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European Journal of Pharmacology 484 (2004) 75–82
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Decreased postsynaptic dopaminergic and cholinergic functions in the ventrolateral striatum of spontaneously hypertensive rat

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Received 25 August 2003; received in revised form 23 October 2003; accepted 31 October 2003

Abstract

Dopamine and acetylcholine receptor functions in spontaneously hypertensive rats (SHR) and in control progenitor Wistar–Kyoto (WKY) rats were assessed, using dopamine D1-like/D2-like receptor-mediated and acetylcholine receptor-mediated jaw movements as readout parameters. Spontaneous behaviours such as locomotor activity, vacuous chewing, grooming, sniffing and rearing occurred significantly more in SHR than in WKY rats. In the anaesthetised rats, a mixture of SKF 38393 (5 μg), a dopamine D1-like receptor agonist, and quinpirole (10 μg), a dopamine D2-like receptor agonist, readily produced repetitive jaw movements in WKY rats, but not SHR, when bilaterally injected into the ventrolateral striatum; such injections into the nucleus accumbens shell were ineffective in each strain. Bilateral injections of carbachol (2.5 μg each side), an acetylcholine receptor agonist, into the ventrolateral striatum elicited repetitive jaw movements in both SHR and WKY rats, but to a far less degree in SHR. The present study demonstrates that spontaneous behaviours are enhanced in SHR, and that postsynaptic dopamine D1-like/D2-like receptors and acetylcholine receptors in the ventrolateral striatum of SHR are hyposensitive when compared to those of WKY rats.

Keywords: Attention-deficit hyperactivity disorder; Spontaneous behaviour; Repetitive jaw movement; Striatum; Ventrolateral; Dopamine D1-like/D2-like receptor; Acetylcholine receptor; Spontaneously hypertensive rat (SHR)

1. Introduction

The spontaneously hypertensive rat (SHR), a hypertensive phenotype derived from the Wistar–Kyoto (WKY) strain (Okamoto and Aoki, 1963; Versteeg et al., 1976; Nagaoka and Lovenberg, 1977), has been used as a genetic animal model for attention-deficit hyperactivity disorder because it exhibits behaviours analogous to those of attention-deficit hyperactivity disorder, such as hyperactivity, impulsivity and inability to sustain attention during behavioural tasks (Boix et al., 1998). Spontaneous behaviours, e.g., locomotor activity and rearing, are higher in SHR than in WKY rats (McCarty and Kirby, 1982; Myers et al., 1982; Fuller et al., 1983; Hynes et al., 1985; Van den Buuse et al., 1986a; Van den Buuse and De Jong, 1987, 1989; Tsai and Lin, 1988; Sagvolden et al., 1992a, 1993; Sagvolden, 2000) and reinforcement mechanisms involving the mesolimbic dopaminergic system are altered in both SHR and attention-deficit hyperactivity disorder children (Sagvolden et al., 1992a,b, 1993). The nigrostriatal dopaminergic projection has been suggested to play a role in attention-deficit hyperactivity disorder and altered striatal dopaminergic mechanisms have been found in SHR (see below).

The striatal and accumbal dopamine release is smaller in SHR than in WKY rats (Linthorst et al., 1990, 1991; Van

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doi:10.1016/j.ejphar.2003.10.050

