Enhancement of Ambulation-Increasing Effect Produced by Repeated Administration of Methamphetamine in Rats and Neurochemical Changes in Catecholaminergic Neurons

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Abstract—Male rats of the Wistar strain were repeatedly given methamphetamine (MAP) at 0.5 mg/kg, s.c., 10 times at a fixed interval of 4 days in different environmental situations. The effects of MAP administration on ambulatory activity and neurochemical parameters in the brain were investigated. MAP (0.5 mg/kg) markedly increased ambulatory activity. The ambulation-increasing effect of MAP was progressively enhanced without accompanying stereotyped behaviors when the drug was repeatedly given in the activity cage. The once enhanced effect was considered to be irreversible. In addition, the pretreatment with MAP in the activity cage produced a decrease in the maximum density of $^3$H-spiperone binding sites in the striatum and that of $^3$H-WB4101 binding sites in the cortex and hippocampus, with decreases in catecholamine and increases in its metabolites. However, the enhancement of the ambulation-increasing effect of MAP and changes in the binding sites or catecholamine metabolism were scarcely observed when the drug was repeatedly given to the rats in the narrow cage where horizontal ambulation of the animals was strongly impaired. These results suggest that the enhancing effect of MAP is closely related to the environmental situations to which the animals have been exposed to under the drug effect. Moreover, it is indicated that there is a correlation between the enhancement of the ambulation-increasing effect of MAP and changes in the neurochemical parameters. The enhancing effect of MAP is supposed to have been partially caused by changes in cerebral catecholaminergic systems, in particular an increase in catecholamine turnover.

Revised administration of psychotropic drugs sometimes produces changes in sensitivity to the drugs such as development of tolerance or enhancement of the sensitivity in experimental animals (1, 2). We have already demonstrated that repeated administration of amphetamines at fixed intervals of 1–7 days produced marked enhancement of their acute effects on ambulatory activity in mice and rats (3–7). The enhancing effects of amphetamines were pointed out to be influenced by the doses given, administration intervals and environmental situations to which the animals were exposed to under the drug effects (8, 9). However, the biological mechanism underlying the enhancing effects has not been elucidated.

The present study was designed to assess the neurochemical background of the enhancing effect of methamphetamine on ambulatory activity produced by repeated administration in rats.

Materials and Methods

Animals
Male rats of Wistar strain weighing 300–350 g at the beginning of the experiment were used. The animals were supplied by the Institute of Experimental Animal Research of the Gunma University School of Medicine. Each rat was housed in a stainless steel wire mesh activity cage with dimensions of 38(D)×25(W)×20(H) cm and given free access to a solid diet, MF (Oriental Yeast Co.,
Tokyo) and tap water. The animal room where the activity cages were set up was artificially illuminated by fluorescent lamps with a 12 hr light-dark cycle (light on 7:00–19:00), and the room temperature was controlled to 24±2°C.

**Apparatus**

The ambulatory activity of each rat was measured by an Ambulo-Drinkometer, an automatic measurement apparatus for ambulation and drinking (GT 7910, O'hara and Co. Ltd., Tokyo), as previously described by Tadokoro et al. (10). Ten of the cages were set on the apparatus. A tilting floor grid, which is set in the activity cage was used for measurement of the ambulatory activity. Any slight tilt of the floor caused by horizontal ambulation of the animals was detected by a microswitch attached to the activity cage. In the present experiment, ambulatory activity alone has been recorded, because changes in ambulatory activity reflected more sensitively the behavioral effects of amphetamines than those in the drinking activity. On the other hand, narrow plexiglass cages with dimensions of 26(D)×14.5(W)×12.5(H) cm were used to impede the ambulatory activity of the animals in Group II after each drug administration.

**Drug used and treatment schedules**

The drug used was methamphetamine hydrochloride (MAP) (Philopon®, Dainippon Pharmaceutical Co., Osaka). MAP was dissolved in a physiological saline vehicle, and the volume administered was made up to 1 ml/kg of body weight. The dose tested (0.5 mg/kg, s.c.) was expressed in terms of the salt form and was adjusted to be optimum to accelerate ambulatory activity in the Wistar strain male rats (11).

