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D_2 Receptors in the Ventrolateral Striatum Are Involved in Feeding Behavior in Rats

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INOUE, K., N. KIRIIKE, Y. FUJISAKI, M. OKUNO, H. ITO AND S. YAMAGAMI. *D_2 receptors in the ventrolateral striatum are involved in feeding behavior in rats.* PHARMACOL BIOCHEM BEHAV **50(2)** 153-161, 1995. – To study the role of dopamine D_1 and D_2 receptors in the ventrolateral striatum in feeding behavior, a D_1 receptor agonist (CY 208-243), a D_1 receptor antagonist (SCH 23390), a D_2 receptor agonist (quinpirole), and a D_2 receptor antagonist [(−)-sulpiride] were perfused via a microdialysis probe into the ventrolateral striatum of rats fasted for 22 h. Then the rats were allowed to feed freely for 6 h. Sulpiride perfusion at a high concentration suppressed food and water intake significantly, whereas dopamine release and the levels of DOPAC and HVA were increased at all concentrations. In contrast, quinpirole perfusion at a high concentration increased food intake by 41%. Dopamine release and the levels of DOPAC and HVA were decreased at all concentrations. On the other hand, neither CY 208-243 nor SCH 23390 changed food intake or dopamine release, but both drugs decreased water intake. These results suggest that D_2 receptors in the ventrolateral striatum have a more important role than D_1 receptors in the feeding behavior of rats.

Feeding behavior D_1 receptor D_2 receptor Dopamine Microdialysis Ventrolataral striatum Sulpiride Quinpirole SCH 23390 CY 208-243

THE MESOLIMBIC dopaminergic system may be primarily involved with the sensory input, reflexes, and reward and memory processes related to feeding behavior (17,18), whereas the nigrostriatal dopaminergic system may be more involved in stereotypic licking, biting, and gnawing movements (5,15, 23). Several investigators have reported a heterogeneity of organization in the striatum (16,29) and have suggested different roles for various striatal subregions in the control of certain motor functions. In the rat, the medial striatum mainly receives projections from the medial frontal cortex and is selectively involved in the performance of spatial learning tasks (11,12,25). In contrast, the lateral striatum mainly receives projections from the dorsolateral frontoparietal cortex and is involved in the motor control of segmental movements such as tongue and forelimb movements (7,28,37). It has recently been shown that the ventrolateral striatum is closely involved in the motor control of oral activity (22,28) and feeding behavior (30). In fact, studies using in vivo microdialysis have demonstrated that dopamine release in the ventrolateral striatum is increased by spaced-interval feeding or time-restricted scheduled feeding (8,21).

Recently, a number of investigators have studied the role of dopamine D_1 and D_2 receptors in the synthesis, release, and metabolism of dopamine using specific D_1 and D_2 receptor agonists and antagonists (2,3,5,34). Previous studies reported that the nigrostriatal dopaminergic pathway is largely regulated by dopamine autoreceptors of the D_2 type (29), and that the release of dopamine from the dorsal striatum was stimulated by D_2 receptor antagonists to a lesser degree than by D_1 receptor antagonists, whereas D_2 receptor agonists decreased dopamine release and D_1 receptor agonists had no effect on it (19). It was demonstrated, by using microdialysis, that a specific dopamine D_2 receptor antagonist (raclopride) dose-dependently increased the release of dopamine and its metabolites [3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] in the ventrolateral striatum (33). A dopamine D_1 receptor antagonist (SCH 23390) also produced an increase of dopamine, DOPAC, and HVA, but to a lesser extent than raclopride, whereas the D_1 agonist SKF 38393 had no influence on the release or metabolism of dopamine at any dose tested. However, the relationship of D_1 and D_2 receptors in the ventrolateral striatum to motor function has never been

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studied. Therefore, the present study was performed to assess the influence of dopamine D_1 and D_2 receptors in the ventrolateral striatum on feeding behavior.

Using the microdialysis technique, a D_1 receptor agonist [CY 208-243 (14,24)], a D_1 receptor antagonist (SCH 23390), a D_2 receptor agonist [quinpirole (35)], and a D_2 receptor antagonist [(−)-sulpiride] were perfused into the ventrolateral striatum. Then the extracellular concentrations of dopamine, DOPAC, and HVA as well as the food intake (as an index of oral activity) were measured hourly during a 6-h free-feeding period following 22 h of fasting.

