Effects of Methamphetamine on Copulatory Behavior in Male Rats

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Many papers have reported the effect of amphetamine and its close relative, methamphetamine on sexual activity in humans. The effect of these drugs on animal sexual behavior is unknown. The present study was done to determine whether methamphetamine modifies the copulatory behavior of male rats. Sexually experienced rats of the Wistar-Imamichi strain, 10 weeks of age, were singly injected intraperitoneally with methamphetamine hydrochloride at doses of 0, 1, 2 or 4 mg/kg body weight. Tests were initiated at 19:30 in the dark period. Observations were conducted for 90 min. At dosages of 1 or 2 mg/kg there were no changes in copulatory behavior ascribed to the administration of methamphetamine. At 4 mg/kg the frequencies of mounting, intromission and ejaculation were greatly decreased but the spontaneous motor activity and stereotypic behavior increased in all males. In a further experiment, males were given methamphetamine by intraperitoneal injection once a week for 8 weeks. The copulatory behavior was tested 5 times at two weeks intervals. In the 4th testing, the percentage showing ejaculation decreased. In the 5th testing, there was no ejaculation and the incidence of intromission decreased. No stereotypic behavior was displayed in any of the males during the testing. From these results, it was concluded that methamphetamine inhibits the intromitting and ejaculating behavior in male rats.

— KEY WORDS: copulation, male, methamphetamine, rat, spontaneous motion.

It is well known that amphetamine and its close relative, methamphetamine, are direct central nervous system (CNS) stimulants and in ordinary therapeutic doses produce the following effects: euphoria, with an increased sense of well-being; heightened mental acuity, until fatigue sets in from lack of sleep; nervousness, with insomnia; and anorexia. In addition, strong sexual desire is often aroused. They are commonly abused by truck drivers, prostitutes, and all-night workers who self-administer the drugs for extended periods of time [10].

Experimental studies in animals have demonstrated the effects of these drugs on locomotor activity, emotionality, and on other kinds of individual or social behavior [4, 9, 13-15]. Nevertheless, the effects of drugs on sexual behavior in animals have not been investigated before.

The present study deals with the effect of methamphetamine on the copulatory behavior of male rats.

Materials and Methods

Subjects: Sexually experienced male rats of the Wistar-Imamichi strain (Imamichi Institute for Animal Reproduction, Omiya, Saitama),
approximately 10 weeks old at the start of the experiments, were used. The animals were kept under controlled light (14 hr light, 10 hr dark; lights off at 19:00) and temperature (22-27°C) conditions. Food (MB-1, Funabashi Farm Ltd., Chiba) and water were available ad lib. Before exposure to the males, the stimulus females of the same strain were rendered sexually receptive by treatment with estradiol benzoate (20 μg/rat, s. c.) and progesterone (0.5 mg/rat, s. c.), dissolved in 0.1 ml of sesame oil, 48 and 4-6 hours, respectively, before the exposure.

Drug: Methamphetamine hydrochloride was obtained commercially from Dainihon Pharmaceutical Ltd. On the day of testing, the drug was dissolved in distilled water and administered intraperitoneal (i. p.) in a volume of 0.1 ml/100 g body weight. Control males were given the same volumes of distilled water.

Copulatory behavior testing: The male was transferred to a semi-circular observation cage (radius 40, height 50 cm) with a Plexiglas front and a floor covered by wood shavings. A few minutes later, the male was given i. p. methamphetamine or vehicle. Then immediately a sexually receptive female was introduced to its cage. Tests lasted 90 min from the introduction of the female. The copulatory items were recorded under a condition of dimmed light by direct observation. The following values were recorded [7]: (a) mount frequency—number of mounts without intromission during 90 min, (b) intromission frequency—number of mounts with intromission during 90 min, (c) ejaculation frequency—number of ejaculations during 90 min, (d) mount latency—the elapsed time between the introduction of the female and the first display of mounting, (e) intromission latency—the elapsed time between the introduction of the female and the first display of intromission, (f) ejaculation latency—the elapsed time from the first intromission of the female to the time of ejaculation, and (g) the post-ejaculatory interval—the elapsed time from ejaculation to the next intromission.

Spontaneous motor activity testing: To measure spontaneous motor activity, males were placed singly in experimental cages (40×26×20 cm) 30 min before the start of the experiment. Methamphetamine (0, 1, 2 and 4 mg/kg) was injected i. p. and the spontaneous motor activity was measured with an MK-ANIMEX (Activity Motor, Model DSE, Muromachi Kikai Ltd., Tokyo) for 90 min.

