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Autonomic mechanisms in the acute cardiovascular effects of cocaine in conscious rats

Jeremy Poon, Maarten van den Buuse *

Baker Medical Research Institute, Prahran, Victoria 8008, Australia

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Abstract

We studied the differential involvement of central dopaminergic activation and autonomic nervous system regulatory mechanisms in the cardiovascular responses to cocaine in conscious rats. Sprague–Dawley rats, Wistar–Kyoto rats (WKY) and spontaneously hypertensive rats (SHR) were instrumented with catheters in the jugular vein and abdominal aorta at least 5 days before the experiment. Intravenous administration of cocaine (0.1–3.0 mg/kg) caused a dose-dependent increase in blood pressure that was biphasic, with a large and rapid increase peaking at 10 s, followed by a mild sustained pressor response. Pressor responses to cocaine were significantly greater in SHR when compared to WKY rats. However, pretreatment with dopamine D_1 receptor antagonist SCH 23390 or the D_2 receptor antagonist raclopride did not influence the effects of cocaine. Pretreatment with the α-adrenoceptor antagonist phentolamine or the ganglion blocker pentolinium blocked the peak response and reversed the more sustained response into a depressor effect. While pretreatment with propranolol alone did not alter the responses to cocaine, in rats pretreated with phentolamine and propranolol neither a pressor response nor a depressor response was observed. In conclusion, cocaine administration caused marked, but short lasting pressor responses that were mediated by sympathetic activation and α-adrenoceptor vasoconstriction with little involvement of central dopaminergic mechanisms. The rapid return of blood pressure towards baseline may be mediated by sympathoinhibition and β-adrenoceptor-mediated vasodilatation, the latter of which being particularly prominent when α-adrenoceptor activation was prevented.

Keywords: Blood pressure; Cocaine; Dopamine; Sympathetic nervous system; α-Adrenoceptor; β-Adrenoceptor; (Rat, conscious)

1. Introduction

Activation of central dopamine receptors by intravenous administration dopamine D_2 receptor agonists results in a rapid increase in blood pressure with little change in heart rate (Van den Buuse, 1992, 1997a). This pressor response is short lasting and blood pressure returns towards baseline after 10–20 min. However, even when blood pressure has normalized, prolonged effects of dopamine D_2 receptor activation can be unmasked. For example, administration of the ganglion blocker pentolinium, 30 min after injection of the D_2/D_3 receptor agonist quinpirole, induces an acute fall in blood pressure which was greater than that in controls, suggesting a prolonged increase in sympathetic vasomotor tone (Van den Buuse et al., 1996). Indeed, in conscious rabbits, quinpirole treatment caused a marked increase in renal sympathetic nerve activity (Van den Buuse et al., 1998). In addition, treatment with centrally-acting antihypertensive drugs such as clonidine and rilmenidine induces little change in blood pressure in quinpirole-treated rats as opposed to the expected hypotensive effect in controls (Van den Buuse et al., 1996; Van den Buuse and Tritton, 1997). Furthermore, whereas pretreatment with the dopamine D_2 receptor antagonist raclopride completely antagonized the pressor response to quinpirole treatment, administration of the blocker 30 min after quinpirole actually caused a fall in blood pressure (Van den Buuse and Tritton, 1997), indicating the occurrence of compensatory mechanisms to normalize blood pressure despite the prolonged presence of drugs such as quinpirole in the circulation. Taken together, these findings show that central dopamine D_2 receptor activation causes a range of prolonged effects on cardiovascular control, the effect on blood pressure being only part of its action.

* Corresponding author. Baker Medical Research Institute, P.O. Box 6492, St. Kilda Road Central, Melbourne, Victoria 8008, Australia. Tel.: + 61-3-952-24-333; Fax: + 61-3-952-11-362; E-mail: maarten.vandenbuuse@baker.edu.au

