Central Effects of Quinpirole on Blood Pressure of Spontaneously Hypertensive Rats

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ABSTRACT
The i.v. administration of the dopamine D-2 receptor agonist quinpirole induced a rapid increase in blood pressure in spontaneously hypertensive rats (SHR). Heart rate showed little change. The pressor response to quinpirole was similar in SHR and normotensive Wistar-Kyoto rats (WKY) at doses of 0.03 to 0.3 mg/kg but, at 1 mg/kg, quinpirole induced a greater increase in blood pressure in SHR than in WKY. In contrast, although both strains showed a decreased locomotor activity after administration of 0.01 to 0.05 mg/kg of quinpirole, only in WKY was activity enhanced by 0.25 to 1.25 mg/kg of quinpirole. The i.v. administration of the dopamine agonists apomorphine, N-propylnorapomorphine, (R(+)-3-(3-hydroxyphenyl)-N-propylpiperidine, but not the putative presynaptic D-2 agonist (S)(-)-3-(3-hydroxyphenyl)-N-propylpiperidine, induced pressor responses in SHR comparable to those after quinpirole administration. The pressor effect of quinpirole was enhanced by pretreatment with the peripheral D-2 antagonist domperidone, but blocked by the centrally acting dopamine antagonists haloperidol or sulpiride. In SHR, which were pretreated centrally with pertussis toxin, quinpirole induced a significantly smaller increase in blood pressure than in control SHR. Pretreatment centrally with 6-hydroxydopamine had no effect on the pressor action of quinpirole in SHR. Thirty minutes after i.v. administration of quinpirole, an additional injection of quinpirole did not significantly change blood pressure. Increasing the interval between two subsequent injections of quinpirole showed that this desensitization slowly reversed, but only after 24 hr had the pressor response to quinpirole fully recovered. These results show that quinpirole and other dopamine agonists cause a centrally mediated pressor response in conscious SHR. The pressor effect of quinpirole is likely to be mediated by pertussis toxin-sensitive dopamine D-2 receptors which show profound desensitization and which are located postsynaptically.

Quinpirole (LY-171555) is a well-recognized agonist selective for dopamine D-2 receptors (Koller et al., 1987; Stoof and Kebabian, 1984; Titus et al., 1983; Tsuruta et al., 1981). The cardiovascular effects of systemic administration of quinpirole to rats include two main components. There is a stimulation of D-2 receptors located on sympathetic nerve terminals, resulting in decreased sympathetic noradrenaline release and a decrease in blood pressure (Clark, 1990; Hahn et al., 1983). This peripheral action of quinpirole can be readily demonstrated in anesthetized rats and dogs (Damase-Michel et al., 1990; Hahn and MacDonald, 1984; Nagahama et al., 1986b). There is also a central component, however, which is especially prominent in conscious rats or after blockade of peripheral dopamine receptors. This central mechanism causes an immediate increase in blood pressure, which appears to be caused by a dual efferent effect (Nagahama et al., 1986a, 1987). A role of vasopressin release was illustrated by the finding that in both vasopressin-deficient Brattleboro rats as well as in rats pretreated with a vasopressin antagonist, the pressor response to quinpirole was attenuated. On the other hand, an increase in sympathetic activity may be involved as well inasmuch as quinpirole caused a marked increase in plasma catecholamine levels and ganglionic blockade inhibited the pressor response (Nagahama et al., 1986a, 1987).

The present study was performed to further investigate the central actions of quinpirole on blood pressure and heart rate. Previously we have shown that SHR show differential changes in central dopaminergic regulation (van den Buuse and De Jong, 1989, van den Buuse et al., 1992) and that depletion of central dopamine stores may inhibit the development of hypertension (van den Buuse et al., 1984, 1986b). Brain dopamine may thus play a role in the development of hypertension. Preliminary results by Kurz and co-workers (1986) showed that quinpirole increased blood pressure in SHR, in which peripheral dopamine receptors were blocked, but no systematic comparison was performed between SHR and normotensive con-
trols. In two mildly hypertensive patients, McNay and co-workers (1987) observed an increase in blood pressure caused by the administration of quinpirole. In view of these results and of the possible role of central dopamine systems in the development of hypertension, in the present study the effect of quinpirole administration on blood pressure was measured in SHR and normotensive WKY and compared to its effect on locomotor activity. The central mechanism of action of quinpirole was investigated by: 1) comparison with other known centrally acting dopamine D-2 receptor agonists; 2) using a number of appropriate dopamine receptor antagonists; 3) comparing the effects of quinpirole before and after central treatment with pertussis toxin; and 4) studying the effects of quinpirole in SHR which were centrally pretreated with 6-OHDA. Finally, desensitization to the pressor action of quinpirole was studied by varying the interval-length between multiple dosing of the compound.

