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Chronic stress impairs rotarod performance in rats: implications for depressive state

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Abstract

Exposure to chronic stress is thought to precipitate or exacerbate several neuropsychiatric disorders such as depression. Here, we examined the effects of chronic stress administered by water immersion and restraint (2 h/day) for 4 weeks followed by a 10-day recovery period on rotarod performance. The time course study revealed that the riding time on a rotating rod was not affected at Day 1 or Week 1 of the stress period, but was significantly decreased at Week 4 and after the 10-day recovery period. However, traction performance and locomotor activity were not changed by chronic stress. We next examined the involvement of a serotonergic mechanism in the impairment of rotarod performance. The poststress administration of a serotonergic antidepressant, trazodone (10 mg/kg, daily for 10 days) significantly ameliorated the impairment of rotarod performance. A microdialysis study also revealed a decrease in the extracellular concentration of serotonin in the prefrontal cortex. These results indicate that chronic stress impairs the rotarod performance in a manner that is not due to muscle relaxation or motor dysfunction, and this impairment may imply a behaviorally depressive state mediated by a serotonergic mechanism. These findings provide insight into the underlying mechanisms of stress-induced neuropsychiatric disorders.

Keywords: Chronic stress; Rotarod performance; Depression; Trazodone; Serotonin; Prefrontal cortex; Rat

1. Introduction

Exposure to chronic stress is thought to play an important role in the etiology of depression (Anisman and Farabollini, 1982). In animals, repeated exposure to stress has often been used in experimental models of depression, such as forced running stress (Hatotani et al., 1977; Kitayama et al., 1994), restraint (Cancela et al., 1991; Albonetti and Farabollini, 1993; Haleen and Parveen, 1994), learned helplessness (Danysz et al., 1988), or unpredictable stress (Biagini et al., 1993; Papp et al., 1994). Recently, we found that rats exposed to chronic stress consisting of water immersion and restraint showed a reduced negative feedback response following administration of a synthetic glucocorticoid, dexamethasone (Mizoguchi et al., 2001). This finding is compatible with the clinical finding that there is generally no suppression of the plasma cortisol level following dexamethasone administration in patients with depression (Carroll et al., 1981; Kalin et al., 1982; Holsboer, 1983; Arana et al., 1985). However, the behavioral changes and neurotransmitter mechanisms involved in its behavioral deficit in our chronically stressed rats are not clear.

Although the neurochemical basis of depression and the mechanisms responsible for neurochemical regulation by stressful stimuli are not well understood, the regulation of some neurotransmitter systems in the brain by stress-sensitive hormones such as glucocorticoids may have an important role in the pathogenesis of depression. For example, treatment of rats with adrenocorticotropic hormone or glucocorticoids decreases the density of serotonin (5-hydroxytryptamine; 5-HT) type-1 (5-HT_1) receptors (Mendelson and McEwen, 1992), 5-HT responsiveness (Karten et al., 1999), or the efficiency of 5-HT transport into synaptosomes (Slotkin et al., 1996), or increases the density of cerebrocortical 5-HT_2 receptors (Kuroda et al., 1992, 1993). These

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mechanisms appear to be involved in the relation between the reduced glucocorticoid feedback response (Carroll et al., 1981; Kalin et al., 1982; Holsboer, 1983; Arana et al., 1985), and such indicators of serotonergic dysfunction in depression as a decrease in the density of 5-HT_{1A} receptors (Drevets et al., 2000), the 5-HT concentration, or the 5-HT transporter (Owens and Nemeroff, 1994) in the brain or an increase in the density of 5-HT_2 receptors in platelets or brain (Pandey et al., 1990; Yates et al., 1990; Deakin, 1991). Indeed, glucocorticoid-suppressive agents (Murphy et al., 1991; Wolkowitz et al., 1993) or glucocorticoid receptor antagonists (Murphy et al., 1993) are useful for hypercortisolemic depressed patients, and 5-HT_2 receptor antagonists (Roccatagliata et al., 1977, 1982; Kellams et al., 1979) or selective 5-HT reuptake inhibitors (Lane et al., 1995; Montgomery, 1996; Perry et al., 1996) are effective for clinical relief of several depressive symptoms. These findings led us to hypothesize that our chronically stressed rats would show behavioral deficits caused by serotonergic mechanisms.

