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EFFECT OF PROPRANOLOL ON ALPHA-ADRENERGIC BLOCKADE IN THE DOG AND ISOLATED RABBIT AORTIC STRIP

BY

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Although propranolol is thought to be a specific blocker of the β-adrenergic receptor (Black, Crowther, Shanks, Smith & Dornhorst, 1964) it is well known that other β-blockers, like dichloroisoproterenol, have sympathomimetic effects (Moran & Perkins, 1958). There are several indications in the literature (Hull, Eltherington & Horita, 1960; Gulati, Gokhale & Udwadia, 1965; Gonçalves & Osswald, 1965) that β-blocking agents such as propranolol can influence the interaction of an α-receptor and α-adrenergic blocking agents, suggesting an effect of the β-blocking agents at an α-receptor site. We have observed (Fig. 1) in the cat that an apparently well-established α-blockade produced by phenoxybenzamine could be virtually completely abolished by administration of the β-blocking agent propranolol. Such an observation seemed to warrant more extensive investigation because of two important implications: (1), do specific β-blocking agents in fact have a previously unrecognized effect on α-receptors ?, and (2), can long-lasting α-blocking agents of the halo-ethylamine type be readily antagonized by β-blocking agents ? The haloethylamine blocking agents are usually considered to act by the formation of alkylated derivatives of the receptors (Harvey & Nickerson, 1954); a finding of ready reversibility by β-blocking agents would be difficult to reconcile with this theory.

The experiments reported in this paper are of two types. In the first, experiments in dogs were designed to demonstrate the cardiovascular effects of catecholamines, the effect of several α-adrenergic blocking agents on the catecholamine responses, and the modification of these responses by the administration of propranolol. In the second type of experiment, isolated strips of rabbit aorta were studied, and the interactions of catecholamines, α-adrenergic blocking agents and β-adrenergic blocking agents were investigated.

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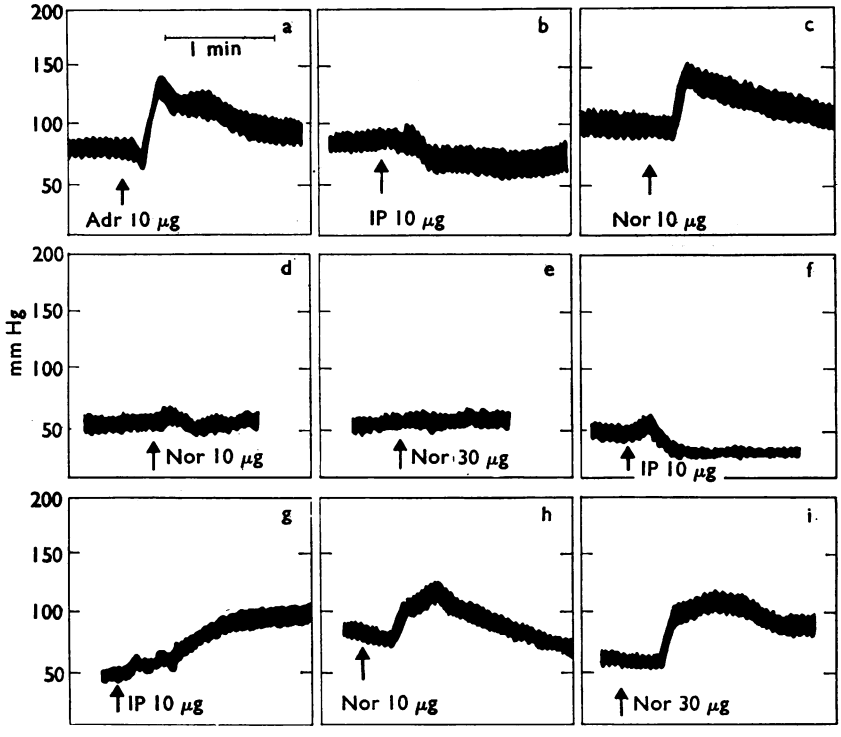

Fig. 1. Blood pressure response to catecholamine administration under conditions of α- and β-blockade in the cat. A 2 kg cat was anaesthetized with dial-urethane and prepared for carotid arterial pressure recording and intravenous drug administration. Ordinate represents carotid arterial pressure in mm Hg. Arrows indicate addition of drugs. Adr, adrenaline; IP, isoproterenol; Nor, noradrenaline. Recordings A, B, and C represent responses to catecholamine administration in the absence of adrenergic blockade. Phenoxybenzamine, 20 mg, was administered between C and D. Propranolol, 1 mg, was given between F and G.