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It has been widely recognized that intranasal or intravenous administration of cocaine causes marked activation of the mesolimbic dopamine system, the extent of which correlates with the 'high' elicited by the drug (Johanson and Fischman, 1989; Volkow et al., 1996, 1997). By virtue of its blocking action on the dopamine transporter, cocaine may induce a relative increase in extracellular levels of dopamine in the brain. In contrast, while it has been equally well-recognized that cocaine intake is accompanied by marked acute cardiovascular effects and that prolonged abuse of cocaine may lead to cardiovascular complications and sudden death (Pitts and Marwah, 1989; Das, 1993), the involvement of central dopamine systems in these cardiovascular effects is unclear. We have recently shown that stimulation of the ventral tegmental area, the region of origin of the mesolimbic dopamine system, induces an increase in blood pressure through central activation of dopamine D_1 and D_2 receptors (Cornish and Van den Buuse, 1995). This finding and the complex central cardiovascular effects of administration of dopamine receptor agonists led us to re-evaluate the effects of cocaine administration on blood pressure in conscious rats. Thus, we investigated the acute effects of intravenous administration of cocaine on blood pressure and heart rate, whether central dopaminergic receptors are involved in these effects, and possible immediate and prolonged compensatory changes in autonomic effector mechanisms. In addition, we compared the effects of cocaine in normotensive rats with those in spontaneously hypertensive rats (SHR) which display a range of changes in central dopaminergic and sympathetic nervous system activity (Van den Buuse, 1997a; Van den Buuse and De Jong, 1992).

2. Methods

We used male Sprague–Dawley rats, Wistar–Kyoto rats (WKY) and SHR of 250–350 g body weight. The animals were obtained from the Baker Medical Research Institute breeding facility and, after surgery, were housed individually with free access to pellet food and tap water. All surgical, post-operative and experimental procedures were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1990) and were approved by the Animal Experimentation Committee of the Alfred Hospital/Baker Medical Research Institute.

2.1. Surgery

All rats were anaesthetised with a mixture of pentobarbitone (Nembutal, 30 mg/kg), methohxitone (Brietal, 40 mg/kg) and atropine sulfate (0.5 mg/kg) and instrumented with a vinyl catheter in a jugular vein and a teflon/vinyl catheter in the abdominal aorta as previously described (Van den Buuse et al., 1996; Van den Buuse and Tritton, 1997). Briefly, the abdominal aorta was exposed through a midline abdominal incision. The aortic cannula consisted of a 60-cm length of vinyl tubing (SV-40, Dural Plastics, Australia) with a 2.5-cm length of teflon (STT 30, Small Parts, Miami, FL) inserted. The teflon tip of this cannula was cut back to approximately 3–4 mm and inserted into the aorta while it was clamped off with non-traumatic vascular clamps. The cannula was fixed to the vessel with a drop of tissue glue (Loctite, Australia). The other end of the cannula was looped 2–3 times in the abdominal cavity before being tunnelled under the skin, exteriorized in the neck of the rat and closed with a pin. The vena cava was catheterized via the jugular vein with a 10-cm length of vinyl tubing (SV-40, Dural Plastics) through an incision lateral to the larynx. This cannula was also tunneled under the skin, exteriorized in the neck, and filled with heparinized saline. Each rat was given 4–5 ml of Hartman's solution intraperitoneally, after which all incisions were sutured, and it was allowed to recover in a warm recovery box. The rats were allowed at least five days of recovery before the commencement of experiments.

2.2. Experiments

On the day of the experiments, the rats were taken to the experiment room, weighed and allowed to acclimatize for at least 30 min. The experiments were performed while the rats were in their home cages. The arterial catheters were connected to Statham P23XL transducers and an eight-channel Neomedix Systems Neotrace recorder. Heart rate was derived off the blood pressure pulse by Baker Medical Research Institute tachographs. Pulsatile blood pressure was digitized and recorded with a National Instruments analogue–digital card and a data-acquisition program written in the Labview programming language (National Instruments, Austin, TX, USA).

Before the experiments, patency of the intravenous catheters was assessed by injection of a 0.1 mg/ml nitroprusside solution. After completion of the experiment, some rats were returned to the animal house and used for additional experiments at least 48 h later. Drug treatments were always randomized between consecutive experiments.

2.3. Experimental compounds

All drugs were administered intravenously (i.v.) and doses are expressed as salt. Cocaine hydrochloride was obtained from Sigma (USA) and administered in doses of 0.1, 0.3, 1, or 3 mg/kg. The involvement of dopamine receptor subtypes was studied by using pretreatment with the dopamine D_2 receptor antagonist raclopride (1 mg/kg, Astra Pharmaceuticals, Södertalje, Sweden) (Hall et al., 1988) or the dopamine D_1 receptor antagonist SCH23390

(0.1 mg/kg, Research Biochemicals, USA) (Iorio et al., 1983), which were administered 15 min before cocaine. The involvement of adrenergic receptor subtypes and sympathetic activation was studied by using pretreatment with phentolamine mesylate (Regitine, 10 mg/kg, Ciba, Australia), propranolol hydrochloride (Inderal, 1 mg/kg, ICI, Australia), pentolinium tartrate (Ansolysen, 10 mg/kg, May and Baker, Australia).