Experimental procedures: In experiment 1, twenty-four and thirty-four male rats were used for copulatory behavior and spontaneous motor activity testings, respectively. The males received a single injection of vehicle or 3 doses of methamphetamine: 1, 2, or 4 mg/kg body weight. In experiment 2, five males were treated once a week with methamphetamine, at a dose of 1 mg/kg for 8 weeks. Their copulatory behavior testing were observed 5 times at 2 weeks intervals. During each interval, each male rat was kept in an individual cage. Also seven males as controls were tested under the same procedure as above. Tests in experiments 1 and 2 were initiated at 19:30 in the dark period.

Statistical analysis: The results from the copulatory behavior testing were analyzed using Fisher's exact probability test and the Mann-Whitney U test and the data for spontaneous motor activity were analyzed by Duncan's multiple t test.

Results

Experiment 1: As shown in Table 1, i. p. administration of 4 mg/kg methamphetamine resulted in a significant decrease in the median number of mount, intromission and ejaculation, compared with vehicle control (P<0.001). Three out of six males at 4 mg/kg showed no ejaculation and of these males, two had no intromission. In the median latencies of mount, intromission, ejaculation and post-ejaculation, there were no significant differences among the four doses, but in some of the animals at 4 mg/kg methamphetamine these latencies increased greatly.

The frequency of spontaneous motion during a 90 min period after administration of methamphetamine (0, 1, 2 and 4 mg/kg) is shown in Fig. 1. There was a dose-dependent increase in the number of spontaneous movements after methamphetamine. The mean number of spontaneous movements in males at 4 mg/kg rose sharply during the first 20 min, increased to a peak level of 414±98 per 10 min at 60 min, and then tended to decline. In males at 2 mg/kg, the mean spontaneous motion increased 10 min after methamphetamine, reached a peak of 262±41 per 10 min at 50 min, then dropped to 137±39 per 10 min at 90 min. After
Table 1. Acute effects of methamphetamine (MAP) on copulatory behavior in sexually experienced male rats (n = 6 for each dose)

<table>
<thead>
<tr>
<th>MAP (mg/kg)</th>
<th>No. of mounts/90 min.</th>
<th>%a</th>
<th>No. of intromissions/90 min.</th>
<th>%</th>
<th>No. of ejaculations/90 min.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>71.5 (17-135)c</td>
<td>100</td>
<td>29.5 (24-55)</td>
<td>100</td>
<td>4.0 (3-6)</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>89.5 (30-222)</td>
<td>100</td>
<td>34.0 (14-61)</td>
<td>100</td>
<td>4.0 (2-6)</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>94.0 (23-124)</td>
<td>100</td>
<td>27.0 (11-71)</td>
<td>100</td>
<td>3.0 (0-4)</td>
<td>83.3</td>
</tr>
<tr>
<td>4</td>
<td>38.0 (0-61)*</td>
<td>83.3</td>
<td>6.0 (0-16)*</td>
<td>66.7</td>
<td>1.0 (0-3)*</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Fig. 1. Spontaneous motor activity in male rats after methamphetamine (1, 2 and 4 mg/kg) or vehicle injection. Each point represents a mean value ± SE.

Fig. 2. Effects of methamphetamine on the percentage of five male rats mounting, intromitting and ejaculating in the time-course study. Open columns represent the control while shaded columns represent methamphetamine treated groups. *p < 0.05 ** p < 0.01

injection of 1 mg/kg of methamphetamine the spontaneous motion during 90 min was similar to that in the vehicle controls.

Stereotypic behavior (i.e. compulsive gna-
Table 2. Mounting behavior displayed by male rats receiving once a week for 8 weeks with methamphetamine (MAP, 1 mg/kg)