METHODS

Whole animal experiments

Mongrel dogs of either sex weighing between 18–25 kg were used. Anaesthesia was induced with methohexital (10 mg/kg intravenously), and maintained with nitrous oxide and oxygen at 4:2 proportion in a non-rebreathing system using a respiratory pump (Harvard apparatus). The animals were immobilized by an intravenous infusion of succinylcholine (1 mg/min in 0.1 ml. of solution).

Both brachiocephalic veins were cannulated, one for an intravenous drip of dextrose, 5% in water, the other for the succinylcholine infusion. A femoral vein was catheterized for drug injections. Atropine was injected at 2 mg/kg at the start of the experiment, and repeated when needed. Atropine was employed to block reflex vagal effects on heart rate. The adrenal glands were left intact, as it was not thought that secretion of catecholamines from the adrenals, if it occurred, would influence the results obtained.

Blood pressure was measured in the left carotid artery by a Statham pressure transducer (either Model P23Db or P23Gb). Recordings were made on an 8-channel Offner polygraph. Mean blood pressure was obtained by electrical damping. Left ventricular pressure was obtained by passing a No. 9 cournand catheter blindly into the ventricle from the left femoral or right carotid artery, and

measured by a Statham pressure transducer (Model P23Db or P23Gb). Placement of the catheter in the ventricle was determined by the contour of the pressure curves. The electrocardiogram (E.C.G.) was recorded using lead II. Heart rate was measured by means of a cardiotachometer coupler which computes heart rate information from the R-R interval of the E.C.G. signal. The ballistocardiogram (B.C.G.) was used as a measure of the force of contraction (Darby, Walton & Gazes, 1959) using an ultralow frequency (0.3 cycles/sec) undamped pendulum bed. Acceleration is transduced in the head-foot direction with a variable capacitance accelerometer. The dog is coupled to the bed with two canvas straps.

In general, the protocol demonstrating reversal of α-adrenergic blocking agents after administration of the β-adrenergic blocking agent was the following:

(a) Isoproterenol, 0.5–1 μg/kg; noradrenaline, 0.1, 0.3, 1, 3 μg/kg, occasionally 10 μg/kg as control.

(b) α-blocking agent, 5–10 mg/kg.

(c) Isoproterenol and noradrenaline series, same doses as control.

(d) Propranolol, 0.5–1 mg/kg.

(e) Isoproterenol and noradrenaline series, same doses as above, 3–5 times after β-blocking agent.

Adrenaline 1–2 μg/kg was used occasionally. Calcium chloride, 30–50 mg/kg, was employed in some experiments. It was administered at the same time as the β-blocking agent. The adrenergic blocking agents, both α and β, as well as the Ca^{++} were injected slowly (20–30 min) by means of an infusion pump. After administration of the α-blocking agent, a period of 30 min to 1 hr was allowed to elapse before testing catecholamine responses.

Isolated aortic muscle strip

Rabbits weighing 2–3 kg were killed with intravenous pentobarbital. The descending thoracic aorta was removed and placed in a Petri dish containing McEwen solution (McEwen, 1956) at room temperature. The whole length of aorta was then cut along a close spiral. The resulting strip, about 4 mm wide and 6–8 cm long, was divided in two parts and placed in separate muscle chambers which contained McEwen solution at 37° and bubbled with 95% O_2, 5% CO_2. The strips were connected to isotonic levers of the gravity type, adjusted to give 5-fold magnification and counterweighted to exert 5 g resting tension. Recording was on a smoked-paper kymograph. Drugs were added to the 50 ml. bath in volumes of 0.5 and 1 ml. All concentrations mentioned refer to final concentrations of free base in the muscle chamber. One strip was used as a control and the other used for drug treatment.

