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# The activities of α- and β-adrenoceptive blocking agents in reducing intestinal relaxation due to sympathetic stimulation in the pithed rat

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A pithed rat preparation, stimulated electrically via the pithing rod left in position, was employed to examine the effects of drugs, administered intravenously, on relaxation of a loop of ileum. Relaxation due to injected isoprenaline could be largely blocked by propranolol but that due to nervous stimulation or injected noradrenaline was blocked to only a lesser extent by either propranolol or phenoxybenzamine alone. The combination of phenoxybenzamine and propranolol was more effective against relaxation from nervous stimulation than either drug alone but was still not as effective against this as against noradrenaline, or as propranolol alone against isoprenaline. It is concluded that intestinal relaxation after nervous stimulation involves both α- and β-adrenergic activity, in variable proportions. Adrenoceptive antagonists are not as effective in blocking these receptors as they are for those concerned in relaxation after injected catecholamines.

Gillespie & Muir (1967) described a preparation of the pithed rat, stimulated electrically in the lumbar region of the cord through the pithing rod left in position. By this means they were able to study the effects upon blood pressure of stimulation of the total lumbar sympathetic outflow. We have used this preparation to study the effects of drugs upon the relaxation of a loop of ileum due to such stimulation.

## EXPERIMENTAL

### *Method*

Sprague-Dawley rats, 250–400 g, were pithed under ether anaesthesia using a No. 14 plastic-covered metal knitting needle, stripped over the length that would lie in the lumbar region of the spinal column. Blood pressure was recorded from a catheter in a carotid artery by means of a Statham transducer. In addition, the abdomen was opened and a small funnel placed over a loop of ileum, which was tied at its base to a wire stretched across the mouth of the funnel while a thread under the apex of the loop was tied to a Devices isometric transducer. Blood pressure and intestinal motility were recorded by a Devices two-channel pen recorder.

Electrical stimulation was given as square waves from a Palmer stimulator, at the rate of 10/s, each of 2 ms width and 80 V, for periods of 30 s. This was applied between the pithing rod and an indifferent electrode clipped to the skin of one hindlimb. Convulsions were reduced by pretreatment with (+)-tubocurarine, 5 mg/kg, intravenously, as used by Gillespie & Muir, though clonic contractions of the limb bearing the electrode still occurred. Responses of blood pressure and ileum to stimulation were rendered more consistent by additional pretreatment with atropine,

1 mg/kg intraperitoneally before pithing and a further 1 mg/kg intravenously later.

Drugs were injected via a jugular catheter and the intestinal relaxation following stimulation compared with that before drug treatment.

## RESULTS

### *The action of β-adrenoceptive blocking agents*

Table 1 and Figs 1 and 2 show the reduction by various doses of propranolol of the relaxation of the loop of ileum due to electrical stimulation and also to the intravenous injection of isoprenaline (1 μg/kg)—a dose just sufficient to cause a similar degree of relaxation. The effectiveness of propranolol against stimulation was much less than against injected isoprenaline. Its effectiveness against injected noradrenaline was also less than against isoprenaline.

Table 1. *Responses of a loop of ileum to injected catecholamines or electrical stimulation of the lumbar cord in pithed rats treated with α- and β-adrenoceptive blocking agents.* Values are expressed as percentage of the appropriate control.

| Relaxation due to | Drug | Dose, mg/kg | Response, % |
|---|---|---|---|
| Isoprenaline, 1 μg/kg .. | None | | 100 |
| | Propranolol | 1 | 75·4, 72·3 |
| | | 2 | 64·5, 68·4, 61·8, 60·0 |
| | | 4 | 46·6, 52·9, 46·6 |
| | | 5 | 40·0 |
| | | 8 | 31·4 |
| Noradrenaline, 2 μg/kg .. | None | | 100 |
| | Propranolol | 2 | 74·9, 82·3, 70·7, 66·8 |
| | | 4 | 58·2, 45·8, 60·6 |
| | | 8 | 51·8, 39·9, 34·6 |
| | Phenoxybenzamine | 2 | 100 |
| | + propranolol | 2 | 62·1, 58·8, 60·0 |
| | | 4 | 51·4, 50·0, 43·8 |
| | | 8 | 38·7, 38·1, 37·5 |
| Electrical stimulation .. | None | | 100 |
| | Propranolol | 2 | 82·8, 86·5, 80·3, 89·8 |
| | | 4 | 76·7, 69·4, 75·0, 70·4 |
| | | 8 | 54·2, 61·4, 59·7, 57·3 |
| | | 10 | 50·8 |
| | | 16 | 43·5, 48·3 |
| | Phenoxybenzamine | 2 | 100 |
| | + propranolol | 2 | 76·2, 66·2, 78·0, 65·6, 67·8 |
| | | 4 | 57·9, 59·3, 61·5 |
| | | 8 | 41·4, 43·3, 54·2, 39·8 |

