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ORIGINAL PAPER

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Spontaneous recurrence of methampetamine psychosis: increased sensitivity to stress associated with noradrenergic hyperactivity and dopaminergic change

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Abstract We studied the factors precipitating spontaneous recurrences of methamphetamine (MAP)-induced paranoid-hallucinatory states (referred to as "flashbacks") in 28 flashbackers, along with 18 non-flashbackers with a history of MAP psychosis. Plasma levels of catecholamines and their metabolites were assayed in the 28 flashbackers, the 18 non-flashbackers, 8 subjects with persistent MAP psychosis, and 33 normal controls (22 MAP users and 11 non-users). The flashbackers had been exposed to significantly higher numbers of stressful events, and/or MAP-induced frightening paranoid-hallucinatory states during previous MAP use, than the non-flashbackers. Factors triggering the flashbacks met the DSM-III-R criteria for a mild psychosocial stressor. During flashbacks, plasma norepinephrine levels increased and plasma levels of 3-methoxytyramine, which is an indicator of dopamine release, showed a smaller increase. It follows that stressful experiences together with MAP use may induce sensitization to mild psychosocial stressors. Noradrenergic hyperactivity and some degree of increased dopamine release may be involved in this process. Stress sensitization may elicit memories of MAP psychosis associated with stressful experiences in response to mild psychosocial stressors, leading to the occurrence of flashbacks. Sensitization to stress associated with noradrenergic hyperactivity, involving increased dopamine release may be central to spontaneous recurrences of MAP psychosis.

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Introduction

Amphetamine (AMP) or methamphetamine (MAP) sometimes induces paranoid-hallucinatory psychosis in non-schizophrenic subjects (Janowsky and Risch 1979). The short-lived psychotic states characterized by vivid visual hallucinations and the absence of thought disorder that occur in AMP or MAP psychosis without marked reduction in functioning appear to be distinct from the later development of schizophrenia (Bell 1965). AMP or MAP induces long-lasting sensitization to stress, suggesting that AMP or MAP psychosis can recur in response to stress during remission (Robinson et al. 1987). It was reported that spontaneous recurrences of MAP psychosis (referred to as "flashbacks") occasionally occur on exposure to psychological stress (Sato et al. 1983). However, there is little information regarding the occurrence of this symptom complex caused by street drug use. The high prevalence of flashbacks due to previous MAP psychosis in Japanese prisoners presents an opportunity to examine the factors precipitating the development of flashbacks.

Animal studies have shown that prior exposure to stressful stimuli induces sensitization to subsequent mild stress (non-specific environmental stimuli) in the brain and peripheral noradrenergic systems (Cassens et al. 1980; Petty et al. 1994). This noradrenergic hyperreactivity to stress may be a precipitating factor in stress-related psychiatric disorders (Cassens et al. 1980). Stress-induced noradrenergic hyperactivity has been implicated in poor coping with mild stress (Petty et al. 1994) and in the pathological encoding and retrieval of traumatic memories in posttraumatic stress disorder (PTSD) (Southwick et al. 1993), involving intrusive reexperiencing of the trauma with hallucinations (DSM-IV 1994). AMP-induced sensitization to stress may be related to enduring hypersensitivity to the psychotogenic effects of stress seen in former AMP ad-

dicts through changes in dopaminergic systems (Robinson et al. 1987). Taking these observations as a whole, it is possible that sensitization to stress associated with noradrenergic hyperreactivity and dopaminergic change is critical in the development of flashbacks due to previous MAP psychosis. The purpose of the present study was to examine the nature and significance of stress sensitization associated with noradrenergic hyperactivity and dopaminergic change in the development of flashbacks. Since plasma levels of catecholamines (e.g., norepinephrine or epinephrine) are used as an indicator of physiological response to stress (Péronnet et al. 1986), we assayed plasma levels of catecholamines and their metabolites in relation to the occurrence of flashbacks.

