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Differential Effects of Quinelorane and Pergolide on Behaviour, Blood Pressure, and Body Temperature of Spontaneously Hypertensive Rats and Wistar-Kyoto Rats

MAARTEN VAN DEN BUUSE[1]

Marion Merrell Dow Research Institute, 16 rue d'Ankara, B.P. 067, 67046 Strasbourg Cedex, France

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VAN DEN BUUSE, M. *Differential effects of quinelorane and pergolide on behaviour, blood pressure, and body temperature of spontaneously hypertensive rats and Wistar-Kyoto rats.* PHARMACOL BIOCHEM BEHAV **50**(3) 389-397, 1995.– The systemic administration of the dopamine agonists quinelorane or pergolide to Wistar-Kyoto rats (WKY) induced a significant increase of locomotor activity at higher doses. In spontaneously hypertensive rats, these compounds induced a significant hypoactivity at low doses, but only a modest, and late, increase in locomotor activity at higher doses. Quinelorane was more potent than pergolide on locomotor activity. In WKY and SHR, which had unilateral lesions of the nigrostriatal dopamine system, quinelorane and pergolide induced similar dose-dependent contralateral turning that, in the case of pergolide, was significantly greater in SHR than in WKY. Both quinelorane and pergolide induced yawning similarly in WKY and SHR, and quinelorane was more potent than pergolide. The intravenous administration of quinelorane induced an immediate and dose-dependent increase in blood pressure in WKY and SHR, which could be completely prevented by pretreating the rats with the dopamine antagonist haloperidol. Pergolide similarly caused a rise in blood pressure in WKY and SHR, but its effect could only partially be blocked by haloperidol. The subcutaneous injection of quinelorane or pergolide induced similar dose-dependent hypothermia in WKY. Pergolide also caused a decrease of body temperature in SHR, but quinelorane had little effect in this strain. These results show differences in the effects of quinelorane and pergolide between various experimental test situations and between WKY and SHR. These differences may be related to the involvement of dopamine receptor subtypes and to the previously described changes in central dopaminergic activity in SHR.

Dopamine agonist Quinelorane Pergolide Locomotor activity Turning Yawning Blood pressure Body temperature Spontaneously hypertensive rats

SPONTANEOUSLY hypertensive rats (SHR) show an age-related rise in blood pressure and behavioural hyperreactivity (18,22,23). A number of reports have described differential changes in central dopaminergic regulation in SHR when compared to normotensive controls [reviewed in (27)]. For example, although in Wistar-Kyoto rats (WKY) the dopamine D_2 receptor antagonist sulpiride induced an inhibition of exploratory locomotor activity, in SHR this compound had little effect (26,29). In contrast, sulpiride induced a normal increase in central dopamine turnover and an exaggerated rise of plasma prolactin concentrations in SHR (29). The dopamine D_2 receptor agonist quinpirole induced an inhibition of locomotor activity at low doses in both SHR and WKY, but the marked hyperactivity induced in WKY by high doses of quinpirol was completely absent in SHR (11,24). The centrally mediated increase in blood pressure in response to intravenous (IV) injection of quinpirole was normal or enhanced in SHR (24).

The significance of changes in central dopaminergic activity in SHR is illustrated by the inhibition of the development of hypertension in these animals after depletion of central dopamine (31,32). Thus, central injection of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) in young, prehypertensive SHR caused an attenuation and retardation

[1] Requests for reprints should be addressed to Maarten van den Buuse at his present address: Baker Medical Research Institute, Commercial Road, P.O. Box 348, Prahran, Vic. 3181, Australia.

of the rise in blood pressure and depletion of central noradrenaline and dopamine (12,28). The effect of 6-OHDA on the development of hypertension could be inhibited by pretreatment with the dopamine uptake inhibitor GBR-12909, which prevented the depletion of central dopamine (32), but not by pretreatment with the noradrenaline uptake inhibitor desipramine, which prevented the depletion of noradrenaline (31). Moreover, discrete lesions in the substantia nigra of young SHR caused an attenuation of the development of hypertension and depletion of central dopamine (30,32). Thus, alterations in central dopaminergic function play a role in the development of spontaneous hypertension and depletion of central dopamine interfered with this mechanism.

Dopaminergic drugs may induce centrally mediated effects on blood pressure (5,6,16,17). Electrical stimulation of ventral midbrain dopaminergic cell groups caused pressor responses in anesthetized, normotensive rats and cats (7,20) and baroreceptor denervation caused changes in dopamine release in the striatum (1), suggesting a link between forebrain dopamine systems and cardiovascular regulation. Studies on central dopamine receptor levels or dopamine concentrations and turnover in SHR have failed to provide a clear neurochemical basis for any changes in this interaction in SHR, however [reviewed in (27)].

