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FURTHER OBSERVATIONS ON THE PRESSOR ACTION OF PROPRANOLOL

BY

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Propranolol was introduced by Black, Crowther, Shanks, Smith & Dornhorst (1964) as a potent β-adrenergic receptor blocking agent. In the previous paper (Kayaalp & Kiran, 1966), evidence was presented for the fact that the sustained pressor response elicited by this drug in the sympathetically denervated perfused hind limbs of the dog is due to the release of catecholamines from the adrenal medulla.

The present work was undertaken to determine if the release of catecholamines from the adrenal medulla is the only mechanism by which propranolol produces a vasoconstrictor response or it causes an increase in the sympathetic nervous activity on the vasculature of the perfused area in addition. An attempt has also been made to elucidate further the mechanism of the sustained pressor response to propranolol, particularly as observed after the blockade of the α-adrenergic receptors.

METHODS

Dogs of either sex, weighing between 12 and 26 kg were used. They were anaesthetized by intravenous injection of sodium pentobarbital (30 mg/kg). The trachea was cannulated for free airway, and the left jugular vein was cannulated for intravenous injection of drugs. The procedures for surgery, perfusion and recording the systemic blood pressure and perfusion pressure were the same as previously described (Kayaalp & Kiran, 1966), except that both hind quarters were autoperfused together as described by Beck (1961).

The sympathetic nerves to the perfused area were kept intact, and this was verified by the occurrence in the perfused area of a reflex vasodilatation in response to the rise in systemic blood pressure elicited by noradrenaline (0.3–0.5 μg/kg, intravenously) or of a pressor response to bilateral occlusion of the common carotid arteries for 50 sec.

Adrenal gland exclusion

In all dogs, except those with spinal cord section or nephrectomy and some of those pretreated with dichloroisoprenaline, the adrenal glands were excluded from the circulation in order to rule out the vasoconstrictor response to propranolol related to the release of catecholamines from the adrenal medulla (Kayaalp & Kiran, 1966). The right adrenal gland was reached through an incision along the lower edge of the last rib ; the left adrenal gland was reached through the incision in the left flank done for the cannulation of the lumbar aorta for perfusion. The vascular connexions of the glands with the surrounding tissue were tied. The glands were left in place. Two hours were allowed to elapse before starting the experiment.

Nephrectomy

In 2 dogs the right kidney was found through an incision in the right flank ; the left kidney was found through the incision in the left flank. They were dissected and removed after ligating the vessels and ureter in the hilus. Two hours were allowed to elapse before starting the experiment.

Section of the spinal cord

In 4 dogs the muscles of the neck were dissected to expose the atlanto-occipital membrane and the spinal cord was then cut through an incision in the membrane. Both common carotid arteries were tied. Three hours were allowed to elapse before beginning the perfusion of the hind quarters.

Drugs used were propranolol hydrochloride (Inderal, I.C.I.), dichloroisoprenaline hydrochloride (Aldrich), phentolamine hydrochloride (Regitine, Ciba), (−)-noradrenaline bitartrate (Hoechst), (−)-adrenaline bitartrate (Boehringer) and (−)-isoprenaline hydrochloride (Winthrop). Doses of the drugs are expressed as salt, except for the last three, which are expressed as the base.

RESULTS

Effect of propranolol on perfusion pressure

Observations were made in 8 dogs. In 7 propranolol (0.3–1.0 mg/kg intravenously) produced a sustained rise in perfusion pressure preceded by a transient fall (Fig. 1). In 1 dog propranolol (0.4 mg/kg intravenously) did not produce an appreciable pressor response. In all dogs, it caused a slowly progressing fall in the systemic blood pressure of slight to moderate magnitude.

The sustained rise in perfusion pressure induced by propranolol reached a plateau within 4 to 13 min. The magnitude of the rise was variable ranging from 10 to 55 mm Hg

