Relapse of Paranoid Psychotic State in Methamphetamine Model of Schizophrenia

by Mitsumoto Sato, Yohtaro Numachi, and Takashi Hamamura

Abstract

The study of the clinical course of methamphetamine (MAP) psychosis yields insights into the biological aspect of the relapse of the paranoid psychotic state with hallucination in schizophrenia. A series of MAP psychosis studies in Japan conducted over a period of more than four decades revealed three types of clinical courses of MAP psychosis after discontinuation of MAP: transient type, prolonged type, and persistent type. Identification of the latter two indicates a lasting change in the brain that produces and maintains a schizophrenia-like paranoid psychotic state without MAP. The characteristic course seen in the transient type is acute recurrence of the psychotic state after a long remission period, almost identical to the initial episode, due to reuse of MAP or to psychological stressors. Such lasting vulnerability of the brain to schizophrenia-like psychotic symptoms may be caused by a lasting sensitization of the brain to the psychotogenic action of MAP resulting from its chronic abuse. Experimental studies using animals sensitized to MAP-induced stereotypy suggest that lasting enhancement of MAP-induced dopamine release in the striatum and nucleus accumbens is related to the development and expression of brain vulnerability to schizophrenic symptoms.

The identification of the etiology of brain dysfunctions underlying schizophrenia has been sought since the time of Kraepelin. More recently, researchers have focused on biological aspects of vulnerability to schizophrenic symptoms because of the high relapse rates after remission (Kane 1987) and the lack of a uniform course and outcome in schizophrenia. Although the neurochemical changes in the brain corresponding to the pathology of schizophrenia or to the patient's vulnerability to schizophrenic symptoms should be investigated in patients with schizophrenia, ethical considerations limit such clinical studies. Consequently, preclinical studies using animal models of schizophrenia have become indispensable in psychiatry as well as in other specialties of physical medicine. When an exogenous agent produces a characteristic clinical feature and a course almost identical to that of schizophrenia, application of such an agent might be suitable for creating an animal model of schizophrenia. Among the many substance-induced psychoses, methamphetamine (MAP) psychosis has been regarded as the dysfunction most analogous to schizophrenia since World War II in Japan. In this report, the concept of MAP psychosis will be discussed in light of clinical studies in Japan with special reference to the dopamine hypothesis of schizophrenia. The onset and relapse of a paranoid psychotic state similar to that of acute schizophrenia will be highlighted to yield insight into vulnerability to schizophrenic symptoms.

Clinical Study on MAP

MAP Abuse and MAP Psychosis in Japan. MAP continues to be the most widely abused central nervous system stimulant in Japan. During World War II, MAP was used both

Reprint requests should be sent to Dr. M. Sato, Dept. of Psychiatry, Tohoku University School of Medicine, 1-1, Seiryo-machi, Sendai-shi, Miyagi, Japan 980.

by members of the Air Force and among civilians engaged in wartime industries to increase productivity (Henmi 1965). Shortly after the dumping of military stores of MAP on the open market in 1945, an epidemic of intravenous MAP abuse occurred in Japan, constituting the first period of MAP abuse (1946–55). The peak of this epidemic occurred in 1954, when the number of MAP abusers was estimated at between 500,000 and 1 million among a population of about 83 million. This initial epidemic dropped off sharply with the revision of the Central Stimulant Control Law in 1954. However, a second epidemic of MAP abuse began in 1970 and continues today. In 1989 the number of MAP abusers was estimated at between 200,000 and 300,000 among a population of about 120 million. The characteristics of these two epidemics are summarized in table 1.

Table 1. Two epidemics of methamphetamine (MAP) abuse in Japan

Characteristic	First epidemic	Second epidemic
Period	1946–1955	1970–present
Origin	Unintentional	Initiated by Yakuza
Social environment	Low economic level, post-war confusion	High economic level
MAP use	Initially legal	Illegal
Abusers		
Age	20	30
Social position	Civilian	Yakuza and related underworld
Motivation	Increased productivity	Curiosity and euphoria
Drug		
Form	Tablet or solution	Powder
Quality	Low	High
Cost	Low	High
Dose	Initial 3 mg/shot; eventually >30 mg	>30–40 mg
Route	Oral or i.v. injection	i.v. injection
Combined abuse with narcotics	Rare	Rare

Note.—Yakuza = organized criminal syndicates in Japan that illicitly imported MAP. Accordingly, abusers had direct or indirect connection with the Yakuza.

