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Original

Altered pre- and postsynaptic dopamine receptor functions in spontaneously hypertensive rat: an animal model of attention-deficit hyperactivity disorder

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Abstract: Dopamine receptor function in spontaneously hypertensive rats (SHR) and in control progenitor Wistar-Kyoto (WKY) rats was assessed from their dopamine D_1-like/D_2-like receptor-mediated jaw movements and dopamine release from the nucleus accumbens and from the ventrolateral striatum measured by an *in vivo* microdialysis technique. Spontaneous locomotor activity and rearing were significantly higher in SHR than in WKY rats. Co-administration of SKF 38393 (1.0, 2.0 and 3.0 mg/kg), a dopamine D_1-like receptor agonist, and quinpirole (1.0 mg/kg), a dopamine D_2-like receptor agonist, produced repetitive jaw movements in WKY rats in a dose-dependent manner. However, this synergism was not evident in SHR. Basal dopamine levels in both the nucleus accumbens and the ventrolateral striatum were lower in SHR than WKY rats, though the levels of dopamine were lower in the nucleus accumbens than the ventrolateral striatum in both strains. After infusion of quinpirole (100 μM for 180 min) the dopamine levels in both regions were reduced. In the nucleus accumbens, the quinpirole-mediated reduction of dopamine release at 40 min and 60 min after infusion was larger in SHR than WKY rats, whereas this difference between the SHR and WKY rats was small in the ventrolateral striatum. The present study therefore suggests that, when compared to WKY rats, postsynaptic dopamine D_1-like/D_2-like receptors in the SHR are hyposensitive, while presynaptic dopamine D_2-like receptors located particularly in the nucleus accumbens are hypersensitive. (J. Oral Sci. 45, 75-83, 2003)

Key words: jaw movement; dopamine release; ventrolateral striatum; nucleus accumbens; presynaptic dopamine D_2-like receptor; postsynaptic dopamine D_1-like/D_2-like receptor.

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Introduction

Spontaneously hypertensive rats (SHR), i.e. the hypertensive phenotype derived from the Wistar-Kyoto (WKY) strain (1-3), are widely used to model the deleterious effects of cardiovascular disease in humans (4-7). In addition, SHR are increasingly used as an animal model for studying attention-deficit hyperactivity disorder (ADHD) because they mimic the fundamentals of behavioral characteristics of ADHD (8-13). In fact, spontaneous behaviors such as locomotor activity and

rearing were found to be higher in SHR than in WKY rats (4,8-11,13-19). In contrast to the spontaneous behaviors, locomotor responses to the indirect dopamine D_1-like/D_2-like receptor agonist, *d*-amphetamine, and to the direct dopamine D_1-like/D_2-like receptor agonist, apomorphine, are smaller in SHR than WKY rats (8,16).

Although the above-mentioned locomotor responses to *d*-amphetamine and apomorphine are considered to be a result of the stimulation of the postsynaptic dopamine D_1-like/D_2-like receptors, the dopamine D_2-like receptor agonist, quinpirole, stimulates the presynaptic dopamine receptors which in turn causes a decrease in the release of dopamine from terminal areas of the nigrostriatal and mesolimbic dopamine projections, the striatum and nucleus accumbens respectively (20-22). Moreover, in an *in vitro* study using brain slices, the ability of quinpirole to decrease dopamine release from the striatum, but not from the nucleus accumbens, was shown to be larger in SHR than WKY rats (12). Though behavioral and biochemical studies have been conducted to elucidate differences in dopamine receptor function between SHR and WKY rats, their details are not completely understood.

The present study, therefore, set out to investigate whether there are any differences between SHR and WKY rats in terms of their responses to dopamine receptor agonists. For that purpose, dopamine D_1-like/D_2-like receptor-mediated jaw movements were used to examine postsynaptic receptor function, and quinoirole-induced decrease of dopamine from terminals of the mesolimbic and nigrostriatal dopamine projections was used to examine presynaptic receptor function. In order to produce dopamine D_1-like/D_2-like receptor-mediated jaw movements, a mixture of the dopamine D_1-like receptor agonist, SKF 38393 (1.0-3.0 mg/kg), and the dopamine D_2-like receptor agonist, quinpirole (1.0 mg/kg), were administered intravenously because this drug combination has been found to be highly effective (23). The jaw movements were measured since they are considered to be selective behavioral indicators of postsynaptic dopamine D_1-like/D_2-like receptor functions (23).

