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Dopamine-receptor stimulation in the prefrontal cortex ameliorates stress-induced rotarod impairment

Kazushige Mizoguchi[a,*], Mitsutoshi Yuzurihara[a], Mitsunobu Nagata[b], Atsushi Ishige[a], Hiroshi Sasaki[a], Takeshi Tabira[c]

[a]*Pharmacology Department, Central Research Laboratories, Tsumura & Co., 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-1192, Japan*
[b]*International Division, Tsumura & Co., 12-7 Nibancho, Chiyoda-ku, Tokyo 102-8422, Japan*
[c]*National Institute for Longevity Sciences, 36-3 Gengo, Morioka, Obu, Aichi 474-8522, Japan*

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Abstract

Exposure to chronic stress is thought to play an important role in the etiology of depression. In this disorder, dopaminergic dysfunction in the prefrontal cortex (PFC) is thought to be involved. Indeed, chronic stress reduces dopaminergic transmission in the rat PFC or induces a behaviorally depressive state. However, a relationship between the reduced dopaminergic activity and the behavior of the chronically stressed rats has not been proven. Here, we examined the effects of local application of a dopamine Type I (D_1) receptor-specific agonist, SKF 81297, in the PFC on the chronic-stress-induced depressive state using a rotarod test. The chronic stress produced by water immersion and restraint for 4 weeks followed by recovery for 10 days impaired the rotarod performance without changing the traction performance or locomotor activity. Although intra-PFC infusion of 1 or 10 ng of SKF 81297 did not affect this impairment, 100 ng of SKF 81297 significantly ameliorated it. These results suggest that the chronic-stress-induced depressive state is caused by a D_1 receptor-mediated hypodopaminergic mechanism in the PFC. These findings will further understanding of the mechanisms underlying the pathophysiology of depression.

Keywords: Chronic stress; D_1 receptor; SKF 81297; Dopaminergic neuron; Prefrontal cortex; Rotarod performance; Depression; Rat

1. Introduction

Exposure to chronic stress is thought to precipitate or exacerbate several neuropsychiatric disorders such as depression (Mazure, 1995). Although the pathogenesis of depression remains unclear, the involvement of dopaminergic dysfunction in the prefrontal cortex (PFC) is suspected. For example, Dolan et al. (1994) provided evidence that neuropsychological symptoms in depression were associated with profound hypometabolism, particularly involving the medial PFC. Drevets et al. (1997) demonstrated that both bipolar and unipolar depressives were identified by decreases in cerebral blood flow and the rate of glucose metabolism in the PFC. Furthermore, agents that enhance dopaminergic transmission, e.g., bupropion, have been used successfully as antidepressants (Calabrese and Markovitz, 1991). Several other antidepressants, fluoxetine, clomipramine, imipramine, and desipramine, also increase the extracellular concentration of dopamine (DA) in the rat PFC (Tanda et al., 1994; Matsumoto et al., 1999). These findings suggest that DA modulation of the neural processes within the PFC is involved in the pathophysiology of depression.

A large number of animal studies indicate that exposure to acute or chronic stress can alter the activity of neurotransmitter systems in the brain that affect behavior. In particular, the mesoprefrontal dopaminergic system shows vulnerability to acute stress (Abercrombie et al., 1989), and chronic stress results in reduction of dopaminergic transmission in the PFC (Mizoguchi et al., 2000). Further, when evaluated by a rotarod test, chronic stress also induces a behavioral deficit that is thought to imply a depressive state (Mizoguchi et al., 2002).

On the basis of these findings, we hypothesized that chronic stress-induced reduction of dopaminergic transmission in the PFC contributes to the behaviorally depressive

* Corresponding author. Tel.: +81-298-89-3859; fax: +81-298-89-2158.
E-mail address: mizoguchi_kazushige@mail.tsumura.co.jp (K. Mizoguchi).

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state. To test this hypothesis, we examined the effects of local application of a DA Type I (D_1) receptor agonist, SKF 81297, in the PFC on the chronic stress-induced depressive state using the rotarod test.

