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Inhibitory and excitatory effects of sympathomimetic amines on muscle strips from the stomach of the guinea-pig

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Summary

1. Responses of muscle strips from the stomach of the guinea-pig have been recorded. Sympathomimetic amines cause inhibitory, motor or biphasic responses.

2. The motor components of the responses of the preparations were greatly enhanced by the removal of the mucosal layers.

3. The inhibitory responses to isoprenaline, noradrenaline and phenylephrine were antagonized by propranolol or by sotalol. The inhibitory responses to noradrenaline and phenylephrine but not isoprenaline were antagonized by phentolamine. Therefore, both α- and β-adrenoceptors may subserve inhibition.

4. The motor responses to noradrenaline and phenylephrine were often potentiated by propranolol or sotalol and were antagonized by phentolamine. Therefore, motor responses to sympathomimetic amines appear to involve α-adrenoceptors.

5. The responses to sympathomimetic amines and their antagonists were not modified by hyoscine or by tetrodotoxin. It is concluded that the adrenoceptors mediating the responses recorded from these preparations are located on the smooth muscle cells rather than on a nervous pathway.

Introduction

Inhibition of gastrointestinal smooth muscle by sympathomimetic amines is well documented. The involvement of both α- and β-adrenoceptors in the sympathomimetic inhibitory response has been demonstrated for the intestine of the gerbil (Goldenberg, 1968), guinea-pig (Kosterlitz & Watt, 1964), rabbit (Lawson & Mackenna, 1969), dog (Levy & Ahlquist, 1967) and of man (Bennett & Whitney, 1966); and for the pyloric region of the stomach of the dog (Daniel, 1966).

Motor responses of gastrointestinal smooth muscle mediated via adrenoceptors have been reported for the small intestine of the guinea-pig (Newman & Thienes, 1933; Munro, 1951, 1952, 1953; Reynolds, Demaree & Heiffer, 1967) and rabbit (Innes, 1962; Woodruff, Agar, Albani, Allen & Folkard, 1969). Similar responses have been recorded from the stomach of the guinea-pig, rat, rabbit and dog (Smith, 1918; McSwiney & Brown, 1926; Lange, 1955; Offermeier, 1966; Ehrreich & Furchgott, 1968; Guimarães, 1969; Innes & Kohli, 1969); from human stomach (Haffner, Liavåg & Setekleiv, 1969) and from ruminant stomach (Duncan, 1954; Sanford, 1968; Titchen, 1968; Van Miert & Huisman, 1968). Oesophageal smooth

muscle from the cat also contracts in response to sympathomimetic amines (Christensen & Daniel, 1966, 1968). Preparations of the isolated muscularis mucosae may contract in response to sympathomimetic amines as described for the intestine of the cat (Gunn & Underhill, 1914) and dog (King & Church, 1923 ; King & Robinson, 1945 ; King, Glass & Townsend, 1947) ; for the human stomach (Walder, 1953) ; and for the oesophagus of the domestic pig (Burnstock, 1960) and guinea-pig (Bailey, 1965).

The present work is an attempt to analyse the motor and inhibitory effects of sympathomimetic amines on isolated preparations from the stomach of the guinea-pig in terms of α- and β-adrenoceptors by means of selective antagonists. Preliminary findings have been reported to the British Pharmacological Society (Bailey, 1968).

