, if substantiated, the effects of the drugs on the regulation of Mg flux across the B—CSF—B and BBB investigated.

Selected neurophysiologic tropics

Acute elevation in systemic extracellular Mg have no effect on the CNS, so long as the B—CSF—B and BBB are intact. However, increasing the CSF-Mg or the concentration of Mg in solutions bathing isolated segments of the brain and spinal cord or cultures of neurons reversibly blocks synaptic transmission [1, 7, 15, 22, 51, 55]. Decreased excitability of normal and epileptogenic neurons develops at higher local extracellular concentrations, but a levels which are still lower than those producing a similar effect on peripheral axons [1, 8, 70]. The roles of Mg and Ca in the exocytosis of potential central neurotransmitters have not been worked out. Some data indicate that Mg blocks the release of certain putative chemical transmitters (ACh, glutamate, aspartate and gamma aminobutyrate) [15, 51]. The postsynaptic effect of Mg may be due to impaired receptor responsiveness to neurotransmitters or to change in the mechanism for generating the action potential [3, 19, 23]. On the other hand, Mg injected iontophoretically into the cytoplasma of the neuronal soma causes spontaneous depolarization, accompanied by a fall in membrane conductance and impaired post-activation hyperpolarization. These effects are opposite to those of Ca and were ascribed to a disturbance in the activation of conductance of potassium [39].

CNS synaptosomes accumulate Mg. Influx seems to be independent of the transmembranous movement of Ca [13]. Synaptosomal uptake of 5-hydroxytryptamine and norepinephrine requires Mg and ATP [15, 30, 67]. The transport of norepinephrine probably involves a Mg/Ca-activated ATPase [67].

Selected neurochemical topics

Evidence indicating a role for Mg in the formation of neurotransmitters is beginning to appear: Mg and ATP are required for the activation of tryptophan-5-monooxygenase, the rate limiting step in the formation of 5-hydroxytryptamine [31, 40, 44 71]. Activation of adenylate cyclase by one class of striatal dopamine receptors involves increased affinity of the enzyme for Mg and guanyl nucleotide [46].

No changes were found in the regional concentration of norepinephrine, dopamine and 5-hydroxytryptamine or in the concentration of taurine and major amino acids (alanine, glutamate, glutamine, aspartate, GABA, glycine, threonine) in Mg-depleted brains from neurologically symptomatic, Mg-deficient rats [17, 68]. The problem of possible changes in the metabolism, release and activity of accepted and proposed central neurotransmitters in the Mg-deficient animals is far from settled.

Microsomal fractions from bovine brain contain a Mg/Ca-dependent ATPase. When this ATPase activity is solubilized and reconstituted into lipsomes, the preparation accumulates Ca in the presence of ATP [54,57]. Efflux of Ca from brain mitochondria involves a Na-Ca exchange which is markedly inhibited by Mg in physiologic concentrations [18].

A non-lysosomal sphingomyelinase has been identified which is dependent on Mg and has its greatest activity in the young brain [27]. As might be expected, magnesium's role in the solubility and polymerization of tubulin is under study [56].

Finally, the concentration of glucose is increased in Mg-depleted brains in rats, without an associated change in fasting plasma glucose or in the single pass uptake of glucose across the BBB [68]. The reasons for this finding have not been worked out.

Clinical-chemical correlations

Based on current limited data in animals and man, the best chemical evidence that symptoms referrable to CNS dysfunction are due to Mg loss is a low CSF-Mg. Acute hypermagnesemia produces peripheral neuromuscular and autonomic blockade but has no significant effect on the CNS, so long as blood pressure and ventilatory functions are supported and the BBB is intact.

