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Enhancement of delayed release of dopamine in the amygdala induced by conditioned fear stress in methamphetamine-sensitized rats

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Abstract

Behavior during conditioned fear stress, a form of psychological stress, and the release of dopamine in the amygdala were measured over time using methamphetamine-sensitized rats, which are considered to be a model of hypersensitivity and vulnerability to emotional stress associated with stimulant-induced psychosis and schizophrenia. Dopamine release in the amygdala showed a delayed increase following completion of freezing behavior induced by conditioned fear stress regardless of the presence or absence of methamphetamine-sensitization. Since methamphetamine treatment did not lower the basal level of dopamine in the amygdala, under the conditions of this study, methamphetamine was presumed not to show neurotoxicity. On the other hand, basal dopamine levels after 15 h of repeated electric foot shock were about 40% lower than those in the control group ($p < 0.0002$). In addition, dopamine release following conditioned fear stress in animals repeatedly treated with methamphetamine increased significantly from 40 to 100 min after conditioned fear stress while the duration of freezing behavior or latency of the appearance of grooming were not different from those in the control group. The above results suggested that delayed dopamine release in the amygdala is a phenomenon strongly associated with the emotional context of conditioned fear stress, and hypersensitivity and vulnerability to stress are at least partially involved with the overreaction to stress.

Keywords: Conditioned fear stress; Amygdala; Dopamine; Methamphetamine; Sensitization

1. Introduction

Methamphetamine or amphetamine-induced sensitization (reverse tolerance phenomena) has been widely investigated as an excellent animal model for stimulant-induced psychosis and schizophrenia in terms of paranoid psychotic state and relapse liability (Robinson and Becker, 1986; Sato et al., 1992; Seiden et al., 1993). This animal model is similar to schizophrenia not only with regards to the behavioral description (a face validity model) but also in terms of drug response (a predictive model), since concomitant treatment with antipsychotic drugs and amphetamine results in lack of sensitization (Kuczenski and Leith, 1981; Kashihara et al., 1984; Kashiwabara et al., 1984; Kuribara et al., 1986; Karler et al., 1990). Since recrudescence and relapse occur in stimulant-induced psychosis patients (Sato et al., 1992) and schizophrenics (American Psychiatric Association, 1997) as a result of environmental changes and emotional stress, it is presumed that there is vulnerability (hypersensitivity) to stress in these psychotic disorders. Thus, investigation of the reaction to emotional stress using this animal model was considered able to yield valuable information about abnormalities of stress reactivity in these psychotic disorders.

In recent years, considerable neurochemical research on stress reaction has been focused on dopamine, yielding significant results. The dopaminergic system is important for reactivity to perturbations in environmental conditions, for selective information processing, and for general emotional responses, all of which are essential functions in the ability (or failure) to cope with the external world (Pani et al., 2000). Research has shown that there is selectivity for the site in the brain, depending on the properties of the stress used to induce the dopamine reaction. For example, although tail shock stress increases dopamine in the striatum (Keefe et al., 1990) and in the nucleus accumbens (Roüge-Pont et al., 1993), the medial prefrontal cortex has primarily been confirmed to be important as the dopamine reactive site in the brain in response to psychological stress, while involvement of the limbic and striatal areas is considered to be only slight

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(Cenci et al., 1992; Cabib and Puglisi-Allegra, 1996; Tidey and Miczek, 1996). On the other hand, there are almost no studies on the amygdala, which is a site of dopaminergic innervation and is known to be deeply involved with emotions. However, Inglis and Moghaddam (1999) investigated dopamine release induced by mild handling, and reported that dopamine release in the amygdala was significantly greater than that in the prefrontal cortex and nucleus accumbens. Thus, in-depth investigation of the role of the amygdala is also considered to be significant with respect to stress vulnerability.

We have measured changes in dopamine levels in the amygdala by in vivo microdialysis in methamphetamine-sensitized rats subjected to conditioned fear stress in order to assess the biological background of hypersensitivity and vulnerability to emotional stress in stimulant-induced psychosis and schizophrenia. Conditioned fear stress is psychological stress based on the classical conditioning theory (Fanselow, 1980). Since this method is not accompanied by physical invasion, it has the advantage that the resulting changes can be directly related with emotional changes, which made it suitable for the objective of this study.

