Is the renal vasodilatation induced by β-adrenoceptor stimulants in the dog mediated through dopamine receptor?

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Summary. In chloralose-anaesthetized dogs the renal vasodilator effect of isoprenaline is depressed by blockade of either dopamine or β-adrenoceptors but the renal vasodilator effect of dopamine is depressed only by blockade of dopamine receptors. This suggests that the vasodilatation induced by β-stimulants within the canine kidney is due in part to activation of dopamine receptors.

The renal vascular bed of the dog contains a population of dilator receptors for dopamine (DA) which are distinct from β-adrenoceptors[4,5]. In addition, β-adrenoceptor stimulants such as isoprenaline cause an increased renal blood flow in the dog, although this is less marked than that produced by DA[4,6,7]. In view of the putative structural similarity of the β-adrenoceptor and the DA-receptor, it is possible that β-adrenoceptor stimulants might activate DA-receptors. We present here some evidence that such activation participates in the dilator effect of isoprenaline within the dog kidney.

Materials and mehods. We anaesthetized adult mongrel dogs of either sex, weighing 8–20 kg, with α-chloralose (70 mg/kg i.v.) following thiopentone induction. In 10 animals the left renal artery was exposed through a retroperitoneal flank incision and in a further 6 animals the left femoral artery was exposed in the groin. Mean blood flow through either renal or femoral bed was monitored using a cuff-type electromagnetic flow probe and a Devices flow meter, and displayed together with aortic blood pressure and heart rate on a Grass 7B polygraph. Intra-arterial injections of drugs were made into the aorta and flow changes were assessed in terms of ml min^{-1} per kg b.wt. The mean systemic blood pressure of all dogs used was 106 mmHg ± 3.7 mm (SEM). The mean resting flow recorded from the left renal artery was 15.56 ± 3.35

Table 1. The effect of propranolol (0.1 mg/kg i.v.) and ergometrine (0.5 mg i.a.) on the responses of femoral blood flow to isoprenaline and acetylcholine in anaesthetized dogs

Agonist	Dose	Increase in femoral blood flow (ml min^{-1} kg^{-1}), n = 6		Increase in femoral blood flow (ml min^{-1} kg^{-1}), n = 3	
		Control	Propranolol (0.1 mg/kg)	Control	Ergometrine (0.5 mg)
Isoprenaline	0.05 μg	1.49 ± 0.40	0.24 ± 0.10[a]	1.19 ± 0.29	1.51 ± 0.16
Isoprenaline	0.5 μg	3.04 ± 0.57	0.53 ± 0.12[a]	4.37 ± 1.51	5.61 ± 0.80
Acetylcholine	0.1 μg	2.38 ± 0.55	1.65 ± 0.30	2.90 ± 0.75	3.40 ± 0.71
Acetylcholine	0.5 μg	3.82 ± 0.94	2.99 ± 0.66	4.7 ± 0.98	4.58 ± 0.45

[a] $p < 0.001$ (single tailed paired *t*-test) Figures presented are mean ± 1 SEM. After reproducible responses to both agonists had been obtained, propranolol was administered and further responses to the agonists obtained. In 3 dogs time was then allowed for the effect of propanolol to wear off and for responses to isoprenaline to return to control values (± 10%), following which the effect of ergometrine on responses to both agonists was determined. Neither propranolol nor ergometrine produced any appreciable change (less than 10%) in resting femoral blood flow.

Table 2. The effect of propranolol (0.1 mg/kg i.v.) and ergometrine (0.5 mg i.a.) on the responses of renal blood flow to dopamine, isoprenaline and acetylcholine in anaesthetized dogs

Agonist	Dose	Increase in left renal blood flow (ml min^{-1} kg^{-1}), n = 10		Increase in left renal blood flow (ml min^{-1} kg^{-1}), n = 10	
		Control	Propranolol (0.1 mg/kg)	Control	Ergometrine (0.5 mg)
Dopamine	5 μg	2.04 ± 0.67	1.88 ± 0.50	1.70 ± 0.46	1.35 ± 0.48[b]
Dopamine	20 μg	2.39 ± 0.58	2.24 ± 0.58	2.25 ± 0.57	1.15 ± 0.25[d]
Isoprenaline	0.05 μg	1.36 ± 0.40	0.79 ± 0.45[a]	1.37 ± 0.65	0.69 ± 0.25[d]
Isoprenaline	0.5 μg	2.20 ± 0.74	0.73 ± 0.31[c]	1.57 ± 0.45	1.08 ± 0.46[d]
Acetylcholine	0.1 μg	1.73 ± 0.52	1.64 ± 0.34	2.04 ± 0.70	1.81 ± 0.51
Acetylcholine	0.5 μg	3.56 ± 0.94	3.16 ± 0.80	3.63 ± 1.21	3.85 ± 1.19

