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Suppression of glucocorticoid secretion induces a behaviorally depressive state in rotarod performance in rat

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ABSTRACT

Glucocorticoid hormones are important in the maintenance of many brain functions, and their receptors distribute abundantly throughout the brain. In patients with several neuropsychiatric disorders such as depression, dysregulation of the glucocorticoid negative feedback system is the consistent observations, which is thought to be caused by reduced glucocorticoid response at the several feedback sites including the brain. In the present study, we examined whether reduced glucocorticoid actions via suppression of circulating glucocorticoids by adrenalectomy (ADX) induced a behavioral depressive state using the rotarod test. We found that ADX impaired the rotarod performance while it did not affect the traction performance and locomotor activity. Moreover, this impairment was significantly reversed by corticosterone replacement treatment and was ameliorated by the infusion of D_1 receptor agonist SKF 81297 into the prefrontal cortex (PFC) in a dose-dependent manner. Considering the previous findings that ADX reduces dopaminergic transmission in the PFC, the present results suggest that suppression of circulating glucocorticoids induces a behaviorally depressive state that is caused by a D_1 receptor-mediated hypodopaminergic mechanism in the PFC. This finding would help to understand the involvement of the dysregulated feedback system in the pathogenesis of depression.

1. Introduction

Glucocorticoid hormones are secreted from the adrenal cortex, and their secretion is facilitated by activation of the hypothalamo–pituitary–adrenal (HPA) axis, such as under a stressful situation (Miller et al., 1992). On the other hand, excessively secreted glucocorticoids or treatment with synthetic glucocorticoids (e.g., dexamethasone) negatively regulate their secretion, which is known as the negative feedback system.

In patients with stress-related neuropsychiatric disorders including depression, schizophrenia, and Parkinson's disease, dysregulation of the feedback system is often observed, which is characterized as dexamethasone-mediated negative feedback resistance (Arana et al., 1985; Rabey et al., 1990; Pariante et al., 1995; Plocka-Lewandowska et al., 2001). Both animal and human studies challenging the HPA system suggest that several depressive symptoms can be attributed to dysregulation of the feedback system (Hatotani et al., 1977; Kuroda et al., 1992; Steckler et al., 1999). This dysregulation is interpreted to imply a reduction of glucocorticoid response at the several feedback sites such as the pituitary (Miller et al., 1992) and the brain including the hypothalamus, hippocampus, and prefrontal cortex (PFC) (Feldman and Conforti, 1985; Magarinos et al., 1987; Kovács and Makara, 1988; Diorio et al., 1993; Feldman and Weidenfeld, 1999; Mizoguchi et al., 2003). Indeed, glucocorticoid receptors distribute abundantly in these regions (Fuxe et al., 1985; Herman et al., 1989; Diorio et al., 1993; Mizoguchi et al., 2003).

In animal experiments, we have shown that chronic stress in rats induces dexamethasone-mediated negative feedback resistance for the corticosterone (CORT) secretion (Mizoguchi et al., 2001), which is caused by reduced glucocorticoid response in the PFC and hippocampus (Mizoguchi et al., 2003). Moreover, we have suggested that these rats show a behaviorally depressive state in the rotarod test (Mizoguchi et al., 2002a). However, the involvement of reduced glucocorticoid response in this behavior is not clear. From these findings, we hypothesized that reduced glucocorticoid response has an important role for the development of the behaviorally depressive state that is similar to chronically stressed rats.

In the present study, we selected the rotarod test to evaluate the behaviorally depressive state, because this test can detect an antidepressive action of several antidepressants such as desipramine and trazodone. Thus, Morimoto and Kito (1994) have indicated that these antidepressants increase the riding time on the rotating rod, but psychostimulant caffeine or anxiolytic diazepam does not affect it. In

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addition, we have shown that chronic stress in rats decreases the riding time and treatment with trazodone reveres this decrease, suggesting that this test can also detect the depressive state (Mizoguchi et al., 2002a). However, it is well known that the riding time is also influenced by a relaxation or weakness of the muscles or motor dysfunction, and these motoric deficits decrease the riding time. Therefore, we also checked the clinging time in the traction test to assess a muscle strength (Kuribara et al., 1977; Mizoguchi et al., 2002a). If the animals tested show a decrease in the riding time concomitant with a decrease in the clinging time, the decreased riding time is thought to be caused mainly by motoric deficits. However, if the decreased riding time is not accompanied by the decreased clinging time, the decreased riding time is thought to be not due to motoric deficits.

