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Pretreatment with quinpirole inhibits the central antihypertensive effects of rilmenidine and α-methyldopa in conscious rats

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Abstract

Treatment of conscious spontaneously hypertensive rats (SHR) with the dopamine D_2 receptor agonist quinpirole causes a short-lasting pressor response and apparent desensitisation to the effects of subsequent injections of quinpirole or central antihypertensives such as clonidine. In the present study, a number of aspects of this apparent desensitisation were investigated. Thirty minutes after intravenous injection of quinpirole into spontaneously hypertensive rats, treatment with the dopamine D_2 receptors antagonist raclopride caused a significant fall in blood pressure. At this time point, circulating levels of vasopressin were not significantly different compared to controls. In Brattleboro rats, the pressor response to quinpirole was reduced in the first 15 min after injection, but no difference in blood pressure was observed at later time points. In SHR which had been treated with quinpirole, the central antihypertensive effects of rilmenidine or α-methyldopa were significantly inhibited. By contrast, the bradycardia induced by these drugs was similar in quinpirole-treated rats and controls. Quinpirole pretreatment caused an enhancement of the hypotension but a reduction of the reflex tachycardia after intravenous treatment with hydralazine. In SHR treated with methylatropine and quinpirole, the upper plateau of the sympathetic baroreceptor-heart rate reflex curve was reduced. These results show that treatment with quinpirole has marked effects on central sympathetic vasomotor mechanisms which are the target of antihypertensive drugs such as rilmenidine and α-methyldopa. At least some of these effects may occur at the level of the sympathetic baroreflex. Moreover, while the effects of quinpirole on sympathetic regulation are prolonged, the initial pressor response is counteracted by an as yet unidentified compensatory mechanism which can be unmasked when quinpirole is displaced from its receptor by dopamine D_2 receptor antagonist treatment.

Keywords: Quinpirole; Dopamine; Dopamine D_2 receptor; Rilmenidine; α-Methyldopa; Hydralazine; Sympathetic nervous system; Vasopressin

1. Introduction

Central dopaminergic mechanisms are involved in cardiovascular regulation in a number of ways. Stimulation of the region of origin of the mesolimbic dopamine system, the ventral tegmental area, caused a long-lasting pressor response and tachycardia (Cornish and Van den Buuse, 1995). This effect was mediated by an interaction of dopamine receptor activation in the brain and the circulatory effects of moderately enhanced levels of vasopressin (Cornish et al., 1997). Several studies have shown changes in indices of central dopaminergic activity in spontaneously hypertensive rats (SHR) (Van den Buuse and De Jong, 1992). For example, in SHR in vivo dopamine release in the striatum was significantly reduced (Linthorst et al., 1991), while dopamine D_2 receptor density in nucleus accumbens was significantly higher (Kirouac and Ganguly, 1993) compared to Wistar-Kyoto controls (WKY).

Administration of dopamine D_2 receptor agonists causes a centrally mediated pressor response with little effect on heart rate (Van den Buuse and De Jong, 1992). This effect has been extensively studied with the selective D_2/D_3 agonist quinpirole (Nagahama et al., 1986; Van den Buuse, 1992) and was found similarly after treatment with the dopamine agonists apomorphine, *N*-propyl-norapomorphine (NPA), (+)-3-PPP (Van den Buuse, 1992), 7-hydroxy-di-propyl-aminotetralin (Van den Buuse, 1993), quinelorane and pergolide (Van den Buuse, 1995). The mechanism behind the pressor action of quinpirole involved an immediate release of vasopressin into the circulation and enhancement of sympathetic vasomotor

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activity (Nagahama et al., 1986; Van den Buuse, 1992). The effect of intravenous injection of quinpirole could be blocked by pretreatment with centrally acting dopamine antagonists such as haloperidol, sulpiride and raclopride, but was enhanced by pretreatment with the peripherally acting dopamine D_2 receptor antagonist domperidone (Van den Buuse, 1992; Van den Buuse et al., 1996), supporting a central site of pressor action of quinpirole.

The nucleus tractus solitarius (NTS) in the dorsomedial medulla oblongata contains a high density of dopamine D_2, but not D_3 receptors (Gehlert, 1993; Lawrence et al., 1995) and has been suggested as the central site of action of quinpirole on blood pressure (Yang et al., 1990). A particularly intruiging aspect of the cardiovascular effects of quinpirole was the occurrence of apparent desensitisation. Firstly, the relatively short duration of the central action of dopamine agonists on blood pressure did not match their long-lasting effects on behaviour (Van den Buuse, 1995). Moreover, 30 min after intravenous injection of quinpirole, when blood pressure had essentially returned to baseline, a second injection produced little effect on blood pressure (Van den Buuse, 1992). Continuous infusion of quinpirole caused only a depressor response which was most likely mediated by peripheral mechanisms (Igarashi et al., 1987). The apparent desensitisation to quinpirole was similar in SHR, WKY and Sprague-Dawley rats and was found similarly after treatment with quinelorane or NPA (Van den Buuse et al., 1996). A surprising finding was that treatment with quinpirole not only caused desensitisation of its own effects, but caused a marked reduction of the antihypertensive action of the centrally acting sympatho-inhibitors clonidine and 8-hydroxy-di-propyl-aminotetralin (8-OH-DPAT) as well (Van den Buuse et al., 1996). By using the acute fall in blood pressure in response to injection of the ganglion blocker pentolinium as a tool, we showed that overall sympathetic vasomotor tone was not inhibited at 30 min after quinpirole treatment (Van den Buuse et al., 1996). We postulated that treatment with quinpirole caused prolonged differential changes in sympathetic vasomotor tone, where long-lasting activation of some neuronal populations or vascular beds by quinpirole caused a compensatory suppression of activity in other populations of vascular beds which caused blood pressure to return to baseline and inhibited the action of further quinpirole treatments or centrally acting sympatholytic agents (Van den Buuse et al., 1996).