Methods

Sample

The subjects were 87 physically healthy females recruited from the inmates at a women's prison. These were made up of 46 with a history of MAP psychosis, of which 28 experienced flashbacks during their 15–20 months of incarceration (flashbackers) and the other 18 did not (non-flashbackers); 8 with persistent MAP psychosis; and 33 age-matched controls (22 MAP users and 11 non-users, none of whom had experienced MAP psychosis or flashbacks). Because MAP psychosis in the 28 flashbackers had disappeared within 730 days prior to blood collection (mean ± SD 210.1 ± 203.5 days), the 18 non-flashbackers were selected based on adjustment of the time of disappearance of MAP psychosis (244.6 ± 201.3 days). The 8 subjects with persistent MAP psychosis, which persisted for at least 6 months (17.6 ± 10.6 months) prior to blood collection, were included to compare with the flashbackers regarding plasma levels of catecholamines and their metabolites. The subject subgroups were age-matched at the time of blood collection (mean age ± SD: the flashbackers during flashbacks 28.0 ± 5.5 years; the flashbackers during remission 28.1 ± 5.8 years; the non-flashbackers 29.2 ± 8.7 years; the subjects with persistent MAP psychosis 25.4 ± 2.6 years; the user controls 29.3 ± 5.2 years; the non-user controls 32.3 ± 8.1 years) (among the subject subgroups, $H = 5.65$, $df = 5$, $P = 0.34$; between single pairs of the subgroups, Z or $Zc = 0.45–1.78$, $P = 0.08–0.64$). Twelve of the 28 flashbackers, 7 of the 18 non-flashbackers, 10 of the 22 user controls, and 3 of the 11 non-user controls had participated in our previous study (Yui et al. 1997). All subjects, except for the 11 non-user controls who had been imprisoned for theft ($n = 7$), arson ($n = 1$), and involuntary manslaughter ($n = 3$), had been incarcerated for violation of the Stimulant Drug Control Law that prohibits both use and possession of stimulant drugs. In Japan, violators of the Stimulant Drug Control Law are usually sentenced to 1–2 years penal servitude in a public court. All subjects were deemed physically healthy based on history, physical and neurological examinations, and biochemical screening. None of the subjects had abused other substances nor experienced any psychiatric disorder in the absence of MAP use. All subjects expressed a wish to participate in the study in order to receive medical examinations from the psychiatrists conducting the investigation, out of concern for their own health. They were free to abstain from participation in the study or to withdraw from it without threat of punishment. Subjects freely gave informed consent prior to their inclusion in the study, which was approved by the Medical Care and Classification Division of the Ministry of Justice.

Diagnostic data were obtained from a structured interview using the DSM-IV checklist. The clinical diagnosis of MAP psychosis was confirmed by two psychiatrists using the DSM-IV criteria for AMP-induced psychotic disorder, based on a structured interview and inmate record review of MAP-related record, which included written evidence recorded at the public prosecutor's office. Subjects who met the DSM-IV criteria for schizophrenia, schizophreniform disorders, brief psychotic disorders, anxiety disorders or PTSD were excluded. To avoid biased recollections of experiences during previous MAP use, subjects who had distinct deviations in recall, learning, and processing of their circumstances, based on neurological examination, were excluded. Flashbacks due to previous MAP psychosis were defined with reference to the DSM-IV criteria for hallucinogen persisting perception disorder (flashbacks), and a general definition of psychedelic drug flashbacks (Matefy et al. 1978) as a spontaneous recurrence of MAP-induced paranoid-hallucinatory states after a period of normalcy, during which the pharmacological effects of MAP had worn off.

Neuroleptic treatment

Of the 28 flashbackers, 13 were maintained on haloperidol (1–3 mg/day), chlorpromazine (25–75 mg/day), or thioridazine (25–75 mg/day) for at least 4 weeks before and during the study (medicated flashbackers). The other 15 flashbackers did not complain of psychiatric symptoms and were unmedicated for at least 3 months before blood collection. However, they received the neuroleptic treatment specified above following blood collection conducted during flashbacks, because of flashback aggravation (later-medicated flashbackers). Defining characteristics and clinical features did not differ between the two subgroups. To determine the effects of the above neuroleptic treatment, we compared plasma levels of catecholamines and their metabolites among the 13 medicated flashbackers, the 15 later-medicated flashbackers, and the 22 user and 11 non-user controls. The 8 subjects with persistent MAP psychosis were treated with haloperidol (1–9 mg/day) or chlorpromazine (25–125 mg/day) for at least 1 month (3.2 ± 1.7 months) prior to blood collection. The 18 non-flashbackers were unmedicated for at least 3 months before and during the study, since they had no psychiatric symptoms. None of the subjects took other medications.

Assessments of stressful experiences and anxiety levels

Data on the pattern of MAP use and symptoms of MAP psychosis during previous MAP use were obtained from structured interviews and inmate record reviews. The interview questions addressed such specific topics as whether the subjects had had stressful experiences and what stressful experiences had occurred during previous MAP use. The interviews were conducted upon admission to the prison before the occurrence of flashbacks. Stress was defined as a physical or psychological factor that poses a threat to the well-being of the subjects, producing a defensive response (Landau et al. 1986). The criteria for stressful events were accordingly based on whether the subjects had been overwhelmingly distressed and whether the events met the DSM-III-R criteria for a severe to catastrophic type of psychosocial stressor. The criteria for MAP-induced frightening paranoid-hallucinatory states (perception of threat) were based on whether the subjects had been overwhelmingly threatened and whether they had taken refuge near or in their houses out of fear (defensive response). Psychosocial stressors were assessed using the Severity of Psychosocial Stressors Scale (axis IV) from the DSM-III-R (1 = none, 6 = catastrophic). When more than one stressor was present, the severity rating was based on the most severe stressor. Auditory and visual hallucinations in the subjects were perceived as originating in the outside world with a quality similar to true perception, so that the subjects felt threatened by their hallucinations. Data on the factors triggering flashbacks were obtained from structured interviews and reports made by prison staff. Each interview involved asking what actually happened before the occurrence of flashbacks and what the subjects believed triggered the flashbacks. All data were verified through follow-up interviews.