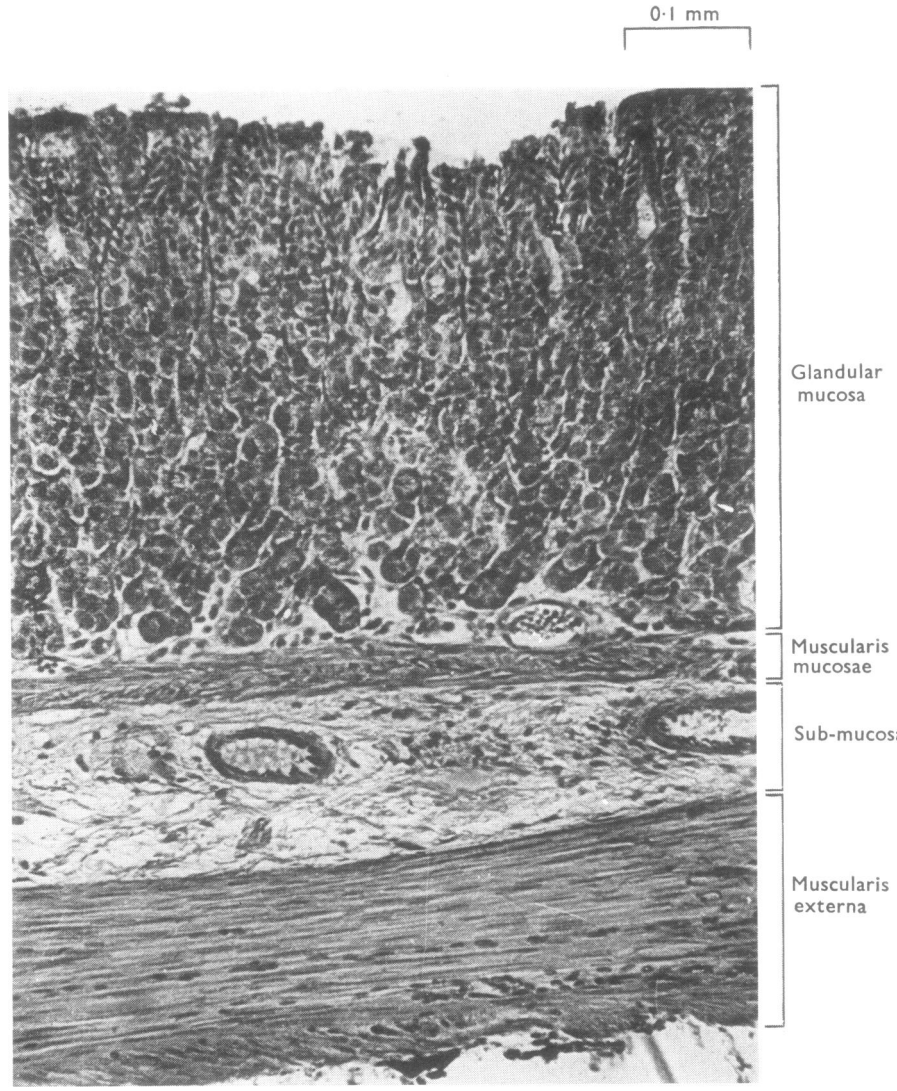

FIG. 1. Photomicrograph of a transverse section through the wall of the stomach of the guinea-pig to illustrate the arrangement of the tissues. (Haematoxylin and eosin stain.)

Methods

Morphology of the guinea-pig stomach

The stomach of the guinea-pig is a reniform structure, there does not appear to be any marked regional variation in the wall. The arrangement of the tissues in a section of the wall of the stomach is shown in Fig. 1. The bulk of the musculature is arranged in a more or less circular direction, with the muscle fibres in the outermost layer being arranged longitudinally. The distinct band of loose submucous connective tissue facilitates the separation of the outer musculature from the mucosa without apparent histological damage to the muscle (Fig. 2). The mucosal layers constitute approximately 60% of the wet weight of the stomach wall.

Preparations

Adult guinea-pigs which had been allowed free access to food and water were killed by stunning and bleeding. The stomach was removed and opened by cutting along the greater curvature. After washing away the contents, the stomach was pinned, under Krebs solution, to a cork mat, mucosal side down, with the wall stretched to its approximate *in situ* size. Strips of the intact wall, 3–4 cm long and 3 mm wide were cut parallel to the lesser curvature so as to preserve the longitudinal muscle or at right angles to the lesser curvature so as to preserve the circular muscle. Care was taken to avoid the mucosa curling and enclosing the muscle. These preparations will be described as ' intact preparations '. ' Mucosa-free preparations ' were made by gently separating the layers with the points of a pair of splinter forceps and peeling away the mucosa from the muscle.

The preparations were then immersed in Krebs solution, gassed with oxygen 95%, carbon dioxide 5% at 39° C. Responses were recorded on a smoked drum using a light, side writing lever with a load on the tissue of 300 mg and a magnification of 10. The preparations were allowed to equilibrate with the experimental environment for 60 min before responses were recorded. The agonists were administered every 15 min with a contact time of 90 seconds. The antagonists were maintained in the bathing fluid by adding the appropriate concentration to the fluid reservoir and allowing at least 30 min before their effects were tested.

