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α-Adrenergic blocking action of propranolol

SIR,—The inhibitory action of catecholamines on the rabbit aorta may be observed *in vitro* in strips pretreated with phenoxybenzamine and contracted by adding carbachol to the bathing fluid. When propranolol was used to block this inhibitory action of the catecholamines, the original excitatory action of these compounds was observed by us. This unexpected effect was of interest because similar concentrations of phenoxybenzamine caused complete blockade of the excitatory action of catecholamines in untreated strips. We are investigating the mechanism of this anti-α-adrenergic blocking action of propranolol and have observed that the drug has an α-adrenergic blocking action.

All experiments were done on spirally cut rabbit aortic strips suspended in Krebs-Henseleit solution maintained at 38° bubbled with 5% carbon dioxide in oxygen. Isotonic contractions against 2 g tension and magnified tenfold were recorded on a kymograph.

In these experiments increasing concentrations of propranolol caused an increasing degree of blockade of the excitatory action of noradrenaline. Propranolol at 10^{-6} g/ml produced 0–45%, and at 10^{-5} g/ml produced 30–72% inhibition of noradrenaline (10^{-8} g/ml). Inhibition of 10^{-7} g/ml noradrenaline was also studied; at 3×10^{-5} g/ml, propranolol caused 20% inhibition, while at 10^{-4} g/ml it caused 67–89% inhibition. Complete recovery from the blocking action of a single dose of propranolol occurred in 60–75 min at all levels of testing. The effect of multiple concentrations of noradrenaline in the presence of propranolol was compared with the effect of a unit concentration of noradrenaline without propranolol. At 3×10^{-5} g/ml of propranolol the dose-ratio was between 3 and 5, at 5×10^{-5} g/ml it was between 5 and 10, and at 10^{-4} g/ml of propranolol the dose-ratio was between 30 and 100. The pA_{10} of propranolol (exposure time 5 min) against noradrenaline, derived from seven experiments, was $3{\cdot}7 \pm 0{\cdot}03$ compared with $6{\cdot}2 \pm 0{\cdot}04$ for phentolamine (exposure time 3 min).

These observations suggested that propranolol had an α-adrenergic blocking action. The nature of this action of propranolol was examined further by

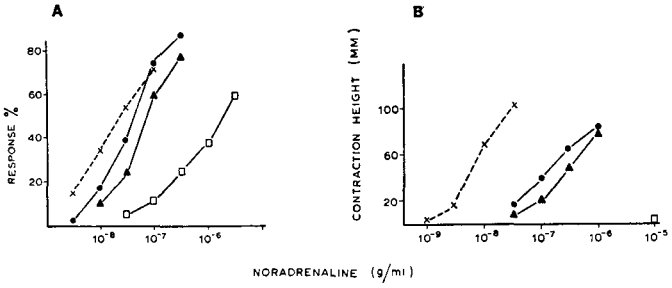

FIG. 1. A. Dose-response curves for noradrenaline with and without propranolol. Concentration of propranolol in g/ml: × - - - ×, 0 (control); ●—●, 10^{-5}; ▲—▲, 3×10^{-5}; □—□, 10^{-4}. B. Protection of noradrenaline responses against blockade by phenoxybenzamine 10^{-7} g/ml (exposure time 5 min). × - - - ×, Control; ●—●, noradrenaline protected; ▲—▲, propranolol protected; □, unprotected. Strips were protected by exposure to the protecting agents for 5 min before and during exposure to phenyoxybenzamine.

making dose-response curves and, also by assessing the ability of propranolol to protect noradrenaline responses against blockade by phenoxybenzamine.