Pergolide is a dopamine agonist with affinity for both dopamine D_1 and D_2 receptors. The affinity values for these receptors vary between studies, but pergolide appeared to have a 20–50-fold selectivity for D_2 receptors over D_1 receptors [reviewed in (10)]. However, recent studies by Wong and colleagues (34) have indicated a K_i of pergolide against [^{3}H]spiperone binding of 75 nM (D_2 receptors) and against [^{3}H]SCH 23390 of 128–158 nM (D_1 receptors), indicating virtually similar affinities for both receptor subtypes. Sokoloff and coworkers (19) found a K_i of 19 nM for dopamine D_2 receptors and an even higher affinity of 2 nM for the recently cloned dopamine D_3 receptors, indicating that at least some of the effects of pergolide could be mediated by this latter receptor subtype. Administration of pergolide to rats induced a range of neurochemical effects, including a rise in striatal levels of acetylcholine, depletion of hypothalamic adrenaline, and reduction of striatal dopamine turnover (10,11,34). Furthermore, several behavioural effects of pergolide have been described, such as changes in locomotor activity in intact rats or the induction of turning behaviour in rats with unilateral lesions of the nigrostriatal bundle (10,13). Pergolide also induced a fall in body temperature in rats (13).

Quinelorane is a dopamine agonist with a structure related to that of pergolide. Agonist affinity of quinelorane at dopamine D_1 receptors has been studied by few authors, although the compound failed to induce an increase in striatal adenylate cyclase activity, an indicator of D_1 agonist activity (4). In vitro binding tests with quinelorane showed a K_i of 340 nM for dopamine D_2 receptors and 4 nM for D_3 receptors (19). Similar to pergolide, quinelorane caused an increase in striatal acetylcholine levels and a reduction of adrenaline levels and dopamine turnover (4,8,9). Quinelorane induced dose-dependent

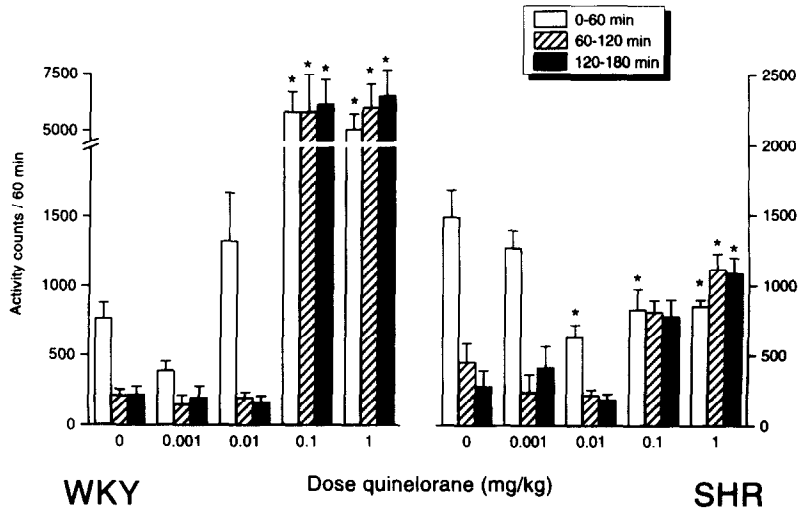

FIG. 1. The effect of IP injection of quinelorane on locomotor activity of WKY (left panel) and SHR (right panel). Data are mean locomotor activity counts ± SEM of six rats per group during the first (open bars), second (hatched bars), or third (filled bars) hour after injection. Note the break in the vertical axis of WKY. *$p < 0.05$ for difference with saline-treated controls during the same time period. ANOVA on data from WKY indicated an overall treatment effect ($F = 31.3, p < 0.001$) and a marked and significant increase of locomotor activity after injection of 0.1 or 1 mg/kg of quinelorane during the entire 3-h measurement period. ANOVA on data from SHR indicated an overall treatment effect ($F = 5.4$, $p = 0.002$), an overall time effect ($F = 29.4$, $p < 0.001$), and a treatment × time interaction ($F = 9.9$, $p < 0.001$), reflecting the decrease of locomotor activity over time in SHR treated with saline, or 0.001 or 0.01 mg/kg, but not in SHR treated with 0.1 or 1 mg/kg of quinelorane. Locomotor activity was significantly reduced in SHR by 0.01–1 mg/kg of quinelorane during the first hour after injection, and moderately, but significantly, enhanced by 1 mg/kg of quinelorane during the second and third hour after injection.

