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Early postnatal stress alters the extinction of context-dependent conditioned fear in adult rats

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Abstract

Fear extinction is hypothesized to be a learning process based on a new inhibitory memory. The present study was conducted to elucidate the effect of early postnatal stress on the extinction of context-dependent fear memory in adult rats, with a focus on the serotonergic system. Extinction was estimated by the expression of freezing behavior during repeated extinction trials (i.e., repeated exposure to contextual fear conditioning) on consecutive days. The decrease in fear expression was attenuated in adult rats that had been subjected to footshock (FS) at the third postnatal week (3wFS), but not in those exposed to footshock at the second postnatal week (2wFS). The decreased attenuation of freezing behavior observed in 3wFS was abolished by repeated treatment with the partial *N*-methyl-D-aspartate receptor agonist D-cycloserine (15 mg/kg, i.p., for 4 days), which has been shown to facilitate cue-dependent extinction. Repeated treatment with the serotonin 5-hydroxytryptamine-1A (5-HT_{1A}) receptor agonist tandospirone (1 mg/kg, i.p., for 4 days) prevented the expression of freezing behavior in 3wFS, whereas diazepam treatment (1 mg/kg, i.p., for 4 days) in 3wFS did not. These results suggest that exposure to early postnatal stress at the third week is responsible for attenuating extinction of contextual fear conditioning and is mediated by a serotonergic 5-HT_{1A} receptor mechanism. In other words, exposure to traumatic events during the early postnatal period might precipitate long-lasting alterations in synaptic function that underlie extinction processes of context-dependent fear memory.

Keywords: Extinction; Contextual fear conditioning; Development; 5-HT_{1A} receptors; Early postnatal stress

1. Introduction

Fear extinction does not result from loss of the fear memory itself, but rather from a learning process based on the formation of new inhibitory associations between conditioned and unconditioned stimuli (Abel and Lattal, 2001; Myers and Davis, 2002; Kim and Jung, 2006). In general, memory consolidation requires gene expression and protein synthesis (Pena de Ortiz and Arshavsky, 2001; Myers and Davis, 2002). For instance, pretreatment with the protein synthesis inhibitor anisomycin prevented recall of extinction of conditioned fear paired with cues such as a tone or light (Quirk et al., 2000; Akirav et al., 2006; Kim and Jung, 2006). Several studies have provided evidence, however, that hippocampus-dependent extinction is involved in contextual encoding processes (Corcoran and Maren, 2001, 2004; Ji and Maren, 2005) and is mediated by protein synthesis-independent mechanisms (Lattal and Abel, 2001; Fischer et al., 2004). Thus, extinction of context-dependent fear memory may be mediated by different neural mechanisms and/or neural circuits other than those associated with cue-dependent extinction.

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Extinction is known to be influenced by stressors of varying types and intensities. Stressful events affect memory function, especially traumatic stress is believed to result in changes in brain regions involved in memory function, such as fear conditioning and extinction. For instance, chronic restraint stress impaired recall of extinction of fear-related freezing on extinction day 2 but did not affect the acquisition or initial extinction of conditioned fear (Miracle et al., 2006). Shumake et al. (2005) reported that rat strains selectively bred for increased susceptibility to learned helplessness showed resistance to extinction of conditioned fear. Interestingly, stress experience alters fear-related behaviors in adult rats depending on the period of exposure. For example, psychogenic stress experienced before puberty in rats impaired the extinction of tone- and context-dependent fear, an effect that varied by gender and age (Toledo-Rodriguez and Sandi, 2007). In preweaning pups, odor/shock conditioning is influenced by maternal presence depending on the context (Moriceau and Sullivan, 2006). These results led us to hypothesize that stress exposed during an early postnatal period affects behavioral responsiveness, including extinction, in adult rats.