Materials and Methods

Animals

Male SHR and normotensive control WKY rats at 9 weeks of age (weighing 200-250 g) were obtained from Funabashi Farms (Chiba, Japan). They were housed in cages (27 × 45 × 20 cm) that were kept at constant room temperature (23 ± 2°C) and relative humidity (55 ± 5%) under a 12 h light/dark cycle (lights on at 0700 h), with free access to food and water.

Behavioral experiments

For the measurement of spontaneous behaviors (i.e. locomotor activity and rearing), the rats were placed singly in experimental boxes (30 cm × 30 cm × 35 cm) with Perspex sides. Locomotor activity was measured with a battery of infrared photocells set 2 cm above the floor (Opto-Varimex, Columbus Instruments Ltd., Ohio, USA) and rearing was counted visually by a trained observer who was unaware of the SHR or WKY rat strain being observed. The animals were habituated to the experimental boxes for a period of 30 min before the observation period began. Locomotor activity was registered automatically by the number of beam interruptions during a 30-min observation period. The method of behavioral measurement employed in this study was based on the one reported previously (24).

For the measurement of drug-induced jaw movements, rats were anesthetized with halothane (0.5-4.0% as needed) and a supplemental dose of ketamine HCl (10.0 mg/kg, i.p.). The surgical and recording procedures were as described previously (25-28). After cannulation of the right external jugular vein, a small light-emitting diode was fixed to the mandible. The animal was placed in a stereotaxic frame so that the head was kept in constant relation to a light-sensitive transducer, which detected the vertical movements of the diode. After surgery, the animals continuously received ketamine in a dose (10.0 mg/kg, i.v.) unable to influence either the jaw movements under study (25) or dopamine metabolism in the striatum (29). Lidocaine HCl (2% gel) was applied to all incisions to ensure complete analgesia. Rectal temperature was maintained at 37.0°C with a thermostatically controlled heating pad. Monitored concentrations of expired O_2 and CO_2 during the experiment were 19-21% and 2.0-2.5%, respectively. The jaw movements were recorded on an eight-channel tape recorder (RD-180T; TEAC) for off-line analyses according to previously described procedures (30). Thus, the recordings were analyzed automatically, using a spike trigger that counted vertical jaw movements every 5 min. The recording period lasted 120 min. The animals were used only once.

In vivo microdialysis experiments

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The anesthetized animals were placed in a stereotaxic apparatus, and a guide cannula was implanted just above the left dorsal striatum or the nucleus accumbens [ventrolateral striatum: antero-posterior (AP) 9.2 mm, medio-lateral (ML) 4.0 mm, dorso-ventral (DV) 3.5 mm; nucleus accumbens: AP 10.6 mm, ML 1.5 mm, DV 4.0 mm from interaural line; Paxinos and Watson (31)]. To avoid the ventricular system, cannulae directed at the

nucleus accumbens were angled 18° from the mid-sagittal plane. After completion of surgery, rats were allowed to recover for 7 to 10 days before experiments were carried out; guide cannulae were kept patent by stainless steel inserts. Each animal was used only once.

A commercially available I-shaped removable-type dialysis probe (2 mm length cellulose membrane, 0.22 mm o.d., 50000 mol. wt. "cut-off," Eicom A-I-8-02 type, Kyoto, Japan) was used. The experiment began by removing the stylus from the guide cannula and inserting the dialysis probe, with only the dialysis tubing protruded from the tip. The probe was secured to the guide cannula by a screw. Each rat was then placed in a plexiglass box (30 × 30 × 35 cm), and the inlet and outlet tubes were connected to a swivel located on a counterbalanced beam to minimize discomfort. The probe was perfused at a rate of 2.0 µl/min with modified Ringer's solution (NaCl 147 mM, KCl 4 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 1.1 mM; pH 7.4) and the outflow was connected by Teflon tubing to a high-performance liquid chromatography system (Eicom, Kyoto, Japan).