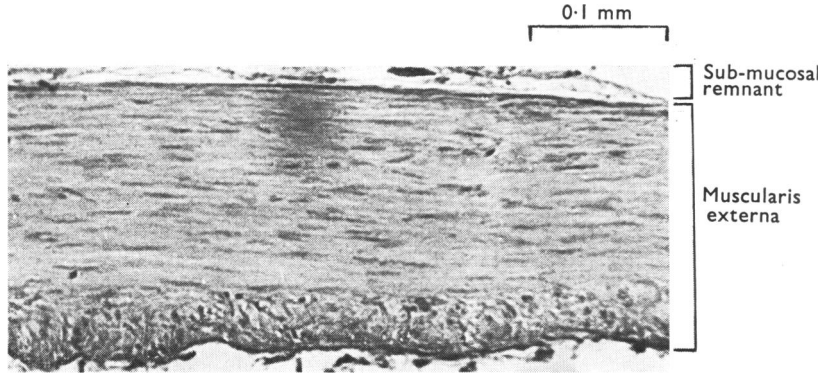

FIG. 2. Photomicrograph of a transverse section through the wall of the stomach of the guinea-pig, after removal of the mucosa. (Haematoxylin and eosin stain.)

Drugs

Drugs used were: (−)-adrenaline acid tartrate, hyoscine hydrobromide, (±)-isoprenaline sulphate, (−)-noradrenaline, phentolamine methane sulphonate, (−)-phenylephrine hydrochloride, propranolol hydrochloride, sotalol hydrochloride, tetrodotoxin. The concentrations are expressed as final bath concentrations in terms of the base. The Krebs solution contained (mM): NaCl, 118; KCl, 4·7; KH_2PO_4, 1·2; $MgSO_4$, 1·2; $NaHCO_3$, 25; $CaCl_2$, 1·9; glucose, 11.

Results

There were no qualitative differences between the responses of strips cut so as to preserve either the longitudinal or the circular muscle. However, since the longitudinal preparations generally gave larger and more reproducible responses than did the circular preparations, longitudinal preparations were used routinely. Removal of the mucosa from a strip of the gastric wall usually enhanced the motor components of all the responses of the preparation. Conversely, inhibitory responses were most readily obtained from intact strips. Therefore, intact preparations were used for a detailed investigation of inhibitory responses, mucosa-free preparations for a detailed investigation of motor responses.

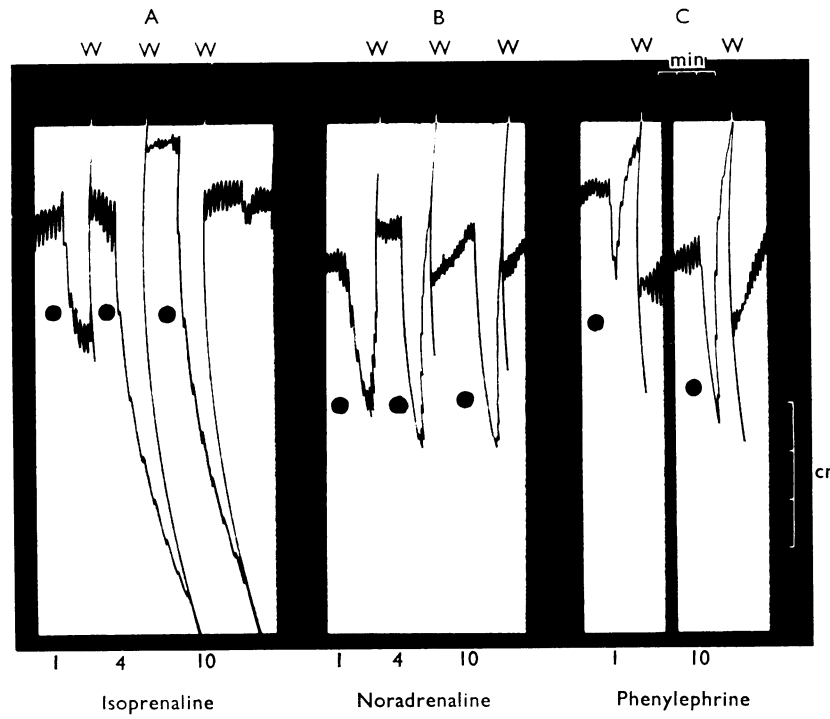

FIG. 3. Effects of sympathomimetic amines on the longitudinal 'intact preparation' from the stomach of the guinea-pig. Isoprenaline in A produced purely inhibitory responses. Noradrenaline in B produced relaxations which were not maintained in the presence of the drug. Responses to phenylephrine in C were biphasic, a brief relaxation followed by a motor response. All doses are expressed as a final concentration (μg/ml) in the bath fluid. W indicates washing.