Methods

Rats, operations and general protocol. Male SHR and normotensive WKY were obtained from Charles Rivers (Paris, France). The animals (250 to 350 g b.wt.) were kept four to five per cage in wire mesh cages with free access to standard pellet food and tap water.

In all the cardiovascular studies, the rats were operated on at least 2 days before the experiment. Pentobarbital was used as an anesthetic (60 µg/kg i.p.) and incisions were made in the skin near the right femoral artery and jugular vein and in the neck. A 3-cm piece of polythene cannula of 0.28-mm inner diameter and 0.61-mm outer diameter (Portex, France), attached to a longer piece of polythene cannula of 0.58-mm inner diameter and 0.96-mm outer diameter was inserted into the femoral artery such that the tip was lying just outside the abdominal aorta. Similarly, a polythene cannula (0.56-mm inner diameter and 0.96-mm outer diameter) was inserted into the jugular vein. Both catheters were tunneled under the skin and exteriorized in the neck. All skin incisions were sutured and the animals were allowed to recover. From then on, the rats were maintained singly.

On the day of the experiments, the rats were taken to a quiet room and allowed to acclimatize for at least 30 min. The arterial catheters were then connected to Statham P23Db transducers, which were connected to a Grass model 7E or a model 79D polygraph, equipped with 7P44 tachographs. In each rat, patency of the jugular catheters was verified with an i.v. injection of nitroprusside (0.1 ml of a 0.1-mg/ml solution). Blood pressure and heart rate were then digitized and recorded with a Metabyte DAS-8 analog-digital card and a Labtech Notebook data acquisition program running on a Compaq 286e computer.

In order to measure the cardiovascular action of quinpirole and other dopamine agonists in SHR and WKY, the following standard protocol was used: 1) a 5-min base-line mean arterial pressure and heart rate reading was taken; 2) saline, 1 ml/kg i.v., was injected and flushed with an additional 0.1 ml of saline; and 3) 10 min later 1 mg/kg of domperidone (1 mg/ml) was injected i.v.; 10 min later quinpirole (or another dopamine D-2 agonist) was injected and cardiovascular responses were measured for 30 min. After the experiments, the rats were returned to the animal room and sometimes used for another experiment at least 48 hr later. As there appeared to be some variation in baseline activity cages (Opto-varimex mini, Columbus Instruments, Columbus, OH), Locomotor activity was measured in 5-min periods for 1 hr.

Antagonist study. In order to test the effect of dopamine receptor antagonists on pressor responses to i.v. quinpirole, the following modifications to the above mentioned general protocol were made. Domperidone (1 mg/kg i.v.) was tested by injecting a number of rats at step 3 with saline and other rats with domperidone. Haloperidol (1 mg/kg i.v.) was tested by injecting it in some animals at step 2 and increasing the interval to 20 min. Thus, haloperidol was injected 30 min before quinpirole. Sulpiride (100 mg/kg) was injected i.p. 1 hr before quinpirole.

Pertussis toxin study. SHR and WKY were anesthetized with pentobarbital and provided with a plastic cannula (Linska Scientific Instruments, Tel-Aviv, Israel) into the lateral cerebral ventricle at least 1 week before the cardiovascular experiments. The stereotactic coordinates for the implantation were 1.8 mm right, 0.2 mm caudal with the bregma as zero and the toothbar set at +5 mm. The cannula was fixed to the skull with 2 or 3 small screws and dental cement. A minimum interval of 24 hr after injection of pertussis toxin is needed for an effect of the toxin to develop (Fujita et al., 1985; Memo et al., 1986; Olianas and Onali, 1987). This time interval was used so that rats could be used as their own controls. Thus, all rats in this experiment were first tested for the effect of i.v. administered quinpirole (see protocol above). Twenty-four hours later they were anesthetized lightly with ether and injected i.c.v. with pertussis toxin. The dose was 2 µg and the injection volume 10 µl. The rats were retested with quinpirole 24 hr later according to the standard protocol. Preliminary experiments showed that a 48-hr time interval does not interfere with the action of quinpirole on blood pressure in control animals. Because the effects of pertussis toxin on the pressor responses to quinpirole in SHR were relatively modest, the effect of this pretreatment was tested in WKY as well.