The mixed use of MAP with narcotics, including cocaine, is extremely rare in Japan. The abusers take a varied dose (mostly 30 to 50 mg/shot) of high quality MAP intravenously 1 to 10 or more times a day. The number of persons rearrested for drug offenses has increased steadily and represented 53.9 percent of all Central Control Law arrests in 1986. This situation in Japan allows us to study the natural course of MAP psychosis and its acute exacerbation by MAP reuse in patients with past MAP psychosis. Although the first case report of amphetamine (AP) psychosis was made by Youngs and Scoville in 1938, two monographs, *The Methamphetamine Psychosis* (Tatetsu et al. 1956) and *Amphetamine Psychosis* (Connell 1958), were published when the disease entity of AP or MAP psychosis was more widely accepted in Japan than the diagnosis of activation of a latent form of schizophrenia.

MAP Psychosis as a Psychosis Analogous to Schizophrenia. The three main reasons for considering MAP psychosis as analogous to schizophrenia in Japan are the similarities of MAP psychosis to schizophrenia in cross-sectional clinical features, the clinical course with frequent relapses, and the response to neuroleptics.

Clinical features. Cross-sectional clinical features of MAP psychosis reported in Japan for four decades coincide with those described by Connell (1958): "The clinical picture is primarily a paranoid psychosis with ideas of reference, delusions of persecution, auditory and visual hallucinations, in a setting of clear consciousness." In fact, 92 percent of Tatetsu's 131 cases, 90 percent of our 82 cases (Sato et al. 1982), and 72.9 percent of Konuma's 192 cases (1984) showed the symptoms of a paranoid psychotic state. Abundant paranoid psychotic delusions frequently accompanied by auditory hallucinations, bizarre ideas (e.g., delusions of being controlled), thought broadcasting, thought insertion, and thought withdrawal, combined with a loosening of associations, were all observed (Sato et al. 1983). Sato and colleagues (1982, 1983) found that auditory hallucinations, with voices commenting on behavior, were more prominent than visual hallucinations, while the sensorium remained clear. Such clinical features in MAP psychosis include some of Schneider's (1959) first-rank symptoms and symptoms in the active phase of schizophrenic disorders in *DSM-III*

(American Psychiatric Association 1980). Thus, the characteristic symptoms of MAP psychosis are virtually indistinguishable from those of schizophrenic disorders based upon cross-sectional psychotic features alone.

The initial paranoid psychotic episode appears after repeated MAP abuse for latent periods ranging from a few months to more than 4 years, except in the case of idiosyncratic reaction (table 2).

Several Japanese researchers (Hayashi 1955; Tatetsu et al. 1956; Sato et al. 1982; Konuma 1984) described diminishing activity and reduced euphoric effects with repeated use of MAP while patients simultaneously developed deeper psychotic symptoms, including a stage in which they displayed greater suspiciousness of those around them. These findings confirm those of Ellinwood and colleagues (1973). This change in the clinical response to MAP may suggest an evolution of brain dysfunction that is produced by the repetition of MAP injection over time. Angrist and Sudilovsky (1978) also suggested that chronic use further affected the response of a given individual to a given stimulant dose because of supersensitivity and tolerance. Experimentally, Klawans and Margolin (1975), Weiner et al. (1979), and Sato (1979) reported that chronic AP or MAP pretreatment resulted in a progressive increase in sensitivity to behavioral stereotypy induced by AP, MAP, cocaine, and apomorphine. It is important to note that such increased sensitivity to catecholamine agonists persists for more than 3 months after the discontinuation of MAP administration in animals.