The present study was undertaken to further investigate the central effects of quinpirole on blood pressure and heart rate, focussing on the apparent desensitisation. The effect of pretreatment with quinpirole on the central antihypertensive effects of rilmenidine and α-methyldopa was measured and compared to that on the systemic vasodilatory action of hydralazine. Since rilmenidine and α-methyldopa reduce blood pressure by inhibition of sympathetic vasomotor and cardiac tone (Head, 1995), the sympathetic baroreceptor-heart rate reflex was investigated in quinpirole-treated SHR. If it was assumed that treatment with quinpirole caused prolonged effects on sympathetic activity, despite blood pressure returning to normal, then acute displacement of quinpirole from its receptors would cause a decrease in blood pressure. To test this hypothesis, the effect of the dopamine D_2 receptor antagonist raclopride was measured on blood pressure and heart rate 30 min after pretreatment with quinpirole. Previous studies have suggested an important role of vasopressin release in the pressor response to quinpirole administration (Nagahama et al., 1986, 1987). A possible involvement of vasopressin in the apparent desensitisation to the cardiovascular effects of quinpirole was investigated by measuring plasma vasopressin levels at 30 min after quinpirole treatment and by comparing the time course of the effect of quinpirole on blood pressure of Brattleboro rats and Long-Evans controls.

2. Materials and methods

Male SHR of 250–350 g were obtained from the Baker Medical Research Institute breeding stock. All experiments, except those in Brattleboro and Long-Evans rats, were performed in conscious SHR, since rats from this strain displayed less locomotor hyperactivity in response to treatment with quinpirole (Van den Buuse, 1992). Brattleboro rats and Long-Evans rats of 250–350 g were obtained from IFFA Credo (L'Arbresle, France). The rats were kept 3–5 per cage with free access to pellet food and tap water.

At least one week before the experiments, the rats were anaesthetized with an intraperitoneal mixture of pentobarbital (Nembutal, 30 mg/kg), methohexital (Brietal, 40 mg/kg) and atropine sulphate (0.5 mg/kg). A vinyl/Teflon catheter (SV-40, Dural Plastics, Australia and STT 30, Small Parts, Miami, FL, USA) was inserted into the abdominal aorta as previously described in detail (Van den Buuse et al., 1996). The rats were also instrumented with a single vinyl (SV-40) cannula or, in case of the baroreflex experiments, a double-lumen vinyl (DV-40) cannula into the jugular vein (Van den Buuse et al., 1996). Each rat was singly housed after surgery.

On the day of the experiments, blood pressure was measured with Statham P23XL transducers and an 8-channel Neomedix Systems Neotrace recorder. Heart rate was derived off the blood pressure pulse by Baker Medical Research Institute tachographs. During the experiments, a standard protocol was used (Van den Buuse, 1992; Van den Buuse et al., 1996), which consisted of (1) a 5-min baseline period; (2) intravenous injection of saline (1 ml/kg) and a 10-min reading of blood pressure and heart rate; (3) intravenous injection of the peripherally acting dopamine D_2 receptor antagonist domperidone (1 mg/kg) and a 10-min reading of blood pressure and heart rate; (4) intravenous injection of saline (1 ml/kg) or quinpirole (0.3

mg/kg) followed by a 30-min reading of blood pressure and heart rate; and (5) intravenous injection of rilmenidine (1 mg/kg), α-methyldopa (50 mg/kg), hydralazine (1 mg/kg) or raclopride (0.5 mg/kg). In the case of baroreflex experiments, the SHR were treated with methylatropine (1 mg/kg i.v. at 20 min before and 20 min after treatment with quinpirole or saline) and baroreceptor-heart rate reflex curves were obtained 30 min after treatment with quinpirole or saline (see below). After completion of the experiment, some rats were returned to the animal house and used for additional experiments at least 48 h later. In the case of plasma vasopressin measurements, 30 min after treatment with quinpirole the rats were decapitated and trunk blood was obtained. Plasma was obtained by centrifugation and concentrations of vasopressin were assessed by radioimmunoassay as previously described (Cornish et al., 1997; Woods and Johnston, 1983).

