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Relation of Drug Action to a Cholinergic Mechanism at Sympathetic Synapses.

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Current pharmacological concepts embrace the possibility that drugs acting at junctions, where acetylcholine plays an important though perhaps not essential rôle in transmission, do so by exerting their influence on some step in the cholinergic mechanism.

The consistency of such a view was examined by studying the effects on a sympathetic ganglion of drugs known to act at the parasympathetic neuro-effector junctions, since both are sites where cholinergic systems operate. Pertinent observations may be found in papers by Langley,[1] by Dale and Laidlaw,[2] etc.

Action potentials of the tonic impulses normally coursing in the superior cervical preganglionic trunk of the rabbit (anesthetized with nembutal) and of the response in the postganglionic fibers were recorded by a Matthews oscillograph after amplification. The waves were also spread out for visual observation by a rotating mirror (speed corresponding to 1.8 meters per second) and converted into sound by a loud speaker.

Pilocarpine, representing the parasympathomimetic stimulants, and atropine, the depressants, were injected into the common carotid artery, all branches except to the ganglion having been ligated and cut and the carotid sinus nerve severed. Thus the ganglionic circulation was retained intact while allowing an effective concentration at the synapse before diffusion into the general circulation. This made possible the observation of local effects uncomplicated by distant actions such as on the central nervous system directly, or indirectly through the remaining innervated carotid sinus responding to vascular changes.

The increase in postganglionic impulses (compare records A and B, C and D) illustrates the stimulant effect of small doses of pilocarpine. This increase, seen again in E, F, took place without any change in the corresponding preganglionic records G and H, and consequently must have been due to a truly peripheral action at the synapse. A larger dose has a paralytic effect.

Atropine caused a reduction in postganglionic response, records

1 Langley, J. N., *J. Physiol.*, 1878, **1**, 339.

2 Dale, H. H., and Laidlaw, P. P., *J. Physiol.*, 1912, **45**, 1.

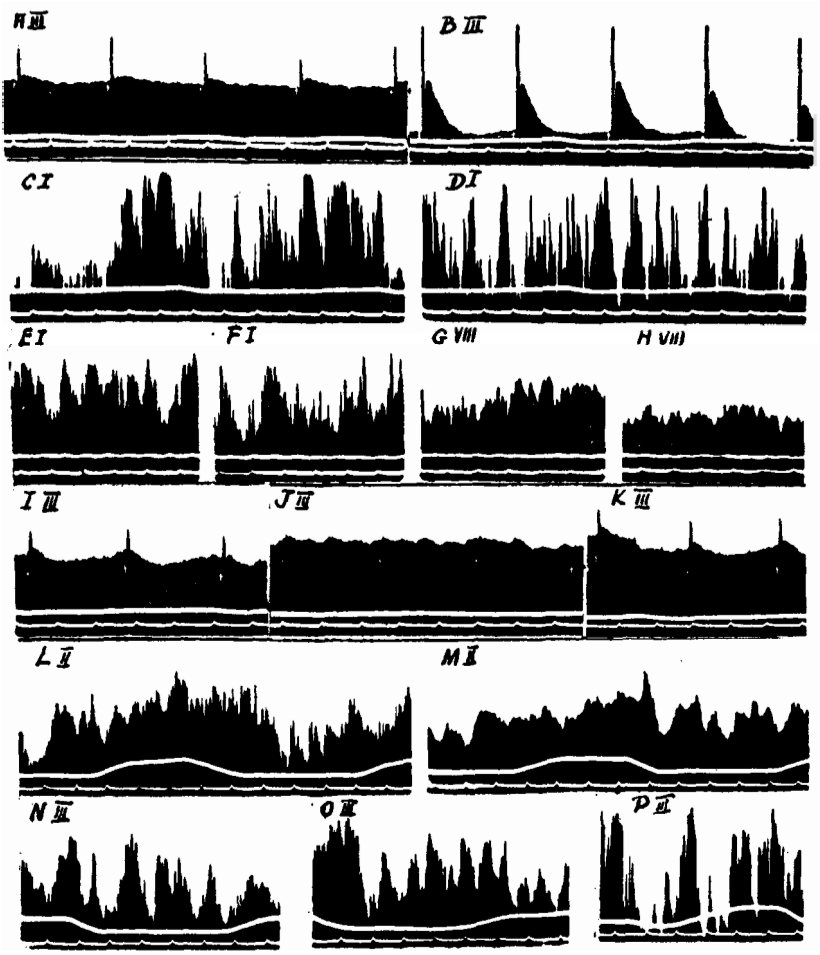

FIG. 1.

Postganglionic Potentials (except Preganglionic G, H).
Time in 1/5 sec. **Inspiration = up, ↑ = submaximal fixed shocks 2/sec.**
Sensitivity mm./10 uV. I = 3, II, = 4, III = 6, VIII = 20, before reduction.
Between A and B 2 mg./kg. (intraven.) Pilocarpine Nitrate.
" C and D, between E. G and F, H. 0.2 cc. 0.05% Pilocarpine Nitrate.
" **I and J 2 mg./kg. (intrav.) Atropine Sulphate.**
" **L and M 0.2 cc. 1% Atropine Sulphate.**
" **N and O 0.2 cc. 1% Sol. Atropine : Pilocarpine = 1:10.**
O to P, Pilocarpine action unmasked by Atropine destruction.

The specificity of the actions of pilocarpine and atropine is testified to by the fact that simultaneous injection of atropine and pilocarpine in the typical ratio of 1 to 10 resulted in an expected mutual

antagonism as described by Cushny[3] for the specific action of these 2 drugs on the salivary gland. Therefore, there is no change in impulses (N, O). Within 5 minutes the atropine is destroyed and the remaining pilocarpine causes an increase in impulses (O, P), which is cut down again by another dose of atropine.

To secure more readily interpretable and quantitative results a fixed stimulus, submaximal impulses (2 per second) from a thyraton stimulator, was used to activate the preganglionic trunk sectioned centrally. Stimulation was continuous from beginning to end of experiment. The rate was slow enough not to result unaided in facilitation at the ganglion, *i. e.*, before exhibiting drugs. Central effects being excluded by the section, the carotid branches were not disturbed and the drugs were injected intravenously. With this technique results identical with the above were more simply and strikingly brought out. Records A, B and I, J, K are examples illustrating the ganglionic effect of pilocarpine and of atropine.

It is concluded that so-called parasympathomimetic drugs act also on sympathetic synapses, responding to spontaneous or test stimuli, and might better be described as cholinotropic.

Cholinotropic is used in a descriptive sense to indicate that the action is exerted on cholinergic systems, but not necessarily through direct action with acetylcholine.

It is suggested that the relation between the action of certain drugs and the cholinergic mechanism at sympathetic synapses is significant and consistent with the view that drugs able to modify the cholinergic neuro-humoral process at this site may, amending predictions based on anatomical classifications, do so at all such sites with quantitative rather than qualitative differences. It is not, however, assumed that drugs may not also act at these sites independently of the neuro-humoral process.

[3] Cushny, A. R., *J. Physiol.*, 1903, **30**, 176.