Chronic Methamphetamine Intoxication Model of Schizophrenia in Animals

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Abstract

The chronic methamphetamine (MAP) intoxication model of schizophrenia in animals is outlined. The idea originated from the clinical and neurochemical similarities between MAP psychosis and schizophrenia that were found during the decade immediately after World War II when MAP abuse occurred in epidemic proportions in Japan. The chronic intoxication model is produced by daily injections of a small dose of MAP into animals for several weeks or months. Behavioral studies with various species of animals from guinea pigs to monkeys produced essentially the same disorders as those observed in human abusers. Specifically, monkeys manifest psychotic behaviors, which appear to result from perceptual-cognitive disturbances, as well as enduring autistic behavior disorders that resemble the defect symptoms in chronic schizophrenia. Furthermore, the psychotic behaviors were found to have a high relapse liability; they recurred readily after the readministration of the drug or under nonspecific stress conditions. The difference and relationship between the chronic MAP intoxication model and the amphetamine stereotypy (acute intoxication) model are discussed.

Origin of the Chronic Methamphetamine Intoxication Model of Schizophrenia

During the decade after World War II, Japanese psychiatrists had the opportunity to observe a number of cases of methamphetamine (MAP) psychosis, which have provided some invaluable lessons. The one conceptualized by H. Utene, working in Matsuzaawa Hospital, Tokyo, at that time, was that chronic MAP intoxication in animals might serve as a model for schizophrenia. The idea was based on two similarities between MAP psychosis and schizophrenia: similarities in clinical features and in the metabolic pattern of the brain.

It is well known that the hallucinatory-paranoid psychosis of chronic MAP intoxication closely resembles paranoid schizophrenia. But MAP addicts have two other clinical features that resemble those of schizophrenic patients. After the psychotic episode they tend to show enduring personality changes, primarily consisting of flattened affect and decreased volition. They also show a strong tendency to relapse after a few subsequent exposures to the drug, sometimes because of alcohol ingestion and sometimes due to psychological stress. These features were described for the first time by S. Tatetsu, who worked in Matsuzaawa Hospital at the same time as Utene (Tatetsu et al. 1956).

During the same period, neurochemical aspects were studied by Utene and his colleagues (Utene and Ezoe 1951; Utene et al. 1955, 1959). In a study investigating glucose metabolism in the excised cerebral cortex obtained from lobotomies of intractably disturbed patients, they observed a peculiar metabolic pattern (a decreased glucose consumption or lactate formation in spite of the control level of respiration) exclusively in schizophrenia and MAP psychosis. However, because the number of cases with MAP psychosis was very limited and the coexistence of schizo-
phrenia in these cases could not be negated, it was not certain whether the metabolic changes were attributable to MAP intoxication. They thus turned to the animal experiment, in which they injected guinea pigs with MAP hydrochloride (HCl) (6 mg/kg) once a day for several weeks, and confirmed that the metabolic pattern could be induced by chronic MAP intoxication.

During the experiment, they noticed behavioral changes in the animals. Over the long-term course of repeated injections, although the animals were excited for several hours after every injection, they gradually became inactive, unresponsive to external stimuli, and easy to handle during the intervals between injections. These changes, which lasted for more than a month after the cessation of injections, seemed suggestive of the personality changes of MAP addicts and the defect state of chronic schizophrenic patients.

It is particularly important to note that the original idea of the chronic MAP intoxication model was aimed at mimicking the residual defect state or negative symptoms of schizophrenia (figure 1). This is in contrast with the amphetamine stereotypy model, which is usually produced by giving a single large dose (5–10 mg/kg) of amphetamine or MAP (acute intoxication) and is regarded as a model for positive psychotic symptoms (Janssen et al. 1967; Randrup and Munkvad 1967).

**Behavioral Studies in Rodents and Cats**

In 1957 Utena started to investigate quantitative behavioral changes in mice, particularly the reduction in spontaneous motor activity, produced by chronic MAP administration (Utena 1961, 1966). Throughout the experiments mice were kept in a revolving wheel cage and the amount and velocity of spontaneous running activity were measured. When mice were injected with small doses of MAP HCl (1.4 mg/kg) once a day for 3–4 weeks, the daily level of the running activity increased slightly at the beginning of the injection period, but later decreased markedly. The decrease persisted up to 10 weeks after the termination of injections. The reduced activity could not be attributed to motor weakness of the animals because the velocity of running was unchanged. It was also found that chlorpromazine restored to some extent the activity in the intoxicated mice, although it had a depressant effect in control animals. Imipramine was also effective in restoring activity (Utena 1961).