In order to assess the baroreceptor-heart rate reflex, the 'steady-state' method was used. Different levels of changes in blood pressure were induced by slow 5–10 s infusions of different volumes of solutions of methoxamine (0.1 mg/ml) or nitroprusside (0.1 mg/ml). Blood pressure was

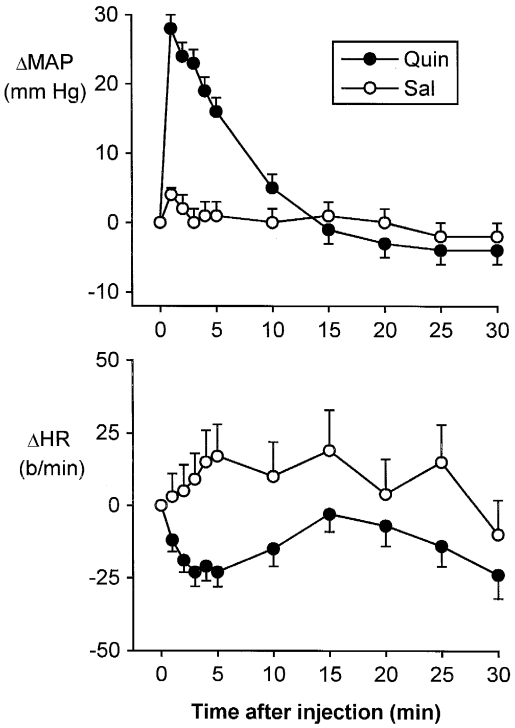

Fig. 1. The effect of i.v. injection of quinpirole (0.3 mg/kg) or saline on mean arterial blood pressure (MAP, top panel) and heart rate (beats/min, bottom panel) of conscious SHR. Injection of quinpirole caused a rapid rise in MAP which was maximum at 1 min after administration. Two-way ANOVA on blood pressure data indicated that the overall effect of treatment and of time, and the time×treatment interaction were significant. Heart rate was reduced in quinpirole-treated SHR compared to controls. Analysis of heart rate data indicated that the overall effects of treatment and of time were significant. The number of rats per group was 15.

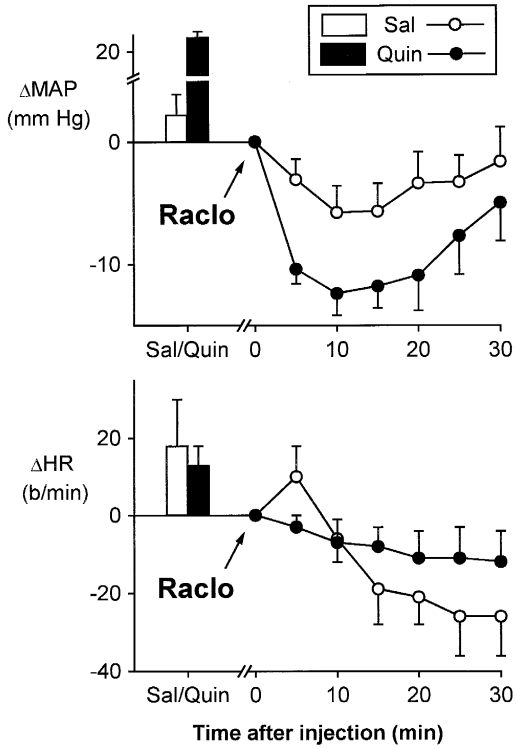

Fig. 2. The effect of i.v. injection of raclopride (0.5 mg/kg) or saline on mean arterial pressure (MAP, top panel) and heart rate (HR, bottom panel) of SHR which were pretreated with saline or quinpirole (0.3 mg/kg i.v.). Bars indicate the maximal change in MAP or HR after saline and quinpirole pretreatments, whereas the curves indicate changes in MAP and HR after injection of raclopride or saline. In SHR pretreated with quinpirole, raclopride treatment induced a decrease in blood pressure, which was significantly greater than that in SHR pretreated with saline. The number of rats per group was 10.

maintained at each level until heart rate had reached a plateau. For each individual rat, the induced changes in blood pressure and observed reflex changes in heart rate were fitted to a logistic sigmoid function using an interative least-squares method using a non-linear regression analysis (Head and McCarty, 1987; Van den Buuse and Itoh, 1993). Baroreflex parameters were group-averaged to construct group baroreflex curves.

Quinpirole HCl and domperidone were purchased from Research Biochemicals International (Natick, MA, USA). Raclopride tartrate was a gift from Astra, Sweden. Rilmenidine was a gift from Servier, France. α-Methyldopa was obtained from Merck, Sharpe&Dome. Other drugs were obtained from Sigma. The doses of the drugs were expressed as their salts. All drugs were dissolved in saline prior to use, except for domperidone, which was first dissolved in a minimal amount of HCl and diluted to the appropriate concentration.

All data are expressed as mean values ± standard error of the mean (S.E.M.). Differences between groups were analyzed with analysis of variance (ANOVA) with repeated measures where appropriate. Further between-group comparisons were performed with Student-Newman Keuls

test or paired and unpaired Student *t*-tests. Differences were considered significant when $P < 0.05$.

3. Results

The i.v. injection of 0.3 mg/kg of quinpirole caused a rapid rise in blood pressure with a maximum at 1 min after administration (Fig. 1). Thereafter, blood pressure gradually decreased towards baseline and tended to be below levels found in saline-treated controls from 15 min after injection. Heart rate was slightly but significantly reduced in quinpirole-treated SHR compared to controls (Fig. 1).