2.4. Data analysis

All data is expressed as means ± standard error of the mean (S.E.M.). One- and two-way analysis of variance was used to analyze overall statistical significance, whereas comparisons with saline-treated controls were done with Bonferroni-corrected *t*-test (Sigmastat, version 1, Jandel Scientific, Australia). Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Time course of cocaine induced pressor response

The i.v. injection of cocaine produced a rapid and dose-dependent increase in blood pressure, which was biphasic. There was a marked and immediate increase in blood pressure (Fig. 1A) and, at higher doses, reflex bradycardia (Fig. 1B), followed by a mild and sustained pressor response which lasted approximately 3 min after which blood pressure returned to baseline. Rats exhibited mild locomotor activation and rearing when administered cocaine. Because of the biphasic nature of the pressor response, for subsequent analysis data were expressed as 'peak' phase (at 10 s) and 'sustained' phase (average of the first 3 min).

3.2. Dose response study

The administration of cocaine (0.1–3.0 mg/kg) produced a dose-dependent increase in blood pressure at 10 s with a plateau at the higher doses ($P < 0.0001$). The immediate pressor response to cocaine was significantly different when compared to controls at all doses ($P < 0.05$, Fig. 1B). In contrast, heart rate responses were not significantly different to those obtained in saline-treated rats other than the 3 mg/kg cocaine dose, even though there was an overall effect of dose ($P = 0.0001$, Fig. 2E). The 'sustained' pressor phase also exhibited an overall effect of dose ($P < 0.0001$) and the pressor responses were statistically different to the control at all doses ($P < 0.05$, Fig. 1C). There was an overall significant effect for the 3 min heart rate responses ($P < 0.05$), although none of the individual doses were significantly different when compared to control responses (Fig. 1F).

The 0.3 mg/kg dose of cocaine was chosen for subsequent pharmacological studies as it resulted in a repro-

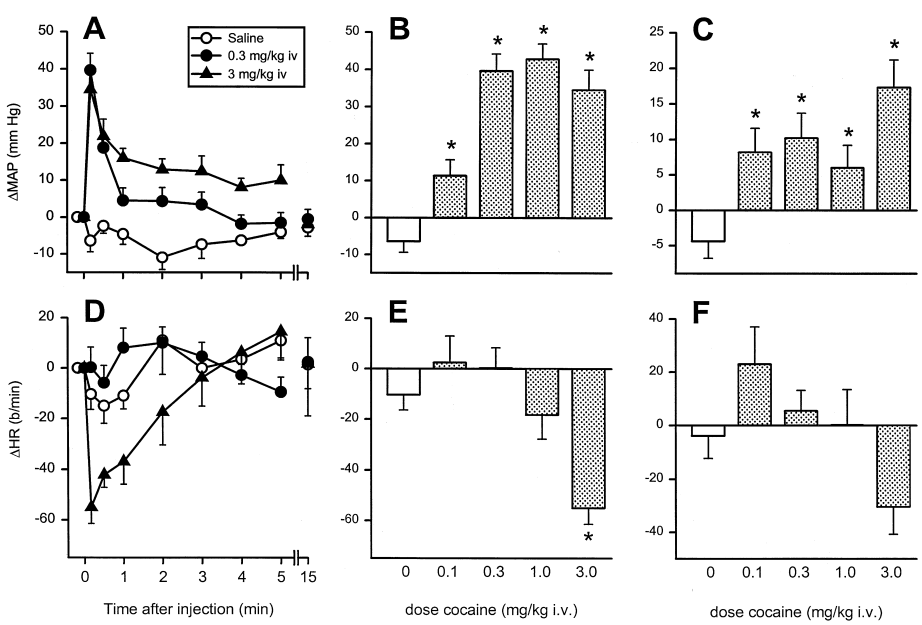

Fig. 1. The effect of i.v. administration of different doses of cocaine on blood pressure (top panels) and heart rate (bottom panels) of conscious Sprague–Dawley rats. Panels A and D show the time-course of responses to injection of saline (open circles), 0.3 mg/kg (closed circles) or 3 mg/kg of cocaine (closed triangles). Panels B and E show peak 10 s responses to different doses of cocaine ($n = 8$ per group) whereas panels C and F show the 'sustained' phase of the responses. Respective baseline values were 100 ± 3, 96 ± 1, 95 ± 3, 99 ± 3, and 105 ± 4 mm Hg for blood pressure and 431 ± 16, 383 ± 12, 411 ± 14, 400 ± 14, and 416 ± 12 b/min for heart rate. * $P < 0.05$ for difference with saline control responses.