References

[1] *Bagust, J. Kerkut, G. A.:* Brain Res. **177**, 410—413, (1979).
[2] *Baker, P. F.:* Fed. Proc. **35**, 2589—2595, (1976).
[3] *Barker, J. L.:* Brain Res. 92, 307—323 (1975).
[4] *Belknap, J. K., Berg, J. H., Cocke, R., Clancy, A. N.:* Exp. Neurol. **57**, 506—616 (1977).
[5] *Belknap, J. K., Berg, J. H., Coleman, R. R.:* Pharmac. Biochem. Behav. 9, 1—6 (1978).
[6] *Belknap, J. K., Berg, J. H., Ondrusek, G., Waddingham, S.:* Psychopharmacol. 59; 299—303 (1978)
[7] *Bindman, L. J., Lippold, C. J., Milne, A. R.:* J. Physiol. **286**, 457—477 (1979).
[8] *Borges, L. F., Gucer, G.:* Epilepsia. **19**, 81—91 (1978).
[9] *Bradbury, M. W., Sarna, G. S.:* Exp. Eye Res. **25** (suppl.): 249—257 (1977.
[10] *Branisteanu, D. D., Miyamoto, M. D., Volle, R. L.:* J. Physiol. **254**, 19—37 (1976).
[11] *Brinley, F. J., Scarpa, A., Tiffert, T.:* J. Physiol. **266**, 545—565 (1977)
[12] *Caldwell-Violich, M., Requena, J.:* J. Gen. Physiol. **74**, 739—752 (1979).
[13] *Carvalho, C. A. M.:* Life Sci. **25**, 73—82 (1979).
[14] *Chutkow, J. G.:* In: *Durlach, J.:* Ed.: First International Symposium on Magnesium Deficit in Human Pathology. Imprimerie Amelot, Brionne, France. 1971. pps. 113—134.
[15] —: In: *Cantin, M., Seelig, M. S.* (Eds.): Magnesium in Health and Disease. Spectrum Publications, New York, 1980. pps. 713—752.
[16] —: Exp. Neurol. **60**, 592—602 (1978).
[17] *Chutkow, J. G., Tyce, G. M.:* J. Neural. Transmission **44**, 297—302 (1979).
[18] *Clark, A. F., Roman, I. J.:* J. Biol. Chem. **255**, 6556—6558 (1980).
[19] *Davies, J., Watkins, J. G.:* Brain Res. **130**, 364—368 (1977).
[20] *DeWeer, P.:* J. Gen. Physiol. **68**, 159—178 (1976).
[21] *Dunnett, J., Nayler, W. G.:* J. Mol. Cell. Cardiol. **10**, 487—498 (1978).
[22] *Erulkar, S. D., Darubach, G. E., Mender, D.:* Brain Res. **66**, 413—424 (1974).
[23] *Evans, R. H., Francis, A. A., Watkins, J. C.:* Experienta. 33, 489—491 (1977).
[24] *Farber, D. B., Lolley, R. N.:* Exp. Eye Res. 22, 219—228 (1976).
[25] *Fleming, L. A., Lenman, J. A. R., Stewart, W. K.:* J. Neurol. Neurosurg. Psychiat. 35, 342—355 (1972).
[26] *Garrahan, P. J., Rega, A. F., Alonso, G. L.:* Biochem. Biophys. Acta **448**, 121—132 (1976).
[27] *Gatt, S., Dinur, T., Leibovitz-Ben Gershon, Z.:* Biochem. Biophys. Acta **531**, 206—214 (1978).
[28] *Gordon, T.:* J. Physiol. **255**, 575—586 (1976).
[29] *Gupta, R. K., Moore, R. D.:* J. Biol. Chem. **255**, 3987—3993 (1980).
[30] *Halaris, A. E., DeMet, E. M.:* J. Neurochem. 31, 591—597 (1978).
[31] *Hamon, M., Bourgoin, S., Hery, F., Simonnett, G.:* Mol. Pharmacol. **14**, 99—110 (1978).
[32] *Heipertz, R., Eickhoff, K., Karstens, K. H.:* J. Neurological Sci. 41—55—60 (1979).
[33] *Hemmingsen, R., Kramp, P.:* Psychopharmacol. **67**, 255—259 (1980).
[34] *Hood, W. F., Harris, R. A.:* Biochem. Pharmacol. **28**, 3075—3080 (1979).
[35] *Ishikawa, K., Harada, E., Kanno, T.:* Jap. J. Physiol. 27, 251—266 (1977).