den Buuse et al., 1991; Russell et al., 1995; Fujita et al., 2003; Russell, 2003) and SHR have a higher density of dopamine D1-like and D2-like receptors than WKY rats (Lim et al., 1989; Kirouac and Ganguly, 1993; Carey et al., 1998; Sadile, 2000). In addition, the dopamine D2-like autoreceptor efficacy in the nucleus accumbens of SHR is different from that found in the nucleus accumbens of WKY rats (Russell, 2000; Fujita et al., 2003). Moreover, there is evidence that the SHR, but not the WKY rats, are marked by an impaired vesicular storage of dopamine in the nucleus accumbens as indicated by a reduced methylphenidate-induced dopamine release (Russell et al., 1998). Remarkably, the D-amphetamine-induced dopamine release from the cytoplasmic stores is larger in the nucleus accumbens of SHR than in that structure of WKY rats (Russell et al., 1998). Despite of all these impairments in the telencephalic, dopaminergic terminals, it has been suggested that the postsynaptic dopamine D2-like receptor function is not altered in SHR relative to WKY rats, because there is no difference between SHR and WKY rats with respect to dopamine D2-like receptor-mediated inhibition of acetylcholine release from the striatal or accumbal slices (Russell et al., 1998). This is difficult to reconcile with the finding that the locomotor response to the indirectly acting dopamine D1-like/D2-like receptor agonist, D-amphetamine, and the directly acting dopamine D1-like/D2-like receptor agonist, apomorphine, is smaller in SHR than in WKY rats (Myers et al., 1982; Hynes et al., 1985). These data suggest that the dopamine receptors that are involved in these locomotor responses, namely the ones that are localised in the nucleus accumbens (Pijnenburg et al., 1976), are less sensitive in SHR than in WKY rats. Similarly, we have provided evidence that the systemic administration of a cocktail of quinpirole, a dopamine D2-like receptor agonist, and [*R*]7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF 38393), a dopamine D1-like receptor agonist, dose-dependently and synergistically induces repetitive jaw movements in WKY rats, but not in SHR (Fujita et al., 2003). Because the postsynaptic dopamine D2-like and dopamine D1-like receptors that are mediating such jaw movements, are localised in the ventrolateral striatum (Koshikawa et al., 1989) and the shell of the nucleus accumbens (Cools et al., 1995), these data also suggests that the function of these receptors differ between SHR and WKY rats. In view of all these findings, we hypothesised that the function of the dopaminergic receptors in striatal and/or accumbal structures that are involved in the display of jaw movements, is decreased in SHR relative to WKY rats.

Apart from the fact that dopamine controls the release of acetylcholine in the striatum, there is evidence that both neurotransmitters can have their own function in the striatum. In fact, we have recently shown that stimulation of dopamine and acetylcholine receptors in the ventrolateral striatum elicits transmitter-specific jaw movements that are funnelled via distinct γ-aminobutyric acid (GABA)ergic output pathways of the striatum (Kikuchi de Beltrán et al., 1992; Adachi et al., 2002; see also: Kelley et al., 1989 and Delfs and Kelley, 1990). Binding studies on cholinergic receptors in the striatum and nucleus accumbens of SHR and WKY rats have shown that the number of muscarinic M_1 receptors is larger in the striatum of SHR than in the striatum of WKY rats, whereas the number of muscarinic M_2 receptors in the nucleus accumbens of SHR is larger than that in this nucleus of WKY rats (Gattu et al., 1997). In view of these findings, one might expect that the functions of the acetylcholine receptors in striatal and accumbal structures differ between SHR and WKY rats. Because only stimulation of cholinergic receptors in the ventrolateral striatum (Kikuchi de Beltrán et al., 1992; Adachi et al., 2002), but not in the nucleus accumbens (unpublished data), result in the display of jaw movements in Sprague–Dawley rats, we hypothesised that the function of the cholinergic receptors in the ventrolateral striatum that are involved in the display of jaw movements, differs between SHR and WKY rats.

In order to investigate these hypotheses, we analysed the effects of bilateral injections of (A) a mixture of SKF 38393 (3 or 5 μg) and quinpirole (10 μg) and (B) the acetylcholine receptor agonist, carbachol (1 and 2.5 μg), into the ventrolateral striatum and the nucleus accumbens; both drugs and their doses were chosen, because these are known to readily produce repetitive jaw movements in Sprague–Dawley rats when administered either into the ventrolateral striatum (Koshikawa et al., 1989; Kikuchi de Beltrán et al., 1992; Adachi et al., 2002) or the shell of the nucleus accumbens (Cools et al., 1995). An additional advantage of the chosen intracerebral route is the fact that it avoids strain differences in the effects of the drugs on blood pressure.