In the present study, to test this hypothesis, we used the rotarod test because it shows higher sensitivity to serotonergic antidepressants such as trazodone, mianserin, and clomipramine than the forced swimming test (Morimoto and Kito, 1994). Furthermore, this test involves no habituation or adaptation to water, which may cause problems in measuring the duration of immobility in the forced swimming test. Using the rotarod test, first, we examined the effects of chronic stress. Second, to test the involvement of a serotonergic mechanism in the chronic stress-induced impairment of rotarod performance, the beneficial effects of trazodone, a 5-HT reuptake inhibitor and 5-HT_2 receptor antagonist (Clements-Jewery et al., 1980) were examined. In addition, the effects of chronic stress on the extracellular concentration of 5-HT in the prefrontal cortex (PFC) were also examined by using a microdialysis technique.

2. Materials and methods

2.1. Drug

Trazodone was purchased from Sigma (St. Louis, MO, USA). The drug was dissolved in distilled water, and the concentration of drug solution was adjusted so that volume administered was constant at 1 ml/kg body weight of the rat.

2.2. 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 ($22 \pm 2^{\circ}C$), humidity ($55 \pm 10\%$), and light (12-h light/dark schedule; lights on at 7:00 AM and off at 7:00 PM)-controlled environment and were given laboratory food and water ad libitum.

Before the beginning of all behavioral experiments, the riding ability of the animals in the rotarod performance test (described below) was checked. Thus, the rats were initially put on a rotating rod, and rats that immediately dropped off (within 10 s) were removed from the experiment. The remaining animals ($n = 142$) were divided into the following two experimental groups: time course study ($n = 92$) and drug treatment study ($n = 50$). For the time course study, half of animals ($n = 46$) were subjected to stress (described below), and the other half of the animals were used as controls. For the drug treatment study, 40 animals were stressed, and 10 animals were used as controls. For the microdialysis study, animals whose behavior was not checked were used ($n = 17$): nine animals were stressed, and eight animals were used as controls.

The procedure of stress exposure was described previously (Mizoguchi et al., 2001). Briefly, the animals were placed in a stress cage (dimensions, 11.8 length × 29.1 width × 19.5 height (cm)), which was divided into 10 compartments and made of wire net, and immersed for 2 h 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). The animals were subjected to this stress session once a day for 4 weeks (chronic stress). To avoid the acute influence of the last stress session, and to evaluate the long-term consequences of the chronic stress, some animals were allowed a 10-day recovery period. In our preliminary experiments, gastric ulcers were not produced by a single or repeated exposure to stress. Thus, although relatively severe, this stress is not intense enough to produce a gastric ulcer.

For the time course study, the behavioral analyses were performed at 24 h following the last stress exposure at Day 1, Weeks 1 and 4, and after the 10-day recovery period ($n = 10$ or 16 rats per group at each time point).

2.3. Drug administration

For the drug treatment study performed from the end of the 4-week stress session, the chronically stressed rats ($n = 50$) were randomly divided into five groups ($n = 10$ per group), and then given daily administration (po) of vehicle or 1, 3, or 10 mg/kg of body weight trazodone during the 10-day recovery period (poststress administration). The naive nonstressed rats used as controls ($n = 10$) were given vehicle daily. Twenty-four hours after the last administration, the behavioral analyses were performed.

2.4. Rotarod test

The experimental procedure was described elsewhere (Dunhan and Miya, 1957; Commissaris and Rech, 1983; Ahmad and Nicholls, 1990). Briefly, the duration (s) that the rats stayed on a rotating rod (diameter, 10 cm; 7 rpm,

Muromachi Kikai, Tokyo, Japan) 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.

2.5. Traction test

After the end of the rotarod test, the traction test was performed. The experimental procedure was described elsewhere (Kuribara et al., 1977). Briefly, a wire (2 mm diameter; 40 cm long) was set horizontally 50 cm above the base. The rat was first forced to grasp the wire with the two forepaws, and the duration of clinging 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.