The protocol used in the isolated strips to demonstrate the reversal phenomenon was the following:

(1) Noradrenaline in graded doses from 2×10^{-9} to 10^{-5} M. Doses were given at 5 min intervals, without changing the bath solution.

(2) Wash.

(3) Phenoxybenzamine, 3×10^{-7} M, left in bath for 10 min. (Experimental strip only.)

(4) Wash.

(5) Noradrenaline series, same as control.

(6) Wash.

(7) Propranolol, 5×10^{-5} M, which was left in the bath.

(8) Noradrenaline series same as control.

(9) Wash.

(8) and (9) were repeated at least twice after propranolol.

The control was treated in the same way as the experimental strip except propylene glycol (the vehicle) was used instead of phenoxybenzamine.

Drugs. The drugs used, and sources of supply, were: Noradrenaline bitartrate monohydrate (Levophed, Winthrop), isoproterenol hydrochloride (Isuprel, Winthrop), epinephrine hydrochloride (Adrenaline, Parke Davis), phenoxybenzamine hydrochloride (Dibenzyline, donated by Smith Kline & French Laboratories), phentolamine methanesulphonate (Regitine, Ciba), tolazoline hydrochloride (Priscoline, Ciba), propranolol hydrochloride (Inderal, donated by Ayerst Laboratories), atropine sulphate and calcium chloride.

RESULTS

Whole animal experiments

Three parameters were chosen for evaluating the results: blood pressure, heart rate and force of cardiac contraction (acceleration BCG). The α-adrenergic blocking agents tested were phenoxybenzamine, tolazoline and phentolamine.

Twenty mongrel dogs of unselected sex were used. Five dogs died before tests were completed, usually during propranolol infusion. Alteration in ECG, decrease in heart rate, depression of contractile force, and fall in blood pressure were observed in these dogs.

Fourteen of the remaining dogs demonstrated reversal phenomenon of α-blockade after propranolol, with one questionable case. Four of 15 dogs were two-day experiments; the α-adrenergic blockade was produced the first day by phenoxybenzamine, and the β-block the next day.

Catecholamines injected at the start of the experiments showed the normal responses: isoproterenol produced a fall in blood pressure, increase in heart rate and contractile force; noradrenaline at increasing doses produced a rise in blood pressure, increase in heart rate and contractile force; and, when adrenaline was used, it resulted in a rise in blood pressure, increase in heart rate and contractile force. Occasionally a decrease in heart rate (vagal effect) was observed, in spite of atropine. The results from a typical experiment are shown in Fig. 2; and the pooled data from all animals are summarized in Table 1.

TABLE 1

CARDIOVASCULAR EFFECTS OF CATECHOLAMINES IN THE ABSENCE AND IN THE PRESENCE OF ADRENERGIC BLOCKING AGENTS

The values in the table represent the means and standard errors of the % change of each parameter in response to catecholamine administration in 9 separate experiments

Agent	% increase (or decrease)		
	Mean blood pressure	Heart rate	Ballisto-cardiogram
Isoproterenol 1 μg/kg (9 dogs)			
Control	—18±2·7	47±16	93±34·8
After phenoxybenzamine	—28±8·7	12± 2·7	51±19·9
After phenoxybenzamine and propranolol	12±5·1	9± 1·9	21± 8·1
Noradrenaline 1 μg/kg (9 dogs)			
Control	51±18·1	33±10·7	90±36·4
After phenoxybenzamine	18± 5·9	5± 0·7	51±24·4
After phenoxybenzamine and propranolol	45±16·5	5± 2·2	22± 7·4