2. Materials and methods

2.1. Animals and stress exposure

All animal experiments were performed in accordance with our institutional guidelines after obtaining the permission of the Laboratory Animal Committee. Naive adult male Wistar rats (Japan Clea, Tokyo, Japan) weighing 300–350 g were used. They were housed four per cage in a temperature (22 ± 2 °C)-, humidity (55 ± 10%)-, and light (12-h light/dark schedule; lights on at 7:00 a.m. and off at 7:00 p.m.)-controlled environment and were given laboratory food and water ad libitum.

Before the beginning of all experiments, the animals were divided into several groups. For this purpose, the rats were initially put on a rotating rod (described below), and rats that immediately (within 10 s) dropped off were eliminated from the experiment. The remaining animals ($n = 60$) were divided into six experimental groups ($n = 10$ per group). For the stress experiment, 40 animals were subjected to stress, and 20 animals were used as naive nonstressed rats.

The procedure of stress exposure was described previously (Mizoguchi et al., 2000, 2001a, 2002). Briefly, the animals were placed in a stress cage made of wire net and immersed to the level of the xiphoid process in a water bath maintained at 21 °C by use of a heating and cooling pump (Coolnit CL-19; Taitec, Tokyo, Japan) for 2 h. After the stress exposure, the animals were returned to the home cage immediately. The animals were subjected to this stress session once a day for 4 weeks (chronic stress) at the same time (10:00 a.m. to 12:00 noon) each day. To avoid the acute influence of the last stress exposure and to evaluate the long-term consequences of the chronic stress, the animals were then allowed a 10-day recovery period. The stressed and nonstressed rats were housed in the same room.

2.2. Infusion procedure

The infusion procedure was described previously (Mizoguchi et al., 2000). Briefly, after a 2-day recovery period following the 4-week stress session, the animals were stereotaxically and bilaterally implanted with a guide cannula (9 mm long, 0.8 mm outer diameter; Bioanalytical Systems, West Lafayette, IN), which was anchored firmly to the skull by dental adhesive and acrylic resin, under pentobarbital anesthesia (45 mg/kg ip). The following coordinates relative to the bregma were used for the cannula implantation in the PFC: anteroposterior, +3.2 mm; lateral, ±1.2 mm; vertical, −2.5 mm (Paxinos and Watson, 1986). Fig. 1 shows the infusion sites in the PFC. The animals were initially treated with Xylocaine (Fujisawa Pharmaceutical, Tokyo, Japan) to minimize pain and were monitored on a daily basis for signs of distress or infection. In the present study, there were no signs of sickness or deficits of the immune system after the 10-day recovery period following the 4-week stress session.

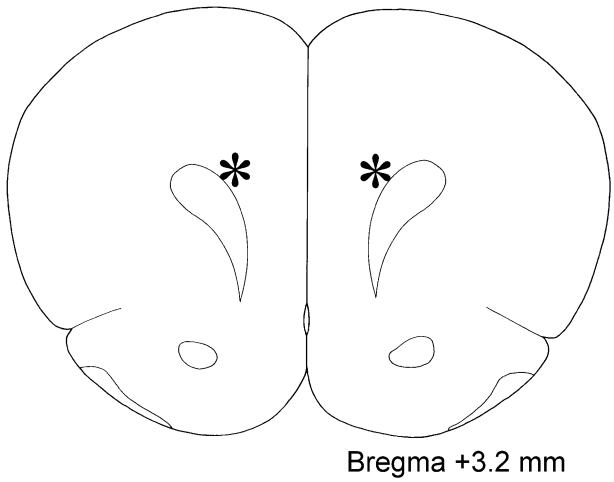

Fig. 1. Location of the drug infusion sites. Asterisks indicate the drug infusion sites in the PFC (anteroposterior +3.2 mm, lateral ±1.2 mm, vertical −2.5 mm from the bregma).