Clinical course of the psychotic state after MAP withdrawal. The clinical course of MAP psychosis in Japan differs basically from that described by Connell (1958) in the duration of the psychotic state after MAP withdrawal. Tatetsu and colleagues (1956), for example, reported that 14.4 percent of 131 inpatients with chronic intravenous MAP intoxication required more than 5 years to recover after MAP withdrawal, and that the psychotic state continued for 8 to 22 years with frequent relapses without MAP reuse in some cases. In contrast, Connell reported on 42 oral

Table 2. Clinical course of stimulant-induced psychosis

	Connell (1958)	Tatetsu et al. (1956)	Sato et al. (1982)	Konuma (1984)
Stimulant	AP	MAP	MAP	MAP
Mode of administration	Oral	i.v.	i.v.	i.v.
Period of abuse before first admission with psychotic episode				
Number of patients	28	100	35	136
<1 month	0	6	0	13
1-6	18	42	17	18
7-12	0	27	3	16
1-4 years	28	22	43	32
>4	43	3	37	20
Undetermined	11	0	0	1
Duration of psychotic state after AP or MAP discontinuation				
Number of patients	30	144	82	192[1]
0-10 days	53	0	64	0
11-30	17[2]	74	18	87
>1 month	7	26[3]	18	13
Undetermined	23	0	0	0

Note.—Numbers are percentages unless otherwise indicated. Difference in number of subjects for each time period depends on the number of subjects available for examination among total subjects. AP = amphetamine; MAP = methamphetamine.

[1]Includes 14 cases (7.3%) of acute MAP intoxication.

[2]The psychotic state disappeared between 2 and 4 weeks.

[3]Includes some cases with prominent affective symptoms other than those of paranoid psychotic state.

AP abusers, and concluded that over half of the patients with AP psychosis recovered within a week unless there was a demonstrable cause for the continuance of symptoms, for example, continuous excretion of the drug or hysterical prolongation of symptoms. However, the psychotic state continued for more than 2 weeks in 24 percent of Connell's 30 cases (table 2).

In addition, at least 12 reports in Japan since 1945 have supported Tatetsu and colleague's (1956) observation. Hayashi (1955) reported on 74 patients with MAP psychosis and indicated that the psychotic state of 23 patients (31 percent) continued for more than 20 days, and in 7 cases (10 percent), the psychotic state continued for more than 2 years. Sato and colleagues (1982) reported on 82 inpatients with MAP psychosis (table 2). Based on these data, Sato and Kashihara (1982) classified their duration of paranoid psychotic state after discontinuation as follows: the transient type (less than 10 days), 64 percent; the prolonged type (10–31 days), 18 percent; and the persistent type (more than 1 month), 18 percent. Konuma (1984) found 13 percent of the persistent type in 192 i.v. MAP abusers. Available Japanese reports suggest that one-third of the patients with MAP psychosis may exhibit symptoms for more than 10 days, although the urinary excretion of MAP ends within 3 to 5 days. However, these reports contained insufficient data on urinary MAP excretion in patients with prolonged and persistent types of psychosis, although most such patients were admitted to hospitals and some were retained there to discontinue drug use. Thus, the Japanese studies suggest that a MAP-induced paranoid psychotic state may not be due to direct psychotomimetic action of the drug on the brain, but to some brain dysfunction that develops during MAP abuse. Angrist and colleagues (1987) reported on the early pharmacokinetics and clinical effects of oral *d*-AP in normal subjects, and found a discrepancy in the peak times between maximum subjective effects and plasma AP levels.

Susceptibility to relapse in patients with previous MAP psychosis. About 82 percent of patients with MAP psychosis recover from the paranoid psychotic state within a month after MAP withdrawal. However, we reported that once the psychotic state develops, recurrence is prompt with subsequent exposure to MAP (Sato 1978, 1986; Sato et al. 1983) or to psychological stressors (Tatetsu et al. 1956; Sato 1979; Konuma 1984). We also proposed that a single dose of less than the amount of the initial injection of MAP reactivates the previous paranoid psychotic state even after a prolonged period, such as after 5 years of abstinence (Sato et al. 1983). This evidence suggests that a long-term sensitization to MAP leads to an acute exacerbation of the psychotic state almost identical to the initial psychotic episode. The cross-sectional clinical features of the paranoid psychotic state in MAP psychosis are indistinguishable from those of schizophrenic disorders; thus, these two disorders may have a common biological triggering mechanism. If this mechanism can be identified in the MAP psychosis model, it will be relevant to the identification of the mechanism in schizophrenic disorders responsible for the estimated 75 percent relapse rate following neuroleptic discontinuation during followup intervals ranging from 6 to 24 months, even after remissions of 6 months to 5 years (Kane 1987).