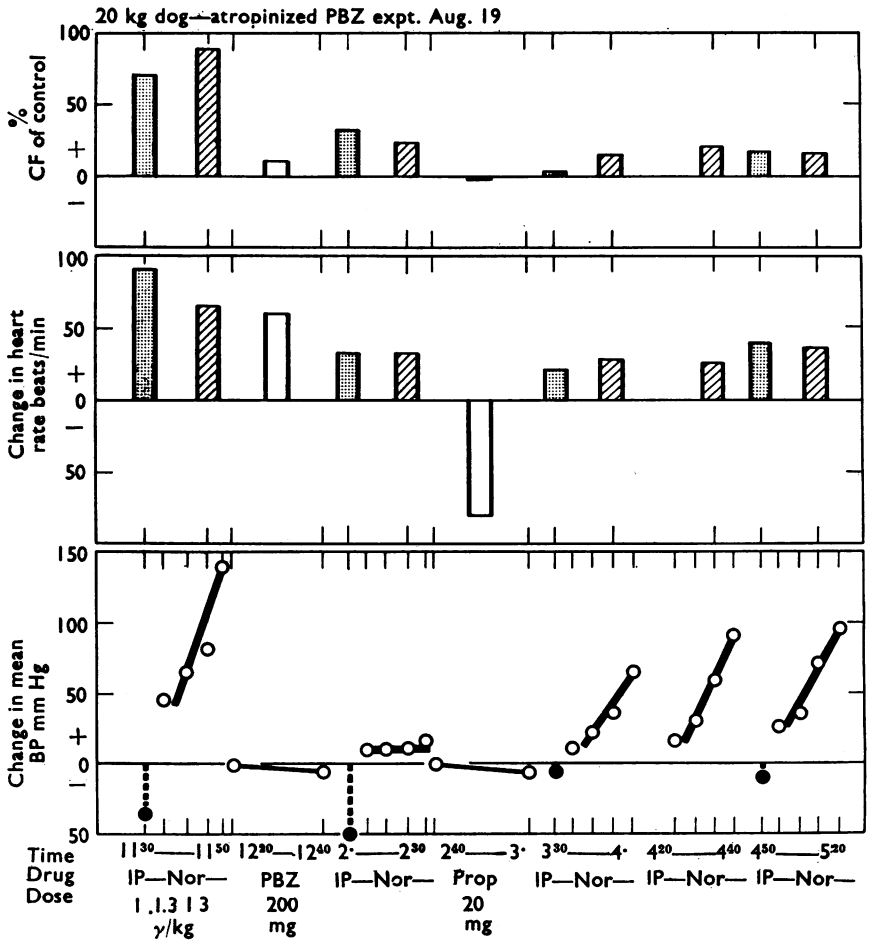

Fig. 2. Cardiovascular effects of isoproterenol and noradrenaline in the dog in the absence of adrenergic blockade and in the presence of α- and β-blocking agents. Change in mean blood pressure to 1 μg/kg isoproterenol (IP), - - - ● ; and in the response to increasing doses (0.1, 0.3, 1 and 3 μg/kg) noradrenaline (Nor), ○—○—○. Changes in heart rate and contractile force (CF) in response to 1 μg/kg IP, stippled bar; to 1 μg/kg Nor, slashed bar ; and to 10 mg/kg phenoxybenzamine (PBZ) or 1 mg/kg propranolol (Prop), open bar.

After phenoxybenzamine, the blood pressure usually fell, but the heart rate and contractile force increased (Fig. 2, Table 2). When tolazoline or phentolamine were used, the blood pressure either did not change or increased slightly, with a rise in heart rate and contractile force.

After administration of the α-blocker, isoproterenol continued to produce the usual, or enhanced, fall in blood pressure. The heart rate and contractile force also increased as usual with isoproterenol (Fig. 2, Table 1). Blood pressure showed a markedly decreased response to noradrenaline, amounting to a depression of 70–90% of control values ; heart rate and contractile force, however, increased. When adrenaline was used,

the pressor response was reversed to a depressor response with increases in heart rate and contractile force.

After the β-blocker propranolol, blood pressure either fell, did not change, or slightly increased; the heart rate and contractile force were always depressed (Table 2).

