Journal of Oral Science, Vol. 45, No. 4, 185-192, 2003

Original

$GABA_A$ receptors in the nucleus accumbens core modulate turning behavior induced by dopamine receptor stimulation

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(Received 5 August and accepted 26 September 2003)

Abstract: The role of $GABA_A$ and $GABA_B$ receptors in the core of the nucleus accumbens in turning behavior of rats was investigated. Unilateral injections into the core of the nucleus accumbens of the $GABA_A$ receptor agonist (muscimol, 50 ng) and antagonist (bicuculline, 200 ng), and the $GABA_B$ receptor agonist (baclofen, 100 ng) and antagonist (2-hydroxysaclofen, 2 μg) did not produce turning behavior. In rats pretreated with unilateral injections of the dopamine D_1-like/D_2-like receptor antagonist, *cis(Z)*-flupentixol (10 μg), into the ventrolateral striatum and saline into the nucleus accumbens core of contralateral side, systemic injection of a mixture of dopamine D_1-like (SKF 38393, 3 mg/kg) and D_2-like (quinpirole, 1 mg/kg) receptor agonists has been found to elicit contraversive pivoting, namely pivoting away from the side of the core injection. This dopamine D_1-like/D_2-like receptor-mediated pivoting was significantly inhibited by injections into the core of the nucleus accumbens of muscimol (50 ng), but not bicuculline (200 ng). In contrast, the dopamine D_1-like/D_2-like receptor-mediated pivoting was suppressed by either baclofen (100 ng) or 2-hydroxysaclofen (2 μg) injected into the nucleus accumbens core. It is therefore concluded that neither $GABA_A$ nor $GABA_B$ receptor stimulation in the core of the nucleus accumbens produces turning behavior, and that $GABA_A$, but not $GABA_B$, receptors in the nucleus accumbens core may modulate dopamine D_1-like/D_2-like receptor-mediated pivoting. (J Oral Sci. 45, 185-192, 2003)

Key words: $GABA_A$ receptor; $GABA_B$ receptor; dopamine D_1-like/D_2-like receptor; turning behavior; nucleus accumbens core.

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Introduction

Unilateral activation of the nucleus accumbens (NAcc) has been shown to elicit two characteristic types of turning behavior in rats, namely circling and pivoting (1-3). It is well known that the NAcc is a heterogeneous structure and is divided anatomically into two structures, i.e., the shell and the core (4-11). Regarding this subdivision, behavioral evidence has been provided that unilateral stimulation of dopamine D_1-like/D_2-like receptors in the shell, but not in the core, of the NAcc produces contraversive pivoting (3,12,13). This pivoting is characterized by abnormal hindlimb stepping, turns of a small diameter (< 20 cm) and spinning around one hindlimb (1,2,12,14).

The NAcc contains abundant γ-aminobutyric acid (GABA) (15,16), and two types of GABA receptors, namely $GABA_A$ and $GABA_B$ receptors (17,18). There is evidence that especially $GABA_A$ receptors exert an inhibitory control upon the release of dopamine within the NAcc, although $GABA_B$ receptors are not devoid of a modulatory role in this respect (19). Behaviorally, evidence

suggests that there is a close relationship between GABAergic and dopaminergic systems in the NAcc for regulation or modulation of locomotor behaviors. For example, $GABA_A$ receptor agonists reduce the hyperlocomotion induced by apomorphine (20-22), and the $GABA_A$ receptor antagonist, picrotoxin, enhances locomotor stimulant effects of dopamine receptor agonists (21,23).

Recently, we examined the role of $GABA_A$ and $GABA_B$ receptors in the shell of the NAcc in turning behavior of rats, and found that neither $GABA_A$ nor $GABA_B$ receptor stimulation in the shell elicits turning behavior. However, $GABA_A$, but not $GABA_B$, receptors in the shell modulate shell-specific dopamine D_1-like/D_2-like receptor-mediated contraversive pivoting (24). Since intrinsic neurons are localized in the core and have extensions into the shell (25) functional connections between the core and the shell can be present. In this context, it can be hypothesized that $GABA_A$ and $GABA_B$ receptors in the core may play either similar or dissimilar roles to that of the shell with regard to modulating shell-specific dopamine D_1-like/D_2-like receptor-mediated pivoting.