6-OHDA study. The protocol used for the pertussis toxin experiments could not be used for the 6-OHDA experiments because the latter involves a much longer treatment schedule and animals cannot be used as their own controls. Parallel groups of saline- and 6-OHDA-treated SHR were therefore used. In this experiment, i.c.v. injections were not used because the treatment with multiple doses of i.c.v. 6-OHDA may cause side effects in the rats such as convulsions and long-lasting weight loss due to aphagia and adipsia. Therefore, the i.c. route of administration, where such side-effects are not observed (van den Buuse et al., 1986a), was chosen. Thus, 5 days before the first 6-OHDA injection, SHR were provided with steel cannulas into the cisterna magna, positioned medial and as far caudal as possible. The operation was otherwise similar to the one described above for the i.c.v. cannulas. 6-OHDA was injected i.c.v. as a 200-µg base in 10 µl of saline with 0.01% ascorbic acid. This treatment was repeated 3 times (5, 7 and 9 days after the operation) in order to get optimal depletion of central dopamine (and noradrenaline) stores (van den Buuse et al., 1984, 1986a). In preliminary experiments, some rats were pretreated i.p. with 20 mg/kg of desipramine in order to protect central noradrenergic neurons from the neurotoxic action of 6-OHDA (van den Buuse et al., 1984). This pretreatment was found not to give different results from those obtained in animals treated with only 6-OHDA. Ten days after the last i.c. injection of saline or 6-OHDA, the rats were again anesthetized with pentobarbital and cannulated in the femoral artery and jugular vein. Three days later the effect of i.v. administration of quinpirole was tested according to the standard protocol.

Desensitization study. The rapid decay of the pressor effect of quinpirole, as opposed to the much longer-lasting behavioral effect (see Locomotor Activity Study) may suggest some desensitization phenomenon. This was studied in SHR by injecting quinpirole i.v. twice with varying intervals between the injections. In the standard protocol a second injection was thus given after the first one. In the case of the 2-hr interval this was preceded by an additional treatment with domperidone. In the case of the 6- and 24-hr interval the standard protocol was applied twice in the same animal. Control SHR received i.v. saline first followed by i.v. quinpirole. Because the pressor response to i.v.
quinpirole in these different control groups was indistinguishable, the control data were pooled. This was also done for the initial pretreatment values.

**Drugs.** The following compounds were obtained from Research Biochemicals (Illkirch, France): quinpirole HCl; the peripherally acting D-2 antagonist domperidone; the dopamine agonists (R)-(+)

-AP0 HCl; (R)-(—)-NPA HCl; and (+)-3-PPP, the putative selective presynaptic D-2 agonist (—)-3-PPP and the catecholamine neurotoxin 6-OHDA with ascorbic acid. All compounds were dissolved in saline immediately before the experiment. Domperidone was dissolved in a minimal amount of 0.1 N HCl and diluted with saline. The preferential D-2 antagonist haloperidol was purchased as a 5-mg/ml solution (Haldol, Janssen Pharmaceutica, Beerse, Belgium) and the selective D-2 antagonist sulpiride as a 100-mg/2-ml solution (Dogmatil, Delagrange, Paris, France). Both of these antagonists act centrally. Pertussis toxin (200 μg/ml of 50% glycerol phosphate buffer) was purchased from Porton Products (Wiltshire, UK). This compound blocks D-2-mediated responses by ribosylating the α-subunit of the G-protein G, to which this receptor is coupled (see "Discussion").

**Data analysis.** Blood pressure and heart rate were averaged over 10-sec periods. These values were taken at 30 sec and 1, 3, 5, 10, 15, 20, 25 and 30 min after quinpirole injection. The values were used to calculate group averages and S.E.M. In most cases, the data were expressed as changes in blood pressure (or heart rate) compared to the values obtained 5 min after injection of domperidone. These relative values are displayed in the time course graphs. In some figures only the maximum pressor effect is displayed. This corresponds to the values obtained at 1 min after administration.