The State-Trait Anxiety Inventory (STAI; Spielberger 1983) was used to assess anxiety levels related to stress. The scale consists of two separate scales intended to measure both levels of transitory anxiety at the time of testing (state anxiety) and more stable enduring anxiety (trait anxiety). STAI data were available for a random subsample of 12 of the 28 flashbackers, at two times (when the flashbacks occurred and at remission), and at one time for random subsamples of 13 of the 18 non-flashbackers, 9 of the 22 user controls, and 8 of the 11 non-user controls (on admission to the prison). Blood pressure and heart rate were measured at the same time as blood sampling.

Checking up on MAP use in relation to the occurrence of flashbacks

All subjects were prohibited from taking MAP or other substances for at least 3 months before and during the study. This was verifiable because of their confinement, which entailed repeated searches at weekly intervals, and whenever the need arose (e.g., after meeting family members) by methods authorized under the Prison Law. To uncover secret possession of MAP, other substances and any other unauthorized article, the prison staff throughly searched prisoners' belongings and clothes, every page of their books and under the mat in their living quarters. All prisoners were prevented from having visitors other than family members and from receiving sealed correspondence. Thus, MAP or other substances have been never used in detention houses or prisons (Ohashi 1996). Because all subjects gave legal consent to be searched, they were not alarmed by the searches. Venous plasma was examined for the presence of MAP in 8 randomly selected flashbackers at the time the flashbacks occurred by gas chromatography/mass spectrometry, as described previously (Yui et al. 1997). The method involved solid-phase extraction, including an extrelut 1 column. Recovery of MAP was 90%. The lowest detectable quantity was 0.5 ng/ml for each product analyzed; all analyses were negative.

Analysis procedure for plasma catecholamines and their metabolites

All subjects received a low-monoamine, alcohol-free, and caffeine-restricted diet for at least 3 months before and during the study while confined in detention houses and in the prison. Blood samples were obtained twice from the 28 flashbackers during their prominent paranoid-hallucinatory flashback states, which occurred within 14 days of the occurrence of flashbacks, and again within 4 weeks after the flashbacks had resolved. The other subjects had a single sample assayed upon admission to the prison. Blood was collected at random by venipuncture between 10:30 a.m. and 12:00 noon. Excessive motor activity (e.g., walking around) was not otherwise allowed in the prison. All prisoners, including our subjects, are allowed to walk in limited areas at fixed times in Japan. Moreover, the subjects remained supine for 20 min before and during blood sampling. Plasma was stored at -80 °C until it was assayed for norepinephrine (NE), normetanephrine (NM), epinephrine (E), dopamine (DA), 3-methoxytyramine (3-MT), and dihydroxyphenylacetic acid (DOPAC), using high-performance liquid chromatography with an electrochemical detector, as described previously (Yui et al. 1997). The sensitivity was 0.01 pmol/ml, except for NM at 0.05 pmol/ml. Intra-assay and interassay coefficients of variation averaged 10.0% and 21.1%, respectively.

Data analysis

Plasma levels of catecholamines and their metabolites were often extremely skewed and far from normally distributed. Thus, a square-root transformation was applied to all monoaminergic values, rendering the distribution normal (Millns 1995). The transformed data were analyzed using one-way analysis of variance (ANOVA) followed by post hoc tests (Fisher's protected least significant difference). As recommended for a repeated mea-

Table 1 Stressful experiences during previous methamphetamine (MAP) use. Percentages do not total 100 because some subjects had more than one event or symptom

