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Further Studies on Action of Physostigmine on Autonomic Ganglia.

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A number of authors[1-6] have described the vasopressor effect of large doses of normally vasodilator choline derivatives in atropinized animals, including the "parasympathetic substance" acetylcholine. The findings of Hunt[7] and Broun and Beaune[8] on these subjects will be discussed in a detailed paper.

All drugs used in these experiments were given intravenously and the doses expressed in milligrams per kg. In 6 cats, 4 rabbits and 10 dogs anesthetized with barbiturates, it was found that acetylcholine in doses of 0.05 to 0.1 mg. did not produce vasopressor effects following the administration of 2 to 5 mg. of atropine sulphate. If the administration of acetylcholine was preceded by 0.3 to 2 mg. of physostigmine salicylate in atropinized animals, acetylcholine produced sharp, epinephrine-like rises in the blood pressure of 50 to 100 mm. of Hg. in cats and dogs, and lesser rises in rabbits. These pressor effects with acetylcholine may be elicited many times over a period of 6 hours in atropinized animals following a single dose of 0.5 to 1.0 mg. of physostigmine salicylate.

This action of physostigmine on the responses of small doses of acetylcholine in atropinized animals may be ascribed to a ganglionic action of this drug in facilitating the cholinergic effect of acetylcholine through the sympathetic synapses.

The injection of 3 mg. of cocaine hydrochloride enhanced the vasopressor effects of acetylcholine under the above conditions, but could not elicit vasopressor responses from small doses of acetylcholine in a physostigmine-like manner.

The injections of 0.1 to 1.0 mg. of pilocarpine produced vasodilator effects which were completely antagonized by atropine. Fol-

1 Schmiedeberg, O., and Koppe, R., *Das Muscarin*, Leipsic, 1869.
2 Jordan, S. N., *Arch. Exp. Path. and Pharm.*, 1878, **8**, 25.
3 Boehm, R., *Arch. Exp. Path. and Pharm.*, 1885, **19**, 99.
4 Mott, F. W., and Halliburton, W. D., *Proc. Roy. Soc.*, 1899, **141**, 211.
5 Hunt, R., and Taveau, R., *U. S. Hyg. Lab. Bull.*, 1911, **73**, 17.
6 Dale, H. H., *J. Pharm. and Exp. Therap.*, 1914, **6**, 147.
7 Hunt, R., *Am. J. Physiol.*, 1918, **45**, 231.
8 Broun, D., and Beaune, A., *C. R. Soc. Biol.*, 1936, **121**, 1589.

lowing atropinization, pilocarpine even in doses of 10 to 50 mg. produced no typical effects in the presence of physostigmine. Pilocarpine, unlike physostigmine, did not elicit pressor effects from small doses of acetylcholine in atropinized animals.

The mechanism of pilocarpine action is fundamentally different from that of physostigmine.

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Further Studies on Physostigmine-Nicotine Antagonism.

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It has been reported by several authors[1-4] that large doses of nicotine (30 to 60 mg. per kg.) prevented the pressor effects of acetylcholine (1 to 5 mg. per kg.) in atropinized animals.

The drugs used in these experiments were all given intravenously and the doses expressed in milligrams per kg. In 6 dogs and 6 cats anesthetized with barbiturates and treated with 2 mg. atropine sulphate and 1 mg. of physostigmine salicylate, pressor effects were elicited in every case following the injection of 0.05 to 0.1 mg. of acetylcholine. The administration of paralytic doses of nicotine salicylate (3 to 6 mg.) in addition to the above drugs changed the effects of acetylcholine injections to uniformly vasodilator responses. Nicotine thus caused a reversal of the hemodynamic action of acetylcholine under the above conditions. In 5 cats and 5 dogs, it was further found that paralytic doses of nicotine are not necessary to obtain this reversal. Doses of nicotine from 0.25 to 2 mg. always diminished and often reversed the hemodynamic effect of acetylcholine. Further doses of physostigmine salicylate again reversed the acetylcholine vasodepressor effects into pressor responses. The administration of nicotine again changed these pressor responses of acetylcholine into depressor effects. This mutual antagonism between physostigmine and nicotine in reversing the acetylcholine blood pressure effects can be demonstrated several times in the same animal.

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1 Dale, H. H., *J. Pharm. and Exp. Therap.*, 1914, **6**, 147.

2 Hunt, R., *Am. J. Physiol.*, 1918, **45**, 231.

3 Fuehner, H., *Biochem. Z.*, 1916, **76**, 232.

4 Feldberg, W., and Minz, B., *Arch. Exp. Path. and Pharm.*, 1931, **163**, 66.