All treatments studied are listed in Table 1. One hundred and twelve animals were divided into four groups. Twenty eight rats of Group I were repeatedly given MAP at 0.5 mg/kg, s.c., 10 times at a fixed interval of 4 days in the activity cages, and the ambulatory activity was measured for 180 min after the drug administration. The animals in Group I were withdrawn from MAP for a month after the 10th administration, and they were given MAP again in the same dose used previously in the activity cages. Another 28 rats of Group II were repeatedly given MAP at 0.5 mg/kg, s.c., 10 times at a fixed interval of 4 days, and they were repeatedly placed in the narrow plexiglass cages for 180 min after each drug administration. These animals were returned to the activity cages after each observation period. The 11th administration of MAP was done 4 days after the 10th administration, and the ambulatory activity was measured for 180 min in the activity cage as described above. Groups III and IV were prepared as controls for Groups I and II, respectively, and they were repeatedly given s.c. saline according to the corresponding schedules described above. In all experiments, administration of the drug or saline was conducted at 12:00 of the light period.

**Receptor assay**

3H-Spiperone (SPP) binding assay: The animals were killed by decapitation at 10 days after termination of repeated MAP or saline administration, and the brains were rapidly removed. Each brain was dissected into 8 regions: cerebral cortex, striatum, hippocampus, hypothalamus, thalamus, mid brain, medulla oblongata/pons and cerebellum, according to the method of Growinski and Iversen (12) with a minor modification. 3H-SPP (18 Ci/mmol, Amersham Japan, Tokyo) binding tests to these regions were performed essentially as described by Usdin et al. (13). In summary, fresh tissues were homogenized by an ultrasonic homogenizer (US-150 Nissei Co. Ltd., Tokyo) in Tris-HCl.

| Groups | Administration (s.c.) | Environmental situations | Number of animals |
|--------|-----------------------|--------------------------|-----------------|
| I      | 0.5 mg/kg/4 days×10   | Activity cage            | 28              |
| II     | 0.5 mg/kg/4 days×10   | Narrow cage              | 28              |
| III    | Saline 1 ml/kg/4 days×10 | Activity cage         | 28              |
| IV     | Saline 1 ml/kg/4 days×10 | Narrow cage            | 28              |
buffer (50 mM, pH=7.7) and centrifuged at 50000 g for 20 min. The resulting pellet was resuspended in another portion of Tris-HCl buffer (50 mM, pH=7.7) and centrifuged again at 50000 g for 20 min. Finally, the pellet was resuspended in Tris-HCl buffer (50 mM, pH=7.1) containing 0.1% ascorbic acid. A particulate suspension containing about 0.5 mg protein was used for the 3H-SPP binding tests (final concentrations 0.11–2 nM). The reaction mixture (1 ml) was incubated at 37°C for 20 min in the presence of ketanserin (final concentration 0.1 nM, ketanserin tartrate, Kyowa Hakko, Tokyo) and was then filtered through a Whatman GF/B filter under vacuum. Ketanserin, a S2-serotonin blocker was used for D2 dopamine receptor binding studies by 3H-SPP, because 3H-SPP simultaneously labels 5-HT receptors as well as dopamine receptors in the brain, particularly in the frontal cortex (14, 15). d-Butaclamol (final concentration 1 μM, butaclamol hydrochloride, Research Biochemicals Inc., Wayland) was used to assess nonspecific binding. The filter was rinsed three times with 5 ml ice cold Tris-HCl buffer (50 mM, pH=7.7). The filters were placed in 10 ml liquid scintillation cocktail and counted 24 hr later by liquid scintillation spectrometry (LSC-673, Aloka, Tokyo).

\[ 3H-WB4101 \] binding assay

\[ 3H-WB4101, \quad \{2-(2',6'-dimethoxy)phenoxyethylamino)methyl benzodioxan\} \quad (27 \text{ Ci/nmol, Amersham Japan, Tokyo}) \] binding tests were carried out by the method of U’Prichard et al. (16). The particulate suspension was obtained in the same way as described above. The reaction mixture (1 ml) consisted of particulate suspension (about 0.5 mg protein), 3H-WB4101 (final concentrations 0.11–2 nM) and phentolamine (final concentration 0.5 mM, Regitin®, Japan Ciba-Geigy Ltd., Takarazuka). 3H-WB4101 has been used as a α1-noradrenaline receptor marker in the brain (17). Phentolamine was used to determine nonspecific binding. The mixture was incubated at 25°C for 20 min followed by filtration through a Whatman GF/B filter under vacuum. The filter was rinsed three times with 5 ml ice cold Tris-HCl buffer (50 mM, pH=7.7). Radioactivity on the filters was counted in the same way as in the 3H-SPP binding assay.

\[ K_d \] and \[ B_{max} \] values were determined by Scatchard analysis only for each case where significant difference in specific binding was observed between saline- and MAP-pretreated groups. Protein concentration was determined by the method of Lowry et al. (18).