One of the major experimental problems in examining this hypothesis is the methodological difficulty in injecting drugs simultaneously into both the core and the shell on the same side of the brain. To resolve this technical problem we employed pivoting evoked by different experimental manipulations as a readout parameter: namely pivoting evoked by intraperitoneal (i.p.) injection of a mixture of dopamine D_1-like/D_2-like receptor agonists in rats with unilateral blockade of dopamine D_1-like/D_2-like receptors in the ventrolateral striatum (VLS) (1,14,26). With this experimental model, it is possible to inject $GABA_A$ and $GABA_B$ receptor agents in the side of the core contralateral to the VLS receiving the dopamine D_1-like/D_2-like receptor antagonist.

In a recent study, we found that in the NAcc shell, 1) the $GABA_A$ receptor agonist muscimol (50 ng) inhibits the shell-specific dopaminergic pivoting and its antagonist bicuculline (200 ng) does not affect the pivoting, and 2) both the $GABA_B$ receptor agonist baclofen (100 ng) and antagonist 2-hydroxysaclofen (2 μg) reduce the pivoting (24). Considering the above-mentioned neuronal connections between the core and the shell (25) together with our recent findings (24), it is reasonable to assume that when GABAergic agents are administered into the core they will also produce effects. To test this possibility in the present study, we used a previously reported methodology to examine pivoting evoked by systemic administration of dopamine D_1-like/D_2-like receptor agonists in rats with unilateral blockade of dopamine D_1-like/D_2-like receptors in the VLS (1,14,26).

Materials and Methods

Animals and surgery

Male Wistar rats (Saitama Experimental Animals Supply, Japan) weighing 190-210 g at the time of the operation were housed in cages (27 × 45 × 20 cm) that were kept at a 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.

For stereotaxic implantation of cannulae, the rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic apparatus (Narishige, Japan). Guide cannulae (0.5 mm o.d., 0.3 mm i.d., 6 mm length) were implanted into the VLS (A 8.6 mm, V 3.0 mm, L 4.0 mm from the interaural line) and the core of the NAcc (A 10.6 mm, V 3.0 mm, L 1.5 mm from the interaural line), according to the atlas of Paxinos and Watson (27). The cannulae were secured to the skull with stainless screws and dental acrylic cement. The NAcc cannulae were angled 21° from the midsagittal plane to avoid the ventricular system. Damage to the target site was minimized by implanting the tips of the guide cannulae 1.2 mm (core) or 1.9 mm (VLS) above the desired injection site. A wire stylet was placed in the guide cannula to prevent occlusion. The rats were then allowed to recover from the operation for a minimum of five days.

The experiments were performed in accordance with Institutional Guidelines in the Care and Use of Experimental Animals. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Intracerebral microinjection and drugs

The drugs used were: muscimol (5-aminomethyl-3-hydroxyisoxazole; Sigma), a $GABA_A$ receptor agonist; (-)-bicuculline methbromide (Research Biochemicals International), a $GABA_A$ receptor antagonist; *R*(+)-baclofen hydrochloride(*R*(+)-β-(aminomethyl)-4-chlorobenzenepropanoic acid hydrochloride; Sigma), a $GABA_B$ receptor agonist; 2-hydroxysaclofen ((+)-3-amino-2-(4-chlorophenyl)-2-hydroxypropane sulfonic acid; Sigma), a $GABA_B$ receptor antagonist; (±)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (SKF 38393, Sigma), a dopamine D_1-like receptor agonist; quinpirole hydrochloride (LY 171555; Research Biochemicals International), a dopamine D_2-like receptor agonist; *cis(Z)*-flupentixol dihydrochloride (Lundbeck), a non-selective dopamine receptor antagonist. All drugs were dissolved in saline (0.9% w/v NaCl solution) immediately before use. For unilateral intracerebral microinjection, the rats were held manually while the

stylets were removed, and the injection needles (0.22 mm) were lowered through the guide cannulae so that they protruded 1.2 mm (core) or 1.9 mm (VLS) beyond the tip. The needles were connected to Hamilton syringes and the drugs were slowly given by hand in a volume of 0.2 μl over 20 s, after which the needles were left in place for a further 20 s. Ten minutes before drug injection, *cis(Z)*-flupentixol was unilaterally administered into the VLS at the side contralateral to the core injection. A mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) was injected intraperitoneally immediately after the core injection. The doses of the drugs employed in the present study have previously been found to be highly effective in studies on locomotion and turning behavior (14,23,28). The animals were used only once.