	Flashbackers $n = 27$[a]	%	Non-flashbackers $n = 18$	%	P
Events					
Stressful events	19	70.4	1	5.6	< 0.001[b]
Being injected with MAP by force	7	25.9	0	0.0	< 0.05[b]
Being assaulted by a male partner	6	22.2	1	5.6	< 0.05[b]
Sexual abuse by a male partner	1	3.7	0	0.0	0.32
Divorce	2	7.4	0	0.0	0.16
Rejecting parents	2	7.4	0	0.0	0.16
Unwanted pregnancy	1	3.7	0	0.0	0.32
Mean DSM-III-R axis IV scores	3.78 ± 1.72		1.22 ± 0.94		< 0.001[b]
Frightening psychotic symptoms	19	70.4	1	5.6	< 0.001[b]
Frightening auditory hallucinations	13	48.2	0	0.0	< 0.001[b]
Frightening visual hallucinatins	7	25.9	0	0.0	< 0.05[b]
Dead body	2	7.1	0	0.0	0.16
Blood-soaked face or face without one eye	2	7.1	0	0.0	0.16
Graveyard, a ghost, long-nose goblin or gore	4	18.5	0	0.0	0.05
Delusions of being killed	4	14.8	0	0.0	< 0.05[b]
Delusions of being pursued	11	70.4	1	5.6	< 0.05[b]
Delusions of being possessed by a devil	1	3.7	0	0.0	0.32

[a] Data were unavailable for one flashbacker
[b] Remains significance difference using X^2 test

sures design (Havilcek and Crain 1988), the transformed data from the flashbackers were analyzed using repeated measures ANOVA with the presence or absence of neuroleptic treatment as between subject factor and flashbacks and no flashbacks as the within subjects repeated factor. Comparison between subject subgroups was performed using the Kruskal-Wallis test followed by the Mann-Whitney U-test and X^2 test.

Results

Clinical characteristics of the subjects

All subjects, except for the 8 non-user controls, had previously abused MAP, averaging 1 to 10 intravenous injections of MAP (30–60 mg per injection) per day during periods of abuse. The mean cumulative duration of MAP use before onset of MAP psychosis did not significantly differ between the 28 flashbackers (15.8 ± 19.4 months) and the 18 non-flashbackers (17.9 ± 25.7 months) (Zc = 0.00, P = 0.99). The flashbackers exhibited a reactivated MAP psychosis, in which the incidence of psychotic symptoms was similar to that of the previous MAP psychosis (X^2 = 19.17, df = 14, P = 0.16) without reexperiencing the original stressful events or the symptoms of PTSD or acute stress disorder listed in the DSM-IV. During flashbacks, these subjects continued to experience paranoid delusions in which they developed transient auditory and visual hallucinations. They did not appear agitated and were able to continue their light prison duties. Paranoid delusions abated after 2 to 282 days. Thus, the total duration of flashbacks was 2 to 282 days (63.8 ± 65.7 days). These subjects returned to a normal psychiatric state once the flashbacks subsided.

Table 2 Factors that triggered the flashbacks. Percentages do not total 100 because some subjects had more than one factor

Factors	Frequency	
	$n = 57$[a]	%
Mild fear of other people	51	89.5
Conflicts or confrontations with inmates	23	40.4
Fear of disciplinary punishment	3	5.3
Fear of emitting body odor	4	7.0
Fear of prison setting, including fear of the prison staff	11	19.3
Being afraid of other inmates' words and actions	7	12.3
Being reproved by the prison staff	3	5.3
Other factors		
Worrying about family	4	7.0
Obligation to perform prison labor	4	7.0
Sleep disturbance due to tension	5	8.8
Somatic discomforts[b]	3	5.3

[a] The 28 flashbackers experienced flashbacks from 1 to 10 times each, for a total of 57 flashbacks
[b] Abdominal pain (n = 1), back pain (n = 1), and general fatigue (n = 1)

Stressful experiences and anxiety levels

The 28 flashbackers had been exposed to significantly higher numbers of threatening, stressful events (X^2 = 8.20), and MAP-induced frightening paranoid-hallucinatory states (X^2 = 8.20) during previous MAP use than the 18 non-flashbackers (Table 1). These events corresponded to severe type (rejecting parents, divorce or unwanted pregnancy, axis IV scores of 4) or extreme type (physical or sexual abuse, axis IV scores of 5) of psychosocial stressors. The axis IV scores in the flashbackers were significantly higher than in the non-flashbackers (Z = 4.45). The 8 flashbackers who had not undergone stressful events had experienced MAP-induced frightening paranoid-hal-