TABLE 2

CARDIOVASCULAR EFFECTS OF ADRENERGIC BLOCKING AGENTS

The values in the table represent the means and standard errors of the % change of each parameter in response to the administration of α- or β-blocking agents for the number of experiments cited in parenthesis in the left-hand column

Agent	% increase (or decrease)		
	Mean blood pressure	Heart rate	Ballisto cardiogram
Phenoxybenzamine 10 mg/kg (9 dogs)	—22± 5·9	30± 9·6	23± 9·6
Propranolol 1 mg/kg (3 dogs)	—31±23·2	—37±20·4	—59±41·1
Propranolol+Ca^{++} 1 mg/kg (6 dogs)	6± 7	—34±13·6	—37±16·4

When catecholamines were tested after the β-blocker, blood pressure now showed responses comparable to control values; the extent of depression of the pressor response was now only 10–30% of control values with noradrenaline (Fig. 2, Table 1). Isoproterenol no longer gave a hypotensive response; in fact there was usually a pressor response (Table 1). Adrenaline no longer showed depressor responses, and the pressor response reappeared. Heart rate and contractile force increased, but remained less than control values, and noradrenaline sometimes produced a decrease in heart rate.

Several experiments were performed over longer time intervals than described above. In the first type of experiment, phenoxybenzamine (10 mg/kg) was given 18 hr before the administration of propranolol. On testing the responses to noradrenaline on the day following phenoxybenzamine, there was good but not complete blockade of the pressor response to noradrenaline. Administration of propranolol resulted in the reversal of α-blockade, with the appearance of responses characteristic of blockade of the β-receptors (Fig. 3). In the second type of experiment, the cardiovascular responses to noradrenaline and isoproterenol were followed for 9 hr subsequent to the administration of propranolol (which had been given after phenoxybenzamine). Although the effects of the propranolol wore off after 4–5 hr (as judged by the reappearance of a normal depressor response to isoproterenol), the α-blockade was not re-established (Fig. 3).

One experiment was performed in which the β-blocker was given first and then the α-blocking agent; the results showed that propranolol interfered with the establishment of an expected α-blockade.

In other experiments, phentolamine or tolazoline were used to produce α-adrenergic blockade. Propranolol reversed the blockade with these agents also.

