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Nature of the Pilomotor Response to Acetylcholine.

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Pilomotor reactions to choline esters[1-4] have been somewhat puzzling in view of the accepted concept of a single sympathetic innervation to the pilomotor muscles.

When 0.1 cc of acetylcholine in dilutions between $1:10^4$ and $1:10^5$ is given intracutaneously in man a goose flesh appears immediately in the area surrounding the puncture and subsides in about 2 minutes. The picture simulates closely that of the physiological pilomotor reaction and differs markedly from the goose flesh produced by intradermal epinephrine injection in concentrations of 1:1000 to 1:100,000, which produce a long lasting goose flesh confined to the vasoconstricted area.

A pilomotor response to intradermal injection of acetylcholine can also be seen in the cat's tail. Furthermore, injection of acetylcholine into the sacrocaudal artery produces a general pilo-erection on the tail. This response is not modified by heavy atropinization or eserinization of the cat. In man, however, physostigmine increases slightly the extent and doubles the duration of response if mixed in a concentration of 1:400,000 to 1:1,200,000 with effective intradermal doses of acetylcholine.

The optimum concentration of acetylcholine (1:40,000) elicits pilo-erection repeatedly if inserted at the same point in the human skin or cat's tail. But if preceded by an injection of acetylcholine 1:5000 or stronger, subsequent doses at the optimum level are ineffective.[4]

The resistance of the response to atropine, the slight augmentation by eserine, and the paralyzing effect of high concentrations all pointed to the nicotine-like action of acetylcholine as being responsible for the pilomotor activity described. Choline, weak in nicotine-like action gives questionable responses. Mecholyl, until recently[5]

1 Kovacs, J., *Am. J. Med. Sci.*, 1934, **188**, 32.

2 Hopkins, J. G., Kesten, B. M., and Hazel, O. G., *Arch. Dermatol. and Syphilol.*, 1938, **38**, 679.

3 Battro, A., and Lanari, A., abstracted by *J. A. M. A.*, 1936, **107**, 890.

4 Brücke, F. T., *Klin. Wochenschr.*, 1935, **14**, 7.

5 Fellows, J., and Livingston, A. E., *J. Pharm. and Exp. Therap.*, 1939, **66**, 13.

thought to be devoid of any nicotine-like action, has a weak effect. Nicotine and alpha-lobeline both produce reactions identical with that by acetylcholine in optimum concentrations of $1:10^5$ and $1:10^6$ respectively.

The rapidly spreading and fleeting nature of the response suggested a mediation through a peripheral nervous mechanism. If the caudal nerves in a cat are cut the characteristic response may still be elicited. But if the nerves are allowed to degenerate local application of nicotine or acetylcholine fails to raise the hairs, though epinephrine is still effective since its action is directly on the muscles. If a piece of skin one centimeter square with its hair is excised from the dorsal surface of the tail and nicotine immediately injected a pilomotor reaction can be observed. This capacity disappears within 2 minutes after excision, though the response to epinephrine can be obtained after 15 minutes. Similarly, if 2 neighboring hair tufts are so close together that both erect when nicotine is injected under one of them, a cut just through the skin between them is sufficient to inhibit the erection of one when the injection is made under the other. If the lateral antibrachial cutaneous nerve in man is blocked by novocaine so that spontaneous physiological goose flesh does not appear in the area supplied by that nerve, nicotine and acetylcholine will still cause the typical pilomotion in the anesthetized area. It can, therefore, be concluded that the pilomotor phenomenon caused by these drugs depends on the integrity of an axon reflex pathway situated wholly within the skin.[6]

In the human skin subcutaneous infiltration of novocaine in dilutions up to 1:50,000, which produce no manifest reduction in cutaneous sensations, inhibits, in the area so treated, both the physiological goose flesh and that ordinarily caused by acetylcholine or nicotine. Mixtures of optimum concentrations of nicotine or acetylcholine with novocaine 1:200,000, apothesin 1:100,000, or cocaine 1:200,000 do not elicit any pilar erection.

It is evident that the nerve fibers carrying to the erector pili muscles impulses initiated by local application of acetylcholine and nicotine are adrenergic since: (1) a local anemia accompanies the goose flesh; (2) ergotamine inhibits the pilomotor response to acetylcholine and to lumbar sympathetic stimulation in the cat; (3) the behavior and appearance of the acetylcholine goose flesh is strikingly similar to that of the physiological phenomenon and to that of sympathetic stimulation, in which liberation of sympathin

[6] A similar mechanism of a pilomotor response to faradic stimulation has been described by Lewis and Marvin, *J. Physiol.*, 1927, **64**, 87.

has been shown;[7] and (4) epinephrine in a concentration of $1:10^9$ injected intradermally in the cat's tail will produce a fleeting piloerection similar to that produced by nicotine, acetylcholine, lumbar sympathetic stimulation or physiological goose flesh stimuli.

Summary. Experiments are cited which indicate that the local pilomotor action following intradermal acetylcholine occurs by virtue of its nicotine-like action, and that this drug as well as nicotine and other drugs possessing nicotine-like action exert this influence through an axon reflex the receptor end of which has several properties characteristic of autonomic ganglia and the effector end of which is evidently adrenergic.

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Nature of a Sweat Response to Drugs with Nicotine-like Action.

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In a preliminary report on the nature of a local pilomotor response to acetylcholine injected intradermally[1] experiments have been cited which indicate that this pilomotor response occurs by virtue of the nicotine-like action of acetylcholine. The same effect can be obtained by nicotine and by alpha-lobeline. Drugs with nicotine-like effect act through an axon reflex in terminal branches of postganglionic sympathetic axons. The receptor end of the axon reflex behaves like an autonomic ganglion, whereas the motor end is evidently adrenergic.

An analogous phenomenon can be shown in the domain of cholinergic nerve endings. If 0.1 cc nicotine 1:100,000, alpha-lobeline 1:1,000,000, or acetylcholine 1:40,000 is injected intradermally in man, drops of sweat appear around the injection wheal in an area about 4 cm in diameter. The sweat secretion can be visualized easily by Minor's iodine-starch method.[2] At high room temperature and humidity and in persons sweating easily the sweat drops can be seen without an indicator.

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[7] Rosenblueth, A., and Cannon, W. B., *Am. J. Physiol.*, 1932, **99**, 398.

[1] Coon, J. M., and Rothman, S., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 229.

[2] Minor, V., *Deutsche Z. f. Nervenheilk.*, 1927, **101**, 302.