To test the hypothesis described above, endogenous glucocorticoids were suppressed by adrenalectomy (ADX) (i.e., shutdown of glucocorticoid actions), and the effects of this suppression on the depressive state were examined and compared with the behavior observed in chronically stressed rats, using the rotarod test. Moreover, the involvement of dopamine (DA) D_1 receptors in the PFC in the ADX-induced behavioral changes was examined, because ADX reduces DA transmission in the PFC (Mizoguchi et al., 2004), and the decrease in the response through D_1 receptors in the PFC have a role for the development of the depressive state (Mizoguchi et al., 2002b).

2. Materials and methods

2.1. Animals

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 fed laboratory food and water *ad libitum*.

2.2. ADX and CORT replacement therapy

The adrenal glands of some animals were removed bilaterally under pentobarbital anesthesia (45 mg/kg, i.p.) (ADX). Either a cholesterol pellet (100 mg, placebo) or a continuous-release CORT pellet (100 mg, 60-day release pellet; Innovative Research of America, Toledo, OH) was implanted subcutaneously in the ADX rats to reproduce the diurnal level of circulating CORT (Holmes et al., 1997). The nocturnal level of circulating CORT was reproduced by adding CORT (50 μg/ml; Sigma, St. Louis, MO) to the drinking solution from 8:00 P.M. to 8:00 A.M. (Marinelli et al., 1994). Control rats underwent the same surgical procedure as the ADX rats, except that the adrenal glands were not removed (Sham group). The Sham rats were given a placebo pellet. The rats were allowed to recover from anesthesia and then placed in cages with both 0.9% saline (for maintaining electrolyte balance) and water for 14 days. We then performed all experiments.

2.3. Infusion procedure

The infusion procedure was described previously (Mizoguchi et al., 2002b, 2004). Briefly, immediately after ADX described above, some 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, i.p.). 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). The animals were initially treated with Xylocaine (AstraZeneca PLC, London, UK) 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 surgery.

After 14 days from the surgery, 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 (Research Biochemicals, Natick, MA), a full D_1 receptor agonist [with activity comparable with that of dopamine 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 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 was begun immediately after the infusion.

2.4. Rotarod test

The experimental procedure was described elsewhere (Dunhan and Miya, 1957; Commissaris and Rech, 1983; Ahmad and Nicholls, 1990; Mizoguchi et al., 2002a). Briefly, the rat was initially put on the rotating rod (diameter, 10 cm; 7 rpm, Muromachi Kikai Co., Tokyo, Japan), and immediately dropped out rats (within 10 s) were removed from the experiments. The remaining animals were then subjected to ADX described above. On the day of the experiment, the rotarod test was performed. Thus, the time (s) 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 of each rat. When the riding time was over 180 s, the rat was released from the rod, and the time was recorded as 180 s.

2.5. 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., 2002a). 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 (s) 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 of each rat. When the clinging time was over 60 s, the rat was released from the wire, and the time was recorded as 60 s.

2.6. 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 Co.), as described previously (Mizoguchi et al., 2002a).

2.7. CORT radioimmunoassay

At the end of all behavioral experiments, the rats were killed by decapitation, and the plasma concentration of CORT was measured by radioimmunoassay. The [^{125}I]-labeled CORT (46.3 kBq) double antibody radioimmunoassay kit for rats (Amersham Biosciences, Tokyo, Japan) was used. To displace CORT from corticosteroid-binding globulin in the plasma, the plasma was heated for 30 min at 60 °C. The assay was carried out in duplicate at room temperature, using rabbit anti-CORT serum as the first antibody and donkey anti-rabbit serum coated on magnetizable polymer particles as a second antibody.

According to the manufacturer, the cross-reactivity is low. The highest cross-reactivity is found with 11-deoxycorticosterone (2.4% in contrast to 100% for CORT). Only ADX animals with CORT levels below the detection threshold (5 ng/ml) were included in the experiment.

2.8. Statistics

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

3. Results

3.1. Effect of suppression of glucocorticoids on rotarod performance

Effects of ADX and CORT replacement treatment on the rotarod performance are shown in Fig. 1A. The riding time on the rotated rod was significantly decreased by ADX [$F(2,27)=5.143$, $p<0.01$]. This decrease was significantly reversed by the CORT replacement treatment [$F(2,27)=5.143$, $p<0.05$]. The clinging time and the activity were not affected by ADX and CORT replacement treatment, respectively (Fig. 1B and C).

