Effects of Dopaminergic Drugs on the Sympathoadrenal System

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Several studies have suggested that dopamine (DA) plays a major role in cardiovascular functions. Dopaminergic receptors have been found on sympathetic nerve terminals (DA2), kidney (DA1, DA2), vascular smooth muscle (DA1) as well as on sympathetic ganglia (DA1, DA2) and adrenal gland (DA1, DA2). Previous studies have shown that DA2 receptor stimulation by a specific DA2 agonist, quinpirole (1) elicits a peripheral depressor action (decreased blood pressure) and a central pressor component involving an increase in both sympathetic tone and vasopressin release and (2) does not affect under in vivo conditions adrenal catecholamine release. The present study investigates the effects of fenoldopam, a specific DA1 receptor agonist on both cardiovascular responses and catecholamine release from the adrenal medulla. In conscious normal dogs, fenoldopam (10, 20 and 40 μg/kg i.v.) elicited a decrease in blood pressure and a marked increase in heart rate associated with a rise in plasma catecholamine levels. The increase in heart rate is only due to baroreflex mechanism since fenoldopam (conversely to DA2 receptor agonists like quinpirole) does not exert a central excitatory component (as shown by the absence of cardiovascular effects after intracisternal injection). Moreover, in sinoaortic denervated dogs (i.e. animals deprived from baroreflex pathways), the decrease in arterial blood pressure was more important than in normal dogs. Heart rate was unchanged. In these animals, DA1 stimulation induced a decrease in sympathetic tone, as shown by the significant fall in plasma noradrenaline levels. These “in vivo” data clearly demonstrate the inhibitory role of ganglionic DA1 receptors. In anesthetized dogs, fenoldopam (5 μg/kg/min i.v.) failed to modify catecholamine release from the adrenal medulla whatever the stimulation frequencies (1, 3 and 5 Hz) of the sectioned splanchnic nerve. Thus, using DA agonists (DA1 : fenoldopam or DA2 : quinpirole see above), we failed to demonstrate any potential role of adrenal dopamine receptors in the control of catecholamine release under in vivo conditions. Since in vivo studies carried out in normal subjects with domperidone, a DA2 receptor antagonist, suggest a modulatory role for adrenal DA receptor during high sympathetic stimulation induced by physical exercise, we further investigate in anesthetized dogs the effects of DA agonists on adrenal catecholamine release. After blockade of alpha and beta adrenergic receptors, we found that haloperidol (1 mg/kg i.v.) elicited an increase in noradrenaline release from the adrenal medulla. In conclusion, the use of experimental models in dogs (sinoaortic denervation, chronic implanted intracisternal cannula and in vivo catheterism of adrenal vein) allows us to demonstrate (1) that the stimulation of ganglionic DA1 receptors induced a decrease in noradrenaline release due to the inhibition of ganglionic transmission and (2) that, under in vivo conditions, the blockade of DA receptors by haloperidol allows to reveal the inhibitory role of adrenal DA receptors on the release of adrenal catecholamines. (Hypertens Res 1995; 18 Suppl. I: S119–S124)

Key Words: fenoldopam, haloperidol, adrenal medulla, catecholamine, sinoaortic denervated dog, intracisternal

Several studies have suggested that dopamine (DA) plays a major role in cardiovascular functions. Dopamine receptors have been found on sympathetic nerve terminals (DA2), kidney (DA1, DA2), vascular smooth muscle (DA1) as well as on sympathetic ganglia (DA1, DA2) and adrenal medulla (DA1, DA2). Previous studies from our group have investigated the effects of quinpirole, a specific DA2 receptor agonist on both cardiovascular responses in conscious dogs as well as catecholamine release from the adrenal medulla in anesthe-
Studies in Conscious Dogs

In order to investigate the effects of DA1 stimulation on cardiovascular parameters, the effects of fenoldopam were studied in normotensive animals after intravenous and intracisterna magna (i.c.m.) injection and in sinoaortic denervated dogs (i.e. animals deprived from baroreflex pathways) after intravenous injection.

Normotensive Animals

1. Intravenous injection

In conscious normal dogs (n=6), intravenous fenoldopam (10–20 and 40 µg/kg i.v.) elicited a decrease in blood pressure and a marked increase in heart rate (Fig. 1) associated with a rise in plasma catecholamines levels (Fig. 2).

