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A NEW MODEL FOR TRANSMITTER RELEASE AT THE PRESYNAPTIC MEMBRANE

David E. Downie

Common to the majority of mechanisms of transmitter release is the initial combination of calcium with a membrane component with subsequent transmitter release mediated by this calcium complex. In Katz and Miledi's work,¹ the calcium complex is positively charged. In the work of Gage and Quastel,² Hubbard et al.³ and Dodge and Rahaminoff,⁴ the component and complex are negatively charged. In a recent paper,⁵ Gage discusses and compares the two variations of the theory, the cationic complex vs. the anionic complex.

We propose here a new model to elucidate the role that divalent cations - in particular, calcium and magnesium - play in the release of transmitter, coupling the anionic complex concept with the recent work of Koshland and his coworkers on cooperative proteins.^{13,6} The latter work is important as the calcium complex is postulated to act in a cooperative mode in the process of transmitter release. The idea of calcium having a cooperative role in transmitter release is not new, having been investigated by several workers.^{3,4,7,8,9,10,11} The membrane component is considered to be negatively charged and is proposed to be a type of carrier molecule. For some workers the cooperative effect was assumed to arise from interaction of the calcium ion with the carrier molecule,^{3,8} while for others from interaction of the anionic complex (calcium ion plus carrier molecule) with some internal membrane site.^{4,9,10,11} In this

proposal we accept the latter viewpoint but suggest a more general model of cooperativity than previously used.

We assume an anionic carrier, restricted to the inside of the presynaptic membrane but capable of moving from the inside of the internal surface of the membrane to the inside of the external surface of the membrane, and back again. It is capable of combining at the external surface with one monovalent or one divalent cation. When combined with a cation, the complex is anionic and still has freedom of intramembranal movement. Upon arriving at the internal surface of the membrane, either the complexed or uncomplexed carrier is capable of combining with one of the subunits of a subunit receptor. To each and every receptor there corresponds a site of transmitter release. When the carrier (complexed or uncomplexed) combines with a receptor subunit, that subunit is activated. When all of the subunits of a receptor are activated the site of transmitter release is "primed". Contact of transmitter containing vesicles with the primed sites of the membrane would result in release of transmitter into the synaptic cleft, thereby attributing the random nature of spontaneous quantal release to the random collision of vesicles with the primed sites.

The special role that calcium plays in transmitter release would be explained by two factors. First, there is a rapid rate of transmitter release by receptors activated by the calcium complex. Second, only the calcium complex is capable of inducing cooperative effects in the subunit receptor.

In Figure 1 the above scheme is illustrated for three

possible receptor ligands: an uncomplexed carrier, a calcium complex, and a magnesium complex. The number of receptor subunits is chosen as four, as the structure most frequently found among receptors (enzymes) involves four similar subunits,¹² and most of the formalism developed to date has been for such receptors. Also, we have shown all three types of ligand acting at the same site of the receptor subunits. This is, of course, not necessarily the case, and the choosing of alternate schemes will change the transmitter release properties.

At the present, the mathematics for one type ligand interaction have been developed for various modes of cooperativity and for these modes the ligand saturation curves have been presented.¹³ For two type ligand interaction the formalism has been developed only for two modes of cooperativity: the allosteric model of Monod et al.,¹⁴ termed the concerted model by Koshland; and the square model of Kirtley and Koshland.⁶ It would be interesting and useful to extend the analysis for two type ligand interactions to the other models of Koshland and to consider such variations as two types of subunits in one receptor, more than two possible subunit states, etc. However, Kirtley and Koshland's treatment of two interacting ligands should be useful in explaining the experiments on transmitter release.

In particular, the two type ligand analysis applied to the model of Figure 1 can, by treating the uncomplexed carrier and the calcium complex as two activation ligands, explain the calcium-independent release mechanism.³ The anomalous magnesium dependence at low calcium concentrations³ can be explained by

Figure 1. In the "round" conformation, subunits have greater affinity for carrier complexes and thus a higher probability of activation.

choosing the magnesium complex and the calcium complex as competitive activators. The model should be able to explain the difference in the calcium mechanism for spontaneous and evoked release in the rat diaphragm, spontaneous release apparently needing the cooperativity of two calcium ions while evoked release requires three.^{3, 8} It is proposed that this difference arises because spontaneous release is measured at a lower concentration of calcium complex than is evoked release. Inspection of the equations of Kirtley and Koshland indicate that at lower concentrations of ligand for a four subunit receptor, the release may go as the k^{th} power of the ligand, where k can be 1, 2, or possibly 3. As the ligand concentration is increased, as would occur during evoked release, k would become closer to 3 and may go as high as 4. Another phenomenon for which this model offers a ready explanation is the great propensity of the action potential to release transmitter. This can be attributed to a combination of two non-linearities: the ability of a large depolarization to mobilize the anionic complex at the inner membrane, to an extent out of proportion to the size of the depolarization; and the cooperative non-linearity of the action of the calcium complex at the receptor. The importance of the latter is underscored by the fact that the magnesium complex, postulated to have little or no cooperative action, is a poor initiator of transmitter release, even under an action potential, while the calcium complex, having a good deal of cooperative action, is an excellent initiator of transmitter release. Finally, this model can be seen to be consistent with

present explanations of the time course of facilitation.^{7,9}

It is proposed to further investigate this model, to fit it to existing data, and to suggest and perform experiments aimed at further defining the mechanism of transmitter release.

Concluding Remarks

We have in this proposal discussed these projects, each aimed at further elucidating the mechanism of action of the synapse. Two of these, the question of the validity of the Poisson distribution approximating the process of transmitter release during an action potential, and the development of a new model of transmitter release, are concerned with the structure and function of the presynaptic membrane. The other project deals with the general question of synaptic membrane cooperativity and results would be of interest in the study of both presynaptic and postsynaptic membranes. A successful treatment of all three of these areas is necessary for the understanding of the synaptic junction and its temporal and spatial characteristics. Only when a self-consistent and complete biophysical model of the synaptic junction has been developed, can we confidently approach the problem of the analysis of more complex nerve networks.

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