We have recently showed that early postnatal stress alters the behavioral response in adult rats during a retention session, but not during acquisition of conditioned fear based on contextual fear memory. Fear-related freezing behavior was markedly reduced during exposure to contextual footshock (FS)-induced fear conditioning in adult rats subjected to aversive stimuli during the second postnatal week. Furthermore, we have suggested, using electrophysiological approaches, that a neuronal serotonin 5-hydroxytryptamine-1A (5-HT_{1A}) receptor mechanism in the hippocampus may be responsible for such behavioral effects (Matsumoto et al., 2005). Early postnatal stress, therefore, may influence not only the retention and/or consolidation of fear memory, but also extinction.

Here, we investigated whether early postnatal stress influences the extinction processes of contextual fear conditioning in 10- to 12-week-old postadolescent rats. The possible involvement of 5-HT_{1A} receptors in mediating the extinction process was examined by investigating the effects of anxiolytic drugs. Extinction was estimated by expression of fear-related freezing behavior during repeated extinction trials (i.e., repeated exposure to contextual fear conditioning).

2. Methods

2.1. Animals

Male Wistar rats were bred in our laboratory, with the exception of the first-breeder adult rats that were supplied by Sankyo Labo Service, Ltd. (Shizuoka, Japan). The day of birth was denoted postnatal day 0 (PND 0). Gender was determined on PND 14, and weaning occurred on PND 21. Rats were housed in a room with a 12 h light/dark cycle with constant temperature (21 ± 2 °C). All animal procedures were performed in accordance with the guidelines of the Care and Use of Laboratory Animals of the Animal Research Committee of Hokkaido University School of Medicine and were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Aversive stress during early postnatal periods

Rats were subjected to early postnatal stress (footshock) as previously described (Matsumoto et al., 2005). Briefly, pups were divided into three groups: footshock at PND 14–18 (2wFS), footshock at PND 21–25 (3wFS), and non-footshock (control). The 2wFS and 3wFS groups were acclimated to the footshock box for 5 min and subjected to five footshocks (shock intensity, 0.5 mA; intershock interval, 30 s; shock duration, 2 s). Rats remained in the test chamber for 5 min after the last footshock stimulation and then were returned to their home cage. Footshock was performed for 5 days. Non-footshock controls remained in the footshock box for 12.5 min without footshock stimuli. Footshock and non-footshock subjects from the same colony were separately housed after weaning.

2.3. Extinction of contextual fear conditioning

During the postadolescent period at 10–12 weeks of age, rats were subjected to contextual fear conditioning. Each rat was acclimated to the footshock box for 5 min and subjected to five footshocks (shock intensity, 0.5 mA; intershock interval, 30 s; shock duration, 2 s; acquisition session). Rats remained in the cage for 5 min after the last footshock and then were returned to their home cage. Twenty-four hours later, rats were placed in the footshock box without footshock stimuli. Behavioral analysis was performed between 11:00 h and 14:00 h to minimize circadian influences. Extinction of fear memory was estimated by measuring freezing behavior (Fanselow, 1980), consisting of 5 min exposure to the conditioning chamber in the absence of footshock stimuli. Extinction trials were repeated for five consecutive days (from the first [Day 1] to the fifth [Day 5] extinction trial). Some rats were subjected to recall of extinction on the second day after the fifth extinction trial.

2.4. Drug administration

Pharmacological experiments were performed during the postadolescent period at 10–12 weeks of age. D-cycloserine (DCS) (15 mg/kg, i.p.) (Sigma, St. Louis, MO, USA), a partial *N*-methyl-D-aspartate (NMDA) receptor agonist, was used to characterize contextual fear conditioning during extinction trials. Diazepam (1 mg/kg, i.p.) (Sigma) and the 5-HT_{1A} receptor agonist tandospirone (1 mg/kg, i.p.) were used as anxiolytic drugs. Doses of these anxiolytics were based on our previous studies (Yoshioka et al., 1998; Mori et al., 2001). Tandospirone was kindly provided by Sumitomo Pharmaceuticals Co. Ltd. (Tokyo, Japan). Drugs were administered 20 min before the second extinction trial (single treatment) and/or 20 min before each extinction trial for four consecutive days (repeated treatment).