Catecholamine assay

In the 10th day after termination of repeated MAP or saline administration, the animals were decapitated after enzyme inactivation by microwave irradiation at 5 kW for 1.5 sec (TMW-6402A, Toshiba, Tokyo), and the brains were rapidly removed for subsequent catecholamine analysis. Regional levels of dopamine (DA), noradrenaline (NA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were measured by high-performance liquid chromatography (L-5000, Yanaco, Kyoto) with electrochemical detection (VMD-501, Yanaco, Kyoto) using the technique of Keller et al. (19), while 4-hydroxy-3-methoxy phenylglycol (MHPG) levels were determined essentially by the method of Semma and Takahashi (20). DA and DOPAC levels were determined only for the regions where significant differences in 3H-SPP specific binding were detected between saline- and MAP-pretreated groups, while NA and MHPG were determined for the regions where significant differences in 3H-WB4101 specific binding were seen.

Statistical analysis

Statistical significance of differences between saline- and MAP-pretreated groups was evaluated by one way ANOVA followed by Student’s t-test. Differences between groups were considered to be significant when the P value was equal or less than 0.05.

Results

Behavioral observation: MAP (0.5 mg/kg) increased the ambulatory activity in Group I for about 180 min with the maximum at 20–30 min, and the total activity counts during the observation period were about 30 times as high as the preinjection level.

The ambulation-increasing effect of MAP was progressively enhanced without accompanying stereotyped behaviors when the drug was repeatedly given at an interval of
4 days. As shown in Fig. 1, mean total activity counts/3 hr obtained in the 3rd administration and thereafter were significantly higher when compared with those obtained in the 1st administration. The maximum enhancement was observed by the 10th administration. In addition, the enhanced sensitivity to the ambulation-increasing effect of MAP had been well maintained when the 11th administration was carried out one month after the 10th administration.

The horizontal ambulation of rats in Group II has been perfectly impeded for 180 min after each administration of MAP. The pretreatment with the drug in the narrow cage produced no significant changes in sensitivity to the ambulation-increasing effect of MAP when the 11th administration was carried out in the activity cage 4 days after the 10th administration (Fig. 1). Thus, the mean total activity counts were almost equal to those obtained in the 1st administration of MAP in Group I, and no enhancement of the ambulation-increasing effect of MAP was observed in Group II. Ambulatory activities observed in preinjection periods in Groups III and IV were scarcely affected by repeated saline administration (preinjection levels, Group III: 3.3±1.4, Group IV: 5.0±1.5; after injection, Group III: 2.4±0.9, Group IV: 3.2±1.6).

**Receptor binding assay**

A significant decrease in the specific binding of $^3$H-SPP in the striatum in Group I was detected when compared with that in Group III, and significant decreases in the $^3$H-WB4101 specific binding were observed in the cortex and hippocampus. Scatchard analyses, therefore, were carried out for these 3 regions in all the groups. In addition, no significant differences in $K_a$ and $B_{max}$ values of $^3$H-SPP and $^3$H-WB4101 binding sites were detected in any region between
Groups III and IV. Thus, mean $B_{\text{max}}$ values calculated from the data obtained in both groups are shown in Fig. 2 as control values (Groups III+IV).

Significant decrease in $B_{\text{max}}$ value of $^3$H-SPP binding sites in the striatum was detected in Group I when compared with that in Groups III+IV; however, no significant difference was observed between Groups III+IV and Group II (Fig. 2, left panel). No significant difference in $K_d$ values of the same binding sites was seen among any group (Groups III+IV: 0.27±0.05, Group I: 0.25±0.01 and Group II: 0.31±0.10).

On the other hand, the $B_{\text{max}}$ value of $^3$H-WB4101 binding sites in the cortex significantly decreased in Group I when compared with those in Groups III+IV, and the value in the hippocampus significantly decreased in Group I when compared with those in Groups III+IV or Group II. However, no significant difference in the $B_{\text{max}}$ values was detected between Groups III+IV and Group II in both brain regions (Fig. 2, right panel).

Significant decrease in the $K_d$ values of $^3$H-WB4101 binding sites was observed only in the hippocampus in Group I (0.74±0.03) when compared with those in Groups III+IV (1.26±0.06) and Group II (1.59±0.21).

**Catecholamine assay:** No significant differences in catecholamine and its metabolites levels were detected in any region between Groups III and IV. Consequently, mean values calculated from data obtained in both the groups are shown in Fig. 3 as control values (Groups III+IV).

The DA level in the striatum significantly decreased in Group I; and on the contrary, it significantly increased in Group II when compared with that in Groups III+IV. DOPAC level in the same region significantly increased in Group I when compared with that in Groups III+IV; however, no significant difference in the level was observed between Groups III+IV and Group II.