Behavioral methods

The rats were placed individually in a circular Perspex chamber (60 cm diameter, 30 cm high) at least 1 h before the start of the experiment. To allow detailed observation of the turning behavior, limb stepping patterns and spinal curvature, a mirror was mounted underneath the chamber at an angle of 30° and the image was recorded on videotape for off-line analysis. Type of turning behavior, i.e., circling or pivoting, was assessed, using the following definitions. Circling is marked by 1) normal hindlimb stepping, 2) normal forelimb stepping, 3) turns with large diameter (> 30 cm), 4) normal, sequential display of lateral movements of the head, torso and pelvis, and 5) running. In contrast, pivoting is marked by 1) abnormal hindlimb stepping that is characterized by the sequential occurrence of a closing and an open step, 2) head-to-tail turns of a very small diameter (< 20 cm), 3) normal, sequential display of lateral movements of the head, torso and pelvis, and 4) spinning around one hindlimb (for details see reference 2). Contraversive and ipsiversive turnings (defined as complete 360° turns) were counted visually by a trained observer. The behavior was analyzed during consecutive 5-min periods for 180 min, starting immediately after injection. Behavioral testing was performed between 1000 and 1700 h.

Histology

At the end of each experiment, the rats were deeply anesthetized with halothane and perfused transcardially with 10% formalin. The brains were removed, sectioned (50 μm) and stained with cresyl violet to visualize the injection sites. Only data of rats with correctly placed injections were included in the analysis (Fig. 1).

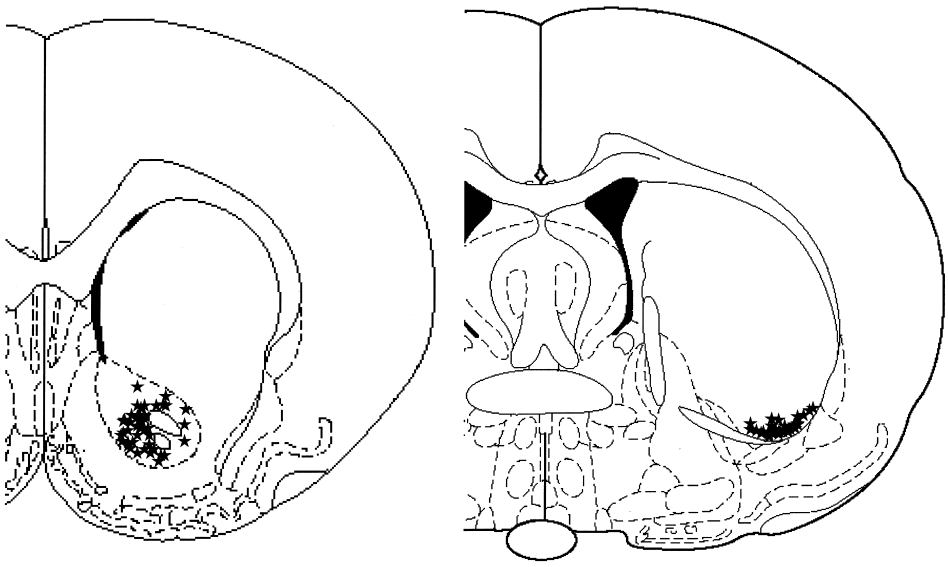

Fig. 1 Location of injection sites in the nucleus accumbens core and ventrolateral striatum. Planes are modified to a series of 2 or 3 sections for each brain area from the atlas of Paxinos and Watson (27); approximate coordinates indicated are in mm anterior to the interaural line.

Data analysis

All values are expressed as mean ± S.E.M. One-way analysis of variance (ANOVA) followed by a post hoc Tukey's test was used to compare groups where appropriate. In addition, a *t*-test assuming unequal variances was used to analyze antagonistic effects where appropriate. Differences were considered significant when $P < 0.05$.

