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BISTABILITY OF THE NERVE MEMBRANE: MECHANICAL AND THERMAL CHANGES IN NERVE FIBERS DURING EXCITATION

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ABSTRACT

In view of the great advancement in recent studies of bistability, oscillating reactions and traveling waves in chemical systems, a renewed interest is aroused in explaining the process of excitation of nerve fibers on the basis of bistability of the nerve membrane. The results of recent measurements of rapid mechanical and thermal changes in nerve fibers during excitation are in consonance with this explanation.

Since the early 1970's, there has been a rapid rise in interest of chemists in studies of bistability, oscillating reactions and traveling waves in homogeneous chemical systems (see chap. 7, 10 and 13 in ref. 1). The lack of interest in the past in oscillating chemical reactions resulted, at least partly, from the lack of a sound theoretical basis for studying such reactions. The advent of thermodynamics of non-equilibrium states (2) kindled the enthusiasm of the chemists working in this field. Although the structure of a nerve fiber is quite complex, there is a close analogy between these phenomena taking place in inanimate chemical systems and what are observed in nerve fibers.

In the field of neurophysiology, a study of bistabilty of the nerve membrane was commenced by the late Prof. Susumu Hagiwara and myself in 1957 (3). Using squid giant axons treated internally with tetraethylammonium ions, it was demonstrated that in the nerve membrane there are two stable states separated by one unstable state, and that the process of excitation can be explained as representing a transition from one stable state to the other (see Fig. 1A). Although this finding was largely ignored by physiologists,

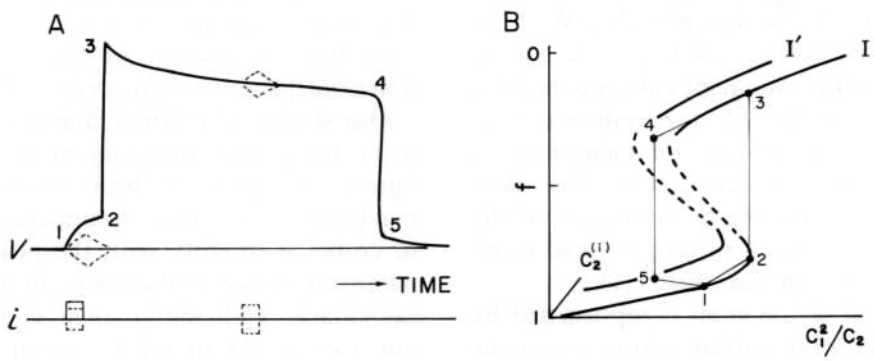

Fig. 1 A: Demonstration of two stable states in the internally perfused giant axon. Note that the perturbations of the membrane potential, V, by application of weak pulses of transmembrane current (i) die away shortly after the end of the pulses, indicating the two potential levels are stable. B: Schematic representation of the process of action potential production. The numerals in this diagram correspond to those in Diagram A. See the text for the details.

sustained efforts have been made in this laboratory to elucidate the physicochemical basis of the bistability of the nerve membrane. We have proceeded from the following premises:

1) The membrane potential observed in axons represents an E.M.F. and is determined by the mobilities and selectivities of the ions in the nerve membrane.

2) An increase of the water-content of the membrane profoundly enhances the ion mobilities. Exchange of monovalent cations for divalent cations in the membrane brings about a rise in ion-mobilities by increasing the water content.

3) The process of action potential production is a 'cooperative' phenomenon. The pathways of ions in the membrane (ion-channels) do not behave independently of one another.

Fig. 1B diagramatically illustrates the process of action potential production on the basis of bistability of the nerve membrane. Here, we are dealing with an axon internally perfused with a salt of monovalent cation (*e.g.* Na^+) and immersed in a medium containing both monovalent and divalent cations (Na^+ and Ca^{2+}). The abscissa of this diagram represents the ratio of the square of monovalent cation concentration, C_1, to the divalent cation concentration in the medium, C_2. The ordinate repesents the fraction, f, of the negatively charged membrane sites cross-linked by divalent cations. The heavy line marked 'I' is an S-shaped theoretical cation-exchange isotherm (4), representing the existence of two stable states (represented by the solid portions of the line) and one unstable state (the broken portion). We have made an additional assumption that there is slow rise in the intracellular divalent cation concentra tion near the inner surface of the membrane, $C_2^{(i)}$, during the period in which the membrane is staying in its highly conductive state. This slow rise brings about a gradual displacement of the isotherm, creating a folded surface referred to by chemists as 'folded slow manifold' (1).

The resting state of the axon is represented by point '1'. A stimulating current pulse lowers the value of f and pushes the state of the axon to '2' by driving monovalent cations into the membrane. The ensuing transition from '2' to '3' is fast. Then, due to interdiffusion of the cations across the membrane, a slow drift of the state from '3' to '4' takes place. The transition from '4' to '5' is fast. The final drift from '5' to '1' brings the axon to the original state. Many aspects of the behavior of internally perfused as well as unperfused axons can be explained on the basis of bistability of the nerve membrane.

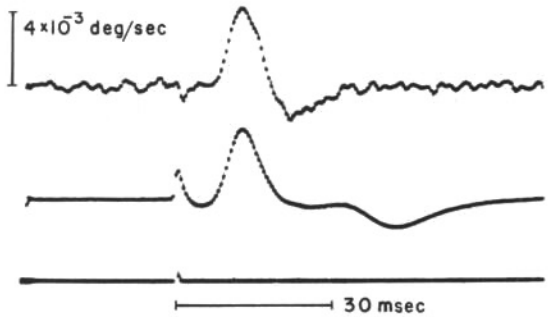

Fig. 2 Top trace: An example of thermal responses of the garfish olfactory nerve. Bottom trace: Action potential recorded from the site of thermal recording. (Tasaki *et al.*, 1989)

In recent years, we have directed our research effort toward detection of rapid mechanical and thermal changes during excitation in various nerve fibers. Using both squid giant axons (5) and garfish olfactory nerves (6), we found that there is, during excitation, a readily detectable radial expansion (*i.e.* swelling). The peak of this swelling coincides fairly accurately with the maximum of the membrane conductance. Furthermore, this swelling is associated with a decrease in the density of the macromolecular structure of the fiber (7), suggesting that the electrostatic repulsion between the charged sites in the membrane is enhanced during excitation. We believe that these findings are quite consistent with the explanation of the process of action potential production described above.

Our studies of thermal changes were performed using the garfish olfactory nerve (Fig. 2). In the figure, the peak of heat production (*i.e.* the maximum of the rate of temperature rise) is seen to coincide roughly with the peak of the action potential. Since replacement of Ca-ions in ion-exchangers with monovalent cations is exothermic (see p. 248 in ref. 4), we attribute the heat production also to the cation-exchange process in the membrane.

The process of action potential production is obviously reversible. Hence, the exothermic process that takes place during the action potential is expected to be followed by an endothermic process. In fact, we found that about 75% of the heat

generated is absorbed by the nerve fibers near and after the end of the action potential.

In conclusion, bistability is the property that plays a crucial role in the process of action potential production. A further investigation of this property is expected to lead us to a better understanding of the mechanism of nerve excitation.

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