Animals were initially adapted to a mock infusion protocol to minimize any stress associated with the procedure before the start of the infusion experiments. After an 8-day recovery period from the surgery (i.e., a total of 10 days recovery), the animals were gently restrained, while the stylets were removed and replaced with an infusion cannula (PC-12; Bioanalytical Systems) that extended 1 mm below the guide cannula. The animals received bilateral infusions of SKF 81297 (2,3,4,5-tetrahydro-6-chloro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine HBr; Research Biochemicals, Natick, MA), a full D_1 receptor agonist (with activity comparable with that of DA itself; Andersen and Jansen, 1990), at a concentration of either 0 (vehicle), 1, 10, or 100 ng in 0.5 μl sterile saline at a rate of 0.1 μl/min, using a microinfusion pump. The naive nonstressed rats also received bilateral infusions of 0 or 100 ng of SKF 81297. The cannula remained in place for 2 min after the completion of the infusion. The stylets were inserted back into the guide cannula, and behavioral testing began immediately after the infusion. Histological verification of cannula placement by dye infusion performed at the end of the experiments demonstrated the correct placement of the cannula in all animals.

2.3. Rotarod test

The experimental procedure was described elsewhere (Dunhan and Miya, 1957; Commissaris and Rech, 1983; Ahmad and Nicholls, 1990; Mizoguchi et al., 2002). Briefly, the rat was put on a rotating rod (diameter, 10 cm; 7 rpm, Muromachi Kikai, Tokyo, Japan), and the time (seconds)

that the rat remained on the rod was recorded automatically in each case for up to 180 s. The trial was conducted five times for each rat, and the mean riding time was used as the mean value for this test. When the duration of riding was over 180 s, the rat was released from the rod, and the riding time was recorded as 180 s.

2.4. Traction test

After the end of the rotarod test, the traction test was performed. The experimental procedure of this test was described elsewhere (Kuribara et al., 1977; Mizoguchi et al., 2002). Briefly, a wire (2 mm diameter, 40 cm long) was set horizontally 50 cm above the base. The rat was forced to grasp the wire with the two forepaws, and the time (seconds) that it clung to the wire was measured for up to 60 s. The trial was conducted three times for each rat, and the mean clinging time was used as the mean value for this test. When the duration of clinging was over 60 s, the rat was released from the wire, and the clinging time was recorded as 60 s.

2.5. Locomotor activity test

After the end of the traction test, the spontaneous locomotor activity of the rat was measured during a 5-min period using an Animex apparatus (ANIMEX AUTO, MK-110, Muromachi Kikai), as described previously (Mizoguchi et al., 2002).

2.6. Statistics

All data were analyzed using one-way analysis of variance (ANOVA). Individual between-group comparisons were made using Fisher's Protected Least Significant Difference test.

3. Results

3.1. Rotarod performance

The effects of chronic stress and bilateral infusions of SKF 81297 into the PFC on the rotarod performance are shown in Fig. 2A. The riding time on the rotated rod was significantly decreased by the chronic stress [$F(8,81) = 5.785$, $P < .001$]. Although intra-PFC infusion of 1 or 10 ng of SKF 81297 did not significantly ameliorate the chronic stress-induced impairment of the performance, the degrees of the significant difference in the stressed rats receiving these doses versus the naive nonstressed and vehicle (0 ng/PFC)-treated control rats were decreased [1 ng, $F(8,81) = 5.785$, $P < .01$; 10 ng, $F(8,81) = 5.785$, $P < .05$]. At 100 ng, SKF 81297 caused a significant amelioration of the impairment of the performance [$F(8,81) = 5.785$, $P < .05$]. The intra-PFC infusion of 100 ng of SKF 81297 did not affect the performance of the naive nonstressed rats.