METHOD

Animals and Drug Treatment

Female Wistar rats (Keari Co., Japan) weighing 180–210 g were used in this study. The rats were housed individually and were fed laboratory chow (24.8% crude protein, 4.4% crude fat, 3.5% crude fiber, 7.0% crude ash, 51.6% nitrogen-free extract, 8.7% water; 345.2 cal/100 g) and water ad lib. They were kept in plastic cages (30 × 30 × 35 cm) with a 12L : 12D cycle (lights on 0800–2000 h) and the ambient temperature regulated to 22 ± 2°C. Animals were cared for in compliance with the Guidelines for Animal Experimentation of Osaka City University.

The following drugs were used: CY 208-243 {(−)-4,6,6a, 7,8, 12b-hexahydro-7-methylindolo[4,3-ab]-phenanthridine (Sandoz Pharmaceutical Ltd., Switzerland)}, SCH 23390 [*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5,-tetrahydro-1*H*-3-benzazepine hydrochloride (Research Biochem, Inc., USA)], (−)-quinpirole hydrochloride (Research Biochem), and (−)-sulpiride (Sigma Chemical Co., USA). CY 208-243, SCH 23390, and quinpirole were dissolved in Ringer's solution (149 mM NaCl, 1.3 mM KCl, and 1.5 mM $CaCl_2$) before use, whereas (−)-sulpiride was dissolved in water with H_2SO_4 and then diluted with Ringer's solution.

Surgery and Microdialysis

Rats were anesthetized with chloral hydrate (400 mg/kg, IP) and a dialysis guide cannula was implanted in the left ventrolateral striatum of each animal according to the following coordinates from the atlas of Paxinos and Watson (27) (AP +0.5 mm, L +3.0 mm, V −3.5 mm from bregma and the dural surface). The cannula was secured to the skull with a screw and dental cement and a wire stylet was placed in the guide to keep it free of debris. A 10-day period was allowed for the rats to recover from surgery.

Drug Perfusion

On the day of the experiment, a dialysis probe with a 3-mm-long cellulose tip was inserted into the guide cannula. Ringer's solution was continuously perfused through the probe at a flow rate of 1 μl/min. After the basal levels of extracellular dopamine, DOPAC, and HVA became stable, six 20-min baseline samples were collected during a 2-h period (0900–1100 h) following 20 h of food deprivation. Then Ringer's solution containing either CY 208-243 (3.3×10^{-2} or 3.3 fg/μl), SCH 23390 (3.24 or 324 pg/μl), quinpirole (2.56×10^{-2} or 2.56×10^{-1} pg/μl), or sulpiride (0.05, 0.5, or 2.5 μg/μl) was perfused into the ventrolateral striatum for 6 h (1100–1700 h) through a microdialysis probe. These doses were determined according to previous reports (1,14,20,31). Perfusion of Ringer's solution alone was performed as a control. Each group consisted of five to seven rats. The animals were allowed free access to food and water, and both the food and water intakes were measured hourly. At the end of the experiment, the animals were killed and their brains were removed and frozen. Examination of the cannula track was carried out using thin sections cut with a razor blade. The track was found to be correctly located and to terminate within the ventrolateral striatum in all rats.

High Performance Liquid Chromatography (HPLC)

To quantify the levels of dopamine, DOPAC, and HVA in the dialysate, samples were collected every 20 min and injected through an automatic injector (AS-10, Eicom, Japan) into a HPLC apparatus with an electrochemical detector (EP-10 and ECD-100, Eicom) and an ODS reverse-phase column (Eicompac MA-5ODS, Eicom). The mobile phase consisted of 80% (v/v) 0.1 M KH_2PO_4, 20% (v/v) methanol, 150 mg/l sodium octane sulphonate, and 10 μM EDTA2Na. Detection was performed using a graphite working electrode coupled to the electrochemical detector.

Statistical Analysis

For the analysis of food and water intake, one-factor ANOVA was performed. Then, if appropriate, comparisons between the control group and each drug-treated groups were carried out using Student's *t*-test (two-tailed).

Due to the large variations of the basal extracellular concentrations of dopamine, DOPAC, and HVA among the individual rats, the data for each parameter were normalized as a percentage of the mean value in the six samples taken prior to the feeding trial. Then Welch's test was used to compare the control and experimental values obtained at any particular period.

RESULTS

Basal Levels of Dopamine and Its Metabolites

The mean ± SEM basal extracellular levels of dopamine, DOPAC, and HVA were 367.67 ± 30.68 fmol/20 μl, 29.10 ± 2.37 pmol/20 μl, and 15.44 ± 1.04 pmol/20 μl, respectively.

Effect of CY 208-243

CY 208-243 (3.3×10^{-2} or 3.3 fg/μl/min) did not change food intake, but it decreased water intake slightly compared with the control level, and the difference was significant in the second and fifth hours (both $p < 0.05$; Tables 1 and 2).