Dose-response curves: control responses of each strip to noradrenaline were obtained at 3–4 dose levels. Each strip was then exposed to a given concentration of propranolol for 5 min and the response to noradrenaline was tested in the presence of the antagonist. Every 25–30 min the same concentration of propranolol was repeated to obtain the dose-response curve of noradrenaline in the presence of propranolol. Propranolol was then discontinued and 60–75 min after washing out the last dose of propranolol, the response of each strip to noradrenaline 3×10^{-5} g/ml was recorded. In all experiments, each response was expressed as % of this near-maximal response. The results of 3–5 experiments at each level of propranolol have been averaged and plotted in Fig. 1A. A progressive shift to the right of the dose-response curve was observed with increasing concentrations of propranolol. Moreover the slope obtained in the presence of 10^{-4} g/ml propranolol was less steep than that of the control.

The ability of propranolol to protect noradrenaline responses against blockade produced by phenoxybenzamine was tested in six experiments. Each experiment was made on three strips taken from the same aorta. A control dose-response curve was obtained for each strip. Two of the three strips were then exposed for 5 min to the protecting agents: one strip was exposed to noradrenaline (3×10^{-5} g/ml) and the other to propranolol (10^{-4} g/ml). All strips were then exposed (without washing) to phenoxybenzamine (10^{-7} g/ml) for the next 5 min. The protecting drugs and the antagonist were then washed out; washings were repeated every 15 min for 75–90 min, at the end of which responses of each strip to increasing doses of noradrenaline were tested. Fig. 1B illustrates the results of a typical experiment. In all six experiments the responses to noradrenaline (10^{-5} g/ml) were fully blocked by phenoxybenzamine in the unprotected strips, while responses to noradrenaline were retained to a variable degree in the strips protected with either noradrenaline or propranolol during exposure to phenoxybenzamine.

These observations indicate that propranolol, considered to be a prototype β-adrenergic blocking drug (Moran, 1967), may also interact reversibly with the α-adrenoceptive receptors and, may cause a reversible and surmountable type of α-adrenergic blockade when used in concentrations higher than those required to produce blockade of β-adrenoceptive receptors.

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Comparative investigation of the effect of cocaine and desipramine on bronchospasm in guinea-pigs

SIR,—Pharmacological examinations of cocaine and desipramine have shown similarities in some of their properties. The essential characteristic common to both drugs is that both inhibit the uptake of noradrenaline and simultaneously potentiate its effect. Yet there are differences in the activity of the two drugs, for while cocaine inhibits the uptake of noradrenaline to a lesser degree than desipramine (Iversen, 1965) it increases more powerfully the activity of exogenously applied noradrenaline. Taking into consideration these common properties we have examined whether any parallelism exists in the effect of two drugs upon bronchospasm in guinea-pigs. We consider this technique appropriate since adrenergic substances block more or less intensively the bronchial spasm provoked by some spasmogens. The investigation of the influence on the bronchospasm was by plethysmography combined with artificial respiration while the thoracic muscles were relaxed by intravenous injection of suxamethonium in doses of 0·1–0·2 mg/kg (Gjuriš, 1965). The animals were anaesthetized with urethane 1·5 g/kg s.c.

The effect of cocaine and desipramine was tested in bronchial spasm provoked by 5-hydroxytryptamine (5-HT), beginning the experiments at the time when the registered reaction to the spasmogen was 50 % of the initial values (5-HT was given in doses 10–20 g/kg, i.v.).

Cocaine, which resembles desipramine in some ways, differs completely in its influence on bronchospasm under these conditions. Thus cocaine in doses of 0·09, 0·2 and 5 mg/kg, i.v. increased bronchospasm by 31, 73 and 93% respectively. On the other hand desipramine inhibited bronchospasm in doses of 1, 5 and 10 mg/kg, i.v. by 11, 48 and 98% respectively. In contrast to our experiments, Foster (1964) found that cocaine potentiated the relaxant effect provoked by transmural stimulation of the trachea at doses less than 25 μg/ml. The two experiments differ in essential ways; we induced bronchospasm with 5-HT in the intact animal whereas Foster stimulated the isolated trachea electrically. The nervous pathways involved may differ.

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