[a] $p < 0.02$, [b] $p < 0.01$, [c] $p < 0.002$, [d] $p < 0.001$ (single tailed paired *t*-test).
Figures presented are mean ± 1 SEM. Reproducible responses to dopamine, isoprenaline and acetylcholine were first obtained. In 5 of the 10 dogs propranolol was then administered and further agonist responses were obtained. Sufficient time was then allowed for all responses to return to their control values (± 10%), following which ergometrine was administered and another series of agonist responses obtained. In the other 5 dogs used the order of administration of propranolol and ergometrine was reserved. Neither antagonist produced any appreciable change (less than 10%) in resting renal blood flow.

ml min^{-1} kg^{-1} (n = 10) and that from the left femoral artery was 6.55 ± 1.15 ml min^{-1} kg^{-1} (n = 6). No deterioration in flow was seen over the 2–4-h-periods of the experiments.

Results and discussion. In several preliminary experiments, dose-response curves were compiled for the dilator effects of intra-arterial injections of DA, isoprenaline (ISO) and acetylcholine (ACh) on renal flow and for ISO and ACh on femoral flow. Both ISO and ACh produced increases of renal and femoral blood flows, together with falls in systemic blood pressure. DA increased renal blood flow and caused a slight fall in systemic blood pressure. In the femoral bed the net effect of DA was vasoconstriction, due to activation of α-adrenoceptors marking the weak dilator effect of DA-receptor activation[8]. For each agonist 2 doses were chosen from the concentration range corresponding to the steepest portion of the dose-response curve. The doses chosen were: ISO 0.05 and 0.5 μg, DA 5 and 20 μg, ACh 0.1 and 0.5 μg.

Propranolol is regarded as a selective antagonist at β-adrenoceptors[9], while ergometrine has been demonstrated recently to behave as a selective antagonist at canine vascular DA-receptors[5,8]. In the present experiments propranolol (0.1 mg/kg i.v.) profoundly reduced femoral dilator responses to ISO, but did not affect renal responses to DA. Ergometrine, in the dose previously reported to be effective in blocking DA receptors (0.5 mg i.a.)[5,8], reduced renal dilator responses to DA but did not affect femoral responses to ISO. Neither antagonist reduced either femoral or renal dilator responses to ACh (tables 1 and 2). These results indicated lack of non-specific depressant activity of propranolol and ergometrine on vascular reactivity and confirmed the absence of cross-antagonism of propranolol on DA-receptors or of ergometrine on β-adrenoceptors. In addition, the absence of any effect of propranolol on renal DA responses indicated that over the dose range used DA did not activate renal β-adrenoceptors. Lack of appreciable β-adrenoceptor stimulant activity has been reported previously for DA in the canine vascular system[6,7,10].

By contrast, both propranolol and ergometrine caused reduction of renal dilator responses to ISO (table 2). In view of their lack of cross-antagonism, this result suggests that the dilator effect of ISO in the canine kidney is mediated partly through activation of DA-receptors. Such non-specificity of action must therefore be considered when assessing the role of β-adrenoceptors in renal function.

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Hormonal manipulation of carrageenin-induced pyresis in rats[1]

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Summary. The intensity of the hyperthermic response in rats promoted by subplantar injection of 1 mg of carrageenin is directly related to the irritant properties of the type of carrageenin. The overall pyretic response is more dramatic in female rats than in male rats. Subtle changes in the time-course hyperthermic profiles are seen after hormonal modifications.

Since the introduction by Winter et al.[2] of the use of carrageenin as an experimental inflammatory agent, much research has been devoted to the characteristics and mechanisms underlying the acute inflammatory insult and testing pharmacologic agents which act to prevent the typical phlogistic reaction promoted by carrageenin. Well-defined studies on the biological properties of carrageenin may be found in a review by DiRosa[3]. In a recent study, Sobanski et al.[4] reported that subplantar injections of carrageenin in the rat produced not only the expected local phlogistic insult but also promoted a dramatic hyperthermic response which was monitored by rectal temperature. Our initial study was designed to determine a possible correlation between the phlogistic efficacy of various types of carrageenin as reported by Moore and Trottier[5] and the hyperthermic profile. A remarkable difference was noted in the hyperthermic response between male and female rats. Hormonal modulation of this response is reported here.

Materials and methods. Male Sprague-Dawley and female Wistar rats, 150–185 g, groups of 10 each, were used in these studies in an environment maintained at 25 ± 1 °C ambient temperature. Rectal temperature was determined using a Yellow Springs Instrument Company thermistor. Carrageenin samples were supplied by Marine Colloids, Rockland, Maine. Carrageenin suspensions (1%) were prepared in 0.9% saline and 0.1 ml volumes were injected s.c. in the plantar surface of the left hind paw. Control groups received 0.1 ml injections of 0.9% saline. Hormonal treatments consisted of: injections of testosterone propionate 2.5 mg per day s.c. × 2 days; estradiol valerate 2.5 mg s.c. × 2 injections on alternate days; and tests accomplished in ovariectomized groups of rats.

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