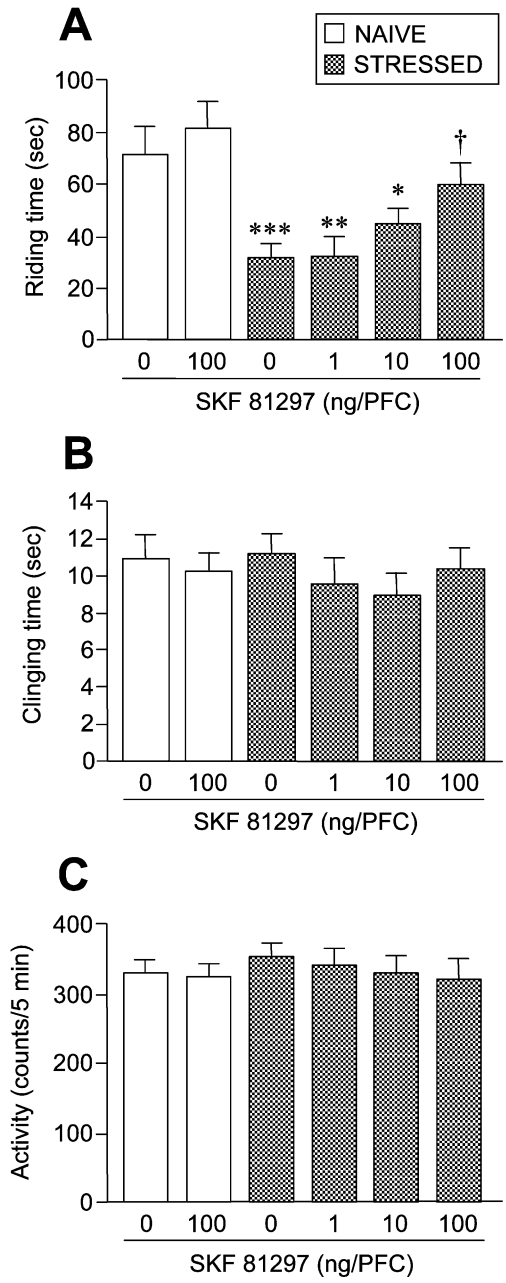

Fig. 2. Effects of chronic stress and bilateral infusions of a DA D_1 receptor agonist, SKF 81297, into the PFC on behavioral performance. (A) Rotarod performance, (B) traction performance, (C) locomotor activity. Each column is the mean ± S.E.M. of 10 rats per group. Asterisks indicate a significant difference from naive nonstressed and vehicle (0 ng/PFC)-treated control rats, $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$; a dagger, a significant difference from stressed and vehicle (0 ng/PFC)-treated control rats, $^{\dagger}P < .05$.

3.2. Traction performance

The clinging time was not affected by the chronic stress or any dose of SKF 81297 tested (Fig. 2B).

3.3. Locomotor activity

The activity was not affected by the chronic stress or any dose of SKF 81297 tested (Fig. 2C).

4. Discussion

The present results suggest that DA D_1 receptor stimulation in the PFC ameliorated the chronic stress-induced behaviorally depressive state.

The validity of intracranial drug injection studies is contingent on the half-life and diffusion of the drug from the injection site of the brain. Since SKF 81297 has a catechol group in its structure, it may be metabolized by catechol-*O*-methyltransferase (COMT) at the synaptic cleft. However, since the metabolic pathway, the half-life, and the degree of diffusion of the intracranially injected SKF 81297 are unclear, the period that this drug is expected to be effective is not determined. For this problem, Zahrt et al. (1997) reported that intra-PFC infusion of 100 ng of SKF 81297 in rats impaired 'spatial working memory' performance of a T-maze task that takes about 30 min per rat after the infusion. We also reported that intra-PFC infusion of 10 ng of SKF 81297 ameliorated chronic stress-induced impairment of the performance of the same task (Mizoguchi et al., 2000). Sorg et al. (2001) reported that enhancement of locomotor activity by intra-PFC infusion of SKF 81297 (30 or 100 ng) on a cocaine-induced increase in the activity in rats was maintained over 30 min. Thus, it is thought that the effect of intra-PFC infusion of SKF 81297 is preserved at least for 30 min. Because the three behavioral tests in the present study were conducted in the same order (first, rotarod test; second, traction test; third, locomotor activity test) and performed within 30 min after the intracranial injection, it is thought that the effect of this drug was preserved throughout the tests.