ANOVA, in appropriate cases with repeated measures, was used to compare different experimental groups. In some cases Duncan's multiple range test was used to further analyze group differences. When P < .05, the difference was considered statistically significant.

**Results.**

**Effect of quinpirole on blood pressure of SHR and WKY.** The i.v. injection of saline or 1 mg/kg of domperidone did not cause significant changes in blood pressure or heart rate (not shown). The i.v. injection of different doses of quinpirole caused an immediate increase in blood pressure, which peaked at 1 min after injection. Thereafter, blood pressure slowly returned to base line. Heart rate showed little change, except that sometimes heart rate variability appeared to be less after quinpirole injection (see fig. 1 for example responses and fig. 2 for group curves). The injection of quinpirole caused some changes in the behavior of the rats. Thus, immediately after injection rats would appear to be aroused and would become hyperactive. Soon after, the hyperactivity was accompanied by various forms of stereotyped behavior, mainly sniffing and occasional grooming or cage-licking. Whereas these behavioral changes were observed in both SHR and WKY, it was clear that their intensity and duration were much less in the former strain than in the latter (see also Locomotor Activity Experiment below).

Quinpirole was injected at doses of 0.03, 0.1, 0.3 and 1.0 mg/kg i.v. in SHR and WKY, and also at 3.0 mg/kg in SHR. All doses showed a similar time course of the effect on blood pressure (see top panel of fig. 2 for the 0.3-mg/kg dose). Peak pressor responses to 0.03 to 0.3 mg/kg of quinpirole did not differ between SHR and WKY, but 1.0 mg/kg caused a significantly greater pressor response in SHR than in WKY. Whereas the dose-response curve for quinpirole appeared to level off at 1.0 mg/kg in WKY, increasing doses of quinpirole caused progressively greater pressor responses in SHR (bottom panel of fig. 2). The dose of 3.0 mg/kg was not studied in WKY because it was anticipated that severe behavioral side-effects would occur which would interfere with the experiment. Because the 0.3-mg/kg dose of quinpirole caused similar effects in SHR and WKY and because the behavioral side-effects were mild, this dose was chosen for further study in SHR.

**Effect of quinpirole on locomotor activity of SHR and WKY.** In order to quantify the observed differences in behavioral responses to quinpirole in SHR and WKY, rats were tested in automated activity meters (fig. 3). Base-line locomotor activity was significantly increased in SHR when compared to WKY. The injection of 0.01 or 0.05 mg/kg of quinpirole caused a decrease in locomotor activity in both SHR and WKY, although this change was greater and statistically significant only in SHR. The injection of 0.25 or 1.25 mg/kg of quinpirole markedly increased locomotor activity in WKY. In contrast, locomotor activity remained significantly decreased in SHR when compared to base-line values. Thus, WKY showed a biphasic response to quinpirole, consisting of a decreased locomotor activity at low doses and a hyperactivity at high doses, whereas SHR showed only the decrease in locomotor activity.

**Effect of other dopamine D-2 agonists.** Injection of 0.3 mg/kg of APO or NPA caused an increase in blood pressure Fig. 1. Representative example of the effect of i.v. injection of 0.3 mg/kg of quinpirole in two SHR. The rats were pretreated with domperidone (1 mg/kg i.v., 10 min before). Top panel, mean and pulsatile blood pressure and heart rate (MAP, BP and HR, respectively) of one SHR; bottom panel, pulsatile BP and HR of another SHR. Immediately after injection of quinpirole (arrows, t = 0), BP increased, reaching a peak at 1 min. Thereafter, BP gradually returned to base line. HR showed little change. B/min, beats/min.
which was comparable to that after 0.3 mg/kg of quinpirole. Thus, blood pressure increased rapidly and returned gradually to base line in the 30 min thereafter. NPA appeared to be slightly more potent than APO (top panel of fig. 4).