2. Materials and methods

2.1. Surgical procedures

Male SHR and normotensive control WKY rats at 9 weeks of age (weighing 200–250 g) were obtained from Charles River Japan (Yokohama, 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.

To measure spontaneous behaviours, i.e., locomotor activity, vacuous chewing, grooming, sniffing and rearing, rats were placed singly in experimental boxes (30 × 30 × 35 cm) with Perspex sides at 0900 h and allowed 30-min habituation. Locomotor activity was measured with a battery of infra-red photocells set 2 cm above the floor (Opto-Varimex, Columbas Instruments, Ohio, USA) and the number of beam interruptions during a 30-min observation period was automatically registered as locomotor activity.

The number of episodes of other spontaneous behaviours was visually counted by a trained observer who was blind to the rat's strain (Koshikawa et al., 1987; Diana et al., 1992; Ikeda et al., 1999). Thus, each episode was scored as a "1". A chewing period consists of distinct bursts of three to about five masticatory movements and lasts 2–5 s. Masticatory movements are characterised by vertical jaw movements in the absence of any chewable material in the rat's mouth.

Immediately after the above-mentioned behavioural observations, the rats were anaesthetised with halothane (0.5–4.0% as appropriate) supplemented with ketamine HCl (10.0 mg/kg, i.p.). The surgical and recording procedures were as described previously (Koshikawa et al., 1989, 1990a,b, 1991; Cools et al., 1995). After cannulation of the right external jugular vein, a small light-emitting diode was fixed to the mandible. The animal was placed in a stereotactic frame so that the head was kept in a constant relation to a light-sensitive transducer, which detected the vertical movements of the diode. Guide cannulas (0.5 mm [o.d.] × 0.3 mm [i.d.] × 6.0 mm [length]), with wire stylets inserted to prevent occlusion, were then implanted bilaterally into the brain as described previously (Koshikawa et al., 1989). The coordinates were, for the ventrolateral striatum: anterior = 8.6 mm from interaural line, vertical = 3.0 mm from interaural line, lateral = 4.0 mm from midline and, for the shell of the nucleus accumbens: anterior = 10.6 mm, vertical = 2.0 mm, lateral = 0.7 mm (Paxinos and Watson, 1998). Cannulas directed at the shell of the nucleus accumbens were angled 21° from the midsagittal plane to avoid the ventricular system (Cools et al., 1995). The injections were made slowly in a volume of 0.2 μl per side over 20 s, and the needle was left in situ for an additional 20-s period after completion of the injection. Damage to the target site was minimised by implanting the tips of the guide cannulae 1.5 mm (ventrolateral striatum) or 2.0 mm (nucleus accumbens shell) above the desired injection site.

After surgery, the halothane was discontinued and anaesthesia maintained with ketamine, 10.0 mg/kg, i.v. per hour, a dose which does not affect either striatal dopamine metabolism or evoked jaw movements (Koshikawa et al., 1988, 1989). Lignocaine HCl (2% gel) was applied to all incisions to ensure complete analgesia. Rectal temperature was maintained at 37.0 °C throughout the experiment with a thermostatically controlled heating pad and concentrations of expired O_2 and CO_2 were monitored and were 19–21% and 2.0–2.5%, respectively. Jaw movements were recorded for 60 or 240 min on an eight-channel tape recorder (RD-180T; TEAC) for automatic off-line analysis with a spike trigger that counted vertical jaw movements per 5 min (Adachi et al., 2002, 2003). The experiments were performed in accordance with institutional guidelines for the care and use of experimental animals and were approved by the Animal Experimentation Committee of Nihon University School of Dentistry.