Responses of 'intact preparations' to sympathomimetic amines

Isoprenaline caused relaxation of the preparations; the responses reached a maximum which was maintained in the presence of the drug (Fig. 3). Adrenaline, noradrenaline or phenylephrine also caused relaxation of the preparations. Relaxations induced by these three drugs reached a maximum within 60 s after which time, in many preparations, in the continuing presence of the drug, the lever returned to its original base line or above. This tendency of the tissue to contract was most marked in the case of responses of phenylephrine (Fig. 3).

Effects of blockade of β-adrenoceptors on the inhibitory responses to sympathomimetic amines

The inhibitory responses of intact preparations to isoprenaline were antagonized by sotalol or by propranolol. An approximately equal displacement of the isoprenaline dose response curve was induced by sotalol, 10 μg/ml, or by propranolol,

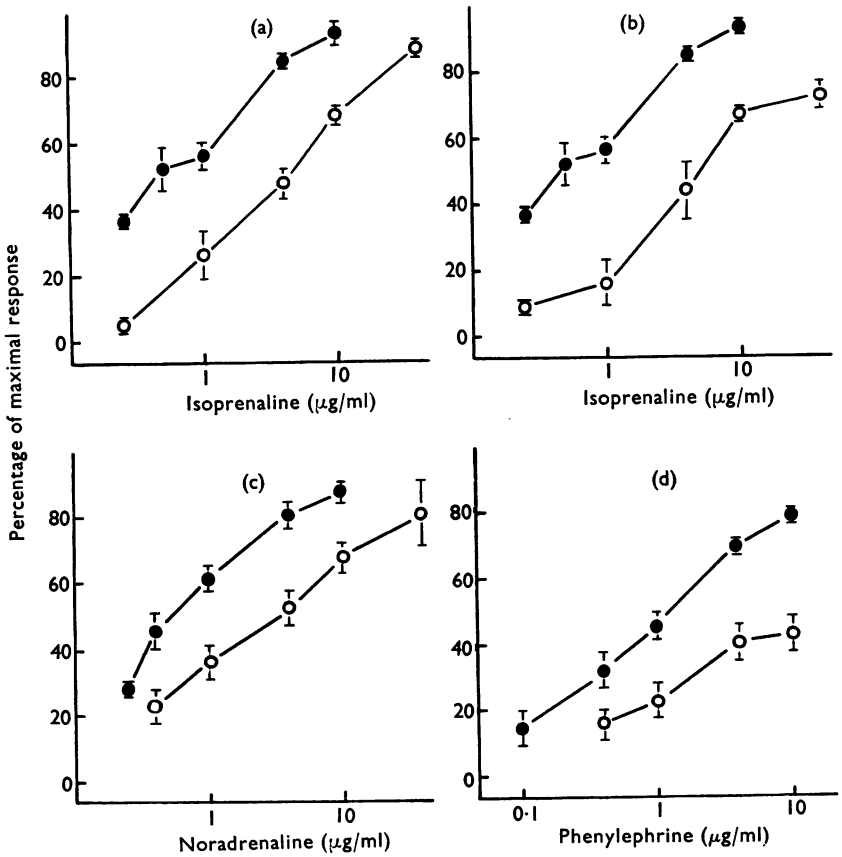

FIG. 4. Effects of antagonists for β-adrenoceptors on the inhibitory responses of strips from the stomach of the guinea-pig to isoprenaline, noradrenaline and to phenylephrine. The results are plotted as a percentage of the maximal response against the dose of agonist in μg/ml on a log scale. Each point is the mean response (ten observations) with its standard error (vertical bar). (●——●), Control responses to the agonists; (○——○), responses in the presence of an antagonist as indicated. (a) Sotalol, 10 μg/ml; (b) propranolol, 2·5 μg/ml; (c) sotalol, 10 μg/ml; (d) sotalol, 10 μg/ml.