2. Subjects and methods

2.1. Experimental animals

Male Wistar rats from Charles River, Japan were used. The rats aged 6 weeks when received, were housed two to a cage in an animal room with temperature set to 25 °C, 45% humidity and light–dark cycle with lights on from 8:00 to 20:00. The cages had automatic water dispensers and cascade-type automatic cleaning systems. The animals were acclimated to the environment for 5–7 days after arrival, being handled frequently during this time. Care was taken that they were not subjected to unexpected stress during administration of drug and subsequent procedures.

All procedures were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the Kitasato University School of Medicine Animal Experiments and Ethics Committee.

2.2. Preparation of methamphetamine-sensitized rats

Methamphetamine was administered following the method for producing the reversed tolerance model in rats as used in our laboratory, and for which behavioral sensitization by re-challenge with methamphetamine has been confirmed (Tanaka et al., 1998). Methamphetamine hydrochloride (Dainippon Pharmaceutical) was dissolved in distilled water (2 mg/ml) and injected subcutaneously into the back of the neck of the rats once a day for 5 consecutive days at 2 mg/kg. This was then stopped for 2 days, and resumed for an additional 5 consecutive days, resulting in a total of 10 administrations (methamphetamine groups). The control groups were given an equal volume of distilled water (distilled water groups).

Following completion of the administration period, a guide cannula was inserted according to the Atlas of the Brain by Paxinos and Watson (1986) under pentobarbital anesthesia (50 mg/kg, mean body weight at surgery: 306 g). The insertion site of the guide cannula in the left amygdala was located 2.8 mm posterior and 4.3 mm lateral to the bregma, and at a depth of 7.2 mm from the bone surface. The stereotaxic instrument manufactured by David Copf was used for stereotaxy, and an ear bar having dulled tips was used for anchoring so as not to damage the eardrums of the rats. Following surgery, the rats were transferred to home cages (black, 30 cm high, 25 cm wide, 15 cm deep) placed in a soundproof room, and were housed individually.

2.3. Procedure for conditioned fear stress and protocol

Fear conditioning was performed once a day for 3 consecutive days starting on the day after insertion of the guide cannula. Fear conditioning was performed by transferring the rats from the home cages to stimulation cages (gray, height 45 cm, width 22 cm, depth 22 cm) still in the soundproof room, and applying an electric foot shock from a floor grid (made of stainless steel rods; diameter, 4 mm at intervals of 8 mm). At this time, an intermittent sound of 2 kHz/80 dB was emitted prior to electric foot shock to serve as a conditioning reinforcement factor. Fear conditioning was performed for 20 min per session, audio stimulation was applied arbitrarily for 30 s per min, and electric foot shock was applied arbitrarily for 15 s during audio stimulation. Electric foot shock was a 2-mA constant-current stimulation produced by a shock generator/scrambler (BRS/LVE) (fear conditioning groups). For the control groups, animals were exposed to audio stimulation under the same conditions but were not subjected to electric foot shock. These latter groups were designated as the sham fear conditioning groups. Following completion of each session of fear conditioning, the animals were immediately returned to the home cages and to the ordinary animal management environment. Following the final conditioning session, a microdialysis probe was inserted and anchored in the left amygdala while the animals were unanesthetized and unrestrained. Measurement of dopamine with the animals in the home cages was begun after at least 15 h had elapsed following insertion of the probe. When the animals had become acclimated to the measuring environment and stable dopamine levels had been obtained from five specimens, this dopamine level was taken to be the basal level, after which, the animals were transferred from the home cages to the stimulation cages. Following conditioned fear stress (only sound, no foot shock), the time-based changes in dopamine were measured and behavior was observed for 180 min.

The animals were divided into the following four groups: (1) group given methamphetamine and subjected to fear conditioning (methamphetamine + fear conditioning + gro-

up), (2) group given methamphetamine and subjected to sham fear conditioning (methamphetamine + fear conditioning – group), (3) group given distilled water and subjected to fear conditioning (methamphetamine – fear conditioning + group), and (4) group given distilled water and subjected to sham fear conditioning (methamphetamine – fear conditioning – group).

In addition, (1) and (2) were classified as methamphetamine groups, (3) and (4) as distilled water groups, (1) and (3) as fear conditioning groups, and (2) and (4) as sham fear conditioning groups according to the particular treatment.

