In trying to inhibit peripheral dopa decarboxylase we used L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)-propionic acid (L-HMD). The L-form was recently shown to be the active component of the racemic mixture[14]. Central inhibition of decarboxylation of aromatic amino acids was attempted with N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl)hydrazine (Ro 4-4602). At 100 mg/kg and higher doses, Ro 4-4602 was reported to inhibit dopa decarboxylase in the brain of rats[15]. Both inhibitors of dopa decarboxylase were administered i.v. 5 min prior to L-dopa. The statistical significance of the changes in arterial pressure and heart rate was determined with the Student's *t*-test.

The results of our experiments are summarized in Tables I and II. In control animals saline produced no significant change in mean arterial pressure (MAP) or heart rate during the 2-h period. L-dopa produced a dose-dependent increase in MAP. L-HMD, 15 mg/kg i.v. or Ro 4-4602, 100 mg/kg i.v. alone had no significant effect on MAP. The pressor effect of L-dopa was reversed by the decarboxylase inhibitors. Pronounced hypotensive response was observed in animals treated with L-HMD + L-dopa, while only slight hypotensive effect was produced by Ro 4-4602 and L-dopa. The difference in the hypotensive response in both groups of animals (groups 6 and 9) was significant statistically ($p < 0.05$).

In animals receiving L-dopa alone at either 25 or 50 mg/kg i.v., heart rate was slowed during the maximal hypertensive response. This can be attributed to reflex bradycardia. In animals receiving L-HMD and L-dopa, in spite of lowered arterial pressure, heart rate was consistently decreased to a greater extent than in control animals in spite of lowered arterial pressure. This may indicate a centrally-induced decrease in sympathetic tone.

Our results suggest that peripheral inhibition of dopa decarboxylase with L-HMD reverses the effects of L-dopa on the arterial pressure of the anesthetized dog. By diminishing dopamine formation in the peripheral organs, cerebral blood concentration of L-dopa was probably increased. We suggest that L-HMD also effectively removed the dopa-decarboxylase blood-brain barrier enabling L-dopa to enter the brain without loss where it was metabolized since L-HMD itself does not enter the brain. Ro 4-4602 probably also removed the enzymatic blood-brain barrier to L-dopa, but Ro 4-4602 may have entered the brain along with L-dopa, inhibiting its metabolism. After pretreatment of our dogs with Ro 4-4602, L-dopa had only slight hypotensive action. It is, therefore, reasonable to assume that a central action of a decarboxylation product of L-dopa is responsible for the observed hypotensive effect. In rats, HENNING and RUBENSON[10,11] found that FLA-63, a disulfiram derivative and an inhibitor of dopamine-β-hydroxylase[16] antagonized the hypotensive effect of DL-HMD and L-dopa combination, while spiroperidol, a dopamine receptor blocking agent, failed to block the hypotensive effect. According to recent findings of BUTUZOV[17], norepinephrine administered into lateral or fourth ventricle of cat brain activates reticulospinal inhibition involved in the control of sympathetic tone. These findings suggest that L-HMD + L-dopa-induced hypotension may be mediated by norepinephrine, which reduces sympathetic tone centrally.

Zusammenfassung. Nach Vorbehandlung mit L-HMD (peripherer Hemmer der Dopa-Dekarboxylase) wird mit L-Dopa (25 und 50 mg/kg i.v.) Blutdruck und Herzfrequenz herabgesetzt.

D. H. MINSKER, A. SCRIABINE, A. L. STOKES, C. A. STONE and M. L. TORCHIANA

Merck Institute for Therapeutic Research, West Point (Pennsylvania 19486, USA), 14 December 1970.

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A Hypothesized Unifying Mechanism in Neural Function[1]

Considering the amount of research being conducted on the nervous system of animals and man, a working hypothesis regarding a unifying mechanism in neural function is needed. If one will consider the results from experiments with various animal nervous systems and test models, there seems to be a reasonable scientific basis for such a hypothesis. I propose that, with or without associated reduction and/or oxidation respectively, ligand complexing with exposed disulfides and/or sulfhydryls in protomers of nerve membranes may be considered as one unifying mechanism in neural function.

The probable importance of complexing, oxidation-reduction and/or one-electron-transfer mechanisms in energy transformation in living systems has been emphasized by SZENT-GYÖRGYI[2], PULLMAN and PULLMAN[3], EDGAR[4] and GREEN and BAUM[5] among others. Complex formation and electron transfer were shown in one type of energy transduction in chemoreception by certain insects[6]. In this research[6], messenger quinones (ligands) complexed with and oxidized sulfhydryls at the receptor sites associated with the dendritic branches of the sensory neurons. Experimental results from other[7] studies of receptor chemical aspects of chemoreception by animals and man appear compatible with such sulfhydryl and disulfide involvement. The importance[8] of the –SH group and –S–S– bond in the basic function of the acetylcholine receptor lends essential support to the hypothesis. The widespread occurrence[2] of such groups and bonds in macromolecules which apparently influence conformational states of protomers in various other biological membranes also suggests a basic role for them.