Thirty minutes after pretreatment with quinpirole, the i.v. injection of the dopamine D_2 receptor antagonist raclopride (0.5 mg/kg) caused a modest, but statistically significant decrease in blood pressure with a maximum effect of −12.4 mmHg at 10 min after injection (Fig. 2). By contrast, injection of raclopride caused little change in blood pressure in SHR which had been pretreated with saline (Fig. 2). From 5–20 min after injection, the average

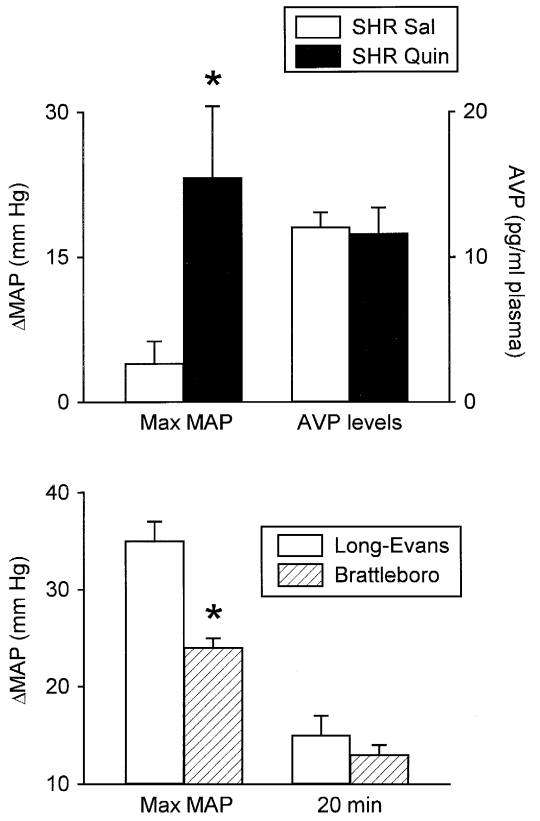

Fig. 3. The involvement of vasopressin in the pressor response and desensitisation to treatment with quinpirole. Top panel shows the maximal change in mean arterial pressure (MAP) in conscious SHR injected with saline ($n = 7$) or quinpirole (0.3 mg/kg i.v., $n = 6$) and plasma concentrations of arginine-vasopressin (AVP) in these rats 30 min later. Bottom panel shows the change in MAP following quinpirole treatment in Long-Evans rats ($n = 10$) or Brattleboro rats ($n = 10$). The maximal pressor responses, but not the changes at 20 min after injection or later, were significantly different between the strains.

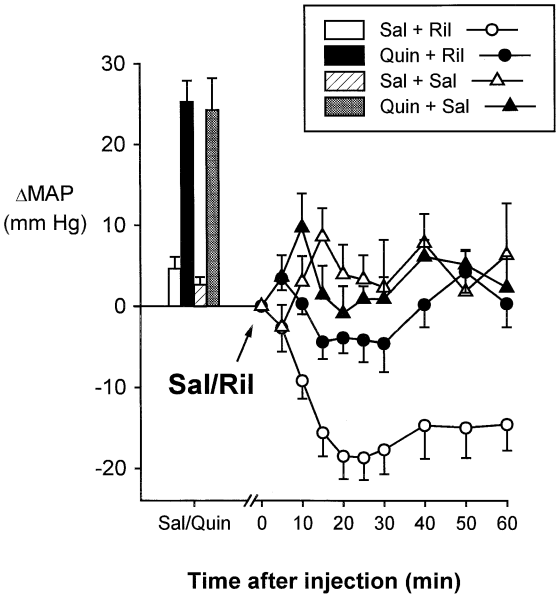

Fig. 4. The effect of i.v. injection of rilmenidine (1 mg/kg) or saline on mean arterial pressure (MAP) of SHR which were pretreated with saline or quinpirole (0.3 mg/kg i.v.). Bars indicate the maximal change in MAP after saline and quinpirole pretreatments, whereas the curves indicate changes in MAP after injection of rilmenidine or saline. In SHR pretreated with saline, rilmenidine treatment induced a marked decrease in blood pressure, which was significantly greater than that in SHR pretreated with quinpirole or after saline treatment in quinpirole-pretreated SHR. The small reduction in MAP observed after rilmenidine treatment in quinpirole-pretreated rats was significantly different from the changes in MAP oberved after saline treatment in quinpirole-treated rats. The number of rats per group was 9, 10, 7 and 7, respectively.