NA level in the hippocampus significantly decreased in Group I, whereas NA level in Group II and MHPG level in Group I in the same region significantly increased when compared with the corresponding levels in Groups III+IV.

**Discussion**

The present experiment demonstrated that the ambulation-increasing effect of MAP was progressively enhanced when the drug was given repeatedly and that the effect once enhanced was considered to be irreversible. The present experiment also showed that the enhancing effect was not produced when the animals were given the drug repeatedly in the narrow cage where their horizontal ambulation was impeded under the drug effect. These results are in agreement with previous results obtained in our laboratory, and the characteristic features of this phenomenon have been reported in detail in other papers (3-9).

The results obtained in the present experiment suggest that the enhancing effect is closely related to the environmental situations to which the animals have been exposed to during the stage of the acute drug effect. Actually, it was confirmed in our laboratory that the enhancing effect of ambulatory activity did not develop enough in a narrow space for free movement even when MAP was repeatedly given in adequate doses at
adequate intervals. The enhancement, for example, developed in mice when the floor space of the round activity cage was over 16 cm in diameter (21).

In the present experiment, marked decreases in the maximum density of $^3$H-SPP and $^3$H-WB4101 binding sites ($B_{\text{max}}$) with simultaneous decreases in brain catecholamine and increases in its metabolites were observed when MAP was repeatedly given in the activity cage. However, no change in both binding sites and catecholamine turnover was detected when the drug was repeatedly given in the narrow cage. These results suggest that there is a correlation between enhancement of the ambulation-increasing effects of MAP and neurochemical changes in cerebral catecholaminergic neurons.

Amphetamines elicit an increase in ambulatory activity in the experimental animals through a stimulation of brain catecholaminergic neurons (22, 23). In addition, it has been reported that the enhanced ambulation-increasing effect is reproduced after readministration of CNS stimulants such as methylphenidate (24), apomorphine (25), cocaine (9), ephedrine (26), and bromocriptine (9, 27), and on the contrary, the effect is antagonized only when antipsychotic drugs are repeatedly given in combination with MAP (9). Much attention, therefore, has been focused on changes in catecholaminergic, in particular dopaminergic, functions as one of the putative mechanisms of the enhancing effect of MAP.

The development of postsynaptic DA receptor supersensitivity (increase in $B_{\text{max}}$ values) has been suggested to be involved in the enhancing effect. However, there are few receptor binding studies supporting such an interpretation (28, 29). On the contrary, a number of reports have indicated a decrease in postsynaptic DA receptor binding sites in several brain regions of animals pretreated repeatedly with amphetamines (30–34). However, these results are inconsistent with those in which the enhanced ambulation-increasing effect was often induced by readministration of amphetamines or several catecholamine agonists (9, 24–27). The development of subsensitivity of DA auto-

receptor, therefore, has been proposed to account for the enhancing effect, and this has actually been reported in the results of binding tests (34), catecholamine measurement (35) or electrophysiological investigations (36). In the present experiment, decrease in $^3$H-SPP and $^3$H-WB4101 binding sites and increase in catecholamine turnover were detected at the steady state. Accordingly, it is supposed that these factors are undoubtedly involved in the enhancement phenomenon as one of the biological factors. However, no details in the mechanism have been elucidated.

There are a number of suggestions about the relationship between the brain regions and behavioral responses. It has been proposed, for example, that amphetamine-induced acceleration of ambulatory activity results from an action on noradrenergic neurons, whereas stereotyped behavior is associated with dopaminergic nerve activity (37). Furthermore, the acceleration of the ambulation and stereotyped behavior were reported to be associated with dopaminergic nerve activity of the nucleus accumbens and the striatum, respectively (38, 39). However, recent findings indicate the presence of another nervous systems capable of mediating the behaviors (40). It is, therefore, very difficult to make a decision about the relationship based on the results obtained in the present experiment alone.

On the other points, the enhancement of sensitivity to behavioral effects of amphetamines has been proposed as one of the useful models for the amphetamine psychosis. However, the mechanism underlying the enhancement may be so complex that our present findings indicate only a part of the neurochemical background. Actually, changes in $\alpha_1$-binding sites and noradrenaline metabolism were detected in the present experiment. Furthermore, changes in $\beta$-noradrenaline receptor (29, 41) or several neuropeptides (42) are reported to be involved in the phenomenon. Further investigations should be required to elucidate the functional mechanisms of the enhanced ambulation-increasing effect of MAP considering other neuronal systems responsible for the phenomenon.
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