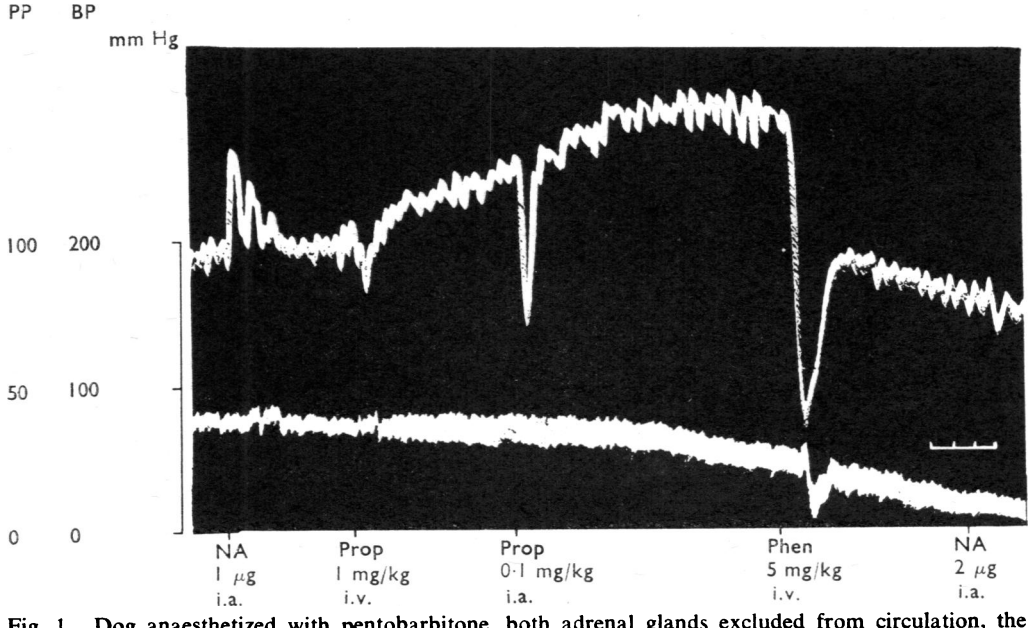

Fig. 1. Dog anaesthetized with pentobarbitone, both adrenal glands excluded from circulation, the hind quarters autoperfused. Recordings of blood pressure (BP, lower) and perfusion pressure (PP, upper). Responses to noradrenaline (NA), propranolol (Prop) and effect of phentolamine (Phen) on these responses are shown. Time marks, 1 min.

and appeared to be independent of the dose. The repetition of the dose, even at a higher level, usually did not elicit any further elevation in perfusion pressure.

In some dogs phentolamine (5 mg/kg intravenously) was given after the pressor response to propranolol reached a plateau, and it decreased the perfusion pressure below the control level. A similar result was obtained with the section of the lumbar sympathetic chains in both sides.

Effect of propranolol in dogs treated with an α-adrenergic blocking agent

In four dogs, phentolamine was infused intra-arterially to the hind quarters at a rate of 5.0 to 5.8 mg/min for 22 to 28 min. Alpha-receptor blockade was verified by the abolition of the pressor response to noradrenaline and the reversal of the response to adrenaline, both given intra-arterially. Phentolamine usually reversed the response to noradrenaline too, though to a smaller extent than the response to adrenaline; it abolished the pressor response in the perfused area to the bilateral occlusion of common carotid arteries. While the infusion was in progress, propranolol (0.5 to 1.0 mg/kg intravenously) was injected and produced a sustained rise in perfusion pressure, reaching a peak in less than 5 min (Fig. 2). It caused a sustained fall in the systemic blood