Prophylactic effect of neuroleptics. In eight patients who developed an initial psychotic episode with subsequent relapse, the paranoid psychotic state did not appear after MAP injection when the patients were concurrently receiving a small dose of a neuroleptic (e.g., 3 mg/day of haloperidol or 100 mg/day of levomepromazine) (Sato et al. 1983). Subsequent discontinuation of haloperidol induced acute recurrence of a psychotic state. This prophylactic effect of neuroleptics on the induction of the psychotic state again suggests a common biological base for recurrence of MAP psychosis and schizophrenic disorders.

Animal Model of Paranoid Psychotic State

Clinical studies on MAP psychosis suggest some characteristics in the development of the paranoid psychotic state that are almost identical to schizophrenic disorders: (1) the psychotic state generally develops gradually during long-term MAP abuse; (2) the psychotic features may continue after MAP withdrawal; (3) once the psychotic state develops, lasting susceptibility to recurrence by exposure to MAP or psychological stress persists without further MAP exposure; (4) recurrent psychotic features are identical to the initial paranoid psychotic episode; and (5) neuroleptics prevent recurrence triggered by MAP use. These results strongly suggest that the repeated pharmacological action of MAP progressively develops into a long-lasting change in brain function, which induces or causes the paranoid psychotic state to recur.

Some of these characteristics can be reproduced in animal experiments. Chronic administration of MAP increases the sensitivity of behavioral

stereotypy to MAP (reverse tolerance phenomenon), with residual effects for some time after MAP withdrawal. In fact, a small dose of MAP initially ineffective in producing behavioral stereotypy is enough to produce the behavior 3 months after the discontinuation of chronic MAP administration (Sato 1979). This phenomenon is identical to the kindling effect (Post and Kopanda 1976), that is, a progressive and lasting increase in seizure susceptibility resulting from the repeated production of localized after-discharges in the brain (Goddard et al. 1969). Once an animal is kindled, even after a long interval, stimulation of the brain at a stimulus intensity initially ineffective in producing the seizure produces generalized convulsive seizures. Moreover, the kindled generalized convulsion may occur spontaneously after kindling (Wada et al. 1974). Both the reverse tolerance phenomenon and the kindling effect indicate that the repeated electrical or chemical stimulation of the brain produces a lasting susceptibility to an abnormal behavior that may be activated spontaneously or by reexposure to the stimulus.

Biological Basis of Susceptibility to Paranoid Psychotic State

Using animals in which the reverse tolerance phenomenon was established by chronic MAP administration, biochemical changes in the brain were studied at two different states: the steady state after chronic MAP treatment, which is related to vulnerability to psychosis, and the state after MAP readministration, which is related to the recurrence of psychosis. As with AP, MAP acts on nerve cells and nerve terminals and results in an increase in dopamine release, inhibition of its reuptake, and inhibition of monoamine oxidase activities. Accordingly, MAP increases dopamine concentration in the synaptic cleft in a dose-dependent manner in rat striatum. Simultaneously, dopamine metabolites (3,4-dihydroxyphenylacetic acid [DOPAC] and homovanillic acid [HVA]) decrease, presumably due to a depletion of dopamine in the cytosol pool (Zetterstroem et al. 1986). Although MAP acts on the noradrenergic and serotonergic systems of the brain as well, repeated MAP administration mainly affects the dopaminergic systems because (1) cross-sensitization is positive to direct and indirect dopamine agonists including cocaine, L-dopa, and apomorphine, but negative to i.c.v. (intracerebroventricular) noradrenalin or the serotonin precursor (5-hydroxytryptophan) and (2) reappearance of developed behavioral stereotypy is blocked by the dopamine D_2 receptor blocker, haloperidol, but not by noradrenalin and serotonin antagonists (Sato 1979; Kashihara et al. 1984). For these reasons, lasting change induced by MAP is presumed to occur mainly in the dopaminergic systems of the brain.