2.2. Drugs

The animals ($n = 5–9$ per experiment) received bilateral injections of a mixture of the dopamine D1-like receptor agonist, SKF 38393 (3 or 5 μg; [*R*]7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; Sigma, St Louis, USA), and the dopamine D2-like receptor agonist, quinpirole (10 μg; Sigma); the non-selective dopamine receptor antagonist, *cis*(*Z*)-flupentixol dihydrochloride (10 μg; Lundbeck, Denmark); the non-selective acetylcholine receptor agonist, carbachol (1 and 2.5 μg; carbamylcholine, Sigma); and the muscarinic receptor antagonist, methylscopolamine (1 μg; Sigma) into the ventrolateral striatum or the nucleus accumbens. The drugs were dissolved in saline immediately before use and the doses were based on our previous studies and refer to the amounts injected into each side (Koshikawa et al., 1989; Kikuchi de Beltrán et al., 1992; Cools et al., 1995; Adachi et al., 2002). The animals were used once only.

2.3. Histology

At the end of each experiment, the rats were deeply anaesthetised with sodium pentobarbitone (80 mg/kg, i.p.)

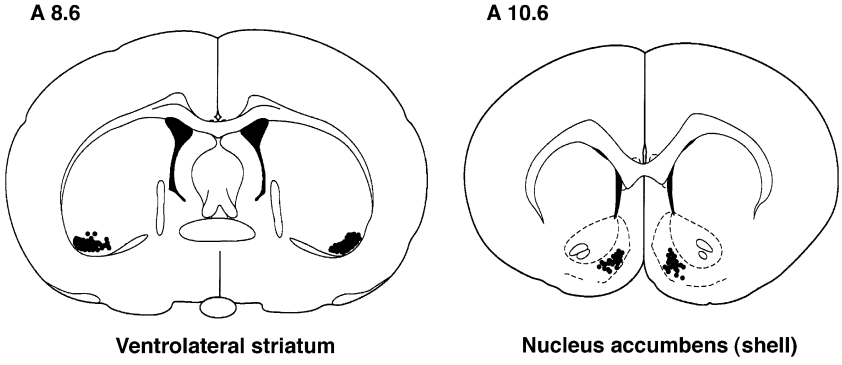

Fig. 1. Location of injection sites in the ventrolateral striatum (left) and the nucleus accumbens shell (right). Planes are modified to a series of two or three sections for each brain area from the atlas of Paxinos and Watson (1998); approximate coordinates indicated are in mm anterior to the interaural line.

and perfused transcardially with 10% formalin. The brains were removed, sectioned at 50 μm and stained with Cresyl violet to visualise the injection site; only data from animals in which the injections were correctly placed were included in subsequent analyses of jaw movements. Fig. 1 gives a survey of the injection sites located in the ventrolateral striatum and the nucleus accumbens.

2.4. Data analysis

All values are expressed as means ± S.E.M. and analysed using one-way analysis of variance (ANOVA) or two-way (group × time) ANOVA, followed by a post hoc Tukey's test where appropriate. In addition, a *t*-test assuming equal or unequal variances was used to analyse differences between two groups (SHR vs. WKY rats; i.e., vacuous chewing, grooming, sniffing, rearing and jaw movements). A probability value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Spontaneous behaviours observed in SHR and WKY rats

Fig. 2 shows that the spontaneous locomotor activity of SHR ($n = 74$) was significantly greater than that of WKY rats ($n = 127$) throughout the 30 min observation period ($F(1,1194) = 2082.62$, $P < 0.0001$, two-way ANOVA). Other spontaneous activities (vacuous chewing, grooming, sniffing and rearing) were also greater in SHR than in WKY rats ($P < 0.001$ in each comparison, *t*-test; Fig. 3).

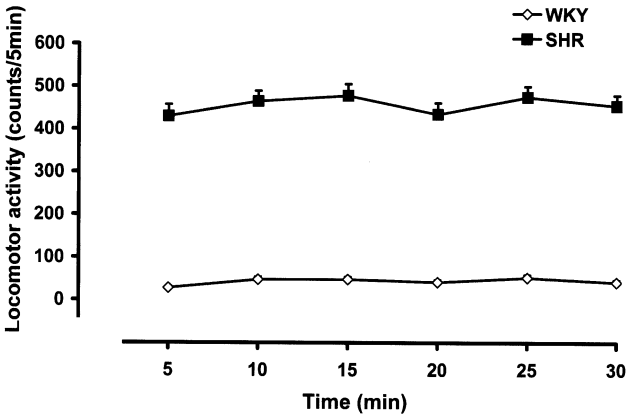

Fig. 2. Time course of spontaneous locomotor activity in SHR ($n = 74$) and in WKY rats ($n = 127$). The data are expressed as the mean number of infrared photocell beam interruptions occurring in 5-min observation periods. Vertical bars indicate S.E.M.