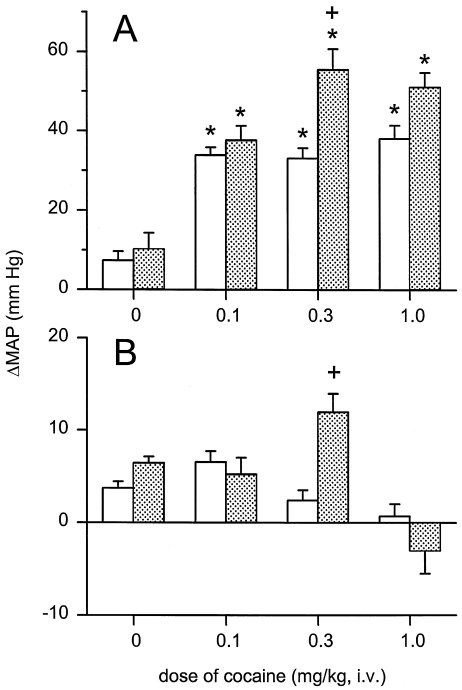

Fig. 2. The effect of i.v. administration of different doses of cocaine on blood pressure of conscious Wistar–Kyoto rats (WKY, open bars) or spontaneously hypertensive rats (SHR, filled bars). Panel A shows the immediate peak pressor response to cocaine injection, whereas panel B shows the 'sustained' phase (see text for explanation). Respective baseline values and number of rats per group were 124 ± 3 ($n = 8$), 117 ± 6 ($n = 7$), 130 ± 3 ($n = 8$) and 129 ± 5 mm Hg ($n = 8$) for WKY and 146 ± 4 ($n = 6$), 151 ± 6 ($n = 6$), 155 ± 5 ($n = 7$) and 153 ± 5 mm Hg ($n = 7$) for SHR. $*$ $P < 0.05$ for difference with saline-treated controls of the same strain; $+$ $P < 0.05$ for difference with WKY treated with the same dose of cocaine (Bonferroni-corrected *t*-test).

ducible peak and sustained pressor effect (39.6 ± 4.6 and 10.2 ± 2.7 mm Hg) with little behavioural side effects.

3.3. Responses in SHR and WKY

The time-course of the cocaine-induced pressor effects was similar in SHR and WKY when compared to Sprague–Dawley rats. The peak response was dose-dependent and tended to be greater in SHR than in WKY rats (Fig. 2A). Indeed, a significant overall strain difference ($P < 0.0001$), dose effect ($P < 0.0001$) and strain × dose interaction ($P = 0.019$) were observed. The pressor responses of SHR and WKY rats to cocaine were significantly different when compared to their controls at all doses ($P < 0.05$). Similar to Sprague–Dawley rats, heart rate responses to cocaine injection were small and no significant difference for strain or dose was observed (not shown). With respect to the 'sustained' phase, there was no overall strain difference between WKY and SHR (Fig. 2B). However, an effect of dose ($P = 0.0061$) and a marginal strain × dose interaction ($P = 0.0484$) was observed which may reflect the greater responses in SHR to the 0.3 mg/kg cocaine dose (Fig. 2B).

Table 1
The effect of intravenous administration of 0.3 mg/kg of cocaine on blood pressure after pretreatment with dopamine receptor antagonists or autonomic blockers

Pretreatment	Baseline	'Peak' phase	'Sustained' phase
Saline ($n = 23$)	97.5 ± 1.3	31.7 ± 2.7	2.8 ± 0.7
Raclopride ($n = 9$)	97.7 ± 2.1	25.0 ± 5.6	2.8 ± 0.9
SCH23390 ($n = 7$)	95.1 ± 1.4	31.4 ± 3.2	2.7 ± 1.1
Pentolinium 10 mg/kg ($n = 8$)	65.9 ± 2.3[a]	-8.0 ± 2.2[a]	-7.1 ± 1.1[a]
Phentolamine 10 mg/kg ($n = 8$)	73.8 ± 2.1[a]	6.4 ± 3.7[a]	-11.5 ± 1.2[a]
Propranolol 1 mg/kg ($n = 9$)	103.9 ± 2.4	32.3 ± 3.3	5.9 ± 1.1
Phentolamine + propranolol ($n = 9$)	81.1 ± 2.9[a]	5.1 ± 2.1	3.0 ± 0.6

Data are baseline blood pressure (mm Hg) or change in blood pressure (mm Hg) expressed as 10 s peak pressor response and 'sustained' phase (average of first 3 min).
Data are means ± S.E.M.
[a] $P < 0.05$ for difference with data obtained in saline-pretreated rats.