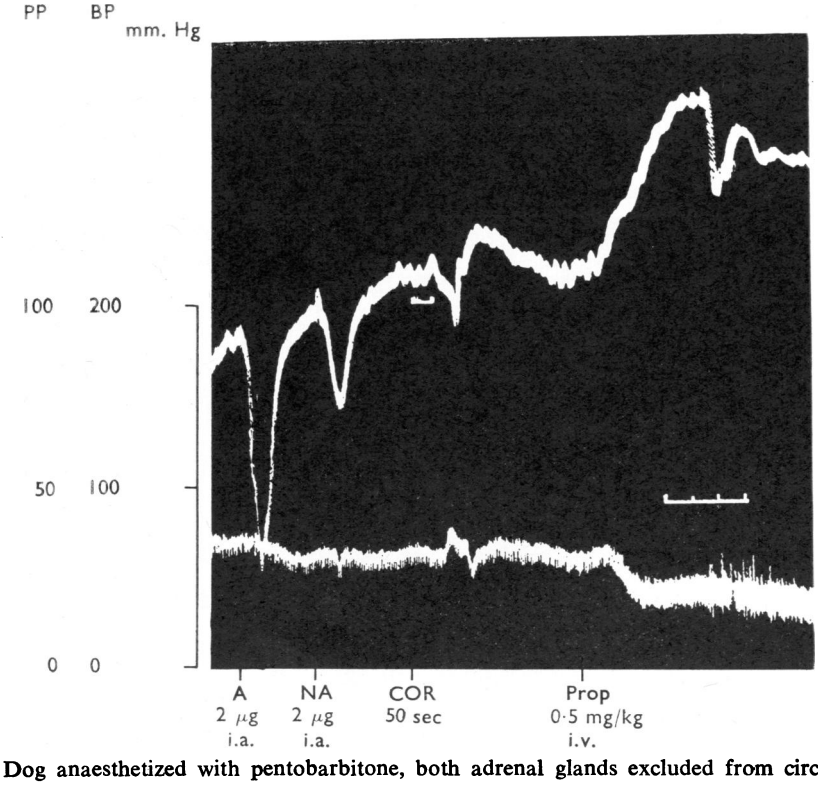

Fig. 2. Dog anaesthetized with pentobarbitone, both adrenal glands excluded from circulation, the hind quarters autoperfused, intra-arterial infusion of phentolamine (5.8 mg/min) in progress. Recordings of blood pressure (BP, lower) and perfusion pressure (PP, upper). Responses to adrenaline (A), noradrenaline (NA), carotid occlusion reflex (COR) and propranolol (Prop) are shown. Time marks, 1 min.

pressure. The magnitude of the rise in perfusion pressure was variable, ranging from 15 to 50 mm Hg. The second dose of propranolol did not cause any further rise in perfusion pressure, but only an initial fall.

In order to rule out the possibility that the pressor response elicited by propranolol after the blockade of the α-adrenergic receptors in dogs with adrenal exclusion, or without it (Kayaalp & Kiran, 1966), might be due to the activation of the renal renin-angiotensin system, experiments were done in 2 additional dogs with bilateral nephrectomy. Their adrenal glands and sympathetic innervation in the perfused area were left intact. The results obtained in one of them is shown in Fig. 3, in which propranolol (1 mg/kg intravenously) given while the infusion of phentolamine was in progress caused a sustained rise of about 50 mm Hg in perfusion pressure ; it also induced an occasional rise in the systemic blood pressure. In the other dog, a similar result was obtained with the exception that propranolol produced a slight fall in the blood pressure.

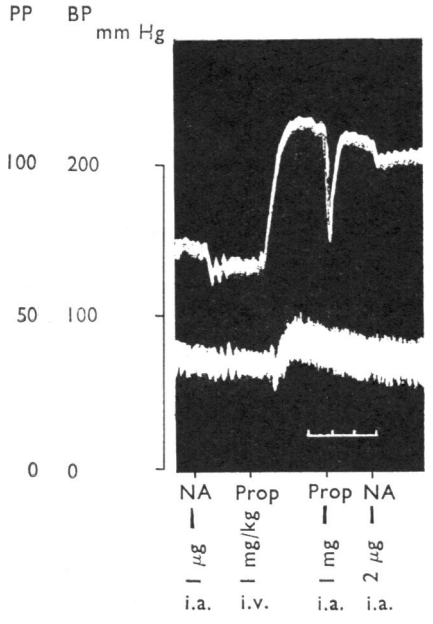

Fig. 3. Dog anaesthetized with pentobarbitone, bilaterally nephrectomized, the hind quarters auto-perfused, intra-arterial infusion of phentolamine (5 mg/min) in progress). Recordings of blood pressure (BP, lower) and perfusion pressure (PP, upper). Responses to noradrenaline (NA), and propranolol (Prop) are shown. Time marks, 1 min.

Effect of propranolol in dogs treated with another β-adrenergic blocking agent

In the first series of experiments in 3 dogs treated with two subsequent intravenous doses of dichloroisoprenaline (5 mg/kg each), propranolol (1 mg/kg intravenously) did not elicit any pressor response in the perfused area in 2 and a slight rise of less than 10 mm Hg perfusion pressure in one. In all of them the adrenal glands and the sympathetic innervation to the perfused area were left intact. At the dose level used, dichloro-

isoprenaline blocked the vasodilator response to isoprenaline (1–2 μg intra-arterially); it depressed to a large extent the rise in perfusion pressure due to the carotid occlusion reflex without reducing the pressor response to noradrenaline (1–2 μg intravenously).

In another series of experiments in 6 dogs (4 with adrenal gland exclusion and all with the sympathetic innervation intact), animals were treated with dichloroisoprenaline (10 mg/kg intravenously) and subsequently the intra-arterial infusion of phentolamine was started at a rate of 4.3 to 5.8 mg/min for about 25 min. Propranolol (0.5–1 mg/kg intravenously), given while the infusion was in progress, did not cause any appreciable rise in perfusion pressure but a slight initial fall in 4 (Fig. 4); it induced a slight sustained pressor response of less than 15 mm Hg in 2.