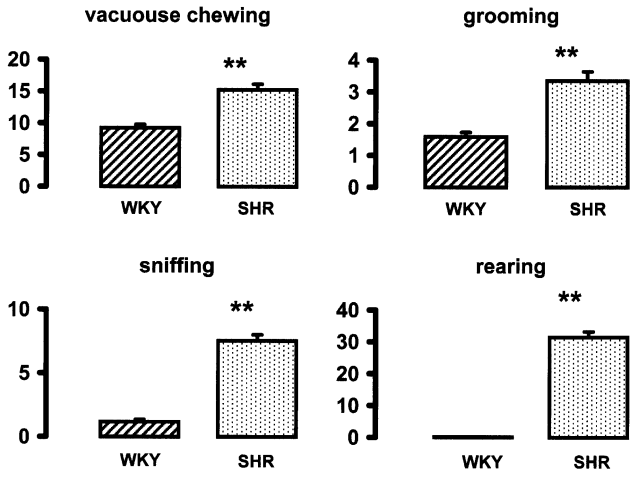

Fig. 3. Spontaneous vacuous chewing, grooming, sniffing and rearing in SHR ($n = 74$) and in WKY rats ($n = 127$). The data are expressed as the mean number of episodes counted during a 30-min observation period. Vertical bars indicate S.E.M. $^{**}P < 0.01$, *t*-test.

3.2. Pattern of jaw movements elicited by dopamine and acetylcholine receptor agonists

Bilateral injections of a mixture of SKF 38393 (5 μg) and quinpirole (10 μg) into the ventrolateral striatum of WKY rats elicited repetitive jaw movements which were marked by continuous series of variable magnitude opening and closing movements of jaw. Opening movements were accompanied by frequent tongue protrusions. On the other hand, jaw movements elicited by bilateral injections of carbachol (2.5 μg) into the ventrolateral striatum of WKY rats were marked by short episodes of jaw movements consisting of 6–10 consecutive, predominantly opening, jaw movements of more consistent magnitude and without tongue protrusions. These characteristics of dopamine D1-like/D2-like receptor-specific and carbachol-specific jaw movements in WKY rats were essentially similar to those reported previously in Sprague–Dawley rats (see Kikuchi de Beltrán et al., 1992; Adachi et al., 2002, 2003).

3.3. Effects of bilateral injections of SKF 38393 and quinpirole mixture into the ventrolateral striatum of SHR and WKY rats

Bilateral injections of SKF 38393 (5 μg) or quinpirole (10 μg) alone did not induce significantly larger number of jaw movements when compared to those seen after injections of saline into the ventrolateral striatum of WKY rats. However, SKF 38393 (3 or 5 μg) synergised with quinpirole (10 μg) to produce characteristic repetitive jaw movements in a dose-dependent manner (saline vs. SKF 38393 (5 μg) + quinpirole (10 μg): $P < 0.05$, Tukey's test; Fig. 4). This effect of the mixture, SKF 38393 (5 μg) + quinpirole (10 μg), was abolished by *cis*(*Z*)-flupentixol (10 μg) given