The effect of CY 208-243 on the extracellular concentrations of dopamine, DOPAC, and HVA is shown in Fig. 1. No significant differences from the control levels were observed at any concentration of CY 208-243, although continuous perfusion with both Ringer's solution and CY 208-243 tended to gradually decrease dopamine release over the 6-h experimental period.

Effect of SCH 23390

SCH 23390 did not change food intake, but it decreased water intake significantly in the second hour at a dose of 324 pg/μl/min (Tables 1 and 2).

The effect of SCH 23390 on the extracellular concentrations of dopamine, DOPAC, and HVA is shown in Fig. 2. There was no change in the release of dopamine, but the DOPAC and HVA levels gradually decreased during the 6-h perfusion period. Although there was no significant difference in the HVA level between the control and SCH 23390-treated

TABLE 1

EFFECT OF VARIOUS DRUGS ON THE FOOD INTAKE OF FASTED RATS

Treatment	n	Food Intake (g) 1 h	2 h	3 h	4 h	5 h	6 h
Ringer's solution (control)	7	3.8 ± 1.0	4.7 ± 1.2	5.3 ± 1.2	7.6 ± 1.6	8.9 ± 1.2	10.5 ± 1.5
CY 208-243							
3.3×10^{-2} (fg/μl/min)	7	2.9 ± 0.7	3.9 ± 0.8	5.1 ± 1.0	6.6 ± 1.3	7.5 ± 1.2	8.4 ± 1.3
3.3 (fg/μl/min)	5	3.6 ± 0.7	4.6 ± 1.0	5.3 ± 0.8	6.2 ± 0.8	7.1 ± 0.9	7.5 ± 1.0
SCH 23390							
3.24 (pg/μl/min)	6	4.1 ± 1.0	5.7 ± 1.7	6.8 ± 1.7	8.1 ± 1.7	10.9 ± 1.8	11.4 ± 1.8
324 (pg/μl/min)	5	3.5 ± 0.3	4.0 ± 0.2	6.2 ± 0.4	7.3 ± 0.7	9.3 ± 1.0	11.1 ± 1.0
Quinpirole							
2.56×10^{-2} (pg/μl/min)	5	2.6 ± 0.4	3.4 ± 0.4	4.6 ± 0.4	5.9 ± 0.7	7.2 ± 0.2	8.8 ± 0.8
2.56×10^{-1} (pg/μl/min)	5	4.6 ± 0.6	5.4 ± 0.4	7.5 ± 0.3*	9.0 ± 0.7	9.8 ± 0.6	12.7 ± 0.9
Sulpiride							
0.05 (μg/μl/min)	5	6.2 ± 0.8	7.4 ± 1.0	9.3 ± 1.5	10.2 ± 1.3	12.7 ± 2.6	13.9 ± 3.0
0.5 (μg/μl/min)	6	5.6 ± 1.1	6.7 ± 1.1	7.7 ± 1.2	8.4 ± 1.0	8.5 ± 1.0	9.2 ± 0.6
2.5 (μg/μl/min)	6	3.7 ± 0.6	4.2 ± 0.8	4.7 ± 0.7	4.9 ± 0.8	5.7 ± 0.6*	6.2 ± 0.6†

Cumulative food intake during perfusion of Ringer's solution, CY 208-243, SCH 23390, quinpirole, and sulpiride into the ventrolateral striatum for 6 h. Values are the mean ± SEM.

*$p < 0.1$, †$p < 0.05$ vs the control group.

groups, the DOPAC level showed a transient significant reduction in the SCH 23390 group ($p < 0.05$).

Effect of Quinpirole

Perfusion with quinpirole at 2.56×10^{-1} pg/μl/min increased food intake nonsignificantly ($0.05 < p < 0.1$) by 41% relative to the control value in the third hour, but did not change water intake throughout the experimental period (Tables 1 and 2).

The effect of quinpirole on the extracellular concentrations of dopamine, DOPAC, and HVA is shown in Fig. 3. Quinpirole perfusion at 2.56×10^{-2} pg/μl/min decreased dopamine release transiently but significantly, and there was a trend toward sustained decrease of dopamine release at 2.56×10^{-1} pg/μl/min. The DOPAC and HVA concentrations were also decreased significantly ($p < 0.05$), with the maximal fall being to about 70% and 50% of the basal level, respectively. The decrease of these dopamine metabolites did not occur in a concentration-dependent manner.