### *The action of α-adrenoceptive blocking agents*

Phenoxybenzamine or phentolamine (1 mg/kg) injected intravenously, reduced intestinal relaxation to electrical stimulation by an extent not reduced further by a second injection. The degree of reduction was quite variable from one animal to another but two injections of 1 mg/kg resulted in no more than 23% reduction. The relaxation due to injected noradrenaline was also less than completely blocked by a total of 2 mg/kg of phenoxybenzamine. This antagonist was, however, quite ineffective against relaxation from injected isoprenaline.

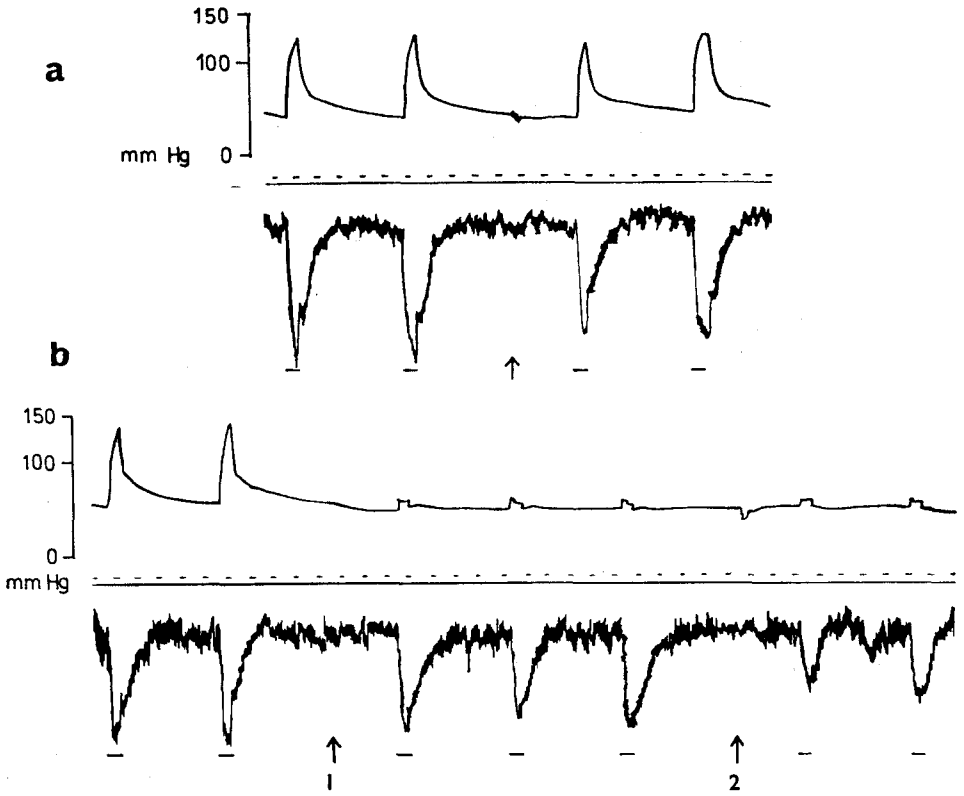


FIG. 1. Record of blood pressure (upper trace) and tone of a loop of ileum (lower trace) in a pithed rat. Horizontal bars represent 30 s periods of electrical stimulation of lumbar cord. (a) At arrow: propranolol 2 mg/kg i.v. (b) At arrows: 1, phenoxybenzamine 2 mg/kg, i.v.; 2, propranolol 2 mg/kg, i.v.