2.4. Measurement of extracellular dopamine

Ringer's solution (147 mM Na^+, 4 mM K^+, 2.3 mM Ca^{2+}, 155.6 mM Cl^-) was used for the perfusate for microdialysis, and samples were collected at a flow rate of 2 μl/min. The BAS PC-12 probe (membrane length: 2.0 mm, outer diameter: 0.5 mm, MW cutoff: 20,000 daltons) was used for the dialysis probe, samples were collected with an Auto Injector (ESA-20: EICOM), and to measure dopamine on a real-time basis, put in a high-performance liquid chromatograph (EP-300: EICOM) every 20 min using CA-5ODS column (2.1 × 150 mm; EICOM) with mobile phase consisting of 80% sodium phosphate buffer, 20% methanol, 700 mg/l sodium octanesulphonate, and 50 mg/l EDTA (2 Na).

This system's detector had a graphite working electrode set at + 0.45 V relative to an Ag/AgCl reference electrode. Use of the Auto Injector enabled dopamine to be measured without any sample decomposition or loss caused by oxidation.

2.5. Histology

Following completion of the post-conditioned fear stress collection period, the animals were given an overdose of sodium pentobarbital (150 mg/kg) and transcardially perfused with physiological saline, followed by 10% buffered formalin. Brains were post-fixed in 10% buffered formalin for 1 day to 1 week, preserved in 20% sucrose for 1 day, frozen, and cut on a sliding microtome into 40-μm sections. Every fourth section was collected in distilled water, mounted on a silane-coated slide, air-dried, and stained with thionine. The accuracy of placements was then assessed.

2.6. Measurement of behavior

The duration of freezing behavior, defined as the absence of observable movement of skeletal muscle and whiskers with the exception of movement related to breathing, was measured. In addition, grooming latency was measured as an indicator of detachment from fear.

2.7. Statistics

A two-way layout analysis of variance of methamphetamine (two conditions) × conditioned fear stress (two conditions) were used for analyses between groups, and Tukey's HDS test was used for multiple comparisons when the primary effect or interaction was significant. A level of $P < 0.05$ was taken as the overall level of significance.

3. Results

The data from 13 rats were excluded from the study for reasons of failed catheterization of the amygdala, presence of comparatively serious hemorrhaging around the membrane or in the insertion path (12 animals) and ineffectiveness of conditioned fear stress (1 animal). Accordingly, the data for a total of 28 animals were analyzed, with the animals divided into four groups of seven animals each.

3.1. Effects of conditioned fear stress on behavior (Table 1)

Freezing duration and grooming latency were compared among the four groups. Freezing duration had a mean value of 707.7 s in the methamphetamine + fear conditioning + group, 8.0 s in the methamphetamine + fear conditioning – group, 513.3 s in the methamphetamine – fear conditioning + group, and 0.1 s in the methamphetamine – fear conditioning – group. Although a significant main effect of conditioned fear stress was found for freezing duration ($F(1,24) = 48.78$, $P < 0.001$), the main effect of neither meth-

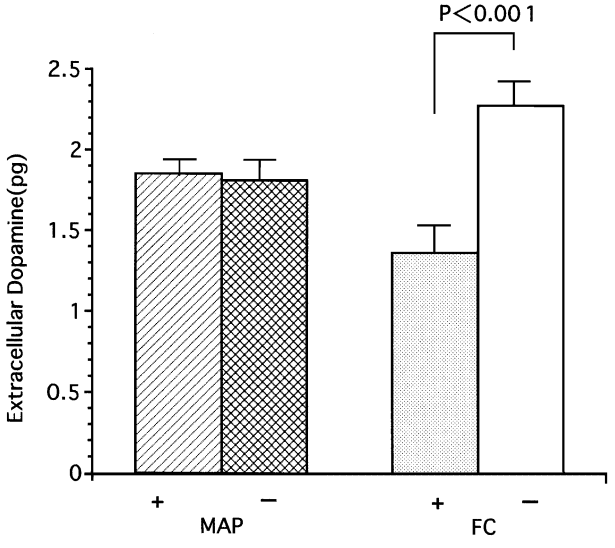

Fig. 1. Effects of electric foot shock on the basal level of extracellular dopamine in the amygdala. Diagonal line bar: methamphetamine groups; hatched bar: distilled water groups; dot pattern bar: fear conditioning groups; white bar: sham fear conditioning groups (see text for grouping). MAP: methamphetamine; FC: fear conditioning; the mean basal levels of dopamine for each group were: methamphetamine + fear conditioning + group, 1.544 ± 0.548; methamphetamine + fear conditioning – group, 2.169 ± 0.597; methamphetamine – fear conditioning + group, 1.221 ± 0.288 and methamphetamine – fear conditioning – group was 2.413 ± 0.755 pg/sample (mean ± S.E.).

amphetamine treatment nor conditioned fear stress by methamphetamine interaction reached significance ($F(1,24) = 1.36$ and $F(1,24) = 1.15$, respectively).