However, the wheel cage did not permit measurement of the changes in responsiveness of the intoxicated animals to environmental stimuli. To measure these changes the cloister cage was devised. The cage was a round narrow (6 cm X 6 cm) runway of 2 m circumference, in which one mouse was housed. It was divided into 20 sectors, some of which were supplied with food and water, and other stimuli such as a view of another mouse. The “pass and stay” of the mice in these sectors were recorded automatically with electronic devices so that the animals’ behavior could be monitored without human interference for a long time. Analysis of these data revealed that in the residual stage of chronic MAP intoxication, responsiveness to the external stimuli or interest in the environment was reduced as was motor activity, and the repertoires of behavior patterns was impoverished. When put into an unfamiliar runway, the chronically intoxicated mice initially showed increased random activity but soon fell into an inactive state with only occasional loitering or feeding and little response to the stimulus mouse.

Yagi (1963) confirmed that long-term administration of small doses of MAP also produces a decrease in motor activity in rats. Furthermore, his group found that the acquisition as well as the extinction of avoidance...
learning was delayed in the chronically intoxicated rats, even a month after the cessation of injections (Moriguchi 1963).

More intricate behavioral changes produced by chronic MAP intoxication in cats were studied by Utena’s group (Funatogawa 1965). Thirty items of behavior patterns were arranged into six categories such as sociability, antisociability, contentment, excitement, defensive hostility, and aggressive hostility. Whereas a single dose (5 mg/kg) of the drug increased excitement and defensive hostility, daily injections of small doses (3 mg/kg) for 30–50 days produced an increase in antisociability and a decrease in excitement and defensive hostility.

The behavioral changes observed in the studies with guinea pigs, rats, mice, and cats were almost the same, comprising reduced spontaneous motor activity, reduced and undifferentiated response to the external stimuli, and an impoverished repertoire of behavior patterns. These abnormalities were a result of chronic intoxication and were long-lasting. They resembled characteristics of the autistic behavior of chronic schizophrenic patients such as loss of initiative, reduced responsiveness, all-or-nothing response tendency, indifference to surroundings, and withdrawal. However, except for acute motor excitement, no definite abnormalities resembling psychotic behaviors in humans were evident.

Behavioral Studies in Monkeys

Human MAP abusers usually develop delusions and hallucinations in the course of repeated injections of the drug. In order to see to what extent one could replicate human pathology in animals, Utena’s group undertook monkey experiments (figure 2; Machiyama et al. 1970, 1974; Utena et al. 1970). Seven of 17 male adult and young Japanese monkeys (*Macaca fuscata*) were subjected to long-term MAP administration. In each experiment, 7–9 monkeys were kept in a big cage to form a group, and 2–3 monkeys were injected with MAP HCl (1–2 mg/kg) every day at 1 p.m. except Sundays for 3–6 months. A crush cage on one side of the cage was used to give injections.

Japanese monkeys usually form a society with a definite order and structure. It was initially found that in a group of male monkeys, individuals of higher rank were generally active in behavior, while those of lower rank were nonactive. When injected with 1 mg/kg MAP HCl, the active ones showed distinct motor excitation, but the nonactive ones showed inhibition rather than excitation. The active/excitatory and nonactive/inhibitory relationship was more pronounced when the monkeys were placed in narrow cages by themselves and tested under these isolated conditions. Consideration was given to the difference in excitatory and inhibitory response types and to the ranking order in the group when monkeys were chosen for long-term MAP injections.

The behavioral changes in the monkeys resulting from chronic intoxication were classified into the following six categories: (1) a decrease in interaction with peer animals; (2) a decrease in motor activity and fixation in location; (3) ‘body-fingering’ behavior; (4) ‘staring’ behavior; (5) inexplicable aggressive or fearful behavior; and (6) ‘splitting’ of behavior.

In the course of repeated injections of the drug, the injected animals gradually stopped interacting with other monkeys, ending activities such as grooming, mounting, play, etc. Closely following this change, a decrease in motor activity, particularly in locomotion, developed, and the monkeys stayed in certain locations in the cage. These changes roughly

Figure 2. Relationship between schizophrenia and chronic methamphetamine intoxication

The Inverted triangle is employed to show that higher animals exhibit more abundant and intricate disorders, which are more similar to the human disorders than to those of lower animals.
paralleled a reduction in variety and intensity of acute excitatory responses to the drug.

After 1 month of daily injections, “body-fingering” behaviors became overwhelming. Body-fingering is a stereotyped repetitive behavior in which one continuously fingers and investigates a fixed part of the body, such as the wrist, thigh, abdomen, penis, or scrotum (figure 3a). The unit pattern of this behavior is almost the same as that of ordinary self-grooming. Because body-fingering first appeared during the period of acute response to the drug and gradually intensified to dominate the whole period, it probably developed from normal self-grooming by the mechanism of reverse tolerance or supersensitivity (cf. Sato et al. 1992, this issue).