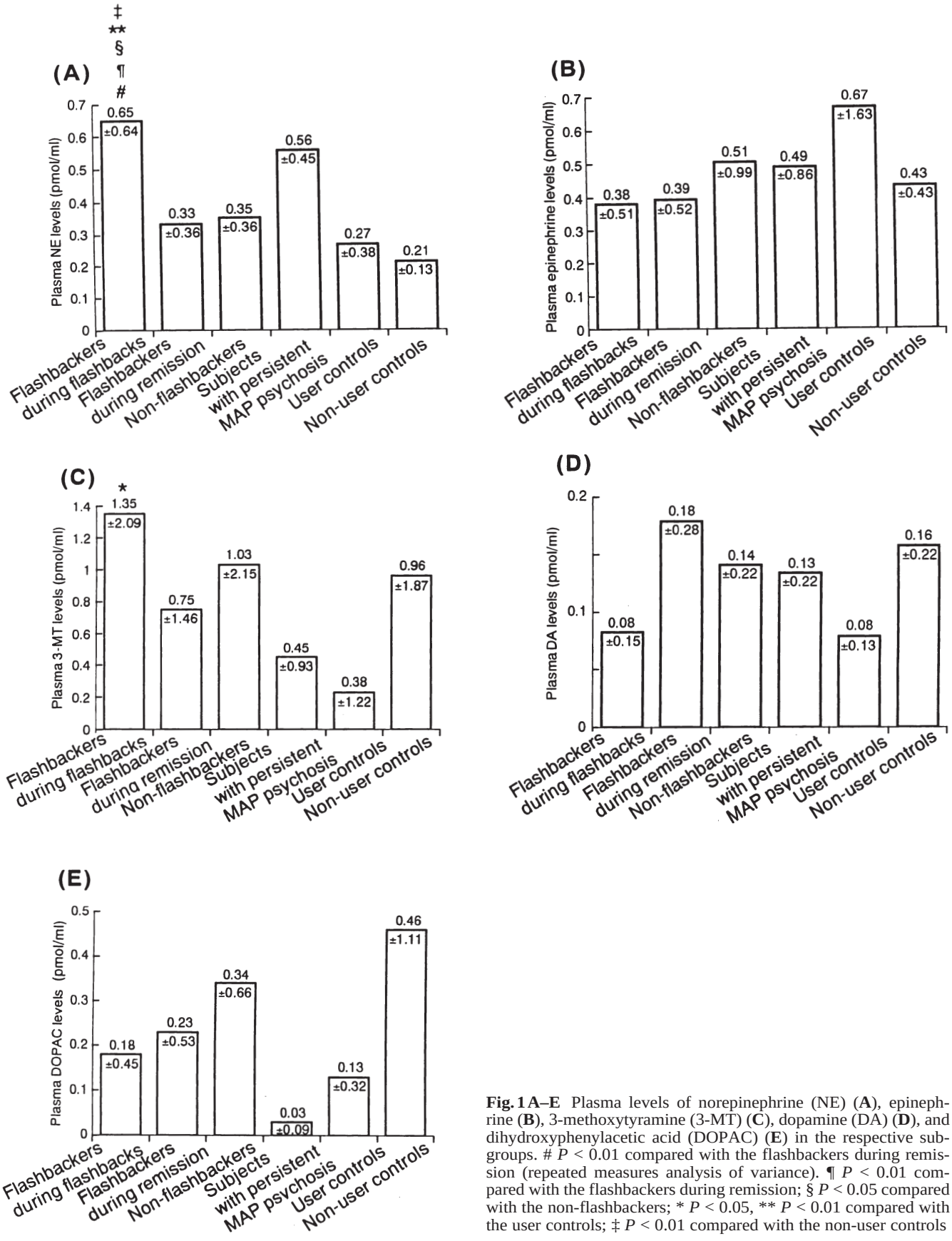

Fig. 1 A–E Plasma levels of norepinephrine (NE) (**A**), epinephrine (**B**), 3-methoxytyramine (3-MT) (**C**), dopamine (DA) (**D**), and dihydroxyphenylacetic acid (DOPAC) (**E**) in the respective subgroups. # $P < 0.01$ compared with the flashbackers during remission (repeated measures analysis of variance). ¶ $P < 0.01$ compared with the flashbackers during remission; § $P < 0.05$ compared with the non-flashbackers; * $P < 0.05$, ** $P < 0.01$ compared with the user controls; ‡ $P < 0.01$ compared with the non-user controls