At 0.3 mg/kg, (+)-3-PPP caused only a small and short-lasting increase in blood pressure (not shown). However, at 3 mg/kg i.v., (+)-3-PPP caused a marked pressor response, which rapidly returned to base line (bottom panel of fig. 4). In contrast, at 3 mg/kg i.v., (−)-3-PPP did not cause a significant increase in blood pressure. That this latter compound was active was shown by three other observations. First, (−)-3-PPP caused a marked increase in heart rate (at 1 min after injection, 161 ± 15 beats/min; at 5 min after injection, 109 ± 17 beats/min; thereafter a gradual return to base line). None of the other compounds tested in this study caused such profound changes in heart rate. Second, injection of 0.3 mg/kg of quinpirole, 30 min after injection of 3 mg/kg of (−)-3-PPP, increased blood pressure (at 1 min after injection, 20 ± 1 mm Hg), but this response appeared to be smaller than in nonpretreated SHR (compare with fig. 2). This shows that treatment with (−)-3-PPP inhibits the response to subsequent treatment with quinpirole. Finally, in behavioral experiments, it was observed that administration of (−)-3-PPP, at doses similar to those used in
the present experiment, caused a decrease of locomotor activity in both SHR and WKY (not shown), similar to the effect seen with low doses of quinpirole. In these behavioral experiments no increase of locomotor activity was seen either in WKY or in SHR, confirming the putative presynaptic selectivity of the effect of (-)-3-PPP. Both (+)- and (-)-3-PPP enantiomers tended to decrease blood pressure from 15 to 30 min after injection. This may be caused by the fact that the pretreatment with 1 mg/kg of domperidone was not able to completely block the peripheral effects of these high doses, and a slight peripherally mediated fall in blood pressure could develop.

The i.v. injection of 3 mg/kg of bromocriptine caused an increase in blood pressure (at 1 min after injection, 22 ± 4 mm Hg). Further quantification of the effect of bromocriptine was difficult, however, as blood pressure in these rats showed short-lasting falls of as much as 50 mm Hg every 3 to 6 min. In between these falls, a response reminiscent of that to quinpirole and the other agonists could be seen (not shown). None of the other compounds tested induced these profound irregularities in blood pressure.

Effect of dopamine antagonists. The i.v. injection of 0.3 mg/kg of quinpirole in SHR pretreated with saline or domperidone caused a pressor response with a similar time course but different magnitude. As illustrated in figure 5, domperidone pretreatment potentiated the pressor action of quinpirole, possibly by inhibiting the peripherally mediated depressor action of this compound. Additional treatment with the centrally acting dopamine D-2 antagonists haloperidol or sulpiride almost completely blocked the pressor action of quinpirole. Haloperidol did not affect basal blood pressure, but sulpiride caused a marked reduction of base-line pressure.

Pertussis toxin pretreatment. The i.c.v. injection of 2 µg of pertussis toxin did not cause overt changes in behavior or general state of the animals. Basal blood pressure was not significantly influenced, although heart rate was increased in WKY (table 1). After pretreatment with pertussis toxin, the i.v. injection of 0.3 mg/kg of quinpirole caused an acute pressor response (fig. 6), which had a smaller magnitude and shorter duration of action when compared to the values before pertussis toxin treatment. Although the effect of pertussis toxin was significant in both strains, the extent of inhibition was greater in WKY. For example, at 1 min after injection the change in blood pressure in WKY was 28 ± 2 mm Hg whereas these values were 14 ± 1 and 22 ± 2 mm Hg (P = .02 for strain comparison), indicating the relatively greater change in response to quinpirole administration by PTX in WKY when compared to that in SHR (see also text). MAP, mean arterial pressure.

**TABLE 1**

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<thead>
<tr>
<th>Strain/Treatment</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
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<tr>
<td>Control</td>
<td>122 ± 2</td>
<td>349 ± 15</td>
</tr>
<tr>
<td>After PTX</td>
<td>131 ± 3</td>
<td>401 ± 14*</td>
</tr>
<tr>
<td>6-OHDA treated</td>
<td>153 ± 2</td>
<td>326 ± 3</td>
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<td>*P &lt; .05 for difference between values before and after treatment.</td>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>164 ± 3</td>
<td>358 ± 10</td>
</tr>
<tr>
<td>After PTX</td>
<td>162 ± 4</td>
<td>379 ± 10</td>
</tr>
<tr>
<td>6-OHDA treated</td>
<td>153 ± 1</td>
<td>326 ± 4</td>
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Fig. 5. Effect of pretreatment with domperidone (DOMP) and haloperidol (HALO) or sulpiride (SULP) on the pressor response to i.v. administration of 0.3 mg/kg of quinpirole. Data are peak changes in blood pressure (n = 6 for the saline (SAL)-, HALO- and SULP-group, n = 18 for the DOMP values). *P < .05 for difference with saline-treated rats. DOMP pretreatment potentiated the effect of i.v. administration of quinpirole, whereas additional treatment with HALO or SULP blocked the quinpirole-induced pressor response. MAP, mean arterial pressure.