Dopamine was separated on an Eicompak CA-5ODS column (particle size, 5 µm, 4.6 × 150 mm, Eicom, Kyoto, Japan) using phosphate buffer (0.1 M) containing octane-sulfonic acid (3.2 mM), EDTA (0.13 mM) and 20% methanol (pH 6.0) in the mobile phase at a flow rate of 1.0 ml/min. Compounds were quantified by electrochemical detection using a glassy carbon working electrode set at +400 mV against a silver-silver chloride reference electrode (Eicom, Kyoto, Japan). The detection limit for dopamine was approximately 0.05 pg per sample. The probes had an *in vitro* recovery rate of approximately 12% for dopamine, but the reported concentrations were not adjusted for recovery *in vivo* because these estimations are inaccurate (32,33). Previous experiments in which we have used the same technique and procedure have shown that dopamine efflux is more or less stabilized 4 h after probe insertion, and that levels seen at that time are largely dependent on neuronal release as most of the release is tetrodotoxin-sensitive and Ca^{2+} dependent (34-39). Perfusate samples were taken every 20 min for quantification of dopamine. Drugs were administered intracerebrally through the dialysis probe at least 20 h after probe insertion.

Drugs

The drugs used were the dopamine D_1 receptor agonist SKF 38393 ([*R*]7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, Sigma, St Louis, USA) and the dopamine D_2-like receptor agonist quinpirole hydrochloride (Sigma, St Louis, USA). For intravenous injection, SKF 38393 and quinpirole were diluted in 0.9% NaCl solution as a cocktail, and for intracerebral administration, quinpirole was dissolved in the modified Ringer's solution that was used for perfusions and was infused via the dialysis membrane for 180 min. All drugs were prepared immediately before use. Doses employed were based on previously published studies (20,21,23).

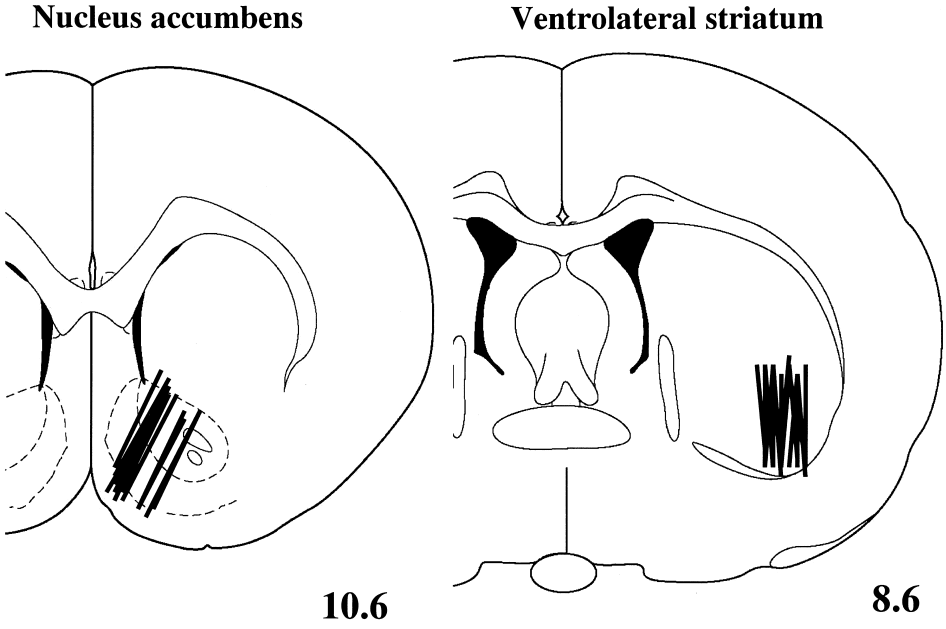

Fig. 1 Location of dialysis probes in the nucleus accumbens (left) and the ventrolateral striatum (right). Planes are modified from the atlas of Paxinos and Watson (1986); approximate coordinates indicated are mm anterior to the interaural line for each plane, with probe locations extending slightly anterior and posterior to each plane.

