TRANSMISSION AT THE MOTOR ENDPLATE AND GANGLIONIC SYNAPSE

W. L. M. PERRY

National Institute for Medical Research, Mill Hill, London, England

Dr. Zaimis and Dr. Paton have been dealing with the analysis of block produced at the neuromuscular junction and at the ganglionic synapse. It has seemed to me for some time that these elegant and refined techniques for classifying the modes of action of the blocking drugs, while serving well—as has been clearly shown by both previous speakers—for the further analysis of the physiology of transmission processes, have also led us into a degree of confusion about the nature of the cell membranes themselves. For all these membranes do share in being specifically reactive to acetylcholine.

From Dr. Zaimis' work, it is now apparent that not only are there differences between species in the response of the muscle membrane to a particular drug, but also that even within one species, the membranes of different muscles display different characteristics; and Dr. Zaimis put the question "what are these differences?"

I had intended, at this stage, to put forward the view that the differences represented not so much variations in the intrinsic structure of these membranes as variations in the "environmental state" of the membrane; but Dr. Loewi and Dr. Bülbring have both forestalled me and have put the case much more clearly than I could hope to do.

Some of the factors which might affect the environmental state of a membrane are: (a) the ionic equilibrium across it; (b) the internal pH of the cell; and (c) the content of myoglobin in the cell, i.e. red or white muscle.

These factors might vary independently of the intrinsic structure of the membrane—and by this term I mean to include the state of the various receptors thereon. Thus, it is possible that a drug might affect the intrinsic structure in one way when the environmental state was normal; but in a totally different way when the environmental state was abnormal.

I would like to illustrate the way in which one factor—namely, the potassium ion concentration—may, by altering the environmental state, also affect the responses of ganglion cells. All the experiments which I quote have been carried out in collaboration with my colleague, Dr. H. Reinert. In the first place, it was shown by Konzett and Rothlin (1) that ouabain potentiated the action of acetylcholine injected into the perfused superior cervical ganglion. This potentiating effect of ouabain is completely absent when the perfusion fluid contains no potassium. In the second place, in the ganglion perfused with Locke's solution, hexamethonium acts by preventing the stimulating effect of acetylcholine. When, however, the ganglion is perfused with Locke's solution containing no potassium, the effect of hexamethonium is altered and the drug now has a stimulating action of its own.

Dr. Reinert and I have also been interested in the changes in the response of the

ganglion cells after preganglionic denervation, and we have found that two compounds, hexamethonium and decamethonium, formerly shown by Paton and myself (2) to act by competition with acetylcholine, seem themselves to be causing stimulation of the denervated ganglion cells. The case of decamethonium interested me particularly since it had always troubled me that this drug should act on normal muscle by depolarization and on normal ganglion by competition, while, at both sites, acetylcholine acted in precisely the same way, namely, by depolarization.

Thus, both reduction of the external potassium concentration and preganglionic denervation can produce changes in the responses of the ganglion cell membranes to drugs. I can offer no explanation of how this is brought about, but I would like to take Dr. Loewi's advice and speculate.

It has often been suggested that the "trophic" effect of the presynaptic fibres depended upon release of the transmitter or on the presence of the normal amount of cholinesterase. I would like to postulate two other possibilities, both subject to experimental check, but not yet—as far as I know—checked:—(a) that the internal potassium concentration of the postsynaptic cells is increased by denervation. This, I believe, is not true of muscle cells where the resting potential of the cell is not increased by denervation, as would be expected with a rise of the internal potassium concentration; (b) that the continuous release of choline from an unstimulated ganglion (3), may play a part in maintaining a trophic effect. I do not know how much choline appears in the effluent of a perfused denervated ganglion, but I suspect that it might be much less than that in the normal ganglion. It is, in any case, feasible that the choline ion may play a part in maintaining a "trophic" state, which determines the normal reaction of the ganglion cell membrane.

I would summarize therefore, by saying that I believe that the mode of action of the ganglionic blocking drugs—and perhaps also of the neuromuscular blocking drugs—may depend more upon the environmental state of the membrane than upon any major difference between the intrinsic structure of the membranes at the different sites; and that structure-action relationships may depend not wholly upon the classical "lock-and-key" receptor fit, but upon the degree to which they can influence the state of the membrane and consequently its response to the normal transmitter.

REFERENCES

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