Fig. 6. The i.c.v. treatment with pertussis toxin (PTX) attenuates the pressor response to i.v. administration of 0.3 mg/kg of quinpirole in SHR (top panel, n = 10) and WKY (bottom panel, n = 10). Data are changes in blood pressure 24 hr before and 24 hr after PTX treatment. ANOVA on the absolute blood pressure values showed in SHR an overall effect of PTX treatment (F = 11.7, P < .001) and of quinpirole (F = 69.3, P < .001), but no significant interaction between these factors. In WKY, there was an overall effect of PTX treatment (F = 4.6, P < .05) and of quinpirole (F = 83.9, P < .001) and also a significant interaction between the two treatments (F = 6.9, P < .001), indicating the relatively greater change in response to quinpirole administration by PTX in WKY when compared to that in SHR (see also text). MAP, mean arterial pressure.
OVA. At 5 min after injection, the effect of quinpirole on blood pressure was 19 ± 2 mm Hg in WKY and 17 ± 2 mm Hg in SHR before pertussis toxin treatment (P > .05) vs. 1 ± 2 and 12 ± 3 mm Hg, respectively, after pertussis toxin treatment (P < .01). At this time point, the effect of pertussin toxin treatment on the quinpirole response was significantly greater in WKY than in SHR (strain-treatment interaction, P = .015). As in previous experiments, i.v. injection of quinpirole did not significantly change heart rate, either before or after pertussis toxin treatment (not shown).

6-OHDA pretreatment. The i.c. injection of 6-OHDA caused an initial decrease in body weight, but by the third treatment body weight had reached pretreatment levels and body weight gain was normal thereafter. There was no significant difference in basal blood pressure or heart rate between SHR treated i.c. with 6-OHDA or control SHR (table I). The i.v. injection of 0.3 mg/kg of quinpirole caused identical pressor responses in both 6-OHDA-treated and control SHR (fig. 7). Heart showed no significant changes in either group (not shown).

Desensitization study. Desensitization to the pressor effect of quinpirole was studied by injection of the compound twice in the same SHRs at varying intervals. Thirty minutes after injection of 0.3 mg/kg of quinpirole, a similar dose did not cause any significant change in blood pressure. SHR, which had been treated with saline initially, showed the normal rapid increase in blood pressure (fig. 8, top panel). After increasing the interval between the two quinpirole treatments to 2 or 6 hr, some of the pressor effect reappeared, but only after an interval of 24 hr were responses similar to saline-treated or nonpretreated controls (see fig. 8, bottom panel, for peak values). In preliminary experiments it was also found that 48 hr after injection of quinpirole an additional injection of this compound could elicit a normal pressor response.

Discussion

The object of the present study was 2-fold: first, the central mechanism of action of quinpirole on blood pressure was studied by the use of dopamine agonists and antagonists, central pretreatment with pertussis toxin or 6-OHDA and by investigating the time course of desensitization of the pressor response. Second, the action of quinpirole was compared between SHR and normotensive WKY, in order to obtain information on possible differences in central dopaminergic responses between these strains. The effect of quinpirole on locomotor activity was also studied in SHR and WKY, as it became obvious from the cardiovascular experiments that differences between the behavioral responses of SHR and WKY to quinpirole administration could be observed. Moreover, previous studies had shown differential changes in the behavioral response of SHR to various dopaminergic treatments (see below).

Central mechanism of action of quinpirole on blood pressure. The main findings were: 1) other centrally acting dopamine agonists with a preferential action on dopamine D-2
receptor mechanisms (Arnt, 1987; Stoof and Kebabian, 1984) caused similar effects of blood pressure; 2) the pressor response to quinpirole was potentiated by the peripherally acting dopamine D-2 antagonist domperidone (see also Nagahama et al., 1986a), but blocked by the centrally acting dopamine D-2 antagonists haloperidol and sulpiride; 3) the pressor response was attenuated after central pretreatment with pertussis toxin; 4) the pressor response was not influenced by central pretreatment with 6-OHDA; and 5) the pressor response showed rapid and long-lasting desensitization.