Histology

At the end of each experiment, the rats were deeply anesthetized with sodium pentobarbital (80 mg/kg, i.p.) and perfused transcardially with 10% formalin. The brains were removed, sectioned at 50 μm and stained with Cresyl violet to permit identification of probe location.

Data analysis

For the behavioral studies, all values are expressed as means ± S.E.M. and analyzed using a one-way analysis of variance (ANOVA), where appropriate. In addition, a Student's *t*-test or a Welch's test was used when necessary. For the microdialysis studies, all values were expressed as a percentage of baseline levels. Comparison of time-course data was performed using two-way ANOVA for repeated measures with the factors treatment and time (repeated). In addition, a Student's *t*-test was used when necessary. A probability value of $P < 0.05$ was considered statistically significant.

These experiments were approved by the Animal Experimentation Committee of Nihon University School of Dentistry, and were performed in accordance with Institutional guidelines for the care and use of experimental animals that are in compliance with the UK Animals Scientific Act 1986. In addition, all efforts were made to minimize animal suffering and to reduce the number of animals used.

Results

Behavioral assessment of SHR and WKY rats

Spontaneous locomotor activity and rearing observed for a 30-min observation time in SHR (n = 15) were significantly larger than those observed in WKY rats (n = 16). Thus, the locomotor activity counts being 1451 ± 137.8 in SHR compared with 844 ± 157.3 in WKY rats ($P < 0.01$, Student's *t*-test) and rearing counts being 13.6 ± 2.07 in SHR compared with 6.4 ± 1.97 in WKY rats ($P < 0.05$, Student's *t*-test) (Fig. 2).

Intravenous injection to WKY rats of quinpirole (1.0 mg/kg) combined with SKF 38393 (1.0, 2.0 and 3.0 mg/kg) synergized to induce jaw movements in a dose-dependent manner (Fig. 3). In contrast, when injected to SHR, SKF 38393 did not synergize with quinpirole (Fig. 3). Therefore, the effects of combination of a fixed dose of quinpirole (1.0 mg/kg) with SKF 38393 (2.0 mg/kg and 3.0 mg/kg respectively) to produce jaw movements were significantly larger in WKY rats than in SHR ($P < 0.01$, Welch's test respectively, Fig. 3).