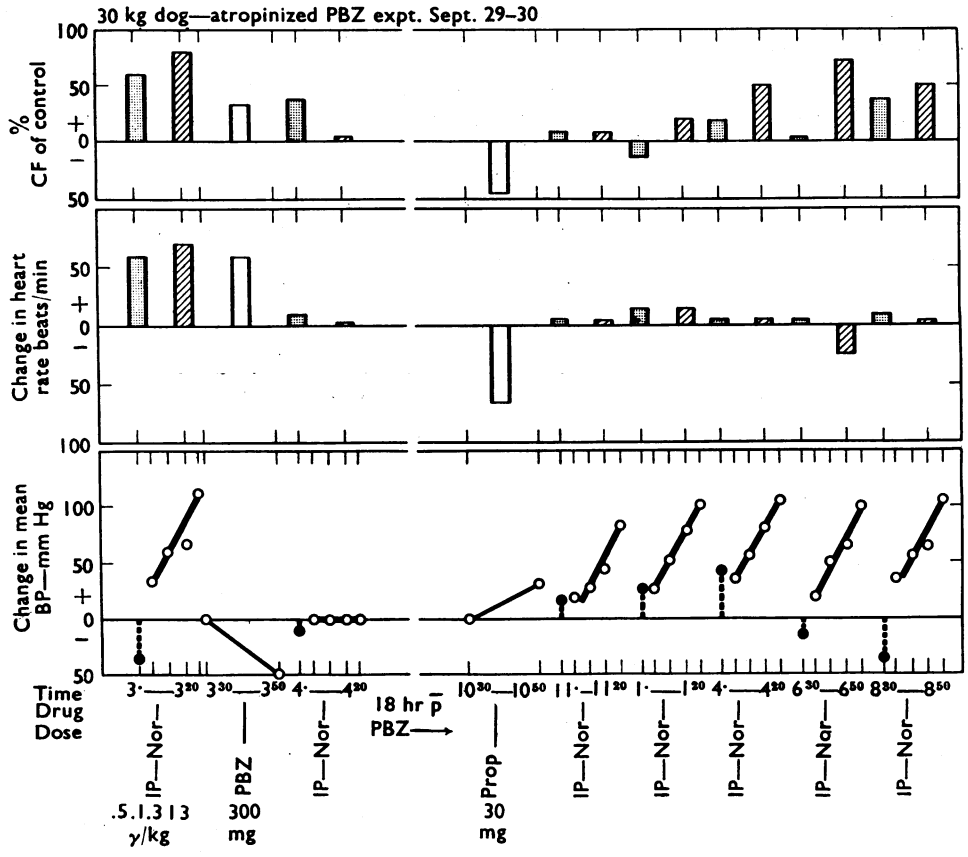

Fig. 3. Reversal of α-adrenergic blockade by propranolol 18 hr after phenoxybenzamine. The data is shown in the same manner as described for Fig. 2.

Isolated aortic strip muscle experiments

Dose-response curves to noradrenaline were obtained in isolated aortic muscle strips from six rabbits, and phenoxybenzamine then introduced in the bath of the experimental strip only. Repetition of the dose-response curve to noradrenaline now showed an almost complete blockade, in comparison to the control (Fig. 4). Addition of propranolol to both strips had no effect on muscle tone or the noradrenaline dose-response curve in the control strip, but the noradrenaline response in the experimental strip was partially restored.

One experiment was carried out to demonstrate that the blockade produced by phenoxybenzamine was not being overcome by the washing procedure. Both aortic strips received phenoxybenzamine, and after 10 min both were washed and the experimental strip received propranolol. The strip which had received only phenoxybenzamine showed the expected blockade of noradrenaline response, while the strip which had been treated with propranolol had partially recovered sensitivity to noradrenaline.

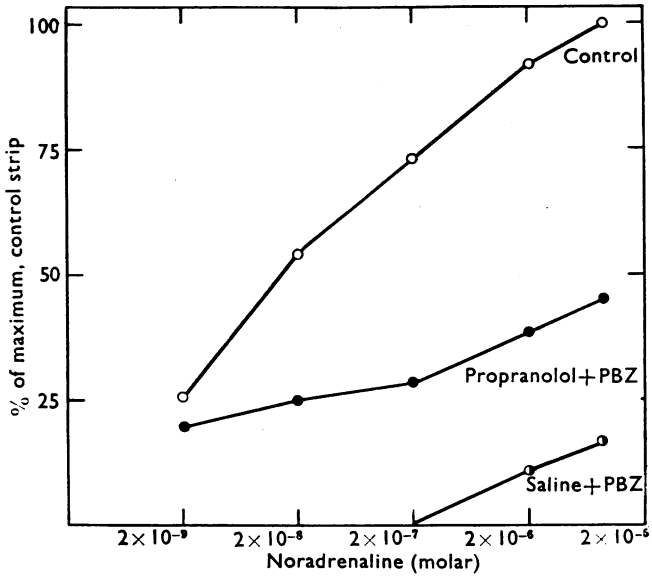

Fig. 4. Effects of phenoxybenzamine and propranolol on the dose-response curve of noradrenaline in the isolated rabbit aortic muscle preparation. A rabbit aortic muscle strip was prepared as described in the text and divided in two equal parts. Each was mounted in a separate bath, one serving as a control, the other as an experimental strip. Both strips were treated in an identical fashion, except that the control strip was not treated with phenoxybenzamine. Ordinate represents per cent of the maximal contraction of the control. Abscissa represents the molar concentration of noradrenaline in the chamber bath. Control preparation, ○——○; experimental preparation after 3×10^{-7} M phenoxybenzamine (PBZ), ◑——◑; and after PBZ followed by propranolol, 5×10^{-5} M, ●——●.