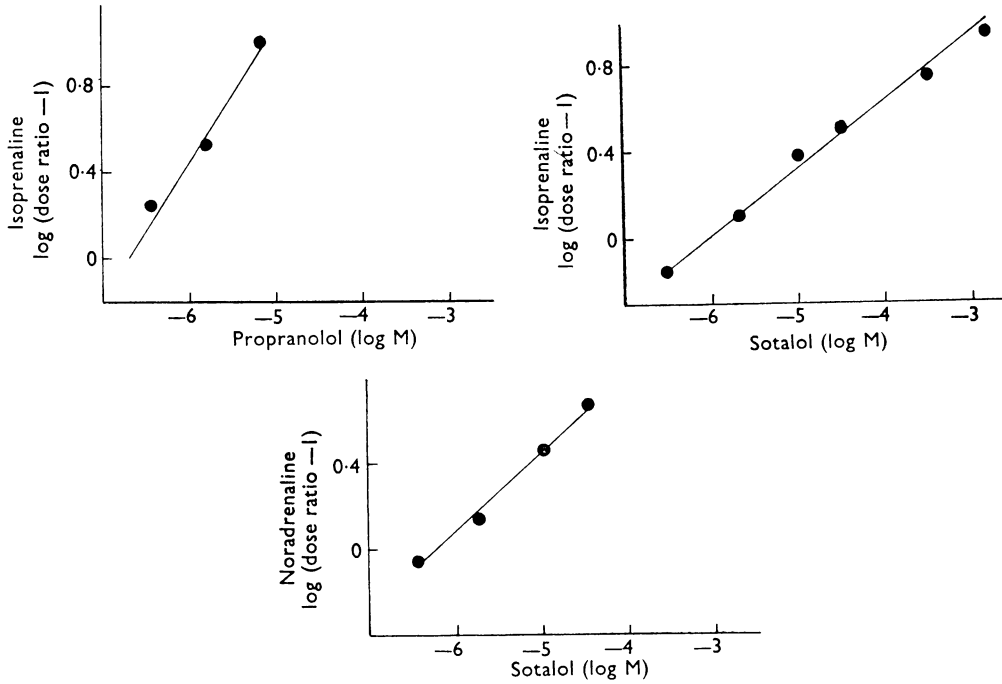

FIG. 5. Effects of antagonists for β-adrenoceptors on the inhibitory responses of longitudinal 'intact preparations' from the stomach of the guinea-pig to isoprenaline and noradrenaline. The log (dose ratio−1) is plotted against log molar concentration of antagonist. Each point is the mean of eight observations.

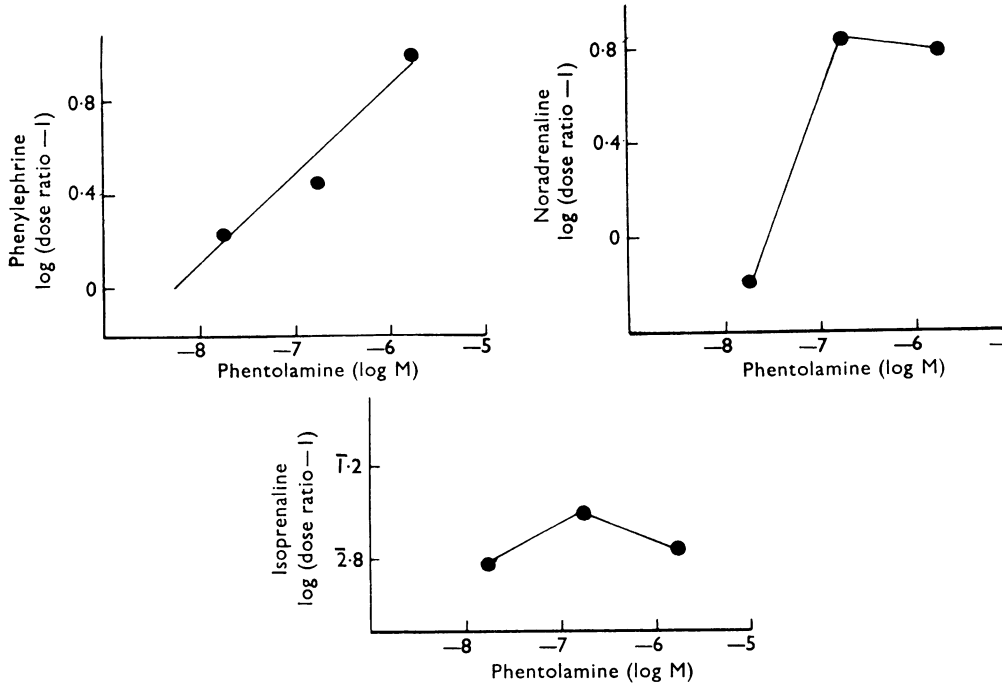

FIG. 6. Effects of phentolamine on the inhibitory responses of longitudinal 'intact preparations' from the stomach of the guinea-pig to phenylephrine, noradrenaline and isoprenaline. The log (dose ratio−1) is plotted against log molar concentration of antagonist. Each point is the mean of eight observations.