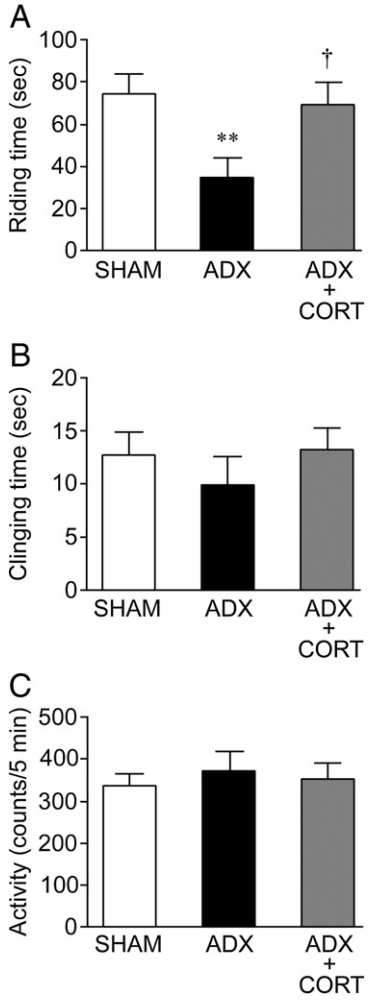

Fig. 1. Effects of ADX and a CORT replacement treatment on rotarod performance. A, rotarod performance; B, traction performance; C, locomotor activity. Each column is the mean±SEM of 10 rats per group. $^{**}p<0.01$, a significant difference from Sham control (placebo-implanted) rats; $^{\dagger}p<0.05$, a significant difference from ADX control (placebo-implanted) rats.

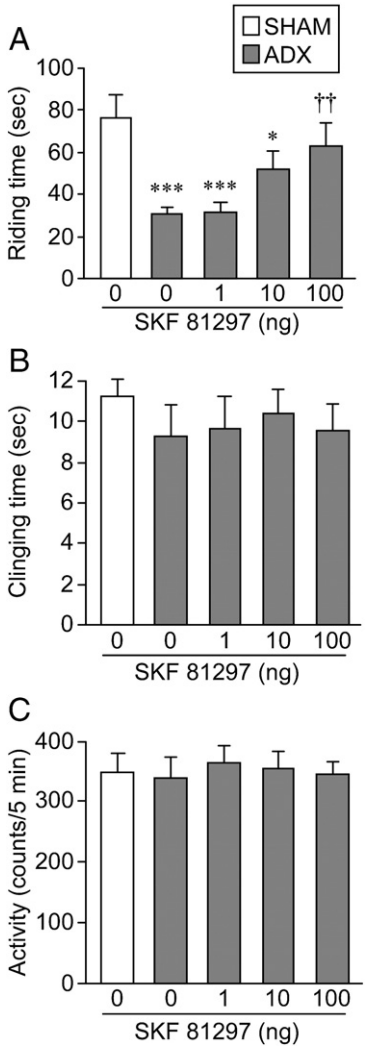

Fig. 2. Effects of bilateral infusions of a DA D_1 receptor agonist SKF 81297 into the PFC on ADX-induced impairment of rotarod performance. A, rotarod performance; B, traction performance; C, locomotor activity. Each column is the mean±SEM of 10 rats per group. $^{***}p<0.001$; $^{*}p<0.05$, a significant difference from Sham control (vehicle (0 ng/PFC)-infused) rats; $^{\dagger\dagger}p<0.01$, a significant difference from ADX control (vehicle (0 ng/PFC)-infused) rats.

3.2. Effect of intra-PFC infusion of D_1 agonist on rotarod performance

The effects of bilateral infusions of SKF 81297 into the PFC on the ADX-induced impairment of the rotarod performance are shown in Fig. 2A. The riding time on the rotated rod was significantly decreased by ADX [$F(4,45)=6.192$, $p<0.001$], which is the same result shown in Fig. 1. Although intra-PFC infusion of 1 or 10 ng of SKF 81297 did not significantly ameliorate the ADX-induced impairment of the performance, the degrees of the significant difference in the ADX rats receiving 10 ng versus the vehicle (0 ng)-treated Sham rats were decreased [$F(4,45)=6.192$, $p<0.05$]. At 100 ng, SKF 81297 caused a significant amelioration of the impairment of the performance [$F(4,45)=6.192$, $p<0.01$]. The clinging time and the activity were not affected by the SKF 81297 infusions, respectively (Fig. 2B and C).