Effect of Sulpiride

Sulpiride perfusion at 2.5 μg/μl/min decreased food intake in the sixth hour ($p < 0.05$), and it decreased water intake at both 0.5 and 2.5 μg/μl/min. The difference in the cumulative

TABLE 2

EFFECT OF VARIOUIS DRUGS ON THE WATER INTAKE OF FASTED RATS

Treatment	n	Water Intake (g) 1 h	2 h	3 h	4 h	5 h	6 h
Ringer's solution (control)	7	6.2 ± 0.8	11.2 ± 1.7	13.7 ± 2.3	18.0 ± 2.9	20.4 ± 2.5	23.9 ± 3.0
CY 208-243							
3.3×10^{-2} (fg/μl/min)	7	4.0 ± 0.4*	6.0 ± 0.3†	8.9 ± 0.8	11.5 ± 1.0*	13.9 ± 1.4*	15.8 ± 1.4*
3.3 (fg/μl/min)	5	4.8 ± 0.9	6.9 ± 1.0*	8.8 ± 1.2	11.0 ± 1.4*	12.9 ± 1.6†	15.2 ± 2.2*
SCH 23390							
3.24 (pg/μl/min)	6	7.3 ± 1.1	9.9 ± 0.9	13.0 ± 1.6	16.0 ± 1.7	19.2 ± 2.1	21.4 ± 2.1
324 (pg/μl/min)	5	5.6 ± 0.4	6.3 ± 1.2†	11.4 ± 0.9	14.0 ± 1.3	17.0 ± 1.5	18.3 ± 1.5
Quinpirole							
2.56×10^{-2} (pg/μl/min)	5	4.6 ± 1.0	6.9 ± 2.4	9.5 ± 1.1	12.2 ± 1.9	14.7 ± 1.5	17.6 ± 2.8
2.56×10^{-1} (pg/μl/min)	5	6.9 ± 0.6	9.2 ± 0.9	12.1 ± 0.8	15.3 ± 0.6	17.0 ± 0.5	20.6 ± 0.5
Sulpiride							
0.05 (μg/μl/min)	5	6.3 ± 0.9	8.5 ± 1.1	13.5 ± 2.7	16.6 ± 3.3	20.4 ± 4.3	22.5 ± 5.2
0.5 (μg/μl/min)	6	4.6 ± 0.5	6.4 ± 1.7*	8.6 ± 1.4	8.9 ± 1.2†	10.2 ± 1.0†	10.6 ± 0.9†
2.5 (μg/μl/min)	6	5.5 ± 0.7	6.6 ± 0.9*	9.0 ± 1.2	10.0 ± 1.4*	11.0 ± 1.8†	12.5 ± 2.4†

Cumulative water intake during perfusion of Ringer's solution, CY 208-243, SCH 23390, quinpirole, and sulpiride into the ventrolateral striatum for 6 h. Values are the mean ± SEM.

*$p < 0.1$, †$p < 0.05$ vs the control group.