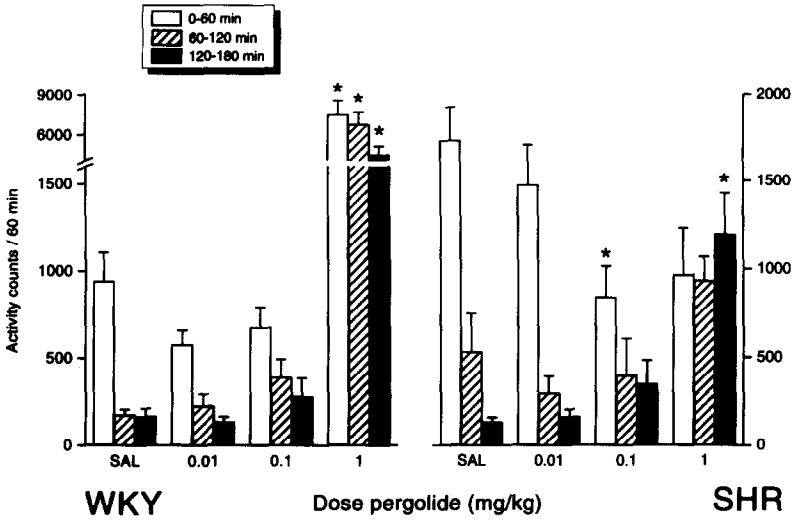

FIG. 2. The effect of IP injection of pergolide on locomotor activity of WKY (left panel) and SHR (right panel). Data are mean locomotor activity counts ± SEM of six rats per group during the first (open bars), second (hatched bars), or third (filled bars) hour after injection. Note the break in the vertical axis of WKY. *$p < 0.05$ for difference with saline-treated controls of the same time period. ANOVA on data from WKY indicated an overall treatment effect ($F = 129.3, p < 0.001$), and of time after injection ($F = 6.7, p = 0.002$), and a treatment × time interaction of borderline significance ($F = 2.4, p = 0.04$). Pergolide (1 mg/kg) induced a significant increase of locomotor activity of WKY during the entire 3-h measurement period. ANOVA on data from SHR indicated an overall time effect ($F = 37.3, p < 0.001$) and a treatment × time interaction ($F = 8.9, p < 0.001$), reflecting the lack of a decrease of locomotor activity over time in SHR treated with 1 mg/kg. At 0.1 mg/kg, pergolide induced a significant reduction of locomotor activity during the first hour after injection, whereas at 1 mg/kg it induced a moderate, but significant, hyperactivity during the third hour after injection.

hypo- and hyperactivity and turning behaviour in rats (9). In these tests, quinelorane displayed higher potency than quinpirole, but comparable potency to pergolide.

In the present study, SHR and WKY were treated with pergolide or quinelorane and were tested in a number of experimental protocols in vivo, some of which have not been extensively studied before in these strains (27). The results extend our earlier knowledge, which was obtained largely with quinpirole (24) and sulpiride (29), and shed more light on central dopaminergic function in these strains.

METHOD

Male SHR and WKY of 225–275 g body weight were obtained from IFFA Credo (l'Arbresle, France) at least 1 week before the experiments. The animals were kept four–five per cage under standard animal house conditions with free access to pellet food and tap water. Quinelorane (LY 163502) and pergolide (LY 127809) were a gift from Lilly Research Laboratories (Indianapolis, IN). The injectable solution of haloperidol (HALDOL, Janssen Pharmaceutics) was used and diluted to the appropriate concentration.

Locomotor Activity

One day before the experiment, naive WKY and SHR were weighed (250–280 g) and randomly assigned to different treatment groups. The next day, the rats were brought to the experiment room, injected intraperitoneally (IP) with saline, quinelorane (0.001, 0.01, 0.1, or 1 mg/kg), or pergolide (0.01, 0.1, or 1 mg/kg), and immediately thereafter were put singly into clear plastic boxes of 33 × 24 × 15 cm. Locomotor activity was measured for 3 h with an Opto Varimex Mini activity meter (Columbus Instruments, Columbus, OH) as the number of infrared photobeam interrupts.

Turning Behaviour

The method was as described previously (25,29). Briefly, male SHR and WKY of 275–300 g body weight were pretreated IP with 20 mg/kg of desipramine (Sigma) and anesthetized with pentobarbital (45 mg/kg, IP). Two microliters of a 5-mg/ml solution of 6-OHDA HBr with 0.01% ascorbic acid (Research Biochemicals, Illkirch, France) was injected over 5 min into the nigrostriatal bundle in the lateral hypothalamus at 2.0 mm posterior and 1.5 mm lateral to bregma, and 10 mm ventral to the surface of the skull at the site of injection. The incisor bar was set at +3 mm. Half of the SHR and WKY were lesioned on the right side and half were lesioned on the left side. The animals were housed singly after the operation.

At least 3 weeks after the operation all rats were tested for turning behaviour twice after a subcutaneous (SC) dose of 2 mg/kg of *d*-amphetamine and twice after a SC dose of 0.5 mg/kg of apomorphine. An eight-channel ROTORAT apparatus (MED Associates, East Fairfield, VT) was used to record the number of turns. Only rats that showed at least 200 ipsilateral (amphetamine) and 200 contralateral (apomorphine)

turns in 60 min were used for further experiments. Thus, nine SHR and 12 WKY were selected, which weighed 350–400 g at the time of the experiments.

The selected rats were injected SC with either 0.001, 0.01, or 0.1 g/kg of quinelorane or 0.01 or 0.1 mg/kg of pergolide, immediately after which the turning behaviour was measured during 2 h. The experiment was repeated with other doses of the compounds at intervals of at least 2 days, such that, at the end of the series, all rats had received all doses of quinelorane or pergolide.

Yawning Behaviour

SHR and WKY of 275–300 g body weight were injected SC with different doses of quinelorane or pergolide and immediately thereafter put singly into clear 2-l observation beakers. The number of yawns displayed by the rats was scored during 30 min.