Next, when a comparison was made for grooming latency, the mean value for the methamphetamine + fear conditioning + group was 1038.0 s, the methamphetamine + fear conditioning – group 358.1 s, the methamphetamine – fear conditioning + group 973.0 s and the methamphetamine – fear conditioning – group 268.7 s. Similar to the freezing duration, conditioned fear stress significantly prolonged grooming latency, regardless of presence or absence of methamphetamine ($F(1,24) = 30.29$, $P < 0.001$). However, there was no significant main effect of methamphetamine treatment ($F(1,24) = 0.38$, $P = 0.55$), or of conditioned fear stress by methamphetamine interaction ($F(1,24) = 0.01$, $P = 0.92$).

3.2. Effect of electric foot shock on basal level of dopamine (Fig. 1)

The basal levels of extracellular dopamine in the amygdala (mean value for five samples prior to conditioned fear stress) are shown in Fig. 1 (mean ± S.E.). The mean level in the methamphetamine groups was 1.857 ± 0.174 pg/sample, while that in the distilled water groups was 1.818 ± 0.184 pg/sample. Thus, methamphetamine administration had no significant effect on basal levels of extracellular dopamine in the amygdala ($F(1,136) = 0.03$, $P = 0.87$). On the other hand, the main effect of conditioned fear stress was significant ($F(1,136) = 14.18$, $P < 0.001$); i.e., the mean level of dopamine was 1.383 ± 0.131 pg/sample in the fear conditioning groups and 2.292 ± 0.202 pg/sample in the sham fear conditioning groups, respectively.

3.3. Effects of conditioned fear stress on dopamine release (Fig. 2)

Fig. 2 shows the respective values as percentages based on a value of 100% for the mean of the basal level of each group. Dopamine release began to increase in samples during conditioned fear stress, and then decreased gradually after reaching a peak after 60 min. Although the increase of the methamphetamine + fear conditioning + group (■) given methamphetamine and subjected to fear conditioning reached 200%, the increase stopped at 148% in the methamphetamine – fear conditioning + group (□). Statistical analysis indicated that the main effect of conditioned fear stress was significant at 40, 60, 80, 100, 120, 140, 160 and 180 min after the treatments ($F(1,24) = 32.1$, 29.0, 28.2, 19.5, 16.5, 12.8, 9.0 and 4.9, respectively, $P < 0.05$) and conditioned fear stress by methamphetamine interaction was also significant at 20, 40, 60, 80 and 100 min after the treatment ($F(1,24) = 8.0$, 7.4, 6.5, 7.1 and 4.9, respectively, $P < 0.05$). Like the results of multiple comparisons, both methamphetamine – fear conditioning+ and methamphetamine + fear conditioning + groups showed significantly increased dopamine release from 40 to 160 min after the treatments.

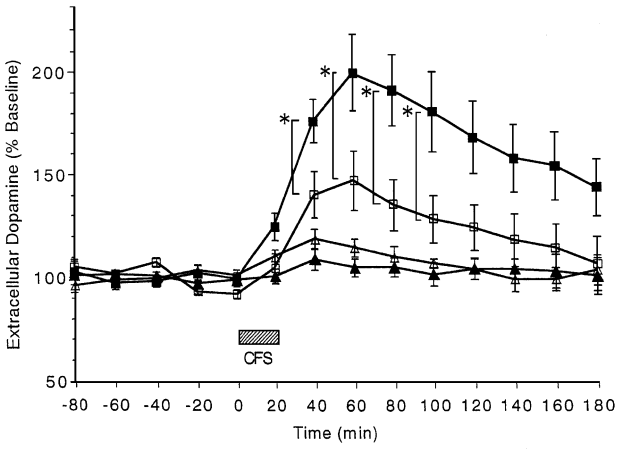

Fig. 2. Effects of conditioned fear stress on dopamine release in the amygdala. Asterisks (*) indicate the presence of a significant difference as determined by multiple comparison ($P < 0.05$). Methamphetamine + fear conditioning + group (■); methamphetamine + fear conditioning – group (▲); methamphetamine – fear conditioning + group (□); methamphetamine – fear conditioning – group (△) (see text for grouping). CFS: conditioned fear stress procedure.