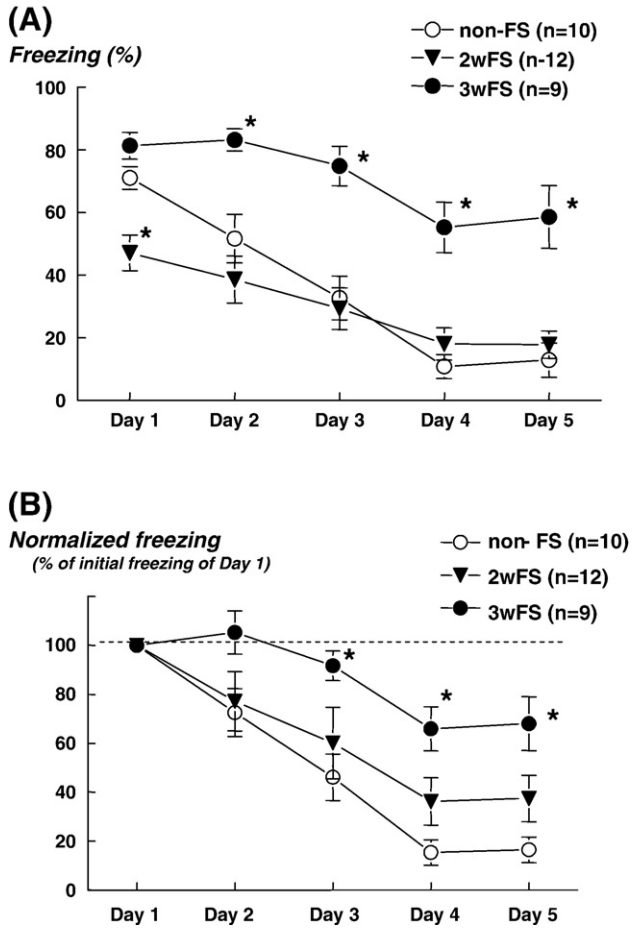

Fig. 1. Effects of early postnatal stress on freezing behavior during extinction. Behavioral experiments were performed during the postadolescent period (10 to 12 weeks old). Extinction was estimated by measuring freezing behavior consisting of 5-min exposure to the conditioning chamber in the absence of footshock (FS) stimuli. Extinction trials were repeated for five consecutive days (from the first (Day 1) to fifth (Day 5) extinction trial) (A) and normalized with respect to the initial post-training session (Day 1) (B). The presence or absence of freezing behavior was estimated every 5 s and is presented as the percentage of each trial. non-FS, pups exposed to the footshock box without footshock; 2wFS and 3wFS, pups exposed to footshock at the second and third postnatal weeks, respectively. Each value represents the mean±SEM. The numbers of rats tested are shown in parentheses. *$P<0.05$ vs. non-FS.

2.5. Statistical analysis

Experimental values are presented as mean±SEM. Freezing behavior was determined every 5 min and is presented as the percentage of each trial. To elucidate the effects of early postnatal stress on extinction, freezing behavior was normalized with respect to the behavior during the initial post-training session among groups. Statistical analysis was performed using repeated-measures one-way analysis of variance (ANOVA), with *Treatment* as the between-subjects factor and *Time* as the within-subjects factor. When appropriate, Dunnett's *post hoc* test was performed. Values of $P<0.05$ were considered statistically significant.

3. Results

3.1. Effects of early postnatal stress on freezing behavior during extinction

Freezing behavior observed immediately after footshock stimuli (acquisition) was similar in the footshock and non-footshock groups (non-footshock control, 91.1±3.2%, $n=10$; 2wFS, 86.8±2.9%, $n=12$; 3wFS, 86.5±3.21%, $n=9$). No significant difference in freezing behavior during the initial post-training session (Day 1) was observed between the 3wFS group (81.0±4.3%, $n=9$) and controls (71.0±3.6%, $n=10$). The 2wFS group showed a significantly lower level of freezing (47.1±5.7%, $n=12$) compared to controls ($P<0.05$). When compared to normalized values (see Methods), freezing behavior diminished depending on the extinction trial, thus conditioned fear was gradually extinguished in all groups. The decrease in freezing behavior, however, was attenuated in the 3wFS group compared to controls (Fig. 1A and B).