Blood Pressure and Heart Rate

The procedure was essentially as described previously (24,25). Briefly, at least 2 days before the experiments, SHR and WKY were anesthetized with pentobarbital and catheters were inserted into a femoral artery and a jugular vein. On the day of the experiments, the arterial catheter was connected to a Statham P23Db transducer, and mean arterial pressure (MAP) and heart rate were recorded on an eight-channel Grass polygraph that was equipped with Grass tachographs. After a baseline reading of 5 min, saline was injected IV and MAP and heart rate were measured for 10 min. Then 1 mg/kg of the peripherally acting dopamine D_2 receptor antagonist domperidone (Research Biochemicals) or 1 mg/kg of haloperidol was injected IV, followed 10 min later by an IV injection of either different doses of quinelorane or pergolide in saline. MAP and heart rate were recorded for 1 h. Some rats were used for another experiment at least 48 h later.

Body Temperature

Body temperature of SHR and WKY of 275–300 g body weight was measured with a Digi-sense thermometer and rectal probe (Cole/Palmer, Chicago, IL). After a baseline reading, the animals were injected SC with either saline or different

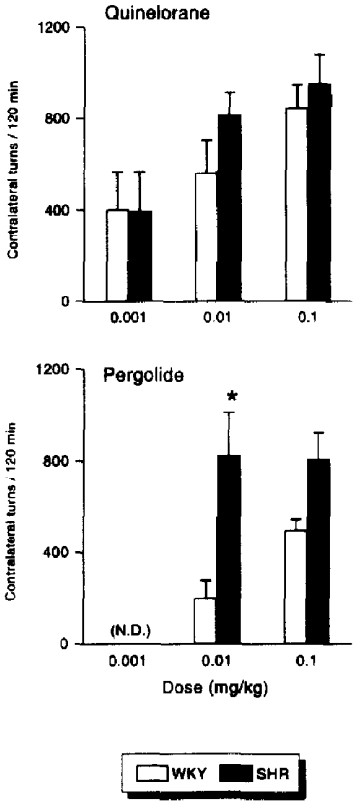

FIG. 3. The effect of different doses of quinelorane (top panel) or pergolide (bottom panel) on turning behaviour of WKY (open bars) and SHR (filled bars) with unilateral lesions of the nigrostriatal dopamine pathway. ANOVA on data from quinelorane-treated rats indicated a significant effect of quinelorane overall ($F = 16.6$, $p < 0.001$) and in WKY ($F = 6.7$, $p = 0.003$) and SHR ($F = 11.0$, $p < 0.001$) separately. ANOVA on data from pergolide indicated a significant overall strain effect ($F = 14.8$, $p = 0.001$) and an effect of dose only in WKY ($F = 4.8$, $p = 0.04$). Moreover, there was a significant strain difference in the response to 0.01 mg/kg of pergolide (*$F = 16.2$, $p < 0.001$). N.D. indicates not determined.

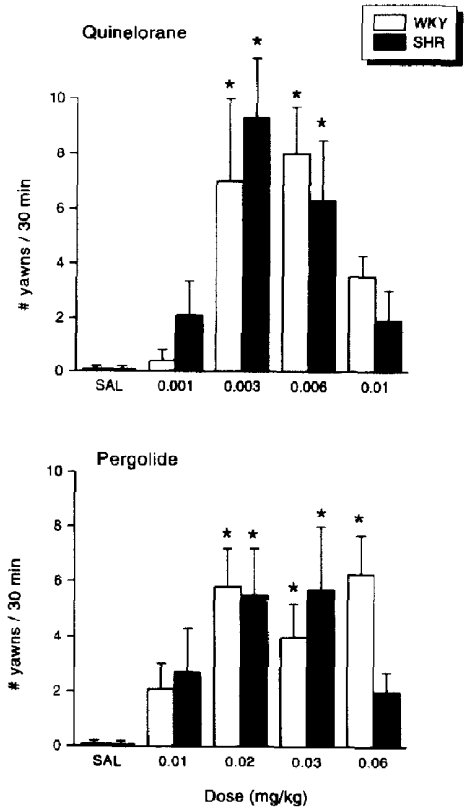

FIG. 4. The effect of different doses of quinelorane (top panel) or pergolide (bottom panel) on yawning behaviour of WKY (open bars) and SHR (filled bars). Data are mean number of yawns per 30 min SEM of six-eight rats per group. *$p < 0.05$ for difference with saline-treated rats of the same strain. ANOVA on data from quinelorane-treated rats indicated a significant treatment effect overall ($F = 10.2$, $p < 0.001$) and for WKY ($F = 5.3$, $p < 0.001$) and SHR ($F = 5.5$, $p < 0.001$) separately. ANOVA on data from pergolide-treated rats showed a similar treatment effect overall ($F = 7.1$, $p < 0.001$) and for WKY ($F = 5.2$, $p < 0.001$) and SHR ($F = 3.5$, $p = 0.006$) separately.

doses of quinelorane or pergolide and their body temperature was measured at 15-min intervals after the treatment.

Data Analysis

All data are expressed as means ± SEM. Differences between groups were analyzed with analysis of variance (ANOVA), followed by Duncan's multiple range test. When $p < 0.05$ the differences between the groups were considered statistically significant.