2·5 μg/ml (Fig. 4). Relaxation induced by noradrenaline or by phenylephrine was also antagonized by sotalol (Fig. 4). Figure 5 shows the increase in the ratio between equi-effective doses of agonist, plotted as log (dose ratio −), with increase in β antagonist concentration. pA_2 values (Schild, 1947) were 6·7 for propranolol against isoprenaline, 6·0 for sotalol against isoprenaline and 6·3 for sotalol against noradrenaline.

Effects of blockade of α-adrenoceptors on the inhibitory responses to sympathomimetic amines

The inhibitory responses of intact preparations to noradrenaline or to phenylephrine were antagonized by phentolamine (Fig. 6). pA_2 values were 8·3 for phentolamine against phenylephrine and 7·5 for phentolamine against noradrenaline.

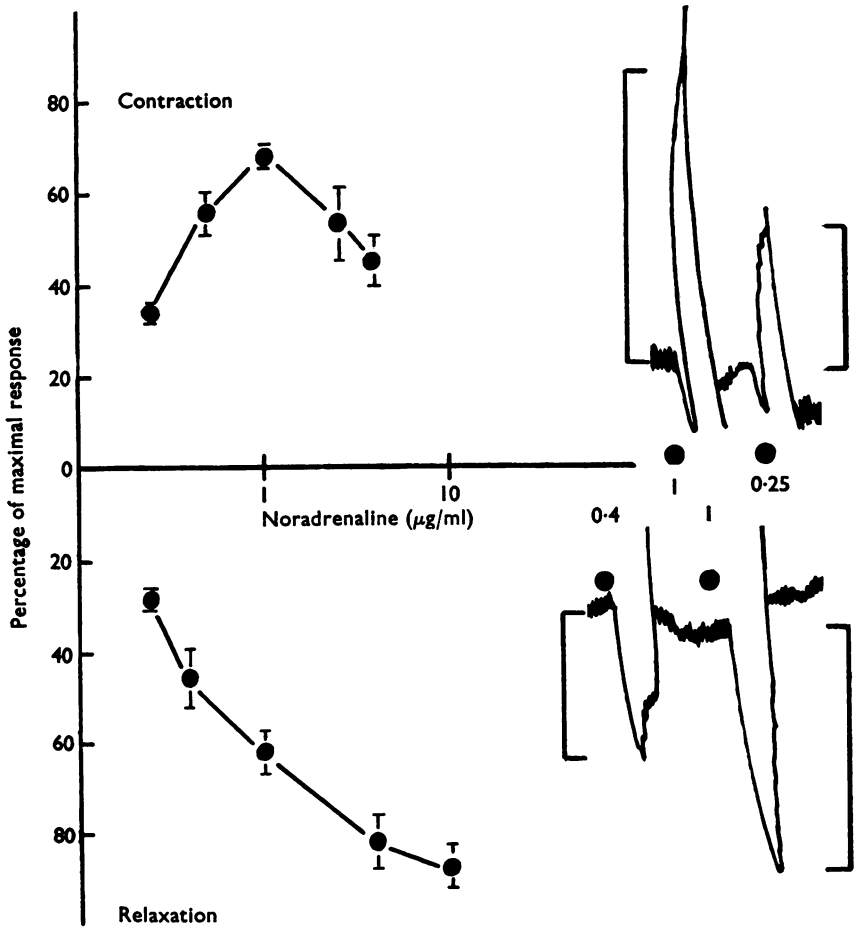

FIG. 7. Effects of removing the mucosa on the responses to noradrenaline of longitudinal preparations from the guinea-pig stomach. The kymograph records show the change in the shape of the responses from predominantly inhibitory in the intact preparation (lower tracing) to predominantly motor in the mucosa-free preparation (upper tracing). The square brackets indicate the measurement made for the 'response'. The average responses of the two preparations to noradrenaline are plotted as a percentage of the maximal response (contraction positive and relaxation negative) against μg/ml noradrenaline on a log scale. Each point is the mean (twelve observations) with its standard error (vertical bar).

The inhibitory action of isoprenaline does not appear to involve α-adrenoceptors since the isoprenaline induced responses were not antagonized by the concentrations of phentolamine used (Fig .6).

Responses of 'mucosa-free' preparations to sympathomimetic amines

After removal of the mucosa from strips of the gastric musculature the response to noradrenaline was changed from a predominantly inhibitory to a predominantly motor effect and the motor component of the phenylephrine response was greatly enhanced. In both intact and mucosa-free preparations, isoprenaline produced a purely inhibitory response, although the magnitude of the maximal relaxation was usually decreased after removal of the mucosa.