In the rotarod test (Fig. 2A), the chronically stressed rats showed a decrease in riding time. It is unlikely that this impaired performance is due to muscle relaxation or motor dysfunction because the chronic stress did not affect the clinging time or locomotor activity (Fig. 2B and C). These results well agree with our recent report (Mizoguchi et al., 2002). The SKF 81297 treatment study revealed that the chronic-stress-induced impairment of the rotarod performance was significantly ameliorated by intra-PFC infusion of SKF 81297 in a dose-dependent manner (Fig. 2A). Since the traction performance and locomotor activity were not affected by the SKF 81297 treatment (Fig. 2B and C), the ameliorating effect of SKF 81297 appears to be caused by an intra-PFC mechanism rather than by an effect on muscle strength or motor function. Considering the facts that SKF 81297 is highly selective for the D_1 family of DA receptors (Andersen and Jansen, 1990) and that the same chronic stress used in the present study reduces dopaminergic transmission in the PFC (Mizoguchi et al., 2000), the present results suggest that the chronic stress-induced impairment of the rotarod performance is caused by a D_1 receptor-mediated hypodopaminergic mechanism in the PFC. This hypothesis is supported by a previous report showing that desensitization of the D_1 receptors in the PFC produced a behavioral deficit in an animal model of depression (Gambarana et al., 1995).

The failure of SKF 81297 to increase the riding time in the rotarod test in the naive nonstressed rats is not thought to be due to a ceiling effect because Morimoto and Kito (1994) reported that a single administration of an antidepressant, desipramine (10 mg/kg po) or trazodone (10 mg/kg po), increased riding time in the rotarod test in normal rats. These effects of antidepressants were also confirmed in our preliminary study (data not shown). In addition, the finding that intra-PFC infusion of 100 ng of SKF 81297 did not affect the locomotor activity in the naive rats is consistent with recent reports (Beyer and Steketee, 2001; Sorg et al., 2001).

The dose–response relationship of SKF 81297 on the behavior of animals is well documented, particularly in 'working memory' performance. For example, a low dose (e.g., 100 ng/kg) of SKF 81297 improved impairment of spatial working memory performance in aged monkeys with naturally occurring DA depletion (Arnsten et al., 1994; Cai and Arnsten, 1997). Intra-PFC infusion of 10 ng of SKF 81297 also improves chronic stress-induced working memory impairment in rats (Mizoguchi et al., 2000). In contrast, stimulation of D_1 receptors by 100 ng of SKF 81297 in the rat PFC (Zahrt et al., 1997) or an increase in dopaminergic activity in response to acute stress in monkeys (Arnsten and Goldman-Rakic, 1998) impairs the performance. These findings have led to the hypothesis that there is an optimal range of DA receptor stimulation for proper PFC function (Zahrt et al., 1997; Arnsten and Goldman-Rakic, 1998), which indicates an important role for DA modulation of the neural processes within the PFC in 'working memory.' However, the dose of SKF 81297 significantly ameliorating the stress-induced impairment of the rotarod performance (i.e., 100 ng in Fig. 2A) was outside the range of the beneficial dose–response relationship of SKF 81297 for working memory performance. Furthermore, intra-PFC infusion of 100 ng of SKF 81297 in the naive nonstressed rats did not affect the rotarod performance (Fig. 2A). These findings suggest that the involvement of the dopaminergic system in the PFC differs in the behaviorally depressive state and working memory performance.