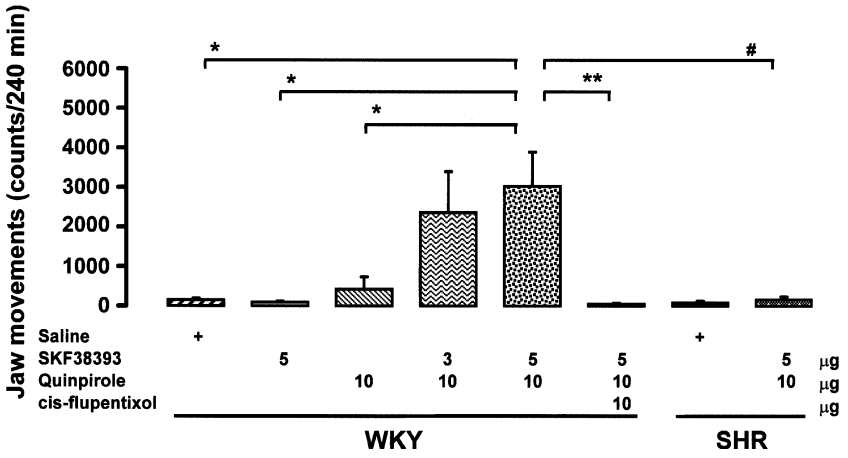

Fig. 4. Effects of bilateral injections of saline, SKF 38393 (5 μg), quinpirole (10 μg) and a mixture of SKF 38393 (3 or 5 μg) and quinpirole (10 μg) into the ventrolateral striatum of SHR and WKY rats on production of jaw movements, and antagonism by *cis*(*Z*)-flupentixol (10 μg). The data are expressed as the mean number of jaw movements occurring in a 240-min observation period ($n=5–9$). Vertical bars indicate S.E.M. (overall among WKY rats groups: $F(5,34)=5.43$, $P<0.001$, one-way ANOVA; post hoc Tukey's test: $^{*}P<0.05$, $^{**}P<0.01$). SHR vs. WKY rats; $^{\#}P<0.05$, *t*-test.

into the ventrolateral striatum ($P<0.01$, Tukey's test; Fig. 4). In contrast, this mixture did not elicit jaw movements when injected into corresponding sites of SHR (SHR vs. WKY rats: $P<0.05$, *t*-test; Fig. 4).

3.4. Effects of bilateral injections of carbachol into the ventrolateral striatum of SHR and WKY rats

Carbachol (1 and 2.5 μg), but not saline, dose-dependently elicited characteristic repetitive jaw movements when injected bilaterally into the ventrolateral striatum of WKY rats ($P<0.01$, Tukey's test). This effect of carbachol (2.5 μg) was abolished by methylscopolamine (1 μg) given into the ventrolateral striatum ($P<0.01$, Tukey's test; Fig. 5). In contrast, carbachol (2.5 μg) produced significantly fewer jaw movements when injected into the ventrolateral part of the striatum of SHR (SHR vs. WKY rats: $P<0.05$, *t*-test; Fig. 5).

3.5. Effects of bilateral injections of SKF 38393 and quinpirole mixture into the nucleus accumbens shell of SHR and WKY rats

Neither saline nor a mixture of SKF 38393 (5 μg) and quinpirole (10 μg) produced a significant amount of jaw movements when injected bilaterally into the nucleus accumbens shell of WKY rats and SHR, though the mixture elicited a slight, but not significant increase of jaw movements in both SHR and WKY rats. Thus, the jaw movements elicited in WKY rats after injections of saline and the mixture of SKF 38393 and quinpirole during a 240-min observation period were 52.3 ± 32.8 ($n=6$) and 151 ± 43.3 ($n=6$), respectively, while the jaw movements elicited in SHR after injections of saline and the mixture of SKF 38393 and quinpirole were 80.0 ± 49.3 ($n=6$) and 261.3 ± 143.3 in ($n=6$), respectively ($F(3,20)=0.54$, $P=0.66$, one-way ANOVA).