Results

Effects of $GABA_A$ and $GABA_B$ receptor agents injected into the core of the NAcc

Unilateral injections of saline (0.2 μl, n = 6; control group) into the core of the NAcc did not elicit significant turning behavior (Table 1). Neither muscimol (50 ng, n = 7) nor bicuculline (200 ng, n = 6) injected unilaterally into the core of the NAcc elicited significant turning behavior when compared to the saline injections. In addition, neither baclofen (100 ng, n = 6) nor 2-hydroxysaclofen (2 μg, n = 6) injected unilaterally into the core elicited significant turning behavior when compared to the saline injections ($F_{4,26} = 1.62$, $P = 0.20$; Table 1).

Effects of $GABA_A$ receptor agents injected into the core of the NAcc on pivoting elicited by the i.p. injection of a mixture of SKF 38393 and quinpirole

As reported previously (14), in rats pretreated with unilateral injections of *cis(Z)*-flupentixol (10 μg) into the VLS and saline into the core of the NAcc of the contralateral side, i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) elicited contraversive pivoting, namely pivoting away from the side of the core injection (n = 7) (Fig. 2). This contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 and quinpirole was suppressed significantly by muscimol (50 ng, n = 7) when injected into the core of the NAcc instead of saline ($P < 0.05$, *t*-test; Fig. 2), while the contraversive pivoting was not affected by injection of bicuculline (200 ng, n = 6) into the same site ($P = 0.73$, *t*-test; Fig. 3).

Table 1 Effects of $GABA_A$ and $GABA_B$ receptor agents injected unilaterally into the core of the nucleus accumbens on rat contraversive turning

Drugs		Contraversive turning / 180min
saline		4.5 ± 0.9
muscimol	50 ng	5.0 ± 1.0
bicuculline	200 ng	10.5 ± 3.8
baclofen	100 ng	4.8 ± 1.7
2-hydroxysaclofen	2 μg	4.9 ± 1.1

(mean ± S.E.M.)

Effects of $GABA_B$ receptor agents injected into the core of the NAcc on pivoting elicited by the i.p. injection of a mixture of SKF 38393 and quinpirole

The contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) was suppressed by baclofen (100 ng, n = 6) when injected into the core of the NAcc instead of saline ($P < 0.05$, *t*-test; Fig. 4). The contraversive pivoting was also suppressed by injection of 2-hydroxysaclofen into the same site (2 μg, n = 6) ($P < 0.05$, *t*-test; Fig. 5).

Discussion

The goal of the present study was to analyze the role of $GABA_A$ and $GABA_B$ receptors in the core of the NAcc in rat turning behavior. In the first series of experiments, the behavioral responses to unilateral injections of $GABA_A$ and $GABA_B$ receptor agonists and antagonists in the core of the NAcc were studied. Once it became evident that none of the GABAergic agents alone elicited turning behavior, we further investigated our hypothesis that $GABA_A$, but not $GABA_B$, receptors in the NAcc core control dopamine-dependent pivoting in a way similar to that of $GABA_A$ receptors in the shell.

The present study demonstrated that neither unilateral injections into the core of the NAcc of the $GABA_A$ receptor agonist muscimol (50 ng) nor the antagonist bicuculline (200 ng) elicited significant changes in turning behavior when compared to that seen with saline injection into the core (Table 1). Additionally neither injections into the core of the NAcc of the $GABA_B$ receptor agonist baclofen (100 ng) nor the antagonist 2-hydroxysaclofen (2 μg) elicited significant changes in turning behavior when compared to saline injection into the core (Table 1). Given that our previous results documented that neither unilateral intra-shell injections of a $GABA_A$ nor $GABA_B$ receptor agonist and antagonist respectively produced significant changes in turning behavior when compared to saline injection into the shell (24), it can be concluded that the $GABA_A$ and $GABA_B$ receptors located in both the shell and the core may not be crucially involved in the production of turning behavior. This conclusion also partly explains previously reported inconsistencies among the studies examining the roles of $GABA_A$ and $GABA_B$ receptors in the production of locomotor behavior (23,29-31).

The contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) after unilateral injection of *cis(Z)*-flupentixol (10 μg) into the VLS and saline into the core of contralateral side of the VLS was inhibited by muscimol (50 ng), but not bicuculline (200 ng) injections into the core of the NAcc

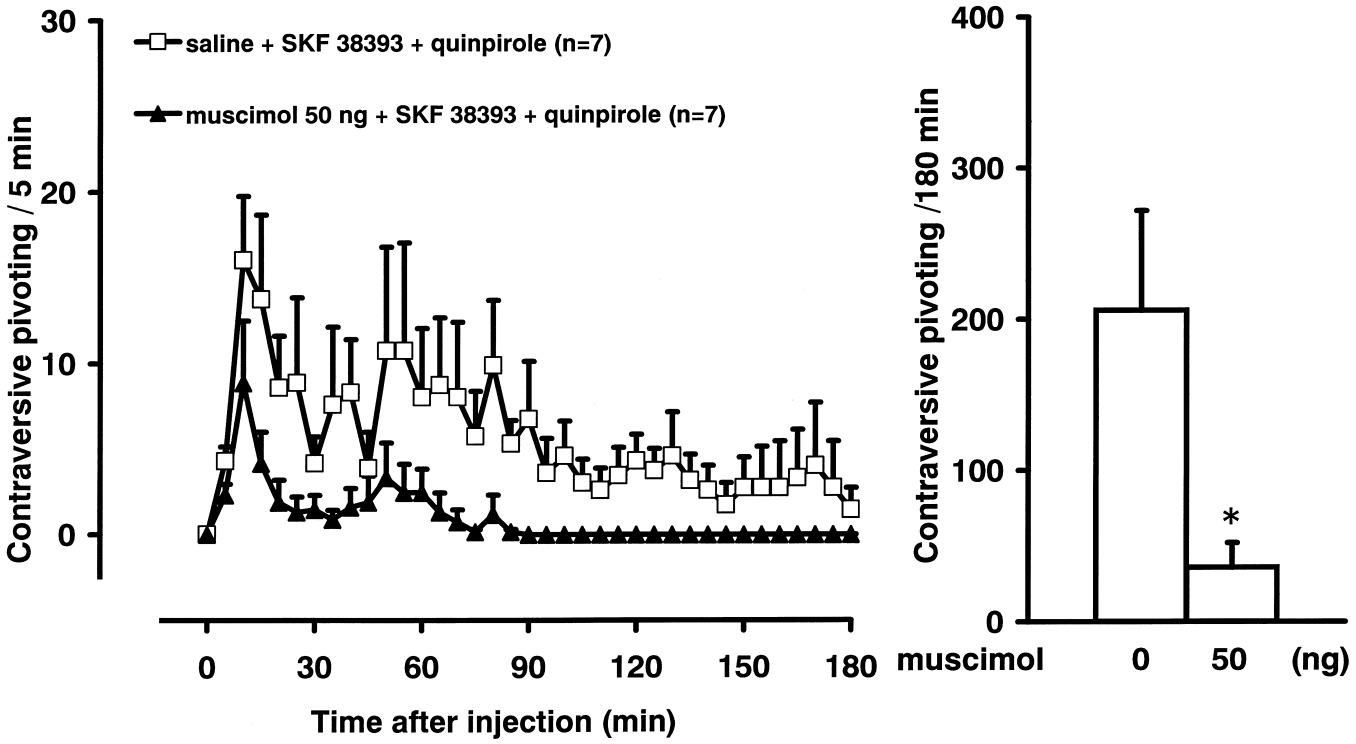

Fig. 2 Effects of muscimol (50 ng: n = 7) injected into the nucleus accumbens core on contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) after unilateral injections of *cis(Z)*-flupentixol (10 μg) into the ventrolateral striatum and saline into the nucleus accumbens core (n = 7). *$P < 0.05$ (*t*-test).

