Stimulation of Renal Vascular "Alpha-Receptors" with Isoproterenol[1] (34707)

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It is generally agreed that isoproterenol stimulates mainly beta-adrenergic receptors (1–3). It is also agreed that stimulation of beta-receptors in vascular smooth muscle results in relaxation and a consequent increase in blood flow (1, 3). However, Spencer (4) reported that intra-arterial bolus injections of isoproterenol into dog kidneys generally decreased renal blood flow. These results suggested that there were probably few beta-receptors in the renal vasculature, and that isoproterenol might stimulate alpha-adrenergic receptors, resulting in vasoconstriction.

The relative lack of responsive beta-receptors in renal vasculature appears to be well established (3, 5). On the other hand, Mark *et al.* (6) were unable to stimulate alpha-receptors with doses of isoproterenol below 32 μg, but in a subsequent study (7) these workers reported that doses above 32 μg produced renal vasoconstriction.

The purpose of the present investigation was to examine changes in canine renal blood flow produced by isoproterenol in the presence and absence of beta-adrenergic and alpha-adrenergic blocking drugs. Results obtained support the view that isoproterenol can stimulate alpha-adrenergic receptors, and are consonant with the concept that beta-receptors in the renal vasculature are few in number.

Methods. Experiments were performed on 18 mongrel dogs of either sex (15–20 kg), anesthetized with sodium pentobarbital (20–25 mg/kg) within 1 hr after premedication with morphine sulfate (3 mg/kg) subcutaneously. Central arterial and venous pressues were monitored continuously with a Grass Model 5 polygraph from catheters inserted into the right femoral artery and vein, and advanced into the thoracic cavity so that their tips were close to the heart. The catheters were attached to Statham P23AC pressure transducers which were connected to the recording polygraph.

The left renal artery was exposed through a flank incision. Renal blood flow was measured with a noncannulating electromagnetic flow sensor (Statham-Medicon), fitted snugly around the renal artery. The zero flow base line was determined by momentarily occluding the artery distal to the flow sensor. Drugs were dissolved in saline, and the bolus was injected (1 ml) into the renal artery through polyethylene tubing connected to a 25-gauge needle which was implanted in the artery. The maximum change in renal blood flow elicited by isoproterenol was expressed as percentage of control blood flow measured just before drug injection. Responses were statistically evaluated by the Student's *t* test (8).

The drugs used were isoproterenol hydrochloride (Winthrop Labs), phentolamine (Ciba), phenoxybenzamine (supplied through the courtesy of Smith, Kline and French Labs), and propranolol (supplied through the courtesy of Ayerst Labs). Phentolamine and propranolol were bolus-injected intra-arterially, but phenoxybenzamine was dissolved in warm saline and infused into the renal artery at a rate of 1.16 ml/min until a total of 5 mg/kg of body weight was delivered. Doses of isoproterenol were expressed in terms of the free base, but doses of all other drugs were expressed in terms of the salt.

Results. Renal vascular responses to close intra-arterial bolus injections of isoproterenol (1–100 μg) are summarized in Fig. 1. No

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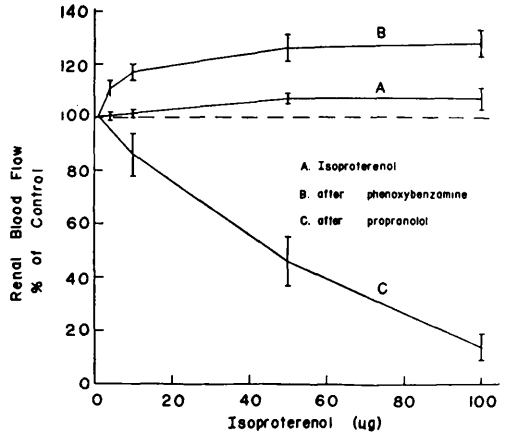

FIG. 1. Effects of isoproterenol on renal blood flow: (--), control blood flow. Mean responses to intra-arterial bolus injections of 1, 5, 10, 50, and 100 μg of isoproterenol are shown. Small vertical bars represent ± 1 SE. (A) Responses to isoproterenol alone in 9 dogs. (B) Responses after intra-arterial infusion of phenoxybenzamine (5 mg/kg) in 4 dogs. (C) Responses after intra-arterial bolus injection of propranolol (5 mg) in 3 dogs.

significant increase in renal blood flow occurred until dose levels of 50 μg were attained (Curve A). With 50 μg, the flow response was 107% $\pm$ 2 SE of control; the increase, although small, was significant at the 0.005 level. In contrast, the response obtained with 100 μg of isoproterenol was not significantly different from control flow.

After alpha-receptor blockade with phenoxybenzamine (Curve B), a significant increase in renal blood flow occurred with 5 μg of isoproterenol. Moreover, increases in flow at all higher doses, though not significantly different from each other, were significantly different from control. The increased renal blood flow observed during isoproterenol administration was abolished by beta-blockade with propranolol.

In 9 dogs, the mean renal flow response to 10 μg of isoproterenol (101% $\pm$ 1 SE) was unaltered by prior administration of phentolamine (5 mg, ia). The effect of this blocking drug thus was decidedly different from that of phenoxybenzamine. The dose of phentolamine, however, was sufficient to block renal vasoconstrictor responses to direct renal nerve stimulation (20 V, 10 cps, 2-msec pulse duration) or to injection of norepinephrine (3 μg, ia).