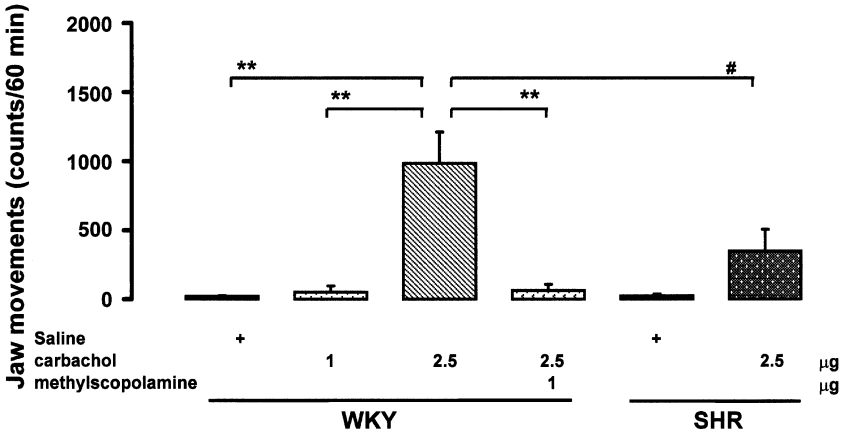

Fig. 5. Effects of bilateral injections of saline and carbachol (1 and 2.5 μg/side) into the ventrolateral striatum of SHR and WKY rats, and antagonism by methylscopolamine (1 μg). The data are expressed as the mean number of jaw movements occurring in a 60-min observation period ($n=5–8$). Vertical bars indicate S.E.M. (overall among WKY rats groups: $F(3,23)=12.50$, $P<0.001$, one-way ANOVA; post hoc Tukey's test: $^{**}P<0.01$). SHR vs. WKY rats; $^{\#}P<0.05$, *t*-test.

4. Discussion

The present study confirmed the previously reported findings that SHR display a greater spontaneous locomotor activity and rearing than WKY rats do (McCarty and Kirby, 1982; Myers et al., 1982; Fuller et al., 1983; Hynes et al., 1985; Van den Buuse et al., 1986a,b; Van den Buuse and De Jong, 1987, 1989; Tsai and Lin, 1988; Sagvolden et al., 1992a, 1993; Sagvolden, 2000). We also found that SHR display more spontaneous activities such as vacuous chewing, grooming and sniffing than WKY rats do. This data is inconsistent with the earlier reported finding that the amount of grooming in SHR is lower than that in WKY rats (Van den Buuse et al., 1986a; Van den Buuse and De Jong, 1987; Linthorst et al., 1992) and that the amounts of sniffing and vacuous chewing do not differ between the two strains (Van den Buuse et al., 1986a; Queiroz et al., 1998). The discrepancy between the outcome of the present study and that of other studies might be due to differences in the procedure used to study the behaviour; for, it is known that parameters of the test situation like habituation time, duration of testing, age, etc. are important in this respect (cf. Sagvolden et al., 1992a, 1993). For example, the difference between the outcome of our study and that of the study of Queiroz et al. (1998) might be due to the fact that our rats were tested at the age of 9 weeks, whereas those of Queiroz et al. (1998) were tested at the age of 5 months. Future studies are required to establish to what extent just methodological factors gave rise to the noted discrepancies.

When the dopamine D1-like receptor agonist, SKF 38393 (5 μg), and the dopamine D2-like receptor agonist, quinpirole (10 μg) are administered together into the ventrolateral striatum of Sprague–Dawley rats, these drugs interact synergistically to produce repetitive jaw movements (Koshikawa et al., 1989). In the present study, this synergism was seen only in WKY rats, although the response to this drug combination was far smaller than that seen in Sprague–Dawley rats (cf. Koshikawa et al., 1989). Anyhow, the fact that SHR did not respond to the drug combination in contrast to WKY rats who did display jaw movements, shows that the dopamine D1-like and/or dopamine D2-like receptors in the ventrolateral striatum are far less sensitive than those in this part of the brain of WKY rats. This finding explains our earlier reported finding that the systemic administration of these drugs elicited jaw movements only in WKY rats, but not in SHR (Fujita et al., 2003). Because binding assays have shown that the number of dopamine D1-like and D2-like receptors in the striatum of SHR is either increased (Kirouac and Ganguly, 1993; Lim et al., 1989) or not different (Linthorst et al., 1993), relative to WKY rats, the noted strain difference in jaw movements cannot be ascribed to a difference in the number of postsynaptic dopamine receptors. Given the fact that the basal release of striatal dopamine in SHR is smaller than that in WKY rats (see Introduction), it can be speculated that the basal release of striatal dopamine was too low in order to stimulate the postsynaptic dopamine receptors in addition to the stimulation caused by the drugs, assuming thereby that the display of jaw movements normally requires a minimum amount of stimulation of postsynaptic receptors that is achieved by a combination of the drug-induced stimulation of these receptors and the stimulation caused by endogenous release of dopamine. Future research is required to provide evidence in favour of this.

