GANGLIONIC AND CENTRAL TRANSMISSION

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Concerning the papers by Drs. Zaimis and Paton, I would like to touch briefly on three points. First, we have some data to contribute to the question of whether acetylcholine influences nerve conduction. For many years we have taken advantage of the situation found in certain autonomic ganglia to compare simultaneously nerve conduction and synaptic transmission. In the inferior mesenteric sympathetic ganglion and also in the ciliary parasympathetic ganglion some fibers run right through the ganglia to synapse at some point distal to the ganglion. The fibers that synapse in the ganglia and those that run right through, receiving the same blood supply, are distinguished from each other by their distinctive postganglionic action potentials. In both the inferior mesenteric ganglia and in the ciliary ganglia acetylcholine enhances synaptic transmission initiated by submaximal preganglionic stimulation but has no effect on the simultaneously recorded conduction in the through and through fibers. Anticholinesterases, either eserine or diisopropylfluorophosphate (DFP), have the same effect. When they are introduced by close arterial injection, so as to achieve a large concentration at the ganglion, transmission is blocked while conduction remains unaffected. Thus, sublethal doses given systemically to an animal do not affect conduction; therefore it is of very little significance for its function *in situ* that immersing a nerve in a solution of anticholinesterase *in vitro* can block conduction.

Second, I should like to vote with Professor Feldberg in favor of submaximal stimulation. In designing experiments there are two pertinent points of view: (1) the convenience of the experimenter and (2) the relevancy of the data. Since synchronized maximal volleys would rarely occur naturally, the data from submaximal volleys are certainly relevant. In fact, we have even found submaximal volleys more convenient in demonstrating either enhancement or depression and have used them in all our work.

The third point has particular reference to Dr. Shaw's communication. Professor von Euler told us of finding adrenaline and noradrenaline in sympathetic ganglia. By staining and by the fluorometric method we have also found catechol amines in the superior cervical sympathetic and in the parasympathetic ciliary ganglia and have shown the origin to be presynaptic, since most of the substance disappeared on preganglionic section with subsequent degeneration.

In Montreal we reviewed some of the evidence that adrenaline and noradrenaline have a primary inhibitory action on transmission in all types of sympathetic ganglia, in the homologous adrenal medulla and in the ciliary parasympathetic ganglion. We also indicated the natural presence of adrenaline and noradrenaline since substances like amphetamine and ephedrine, which may have a preservative action on these amines, also inhibit transmission in autonomic ganglia.

We therefore want to suggest that among the synaptic transmitter substances there is not only a humoral excitor that is acetylcholine-like but also a humoral inhibitor that is adrenaline-like along perhaps with other possible agents including ions or along with direct electrical transmission.

Professor Feldberg has introduced into this meeting the commendable practice of defining one's bias—sometimes dignified as hypothesis. Our own bias has been the expectation that our findings in autonomic ganglia might also be true in the central nervous system. As has already been mentioned, the ganglia are monosynaptic pathways. In order to duplicate this situation in the central nervous system we have been utilizing the pathway connecting the two optic cortices of the cat. This is essentially a monosynaptic pathway. At any rate we are able to record the electrical events at the terminal synapse so that on stimulating one cortex the electrical record of the contralateral cortex records the input and the output from the final synapse. When the input stays constant and the output varies, we regard this as evidence of synaptic action and it is only this type of data that we regard as significant. Using submaximal stimuli we find that on the one hand acetylcholine enhances the evoked response which atropine and also curare block. On the other hand adrenaline and noradrenaline inhibit. Furthermore, preservatives and preservative-like substances are effective in each instance, i.e., anticholinesterases have an acetylcholine-like action and amphetamine and ephedrine an adrenaline-like action, thus suggesting the natural presence of acetylcholine and adrenaline or noradrenaline-like substances.

The simplest explanation of these data is that at these synapses, which incidentally are on the afferent side, there is a "cholinoceptive" excitatory and an "adrenoceptive" inhibitory mechanism.

Finally, I would like to express a pure speculation in the form of a question. It has been emphasized that in ganglia the cholinesterase is to be found at the endings of the preganglionic nerves, so that on section of the preganglionic nerves and subsequent degeneration the major part of the true cholinesterase disappears, while in skeletal muscle the cholinesterase is concentrated in the endplate region and does not disappear on section of the motor nerves. Furthermore, if the postganglionic nerve is cholinergic, cholinesterase is concentrated in its endings. If we extend Langley's analogy of the ganglion to the endplate region of skeletal muscle, could we not regard the endplate as a condensed ganglion and postganglionic nerve? If so, the cholinesterase of the endplate region would be analogous to that at the endings of postganglionic nerves and would not be expected to disappear on preganglionic section.