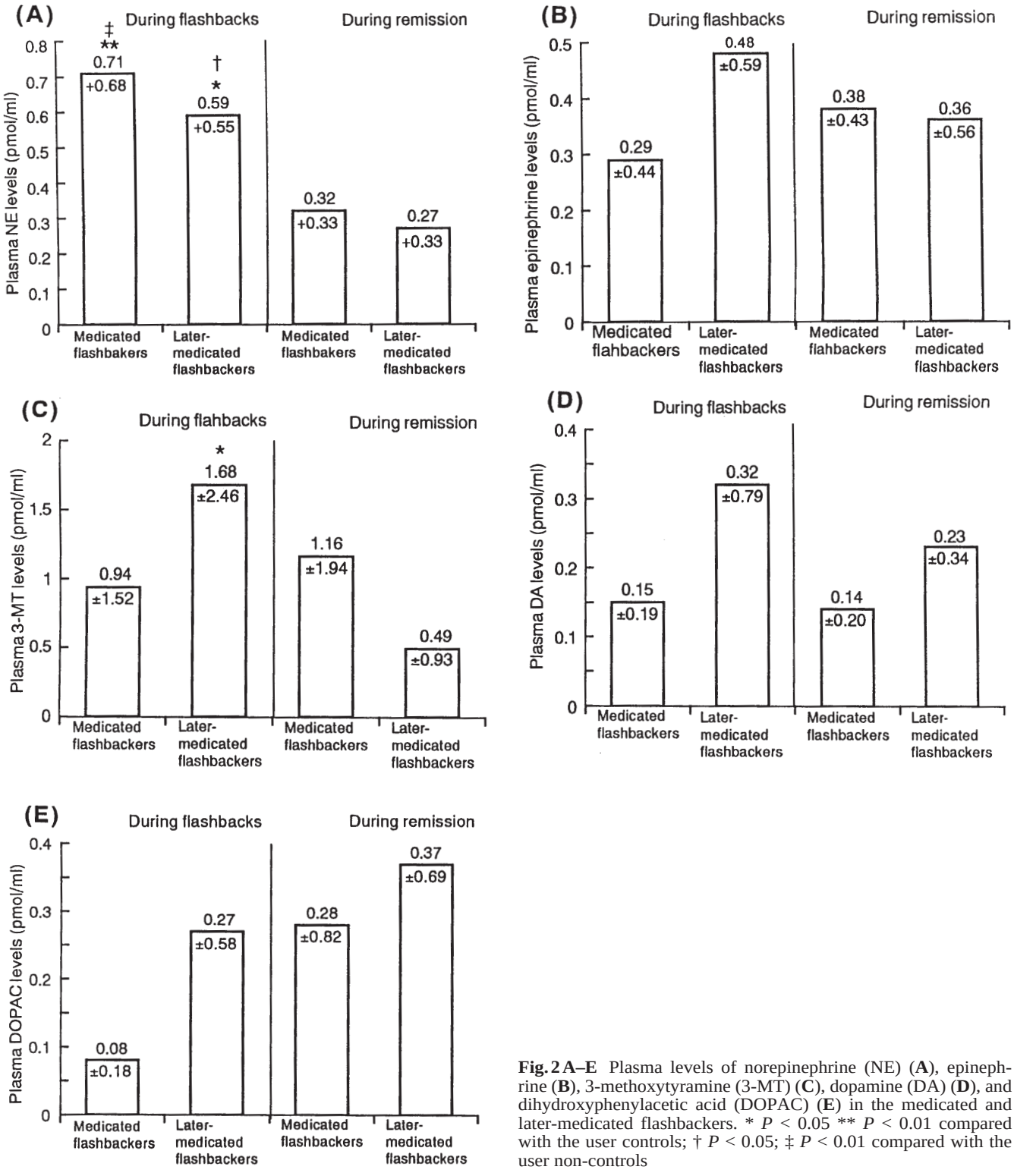

Fig. 2 A–E Plasma levels of norepinephrine (NE) (**A**), epinephrine (**B**), 3-methoxytyramine (3-MT) (**C**), dopamine (DA) (**D**), and dihydroxyphenylacetic acid (DOPAC) (**E**) in the medicated and later-medicated flashbackers. * $P < 0.05$ ** $P < 0.01$ compared with the user controls; † $P < 0.05$; ‡ $P < 0.01$ compared with the user non-controls

lucinatory states, i.e., hallucinations threatening the subject with death ($n = 3$), frightening visual hallucinations (a vampire, a hanging dead body or blood on the floor) ($n = 3$), or delusions of being possessed by a devil ($n = 1$), delusions of being killed by a person concerned ($n = 2$) or delusions of being pursued by a mobster or the police ($n = 5$). Thus, compared with the non-flashbackers, all flashbackers had been exposed to threatening, stressful events or frightening psychotic symptoms during previous MAP use. The factors that triggered the flashbacks were found to meet the DSM-III-R criteria for a mild type of psychosocial stressor (axis IV scores of 2), involving mainly

a mild fear of other people, and this was stimulated by personal conflicts in the prison (Table 2). These factors represent non-specific psychosocial stressors that occur in ordinary conflicts in the prison.

The STAI-state scores did not differ significantly among the subject subgroups (during flashbacks 58.3 ± 9.9, at remission 54.8 ± 11.9, non-flashbackers 52.5 ± 7.2, user controls 50.7 ± 5.6, non-user controls 53.3 ± 10.6) (H = 3.37, df = 4, P = 0.50). STAI-trait scores during flashbacks (60.8 ± 9.2) were significantly higher than in random subsamples of 13 of the 18 non-flashbackers (50.0 ± 8.5) (Z = 2.60, $P < 0.01$), 9 of the 22 user controls (45.2 ± 8.1) (Z = 3.06, $P < 0.01$), and 8 of the 11 non-user controls (48.8 ± 14.3) (Z = 2.24, $P < 0.05$). The STAI-trait scores during remission (59.1 ± 13.0) were significantly higher than in the 13 non-flashbackers (Z = 2.02, $P < 0.05$) and the 9 user controls (Z = 2.49, $P < 0.05$). Blood pressure and heart rate did not increase during flashbacks.