3.4. Pharmacological study

Pretreatment of the rats with raclopride or SCH23390 did not significantly affect either the peak pressor phase or 'sustained' phase after injection of 0.3 mg/kg of cocaine (Table 1). Similarly, pretreatment with propranolol had no significant effect on either part of the response, although

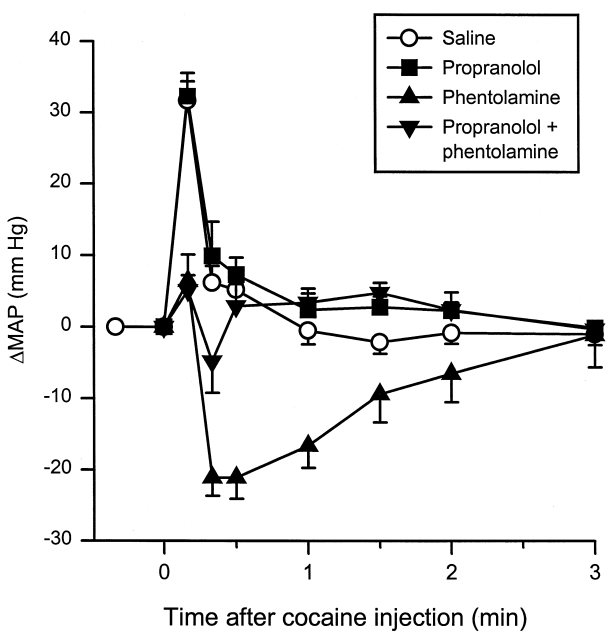

Fig. 3. The effect of intravenous administration of 0.3 mg/kg of cocaine on blood pressure of conscious Sprague–Dawley rats after pretreatment with either saline (open circles), 1 mg/kg of propranolol (closed squares), 10 mg/kg of phentolamine (closed up triangles), or propranolol and phentolamine combined (closed down triangles). Data are mean change of mean arterial pressure (ΔMAP) ± S.E.M. For baseline values, number of rats and statistical comparisons (see Table 1).

the 'sustained' pressor response tended to be greater (Table 1). In contrast, pretreatment with either phentolamine or pentolinium abolished the peak pressor phase ($P < 0.05$) (Table 1; Fig. 3) and reversed the 'sustained' phase into a significant depressor effect ($P < 0.05$, Table 1; Fig. 3). In rats which received combined pretreatment with propranolol and phentolamine, cocaine injection did not induce either an immediate peak response, a 'sustained' pressor phase, or a 'sustained' depressor effect (Table 1; Fig. 3). Peak or 'sustained' heart rate responses were not significantly affected by receptor antagonist pretreatment (not shown).

4. Discussion

The principal aim of this study was to evaluate the effects of cocaine on blood pressure in conscious, freely moving normotensive and hypertensive rats and to investigate autonomic and compensatory mechanisms involved in these effects. Similar to the centrally-mediated pressor response to intravenous treatment with dopamine D_2 receptor agonists (Van den Buuse, 1992), cocaine injection evoked a rapid, but short lasting increase in blood pressure. Similar to direct dopamine D_2 receptor agonists, such as quinpirole, the relatively short duration of action of cocaine on blood pressure is inconsistent with its plasma half-life after intravenous administration. In humans, the plasma half-life of cocaine has been reported to be 40–60 min after either intravenous or intranasal administration, and plasma levels and the subjective psychopharmacological effects of cocaine appear to parallel each other (Johanson and Fischman, 1989; Volkow et al., 1997). Clearly, autonomic compensatory mechanisms limit the pressor response, similar to what we have proposed for direct dopamine D_2 agonists (Van den Buuse et al., 1996; Van den Buuse, 1997b).