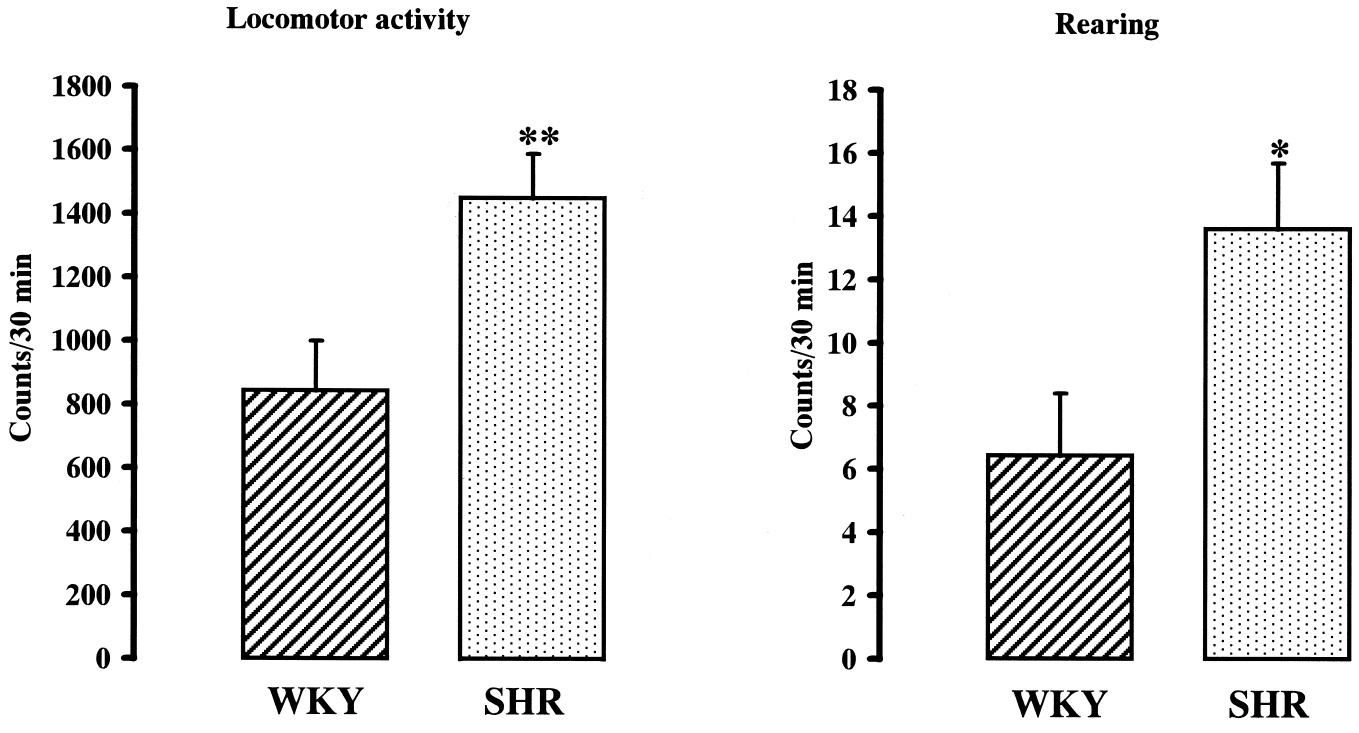

Fig. 2 Spontaneous locomotor activity and rearing in spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats observed during a 30-min observation period.

In vivo microdialysis measurements of dopamine in SHR and WKY rats

Placements of the dialysis probes in the nucleus accumbens and the ventrolateral striatum were given in Fig. 1.

Approximately 20 h after probe insertion, concentrations of dopamine in dialysates of the nucleus accumbens [SHR: 2.6 ± 0.3 (n = 7), WKY: 3.1 ± 0.5 (n = 7)] and the ventrolateral striatum [SHR: 4.7 ± 0.8 (n = 7), WKY: 5.2 ± 0.9 (n = 8)] reached a stable baseline value and remained stable over the subsequent 3-h study period. The dopamine levels in both brain regions were lower in SHR than in WKY rats. A 180-min infusion of quinpirole (100 μM) significantly reduced extracellular levels of dopamine in the nucleus accumbens and the ventrolateral striatum of SHR and WKY rats [nucleus accumbens: SHR, $F(11, 72) = 10.13$, $P < 0.0001$; WKY, $F(11, 69) = 2.01$, $P < 0.05$; ventrolateral striatum: SHR, $F(11, 72) = 9.35$, $P < 0.0001$; WKY, $F(11, 84) = 4.52$, $P < 0.0001$]. The time-dependent effect of quinpirole in each experimental group, shown in Fig. 4, clearly illustrates that the effect started nearly immediately after infusion, reached maximum around 60 min, and then continued over 180 min.

The reduction rate of quinpirole-mediated dopamine release in the nucleus accumbens at 40 min and 60 min after treatment was significantly larger in SHR than it was in WKY rats, though their levels of reduction were small. However, the reduction rate of the quinpirole-mediated dopamine release in the ventrolateral striatum in SHR was not significantly larger than that of WKY rats (Fig. 5).

Discussion

In accordance with the previous reports (4,8-11,13-19), the present study demonstrates that spontaneous locomotor activity and rearing are higher in SHR than in WKY rats. When increasing doses (1.0, 2.0 and 3.0 mg/kg) of the dopamine D_1-like receptor agonist, SKF 38393, was co-administered with a fixed dose (1.0 mg/kg) of the dopamine D_2-like receptor agonist, quinpirole, SKF 38393 synergized with quinpirole to induce jaw movements in a dose-dependent manner in WKY rats. In contrast, SKF 38393 did not synergize with quinpirole in SHR. The inability to induce dopamine D_1-like/D_2-like receptor-mediated jaw movements in SHR is not surprising. Earlier studies measuring locomotor hyperactivity after administration of *d*-amphetamine (8,16) and apomorphine (16) showed a similar inability or reduced locomotor activity. Although much of the data in receptor binding studies are contradictory (i.e. striatal dopamine D_1-like and D_2-like