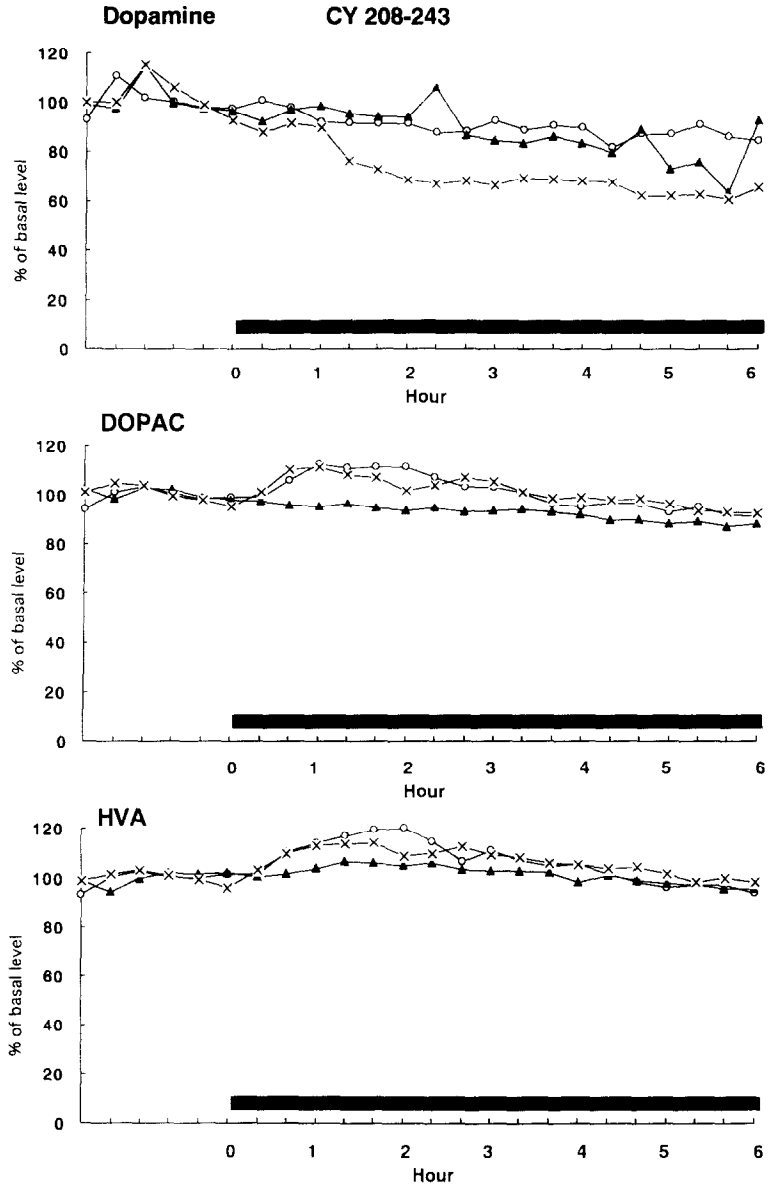

FIG. 1. Changes of the striatal extracellular concentrations of dopamine, DOPAC, and HVA during perfusion of CY 208-243 (black bar) into the ventrolateral striatum for 6 h. Empty circles, filled triangles, and crosses represent the control group ($N = 7$), the 3.3×10^{-2} fg/μl/min group ($N = 7$), and the 3.3 fg/μl/min group ($N = 5$), respectively. Mean values are shown. $*p < 0.05$ vs. the control group.

water intake was significant ($p < 0.05$) after the fourth hour of perfusion at 0.5 μg/μl/min and after the fifth hour of perfusion at 2.5 μg/μl/min (Tables 1 and 2).

The effect of sulpiride on the extracellular concentrations of dopamine, DOPAC, and HVA is shown in Fig. 4. Sulpiride increased dopamine release within 1 h at each concentration tested, but the increase was significant only in the 2.5 μg/μl/min group. In addition, the extent and duration of dopamine release were not dependent on the concentration of sulpiride, with the increased release persisting for at least 4 h and then gradually lessening. The DOPAC and HVA concentrations were significantly increased ($p < 0.05$), with the maximal changes being about 80% and 120%, respectively. These increases were not concentration dependent.

DISCUSSION

In this study, neither perfusion of a D_1 receptor agonist (CY 208-243) nor a D_1 receptor antagonist (SCH 23390) into the ventrolateral striatum changed dopamine release or food intake in rats fasted for 22 h. However, water intake was slightly decreased by perfusion with these agents. In contrast, perfusion with a D_2 receptor agonist (quinpirole) at a high concentration tended to increase food intake while it de-

