A Quantity of Stereotyped Behavior of ddY Mice Induced by Low-dose Methamphetamine

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Abstract: It is reported that high-dose methamphetamine (8 mg/kg) induces stereotyped behavior in ddY mice in an open field, but it is still not certain that low-dose methamphetamine (less than 2 mg/kg) can induce the stereotyped behavior in ddY mice in a narrow space. In order to investigate the problem, we evaluated the quantity of stereotyped behavior of ddY mice by using a mouse wheel-running apparatus. In this method, we have come to recognize an increase in the stereotyped behavior depending on the dose of methamphetamine and the reverse-tolerance phenomenon as a decrease in the wheel-revolution counts. The present findings indicate that low-dose methamphetamine can promote stereotyped behavior in ddY mice under conditions in which the ambulation is restricted to a narrow wheel space.

Key words: ddY mouse, methamphetamine, stereotyped behavior

Hirabayashi and Alam [1] have reported that methamphetamine hydrochloride (MAH) promotes ambulatory activity and stereotyped behavior in ddY mice in an open field. This stereotyped behavior is mainly observed in the form of continuous sniffing, head twitching or circular movement. Following repeated administration of MAH, both the stereotyped behavior and the ambulation readily appear (reverse-tolerance phenomenon). The authors have also reported that the ambulation is promoted by MAH 1 mg/kg, but that the stereotyped behavior is not found till the mice are injected with MAH 8 mg/kg. Though the authors have referred to competition between ambulation and stereotyped behavior, it is still not certain that low-dose MAH can induce stereotyped behavior in ddY

mice under conditions in which ambulation is restricted. In this study, we tried to evaluate the quantity of the stereotyped behavior in ddY mice induced by low-dose MAH (less than 2 mg/kg) as a decrease in the counts of the wheel-revolutions in the narrow space in a mouse wheel-running apparatus.

Animals: Seventy male Slc: ddY mice, aged 8 weeks, weighing 26 to 28 g, were used. The mice were divided into 10 groups of 7 animals and housed in a communal plastic cage, 338 mm wide, 140 mm high and 225 mm deep, and were given a solid diet (F₂: Funabashi Co., Japan) and tap water *ad lib*. The room in which the mice dwelt was kept at a temperature of 21 to 25°C and at a humidity of 50 to 60% with lights on from 7:00 to 19:00.

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Fig. 1. Temporary change in the wheel-revolution decreasing (stereotyped behavior-increasing) effect induced by MAH 0.5, 1 and 2 mg/kg and physiological saline (PS) in mice. □: MAH 2 mg/kg, △: MAH 1 mg/kg, ○: MAH 0.5 mg/kg, ×: PS. Each point is the mean count for a 5 min period. The black symbols are significantly different from the PS control ($P < 0.01$; Wilcoxon's U test). $N = 7$ in all doses.

Procedures: MAH (Dainihon Seiyaku Co., Japan) was diluted in 0.9% NaCl (physiological saline: PS). The mice were injected with MAH (0.5, 1 and 2 mg/kg) subcutaneously into the back at 10 μ l/g. The control injections were of PS only. The injection of MAH or PS was repeated 10 times at intervals of 3 to 4 days in the housing cage and the 11th injection was performed 14 days after the 10th. Immediately after the 1st, 10th and 11th injections, the mice were separately placed in a mouse wheel-running apparatus (Natsume Co., Japan) and the number of wheel-revolutions caused by their running was counted every 5 min for 60 min. The counting was carried out between 9:00 and 16:00. Counts for successive 5 min segments were statistically analyzed by Wilcoxon's U test.

Continuous sniffing appeared in all of the mice injected with MAH 2 mg/kg soon after the injection. Head twitching and circular movement were sometimes found in the mice. Continuous sniffing also appeared in the mice injected with MAH 1 mg/kg soon after the injection, but the frequency and the duration of the sniffing were lower and shorter than those of the mice injected with MAH 2 mg/kg. In the mice injected with MAH 0.5 mg/kg, continuous sniffing appeared 30 min after the injection. This finding may

indicate that MAH 0.5 mg/kg requires time to evoke continuous sniffing by ddY mice. As the mice with these stereotyped behavior patterns did not run in the wheel, a decrease in wheel-revolution counts indicated, conversely, an increase of stereotyped behavior. The MAH effect decreasing wheel-revolutions was found to be dose-dependent. In the mice injected with PS, none of the stereotyped behavior patterns was found. As the mice were continuously running in the wheel, their wheel-revolution counts slightly increased (Fig. 1). The wheel-revolution was also counted after the 10th and 11th injections. Figure 2 shows the wheel-revolutions after the 1st, 10th and 11th injections of MAH 0.5 and 1 mg/kg on the same arrangement to Fig. 1. The stereotyped behavior-increasing effect of MAH 0.5 mg/kg was enhanced following the 10th injection (reverse-tolerance phenomenon) and the effect was also found following the 11th. In the mice injected with MAH 1 mg/kg, the reverse-tolerance phenomenon was found following the 10th injection and even the 11th. The reverse-tolerance phenomenon in the mice injected with MAH 2 mg/kg was also found following the 10th and 11th injections, but repeated injections of PS did not affect the wheel-revolution by the mice.

Fig. 2. Comparisons of changes in the wheel-revolution decreasing (the stereotyped behavior-increasing) effect following the 1st, 10th and 11th injections of MAH 0.5 and 1 mg/kg. The 11th injection was performed 14 days after the 10th. □: 1st, △: 10th, ○: 11th. Each point is the mean count for a 5 min period.

The present conventional methods [1, 2] must be used to observe the patterns of the stereotyped behavior of ddY mice, but the quantity of the stereotyped behavior could be evaluated by means of our method. Considering the findings in our study, the stereotyped behavior of ddY mice can be promoted by low-dose MAH (less than 2 mg/kg) when ambulation is restricted. As MAH 0.5 mg/kg could induce the reverse-tolerance in ddY

mice, the mice may be very sensitive to MAH in the promotion of stereotyped behavior.

References

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