Remarkably, the administration of a cocktail of SKF 38393 and quinpirole into the shell of the nucleus accumbens was ineffective in both SHR and WKY rats, despite of the fact that the doses used have been found to be highly effective in eliciting jaw movements, when administered into the shell of the nucleus accumbens of Sprague–Dawley rats (Cools et al., 1995). The finding that this cocktail was ineffective in SHR, indicates that the dopamine D1-like and dopamine D2-like receptors in the nucleus accumbens that are normally involved in the display of jaw movements, are less sensitive in SHR than those in Sprague–Dawley rats. Again, the noted difference in jaw movements cannot be ascribed to a difference in number of postsynaptic dopamine D1-like receptors, because the nucleus accumbens of SHR contains more dopamine D1-like and dopamine D2-like receptors than this nucleus of Sprague–Dawley rats does (Kujirai et al., 1990). Therefore, analogous to the reasoning above, it can be speculated that the basal release of accumbal dopamine was too low in order to stimulate the postsynaptic dopamine receptors in addition to the stimulation caused by the drugs. This explanation does not hold true for WKY rats. There are no studies indicating that the dopaminergic mechanism in the nucleus accumbens of WKY rats significantly differ from those found in this nucleus of Sprague–Dawley rats. At the moment, we have no valid explanation for the ineffectiveness of the cocktail of SKF and quinpirole when administered into the shell of the nucleus accumbens of WKY rats.

A major novel finding in the present study was the demonstration of altered cholinergic function in the ventrolateral striatum of SHR. Thus, the acetylcholine receptor agonist, carbachol, dose-dependently elicited characteristic repetitive jaw movements when injected bilaterally into the ventrolateral striatum of WKY rats, but produced significantly less jaw movements when injected into this brain structure of SHR. Apparently, the striatal, cholinergic receptors that are involved in the display of jaw movements in SHR, were less sensitive than those in WKY rats. Again, this cannot be ascribed to a change in the number of cholinergic, postsynaptic receptors, because the striatum of SHR contains more muscarinic M_1 receptors than WKY rats (Gattu et al., 1997). Although carbachol also has an affinity for muscarinic M_2 receptors, the difference in carbachol-induced jaw movements between SHR and WKY rats cannot be ascribed to a differential involvement of M_2 receptors, because the number of these receptors in the striatum of SHR does not differ from that in the striatum of WKY rats (Gattu et al., 1997). The present study clearly

reveals that the cholinergic function in the ventrolateral striatum of SHR is reduced in comparison with the normotensive WKY rats. In Sprague–Dawley rats, stimulation of dopamine and acetylcholine receptors in the ventrolateral striatum produces different types of repetitive jaw movements (Kikuchi de Beltrán et al., 1992), that are funnelled via distinct GABAergic output channels (Adachi et al., 2002). The present study clearly shows that these two neuronal systems are also present in WKY rats and SHR, and that both systems are less sensitive in SHR than in WKY rats.

In conclusion, the present study demonstrates that spontaneous behaviours are enhanced in SHR, and that SHR have reduced postsynaptic dopamine D1-like/D2-like receptor and acetylcholine receptor functions in the ventrolateral striatum when compared to WKY rats.

Acknowledgements

These studies were supported by a Nihon University Multidisciplinary Global Research Grant (NK, ARC), the Sato Fund (NK), the Promotion and Mutual Aid Corporation for Private Schools of Japan (NK, SF, JL), and a grant for promotion of multidisciplinary research projects (NK, ARC) and a grant-in-aid for scientific research (# 14370609 to NK) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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