After 2 months of daily injections, the intoxicated monkeys began to show unusual investigative or exploratory “staring” behaviors. They stared incredulously at certain parts of their own bodies (figure 3a), or at the faces or other parts of the bodies of cagemates (figure 3b), at times actually touching with fingers (figure 3c). The intoxicated monkeys also stared at certain areas on the floor (figure 3d), around the cage apparently searching for something, and into space vacantly (figure 3e). These bizarre behaviors indicate a psychosis of some sort and strongly suggest that the animals had perceptual disorders. Such behaviors have so far been observed only in the monkeys with chronic MAP intoxication (Ellinwood 1971; Kashiwabara 1983) and have never been reported by primate ethologists with animals in the wild or in captivity.

It is noteworthy that body-fingering and staring behaviors have an investigating component in common, and that apparently the former is the

**Figure 3. Abnormal behaviors in monkeys produced by chronic methamphetamine administration: “Body-fingering” and “staring” behaviors**

(a) Monkey J (left) involved in thigh-fingering. For several hours after the injection, he continues to finger a fixed part of body, in a fixed manner, in a fixed posture, and on a fixed location of the stand. Monkey G (right) is now staring and investigating his own abdomen. Staring alternates with fingering. The behavior is fairly stereotyped. (b) Monkey J (middle) exhibiting bizarre staring at monkey D (left), who seems rather perplexed. He has also been injected, but shows little change in behavior. Monkey G (right) has stopped abdomen-fingering at being approached by J of upper rank. (c) Monkey J (left) stared for a while at monkey H’s (right) thigh and began to investigate by touching with fingers. The behavior is quite different from the ordinary grooming and the stereotyped fingering. H is not injected. (d) Monkey J staring at a small area on the floor. (e) Monkey J staring into space vacantly.
antecedent of the latter. Indeed, some mixed body-fingering and body-staring behaviors were observed in the experiments. The close relationship between stereotyped repetitive behaviors and psychosis among human stimulant abusers has been reported (Ellinwood 1967; Rylander 1972).

Inexplicable aggressive and fearful behaviors were observed in two monkeys who had been injected with MAP HCI for more than 4 months. It should be stressed that most of these behaviors appeared in the residual stage of chronic intoxication. The intoxicated monkeys abruptly exhibited those behaviors to certain members of the group for no apparent reason. Because social signals in monkey groups may be elusive for human observers, social behaviors of all the members were sociometrically examined. The results showed that these behaviors were unique to the intoxicated monkeys and strongly suggested that their cognition of social signals was disordered.

"Splitting" or disorganization of behavior, in which all the chronic symptoms were exhibited in the same time without regularity, was observed in only one monkey in the later stage of the second series of daily injections. In the earlier stages, body-fingering was dominant and only occasionally interrupted by staring or aggression. Moreover, the fingered body parts and the objects that were stared at were fairly fixed. But during splitting, the monkey was restless and irritable, and the behaviors and their objects frequently changed.

After the termination of daily injections, the behavioral abnormalities of the monkeys gradually diminished, but the degree of recovery markedly differed between behavior items. Staring and splitting diminished rather rapidly and to a considerable extent, while there was much less recovery in motor activity, fixation in location, and interaction with peer animals; body-fingering held the intermediate position. As mentioned earlier, inexplicable aggression and fear were observed more frequently than before, although they were very transient each time.

Two interesting findings were obtained in this period. One is that injections of physiological saline into the animals under the same conditions as MAP injections caused the staring and body-fingering behaviors to increase or reappear. This is in accordance with the findings of Antelman and colleagues (1980) which noted that a stressor (mild tail pressure) and amphetamine are equally effective in sensitizing rats to stereotypy. The other is that readministration of MAP 4–12 months after the drug suspension exacerbated the abnormal behaviors and caused them to reappear and increase to their previous levels within a couple of days. These findings clearly show that latent abnormalities that determine a high relapse liability persist in the residual stage of chronic intoxication. This problem is discussed by Sato and colleagues (1992, this issue).

There were marked individual differences in the behavioral changes produced by MAP administration. Some monkeys showed the severe disorders described above, even in the residual stage. The abnormal behavior of the monkey who showed the most severe disorders persisted for so long that years later uninformed observers could easily identify this monkey as the one with chronic intoxication. On the other hand, other monkeys exhibited only mild changes which disappeared almost completely when drug injections were terminated. As to the causes of individual differences, we know about four variables: ranking order, behavior traits, type of acute response, and age. We can say only that the order of liability to chronic intoxication is, for ranking order, middle > upper > lower; for behavior traits, active > nonactive; and for type of acute response, excitatory > inhibitory. Age seems irrelevant.