With respect to the comparison between quinpirole and other dopamine D-2 agonists, it is noteworthy that (−)-3-PPP did not induce any pressor response in SHR, whereas (+)-3-PPP induced effects similar to the other agonists, albeit less potently. Whereas (+)-3-PPP is a potent ligand for central sigma receptors, there is abundant evidence that it modulates central dopamine systems as well (see Clark et al., 1985, 1991 and references therein). In this respect (−)-3-PPP is a partial agonist and has been shown to be active as an agonist only in tests which involve presynaptic dopamine receptors (autoreceptors). At postsynaptic receptors it may act as an antagonist. The underlying mechanism of this difference might be a greater receptor reserve of pre- as opposed to postsynaptic dopamine receptors (Clark et al., 1985; Meller et al., 1987).

The lack of effect of (−)-3-PPP on blood pressure may thus indicate that the dopamine receptors involved in the pressor responses have similar characteristics to postsynaptic dopamine D-2 receptors involved in behavioral responses. The apparent inhibition of the quinpirole-induced pressor response in animals treated with (−)-3-PPP might be due to the postsynaptic "antagonist" action of the latter compound. The experiments with 6-OHDA-treated SHR confirm a postsynaptic location of these receptors. Thus, depletion of central dopamine by the presently used method (van den Buuse et al., 1984, 1986a) did not influence the pressor action of quinpirole, indicating that the presence of dopamine neurons, including presynaptic receptors, is not essential for this response. Interestingly, as 6-OHDA depletes noradrenaline stores as well (van den Buuse et al., 1984, 1986a), it is unlikely that the dopamine receptors involved in the quinpirole-induced pressor response are located on central noradrenergic neurons. A further indication for a single population of dopamine receptors involved in the pressor action of quinpirole comes from comparing the dose-response curves for the behavioral action and for the cardiovascular action of this compound. Whereas in WKY and other normotensive rats (Eilam and Szechtman, 1989; Fuller et al., 1983; present results) quinpirole showed a biphasic effect on locomotor activity, the cardiovascular effect of a similar dose range was only pressor. The biphasic dose-response curve for the behavioral action has been suggested to be caused by an action at presynaptic dopamine receptors at low doses, resulting in hypoactivity, and an action at postsynaptic dopamine receptors at higher doses, resulting in hyperactivity (Arnt, 1987; Eilam and Szechtman, 1989). In SHR, both the behavioral and the pressor action of quinpirole showed a monophasic dose-response curve (see below).

Central treatment with pertussis toxin caused an inhibition of the effect of quinpirole on blood pressure. Pertussis toxin is known to inhibit dopamine D-2 receptor-mediated responses such as the inhibition of adenylyl cyclase and certain behavioral effects by ADP-ribosylating the α-subunit of the G-protein G, to which this receptor is coupled (Boyajian et al., 1989; Fujita et al., 1985; Olianas and Onali, 1987; and references therein). Interestingly, it has been suggested that pertussis toxin treatment does not affect responses mediated by presynaptic dopamine D-2 receptors located on corticostriate and nigrostriate terminals (Memo et al., 1988), which would be further evidence that the receptors involved in the quinpirole-induced pressor response have the characteristics of striatal postsynaptic dopamine D-2 receptors.

After an injection of quinpirole, blood pressure responses to a subsequent dose were significantly reduced in a time-dependent manner. Although measurement of the half-life of the drug and its plasma levels would be needed to rule out any pharmacokinetic effects, these data may suggest desensitization of the central D-2 receptors involved in the cardiovascular response to quinpirole administration. One important aspect of the present results is that, although quinpirole may act at postsynaptic dopamine D-2 receptors to increase blood pressure, these receptors are apparently not tonically activated in the conscious animal. This latter interpretation comes from the findings that: 1) injection of centrally acting dopamine D-2 antagonists does not decrease blood pressure; 2) depletion of central dopamine by treatment with 6-OHDA does not change basal blood pressure; and 3) the rapid desensitization of these dopamine receptors would prevent any tonic effects.

The present results are in line with previous work which showed that the centrally acting dopamine antagonist metoclopramide blocked the pressor response (Nagahama et al., 1986a). Desensitization to the pressor action of quinpirole was suggested by the finding of Igarashi et al. (1987) that continuous infusion of the compound in conscious rats not treated with domperidone caused only a transient increase in blood pressure followed by a prolonged decrease. It is interesting to note that Yang et al. (1990) could induce a pressor response in the conscious, decerebrate rat by injecting quinpirole into the nucleus tractus solitarii. The authors suggested that this nucleus was the central site of action of quinpirole on blood pressure. However, it has been found that catecholamine metabolism in a number of other brain regions such as the hypothalamus is affected by injection of quinpirole (Chen et al., 1987; Fuller and Hemrick-Luecke, 1985), indicating that these regions may influence the cardiovascular response as well. Moreover, stimulation of other dopaminergic regions, such as the ventral tegmental area, also induces a pressor response (van den Buuse et al., 1988).