*The combined action of α- and β-adrenoceptive blocking agents*

As shown in Table 1 and Fig. 2, propranolol was more effective in reducing the intestinal relaxation due to electrical stimulation remaining after pretreatment with phenoxybenzamine (2 mg/kg) than when used alone. The dose-response relation may be seen to have moved nearer to that for antagonism of propranolol alone to injected isoprenaline, though the blocking agent did not reach its degree of effectiveness against the amine (despite the fact that it was frequently acting on a lesser degree of relaxation). When used after phenoxybenzamine, propranolol was also more effective against noradrenaline than when given alone and it may be noted that in this case its effectiveness matched that when used alone against isoprenaline.

## DISCUSSION

The results presented here demonstrate that stimulation of the visceral nerve supply causes relaxation and inhibition of intestinal motility by processes involving both α- and β-types of receptor. This is in agreement with earlier findings that both α- and β-adrenoceptive blocking agents are necessary to block intestinal inhibition due to adrenaline or noradrenaline (Ahlquist & Levy, 1959; Furchgott, 1960) or periarterial nerve stimulation (Day & Warren, 1968). The variable extent to which

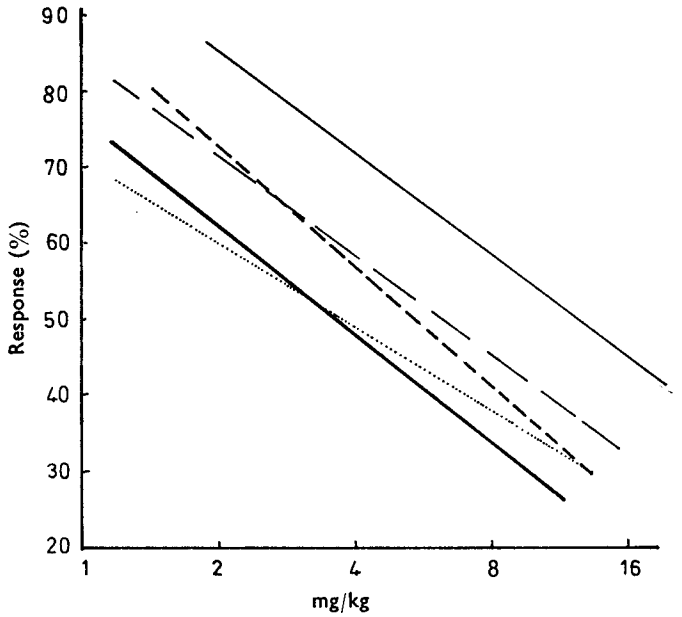


FIG. 2. Dose-response relations for the antagonism by propranolol to the effects on the tone of a loop of ileum in the pithed rat of: — Intravenous isoprenaline, 1 μg/kg (b = −47·5 ± 9·0; N = 11; ED50 = 3·8 (3·2–4·1) mg/kg). — Electrical stimulation of the lumbar cord (b = − 44·6 ± 6·1; N = 15; ED50 = 12·3 (10·7–14·3) mg/kg). — — Electrical stimulation, after phenoxybenzamine, 2 mg/kg, i.v. (b = −43·1 ± 13·1; N = 12; ED50 = 6·2 (5·0–7·6) mg/kg). – – – Intravenous noradrenaline, 2 μg/kg (b = −52·9 ± 21·4; N = 10; ED50 = 5·4 (4·3–6·9) mg/kg). . . . . Intravenous noradrenaline, 2 μg/kg, after phenoxybenzamine, 2 mg/kg, i.v. (b = −36·9 ± 7·7; N = 9; ED50 = 3·7 (3·3–4·2) mg/kg). The ranges quoted for ED50 values are the calculated 95% fiducial limits.

phenoxybenzamine affected the response to electrical stimulation in different animals suggests that the contributions of α- and β-actions are variable.

In the presence of maximal amounts of phenoxybenzamine, propranolol was as effective against relaxation after injected noradrenaline as it was, used alone, against relaxation seen after isoprenaline, suggesting that both catecholamines are interacting with the same β-adrenoceptors. Against relaxation due to electrical stimulation in the presence of complete α-block, however, propranolol was less effective than it was against injected catecholamines. This suggests either that nerve stimulation releases the transmitter in such a way that the β-receptors are less susceptible to block by propranolol than when they are stimulated by injected catecholamines or that different receptors are involved.

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