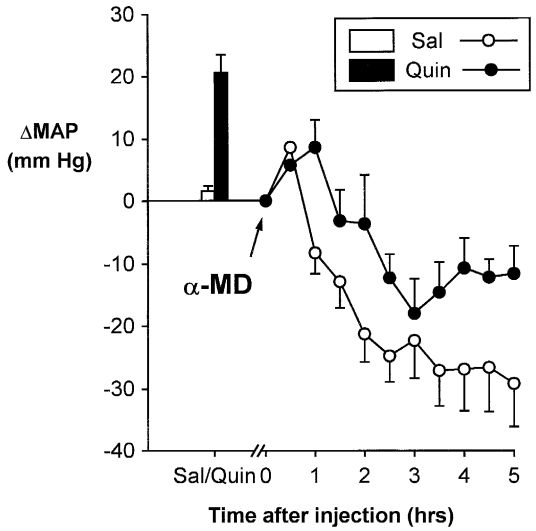

Fig. 5. The effect of i.v. injection of α-methyldopa (50 mg/kg) or saline on mean arterial pressure (MAP) of SHR which were pretreated with saline or quinpirole (0.3 mg/kg i.v.). Bars indicate the maximal change in MAP after saline and quinpirole pretreatments, whereas the curves indicate changes in MAP after injection of α-methyldopa or saline. In SHR pretreated with saline, α-methyldopa treatment induced a marked decrease in blood pressure, which was significantly greater than that in SHR pretreated with quinpirole. The number of rats per group was 10.

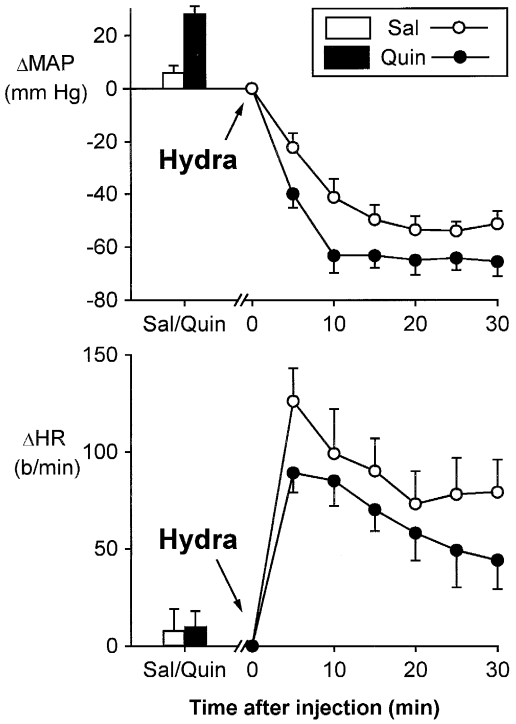

Fig. 6. The effect of i.v. injection of hydralazine (1 mg/kg) or saline on mean arterial pressure (MAP, top panel) and heart rate (HR, bottom panel) of SHR which were pretreated with saline or quinpirole (0.3 mg/kg i.v.). Bars indicate the maximal change in MAP or HR after saline and quinpirole pretreatments, whereas the curves indicate changes in MAP and HR after injection of hydralazine or saline. In SHR pretreated with quinpirole, hydralazine treatment induced a marked decrease in blood pressure, which was significantly greater than that in SHR pretreated with saline. Conversly, the bradycardia, which occurred after treatment with hydralazine, was significantly smaller in SHR pretreated with quinpirole compared to control SHR. The number of rats per group was 7.

raclopride-induced decrease in blood pressure was -11.4 ± 1.8 mmHg in quinpirole-pretreated SHR vs. -4.5 ± 1.9 mmHg in saline-pretreated SHR ($P < 0.05$). Raclopride treatment did not cause significant changes in heart rate (Fig. 2).

Plasma levels of vasopressin were not significantly different between SHR which had been pretreated 30 min previously with saline or with quinpirole (Fig. 3). In Brattleboro rats and Long-Evans control rats, i.v. injection of quinpirole caused a similar rapid rise in blood pressure as in SHR with the maximum increase occurring at 1 min after injection and blood pressure gradually returning to baseline thereafter. The maximal increase in blood pressure was significantly greater in Long-Evans rats compared to Brattleboro rats (Fig. 3). By contrast, at 20 or 30 min after treatment blood pressure was not different between these strains (Fig. 3).

The i.v. injection of rilmenidine in saline-pretreated control SHR caused a reduction in blood pressure with a maximum of -18.7 mmHg at 25 min after administration (Fig. 4). By contrast, in SHR which had been pretreated with quinpirole, the i.v. injection of rilmenidine induced only a minor change in blood pressure (-4.2 mmHg at 25 min). Injection of saline into SHR which were pretreated with saline or quinpirole induced little change in blood pressure (Fig. 4). The average change in MAP from 10–60 min after administration of rilmenidine was -15.5 ± 1.2 mmHg in saline-pretreated rats vs. -1.5 ± 1.0 mmHg in quinpirole-pretreated rats ($P < 0.05$). These values were 4.6 ± 1.5 and 3.2 ± 1.2 mmHg after saline injection. The average changes in MAP after rilmenidine treatment, either in saline- or quinpirole-pretreated SHR, were significantly different from those after saline treatment.

The i.v. injection of rilmenidine caused a bradycardia which was similar in SHR which were pretreated with saline or quinpirole (Fig. 7). The maximum fall in heart rate was at 25 min after administration (-64 ± 10 beats/min vs. -58 ± 7 beats/min, respectively). In SHR which were injected with saline, there were little changes in heart rate.