Central dopaminergic regulation in SHR. The development of hypertension in SHR was inhibited by selective depletion of central dopamine (van den Buuse et al., 1984). Similarly, discrete lesions of the substantia nigra in prehypertensive SHR attenuated the rise in blood pressure in these rats (van den Buuse et al., 1986b). This suggested that brain dopamine, most likely the nigrostriatal system, was involved in the development of spontaneous hypertension. Further work showed differential changes in central dopaminergic function in SHR (van den Buuse and De Jong, 1989).

Quinpirole induced a pressor response in SHR which was similar at lower doses, but greater at higher doses, than that observed in WKY. Although a higher dopamine D-2 receptor sensitivity in SHR compared to WKY cannot be excluded, such a change would most likely cause a difference in the pressor response at all doses. Alternatively, the SHR could be showing a less marked desensitization to the pressor action of the 1-mg/kg dose of quinpirole or show some differences in transduction coupling of their dopamine D-2 receptors. This latter
possiibility is supported by the somewhat greater effect of pertussis toxin on the quinpirole-induced pressor response, but it is unclear why such a difference in transduction mechanism would not be apparent at the lower doses of quinpirole. A full quinpirole dose-response curve before and after pertussis toxin pretreatment would be needed in the two strains before a definite conclusion can be drawn.

During the experiments it was observed that treatment with quinpirole, especially at the higher doses, induced more intense behavioral activation in WKY than in SHR. This was confirmed by a markedly increased locomotor activity of WKY after treatment with higher doses of quinpirole, whereas SHR showed no such behavioral activation (see also Fuller et al., 1983). Thus, it is possible that the effects of quinpirole on other dopamine systems (e.g., Chen et al., 1987), resulting in marked behavioral effects in WKY, but not SHR, influence in some way the cardiovascular responses. Nevertheless, the pressor response to quinpirole was not reduced in SHR when compared to WKY, in contrast to the difference in behavioral response. Previous work has shown other differential changes in dopaminergic regulation of SHR when compared to WKY (for a review, see van den Buuse and De Jong, 1992). In a recent series of experiments we used treatment with the dopamine D-2 antagonist sulpiride in a number of tests of dopaminergic function in SHR and WKY (van den Buuse et al., 1992). It was found that at low doses sulpiride enhanced locomotor activity of SHR, but not WKY, whereas at higher doses it decreased locomotor activity in WKY, but not SHR. Furthermore, at higher doses sulpiride significantly decreased amphetamine-induced turning in WKY, but not SHR, with unilateral 6-OHDA-induced lesions of the ascending dopaminergic pathways. Sulpiride also enhanced salt-sensitivity in SHR and WKY. Taken together, these data could suggest two groups of dopamine D-2 receptor responses, one of which is diminished markedly in SHR, and the other normal or upregulated. The presently described quinpirole-induced pressor response would then belong in the latter group, whereas the increase in behavioral activity would belong to the former. The underlying neurochemical difference in these two groups of dopamine D-2 receptor-mediated responses is as yet unclear. It is unlikely to be due to the pre- vs. postsynaptic location of the receptors, as the group of “normal” responses in SHR includes D-2-induced hypoactivity via presynaptic receptors, but also D-2-mediated prolactin release and pressor responses (present results) via postsynaptic receptors. One possibility is that different subtypes of the D-2 receptor or different transduction mechanisms are involved, one being downregulated in SHR and the other either normal or upregulated. Further experiments are needed to explore these possibilities. The results of such experiments may give further insight into the role of central dopamine systems in cardiovascular regulation and the development of hypertension.

In conclusion, the present experiments showed that SHR showed normal or greater pressor responses to quinpirole treatment than WKY. The pressor response to quinpirole was shown to involve central, postsynaptic, dopamine D-2 receptors, which were sensitive to pertussis toxin treatment and showed a marked and long-lasting desensitization.

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References


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