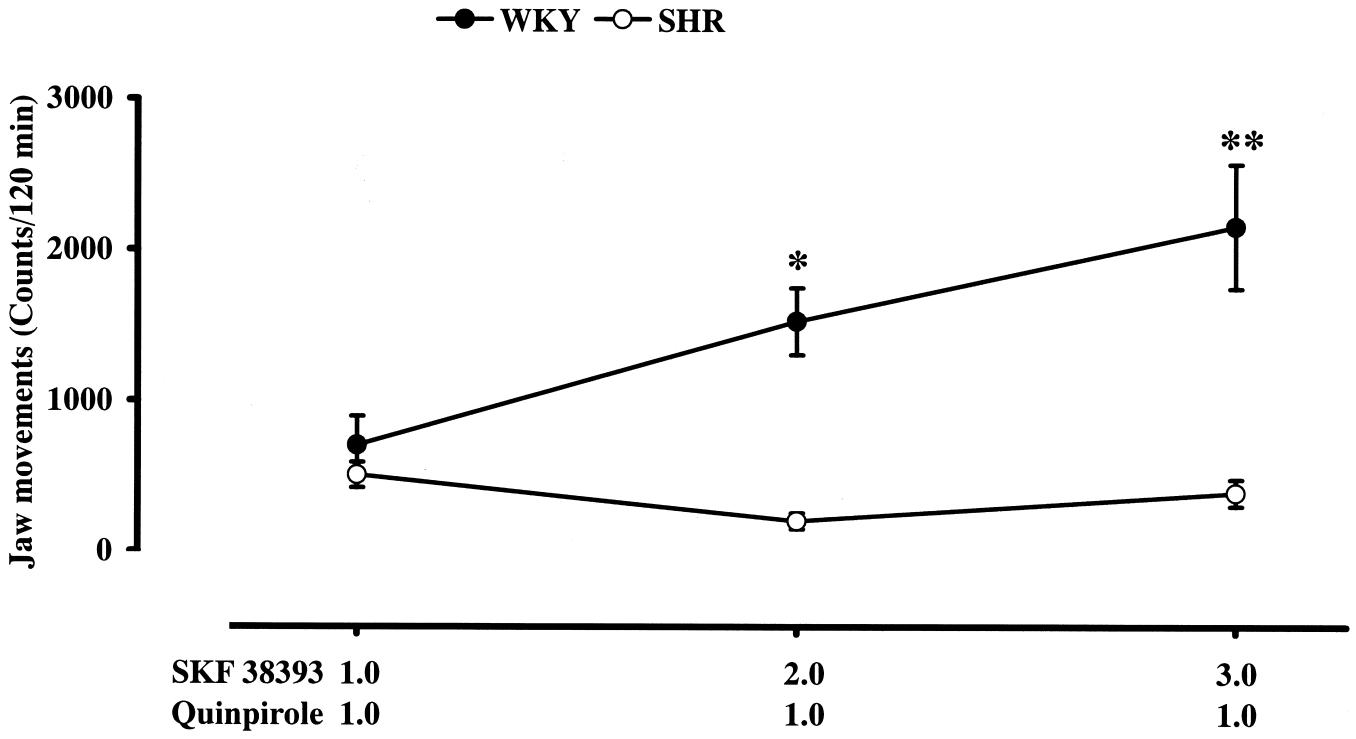

Fig. 3 Effects of SKF 38393 (1.0, 2.0 and 3.0 mg/kg) injected intravenously in combination with quinpirole (1.0 mg/kg) on production of jaw movements in spontaneously hypertensive rats (SHR, ●) and in Wistar-Kyoto (WKY, ○) rats. The data are expressed as the mean number of jaw movements occurring in a 120-min observation period (n = 5-6). Vertical bars indicate S.E.M.

receptors are increased (7,40) or are not different (41) in SHR compared to WKY rats) the present study and previous behavioral studies (8,16) provide firm evidence that postsynaptic dopamine D_1-like and/or D_2-like receptors in SHR are far less sensitive than those in WKY rats. Moreover, these dopamine D_1-like/D_2-like receptor-mediated jaw movements are probably accumbens- and/or ventrolateral striatum-specific because local injection of SKF 38393 and quinpirole combinations into these particular regions of Sprague-Dawley rats is known to readily elicit dopamine D_1-like/D_2-like receptor-mediated jaw movements (25,28,42).

