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### Attempt to assess the selectivity of $\beta$ -adrenoceptive blocking agents towards the effects of electrical stimulation of the spinal cord on different organs

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In the pithed guinea-pig, propranolol was reported to block the effectiveness of cord stimulation in reducing bronchoconstriction at lower doses than those blocking tachycardia, whereas practolol reduced both effects at the same doses (Burden, Parkes & Gardiner, 1971). Selectivity of blocking agents towards the consequences of sympathetic nerve stimulation of different organs may reflect not only their effectiveness in blocking the neurotransmitter at the respective sites, but also differences in innervation, and the effectiveness of stimulation, which determine the amounts of neurotransmitter involved.

In this study, we compared the effectiveness of cord stimulation for  $\beta$ -adrenoceptive responses in different organs with that of injected catecholamines, as reference. This was necessary since the parameters of the responses studied did not permit direct comparison.

Heart rate and air overflow were measured in the pithed guinea-pig, bronchoconstriction being produced by methacholine; heart rate and the tone of a loop of

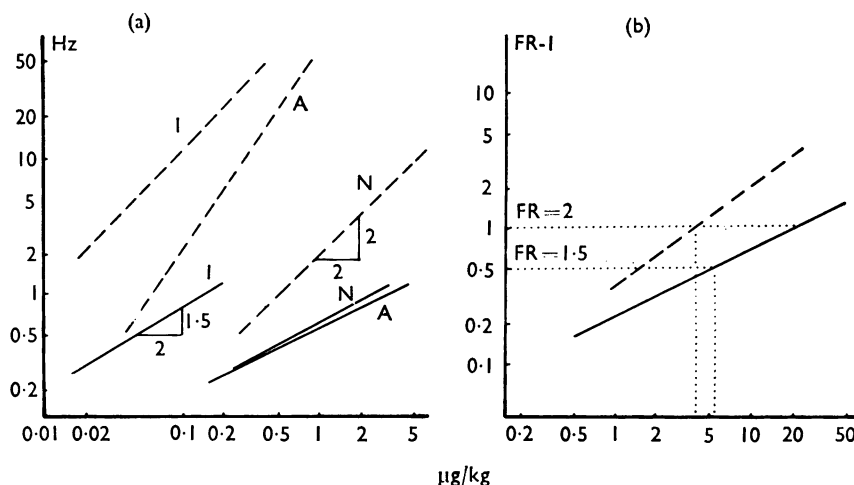


FIG. 1. (a) Relationship between the frequency (80V) of stimulation of the spinal cord of the pithed guinea-pig for 20 s and the intravenous dose of catecholamines for equal effect on — heart rate; - - - air overflow (log-log plots derived from computed regression lines). N—noradrenaline; A—adrenaline; I—isoeprenaline, DR=dose ratio; FR=frequency ratio.

(b) Relationship between intravenous dose of propranolol and frequency ratio for effects of cord stimulation on — heart rate; - - - air overflow, in the pithed guinea-pig (log-log plots of dose against FR-I).

ileum in the pithed rat. The cord was stimulated supraximally via the pithing rod in the thoracic region of the guinea-pig and totally in the rat; responses other than  $\beta$ -adrenoceptive were blocked by tubocurarine, phenoxybenzamine, and in the rat, atropine.

The range of stimulus pulse frequencies giving responses matching those to injected catecholamines differed from one organ to another; the relationship between frequency and equi-effective dose also differed (Fig. 1a).

When the effectiveness of  $\beta$ -adrenoceptor blocking agents against cord stimulation was expressed by displacement of the stimulus frequency-response relationship, the relation of this to dose of blocking agent was found to differ for different organs (Fig. 1b). Comparison of relative blocking activity for different organs may be made from the doses corresponding to the frequency ratio that is equivalent, for each organ, to a reference dose ratio for injected amine.

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#### Effects of $\beta$ -adrenoreceptor blocking drugs on isolated skeletal and cardiac muscle

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Propranolol, oxprenolol and practolol produce differential effects on the chronotropic and inotropic actions of isoprenaline in the denervated dog heart (Harry, Kappagoda, Linden & Snow, 1971). An explanation of these results may be that these drugs have a negative inotropic action on the dog heart over and above their activity as  $\beta$ -adrenoceptor antagonists. In an attempt to test this hypothesis the actions of propranolol, oxprenolol and practolol on the isolated rat diaphragm and the isolated rabbit papillary muscle were investigated.

The isolated muscles were bathed in Krebs solution maintained at 32.5°C bubbled with 95% CO<sub>2</sub> and 5% O<sub>2</sub> and containing tubocurarine (10<sup>-5</sup> g/l.). Supramaximal stimulation was used to produce a maximal isometric twitch tension from a constant resting tension of about 1 g. Each muscle was subjected to increasing concentrations of the drugs (0.2-1000  $\mu$ g/ml) for 10 min after which the twitch tension was recorded. The relationship between isometric tension produced by the muscles and the concentration of  $\beta$ -blocking agents in the bath fluid was obtained. A separate group of control muscles was examined over the same periods of time but with no drugs added to the bathing fluids.

Each blocking agent was tested on at least five muscles. The results are summarized in Table 1.

TABLE 1. Lowest bath concentrations ( $\mu$ g/ml) of propranolol, oxprenolol and practolol which produce statistically significant depression of isometric twitch tensions

	Propranolol	Oxprenolol	Practolol
Rat diaphragm	20	100	1000
Rabbit papillary muscle	20	100	1000