3.2. Effects of D-cycloserine (DCS) on freezing behavior during extinction in 3wFS rats

DCS is well known to facilitate cue-dependent extinction (Walker et al., 2002; Ledgerwood et al., 2004; Parnas et al., 2005). To confirm whether freezing behavior is an appropriate measure for estimating extinction of context-dependent fear memory, we examined the effects of DCS on this behavior. Repeated treatment with DCS (15 mg/kg, i.p., for 4 days) markedly decreased freezing behavior in the 3wFS group (Fig. 2). Furthermore, DCS significantly prevented the expression of freezing behavior after a 2-day extinction trial interval compared to the saline-administered

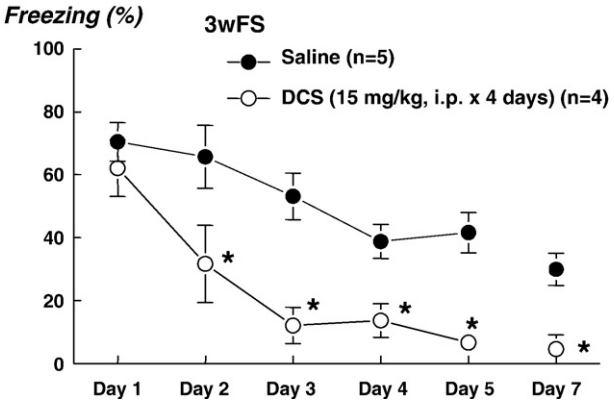

Fig. 2. Effects of D-cycloserine (DCS) on freezing behavior during extinction in 3wFS rats. The partial *N*-methyl-D-aspartate receptor agonist D-cycloserine (DCS) (15 mg/kg, i.p., for 4 days) or saline (2 ml/kg, i.p.) was administered 20 min before each extinction trial for four consecutive days (from Day 2 to Day 5) in 3wFS at postadolescent period (10–12 weeks old). Rats were submitted to recall of extinction memory on the second day (Day 7) after the fifth (Day 5) extinction trial to determine whether spontaneous recovery of fear or long-term maintenance of extinction occurred. The presence or absence of freezing behavior was estimated every 5 s and is presented as the percentage of each trial. Each value represents the mean±SEM. The numbers of rats tested are shown in parentheses. *$P<0.05$ vs. saline-administered group.

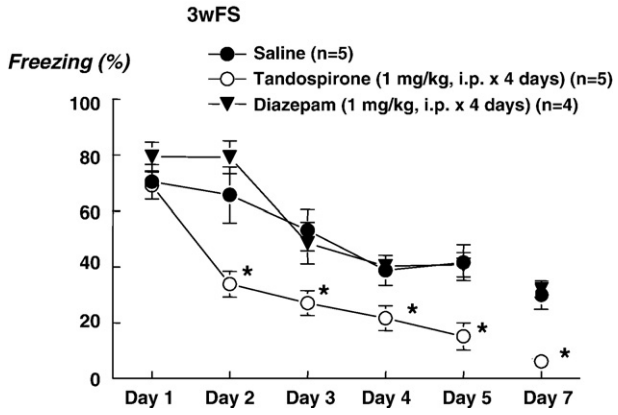

Fig. 3. Changes in freezing behavior during the extinction trial in 3wFS rats following anxiolytic administration. Diazepam (1 mg/kg, i.p., for 4 days), the 5-HT_{1A} receptor agonist tandospirone (1 mg/kg, i.p., for 4 days) or saline (2 ml/kg, i.p.) was administered 20 min before each extinction trial for four consecutive days (from Day 2 to Day 5) in 3wFS at postadolescent period (10–12 weeks old). Rats were subjected to recall of extinction memory on the second day (Day 7) after the fifth (Day 5) extinction trial. The presence or absence of freezing behavior was estimated every 5 s and is presented as the percentage of each trial. Each value represents the mean± SEM. The numbers of rats tested are shown in parentheses. *$P<0.05$ vs. saline-administered group.