The i.v. injection of α-methyldopa in control SHR caused a gradually developing marked reduction in blood pressure and heart rate which was maintained for the duration of the observation period. In SHR which had been pretreated with quinpirole, the hypotensive action of α-methyldopa was significantly inhibited (Fig. 5). By con-

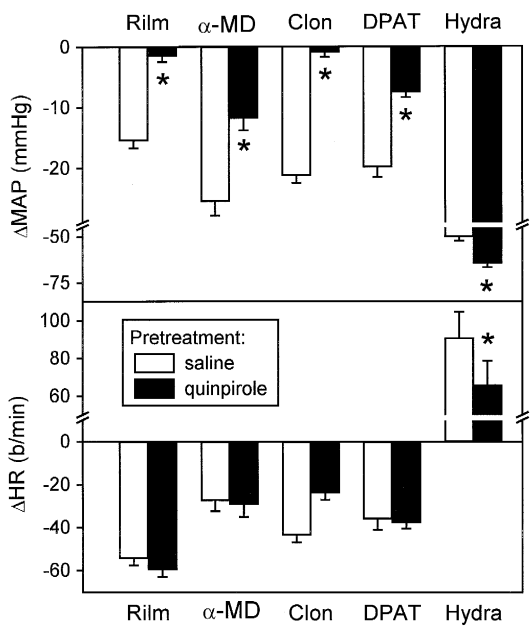

Fig. 7. Average changes in mean arterial pressure (MAP, top panel) and heart rate (HR, bottom panel) after i.v. treatment with rilmenidine (1 mg/kg), α-methyldopa (50 mg/kg), clonidine (0.01 mg/kg), 8-OH-DPAT (0.1 mg/kg) or hydralazine (1 mg/kg) in conscious SHR which were pretreated with saline (open bars) or quinpirole (0.3 mg/kg, closed bars). Data were calculated as the average decrease in blood pressure or heart rate from 10–60 min (rilmenidine), 2–5 h (α-methyldopa), 5–60 min (clonidine, 8-OH-DPAT) or 10–30 min (hydralazine) after injection. Data for clonidine and 8-OH-DPAT were taken from Van den Buuse et al. (1996) and included for comparison.

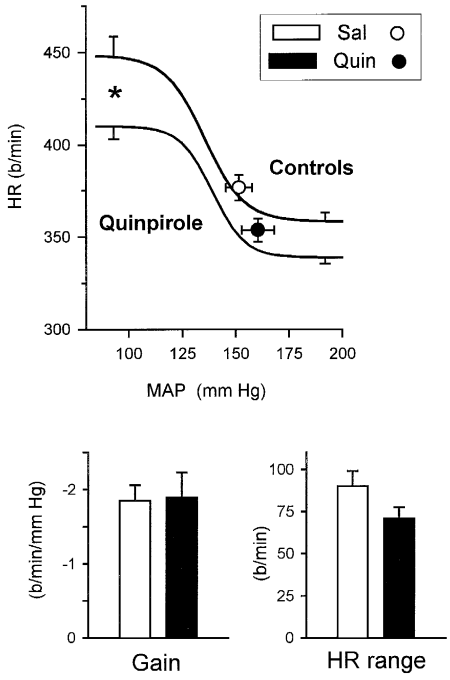

Fig. 8. The effect of pretreatment with quinpirole (0.3 mg/kg) or saline on sympathetic baroreceptor-heart rate (HR) reflex parameters in conscious SHR. Injection of quinpirole caused a pressor response of 25.7 ± 2.7 mmHg with little effect on HR. Baroreflex data were obtained at 30 min after treatment. The top panel shows group baroreflex curves constructed from the individual baroreflex parameters, whereas the bottom panels show average gain and HR range. In SHR pretreated with quinpirole the upper plateau of the baroreflex curve was significantly lower than that in saline-pretreated controls. Average gain, HR range or any other baroreflex parameters were not different between the groups. The number of rats per group was 7.

trast, there was no difference in the α-methyldopa-induced bradycardia between the two pretreatment groups (Fig. 7).

The effect of pretreatment with quinpirole on the hypotensive and bradycardic action of rilmenidine and α-methyldopa was similar to previous results with clonidine and 8-OH-DPAT (Fig. 7). In those experiments, we observed that pretreatment with quinpirole markedly inhibited the effect of clonidine and 8-OH-DPAT on blood pressure, but had less effect on the bradycardic action of these drugs (Van den Buuse et al., 1996).

The i.v. injection of hydralazine caused a marked fall in blood pressure which was associated with a marked tachycardia. The hydralazine-induced decrease in blood pressure was significantly greater in SHR which had been pretreated with quinpirole compared to saline-pretreated controls (Figs. 6 and 7). By contrast, the hydralazine-induced tachycardia was significantly reduced in quinpirole-pretreated SHR compared to controls (Figs. 6 and 7).

Sympathetic baroreceptor-heart rate reflex curves were constructed 30 min after the i.v. injection of quinpirole or saline in SHR which had been pretreated with methylatropine. Methoxamine-induced pressor responses and nitroprusside-induced depressor responses caused reflex bradycardic and tachycardic responses, respectively, which reached a plateau upon large blood pressure changes (Fig. 8). The upper plateau of the baroreflex curve was significantly lower in SHR which had been pretreated with quinpirole. Other baroreflex parameters, including baroreflex gain and heart rate range, were not significantly different between the groups (Fig. 8).