The shape of the responses to noradrenaline before and after the removal of the mucosa is illustrated in Fig. 7 and the dose-response relationship for noradrenaline on the two preparations is also shown. As the concentration of noradrenaline was increased the motor responses of the mucosa-free preparations reached a maximum after which a further increase in the concentration produced a decrease in the response.

Effects of blockade of adrenoceptors on the motor responses to noradrenaline

The motor responses induced by noradrenaline in mucosa-free preparations were often enhanced by sotalol or by propranolol. Figure 8 illustrates the average dose-response lines to noradrenaline in the presence and absence of sotalol, 10 μg/ml. In eleven out of nineteen experiments the responses were potentiated and in the remaining eight experiments there was no change or a very slight reduction in the

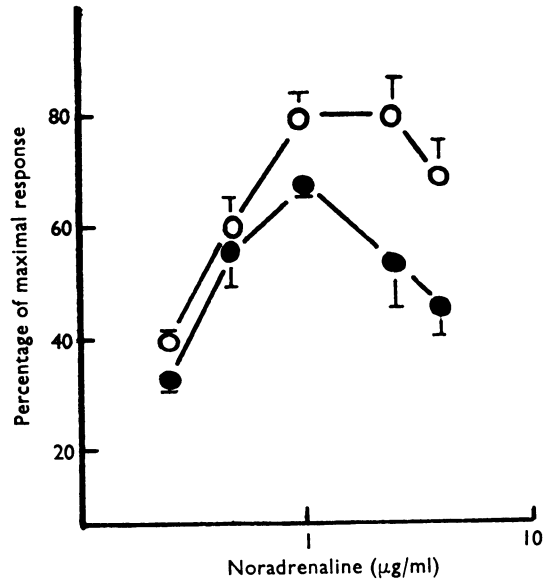

FIG. 8. Effect of sotalol on the noradrenaline induced motor responses of longitudinal mucosa-free preparations from the stomach of the guinea-pig. Results are plotted as a percentage of the maximal response against the dose of noradrenaline (μg/ml) on a log scale. Each point is the mean response (nineteen observations) with its standard error (vertical bar). (●——●), Control responses to noradrenaline; (○——○), responses in the presence of sotalol, 10 μg/ml.

responses. Similar results were obtained with propranolol at a concentration of 1 μg/ml. The motor responses induced by noradrenaline in mucosa-free preparations were antagonized by phentolamine (Fig. 9).

Effects of hyoscine and tetrodotoxin on the responses to sympathomimetic amines

In the presence of tetrodotoxin, 0·1 μg/ml, the responses of intact and mucosa-free preparations to noradrenaline were unchanged. The presence of hyoscine, 0·1 μg/ml, in the bathing fluid caused a slight reduction in the inhibitory responses to phenylephrine but did not modify the antagonism by phentolamine of these inhibitory responses. The noradrenaline induced motor responses of mucosa-free preparations were not modified by this concentration of hyoscine.

Discussion

Inhibitory responses to sympathomimetic amines

The present results provide evidence for an inhibitory action of sympathomimetic amines on the smooth muscle of the stomach of the guinea-pig mediated by both α- and β-adrenoceptors. Propranolol or sotalol antagonized the responses to isoprenaline, noradrenaline or phenylephrine, indicating an action of all three amines on β-adrenoceptors in these preparations. The pA_2 value calculated for the antagonism of isoprenaline by propranolol in these experiments (pA_2 6·7) is comparable with the value which can be derived from the data of Furchgott (1967) for propranolol on β-receptors in the stomach of the rabbit (pA_2 6·7). However, in the present experiments no attempt was made to block uptake mechanisms for sympatho-

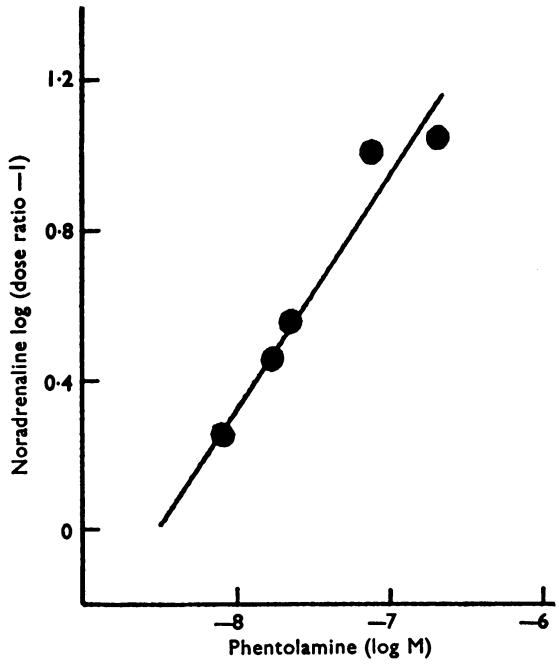

FIG. 9. Effects of phentolamine on the motor responses of longitudinal mucosa-free preparations from the stomach of the guinea-pig to noradrenaline. The log (dose ratio—1) is plotted against the log molar concentration of antagonist. Each point is the mean of six observations.