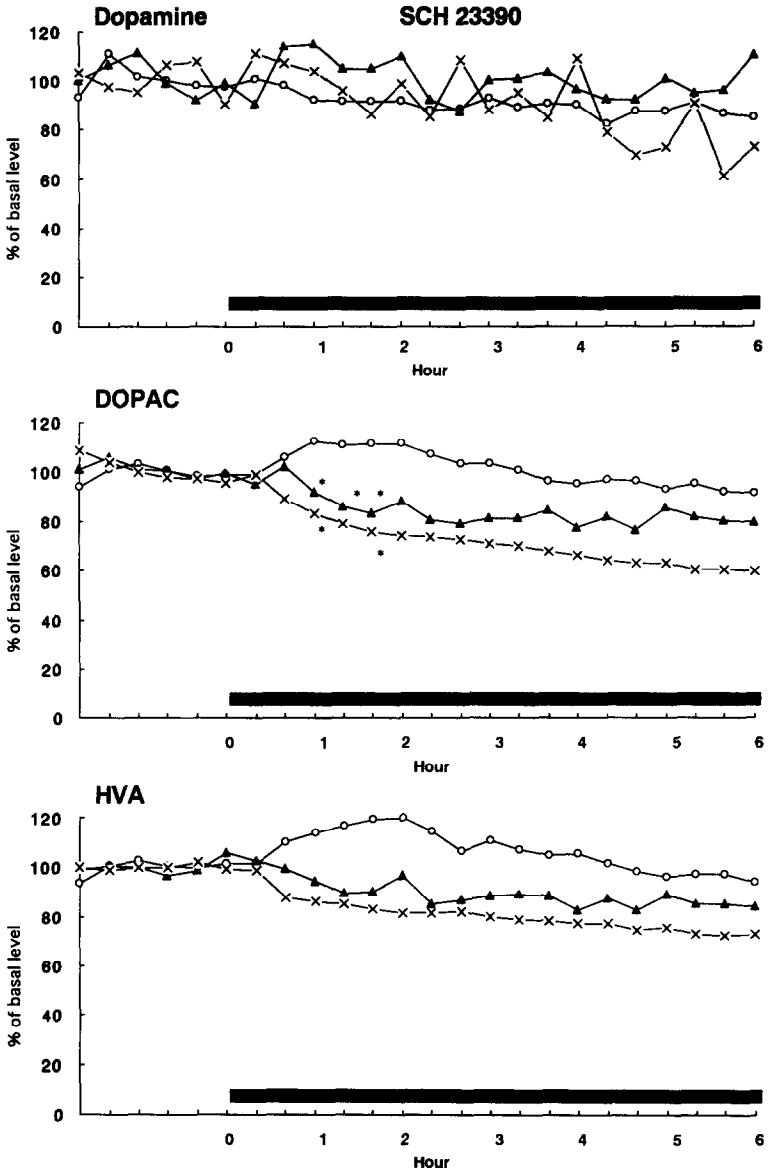

FIG. 2. Changes of the striatal extracellular concentrations of dopamine, DOPAC, and HVA during perfusion of SCH 23390 (black bar) into the ventrolateral striatum for 6 h. Empty circles, filled triangles, and crosses represent the control group (N = 7), the 3.24 pg/μl/min group (N = 6), and the 324 pg/μl/min group (N = 5), respectively. Mean values are shown. *$p < 0.05$ vs. the control group.

creased the release of dopamine and dopamine metabolites at all concentrations, whereas perfusion with a D_2 receptor antagonist (sulpiride) at a high concentration decreased both food and water intake. Furthermores, sulpiride perfusion at all concentrations increased the release of dopamine and the levels of its metabolites.

Previous studies have reported that intraperitoneal and subctaneous injection of a D_1 receptor agonist (SKF 38393) had no effect on dopamine (19,33). However, the reported effects of SCH 23390 on dopamine metabolism are inconsistent. For example, intraperitoneal injection of SCH 23390 has been variously reported to increase dopamine release (19,33) or to have no effect (39), whereas intrastriatal infusion of SCH 23390 through a dialysis probe has also been reported to increase dopamine release (20) or to have no effect (36). In this study, perfusion of the D_1 receptor agonist CY 208-243 into the ventrolateral striatum did not change dopamine release or the levels of DOPAC and HVA. These findings are consistent with the results of previous studies. SCH 23390 did not change dopamine release or the HVA level, although it transiently decreased the DOPAC level. These results are in accordance with the results of Watanabe's study (36), and suggest that SCH 23390, a D_1 receptor antagonist, did not alter the release or metabolism of dopamine.

Previous studies showed that intraperitoneal injection of the D_2 receptor agonist quinpirole (0.03, 0.1, and 0.3 mg/kg)

