STUDIES OF TWO NOVEL PRESYNAPTIC TOXINS

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INTRODUCTION

The use of toxins has been widespread in examining a number of biological phenomena. Every undergraduate in an introductory course in biochemistry is aware of the toxins which inhibit the electron transport system and oxidative phosphorylation, and appreciates the value of these molecules in the understanding of complex biological processes. Our laboratory has long agreed with others in our field that toxins would be useful - in fact, would probably be essential - in unravelling the molecular mechanisms which control release of neurotransmitters at synaptic terminals. We have limited our work to toxins which are active at the presynaptic terminal, for we wish to consider only the relese of neurotransmitter. We have further restricted our attention to toxins which stimulate

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I. Hanin (ed.), *Dynamics of Cholinergic Function*

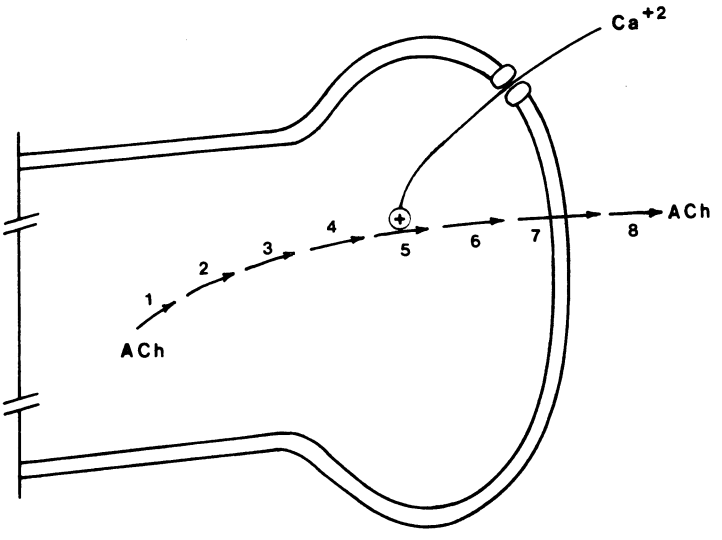

Figure 1. Simplified scheme for the reactions involved in the release of acetylcholine (ACh) at a nerve terminal. ACh is indicated moving from an initial internal state through a series of transitions which finally cross the membrane (Step 7) and lead to ACh in the cleft, free of association with presynaptic elements. Each step refers to a change in state of the ACh, but does not imply a change in the covalent bond structure of the neurotransmitter. Synaptic vesicles are involved in some of the defined states, but we do not now know which ones. For the sake of description, eight reactions are considered, of which six are internal and one external to the membrane. The actual number of steps is unknown.

release, and have avoided working with those which inhibit release. It is worthwhile to examine the logic behind this decision. In Fig. 1 is presented a sketch of the biochemical steps involved in a mechanism of release of the neurotransmitter, acetylcholine (ACh).

In this model the numbered steps indicate any change in the chemical state of a molecule of ACh. A change in state could involve a movement from one intracellular site to another, such as being introduced into or expelled from a vesicle. It could also involve simply a change in binding, as a transfer of ACh from one protein to another, or from a bound to an unbound state. The model presented here is greatly simplified, but not to the point of being unrealistic. Almost any mechanism of release can be reduced to a description similar to that of Fig. 1.

The choice of which of several toxins to study can be clarified to some extent by considering the logic associated with Fig. 1. It is clear that a toxin which blocks any of the steps of Fig. 1