4. Discussion

This study suggests that pretreatment with the dopamine agonist quinpirole induces a number of effects on sympathetic regulation which surpassed the initial pressor action of this compound whereas the initial effect on vasopressin release was short lasting. At 30 min after treatment, when the quinpirole-induced pressor response had dissipated, the central antihypertensive actions of rilmenidine and of α-methyldopa were markedly inhibited, whereas the hypotensive effect of the vasodilator hydralazine was enhanced. We have postulated that treatment with quinpirole caused prolonged differential changes in sympathetic vasomotor tone, where long-lasting activation of some neuronal populations or vascular beds by quinpirole caused a compensatory suppression of activity in other populations of vascular beds which caused blood pressure to return to baseline and inhibited the action of further quinpirole treatments or centrally acting sympatholytic agents (Van den Buuse et al., 1996).

We focussed on the 30 min time-point after i.v. administration of quinpirole. Previously, we found that, at this time point, a second injection of quinpirole did not induce a pressor response, suggesting desensitisation. This apparent desensitisation was similar in SHR, Wistar-Kyoto controls and Sprague-Dawley rats, and was found similarly after treatment with the dopamine agonists quinelorane or *N*-propyl-norapomorphine (Van den Buuse et al., 1996). The apparent desensitisation was long lasting. At 2, 4 and 6 h after quinpirole administration, the effect of a second injection of this drug was significantly reduced (Van den Buuse, 1992; Van den Buuse et al., 1996). It is likely that this prolonged action of quinpirole reflects its long-lasting presence in the circulation and brain. Pharmacokinetic studies with the chemically closely related compounds quinelorane and pergolide have shown that these drugs, or active metabolites, remain in the circulation for several hours after their administration (Clemens et al., 1993; Franklin et al., 1994). Indeed, the effects of quinpirole and related compounds on behaviour were maintained for several hours (Eilam and Szechtman, 1989; Van den Buuse, 1995). However, the pressor effect of quinpirole was maintained for a short time only. It is likely that the return of blood pressure towards baseline was induced by an as yet unidentified compensatory mechanism which was activated by the immediate rise in blood pressure induced by quinpirole. It has been suggested that the pressor effect of

quinpirole is mediated by an increase in vasopressin release into the circulation and by an increased sympathetic nervous system activity, as measured by increased plasma levels of noradrenaline and adrenaline (Nagahama et al., 1986, 1987). Our results support an involvement of vasopressin in the initial pressor response as the maximal increase in blood pressure was significantly reduced in Brattleboro rats which are unable to synthesize vasopressin. Part of the compensatory mechanism to the quinpirole-induced pressor response appears to be to shut off the increased vasopressin release. The initial difference in the extent of the quinpirole-induced pressor response between Long-Evans rats, which are able to release vasopressin, and Brattleboro rats, which are not, was not maintained, suggesting that the effects of quinpirole do not rely on the release of vasopressin at later time points. Moreover, at 30 min after administration of quinpirole, plasma levels of vasopressin were not different between SHR which were treated with quinpirole or with saline. It is unclear how systemic administration of quinpirole caused release of vasopressin and how, despite maintained presence of the stimulus, this vasopressin release was subsequently normalized. The major source of vasopressin in the neurohypophysis are the hypothalamic supraoptic and paraventricular nuclei (Silverman and Zimmerman, 1983; Swanson and Sawchenko, 1983). Direct application of dopamine into the supraoptic nucleus of the hypothalamus caused an antidiuretic response (Urano and Kobayashi, 1978), suggesting that the effect of quinpirole could have been due to a direct action on vasopressin synthesizing cell bodies in the hypothalamus. Both the paraventricular and the supraoptic nucleus receive dense innervation from hindbrain region involved in cardiovascular control, and particularly noradrenergic projections from the A1 nucleus have been implicated in changes in vasopressin release in response to cardiovascular challenges (Cunningham and Sawchenko, 1991; Renaud and Bourque, 1991). It is possible that such projections play a role in counteracting the effect of quinpirole in the hypothalamus, in an attempt to dampen the increase in vasopressin release and return blood pressure to normal.

The prolonged apparent desensitisation shows that effects of quinpirole on sympathetic control were not directly reduced by any compensatory mechanism, in contrast to vasopressin release. The return of blood pressure to a level slightly below baseline appears to be due to an active hypotensive mechanism which may be unmasked when quinpirole is acutely displaced from its receptor by treatment with the dopamine receptor antagonist raclopride. The nature of this hypotensive mechanism is as yet unclear, but is unlikely to involve changes in the release of atrial natriuretic peptide or in haematocrit (Van den Buuse et al., 1996). A similar situation occurred with infusion of glutamate into the rostral ventrolateral medulla of anaesthetized rabbits which caused a pressor response which returned to baseline despite continued stimulation and persistence of increased renal sympathetic nerve activity levels (Malpas et al., 1996). Similarly, intravenous infusion of angiotensin in rabbits caused an initial pressor response which subsequently returned to baseline despite continued infusion (Hirooka et al., 1996). Interestingly, baroreceptor denervation enhanced the effects of angiotensin infusion on blood pressure and prevented the return to baseline (Hirooka et al., 1996). This suggests that at least part of the cardiovascular compensation to a pressor stimulus such as angiotensin infusion (and possibly injection of quinpirole) is a resetting of central sympathetic vasomotor responses. While the present study has assessed the baroreceptor-heart rate reflex, it would be of great interest to measure the effect of quinpirole treatment on the sympathetic vasomotor reflex.