group. There was no significant difference in freezing behavior during the initial post-training session (Day 1) (saline-treated 3wFS, 70.5±6.1%, $n=5$; DCS-treated 3wFS, 62.1±9.0%, $n=4$).

3.3. Changes in freezing behavior during extinction in 3wFS rats following anxiolytic administration

We further investigated the effects of anxiolytic treatment on the impairment of extinction observed in the 3wFS group. The same data from saline-treated 3wFS were used as control data. Repeated treatment with the 5-HT_{1A} receptor agonist tandospirone (1 mg/kg, i.p., for 4 days) induced a significant decrease in freezing in the 3wFS group, to levels that were similar to non-footshock controls. Tandospirone also significantly prevented freezing after the 2-day extinction trial interval compared to the saline-administered group. Repeated treatment with diazepam (1 mg/kg, i.p., for 4 days) did not affect the freezing response (Fig. 3). A single treatment with tandospirone (1 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) did not affect the freezing response in the 3wFS group (data not shown). No significant difference in freezing behavior during the initial post-training session (Day 1) was observed among groups (saline-treated 3wFS, 70.5± 6.1%, $n=5$; tandospirone-treated 3wFS, 69.1±4.8%, $n=6$; diazepam-treated 3wFS 79.4±5.2%, $n=4$).

4. Discussion

The present study demonstrated that early postnatal stress affects extinction of context-dependent fear memory. In 3wFS group, freezing behavior during the initial post-training session (Day 1) was similar to that in non-FS control, but the decrease in freezing was attenuated. These results suggest that exposure to aversive stimuli at the third postnatal week might influence the neural circuits and/or neural mechanisms that mediate extinction of context-dependent fear memory. In the 2wFS group, low levels of freezing behavior were observed during the post-training session (Day 1). This phenomenon was consistent with our previous report showing that 2wFS exhibited remarkable decreases in freezing behavior during the retention session of contextual fear conditioning (Matsumoto et al., 2005). Nevertheless, 2wFS showed a decrease in freezing behavior that did not significantly differ from controls during each extinction trial. Thus, the behavioral response to contextual fear conditioning seems to depend on the early postnatal period in which animals are subjected aversive stress.

We cannot fully explain the remarkable attenuation in freezing behavior during the initial post-training session found in the 2wFS group, but it is possible that the retention and/or consolidation for fear memory were disrupted by aversive stimuli experienced during the second postnatal week. In general, during the first two weeks, pups show a markedly diminished adrenocortical response to stress, termed the stress-hyporesponsive period. Interestingly, Moriceau and Sullivan (2006) reported that odor/shock conditioning in preweaning pups is influenced by maternal presence depending on the context. They proposed that maternal presence suppresses stress-induced corticosterone release and neuronal activity in the amygdala, which was enhanced by learned odor aversion originating with the initial aversive conditioning (Sullivan et al., 2000). Therefore, the abnormal response in 2wFS observed in the present study may be due to functional neuronal changes associated with fear memory, but further studies are required.

In this study, we chose at least one pup from each colony to serve as a non-footshock control. Controls were housed in the same cage with their mother until the weaning period. After weaning, they were individually housed (2–4 pups per cage), i.e., footshock and non-footshock pups were separately housed in the cage. Non-footshock controls were subjected to similar conditions as the footshock groups (i.e., they remained in the footshock box for 12.5 min without footshock stimulation for 5 days). Although we cannot exclude the possible influence of weaning on extinction, we compared the behavioral response of early postnatal-stressed rats with non-footshock controls. Therefore, we consider that the freezing behavior observed in this study was evaluated with or without aversive stress.