RESULTS

Locomotor Activity

The effect of IP administration of different doses of quinelorane or pergolide on locomotor activity of SHR and WKY is shown in Figs. 1 and 2, respectively. Similar to previous observations (24-26), basal locomotor activity was higher in SHR than in WKY, which lasted throughout the 3-h observation period. At 0.001 mg/kg, quinelorane tended to inhibit locomotor activity of WKY, but this effect (−49%) failed to reach statistical significance. In contrast, in SHR quinelorane caused a significant reduction of locomotor activity at 0.01 (−58%), 0.1 (−44%), and 1 mg/kg (−42%) during the first hour after administration, but a significant increase in locomotor activity at 1 mg/kg during the second and third hours of observation compared to values from saline-treated SHR during the same time periods. It should be noted that this increase was marginal when compared to the marked hyperactivity seen in WKY at these doses (Fig. 1).

Pergolide induced effects on locomotor activity of WKY and SHR that were similar to those of quinelorane, although pergolide appeared to be about 10 times less potent (Fig. 2). After treatment with 1 mg/kg of pergolide, a marked hyperactivity was observed in WKY throughout the observation period, whereas in SHR, pergolide at 0.1 mg/kg reduced locomotor activity during the first hour of observation and at 1 mg/kg only moderately increased activity during the third hour of observation (Fig. 2).

Turning Behaviour

WKY and SHR with unilateral 6-OHDA-induced lesions of the nigrostriatal bundle showed little spontaneous turning behaviour, but similar ipsilateral turning after treatment with amphetamine. The rats showed contralateral turning after treatment with apomorphine, which was more pronounced in SHR (not shown). The SC administration of quinelorane caused dose-dependent contralateral turning behaviour, which was not significantly different in magnitude between SHR and WKY (Fig. 3). In contrast, after treatment with pergolide, SHR showed significantly more contralateral turning than WKY (Fig. 3). Quinelorane and pergolide were approximately equipotent on turning behaviour of SHR, whereas in WKY pergolide induced somewhat smaller effects than quinelorane.

Yawning Behaviour

Saline-treated rats displayed little spontaneous yawning. The SC administration of quinelorane or pergolide to WKY

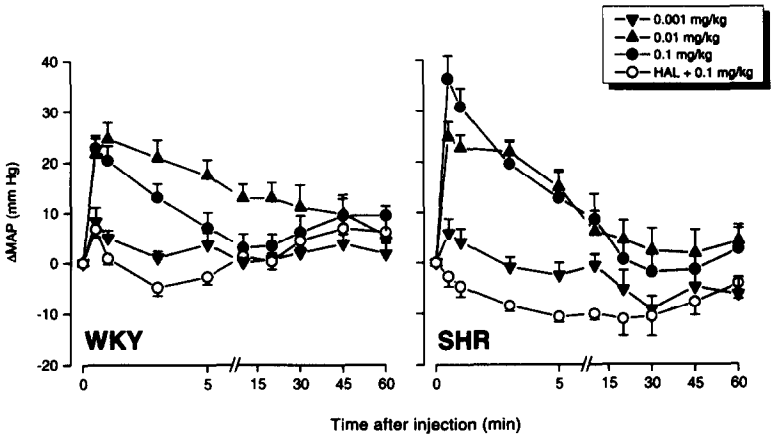

FIG. 5. The effect of IV injection of quinelorane on blood pressure of WKY (left panel) and SHR (right panel). Data are expressed as mean change of baseline mean arterial pressure (MAP) ± SEM of six-eight rats per group. Note the break in the horizontal axes to emphasize the effects in the first 5 min after injection. ANOVA on data from WKY indicated a significant overall treatment effect ($F = 15.9$, $p < 0.001$), time effect ($F = 23.0$, $p < 0.001$), and treatment × time interaction ($F = 6.5$, $p < 0.001$), reflecting the pressor response to injection of 0.01 (at all time points) or 0.1 mg/kg (all time points except at $t = 10$ and 20 min) of quinelorane, but the relative lack of effect in WKY treated with 0.001 mg/kg of quinelorane or with 1 mg/kg of haloperidol followed by 0.1 mg/kg of quinelorane (significant only at $t = 30$ s and 45 and 60 min). ANOVA on data from SHR similarly indicated an overall effect of treatment ($F = 5.2$, $p = 0.008$), time ($F = 33.6$, $p < 0.001$), and an interaction between these factors ($F = 64.5$, $p < 0.001$). The pressor effect of 0.01 mg/kg of quinelorane was significant at $t = 30$ s and 1, 3, and 5 min after injection. The pressor effect of 0.1 mg/kg was significant at $t = 30$ s and 1, 3, 5, and 10 min after injection. Blood pressure was significantly reduced after treatment with haloperidol and 0.1 mg/kg of quinelorane at all time points except 30 s and 1 and 60 min after injection.