4. Discussion

In this study, conditioned fear stress clearly caused an increase in dopamine release in the amygdala. In addition, this increase was significant from 40 to 160 min after conditioned fear stress (Fig. 2). Since mean grooming latency was 707.7 s (methamphetamine + fear conditioning + group) and 513.3 s (methamphetamine – fear conditioning + group) (Table 1), this significant increase still persisted after more than 2 h following both termination of freezing behavior, a behavioral stress reaction induced by conditioned fear stress, and the appearance of grooming behavior, an indicator of detachment from the fear. There have been only few reports thus far describing increases in dopamine in the amygdala due to conditioned fear stress and other forms of psychological stress. One reason for this is probably that in much of the research conducted thus far, the animals were decapitated immediately after stress, and the resulting dopamine in brain tissue was measured biochemically in an attempt to simultaneously measure several monoamines and their metabolites (e.g., Inoue et al., 1994; results of rats in Konstandi et al., 2000). However, as we have showed, increases in dopamine in the amygdala induced by conditioned fear stress were delayed even after behavioral changes had terminated. Therefore, it is believed that this was shown for the first time as a result of being observed over time, using in vivo microdialysis. Dopamine in the amygdala has, so far, not been measured in studies combining psychological stress and microdialysis (Yoshioka et al., 1996; Feenstra and Botterblom, 1996; Tidey and Miczek,

Table 1
Effect of conditioned fear stress on behavior

Treatment group	Freezing duration	Grooming latency
MAP + FC +	707.7 ± 135.2	1038.0 ± 93.0
MAP + FC −	8.0 ± 5.5	385.1 ± 147.8
MAP − FC +	513.3 ± 108.9	973.0 ± 87.6
MAP − FC −	0.1 ± 0.1	268.7 ± 158.4

Results represent the mean ± S.E. (in seconds).
See the text for grouping and statistical results.
MAP: methamphetamine; FC: fear conditioning.

1996; Wu et al., 1999). In addition, handling stimulation was used in a study that reported an increase in dopamine in the amygdala during stress loading (Inglis and Moghaddam, 1999). Increases in dopamine in the amygdala under these latter conditions were characterized as occurring earlier than those in the prefrontal cortex and the nucleus accumbens, and are clearly different from those induced by conditioned fear stress. Differences in the dopamine reaction between that induced by handling and that by conditioned fear stress are probably brought about by differences in the experimental conditions.

The amygdala is an important anatomical structure that plays a central role in the emotional memory system (LeDoux, 1993a,b), which is a latent memory process for learning and storing information relating to the emotional importance of events. The amygdala has been reported to enhance the synaptic response of the hippocampus and septonuclear system by context conditioning in animal experiments (Desmedt et al., 1998). Research on human subjects has also shown that the amygdala is activated in encoding of emotional stimulation regardless of whether there is pleasure or aversion (Hamann et al., 1999), and that involvement of the amygdala in this process is characteristically long-lasting (Cahill et al., 1996; Büchel and Dolan, 2000). Thus, the delayed increases in dopamine induced by conditioned fear stress which we have now observed are considered to be a phenomenon intimately related to the emotional memory system.

In the present study, repeated administration of methamphetamine did not decrease the baseline levels of dopamine in the amygdala (Fig. 1). Although decreases in basal levels of dopamine in the ventral striatum following repeated administration of amphetamine have been reported by others (Rossetti et al., 1992; Weiss et al., 1997), this contradiction can be explained by a decrease in the activity of tyrosine hydroxylase following repeated administration of methamphetamine at high dose levels (Hotchkiss and Gibb, 1980). Thus, neurotoxicity associated with methamphetamine could be considered not to have appeared under the conditions we used. On the other hand, dopamine basal levels in the amygdala decreased by about 40% 15 h after three sessions of electric foot shock (Fig. 1). Since this type of decrease has not been reported to occur in brain tissue obtained by decapitation immediately following electric foot shock (Tsuchiya, 1999), it is presumed that this change begins gradually after electric foot shock.