At least some of the autonomic compensatory mechanisms associated with the cardiovascular effects of cocaine were unmasked when we pretreated the rats with either the α_1-adrenoceptor antagonist phentolamine or the ganglion blocker pentolinium. In these rats, a pronounced depressor response was observed after cocaine injection, which could be prevented by additional pretreatment with propranolol. Thus, the effect of cocaine on blood pressure appears to consist of the sum of a number of autonomic responses. The immediate 'peak' pressor response could be blocked by pretreatment with either phentolamine or pentolinium and thus appears to be the result of an increase in sympathetic vasomotor tone leading to α_1-adrenoceptor-mediated vasoconstriction. This conclusion is consistent with earlier work on the cardiovascular effects of cocaine (Wilkerson, 1988; Kiritsy-Roy et al., 1990; Branch and Knuepfer, 1992; Schindler et al., 1992). After the initial 'peak' response, blood pressure returns to values close to baseline (the 'sustained' phase) despite cocaine's continued presence in the circulation. This compensatory return of blood pressure towards baseline may be due to centrally-mediated sympatho-inhibition and a β-adrenoceptor-mediated vasodilatation. Inhibition of sympathetic vasomotor tone has been described previously as a result of cocaine administration (Knuepfer and Branch, 1992) and could be a result of activation of the baroreflex by the immediate pressor response. Indeed, when the acute pressor response to cocaine was prevented by co-infusion of nitroprusside, the observed sympatho-inhibition was reversed to a marked and prolonged sympatho-excitation (Jacobsen et al., 1997). Central α_2-adrenoceptor mechanisms in the rostroventrolateral medulla mediate at least part of the sympatho-inhibition (Abrahams et al., 1996). β-Adrenoceptor-mediated vasodilatation has also been suggested by others (Branch and Knuepfer, 1992; Tella et al., 1993b) and could result from increased adrenaline release from the adrenal glands. This effect on the adrenal does not appear to be mediated by sympathetic innervation of the gland, as neither ganglion blockade by pentolinium nor α_1-adrenoceptor blockade by phentolamine prevented its occurrence. It should be mentioned that treatment with chlorisondamine, a non-competitive ganglion blocker, blocked the pressor action of cocaine in squirrel monkeys, which may be due to the different mode of action of this drug (Tella et al., 1993a). In conclusion, the balance of sympathetic excitation, reflex sympathetic inhibition and possibly β-adrenoceptor-mediated vasodilatation appears to determine the net effect of cocaine on blood pressure.

While similarities exist between the effect of direct dopamine D_2 receptor agonists, such as quinpirole, and those of cocaine, there are clearly marked differences as well. The most importance difference would be that pretreatment with the dopamine D_2 receptor antagonist raclopride (Hall et al., 1988) had no effect on either the 'peak' response or 'sustained' response to cocaine, whereas it completely prevented the pressor action of quinpirole (Van den Buuse et al., 1996). Because pretreatment with the dopamine D_1 receptor antagonist SCH23390 (Iorio et al., 1983) did not appear to influence the cardiovascular effects of cocaine either, it has to be concluded that central dopaminergic stimulation does not play a major role in the acute cardiovascular actions of cocaine, as suggested also by other authors (Kiritsy-Roy et al., 1990; Schindler et al., 1995; Tella, 1996). As indicated above, this is in marked contrast to the effect of direct dopamine D_2 receptor agonist, and is also unlike the subjective psychopharmacological and rewarding effects of cocaine (Johanson and Fischman, 1989; Volkow et al., 1996, 1997).

Spontaneously hypertensive rats display several differences with normotensive rats in central dopaminergic activity and behavioural responses to dopaminergic drugs (Van den Buuse and De Jong, 1992; Van den Buuse, 1997a). The pressor effects of the dopamine D_2 receptor agonists quinpirole, quinelorane and pergolide on blood pressure were identical in normotensive or spontaneously

hypertensive rats (Van den Buuse et al., 1996), except at higher doses (Van den Buuse, 1992). Because spontaneously hypertensive rats showed markedly less locomotor hyperactivity to higher doses of dopamine D_2 receptor agonists, we postulated that this strain difference in behavioural responses could influence concomitant cardiovascular responses (Van den Buuse, 1992). Although we did not quantify behavioural responses to cocaine in our experiments, similar differential behavioural 'side effects' of cocaine could have influenced the cardiovascular responses. Alternatively, differences in central noradrenergic and sympathetic mechanisms (Head and De Jong, 1986; Folkow, 1987) could explain the tendency of spontaneously hypertensive rats to show greater pressor responses to cocaine.

In conclusion, the intravenous injection of cocaine induced a marked pressor response, which is mediated by sympathetic activation and α_1-adrenoceptor stimulation. Activation of dopamine receptors appears to play little role in the pressor action of cocaine, unlike with direct dopamine receptor agonists. The hypertensive effect of cocaine was short lasting because of the rapid recruitment of compensatory mechanisms to normalize blood pressure, including β-adrenoceptor-mediated effects.

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