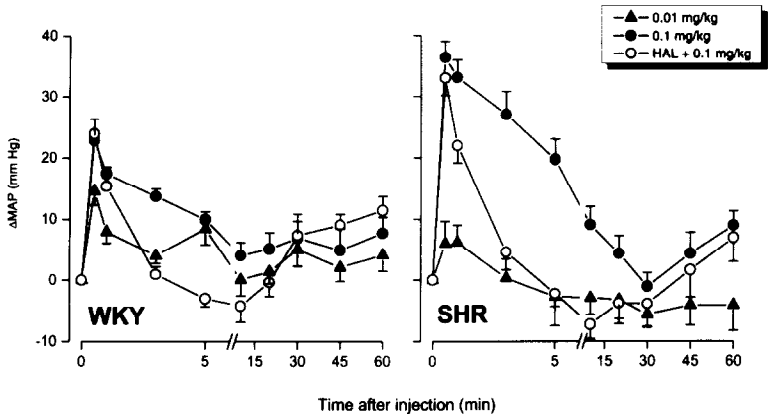

FIG. 6. The effect of IV injection of pergolide on blood pressure of WKY (left panel) and SHR (right panel). Data are expressed as mean change compared to baseline in mean arterial pressure (MAP) ± SEM of six-eight rats per group. Note the break in the horizontal axes to emphasize the effects in the first 5 min after injection. ANOVA on data from WKY indicated a significant overall treatment effect ($F = 4.5$, $p = 0.025$), time effect ($F = 30.8$, $p < 0.001$), and treatment × time interaction ($F = 4.2$, $p < 0.001$), reflecting the pressor response to injection of 0.1 (significant at all time points except $t = 10$, 20, and 45 min), and to a lesser extent 0.01 mg/kg of pergolide (significant at $t = 30$ s and 1 and 5 min). For HAL + 0.1 mg/kg of pergolide, the effect was significant at $t = 30$ s and 1 min and at $t = 30$, 45, and 60 min. Pretreatment with haloperidol thus partially prevented the pressor response induced by 0.1 mg/kg pergolide. ANOVA on data from SHR indicated an overall effect of time ($F = 42.3$, $p < 0.001$) and an interaction between treatment and time ($F = 6.8$, $p < 0.001$). At 0.1 mg/kg pergolide induced a significant pressor effect ($t = 30$ s, 1, 3, 5, 10, and 60 min), but the dose of 0.01 mg/kg had no effect. After treatment with haloperidol and 0.1 mg/kg of pergolide, blood pressure signficantly increased at 30 s and 1 min after injection.

and SHR induced similar dose-dependent yawning, although quinelorane was about 10 times more potent than pergolide. The dose-response curve of quinelorane was narrow and bell-shaped, with a peak effect at 0.003–0.006 mg/kg and little effect at higher or lower doses (Fig. 4). The dose-response curve of pergolide showed a maximal effect at 0.02–0.06 mg/kg in WKY and at 0.02–0.03 mg/kg in SHR (Fig. 4). Higher doses of either compound induced hyperactivity in both strains.

Blood Pressure

Baseline blood pressure was 110–125 mmHg in WKY and 150–165 mmHg in SHR. The IV injection of saline or of 1 mg/kg of domperidone or haloperidol did not significantly alter blood pressure (not shown). The IV injection of quinelorane or pergolide similarly induced a pressor response in WKY and SHR, although quinelorane appeared to be more potent than pergolide (Figs. 5 and 6). The maximum effect was reached between 30 s and 1 min after injection, and blood pressure gradually returned to baseline thereafter. Heart rate showed little change after any of the treatments (not shown). In WKY, the pressor response to quinelorane was greatest and lasted longest at 0.01 mg/kg. The effect of 0.1 mg/kg of quinelorane was somewhat smaller in WKY, and could be completely blocked by pretreatment with haloperidol (Fig. 5). In SHR, the effect of 0.1 mg/kg of quinelorane was slightly greater than that of 0.01 mg/kg, and could be completely antagonized by pretreatment with haloperidol (Fig. 5). In SHR, which were treated with haloperidol and 0.1 mg/kg of quinelorane, blood pressure was actually slightly reduced when compared to baseline at almost all time points during the time of measurement.

In WKY, the pressor response to pergolide was greatest at 0.1 mg/kg, whereas 0.01 mg/kg had little effect. Pretreatment with haloperidol did not antagonize the initial peak pressor response to injection of 0.1 mg/kg of pergolide, but blood pressure returned to baseline much faster than in WKY pretreated with only domperidone (Fig. 6). Similarly, in SHR pergolide induced a much greater effect at 0.1 mg/kg than at 0.01 mg/kg, and the pressor response was only shortened by pretreatment with haloperidol (Fig. 6).

Body Temperature

Baseline body temperature was higher in SHR than in WKY, but this differences disappeared over repeated measurements. For example, saline-treated SHR and WKY from the quinelorane experiment had baseline body temperatures of 37.5 and 36.2°C, respectively, but at the end of the experiment these values were 36.8 and 36.2°C, respectively (see Fig. 7). Quinelorane and pergolide induced dose-dependent hypothermia to a similar extent in WKY (Fig. 7). The peak effect was reached with 0.1 mg/kg at 60 min after injection and temperature started to gradually return towards baseline thereafter. The effect of 0.01 mg/kg of quinelorane was significant in WKY, but of much smaller magnitude than that of 0.1 mg/kg. In SHR, 0.01 mg/kg of quinelorane induced a slightly greater hypothermia than 0.1 mg/kg. The latter dose had a much smaller effect in SHR than in WKY (Fig. 7). In SHR, 0.1 mg/kg of pergolide induced a significant hypothermia, which was of similar magnitude to that in WKY, despite