The present study using an *in vivo* microdialysis technique clearly demonstrated that basal extracellular levels of dopamine in both the nucleus accumbens and the ventrolateral striatum were lower in SHR than in WKY rats, though the levels of dopamine were lower in the nucleus accumbens than the ventrolateral striatum in both strains. The present study indicates that dopamine levels in the striatal region were lower in SHR than in WKY rats and confirms the previous finding provided by studies using a similar *in vivo* microdialysis technique (22) and brain slices (12). Infusion of quinpirole at a concentration of 100 µM into the nucleus accumbens and the ventrolateral striatum for 180 min significantly decreased extracellular levels of dopamine in the respective areas. In the nucleus

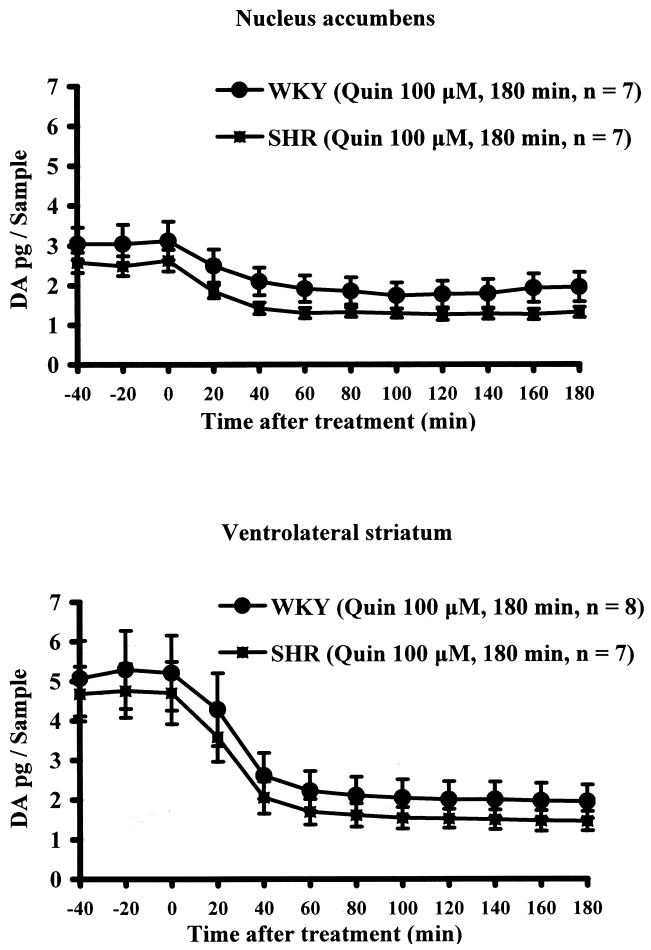

Fig. 4 Effects of quinpirole (100 μM) on extracellular levels of dopamine measured in a 40-μl dialysate collected for every 20-min from the nucleus accumbens (upper panel) and the ventrolateral striatum (lower panel) of spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. The data are expressed as the mean dopamine contents (pg) in 20-min dialysates (n = 7-8). Vertical bars indicate S.E.M.