2.6. 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).

2.7. Brain microdialysis

Microdialysis was performed in freely moving animals according to the methods described previously (Mizoguchi et al., 2000). Briefly, after a 2-day recovery period following the 4-week stress session, the animals were stereotaxically 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 brain atlas of Paxinos and Watson (1982) was used to determine the coordinates. The following coordinates relative to the bregma were used for the cannula implantation in the PFC: anteroposterior, +3.2; lateral, +1.2; ventral, −2.5. The animals were allowed at least 8 days to recover from the surgery. On the day of the experiment (i.e., after the 10-day recovery period following the 4-week stress session), a microdialysis probe (PC-12; tip length, 4 mm; tip diameter, 0.5 mm; Bioanalytical Systems) was inserted into the guide cannula, and Ringer's solution (in mM: Na, 147; K, 4.0; $CaCl_2$, 3.0) was perfused at a rate of 0.6 μl/min. After an equilibration period of 3 h, the perfusate was collected every 70 min. To examine the response to stimuli, the KCl concentration was raised to 100 mM. Each perfusate (35 μl) was injected immediately into an HPLC system in conjunction with a coulometric electrochemical detector (ECD-200; Eicom, Kyoto, Japan) to determine the level of 5-HT in the perfusate. A reverse-phase ODS column (CA-5; Eicom) was used with a mobile phase consisting of 82 mM sodium phosphate, pH. 6.0, 800 mg/l sodium 1-octanesulfonate, 50 mg/l EDTA, and 180 ml/l methanol.

2.8. Statistics

All data were initially analyzed using one-way analysis of variance (ANOVA). Individual between-groups comparisons were performed as follows: the Mann–Whitney *U* test for the time course study; Fisher's Protected Least Significant Difference test for the effects of poststress administration of the drug on the performance; the unpaired *t* test for the microdialysis study.

3. Results

3.1. Time course of behavioral changes

The time courses of changes in the behavioral performance during the 4-week stress session and the 10-day recovery period are shown in Fig. 1. In the rotarod performance test (A), the riding time was not affected at Day 1

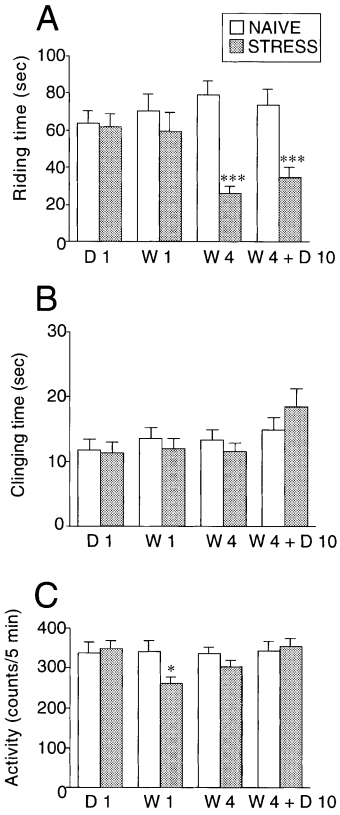

Fig. 1. Time course changes in behavioral performance during a 4-week stress session and a 10-day recovery period. A, rotarod performance; B, traction performance; C, locomotor activity. Each column is the mean ± S.E.M. of ten or sixteen rats per group. Asterisks indicate a significant difference from naive nonstressed rats, * $P < .05$; *** $P < .001$. D, day; W, week.

and Week 1 of the stress period. However, the time was significantly decreased at Week 4 [$F(1,18)=37.561$, $P<.001$] and after the 10-day recovery period [$F(1,29)=13.041$, $P<.001$]. In the traction performance test (B), the clinging time was not changed at any of the stress duration. In the locomotor activity test (C), the activity was significantly decreased at Week 1 of the stress period [$F(1,18)=6.811$, $P<.05$], but was not affected at Day 1 and Week 4 of the stress period and after the 10-day recovery period.