Animals with amygdala kindling epileptogenesis also serve as animal models of a kind of hypersensitivity and vulnerability. Although these animal models have been reported to exhibit increases in dopamine levels in the amygdala following stress (McIntyre et al., 1999), the experimental animals we have used here not only serve as a behavioral hypersensitivity model, but also a predictive model of psychosis (Tanaka et al., 1998). It was also presumed that in this study, methamphetamine showed almost no neurotoxicity. In this animal model, biochemical hypersensitivity was confirmed by the release of dopamine in the amygdala in response to conditioned fear stress (Fig. 2). Since the delayed nature of this excessive dopamine release was unchanged (Fig. 2), without being accompanied by changes in the duration of freezing behavior or the latency of appearance of grooming behavior (Table 1), it is believed to be a phenomenon involving an excessive reaction to the emotional context associated with conditioned fear stress. Although Tsuchiya (1999) also measured the levels of dopamine and its' metabolites in the brain following conditioned fear stress using methamphetamine-sensitized rats, the results differed from ours, namely in that freezing behavior was prolonged and dopamine levels in the brain, including those in the amygdala, did not increase. This discrepancy is considered to be the result of the dose of methamphetamine used being higher, and the animals having been decapitated immediately after conditioned fear stress and the use of the resulting samples for measurement. Our findings are rather similar to those of Harmer and Phillips (1999), who used an appetitive Pavlovian conditioning task in terms of dopamine release in the amygdala and its enhancement by repeated pretreatment with amphetamine, strongly suggesting a role of the amphetamine in emotional associative learning, unlike that of the hippocampus in non-emotional memory (Akire et al., 1998). The longer-lasting dopamine release in the conditioned fear stress animals compared to those of the abovementioned ones may implicate the differences in conditioning, such as nature of stimuli used (pleasure and aversion) and/or complexity of association.

The molecular biological mechanism underlying the excessive dopamine release reaction to conditioned fear stress in methamphetamine-sensitized rats is not clear. Dopamine transporter levels have recently been reported to be decreased in the striatum of methamphetamine abusers (Volkow et al., 2001), and this phenomenon could be explained if there were similar changes in the amygdala as well. The biochemical sensitization observed in the conditioned fear stress animals could be a case of time-dependent sensitization (see for review: Antelman et al., 1997), a phenomenon widely seen in neuropharmacology.

Increased concentrations of dopamine in the amygdala (especially in the left side) from post-mortem brain tissues of patients with schizophrenia were described by Reynolds (1983). Based on our results, along with those of studies involving measurement of dopamine in animals sensitized

with amphetamine or methamphetamine, the following series of changes can be assumed to take place: dopamine release increases in the prefrontal cortex as the sensory stage immediately after stress (Hamamura and Fibiger, 1993; Tsuchiya, 1999), but decreases in the ventral striatum in contrast to that in normal animals (Weiss et al., 1997) in which a trend reciprocal to that in the cortex is observed as a result of being under inhibitory control from this site (Le Moal and Simon, 1991), and is further delayed and increased in the amygdala as part of the emotional reaction process (Fig. 2). Due to this series of abnormal reactions, a chain of failures probably occurs in the reaction to cope with stress, and is presumed to eventually lead to the formation of a psychotic state.

The present results suggest that an abnormality in the dopamine system is a background factor of stress vulnerability. However, additional studies are needed on the relationship with neurotransmitters other than dopamine if one is to reach a comprehensive understanding of stress vulnerability. According to modern integrative physiology of the aminergic systems, each projection interacts through a subtle imbalance and it is never one projection alone that is involved (e.g., Darracq et al., 1998). Although numerous studies have been conducted on the response of the serotonin system (see for review: Takeda et al., 2000) and the noradrenaline system (see for review: Tanaka et al., 2000) to stress, their abnormalities were almost never studied using a stress-vulnerable animal model. The only report thus far is that by McIntyre et al. (1999), which stated that serotonin, noradrenaline and their metabolites exhibit abnormal variations at sites covering a wide area of the brain in the same manner as does the dopamine system when the effects of ferret exposure and restraint were observed in amygdala kindled rats. It will therefore be necessary in the future to conduct studies on the vulnerability to emotional stress of psychotic patients for neurotransmitter systems other than the dopamine system using animal models considered to more closely approximate human psychosis, such as the methamphetamine-sensitized rat model.

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