3.3. Plasma CORT levels

The plasma CORT levels in the rats with Sham, ADX, and ADX implanted with the CORT pellet are shown in Table 1. The CORT levels significantly decreased in the ADX rats compared with the Sham rats

Table 1
Plasma CORT levels in the rats with Sham, ADX, and ADX plus CORT replacement treatment

	Plasma CORT levels (ng/ml)	
	Light	Dark
Sham	56.3±9.9	574.6±106.9
ADX	4.6±0.3***	4.5±0.4***
ADX+CORT	60.1±10.9†††	476.4±43.8†††

Each value is the mean±SEM of 10 rats per group. ***$p<0.001$, a significant difference from Sham control (Sham; placebo-implanted) rats; †††$p<0.001$, a significant difference from ADX control (ADX; placebo-implanted) rats.

in both diurnal [$F(2,13)=16.291$, $p<0.001$] and nocturnal [$F(2,13)=25.359$, $p<0.001$] situations. These decreases were significantly revered by the CORT replacement treatment [diurnal, $F(2,13)=16.291$, $p<0.001$; nocturnal, $F(2,13)=25.359$, $p<0.001$], and the plasma CORT levels during this CORT replacement treatment were in the normal physiological range.

4. Discussion

In the present study, we indicated that ADX impaired the rotarod performance and this impairment was ameliorated by the CORT replacement treatment or D_1 receptor stimulation in the PFC. These results suggest the involvement of the glucocorticoid system and dopaminergic mechanisms in the ADX-induced rotarod impairment. Interestingly, this ADX-induced impairment was very similar to chronic stress-induced behavioral deficit, because chronic stress also impairs the rotarod performance (Mizoguchi et al., 2002a).

The rotarod test was established for evaluating pharmacological actions of psychotropic agents such as skeletal muscle relaxants and anticonvulsants in the central or peripheral nervous system (Dunhan and Miya, 1957). Thereafter, it has been indicated that this test is useful to evaluate not only the antidepressive effects of several antidepressants (Morimoto and Kito, 1994), but also a behaviorally depressive state of chronically stressed rats (Mizoguchi et al., 2002a). Thus, the impairment of the rotarod performance has been thought to reflect, at least in part, a behaviorally depressive state.

As shown in Fig. 1, ADX impaired the rotarod performance, and this impairment is thought to be not due to muscle relaxation and motor dysfunction, because ADX did not affect the clinging time and locomotor activity. This ADX-induced rotarod impairment was sufficiently ameliorated by the CORT replacement treatment that reproduced appropriate concentrations of plasma CORT between a physiological range (Table 1), suggesting that the endogenous glucocorticoids are essential hormones to maintain the rotarod performance.

Since the same ADX procedure used in the present study reduces dopaminergic transmission in the PFC (Mizoguchi et al., 2004), and D_1 receptors in the PFC are involved for maintaining the rotarod performance (Mizoguchi et al., 2002b), we next examined the effects of D_1 receptor stimulation in the PFC on the ADX-induced rotarod impairment. As shown in Fig. 2, the ADX-induced rotarod impairment was sufficiently ameliorated by the intra-PFC infusions of SFK 81297 in a dose-dependent manner. 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), the present results suggest that the ADX-induced rotarod impairment is caused by the reduced response through D_1 receptors in the PFC.

Reversal of the SKF 81297 response by D_1 receptor antagonists such as SCH 23390 would be necessary to further confirm the D_1 receptor mechanism. As shown in previous reports (Zahrt et al., 1997; Mizoguchi et al., 2000), 10 μg/kg (i.p.) of SCH 23390 is needed to antagonize the intra-PFC response of 10 ng of SKF 81297 in rats. In the present study, because 100 ng of SKF 81297 was required to ameliorate the ADX-induced rotarod impairment (Fig. 2), 100 μg/kg of SCH 23390 would need theoretically to reverse the SKF 81297 response. However, this dose of SCH 23390 in rats decreased greatly their locomotor activity, indicating a strongly sedative action (data not shown). Thus, the antagonistic effect of SCH 23390 could not be examined.