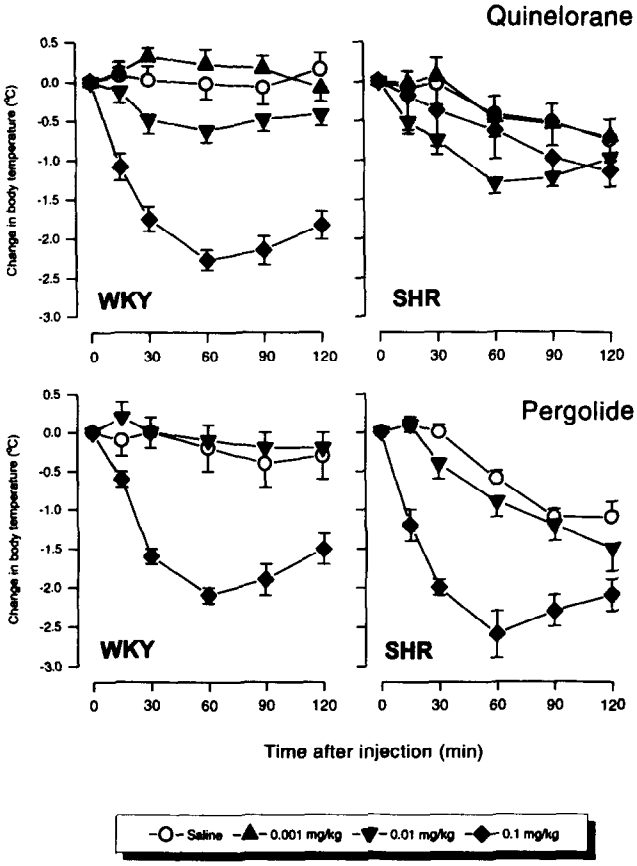

FIG. 7. The effect of SC injection of different doses of quinelorane (top panels) or pergolide (bottom panels) on body temperature of WKY (left panels) or SHR (right panels). Data are expressed as mean change of temperature ± SEM of six rats per group. In quinelorane-treated WKY, there was a significant treatment effect ($F = 7.4$, $p < 0.001$), time effect ($F = 19.8$, $p < 0.001$), and treatment × time interaction ($F = 13.5$, $p < 0.001$), reflecting the lack of effect of saline or 0.001 mg/kg of quinelorane, but the significant hypothermia after 0.01 mg/kg (at all time points except $t = 15$ min) or 0.1 mg/kg (at all time points). In quinelorane-treated SHR, there was a significant treatment effect ($F = 6.6$, $p = 0.002$) and time effect ($F = 17.9$, $p < 0.001$). Temperature was significantly reduced after treatment with saline (at $t = 120$ min), 0.001 mg/kg ($t = 90$ and 120 min), 0.01 mg/kg (all time points), and 0.1 mg/kg of quinelorane ($t = 60$, 90, and 120 min after injection). In pergolide-treated WKY, there was a significant effect of treatment ($F = 29.5$, $p < 0.001$) and of time ($F = 24.0$, $p < 0.001$), and a treatment × time interaction ($F = 12.6$, $p < 0.001$), reflecting the significant decrease of body temperature after injection of 0.1 mg/kg only (at all time points). In SHR, there similarly was an effect of treatment ($F = 22.2$, $p < 0.001$), of time ($F = 78.3$, $p < 0.001$), and an interaction between treatment and time ($F = 10.1$, $p < 0.001$). A significant decrease in body temperature was observed after injection of saline ($t = 60$, 90, and 120 min), 0.01 mg/kg ($t = 30$, 60, 90, and 120 min), and 0.1 mg/kg of pergolide (all time points).

the change in body temperature occurring in saline-treated SHR. Thus, the difference with values from saline-treated rats at 60 min was 2.0°C in SHR and 2.3°C in WKY.

DISCUSSION

This study shows a number of effects of the potent dopamine agonists quinelorane and pergolide in WKY and SHR. The main findings were that SHR differed in their responses from WKY in that they lacked the hyperactivity induced by higher doses of quinelorane or pergolide, and showed more intense turning behaviour after treatment with pergolide, but less hypothermia after treatment with quinelorane. Quinelorane differed from pergolide in that it was more potent on locomotor activity in intact WKY and SHR, to induce turning and hypothermia in WKY, and to induce yawning in both WKY and SHR. In addition, whereas the quinelorane-induced pressor response could be antagonized completely by pretreatment with haloperidol, the effect of pergolide was only partially prevented.

In normotensive rats, dogs, or man, quinelorane and pergolide have been shown to cause several endocrine, behavioural, and neurochemical effects. Endocrine effects of both compounds include a reduction of plasma prolactin concentrations and an increase of plasma corticosterone concentrations (9,10). Behavioural effects include dose-dependent changes in locomotor activity in intact animals and contralateral turning in rats with unilateral nigrostriatal lesions (3,13). Neurochemical effects include a decrease in central dopamine turnover and release (4,8,9,13). Furthermore, pergolide and quinelorane may cause changes in body temperature and influence cardiovascular regulation [(5,6,9,10), and references therein]. Recently, it was shown that, in addition to being potent agonists at dopamine D_2 receptors, quinelorane and pergolide showed high affinity for dopamine D_3 receptors (19).