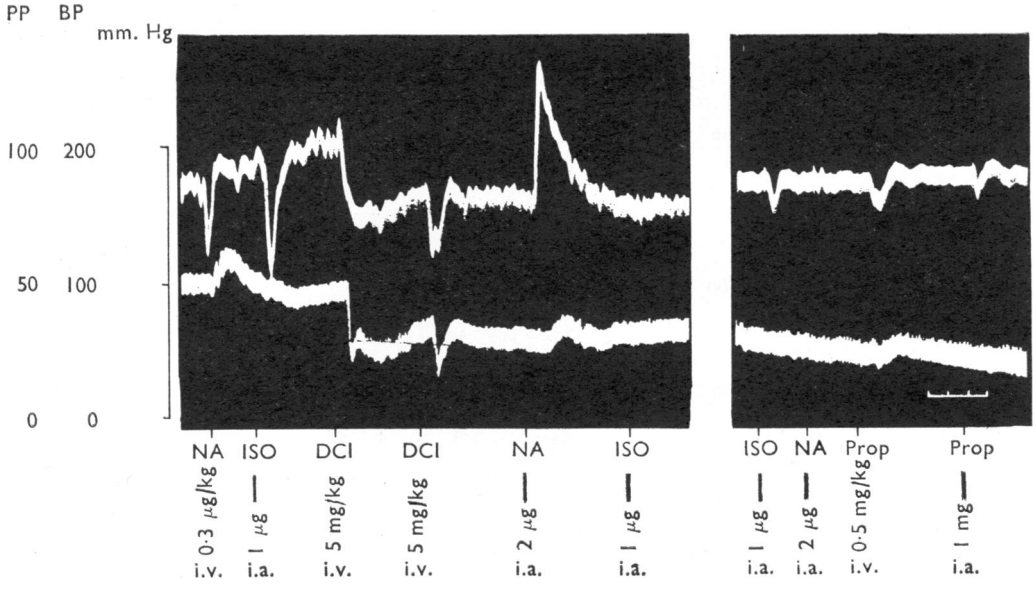

Fig. 4. Dog anaesthetized with pentobarbitone, both adrenal glands excluded from circulation, the hind quarters autoperfused. Recordings of blood pressure (BP, lower) and perfusion pressure (PP, upper). Responses to noradrenaline (NA), isoprenaline (ISO), dichloroisoprenaline (DCI) and propranolol (Prop) are shown. In the right panel, intra-arterial infusion of phentolamine (4.4 mg/min) in progress. Interval between left and right panels is 10 min. Time marks, 1 min.

In the majority of the dogs treated with dichloroisoprenaline, propranolol elicited a slight and fairly sustained rise in the systemic blood pressure. On the other hand, dichloroisoprenaline itself invariably caused a sustained fall in both perfusion and systemic blood pressures.

Effect of propranolol in spinal dogs

In 4 spinal dogs with the adrenal glands and sympathetic innervation otherwise intact, propranolol (0.5–1.0 mg/kg intravenously) did not produce any pressor response but only an initial transient fall in the perfused area (Fig. 5).

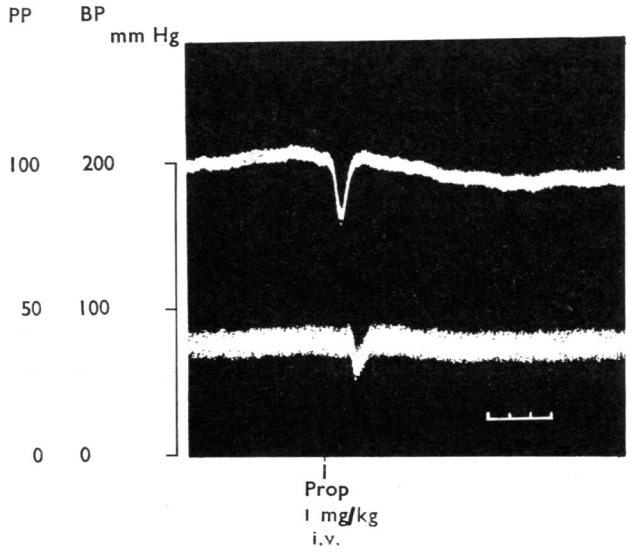

Fig. 5. Spinal dog anaesthetized with pentobarbitone and maintained on artificial ventilation, both lumbar sympathetic chains and adrenal glands intact, the hind quarters autoperfused. Recordings of blood pressure (BP, lower) and perfusion pressure (PP, upper). Response to propranolol (Prop) is shown. Time marks, 1 min.