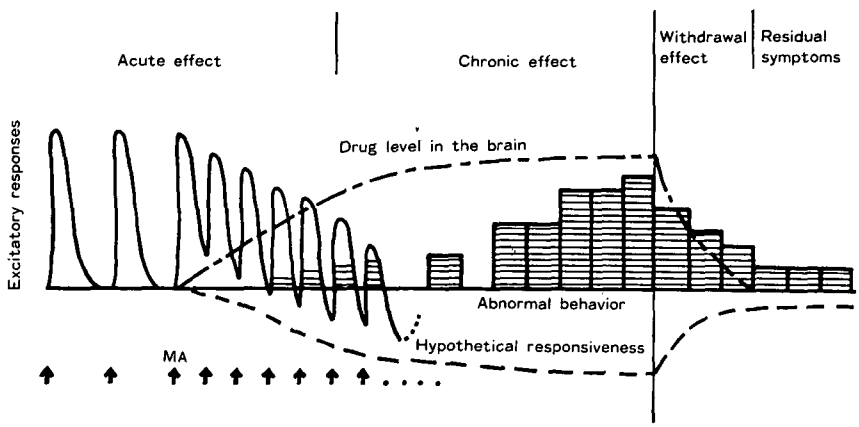
Dopaminergic Systems in Steady State After Chronic MAP Administration. In animals, more than 7 days after chronic treatment with MAP or AP, the dopamine concentration is unchanged or decreased in the striatum, and decreased in the limbic forebrain, hypothalamus, and cerebral cortex. DOPAC and HVA concentrations are also unchanged or decreased in the striatum and limbic forebrain (see Sato and Kashihara 1986). Nishikawa and colleagues (1983) reported no change in dopamine and DOPAC levels, DOPAC/dopamine ratio, and tyrosine hydroxylase activity in rat striatum. ^{3}H-spiperone binding with a competitor of butaclamol decreased in the striatum and frontal cortex, while it increased in the nucleus accumbens (Akiyama et al. 1982). In addition, studies that determined extracellular dopamine concentration by in vivo microdialysis showed no change more than 1 week after MAP or AP withdrawal following chronic administration in the steady-state extracellular dopamine concentrations in the striatum and nucleus accumbens (Robinson et al. 1988; Kazahaya et al. 1989). These results suggest that repeated MAP administration induces no lasting change or decrease in dopamine concentration, its metabolites, and receptors in the striatum in the steady state.

The State After MAP Readministration. Recently, Kazahaya and colleagues (1989), using in vivo dialysis, found that the readministration of both MAP and cocaine after a 7-day interval free from chronic MAP treatment caused a marked increase in dopamine and a decrease in DOPAC and HVA under behavioral sensitization in the rat striatum. They concluded that the enhanced efflux of dopamine in the synaptic cleft may play a role in the MAP-induced behavioral sensitization and cross-sensitization to cocaine. This finding is consistent with earlier findings by Robinson and Becker (1982), Kolta and colleagues (1985), and Yamada and colleagues (1988) that the AP-stimulated release of dopamine increased in striatal slices of sensitized animals. In addition, Robinson and colleagues (1988) found that AP-induced long-term hypersensitivity was accompanied by a significantly elevated dopamine release in the nucleus accumbens of rats with previous repeated AP treatment. They