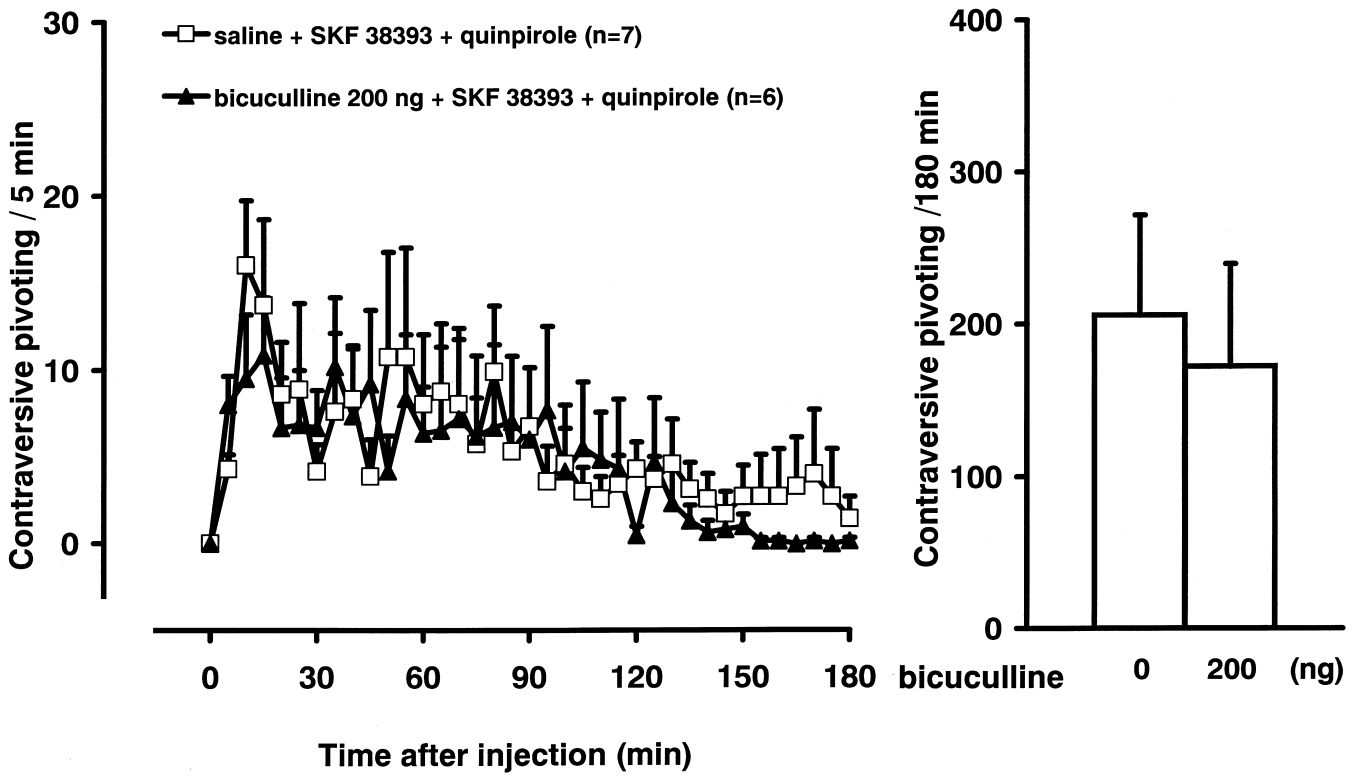

Fig. 3 Effects of bicuculline (200 ng: n = 6) injected into the nucleus accumbens core on contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) after unilateral injections of *cis(Z)*-flupentixol (10 μg) into the ventrolateral striatum and saline into the nucleus accumbens core (n = 7).