Plasma levels of catecholamines and their metabolites

As shown in Fig. 1, repeated measures ANOVA revealed a significant difference between flashbacks and remission only in plasma NE levels (F(1,26) = 10.44). No significant interaction between neuroleptic treatment and testing time was recognized for plasma levels of NE (F(1/26) = 0.09, P = 0.77) or other monoamine metabolites (F(1/19–26) = 0.16–3.42, P = 0.08–0.69). There was no significant effect of neuroleptic treatment on plasma levels of NE (F(1/26) = 0.52), P = 0.48) or other monoamine metabolites (F(1/19–26) = 0.008–3.68, P = 0.07–0.93). Plasma NE levels during flashbacks were significantly higher than during remission and were significantly higher than in the non-flashbackers, and the user and non-user controls. Plasma 3-MT levels during flashbacks were significantly higher than in the user controls. Plasma levels of NE (P = 0.052–0.13) and other monoamine metabolites (P = 0.10–0.97) in the 8 subjects with persistent MAP psychosis were not significantly different from the user and non-user controls. Plasma E levels did not differ significantly between the subject subgroups (P = 0.29–0.97). During flashbacks, both the 13 medicated and the 15 later-medicated flashbackers had significantly higher NE levels than the user and non-user controls. The later-medicated flashbackers had significantly higher 3-MT levels during flashbacks than the user controls (Fig. 2).

Discussion

Previous paranoid-hallucinatory states in the 28 flashbackers had occurred after the ingestion of MAP, but not after exposure to any marked stressor. The flashbackers developed transient psychotic aspects of flashbacks, which manifested as paranoid-hallucinatory states closely resembling their previous MAP psychosis, with no gross impairment of awareness of reality or marked reduction in functioning, under conditions that provoked mild psychosocial stress. There was no possibility of secret use of MAP or other substances. Thus, the flashbacks did not meet the DSM-IV criteria for delusional disorder or brief psychotic disorders, but most likely occurred as a spontaneous psychosis due to previous MAP psychosis. With reference to the reported finding that psychedelic drug flashbacks persist for 1–2 years (Matefy et al. 1978), or even 5 years or longer (DSM IV 1994), the total duration of flashbacks appears to be consistent with that of psychedelic drug flashbacks. In view of the relatively prolonged flashback states and the fact that the flashbacks were recrudescence of previous MAP psychosis, the flashbacks reported here may appropriately be termed “recurrence of MAP psychosis” (Hausner 1980).

The most important finding is that the flashbackers had been exposed to significantly higher number of frightening, stressful experiences than the non-flashbackers during previous MAP use, and then exhibited flashbacks in situations of mild psychosocial stress, involving mainly mild fear of other people. Mild psychosocial stressors disturbed the well-being of the subjects (usually stimulating a mild fear of other people) and, thus, met the general definition of stress (Landau et al. 1986). Animal studies have shown that stressful stimuli result in sensitization of the brain and peripheral noradrenergic mechanisms to subsequent stress that is mild enough to have no measurable effect on non-exposed animals (Cassens et al. 1980; Petty et al. 1994). AMP induces enduring sensitization to stress through dopaminergic changes (Robinson et al. 1987). Importantly, stressful experiences together with MAP use would appear to be irrational and may consequently have greatly increased the sensitivity to subsequent mild (non-specific) stressors. Under this condition, mild psychosocial stressors were able to trigger the flashbacks.

The plasma NE levels reported here were within or not over-below normal Japanese values (0.04–0.4 ng/ml, 0.237–2.37 pmol/ml) (Ozawa 1991). Normal Japanese limits for plasma 3-MT levels have not been reported. Plasma 3-MT levels in this study were not outside levels found in several healthy Japanese subjects (1.6 pmol/ml) (Wang et al. 1975). The present results of monoamine metabolite analysis suggest that increased noradrenergic activity is related to the occurrence of flashbacks. Plasma levels of 3-MT, which is a more sensitive indicator of preferential flux of DA release than either DOPAC or HVA (Wood and Altar 1988; Heal et al. 1990), were elevated during flashbacks. There is evidence of an important correlation between peripheral and brain 3-MT (Kent et al. 1990). A recent animal study reported that repeated stressful stimuli sensitize 3-MT release to subsequent stress (Chrapusta et al. 1997). Thus, the higher 3-MT levels may reflect an increase in DA release. Overall, stressful experiences together with MAP use may have induced sensitization to stress associated with noradrenergic hyperactivity and some degree of increased DA release. High trait anxiety in the flashbackers may reflect such noradrenergic hyperreactivity (Péronnet et al. 1986).