A normal basic function in a nervous system involves the highly ordered transmission of energy through and between nerve cells; this being especially regulated by membranes and associated intra- and extra-cellular molecules and ions. This rigorously channeled energy must be rapidly and repeatedly converted from molecular to ionic form, and vice versa, such that a) energy transductions in receptor macromolecules occur; b) action potentials are generated in and conducted through neurons; c) synaptic transmissions result; and d) learning may occur and learned information is stored and can be retrieved. Experimental evidence that each of the above

actions entails the hypothesized unifying mechanism includes the following. Our findings[6] proved the fundamental involvement of the proposed mechanism at the energy-transduction interface between the nervous system and the external environment. This basic mechanism[6] involving two counteracting phases provides a molecular and/or ionic basis for information coding in the neuron and the nervous system, and also certainly encompasses the ordered transfer of the informational energy from site-specific ligands to protomer-conformational states to altered ionic flows and vice versa. The excellent work of KARLIN and BARTELS[9] indicated that disulfides and sulfhydryls are vital to the functioning of the acetylcholine receptor, the generation of the action potential and the intra-neural transmission of the impulse. This research[9] and other studies summarized and interpreted by NACHMANSOHN[8] also revealed the basic involvement of disulfides and thiols in the regulation of synaptic transmission. Finally, there is evidence that this hypothesized mechanism probably provides the essential framework for learning, and the storage and retrieval of information. The work of LENHOFF et al.[7], GALUN et al.[7], and/or HENKIN et al.[7] indicated that sensitivity to concentrations of specific ligands probably varies naturally within and among neurons; and can be altered predictably by administration of agents which specifically alter the state of –SH to –S–S–. KARLIN and BARTELS[9] also showed specifically that the sensitivity of the acetylcholine receptor to species and quantities of stimulant molecules could be predictably altered by changing the state of disulfides versus thiols at the receptor through the use of the thiol reagents and disulfide-reducing agents. Thus, one or more systems for change (i.e. learning) in neuron sensitivity to stimuli, based on shifts in the equilibrium between disulfides and sulfhydryls, are apparently involved naturally.

Is there a natural system in nerve membrane, or intimately associated, which would seem capable of aiding change in this equilibrium between disulfides and sulfhydryls at a receptor in response to a significantly altered stimulus, and of then buffering the altered state? Glutathione, which is an almost universal constituent of functioning biological systems[10] and is common in neurons, both catalyzes and buffers disulfide-thiol interchange reactions in cells[10]. Dehydroascorbic acid (DHA) is widely dispersed in tissues and functions as an antagonist to reduced glutathione (GSH)[4]. It thus oxidizes glutathione (GSH) to G–S–S–G and becomes reduced to ascorbic acid (AA). Such interaction between glutathione and DHA–AA apparently could constitute a natural system to regulate the state and binding functions[11] of given neural membranes. There are good experimental data which indicate that both glutathione[7] and DHA–AA[12] are fundamentally involved in altering the above functions[11]. Thus, learning in a neuron could be reduced to a shift in the interrelationship between the binding and state functions[11] in a neuronal macromolecule. Storage (retention) of learned information would necessitate the maintenance of an experienced shift in the interrelationship between binding and state functions. According to the hypothesis, this could be accomplished by a stabilization of the new threshold-potential equilibrium between –SH groups and disulfide bonds in the learned macromolecule. A stabilized redox buffer system involving glutathione and/or DHA–AA could provide for retention of the learned state. Some other ordered incorporation of lipids, polypeptides, proteins, and/or nucleic acids into the longer-term stabilization of a learned interrelationship between functions[11] in a neuronal membrane also is probable. Basic retrieval of learned information would necessitate that the nervous system or its environment present at the learned receptor of the neuron enough complexing energy, with or without disulfide reduction and/or sulfhydryl oxidation, to trigger the generation of the threshold potential of the nerve membrane.

This statement does not discuss hierarchies of neural function, such as levels of integration of neural impulses in the central nervous system. However, the author believes that clarification of the mechanisms of learning, and information storage and retrieval at the levels of the neuron or series of a few neurons will provide the basic insight to the more complex brain functions.

Enzymatic and non-enzymatic reactions have not been distinguished in this statement. This was not done because the author considers such differences, as vital as they obviously are in the continued functioning of the nervous system, as basically accessory to (auxiliary to) the hypothesized unifying mechanism in neural function.

Zusammenfassung. Es wird die Hypothese aufgestellt, wonach alle nervösen Prozesse auf Ligandenkomplexierung mit Rezeptordisulfiden und/oder Sulfhydrylprotomeren der Nervenmembranen beruhen und diese Prozesse mit Reduktions- bzw. Oxydationsprozessen gekoppelt sein könnten. Lernprozesse würden auf dem gleichen Mechanismus beruhen.

D. M. NORRIS[13]

Department of Entomology, University of Wisconsin, Madison (Wisconsin 53706, USA), 30 November 1970.

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[13] Temporary address: Visiting Scientist, Entomological Pioneering Research Laboratory, Department of Biology, University of Puerto Rico at Mayaguez, Mayaguez (P.R. 00708).