The factors that contribute to the stress-induced dopaminergic dysfunction in the PFC are unknown. It is possible that some stress-sensitive neurotransmitters or hormones are involved in the dysfunction. Two principal mechanisms may be projected. First, several reports have shown that dopaminergic and serotonergic neurons in the PFC are closely linked. For example, dopaminergic activity in the PFC is positively regulated by serotonin (5-HT) Type I receptor-stimulation (Wedzony et al., 1996; Sakaue et al.,

2000) or by an increase in 5-HT levels via local application of a 5-HT reuptake inhibitor in the PFC (Tanda et al., 1994; Matsumoto et al., 1999). Indeed, our recent report (Mizoguchi et al., 2002) showed that the same chronic stress used in the present study reduced serotonergic transmission in the PFC. Thus, it is possible that chronic stress-induced serotonergic dysfunction in the PFC causes the dopaminergic dysfunction.

Second, altered regulation by glucocorticoids may be involved in the dopaminergic dysfunction. Glucocorticoid secretion is potently activated by exposure to stresses, such as immobilization (Sapolsky et al., 1984) as well as water immersion and restraint (Mizoguchi et al., 2001). Mesencephalic and mesoprefrontal dopaminergic neurons have glucocorticoid receptors (Härfstrand et al., 1986; Diorio et al., 1993), and the administration of glucocorticoids can modify DA metabolism (Versteeg et al., 1983; Rothschild et al., 1985) and increase the DA release in the PFC (Imperato et al., 1989). Thus, glucocorticoids can positively regulate the dopaminergic activity in the PFC. Also, several reports have shown that the response to exogenous glucocorticoids is reduced in chronically stressed rats. For example, in chronically footshocked rats, the plasma levels of corticosterone (Haracz et al., 1988) or β-endorphin (Young et al., 1990) are not decreased by the administration of glucocorticoids. Recently, we also found similar reduced glucocorticoid negative feedback in rats that were exposed to the same chronic stress used in the present study (Mizoguchi et al., 2001). Since the reduced response to glucocorticoids is considered to reduce the actions of glucocorticoids at the feedback sites, including the PFC (Diorio et al., 1993), the reduction of glucocorticoid-induced actions may be involved in the dopaminergic dysfunction in the PFC, which in turn causes the depressive state. Indeed, the reduced feedback is one of the most consistent findings in patients with depression (Carroll et al., 1981; Kalin et al., 1982; Holsboer, 1983; Arana et al., 1985) and is thought to contribute to some of the depressive symptoms (Steckler et al., 1999). Thus, it is possible that the disruption of the glucocorticoid feedback system in depressives relates to the depressive symptoms through dopaminergic dysfunction in the PFC.

The response of the central nervous system to stress is often critical for the adaptation of an organism to a stressful environment. However, in humans, an over-response to stress can be maladaptive, resulting in the expression or exacerbation of many neuropsychiatric disorders, including a number of features that indicate abnormal functioning of the PFC (Mattes, 1980; Deutch, 1993; Weinberger et al., 1986; Fibiger, 1995). The influence of dopaminergic neurons on the PFC functions in stress-related neuropsychiatric disorders remains obscure, but some observations support the idea that dysfunction of these neurons is involved in the pathogenesis of depression (Calabrese and Markovitz, 1991; Tanda et al., 1994; Fibiger, 1995). In addition, negative symptoms of schizophrenia such as low volition, social withdrawal, and impairment of working memory, insight, and judgment are suspected to be attributable to the reduced dopaminergic transmission in the PFC (Knable and Weinberger, 1997). Thus, since dopaminergic neurons in the PFC are thought to play an important role in several neuropsychic activities, the present findings provide important information for prevention and treatment of stress-related neuropsychiatric disorders.

In conclusion, the present study provides additional evidence of the significance of the chronic stress-induced reduction of dopaminergic transmission in the PFC. Thus, chronic stress induces both working memory impairment (Mizoguchi et al., 2000) and a depressive state (present study), which are both caused by a hypodopaminergic mechanism in the PFC. These findings will further understanding of the mechanisms underlying the pathogenesis of stress-related neuropsychiatric disorders such as depression.

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