[36] *Koenigsberger, R., Parsons, S. M.:* Biochem. Biophys. Res. Commun. **94**, 305—312 (1980).
[37] *Kramp, P., Hemmingsen, R., Rafaelsen, O. J.:* Psychiatr. Res. **1**, 161—171 (1979).
[38] *Krasts, I. V., Chemeris, N. K., Veprintsev, B. N.:* Comp. Biochem. Physiol. **61**, 519—527 (1978).
[39] *Krnjevic, K., Puil, E., Werman, R.:* Canad. J. Physiol. Pharmacol. **54**, 73—77 (1976).
[40] *Kuhn, D. M., Vogel, R. L., Lovenberg, W.:* Biochem. Biophys. Res. Commun. **82**, 759—766 (1978).
[41] *Kunze, D. L.:* Circ. Res. **45**, 815—821 (1979).
[42] *Lang, F., Cleveland, M. B., Atwood, H. L.:* J. Neurobiol. **10**, 609—614 (1979).
[43] *Lang, R. J.:* Br. J. Pharmac. **67**, 39—49 (1979).
[44] *Lysz, T. W., Sze, P. Y.:* J. Neurosci. Res. 3, 411—418 (1978).
[45] *Maguire, M. E., Erdos, J. J.:* J. Biol. Chem. **255**, 1030—1035 (1980).
[46] *McSwigen, J. D., Nicol, S. E., Gottesman, I. I., Tuason, V. B., Frey, W. H.:* J. Neurochem. **34**, 594—601 (1980).
[47] *Mullins, L. J., Brinley, F. J.:* J. Membrane Biol. **43**, 243—250 (1978).
[48] *Mullins, L. J., Brinley, F. J., Abercrombie, R. F.:* J. Gen. Physiol. **69**, 389—400 (1977).
[49] *Nagasaki, K., Kasai, M.:* J. Biochem. **87**, 709—716 (1980).
[50] *Pinto, J. E. B.:* Horm. Metab. Res. **11**, 404—407 (1979).
[51] *Potashner, S. J.:* J. Neurochem. **31**, 187—195 (1978).
[52] *Reed, D. J., Yen, M. H.:* J. Physiol. **281**, 477—485 (1978).
[53] *Robertson, D., Johnstone, B. M.:* Pflügers Arch. **380**, 7—12 (1979).
[54] *Robinson, J. D.:* Arch. Biochem. Biophys. **176**, 366—374 (1976).
[55] *Rogers, H. R., Levy, W. B.:* Brain Res. 139, 183—198 (1978).
[56] *Rosenfeld, A. C., Zackroff, R. V., Weisenberg, R. C.:* FEBS Letters **65**, 144—147 (1976).
[57] *Saermark, T., Vilhardt, H.:* Biochem. J. **181**, 321—330 (1979).
[58] *Schmidt, R., Zimmermann, H., Whittacker, V. P.:* Neuroscience 5, 625—638 (1980).
[59] *Sims, M. H., Bell, M. C., Ramsey, N.:* J. Anim. Sci. **50**, 539—546 (1980).
[60] *Singh, Y. N., Marshall, I. G., Harvey, A. L.:* Br. J. Anaesth. **51**, 1027—1033 (1979).
[61] *Souza, D. O. G., de Meis, L.:* J. Biol. Chem. **251**, 6355—6359 (1976).
[62] *Spah, F., Fleckenstein, A.:* J. Mol. Cell. Cardiol. **11**, 1109—1127 (1979).
[63] *Stach, R. W., Stach, B. M., West, N. B.:* J. Neurochem. 33, 845—855 (1979).
[64] *Stephenson, E. W., Podolsky, R. J.:* J. Gen. Physiol. **69**, 1—16 (1977).

[65] —, —: J. Gen. Physiol. **69**, 17—35 (1977).
[66] *Stieve, H., Bruns, M.:* Z. Natur. forsch. **33**, 574—579 (1978).
[67] *Toll, L., Gundersen, G. B., Howard, B. D.:* Brain Res. **136**, 59—66 (1977).
[68] *Tyce, G. T., Chutkow, J. G.:* Unpublished data.
[69] *Washio, H. M., Inouye, S. T.:* J. Exp. Biol. **75**, 101—112 (1978).
[70] *Wojtowicz, J. M., Marshall, K. C., Hendelman, W. J.:* Canad. J. Physiol. Pharmacol. **55**, 367—372 (1977).
[71] *Yamauchi, T., Fugisawa, H.:* Arch. Biochem. Biophys. **198**, 219—226 (1979).