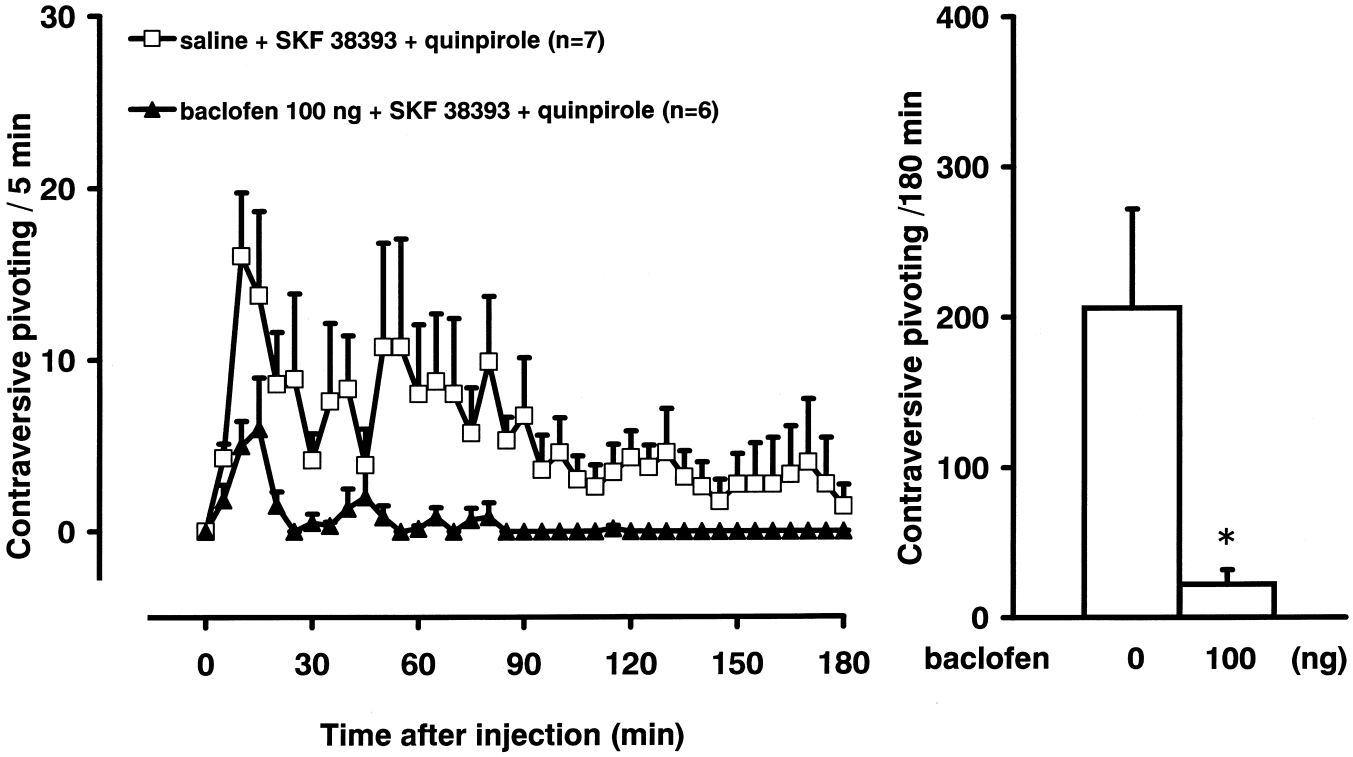

Fig. 4 Effects of baclofen (100 ng: n = 6) injected into the nucleus accumbens core on contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) after unilateral injections of *cis(Z)*-flupentixol (10 μg) into the ventrolateral striatum and saline into the nucleus accumbens core (n = 7). $^*P < 0.05$ (*t*-test).