The effect of raclopride on blood pressure in quinpirole-pretreated SHR resembles the fall in blood pressure which occurred after discontinuation of intravenous infusion of vasopressin, phenylephrine or angiotensin (Chiu and McNeill, 1985, 1986). Here too, the interpretation of this result was that the infusion of pressor agents triggered a hypotensive mechanism which, upon removal of the initial pressor stimulus, led to a fall in blood pressure. The identity of this hypotensive mechanism has not been clarified yet.

We previously assessed baroreceptor-heart rate reflex function in quinpirole-treated rats by the ramp technique (Van den Buuse et al., 1996). However, because of the relatively rapid changes in blood pressure and heart rate, this technique over-emphasizes the vagal component of this reflex. We found a reduced upper plateau of the ramp baroreflex curve (Van den Buuse et al., 1996), an effect which could represent reduced maximal sympathetic cardiac tone. Our present findings corroborate this result by selectively measuring the sympathetic component of the baroreceptor-heart rate reflex with the ‘steady-state technique’ (Head and McCarty, 1987). Funtionally, the reduced upper plateau will be reflected by an inhibited ability of the heart to adequately respond to relatively large changes in blood pressure and thereby provide less buffering of these changes.

This effect of quinpirole pretreatment on the cardiac baroreflex could at least partly explain the enhancement of the hypotensive effect of hydralazine, as the vasodilatation was buffered less by a reflex increase in heart rate, allowing a greater fall in blood pressure to develop. Indeed, in quinpirole-pretreated rats, the tachycardia associated with the hydralazine-induced hypotension was significantly reduced, in line with the effect of quinpirole on the upper baroreflex plateau.

Given the effect of quinpirole on baroreflex control and the action of hydralazine, it was surprising that, despite a clear effect on the antihypertensive effects of rilmenidine and α-methyldopa, quinpirole pretreatment did not significantly alter the bradycardia induced by these agents. One possibility to explain this apparent contradiction is that the

apparent desensitisation caused by quinpirole is specific to certain sympathetic vasomotor pathways, including those which mediate the antihypertensive action of clonidine, rilmenidine, α-methyldopa and 8-OH-DPAT (Van den Buuse et al., 1996). However, this would not take into account any possible effects on baroreceptor-heart rate reflex mechanisms. Another possibility is to consider that the bradycardia induced by treatment with rilmenidine and α-methyldopa is actually built up from a number of components. Firstly, these drugs are known to cause a reduction in cardiac sympathetic nerve firing (Esler et al., 1992; Ramage and Wilkinson, 1989), an effect which may be subject to inhibition by pretreatment with quinpirole. On the other hand, the fall in blood pressure which is induced by these centrally acting antihypertensive drugs would trigger a reflex increase in heart rate which would normally counteract to some extent the direct bradycardia. If quinpirole is acting to inhibit both the reflex tachycardia component by its effect on the upper heart rate plateau as well as the direct bradycardia component, the net effect of its action would seemingly be no change of the effects of centrally acting antihypertensives on heart rate.

In summary, this study shows that pretreatment with quinpirole caused an inhibition of the central antihypertensive action of rilmenidine and α-methyldopa, but not of the vasodilator hydralazine. The immediate pressor effect of quinpirole was not maintained because the initial increased release of vasopressin was returned to normal and an active hypotensive mechanism compensated for the enhanced sympathetic vasomotor tone. While the bradycardia caused by these agents was not significantly altered by quinpirole treatment, the upper plateau of the sympathetic baroreceptor-heart rate reflex and reflex tachycardia to the hypotensive effect of hydralazine were significantly reduced.

Our findings could have important functional and clinical implications. On a functional level, the data suggest that activation of central dopaminergic receptors may induce a shift in the balance of cardiovascular regulatory mechanisms, which becomes apparent when additional stimuli, such as central sympatho-inhibitory antihypertensives, are used. It would be of great interest to study the effects of pretreatment with quinpirole on central sympathetic responses triggered by environmental stimuli such as behavioural stress or changes in salt and water balance. Clinically, centrally acting dopaminergic agonists, such as pergolide and bromocriptine, are used for the treatment of Parkinson's disease and hormonal disorders such as hyperprolactinaemia (Lancranjan, 1981; Mizuno et al., 1995; Montastruc et al., 1993). The present data suggest that these drugs may cause changes in central sympathetic and humoral mechanisms which may have gone unnoticed because, after an initial pressor response (McNay et al., 1987), blood pressure is apparently maintained at normal levels.

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