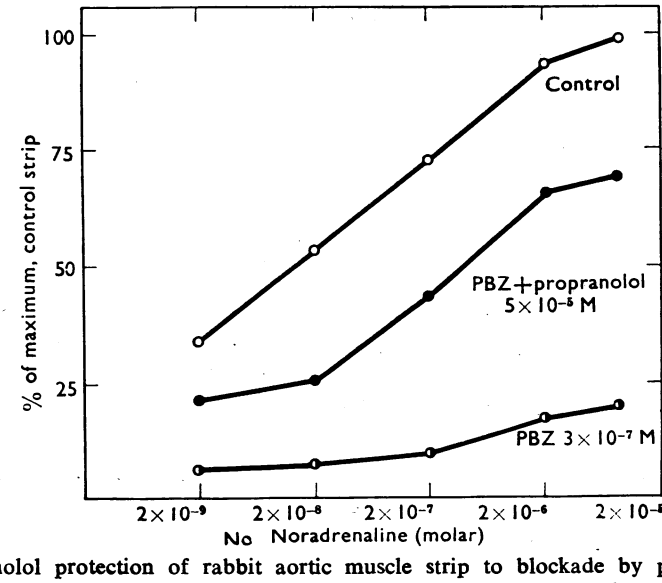

Fig. 5. Propranolol protection of rabbit aortic muscle strip to blockade by phenoxybenzamine. The graph shows dose-response curves to noradrenaline in a pair of aortic strips and the subsequent dose-response curves to noradrenaline following simultaneous 10 min exposure to propranolol (or saline) and 3×10^{-7} M phenoxybenzamine (PBZ). The experimental strip received propranolol, 5×10^{-5} M. Control, ○——○; after saline and PBZ, ◑——◑; and after propranolol and PBZ, ●——●. Units of the abscissa and ordinate as in Fig. 4.

One protection experiment was designed in which the experimental strip received propranolol (5×10^{-5} M) and the control strip an equal volume of saline. Phenoxybenzamine (3×10^{-7} M) was then added to both strips, and allowed to remain in the bath for 10 min. After washing, dose-response curves were obtained to noradrenaline. As expected, the control showed almost complete blockade. However, the strip which was exposed to both propranolol and phenoxybenzamine showed larger responses to noradrenaline over the range of doses used (Fig. 5).

DISCUSSION

In interpreting these results, it is important to consider that noradrenaline might have, as a small component of its action, an effect on β-receptors. If propranolol blocked this effect, the net result of sequential administration of a β- and α-blocking agent might appear to be an enhanced α response, or an apparent reversal of the α-receptor blockade (Karim, 1964). It is well known that noradrenaline does have some β-stimulating properties (Burn & Hutcheon, 1949 ; Parratt, 1965). Nevertheless, several considerations make it unlikely that this is the basis of our results. First, propranolol very nearly eliminates the α-blockade ; the effect is rather larger than one might expect if, in fact, the sole effect of the β-blocking agent were to eliminate a β-response and unmask a small residual α-response.

Another possibility might be that the α-blockade had not been well established, and propranolol interfered with its establishment. Our experimental design, however, allowed 30 min to 1 hr to elapse after administration of phenoxybenzamine before the catecholamine response was tested, and propranolol was not given until another 30 min or more had elapsed (for example, Fig. 2). The amount of phenoxybenzamine given, 10 mg/kg, is a large dose and it is known that doses of this magnitude promptly produce a blockade which lasts, ordinarily, 2 or 3 days (Brodie, Aronow & Axelrod, 1954). Further, in a few experiments (Fig. 3) propranolol was not administered until the following day. Although the blockade of α-receptors was still quite apparent at this time (not shown in the figure), propranolol administration produced a prompt " unblocking " effect. It should be noted that the α-blockade, once it has been interrupted by propranolol, does not re-appear after the β-blocking agent has worn off (Fig. 3), suggesting that in fact we have unblocked an α-receptor site.