It has been reported that memories of stressful events are synthesized into symbolic form and then transcribed

into personal narratives (van der Kolk and Fisler 1995). All flashbackers had narrative memories of frightening, stressful experiences closely related to MAP psychosis, which may therefore have been synthesized into frightening images. Mild psychosocial stressors, involving mainly a mild fear of other people, may have actualized the encoded frightening images through sensitization to stress associated noradrenergic hyperreactivity, involving increased DA release. Thus, memories of MAP psychosis may have been elicited, triggering the flashbacks, including increased NE levels and a smaller increase in 3-MT levels.

Plasma levels of catecholamines and their metabolites do not accurately reflect brain neurotransmitter activity, despite the strong correlations found between plasma and cerebrospinal fluid (CSF) levels of NE (Roy et al. 1988) and 3-MT (Kent et al. 1990). The measurement of plasma catecholamines and their metabolites nevertheless remains the least invasive method available for evaluating central catecholamine metabolism.

It has been reported that plasma NE levels were increased by exercise through increased production of endothelin-1 which induces changes in distribution of blood flow in skeletal muscles (Maeda et al. 1997). Although motor activity of the flashbackers was highly restricted in the prison, the possibility that the elevated NE levels may be attributable to excessive motor activity cannot be wholly ruled out. The elevated NE levels (Peronnet et al. 1986) and 3-MT levels (Charapusta et al. 1997) may be secondary to heightened sympathetic activity related to stress or anxiety. However, plasma E levels, which reflect fluctuations in emotional stress (Dimsdale and Moss 1980), STAI-state scores, heart rate, and blood pressure were not affected by the flashbacks. A stimulus of sufficient intensity, as indicated by heart rate, can activate peripheral noradrenergic systems (Abercrombie and Jacobs 1987). Taking these observations into account, the elevated NE and 3-MT levels are not necessarily due to increased sympathetic arousal.

The neuroleptics used may affect plasma NE and 3-MT levels. A previous study on patients with schizophrenia showed that haloperidol (5–10 mg/day or 10–20 mg/day) reduced plasma NE levels over the course of 6 weeks of treatment (Green et al. 1993). Other studies have showed that treatment with haloperidol (4–8 mg/day) or thioridazine (150–400 mg/day) for at least 10 days (Tuck 1973), or haloperidol (4 mg/day) for 5 weeks (Breier et al. 1994) had no significant effect on peripheral noradrenergic activity. Infusion of chlorpromazine (25 mg) has been shown to decrease plasma NE levels (Risbo et al. 1983). Although a CSF study is not the same as a plasma study, treatment with haloperidol (585 ± 755 mg/day in chlorpromazine equivalents) for at least 3 weeks increased CSF levels of NE in schizophrenic patients (Gattaz 1983). Comparative clinical studies of the effect of neuroleptics on plasma 3-MT levels are scarce. Preclinical studies have reported that haloperidol (0.5 mg/kg) or chlorpromazine (20 mg/kg) have no significant effect on brain 3-MT levels (Westerink and Spaan 1982). However, brain 3-MT levels have been reported as increasing after treatment with haloperidol (0.12–1.0 mg/kg), chlorpromazine (2.3 or 14 mg/kg), and thioridazine (5 or 30 mg/kg) (Wood and Altar 1988). Thus, neuroleptic effects on plasma NE levels and brain 3-MT levels remains controversial, due possibly to differences in subject selection criteria or the type of study. In the present study, both medicated and later-medicated flashbackers had significantly higher NE levels during flashbacks than the user and non-user controls. The later-medicated flashbackers had significantly higher 3-MT levels during flashbacks, at which point they had not yet received neuroleptic treatment, than the user controls. Thus, our neuroleptic treatment may not be significant in raising the NE and 3-MT levels. Since our analysis of the differences between the subject subgroups took into account subjects with and without neuroleptic treatment, influence of neuroleptics on plasma NE and 3-MT levels cannot be completely ruled out, to answer this question, further investigation is necessary.

In conclusion, frightening stressful experiences together with MAP use may increase sensitivity to subsequent mild psychosocial stressors. Noradrenergic hyperactivity and increased DA release may be included in this process. This sensitization to stress may elicit memories of frightening, stressful experiences closely related to MAP psychosis in response to mild psychosocial stressors, causing flashbacks to occur. The present findings suggest that sensitization to stress associated with noradrenergic hyperactivity, involving increased DA release is central to spontaneous recurrences of MAP psychosis.

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