3.2. Effects of poststress administration of drug

The effects of poststress administration of trazodone on the behavioral performance are shown in Fig. 2. In the rotarod performance test (A), the riding time was significantly decreased in the chronically stressed rats [$F(8,81)=6.192$, $P<.001$]. This decrease in the riding time was not reversed by trazodone at a dose of 1 or 3 mg/kg, but was significantly reversed by 10 mg/kg trazodone [$F(8,81)=6.192$, $P<.01$]. The clinging time in the traction performance test (B) and locomotor activity (C) were not affected by chronic stress or any dose of the drug tested.

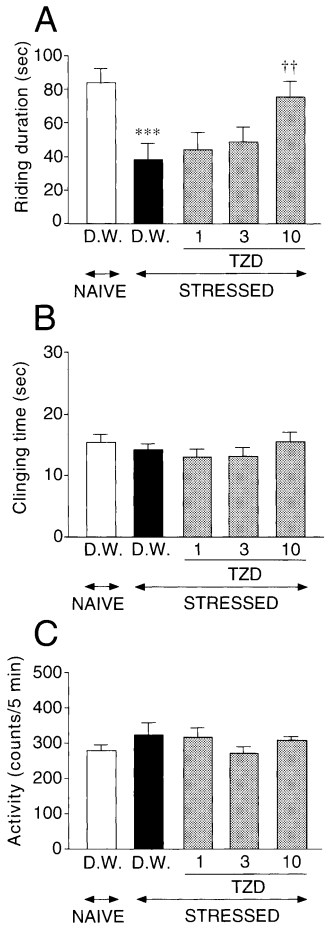

Fig. 2. Effects of poststress administration of trazodone (TZD) on behavioral performance. A, rotarod performance; B, traction performance; C, locomotor activity. The animals were stressed for 4 weeks, and then given daily administration (po) of 1, 3, or 10 mg/kg of drug during a 10-day recovery period. Each column is the mean ± S.E.M. of 10 rats per group. Asterisks indicate a significant difference from naive nonstressed and vehicle distilled water (D.W.)-treated rats, *** $P<.001$; daggers, a significant difference from stressed and D.W.-treated rats, †† $P<.01$.

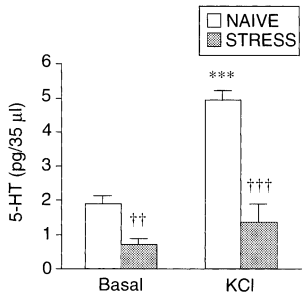

Fig. 3. Effects of chronic stress on the extracellular concentration of 5-HT in the prefrontal cortex under basal or KCl-stimulated conditions. The microdialysis study was performed after a 10-day recovery period following a 4-week stress session. Each column is the mean ± S.E.M. of eight or nine rats per group. Asterisks indicate a significant difference from the basal levels, *** $P<.001$; daggers, a significant difference from naive nonstressed rats, †† $P<.01$, ††† $P<.001$.

3.3. Extracellular concentration of 5-HT

The extracellular concentration of 5-HT in the PFC under the basal or KCl-stimulated conditions was compared between chronically stressed and naive nonstressed rats (Fig. 3). The basal concentration of 5-HT in the chronically stressed rats was significantly lower than that in the naive nonstressed rats [$F(1,15)=14.025$, $P<.01$]. Although a significant increase in the 5-HT concentration was caused in the naive nonstressed rats by perfusion of high KCl [$F(1,14)=46.049$, $P<.001$], this increase was significantly attenuated in the chronically stressed rats [$F(1,15)=35.591$, $P<.001$].

Histological verification of the cannula position by dye infusion performed at the end of the experiments demonstrated the correct position of the cannula in all animals.

4. Discussion

Our results revealed that chronic stress could impair the rotarod performance of rats. This impairment might be caused by dysfunction of the serotonergic system.

The rotarod test was established for evaluating pharmacological actions of psychotropic agents such as skeletal muscle relaxants, anticonvulsants, and antidepressants in the central or peripheral nervous system (Dunhan and Miya, 1957). Morimoto and Kito (1994) demonstrated that this test was useful, in particular, to evaluate the antidepressive effects of serotonergic antidepressants.