Finally, the responses of the isolated aortic muscle strip are quite clear cut. This preparation seems to respond almost entirely as an α-receptor preparation. Isoproterenol has little or no effect on these strips (Furchgott & Bhadrakom, 1953), nor does propranolol, either directly or an as antagonist of noradrenaline. Yet, propranolol partially reverses a phenoxybenzamine-induced blockade of this strip *in vitro*, and also interferes with the establishment of an α-blockade.

Gulati *et al.* (1965) examined pronethalol against phentolamine in a similar series of experiments, and by reciprocal analysis, before and after pronethalol, indicated that the antagonism of adrenergic blockade was competitive.

On the basis of the results presented, we conclude that propranolol has an effect on the α-receptor as well as blocking β-receptors. The α-effect is such that propranolol can restore the sensitivity of a previously blocked receptor to noradrenaline. This is true

for all three α-blocking agents studied, including the long-lasting, supposedly irreversible blocking agents of the phenoxybenzamine type. Although we cannot pretend fully to understand the mechanism of the "unblocking" effect of propranolol, one possibility is that these supposedly irreversible α-blocking agents are in fact not covalently linked to the α-receptor. Brodie, Aronow & Axelrod (1954) showed that the drug was present in an unchanged form in fat depots for very long long periods of time, and, despite a considerable accumulation of data suggesting an alkylation of receptor sites, it is still possible that the drug acts either as the unchanged moiety or as the ethyleneimmonium derivative, and not by irreversible alkylation of receptors.

Five dogs in this series of experiments died either during or shortly after propranolol administration due to its effects on the heart. Depressor action on the heart by β-blocking agents has been reported (Moran & Perkins, 1958; Somani & Lum, 1965). Shanks (1965) considers propranolol to be not free of such action and we concur. One of us (Smith, 1966) has observed that dogs under β-adrenergic blockade are more sensitive to a decrease in serum calcium ions produced by citrate infusion than are control animals. We decided to inject Ca^{++} (30–50 mg/kg $CaCl_2$) after propranolol administration was started in order to protect the heart from the deleterious cardiac effects of propranolol. Of the eight dogs which received propranolol and calcium, none died. However, decreases in cardiac contractile force and heart rate were not avoided (Table 2). The relationship of calcium and β-blocking agents deserves further study. It should be emphasized that these deleterious effects (cardiac slowing and decreased force of contraction) of propranolol on the heart are seen in dogs only after they had been previously treated with large doses of potent α-adrenergic blocking agents.

SUMMARY

1. The effects of propranolol (1 mg/kg) upon α-adrenergic blockade produced in 20 dogs by phenoxybenzamine (6–10 mg/kg), phentolamine (10 mg/kg) and tolazoline (10 mg/kg) were studied. Propranolol reversed the α-blockade produced by all three agents, restoring a practically normal pressor response to noradrenaline. The reversal was evident within 5 min after propranolol administration, and reached a maximum 1–2 hr later.

2. The α-blockade did not re-appear after the effects of the β-blocking agent disappeared (as measured by the return of a normal hypotensive response to isoproterenol).

3. Prior administration of propranolol interfered with the establishment of an α-blockade in the intact dog.

4. The response of isolated aortic muscle strips to noradrenaline could be blocked by phenoxybenzamine; this blockade was also reversed by propranolol. Similarly, propranolol interfered with the establishment of α-blockade in this preparation.

5. The possibility that propranolol, by blocking the weak β response of noradrenaline, unmasked a small, residual α-stimulation which the α-adrenergic blocking agents had not completely blocked was discussed and rejected. It was therefore concluded that propranolol interacts with a previously blocked α-receptor, in some undefined way, to displace α-blocking agents. This is true even with the long-lasting, supposedly irreversible blocking agents like phenoxybenzamine.

6. Five dogs in this series died, due to the deleterious effects of propranolol on the heart, in animals which had already been heavily treated with potent α-adrenergic blocking agents. No deaths were observed when Ca^{++} infusions were given along with propranolol. These observations suggest it would be wise to be cautious in the use of this potent β-adrenergic blocking agent for the treatment of arrhythmias and other cardiac diseases.

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