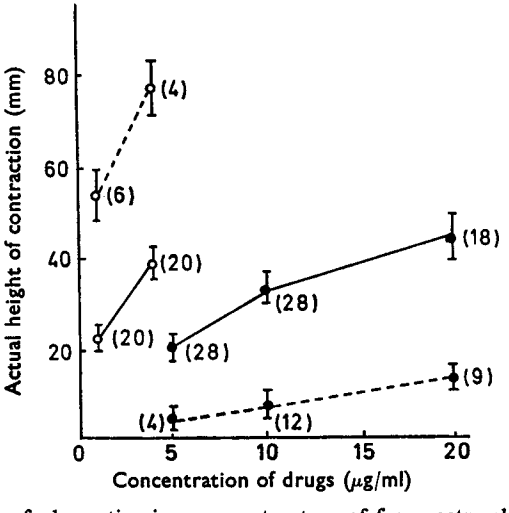
Modification by physostigmine of response to ganglion stimulant drugs

SIR,—Recently it has been shown that pharmacological actions of physostigmine cannot be explained wholly by its cholinesterase inhibition (Holmstedt, 1965). During a study of the pharmacological effects of 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343) and *N*-benzyl-3-pyrrolidyl acetate methobromide (AHR-602), which are known sympathetic ganglion stimulants (Jones, 1963), it was found that physostigmine inhibited the responses to McN-A-343 in the frog rectus abdominis isolated muscle, and that physostigmine reversed an inhibitory response of the isolated atria of the tortoise to both drugs (Kim & Shin, 1965).

As already shown by Roszkowski (1961), the frog rectus skeletal muscle was contracted by McN-A-343 (5–20 μg/ml), an action not antagonized by atropine. In the presence of physostigmine sulphate (100 μg/ml) in the bath, the contraction to McN-A-343 was much inhibited, whereas the acetylcholine contraction was potentiated (Fig. 1).

The isolated atria of the tortoise responded with a gradual depression of spontaneous movements to 100–200 μg/ml of McN-A-343 and to AHR-602. After exposing the atria to physostigmine (1 μg/ml) for more than 15 min, the response to McN-A-343 and AHR-602 was changed. An augmentative response was produced in 8 out of 20 experiments to McN-A-343 and 11 out of 15 experiments to AHR-602. The inhibitory effect of acetylcholine bromide (0·1 μg/ml) was more marked in the physostigmine-treated atria. Atropine sulphate (0·01 μg/ml) did not affect the augmentative response in the presence of physostigmine. Atropine or physostigmine changed the depressive response to both substances to an augmentative one, but scarcely affected the acetylcholine response.



FIG, 1. Effects of physostigmine on contracture of frog rectus skeletal muscle by McN-A-343 (●) and acetylcholine (○). Actual height of contraction on drum (mm) was plotted against the dose (μg/ml) of each drug. Each point denotes the mean from the indicated number (in brackets) of preparations with the standard error. The difference in the response to the same dose of each drug was statistically significant. Continuous lines represent control response; broken lines represent response in the presence of physostigmine.

The augmentative response of physostigmine-treated atria to AHR-602 was abolished by pretreatment of the preparations with pronethalol (2 μg/ml). Of the atria from 12 tortoises treated with reserpine (0·1 mg of reserpine phosphate/100 g body weight i.p. 48 to 72 hr previously), two responded to AHR-602 with augmentation in the presence of physostigmine. In the controls, which were given saline instead of reserpine, 6 out of 8 responded to AHR-602 with a positive inotropic effect. The difference was statistically significant ($P < 0.05$).

It is obvious that the modification by physostigmine of the responses to McN-A-343 and AHR-602 shown in the present experiment was not related to its anticholinesterase property. Rather, the action of physostigmine on the tortoise atria mimics that of atropine, and the action on the frog rectus skeletal muscle mimics that of (+)-tubocurarine. Smith (1966) reported inhibition by physostigmine of the pressor response to McN-A-343 in the cat arterial blood pressure by an action on the sympathetic ganglia. The present experiment indicates that the antagonism is not confined only to the sympathetic ganglia.

It is noteworthy that the response to McN-A-343 and AHR-602 in the isolated atria of the tortoise was reversed by physostigmine, and that the reversed effects are related to the sympathetic activity. These facts imply that the pharmacological properties of McN-A-343 and AHR-602, as well as those of physostigmine, are diverse.

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Department of Pharmacology,
Chonnam University Medical School,
Kwangju, Korea.
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Y. I. KIM
P. C. SHIN
J. K. HWANG

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