In the time course study (Fig. 1), when the chronic stress-induced impairment of rotarod performance was observed (i.e., at Week 4 and after the 10-day recovery period, but not

at Day 1 and Week 1), the traction performance and locomotor activity were not changed. These results suggest that the chronic stress-induced impairment of rotarod performance is not due to muscle relaxation or motor dysfunction. In addition, these results indicate that the impairment of rotarod performance is not due to an acute stress effect, but appears to be a cumulative consequence of stress. Interestingly, this time course characteristic of the rotarod performance is consistent with our recent observation that a reduced glucocorticoid negative feedback response for the basal secretion of corticosterone following dexamethasone administration is initially expressed at Week 4 of the stress period, but not at Week 1, and is maintained after the 10-day recovery period (Mizoguchi et al., 2001). Hence, it is possible that the dysregulation of the hypothalamo-pituitary–adrenocortical system is involved in the chronic stress-induced impairment of rotarod performance.

In general, rats repeatedly exposed to the same stress acquire habituation or adaptation to the stress response. Such adaptation is sometimes observed in tests of the locomotor activity (Kennett et al., 1985). The finding that the decrease in locomotor activity seen at Week 1 of the stress period was not seen at Week 4 (Fig. 1C) suggests that the chronically stressed rats acquired some adaptation. It is possible that the impairment of rotarod performance is advanced by chronic stress despite the fact that chronically stressed rats acquire habituation or adaptation to the stressor.

We next conducted experiments to test the involvement of a serotonergic mechanism in the impaired rotarod performance. For this purpose, we examined the beneficial effects of a serotonergic antidepressant, trazodone, on the chronic stress-induced impairment. In order to evaluate the resultant behavioral deficits of the stressed rats and to eliminate any protective action such as an antistress effect, trazodone was administered during the recovery period but not during stress exposure. As shown in Fig. 2, the chronic stress-induced impairment of rotarod performance was significantly ameliorated by trazodone in a dose-dependent manner (Fig. 2). Morimoto and Kito (1994) reported that a single administration of trazodone (10 mg/kg, po) significantly increased the riding duration in the rotarod performance test, suggesting an antidepressive action. Therefore, it is suggested that the effective dose and administration route of trazodone used in the present study (i.e., 10 mg/kg, po) exert an antidepressive effect. Thus, the ameliorating effect of trazodone on the chronic stress-induced impairment of rotarod performance is thought to be based on an antidepressive effect. Considering the facts that trazodone has a 5-HT reuptake inhibitory action and 5-HT_2 receptor antagonistic action (Clements-Jewery et al., 1980), it was possible that the chronic stress-induced impairment of rotarod performance was caused by the dysfunction of the serotonergic system. To examine this possibility, we further examined the effects of chronic stress on the extracellular concentration of 5-HT in a brain region that might be related to several depressive symptoms in patients with depression, i.e., the PFC. For example, Dolan et al. (1994) provided evidence that neuropsychological symptoms in depression were associated with profound hypometabolism, particularly involving the PFC. Drevets et al. (1997) also demonstrated that both bipolar and unipolar depressives showed decreases in cerebral blood flow and the rate of glucose metabolism in the PFC. As shown in Fig. 3, the extracellular concentrations 5-HT in the PFC under the basal and KCl-stimulated conditions in the naive non-stressed rats were decreased by chronic stress. These findings are in agreement with those of previous reports (Fontenot et al., 1995; McKittrick et al., 2000). Takao et al. (1995) also reported that chronic stress increased 5-HT_2 receptors in the frontal cortex. Since these serotonergic abnormalities are thought to be involved in the pathogenesis of depression (Yates et al., 1990; Deakin, 1991), the chronic stress-induced impairment of rotarod performance may imply a behavioral depressive state caused by the serotonergic dysfunction.

In conclusion, the present results suggest that chronic stress impairs rotarod performance in a manner predominantly mediated by a serotonergic mechanism in the brain. Although the mechanisms of the influence of chronic stress on behavior remain to be clarified, these chronically stressed rats may be useful as a depression model with depressive behavior or reduced glucocorticoid negative feedback response.

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