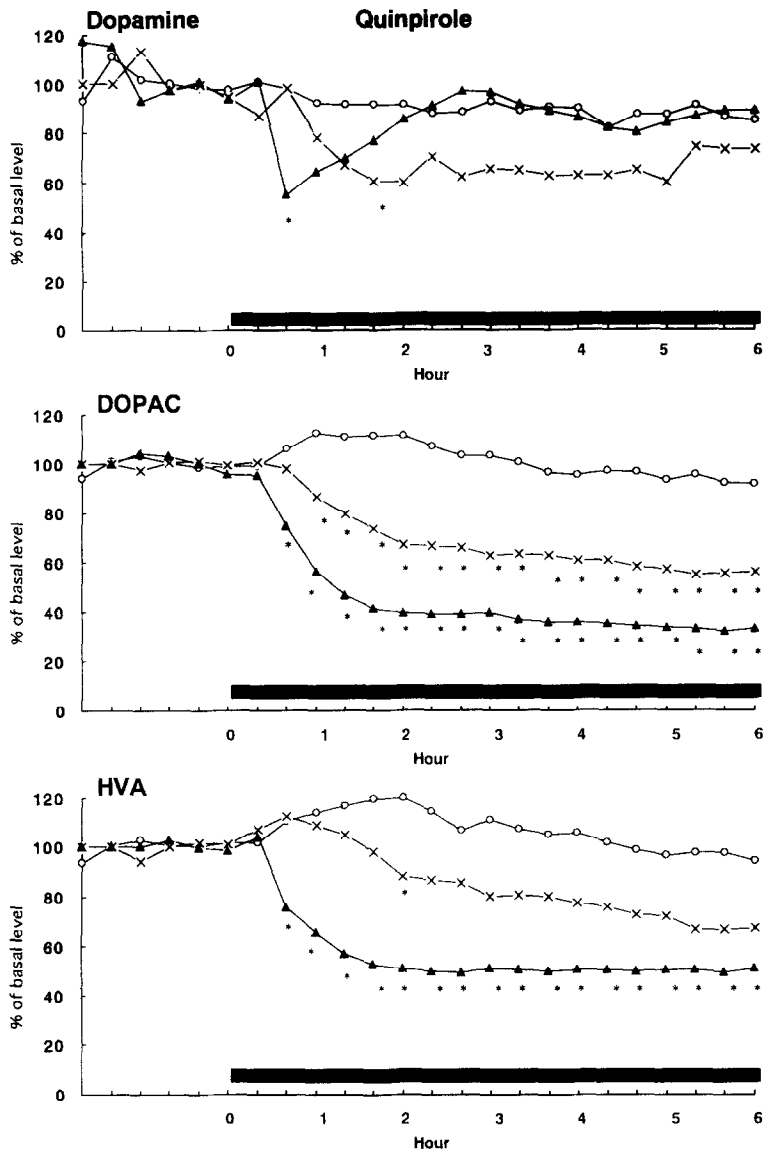

FIG. 3. Changes of the striatal extracellular concentrations of dopamine, DOPAC, and HVA during perfusion of quinpirole (black bar) into the ventrolateral striatum for 6 h. Empty circles, filled triangles, and crosses represent the control group (N = 7), the 2.56×10^{-2} pg/μl/min group (N = 5), and the 2.56×10^{-1} pg/μl/min group (N = 5), respectively. Mean values are shown. *$p < 0.05$ vs. the control group.

caused a dose-dependent decrease in the levels of dopamine, DOPAC, and HVA in the ventrolateral striatum (33). Intraperitoneal injection of the D_2 receptor antagonist raclopride dose-dependently increased the levels of dopamine, DOPAC, and HVA in the ventrolateral striatum (33). LY 171555 (quinpirole) reduced dopamine release when applied locally to the caudate via a dialysis probe at concentrations of 10^{-6} and 10^{-7} M, whereas DOPAC and HVA release remained unchanged (20). In the present study, perfusion of the ventrolateral striatum with quinpirole at 10^{-5} and 10^{-4} M (2.56×10^{-2} and 2.56×10^{-1} pg/μl) decreased not only dopamine release but also the DOPAC and HVA concentrations in a non-dose-dependent manner. In addition, sulpiride perfusion increased the release of dopamine, DOPAC, and HVA at all concentrations. These results are in accordance with See's findings regarding systemic administration of a D_2 receptor agonist and antagonist.

A few studies have already assessed the effect of D_1 receptor agonists and antagonists on feeding behavior. Peripheral administration of D_1 receptor agonists (CY 208-243 and SK&F 38393) reduced sucrose sham feeding in rats (10), whereas D_1 receptor antagonists had no effect on food intake but decreased water intake (9). However, no previous study assessed the effect of local administration of a D_1 receptor agonist and