As shown in Curve C of Fig. 1, renal vasoconstriction occurred in response to isoproterenol after administration of propranolol (5 mg, ia). In contrast to the responses shown in Curves A and B, the responses after propranolol did not reach a maximum at isoproterenol doses of 50 μg. Rather, greater constrictor responses were obtained with further increases in the dose of isoproterenol.

A renal vasoconstrictor response to isoproterenol, unmasked by propranolol, is shown in Fig. 2. The upper panel shows the response to 50 μg of isoproterenol before propranolol. Following the injection artifact, a slight increase in renal blood flow occurred which was followed immediately by a marked secondary decrease in flow coincident with a systemic depressor response. After giving propranolol, the lower record shows that 50 μg of isoproterenol decreased flow to 20% of control, long before the systemic response ap-

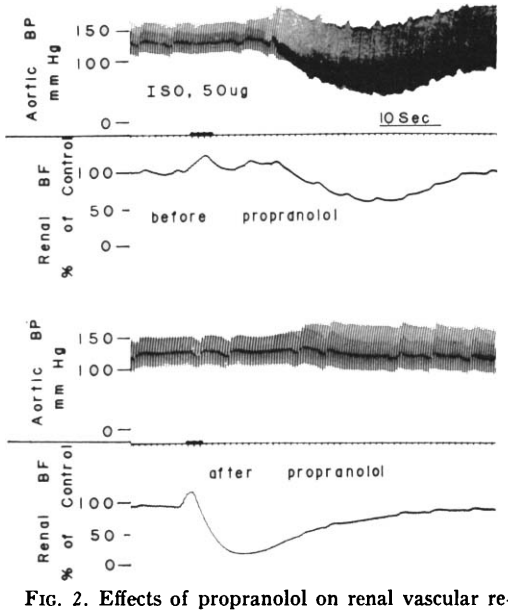

FIG. 2. Effects of propranolol on renal vascular response to isoproterenol. Upper panel shows the response to intra-arterial bolus injection of 50 μg of isoproterenol. Lower panel shows the response after giving propranolol (5 mg, ia). The slight renal vasodilator action of isoproterenol was converted to a marked vasoconstrictor action after pretreatment with propranolol.

peared. Such vasoconstrictor responses to isoproterenol were abolished with either phentolamine or phenoxybenzamine.

Discussion. With close intra-arterial injections of isoproterenol into the renal artery, the initial flow responses occurred well before any response could be detected in the recordings of arterial or venous pressure (Fig. 2). Thus, there was no difficulty in dissociating primary responses in the renal vasculature from secondary responses due to drug actions on the heart or other vascular beds.

Increases in renal blood flow elicited by isoproterenol reached a maximum with relatively low doses, and were small in magnitude at all doses (Fig. 1, Curve A). This suggests that available beta-receptors were saturated with isoproterenol, and that they were few in number. Potentiation of these responses following alpha-blockade with phenoxybenzamine suggests that a fraction of the injected isoproterenol was bound by alpha-like receptors (Fig. 1, Curve B). Since the dose–response curves for isoproterenol in the presence and absence of phenoxybenzamine were parallel, it is reasonable to suspect that the increases in renal blood flow resulted from stimulation of the same or similar receptors. This hypothesis is supported by the finding that all dilator responses to isoproterenol were abolished by beta-blockade with propranolol.

The reasons for the failure of alpha-blockade with phentolamine to potentiate dilator responses to isoproterenol are unclear, but may be related to differences in affinity between isoproterenol, phenoxybenzamine, and phentolamine for alpha-receptors, or to differences between phenoxybenzamine and phentolamine in the mechanisms whereby alpha-blockade is produced (9). Alternatively, it is possible that the dosage of phentolamine was insufficient to demonstrate potentiation of dilator responses to isoproterenol, despite the fact that this dose almost completely blocked constrictor responses produced by direct stimulation of nerves to the kidney. Direct stimulation of alpha-receptors by isoproterenol was strongly suggested by production of marked vasoconstrictor responses following beta-blockade with propranolol (Fig. 1, Curve C), which in turn were abolished by alpha-blockade either with phentolamine or phenoxybenzamine.

Mark *et al.* (7) also demonstrated constrictor responses to large doses of isoproterenol after propranolol, but they were unable to demonstrate potentiation of dilator responses after phenoxybenzamine. The difference may be due simply to the fact that they used a much smaller dose of this blocking agent. In any event, the present study and that of Mark *et al.*, both demonstrate a relatively low order of beta-adrenergic receptor activity in the canine kidney, and demonstrate that isoproterenol can combine with alpha-adrenergic receptors, producing under some circumstances an overt vasoconstriction.

Summary. Changes in canine renal blood flow in response to intra-arterial bolus injections of isoproterenol were studied in the presence and absence of adrenergic blocking agents. In the absence of blocking drugs, isoproterenol produced small increases in renal blood flow. Alpha-adrenergic blockade with phenoxybenzamine potentiated the vasodilator action of isoproterenol. In contrast, beta-adrenergic blockade with propranolol reversed the dilator action of isoproterenol to a marked constrictor action, which in turn was abolished by alpha-blockade. These results support the view that few responsive beta-receptors are present in renal vascular smooth muscle, and that isoproterenol can stimulate alpha-receptors, resulting in vasoconstriction.

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