2. Intracisterna magna injection

Experiments were performed in Beagle conscious dogs weighing 10 to 15 kg (n=8) and trained to keep quiet in a Pavlov-type stand. In order to allow the intracisternal (i.c.) injection in conscious animals, dogs were operated 3 days before under general anaesthesia (alpha-chloralose, 80 mg/kg i.v.). Skin and muscles of the posterior side of the neck were dissected. The distal extremity of a catheter (flexopulmocath) was inserted into the cisterna magna and fixed to the atlanto occipital membrane. The catheter was running under the skin and came out at level of back of the dog. The proper position of the catheter in the cisterna magna was

![Diagram](image-url)
demonstrated by the bradycardia and hypotension induced by a clonidine injection (1.5 μg/kg) through the catheter. The dogs were deprived of food the morning of the experiment but had free access to water *ad libitum* in order to be normally hydrated. Before injection of the drug, each animal received a preliminary i.c. injection of the same volume of saline to confirm the absence of non-specific cardiovascular effects. Blood pressure (BP), heart rate (HR) and noradrenaline plasma levels were measured 1 min before and 2, 5 and 10 min after injection of the drug. The same procedure was performed using a central injection of a similar volume of saline to obtain sham values.

Central intracisternal injection of 1 μg/kg fenoldopam neither modified cardiovascular parameters, nor noradrenaline plasma levels when compared to a sham group (the same volume was injected instead of fenoldopam).

Thus, the lack of central effect of fenoldopam suggest that the increase in heart rate observed in normal dogs is only due to a baroreflex mechanism (and not to a central activation).

**Sinoaortic Denervated Dogs**

In order to explore the importance of baroreflex pathways in the cardiovascular responses to drug injection, six chronic sinoaortic denervated (SAD) dogs (beagle of either sex, 14-24 kg) were examined. The animals were made SAD as described previously (2). Briefly, carotid and aortic nerves were cut under chloralose anesthesia (80 mg/kg i.v.) during two successive procedures, one at time 0 and the second one 7 weeks later. During the surgery, care was taken to keep intact both vagal and sympathetic fibers in the vagus. The effectiveness of baroreceptor denervation was checked by the failure of NA and phenylephrine to induce bradycardia and nitroglycerin to induce tachycardia. The present protocol was performed at least 4 months after surgery, i.e., the period in which plasma catecholamine levels has returned to normal values when blood pressure remained elevated (3). In fact, we previously used this SAD model for the study of other antihypertensive drugs (2, 4-6).

In SAD dogs, whatever the dose, i.v. fenoldopam (10, 20 and 40 μg/kg i.v.) induced a decrease in blood pressure which was more pronounced than in normal dogs (Fig. 3). Simultaneously, we noted a significant decrease in heart rate 5 min after the i.v. injection of fenoldopam at the dose of 20 μg/kg whereas no effects were observed for the other doses. These cardiovascular effects were associated with a significant reduction in plasma noradrenaline levels 2 min after i.v. fenoldopam at the dose of 20 μg/kg and 2 and 5 min after the injection for the higher dose of 40 μg/kg (Fig. 4).

Thus, under “in vivo” conditions after exclusion of baroreflex pathways and central effects, we were able to reveal a decrease in sympathetic tone from peripheral origin after stimulation of peripheral D1 receptor. We hypothesized that the involved D1 receptors are from ganglionic location since several authors have characterized D1 receptors at ganglionic level (7-9). Thus, Sabouni et al. (9) described that fenoldopam causes a significant inhibition of ganglionic transmission in both isolated and perfused dog stellate and rat superior cervical ganglia. These D1 receptor appear to be different from the vascular D1 receptor since Lokhandwala et al. (8) and Sabouni et al. (7) show that SCH 23390, a potent and selective D1 receptor antagonist, fails to antagonize the action of fenoldopam in the ganglia, although it does prevent the hypotensive effect of fenoldopam. In contrast, these ganglionic D1 receptors partially resemble the D1 receptors de-
scribed in the brain (10). Finally, these present "in vivo" data provide additional evidence for the inhibitory role of ganglionic DA1 receptor on sympathetic neurotransmission.

Studies in Anaesthetized Dogs
In order to further precise the peripheral effects of DA stimulation on the sympathoadrenal system, we decided to investigate the effects of fenoldopam on the release of catecholamine of adrenal medulla.

Methods
Beagle dogs of either sex weighing 10 to 18 kg were anaesthetized with alpha-chloralose (80 mg/kg i.v.), curarized by gallamine (2 mg/kg i.v.) and artificially ventilated with an Ideal Palmer pump (insufflated air volume : 15 ml/kg with frequency of 16/min).