Previously, we (24) and others (11) have shown that the administration of moderately high doses of quinpirole, an ergoline derivative closely related to quinelorane, induced only an inhibition of locomotor activity in SHR, whereas in WKY it induced marked hyperactivity. When a longer observation period was used, a slight, and late, quinpirole-induced increase in locomotor activity became apparent in SHR, an effect that was marginal compared to that in WKY (Van den Buuse, unpublished observations). The present results show that quinelorane and pergolide share this effect with quinpirole, inasmuch as only a slight, and late, increase in behavioural activity was observed in SHR, in contrast to the marked hyperactivity observed in WKY. Thus, intact SHR show a reduced sensitivity to the locomotor stimulant effects of dopamine D_2 receptor agonists. Surprisingly, in SHR and WKY with unilateral 6-OHDA-induced lesions of the nigrostriatal system, quinelorane induced similar contralateral turning behaviour, whereas pergolide had greater effects in SHR than in WKY. This finding raises two questions—about the difference between the response of intact and lesioned rats, and about the differential effects of quinelorane and pergolide. The microinjection of 6-OHDA in the nigrostriatal bundle is likely to have caused a significant depletion of dopamine in terminal regions such as the caudate nucleus and nucleus accumbens. It is possible that this depletion altered the responsiveness of dopamine D_2 (or D_3) receptors, which rendered the SHR equisensitive or more sensitive to the effect of agonists than WKY. It is well known that unilateral lesions in central dopamine systems cause postsynaptic dopamine receptor supersensitivity and an uncoupling of the otherwise obligatory "permissive" role of D_1 receptor activation in D_2 receptor-mediated effects (2,33). Lesions in brain dopamine systems caused an inhibition of the development of hypertension (31,32) and it is tempting to speculate that this inhibition and the "normalizing" effect of 6-OHDA lessions on locomotor activity in the present study represent similar mechanisms. However, this does not explain the differential effect of the lesions for quine-

lorane and pergolide. It is possible that the mixed D_1/D_2 agonist activity of pergolide renders it more effective than the "pure" D_2 agonist quinelorane to induce turning, but further experiments with combined treatment with D_1 and D_2 agonists will be needed to test this hypothesis. Indeed, the contribution of stimulation of dopamine D_1 receptors in the effects of pergolide has been questioned in some studies [for a review, see (10)].

The normal yawning reponse of SHR after treatment with quinelorane or pergolide suggests that dopamine receptors involved in this response are normal in this strain. Some authors have suggested that yawning is induced after activation of presynaptic dopamine D_2 receptors, but this was disputed by others and it was suggested that, instead, a population of postsynaptic D_2 receptors with high sensitivity for agonists may be involved [reviewed in (21)]. Presynaptic D_2-mediated inhibition of dopamine release was greater in SHR in vivo and in vitro (14,15), but in this study no evidence for a strain difference in yawning was observed.

The immediate pressor response to injection of quinelorane and pergolide is in line with results obtained with quinpirole and other dopamine agonists (17,24). The relatively short-lasting effect of these compounds may be explained by a rapid desensitization of the dopamine receptors involved or by systemic compensatory mechanisms, such as changes in vasopressor or vasodepressor hormone levels, which bring blood pressure back to baseline (24). The complete antagonistic effect of pretreatment with haloperidol suggests that, similar to quinpirole (24), quinelorane acts primarily on dopamine D_2 receptors to mediate its effect on blood pressure. In contrast, pergolide appears to have an additional effect on receptors that were not blocked by haloperidol. Although this could represent the action of pergolide on dopamine D_1 receptors, a further pharmacological analysis of the central effect of pergolide is needed to prove this. In any case, there was little difference between WKY and SHR with regard to their overall cardiovascular response to injection of either quinelorane or pergolide. Similar to quinpirole (24), at high doses of quinelorane SHR tended to have a greater pressor response than WKY, but this was at least partly because the response in WKY tended to become smaller at further increasing the dose. Although at such doses WKY showed hyperactivity and stereotypy, SHR showed few behavioural effects, and this difference in behavioural response may influence the cardiovascular effects (24).

The hypothermia induced by treatment with apomorphine or L-DOPA was greater in SHR than in WKY [for references, see (27)]. In the present study, pergolide induced similar hypothermia in these strains, whereas quinelorane had less effect in SHR than in WKY. The explanation for this difference is unclear, but again could be related to the different receptor selectivity of these compounds (i.e., a significant contribution of dopamine D_1 receptors in the action of pergolide).

In conclusion, in the present study, central dopamine function in WKY and SHR was investigated by using two well-characterized dopamine receptor agonists. The differences in the effects of these compounds between the two strains suggests selective alterations of dopamine receptor subtype density or coupling mechanisms in the SHR, which could play a role in the development of hypertension in these rats. Further analysis of the changes in central dopamine systems in SHR with selective antagonists for dopamine D_1 or D_2 receptors could provide more details on these alterations.

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