The 3wFS group underwent the extinction process and continued to show similar levels of freezing 2 days after the extinction trial, suggesting that the extinction memory was retained for long periods after the 2-day interval. Additionally, treatment with DCS, which has been demonstrated to facilitate cue-dependent extinction (Walker et al., 2002; Ledgerwood et al., 2004; Parnas et al., 2005), diminished the expression of freezing in 3wFS after the 2-day interval. These findings suggest that cue- and context-dependent extinction processes are mediated by fundamentally similar molecular mechanisms, perhaps by NMDA receptors in which calcium-dependent mechanisms are involved. In other words, the present results indicate that the behavioral protocol used in this study is appropriate for estimating context-dependent extinction. Recent studies have shown that DCS facilitates fear extinction in people with anxiety (Ressler et al., 2004; Guastella et al., 2007). DCS may have significant clinical

value in the treatment of anxiety-related disorders, such as exposure therapy, by enhancing extinction of fear memory.

Interestingly, repeated treatment with the 5-HT_{1A} receptor agonist tandospirone abolished the differential response observed in the 3wFS group. Because tandospirone treatment also facilitated extinction in non-footshock controls (data not shown), the recruitment of serotonergic systems mediated by 5-HT_{1A} receptors appears to contribute to the extinction process. Thus, activation of 5-HT_{1A} receptors induced by tandospirone may trigger the onset of fear extinction, and consequently might result in long-term storage of fear extinction memory. These results are consistent, in part, with a study showing that another 5-HT_{1A} receptor agonist, buspirone can facilitate the responses during extinction of conditioning (Bond et al., 2003). The deficit of extinction observed in the 3wFS group in the present study might be due to dysfunction of serotonergic mechanisms mediated by 5-HT_{1A} receptors.

Recently, we demonstrated that 5-HT immunoreactive cells in the median raphe nuclei of 3wFS rats was markedly reduced compared to non-footshock controls and 2wFS rats (Konno et al., 2007). These findings led us to theorize that somatodendritic 5-HT_{1A} receptors located in median raphe nuclei and/or postsynaptic 5-HT_{1A} receptors in median raphe terminal regions are influenced by aversive stress experienced at the third postnatal week. Several studies have shown that blockade of 5-HT_{1A} receptor-mediated hyperpolarization (Joëls et al., 1991) or decreases in hippocampal 5-HT_{1A} receptors (Czyrak et al., 2002) are caused by enhancement of corticosterone levels. It is possible, therefore, that exposure to aversive stress during the third postnatal week causes enhanced and prolonged corticosterone levels, might lead to long-lasting changes in neural circuits, and consequently result in dysfunction of the serotonergic 5-HT_{1A} receptor system, thus regulating extinction processes. The present findings suggest that establishment of normal extinction processes in adults requires a functionally intact mechanism mediated by 5-HT_{1A} receptors during development.

Numerous reports have shown that the γ-aminobutyric acid (GABA) system has a facilitatory role in the extinction process (Harris and Westbrook, 1998; Foltin, 2004; Chhatwal et al., 2005). However, in the present study, repeated treatment with diazepam did not affect the deficit of extinction observed in 3wFS. Although we cannot completely exclude the possible involvement of the GABAergic system in mediating extinction, it seems unlikely that GABAergic mechanisms contribute to the differential extinction processes observed in 3wFS, at least under the present experimental conditions.

In summary, the present study demonstrated that exposure to early postnatal stress at the third week impaired extinction of context-dependent fear memory during the postadolescent period, an effect possibly mediated by the serotonergic 5-HT_{1A} receptor system. Deficits in extinction of conditioned fear are known to cause certain anxiety disorders, such as posttraumatic stress disorder (Li et al., 2005; Adamec et al., 2006). A better understanding of the neural mechanisms of the deficit of extinction induced by early postnatal stress, therefore, could help clarify the pathophysiological processes of anxiety disorders in which fear extinction is compromised.

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