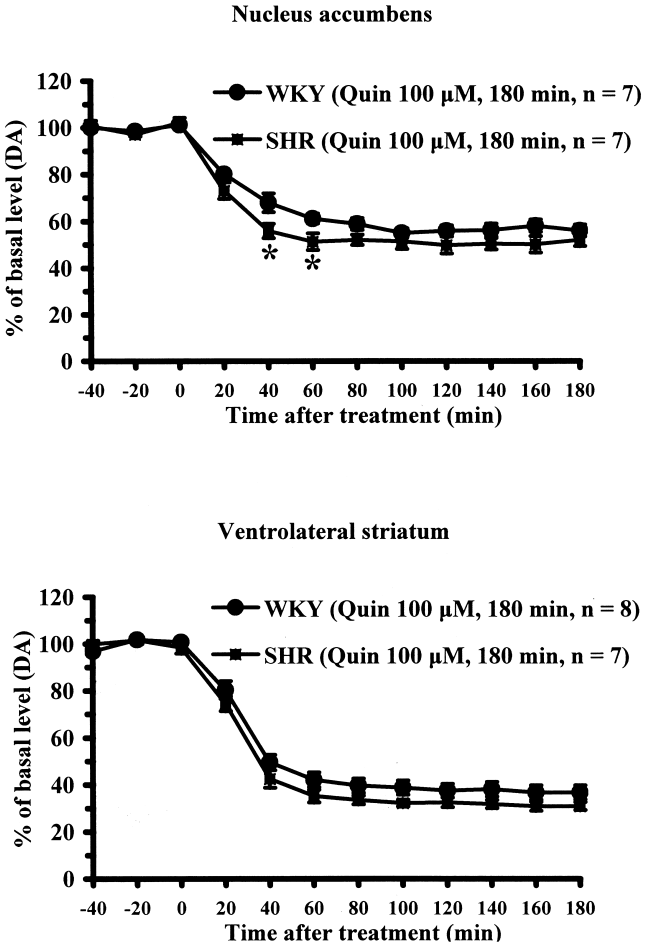

Fig. 5 Effects of quinpirole (100 μM) on extracellular levels of dopamine measured in a 40-μl dialysate collected for every 20-min from the nucleus accumbens (upper panel) and the ventrolateral striatum (lower panel) of spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. Baseline levels of dopamine are the mean of the last three 20-min dialysate samples before drug administration and all values given in this figure are expressed as a percentage of baseline levels. Vertical bars indicate S.E.M. (n = 7-8).

accumbens, a similar reduction of extracellular levels of dopamine has been reported after infusion of the same concentration of quinpirole (21). Such a reduction in extracellular levels of dopamine achieved by acute and local quinpirole infusion has been suggested to be a valid tool for revealing subtle differences in the function of presynaptic dopamine receptors that regulate the release of dopamine (12). As for the reduction rate of quinpirole-induced dopamine release, it was found that the reductions in the nucleus accumbens at 20 min and 40 min after treatment were significantly larger in SHR than in WKY rats: the difference between SHR and WKY rats in the ventrolateral striatum was only marginal.

In view of this data, it is concluded that presynaptic autoreceptors (i.e. D_2-like receptors which regulate the release of dopamine) are hypersensitive in SHR when compared to that of WKY rats, and this is more prominent in the nucleus accumbens. This finding of regional specificity is not entirely consistent with the previously reported results that showed a higher reduction of quinpirole-induced dopamine release in the striatum in SHR than WKY rats using *in vivo* brain microdialysis (22) and brain slices (12). However, the above-mentioned conclusion validates the behavioral finding that quinpirole-induced hypolocomotion, a widely used behavioral tool for assessing presynaptic D_2-like receptor function in the nucleus accumbens, is larger in SHR than WKY rats (15). Moreover, binding studies have indicated that dopamine D_2-like receptor density is increased in SHR (7,40) thus supporting the suggestion that increased autoreceotor-mediated inhibition of dopamine release is due to an increased number of dopamine D_2-like receptors.

In conclusion, it is hypothesized from the present study that, in SHR when compared to WKY rats, presynaptic dopamine receptors are hypersensitive and postsynaptic dopamine receptors are hyposensitive. Future research is required to validate this hypothesis, but both behavioral and neurochemical data clearly reveal that SHR (i) did not show dopamine D_1-lile/D_2-like receptor-mediated jaw movements and (ii) had enhanced response to reduce dopamine release by quinpirole in the nucleus accumbens.

Acknowledgments

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