The vagus nerves were cut at the cervical level (C4). A constant level of anaesthesia was maintained by an injection of 15 to 20 mg/kg of chloralose each hour. Body temperature of the animals was maintained at a constant level around 38°C and arterial pH monitored using a Metrohm pH meter.

Adrenal venous blood sampling was made according to our previously described technic (11). Briefly, the right adrenal vein was dissected and its collaterals occluded. The animal was heparinized (500 U kg⁻¹ every 2 h) and the adrenal vein occluded at the level of its junction with the inferior vena cava whereas the other end was cannulated in order to enable blood sampling. When not being sampled, adrenal venous blood was returned directly to the femoral vein via a cannula. After completion of the preparation 30 to 45 min were allowed for stabilization. Thus, blood sampling started 30 min after

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Fig. 3. Effects of i.v. administration of fenoldopam (10, 20 and 40 µg/kg) in sinoaortic denervated dogs (n=6) on blood pressure (upper panel, millimeters of mercury), heart rate (lower panel, beats per minute). Statistical analysis was made with the Wilcoxon test for paired comparisons. Mean values are given. Vertical lines show SEM. *p <0.05 when compared with pretreatment values.
adrenal vein cannulation. Each blood sample (2 ml) was collected in a tube containing anticoagulant heparin (0.1 %) and frozen immediately. Plasma was separated immediately by centrifugation and stored below -80°C. Adrenal plasma flow rate (milliliters per kilogram per minute) was measured and catecholamine output (A and NA) expressed as nanograms per kilogram per minute.

The right great and lesser splanchnic nerves were dissected and cut below the diaphragm and the surrounding tissue containing sympathetic fibers destroyed cautiously in order to obtain a fairly complete denervation. Section of the splanchnic nerve was made 1 h before blood collection was started. The peripheral end of the great splanchnic nerve was stimulated via a bipolar stainless-steel electrode. The stimuli consisted of rectangular pulses of supramaximal intensity (5 V), 0.5 msec duration. Stimulus frequency was raised stepwise from 1 to 3 and 5 Hz at 2 min 30 s intervals during a 7 min 30 s stimulus period. Stimulation of the splanchnic nerve (SNS) was repeated twice for periods of 7 min 30 s each separated by 30 min. Adrenal venous blood was collected (3 min) before each stimulation period and 90 s after the beginning of each stimulation.

Results
For a 1 Hz frequency adrenal catecholamine secretion rates were almost identical with the basal values measured when adrenal nerve is intact. Moreover, the effects of drugs on splanchnic nerve stimulation could be dependent on the stimulation frequency. Under our experimental conditions, catecholamine release from the gland was frequency-dependent. Fenoldopam (5 μg/kg/min) failed to modify catecholamine release from the adrenal medulla whatever the frequencies of stimulation. The lack of effect of DA agonist on adrenal catecholamine release was also demonstrated previously by the use of the DA2 receptor agonist quinpirol (6). Thus, the use of DA agonists (DA1 or DA2) unable to demonstrate the potential role of adrenal dopaminergic receptors in the control of catecholamine release under “in vivo” conditions although “in vitro” studies have shown that dopaminergic receptors could modulate catecholamine release from the cat adrenal gland (12).

However, “in vivo” studies carried out in normal subjects with domperidone, a DA2 receptor antagonist during high sympathetic stimulation induced by physical exercise, suggest a modulatory role for adrenal dopaminergic receptors (13). For this
reason, we further investigate in anesthetized dogs the effects of dopamine receptor antagonist (haloperidol) on adrenal catecholamine release. The effects of haloperidol (1 mg/kg i.v.) on adrenal catecholamine release were studied after blockade of both alpha adrenoceptors by phentolamine (1 mg/kg i.v. and beta adrenoceptors by propranolol (1 mg/kg i.v.). With a 5 Hz frequency of splanchnic nerve stimulation, haloperidol elicited a significant increase in noradrenaline release from the adrenal gland (Fig. 5). Further studies are needed to characterize the subtype (DA1 or DA2) of the involved DA receptors.

These data suggest an inhibitory role of adrenal dopaminergic receptors on the release of noradrenaline from the adrenal gland.

In conclusion, the use of appropriate experimental models in dogs: sinoaortic denervation, chronic implanted intracisternal cannula and in vivo catheterism of adrenal vein allows us to demonstrate that the in vivo stimulation of peripheral DA1 receptors decreases plasma noradrenaline release. This decrease in sympathetic tone may be due to the inhibition of ganglionic transmission. Under “in vivo” conditions, the blockade of DA receptors allows to reveal the inhibitory role of adrenal DA receptors on the release of adrenal catecholamines.

References