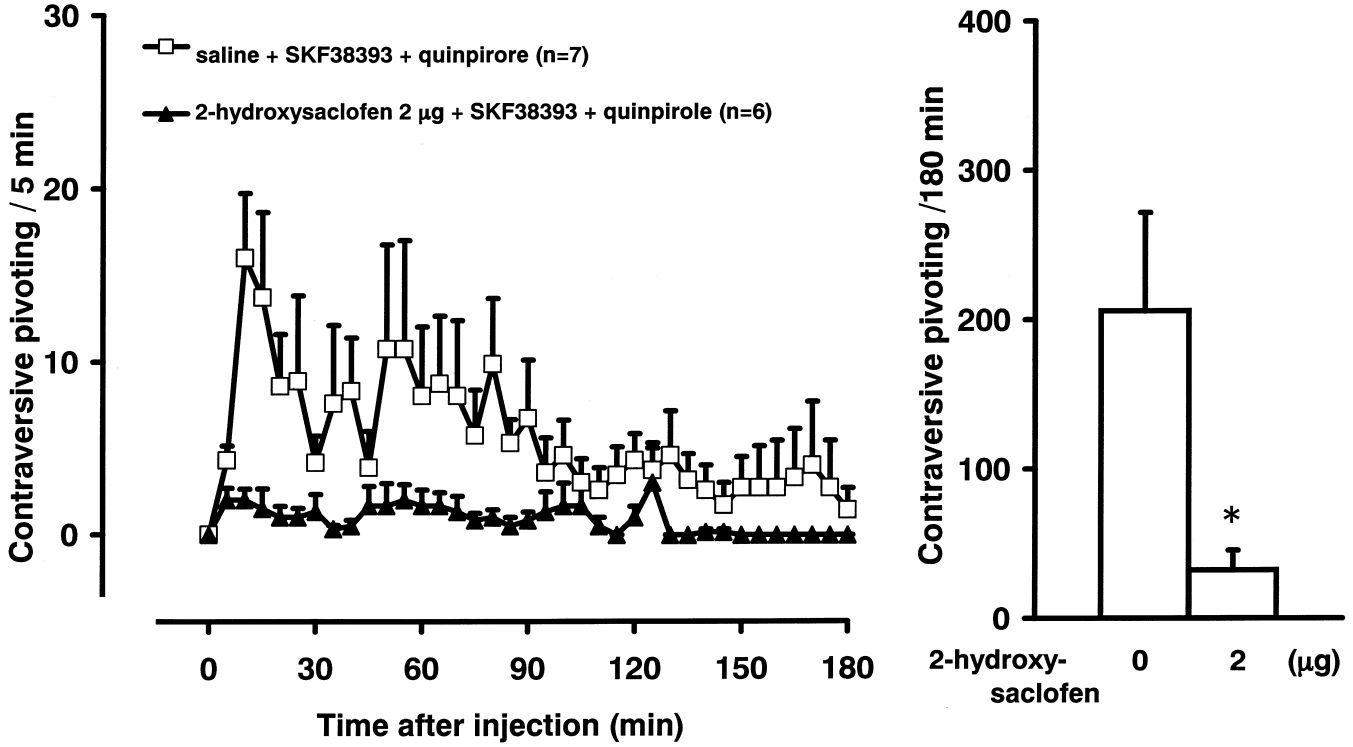

Fig. 5 Effects of 2-hydroxysaclofen (2 μg: n = 6) injected into the nucleus accumbens core on contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 (3 mg/kg) and quinpirole (1 mg/kg) after unilateral injections of *cis(Z)*-flupentixol (10 μg) into the ventrolateral striatum and saline into the nucleus accumbens core (n = 7). $^*P < 0.05$ (*t*-test).

(Figs. 2 and 3). These results are very similar to our previous results in the shell that showed that muscimol (50 ng), but not bicuculline (200 ng) inhibited shell-specific dopamine D_1-like/D_2-like receptor-mediated pivoting (24). The present results are also consistent with the previous reports showing inhibitory control of accumbal $GABA_A$ receptors upon dopamine release (19) and dopamine-dependent hyperlocomotion (20-22). Taking all these reports into consideration, it can be concluded that the inhibitory effect of muscimol injected into the core on dopamine D_1-like/D_2-like receptor-mediated pivoting was $GABA_A$ receptor specific.

On the other hand, the contraversive pivoting induced by i.p. injection of a mixture of SKF 38393 and quinpirole after unilateral injection of *cis(Z)*-flupentixol into the VLS was inhibited by both baclofen (100 ng) and 2-hydroxysaclofen (2 μg) (Figs. 4 and 5). Given the previous results that the shell-specific dopamine D_1-like/D_2-like receptor-mediated pivoting is also inhibited by both baclofen (100 ng) and 2-hydroxysaclofen (2 μg) injected into the shell (24), it is unlikely that $GABA_B$ receptors in the NAcc modulate the dopamine-dependent contraversive pivoting because both agonist and antagonist of the $GABA_B$ receptor show similar inhibition in both the core and the shell. Thus, the inhibition induced by baclofen and 2-hydroxysaclofen is unlikely to be due to a pharmacological but rather due to an unknown functional inhibition.

In conclusion, the present study demonstrates that neither $GABA_A$ nor $GABA_B$ receptor stimulation in the core of the NAcc produce turning behavior, and it is suggested that $GABA_A$ receptors, but not $GABA_B$ receptors, in the core of the NAcc modulate the contraversive pivoting induced by dopamine D_1-like/D_2-like receptor stimulation.

Acknowledgments

This work was supported by Research Grants from the Sato Fund (N.K.) and the Dental Research Center (N.K), Nihon University School of Dentistry; a grant for promotion of multidisciplinary research projects (N.K.) and a grant-in-aid for scientific research (# 14370609 to N.K.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan; and The Promotion and Mutual Aid Corporation for Private Schools in Japan (G.A., S.M., N.K.).

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