In summary, the intoxicated monkeys exhibited psychotic behaviors such as staring, inexplicable aggression and fear, and splitting, as well as such autistic behavior disorders as decrease in motor activity, fixation in location, and decrease in interaction with peer animals. While the former behaviors were temporal, the latter disorders were rather long-lasting. These results were essentially the same as those observed in experiments with lower animals such as mice. Furthermore, the monkeys’ psychotic behaviors could easily be reinduced by the readministration of the drug or by the nonspecific stress conditions.

Thus, the monkey experiments clearly showed that nearly all the varieties of symptoms and disorders of human MAP psychosis can be reproduced in the higher species of animals. The higher the animals are in the phylogenetic order, the more similar the elicited disorders are to those of humans (figure 2).

Two Kinds of Amphetamine Models of Schizophrenia

As stated earlier, MAP psychosis strongly resembles schizophrenia in the following three clinical features: (1) an episode of hallucinatory-paranoid psychosis; (2) an enduring residual stage of personality changes; and (3) a high relapse liability of the psychosis. MAP psychosis has been proposed as a model of schizophrenia not merely because of the similarity of the type of psychosis, but also because of the similarity in the symptom structure (figure 4) and the
high relapse liability of the psychosis (Machiyama et al. 1970; Utena 1974). With the chronic MAP intoxication model in animals, we may be able to gain knowledge of these other aspects of schizophrenia.

This model differs greatly from the amphetamine stereotypy model or acute amphetamine intoxication model, which represents only the psychotic symptoms. The stereotypy apparently resembles a catatonic psychomotor agitation. It could also be regarded as an equivalent of paranoid ideation, because it is a forced accentuation of one particular behavior pattern and involves an inability to switch to another.

It is worth remembering that the body-fingering behaviors developed in the course of repetitive MAP injections were also highly stereotyped. They seem to be a monkey equivalent of the chronic stereotyped repetitive behaviors in human stimulant abusers, called the “punding” syndrome by Rylander (1972). Although the chronic stereotypy differs from the acute one in the underlying mechanisms, it may fill the role of linking the chronic and the acute intoxication models. The possibility that sensitization or kindling mechanisms are capable of transforming psychological stresses to somatic events (Antelman et al. 1980; Robinson and Becker 1986) and the involvement of those mechanisms in the development of recurring stereotypies in chronic MAP intoxication and of psychotic symptoms in schizophrenia are fascinating topics.

References


Sato, M.; Numachi, Y.; and Hama-
mura, T. Relapse of paranoid psy-
chotic state in methamphetamine
model of schizophrenia. Schizophre-
Tatetsu, S.; Goto, A.; and Fujiwara,
T. The Methamphetamine-Psychosis.
Utena, H. A special type of model
psychosis: A chronic methampheta-
mine intoxication in man and ani-
mal. Brain and Nerve, 13:687–692,
1961.
Utena, H. Behavioral aberrations in
methamphetamine-intoxicated ani-
mals and chemical correlates in the
brain. Progress in Brain Research,
Utena, H. On relapse-liability:
Schizophrenia, amphetamine psychosis,
and animal model. In: Mitsuda,
H., and Fukuda, T., eds. Biological
Mechanisms of Schizophrenia and
Schizophrenia-Like Psychosis. To-
285–287.
Utena, H., and Ezoe, T. Studies on
the carbohydrate metabolism in
brain tissues of schizophrenic pa-
tients. Psychiatria et Neurologia Ja-
Utena, H.; Ezoe, T.; and Kato, N.
Biochemical studies on addiction due
to β-phenylisopropylmethylamine:
1. Tissue distribution and secretion
of the amine; 2. Effect on glucose
metabolism in brain tissue. Psychi-
atria et Neurologia Japanica,
Utena, H.; Ezoe, T.; Kato, N.; and
Hada, H. Effects of chronic adminis-
tration of methamphetamine in enzy-
matic patterns in brain tissue. Jour-
nal of Neurochemistry, 4:161–169,
1959.
Utena, H.; Machiyama, Y.; and Ki-
kuchi, M. “Behavioural Disorders in
Monkeys Produced by the Long-
Term Administration of Metham-
phetamine: An Animal Model for
Schizophrenia.” Movie film, 16mm,
32 min., sound (with English narra-
Yagi, M. Factors influencing the gen-
eral activity in rats: 2. Effect of
methamphetamine. Annual of Ani-

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