Taken together, the present results suggest that the suppression of glucocorticoid secretion impaired rotarod performance, which is caused by a D_1 receptor-mediated hypodopaminergic mechanism in the PFC. This mechanism occasionally causes a behaviorally depressive state. For example, desensitization of D_1 receptors in the PFC produces a behavioral deficit in an animal model of depression (Gambarana et al., 1995). Moreover, several antidepressants increase DA levels in the PFC (Tanda et al., 1994), and agents such as bupropion that enhance dopaminergic transmission have been used successfully as antidepressants (Calabrese and Markovitz, 1991). Previously, we indicated that the suppression of glucocorticoids induced impairment of working memory because of reduced dopaminergic transmission in the PFC (Mizoguchi et al., 2004). From the present study, we provide the additional significance of the glucocorticoid suppression, that is a behaviorally depressive state. However, this state should be evaluated by the other behavioral tests such as the forced swimming test or the tail suspension test, because O'Reilly et al. (2006) reported that the rotarod performance was not impaired in the mice showing prolonged immobility in the forced swimming test.

Although the hypodopaminergic mechanisms in the PFC by glucocorticoid suppression have yet been unclear, glucocorticoids may modulate extracellular concentration of DA by acting directly on DA neurons, which express glucocorticoid receptors (Härfstrand et al., 1986). For example, glucocorticoids may enhance DA synthesis by increasing the levels of tyrosine hydroxylase, a rate limiting enzyme for DA synthesis, in the ventral tegmental area (VTA), an originating area of DA neurons in the PFC (Ortiz et al., 1995). However, Piazza et al. (1996) and we (Mizoguchi et al., 2004) have confirmed that ADX does not affect the number of DA neurons in the VTA. Therefore, the other mechanisms should be considered. For example, glucocorticoids may decrease DA catabolism by acting as reversible monoamine oxidase inhibitors (Veals et al., 1977) or they may decrease catecholamine reuptake by inhibiting its transporters (Gilad et al., 1987; Arnsten, 2000). Glucocorticoids may also regulate extracellular concentration of DA through neural mechanisms extrinsic to the DA neurons. For example, opioid, gamma-aminobutylic acid, excitatory amino acid, and serotonergic transmissions are affected by glucocorticoids (Joëls and de Kloet, 1994) and can modulate the activity of DA neurons (Kalivas, 1993).

Although CORT is the primary "glucocorticoid" in rodents, this hormone also binds to mineralocorticoid receptors (Reul and de Kloet, 1985). Therefore, the involvement of mineralocorticoid receptors in the interpretation of the present findings is not ruled out, because the receptors distribute abundantly in the PFC (Diorio et al., 1993).

A number of studies have indicated dysregulation of the glucocorticoid feedback system in patients with depression. Over the several past decades, a large number of studies has focused on the role of excess glucocorticoids on brain function to address the pathogenesis of depression, because the reduced feedback response can induce an elevation of the plasma glucocorticoid levels, which is also seen in depression (Arana et al., 1985; Rabey et al., 1990; Pariante et al., 1995; Plocka-Lewandowska et al., 2001). Consequently, several theories are considered that the high level of cortisol is associated with altered neurotransmitter function, e.g., diminished synthesis of serotonin in the brain, low levels of 5-hydroxyindole-3-acetic acid in the cerebrospinal fluid, and increased noradrenergic

activity (Dinan, 1996; McAllister-Williams et al., 1998; Meijer and de Kloet, 1998; Hanley and Van de Kar, 2003). However, conversely, the present findings would lead to a hypothesis that the reduced actions of glucocorticoids are also involved in depressive psychopathology. Indeed, the ADX-induced behaviorally depressive state in the present study is greatly consistent with the behavior observed in chronically stressed rats. Thus, these rats show the behaviorally depressive state concomitant with the dysregulated negative feedback system that is caused partially by the reduced glucocorticoid response in the PFC (Mizoguchi et al., 2001, 2002a, 2003). As supporting this hypothesis, Boyle et al. (2005) have demonstrated that the mice showing impairment of glucocorticoid receptor function in the forebrain develop behavioral abnormality that mimics major depression in humans.

In conclusion, the present results suggest that suppression of glucocorticoid secretion induces a behaviorally depressive state in the rotarod performance because of a hypodopaminergic mechanism in the PFC. This finding provides understanding of the involvement of the reduced glucocorticoid response in the development of depressive state seen in stress-induced neuropsychiatric disorders.

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