INTERNAL ACTIVITY, INDEPENDENT ANTAGONISM, AND RELATIONSHIP OF EFFECT TO DEGREE OF ACTIVATION OF RECEPTORS

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Absolute values of maximal effects on acetylcholine and pilocarpine and also the relative effect of different concentrations of one agonist are affected differently by a change in the degree of stretching of a smooth-muscle preparation and by the action of the independent antagonist adrenalin. It is assumed that a nonlinear relationship between the number of occupied receptors and the effect is the explanation of this phenomenon.

For a long time the character of the relationship between the effect and degree of activation of a receptor was discussed purely within the framework of the more general question of the quantitative relationship between effect and concentration of the substances tested [2, 3]. It is evident that if this relationship is one of direct proportion, the " log concentration–effect" curve will directly reflect the degree of activation of the receptors, and with a quantitative change in the relationship (specifically, a change in the effectiveness of coupling) the relative maximal effect of the agonists (their internal activity) and the relative magnitudes of the effects of different concentration of the same agonist will not change. The opposite result may be observed in the absence of a linear relationship.

The effect of a change in the load on a smooth-muscle preparation contracting under isotonic conditions on the magnitude of the maximal effects of acetylcholine and pilocarpine and also on the shape of the "log concentration–effect" curve of these substances was accordingly investigated. This procedure alters the magnitude of the responses without evidently altering the interaction between the substance and the receptor. Similar properties are possessed by independent antagonists which act on "functionally different and independent receptive structures of the same cells" [2]. Adrenalin and papaverine were used as independent antagonists.

TABLE 1. Maximal Effects of Smooth-Muscle Stimulators (M ± m)

Stimulator	Maximal effect (in mm/cm)			
	stomach		bladder	
	load 2g	load 5 g	load 0.5 g	load 2 g
Acetylcholine	58±2,2 (24)	43,7±6,5 (10)	43,9±2,3 (6)	34,9±2,5 (22)
Pilocarpine	54±3,4 (6)	21,1±2,6 (6)	9,2±2,1 (8)	5,2±1,9 (6)
Depolarizing solution	38±2,7 (24)	15,3±2,4 (10)	41,5±3,1 (6)	28,2±1,8 (31)

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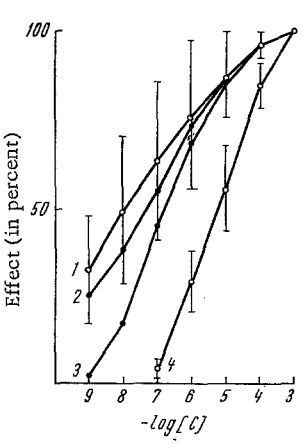

Fig. 1

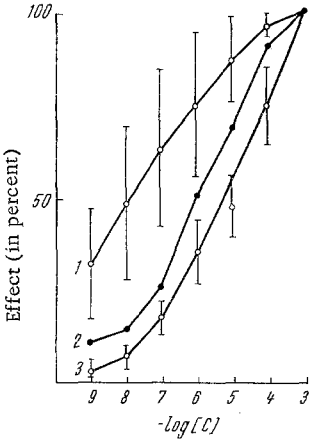

Fig. 2

Fig. 1. Effect of adrenalin on "log concentration–effect" of acetylcholine curve (strip of rat stomach): 1) control; 2, 3, 4,) adrenalin in concentrations of 10^{-6}, $2.5 \cdot 10^{-6}$, and 10^{-5} g/ml respectively. Here and in Fig. 2, vertical lines show confidence interval at $P < 0.05$.

Fig. 2. Effect of change of load on "log concentration – effect" curve of acetylcholine (strip of rat stomach): 1) load 2 g; 2) load 5 g; 3) load 10 g.

EXPERIMENTAL METHOD

Isolated strips from the fundus of the stomach and the urinary bladder of rats, kept in a thermostatically controlled (37° C) bath, were used. The bath was filled with Tyrode solution aerated with oxygen. Contractions were recorded isotonically with a magnification of 1:10. The absolute magnitude of the contractions was expressed in millimeters of deviation of the lever per centimeter initial length of the preparation, and their relative magnitude was expressed as a percentage of the maximal effect. The load on the preparation in the various series of experiments was 0.5, 2, 5, and 10 g. The "log concentration–effect" curves of acetylcholine (or pilocarpine) were obtained cumulatively within the concentration range 10^{-9}–10^{-3} g/ml. A depolarizing solution, consisting of isotonic potassium chloride solution, was used as the control agent inducing contraction.

Statistical analysis was carried out by the usual methods [1]. Each series was reproduced on at least five strips.

EXPERIMENTAL RESULTS AND DISCUSSION

The maximal effects of acetylcholine, pilocarpine, and depolarizing solution on strips of stomach and urinary bladder loaded under different conditions are given in Table 1.

The results given in Table 1 show that an increase in load reduced the absolute values of the maximal effects of all contraction-inducing agents including the depolarizing solution. This suggests that the effects were reduced not through a change in interaction between the substance and the receptor, but through a more distal action. The maximal effects of acetylcholine and pilocarpine underwent different changes: although practically equal in the experiments on the stomach when the load applied was 2 g, they differed by 2.1, 4.6, and 6 times under other experimental conditions.

The results given in Figs. 1 and 2 show that adrenalin and loading altered the relative values of the contractions induced by different concentrations of agonist unequally. The lower the concentration and the smaller the corresponding effect, the more strongly it was inhibited by an increased load or by preliminary administration of the independent antagonist. As a control of the reproducibility of the results the effect of papaverine, in concentrations of 10^{-5} and 10^{-4} g/ml, on the "log concentration–effect" curve of acetylcholine and also the effect of adrenalin (10^{-5}/ml) on the same curves for arecoline and serotonin

and the effect of loads (5 g) on the "log concentration–effect" curve of pilocarpine were studied. The results obtained were similar to those given in Figs. 1 and 2.

The facts described above are evidence that the effect is not directly proportional to the degree of activation of the receptors because the absolute values of the maximal effects of acetylcholine and pilocarpine, and also the relative effects of the same agonist undergo different changes in response to an equal change in the experimental conditions not influencing the process of agonist - receptor interaction. The use of relative maxima to assess internal activity, is therefore valueless. The second conclusion from the result of these experiments is that the effects of independent antagonists differ from those of noncompetitive antagonists, for the latter change the relative effects of agonists by an equal degree.

LITERATURE CITED

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