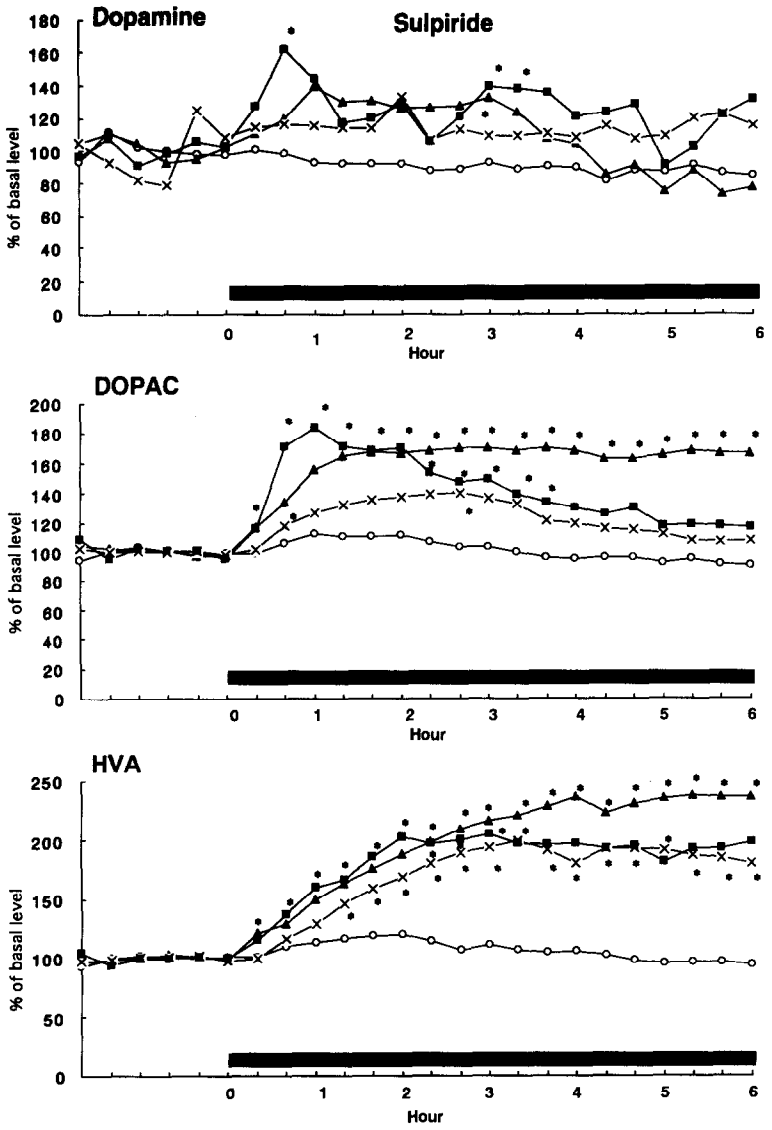

FIG. 4. Changes of the striatal extracellular concentrations of dopamine, DOPAC, and HVA during perfusion of sulpiride (black bar) into the ventrolateral striatum for 6 h. Empty circles, filled triangles, crosses, and filled squares represent the control group (N = 7), the 0.05 μg/μl/min group (N = 5), the 0.5 μg/μl/min group (N = 6), and the 2.5 μg/μl/min group (N = 6), respectively. Mean values are shown. *$p < 0.05$ vs. the control group.

antagonist into a specific brain region on food intake. Our study showed that neither CY 208-243 nor SCH 23390 changed food intake when directly perfused into the ventrolateral striatum of rats fasted for 22 h, but both agents decreased water intake. Central rather than peripheral administration of drugs is more likely to directly reflect the relationship between function and specific brain regions. If D_1 receptors were involved in water intake regulation, an opposite effect on water intake should have occurred during perfusion with a D_1 receptor agonist and antagonist. However, this was not the case, suggesting that the decreased water intake of fasted rats was not mediated by D_1 receptors in the ventrolateral striatum. Thus, our results, taken together with previous findings, suggest that D_1 receptors in the ventrolateral striatum may not be involved in the regulation of food and water intake.

Previous studies have reported that subcutaneous and intraperitoneal administration of D_2 receptor agonists reduced food intake in the rat (4,38), whereas administration of D_2 receptor antagonists increased food intake (38). It was also reported that intraperitoneal injection of lisuride (a D_2 receptor agonist) reduced food intake at all doses, although another D_2 receptor agonist, CQ 32-084, had no effect (13). On the other hand, a D_2 receptor antagonist has also been reported to suppress food intake after systemic administration (32). Thus, the effects of systemic administration of D_2 receptor agonists and antagonists on food intake are inconsistent. Intrahypo-

thalamic injection of sulpiride has been reported to suppress food intake (26). However, the effect of local administration of D_2 receptor agonists and antagonists into the ventrolateral striatum has not been assessed previously. We found that quinpirole perfusion into the ventrolateral striatum at a high concentration increased food intake by 41% relative to the control value in the third hour, whereas sulpiride perfusion at 2.5 $\mu g/\mu l$/min suppressed both food and water intake. These results suggest that D_2 receptors in the ventrolateral striatum are involved in the regulation of food intake in the rat. Water intake was suppressed by sulpiride but was not changed by quinpirole, so the effect of sulpiride perfusion on water intake may be related to its suppression of food intake.

In summary, perfusion of the ventrolateral striatum with a D_1 receptor agonist (CY 208-243) or a D_1 receptor antagonist (SCH 23390) had no effect on food intake or dopamine release. In contrast, perfusion with a D_2 receptor agonist (quinpirole) at a high concentration increased food intake by 41% relative to the control value and decreased dopamine release. In addition, perfusion with a D_2 receptor antagonist (sulpiride) at a high concentration reduced food intake significantly and increased the release of dopamine and its metabolites. These results suggest that D_2 receptors in the ventrolateral striatum rather than D_1 receptors are involved in the regulation of feeding behavior in rats.

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