mimetic amines in the tissues, neither were the α-adrenoceptors blocked before measuring the effects on β-adrenoceptors.

Phentolamine antagonized the responses to noradrenaline or to phenylephrine but did not modify the responses to isoprenaline in the present experiments. The value calculated for the antagonism of the noradrenaline induced inhibitory responses by phentolamine (pA_2 7·5) is similar to the value derived from the data of Furchgott (1967) for phentolamine on α-adrenoceptors in the duodenum of the rabbit (pA_2 8·1).

It has been suggested by Kosterlitz & Watt (1964) and Kosterlitz, Lydon & Watt (1970), that for the ileum of the guinea-pig β-adrenoceptors but no α-adrenoceptors are present on the cells of the longitudinal muscle. The α-adrenoceptors in the ileum of the guinea-pig appear to be situated on a cholinergic pathway since their activation results in a decrease in acetylcholine release (Kosterlitz *et al.*, 1970; Paton & Vizi, 1969). Denervation by means of storage in the cold of the jejunum isolated from the rabbit appears to result in a selective loss of inhibitory responses mediated by α-adrenoceptors (Lum, Kermani & Heilman, 1966). However, evidence for the presence of α-adrenoceptors on the smooth muscle cells has been reported by Jenkinson & Morton (1967) for the taenia coli of the guinea-pig and by Bowman & Hall (1970) for the small intestine of the rabbit. Gershon (1967) found that for the intact stomach, isolated from the guinea-pig, the removal of nervous influences with tetrodotoxin did not reduce the inhibitory responses to noradrenaline. This finding has been confirmed in the present experiments for strips of the gastric musculature from the guinea-pig. If the α-adrenoceptors subserving inhibition were located exclusively on a cholinergic pathway, antagonism of the released acetylcholine at its site of action on the muscle with hyoscine, should abolish or at least reduce inhibition mediated via α-adrenoceptors. In the present experiments, a component of the inhibitory response to noradrenaline blocked by phentolamine was present after treatment of the tissues with hyoscine. Thus, for the stomach of the guinea-pig, α-adrenoceptors subserving inhibition do not appear to be located exclusively on a cholinergic pathway.

Motor responses to sympathomimetic amines

The present results also provide evidence for an excitatory action of sympathomimetic amines on the smooth muscle of the stomach of the guinea-pig mediated via α-adrenoceptors. Motor responses to sympathomimetic amines were most readily observed in mucosa-free preparations, which appeared to be more fully relaxed in the resting state than were the intact preparations. Motor responses were also generally enhanced by blockade of the β-receptors subserving inhibition. However, even in intact preparations, in the absence of any antagonist, motor components were apparent in the responses to noradrenaline and particularly to phenylephrine. Similar results with the whole stomach isolated from the guinea-pig have been described by Guimarães (1969). In view of the numbers of reports of motor effects of sympathomimetic amines on gastrointestinal smooth muscle, it would appear that this is a fundamental response of the muscle, masked by the inhibitory effects which predominate under many experimental conditions. A similarity between receptors mediating noradrenaline motor responses of smooth muscle and tryptamine receptors has been suggested (Innes, 1962, 1963; Innes & Kohli, 1969; Offermeier, 1966). Strips of muscle isolated from the stomach of the guinea-pig were very insensitive to 5-hydroxytryptamine and a full investigation of this phenomenon was not possible.

Three sympathomimetic effects—inhibition involving both α- and β-adrenoceptors and excitation involving α-adrenoceptors—have been described for the stomach (Guimarães, 1969 ; Haffner *et al.*, 1969 ; and the results presented here). The preparations of gastric smooth muscle isolated from the guinea-pig and described in the present experiments appear to provide a unique opportunity for the simultaneous observation of these three sympathomimetic effects.

I wish to thank Professor G. Brownlee for his helpful advice during the course of this work.

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