also noted no change in the basal extracellular concentrations of dopamine, and concluded that the sensitization produced by chronic AP use was due to the releasability of dopamine. Thus, MAP- and AP-induced behavioral hypersensitivity appears, at least partially, to be due to an increased releasability of dopamine in the striatum and nucleus accumbens. The precise mechanism of this long-term increase in dopamine releasability is unknown. In their review of previous reports, Robinson and Becker (1986) pointed out two possibilities: (1) subsensitivity of autoreceptors located on the presynaptic terminal regulating dopamine release and (2) presynaptic facilitation by hyperpolarization of the dopamine terminal via a presynaptic input or a shift in the distribution of dopamine from a storage pool to a more releasable pool. We postulated that chronic MAP administration results in a long-term change in presynaptic cell membrane at the nerve terminal that may cause an increase in both MAP and dopamine uptake with an increased release of dopamine at the synaptic cleft. It will be important to examine this impaired-membrane theory in the future because of our two findings: a lasting increase in ^{14}C- and ^{11}C-MAP radioactivity in both the striatum and nucleus accumbens of animals sensitized to MAP (figure 1; Numachi et al. 1990) and more cross-sensitivity to cocaine than to L-dopa and apomorphine in those animals (Sato 1979).

While the cocaine- and the MAP-induced increases in extracellular dopamine depend on the presynaptic vesicular pool and cytosol pool, respectively, the uptake site is key in these drugs exerting their pharmacological effects. Cocaine blocks dopamine reuptake and MAP or AP exerts a releasing effect through their

Figure 1. Differential absorption ratio (DAR) of ^{14}C-methamphetamine in rat brain



Animals in the methamphetamine (MAP) and control groups (n = 17 each) were pretreated with MAP and saline, respectively, for 21 days. DAR was determined 7 days after pretreatment using beta counting method. Statistical analysis was made by t-tests.

uptake into cytosol (Fisher and Chao 1979; Bonnet et al. 1984; Butcher et al. 1988; Parker and Cubeddu 1988). A change in the dopamine uptake site on the nerve terminal may explain the potent cross-supersensitivity to cocaine in animals sensitized to MAP. Using an in vivo dialysis method, Butcher and colleagues (1988) found no change in dopamine release in the presence of a low concentration of veratrine or ouabain which enhanced dopamine reuptake. However, under the same conditions, a MAP challenge test enhanced dopamine release remarkably. This may be a state similar to the one we postulated as impaired-membrane theory in the model of MAP psychosis.

Cross-Sensitivity to MAP and Psychological Stressors. Clinically, a paranoid psychotic state can recur spontaneously in patients with past MAP psychosis (Tatetsu et al. 1956; Sato 1978; Konuma 1984). In these cases, it is almost impossible to differentiate MAP psychosis from some schizophrenic disorders. However, animal studies that support the relapse of the psychotic state with psychological stressors have been reported. Antelman and colleagues (1980) have proposed that AP may be interchangeable with nonpharmacological stressors in its ability to induce long-term sensitization. Robinson and Becker (1986) reviewed these articles and concluded that previous exposure to stressors enhances AP-induced behavior, and also that previous exposure to MAP influences the effects of subsequent stressors. Such interchangeability of behavioral hypersensitivity to stimulants and psychological stressors again supports the traditional clinical observation in Japan that MAP psychosis, once it has developed, results in a lasting susceptibility to the paranoid psychotic state, and is easily activated by a small dose of MAP and psychological stressors.

Summary

Clinical studies of MAP psychosis for four decades in Japan strongly suggest a possibility of prolongation and continuation of a MAP-induced paranoid psychotic state that is indistinguishable from that of some schizophrenic disorders after the discontinuation of MAP. A frequent recurrence of the psychotic state identical to the initially developed psychotic episode is common after the reuse of MAP or nonspecific psychological stress. These clinical characteristics suggest an evolution of a lasting vulnerability to the paranoid psychotic state in the brain during chronic MAP abuse. Animal studies suggest a lasting change in the brain dopaminergic system, and increased releasability of dopamine. Such increased releasability may be, at least partially, due to an impaired cell membrane at a presynaptic nerve terminal that may lead to an increased MAP and dopamine uptake with subsequent shift of the dopamine pool. The increased releasability of dopamine from presynaptic terminals may be related to the onset of a paranoid psychotic state or a relapse into one.

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The Authors

Mitsumoto Sato, M.D., is Professor, and Yohtaro Numachi, M.D., is Staff Psychiatrist, Department of Psychiatry, Tohoku University School of Medicine. Takashi Hamamura, M.D., is Staff Psychiatrist, Department of Neuropsychiatry, Okayama University Medical School, Japan.