DISCUSSION

The results show that propranolol induces a sustained pressor response in the perfused area with intact sympathetic innervation in dogs whose adrenal glands were excluded from the circulation. This response may be due to a reflex increase in the sympathetic activity on the vessels resulting from the fall in the systemic blood pressure or any other haemodynamic chance due to propranolol. A similar postulate was put forward by Nakano & Kusakari (1965, 1966) as to the cause of the pressor response to propranolol. Such a possibility is favoured by the lack of the response in the spinal dogs, and in dogs with bilateral adrenal gland exclusion plus sympathetic denervation (Kayaalp & Kiran, 1966). Accordingly, the complete or near complete abolition of the response in dogs treated with dichloroisoprenaline, another β-adrenergic receptor blocking agent (Powell & Slater, 1958), might be due to a depressant action of this drug on the sympathetic outflow. Dichloroisoprenaline, and also pronethalol, have been shown to reduce the pressor responses to the preganglionic stimulation of the sympathetic nerves about 50% simultaneously with a slight increase in the pressor response elicited by intra-arterial noradrenaline in the similar preparation in dog (Kayaalp, 1966). Dichloroisoprenaline depressed also the pressor response to the carotid occlusion reflex.

Another explanation for the effective antagonistic action of dichloroisoprenaline on the pressor response to propranolol may be put forward. The catecholamines released from the adrenal medulla and sympathetic nerve endings under the tonic sympathetic discharges from the central nervous system are likely to create a minor vasodilator influence mediated via the vascular beta adrenergic receptors and overshadowed by the predominant vasoconstrictor influence. On the basis of this assumption, propranolol is expected to produce

a " passive " vasoconstriction by a selective blockade of the β-adrenergic receptors underlying the minor vasodilator influence. On the other hand, dichloroisoprenaline, which also blocks the same receptors, is not expected to cause a similar pressor response, possibly because of its remarkable non-specific depressant action on the vascular tone as evidenced by the large sustained fall in perfusion pressure elicited by this drug (Fig. 4). After the blockade of the β-adrenergic receptors by dichloroisoprenaline, propranolol is not likely to produce a pressor response in the perfused area.

The aforementioned two possible mechanisms of action may take part together in the pressor response to propranolol. On the other hand, the interesting pressor response to propranolol after the blockade of the α-adrenergic receptors by phentolamine might be mainly due, if not wholly, to the latter mechanism of action mentioned above—namely, the passive vasoconstriction arising from the blockade of the β-adrenergic receptors. In that case, the former mechanism was rendered already ineffective by the blockade of the α-adrenergic receptors. The α-adrenergic blocking agents were shown to raise the output of the sympathetic transmitter in the venous blood from the spleen when the splenic nerves are excited (Blakeley, Brown & Ferry, 1963). By such an action, the infusion of phentolamine which blocks the α-adrenergic receptors might make available more transmitter to activate the nearby β-adrenergic receptors and consequently might exaggerate the possible vasodilator influence.

Phentolamine, when given intra-arterially at the rate used in this study, unmasked the slight β-adrenergic action of noradrenaline (Ahlquist, 1948). The blockade of the α-adrenergic receptors has already been shown to reverse the pressor action of noradrenaline (Karim, 1964).

The pressor response to propranolol given during the α-adrenergic blockade did not seem to be due to the activation of the renal renin-angiotensin system which accompanies the fall in the blood pressure in some instances (Hodge, Lowe & Vane, 1966). The response was not abolished by the removal of both kidneys.

The discrepancy between the pressor action of propranolol in the perfused area and its depressor action in the systemic circulation was explained in the previous paper by Kayaalp & Kiran (1966) on the basis of the fact that the depressant action of this drug on the heart arising from the β-receptor blockade can overcome the pressor action. The observation that propranolol usually produced a slight rise in the systemic blood pressure in dogs treated with dichloroisoprenaline appears to be in favour of this suggestion.

SUMMARY

1. Propranolol induces a sustained pressor response in the perfused hind quarters of the dogs whose both adrenal glands are excluded from the circulation, possibly by a reflex increase in the sympathetic activity on the vessels, at least in part. This response does not occur in spinal dogs. It is almost completely abolished in dogs treated with dichloroisoprenaline.

2. Even during the blockade of the α-adrenergic receptors by phentolamine, propranolol causes a similar sustained rise in the perfusion pressure. The previous treatment of the dog with dichloroisoprenaline prevents the latter response.

3. The results suggest that a " passive " vasoconstriction arising from the abolition by propranolol of a minor vasodilator tonic influence mediated *via* the vascular β-adrenergic receptors may take part in the pressor response to propranolol.

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