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (5)</td>
<td>105*</td>
<td>135</td>
<td>129*</td>
<td>147</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>(65-130)</td>
<td>(73-191)</td>
<td>(120-237)</td>
<td>(46-169)</td>
<td>(39-182)</td>
</tr>
<tr>
<td>Cont. (7)</td>
<td>81</td>
<td>74</td>
<td>80</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

a) The copulatory behavior testing given 5 times at two weeks intervals

b) Latency in seconds

c) Median (range) * P < 0.05 vs Control

Discussion

In the 1st experiment, our data indicate that methamphetamine administered singly to male rats apparently does not facilitator copulatory behavior. Rather, at a 4 mg/kg dose the drug greatly inhibits the behavior. Indeed the numbers of mountings, intromissions and ejaculations with 4 mg/kg methamphetamine were suppressed during 90 min. On the other hand, when given this dose of methamphetamine the spontaneous motor activity was accelerated twofold to fourfold over the control activity and stereotypic behavior was also induced. Utena [16] and Randrup et al. [12] demonstrated the characteristic stereotyped pattern of abnormal behavior elicited by amphetamine, methamphetamine and cocaine. In summary, i.p. single injection of methamphetamine which increased the spontaneous motor activity has no effect on copulatory behavior. The inhibition of copulatory behavior by the high dose of methamphetamine may result from the appearance of stereotypic behavior. These results indicate that there is no relation between the effects of methamphetamine on copulatory behavior and the effects on spontaneous motion and stereotypic behaviors in male rats.

In the 2nd experiment, we checked the chronic effects of methamphetamine on the copulatory behavior of male rats. We found a significant decrease in the ejaculating and intromitting behaviors in males given 6 and 8 weekly doses of 1 mg/kg methamphetamine in the 4th and 5th testing, respectively. All males receiving the same dose of drug displayed mounting behavior and no change in mounting frequency during the testing. At 1 mg/kg there was no stereotypic behavior in males until the 5th testing. Gross indications were that the spontaneous motion in these animals through a period of copulatory behavior testing was similar to that in controls. These results suggest that even a small dose of methamphetamine directly suppresses ejaculating and intromitting behaviors of males when given continuously once a week.

Our results of rat copulatory behavior are similar to those of men methamphetamine users. Angrist and Gershon [1, 2], Greaves [6] and Nail et al. [11] reported some instances of increased sexual feelings and of delayed ejaculation in amphetamine-abusers. Jones [8] postulated that amphetamine and a similar drug, methamphetamine, stimulated pleasurably mental excitement by blocking the sexual
climax. These drugs were thought to be aphrodisiac but they merely postponed the climax by interfering with the sensual progression in the sex act. In our 5th testing, each pair of rats was left in the observation cage after the 90 min observation. Next morning the vaginal plug was obtained from all females. Showing that they had delayed ejaculation. This is in agreement with the human results cited above [1, 2, 6, 11].

The question addressed was why the male rats with acute administration of methamphetamine showed no changes on copulatory behavior, but chronic injection inhibited ejaculating and intromitting behaviors. Generally, upon chronic administration of amphetamine or its close relative, methamphetamine, it is possible to produce an eventual depletion of brain norepinephrine, perhaps owing to displacement of norepinephrine in the neuron and/or inhibition of its synthesis. Also, as indicated earlier, amphetamine inhibits neuronal activity in catecholamine neurons [3]. It is known that catecholamine systems play a relative role in displaying copulatory behavior [5]. Therefore the inhibitory effect of copulatory behavior by chronic administration of methamphetamine may result from a depletion of catecholamines. Further studies are necessary to clarify these points.

In conclusion, results in the present experiments are the first to show that methamphetamine inhibits intromitting and ejaculating behaviors in male rats.

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**References**


雄ラットの交尾行動に対する覚醒剤
メタンフェタミンの影響

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覚醒剤の性行動に対する報告はヒトに数多くみられるが、小動物に対するその研究はほとんど行われていない现状である。今回 の報告はラットの交尾行動に対する覚醒剤の単回および連続投与の影響について検討したものである。動物には交尾行動の経験を有する生後10週齢の Wistar-Imamichi 系の雄ラットを用い、メタンフェタミン（単回投与群：1, 2, 4 mg/kg、連続投与群：1 mg/kg）を腹腔内に投与し、その後 90 分間の交尾行動を暗期の 19 時30分より赤色ライト下で観察した。その結果、単回投与におけるメタンフェタミン 1 および 2 mg/kg 群の交尾行動パターンは溶媒対照群と同じ傾向を示し、4 mg/kg 群では、マウント、イントロミッションおよび射精回数の有意な減少（p < 0.001）を認めた。この投与群の動物には自発運動の亢進ならびに同動行動の出現が見られた。連続投与、即ち 1 週間に 1 回メタンフェタミンを投与し、2 週間毎に投与直後より交尾行動を観察した結果、第 4 回目の観察（7 回目のメタンフェタミン投与直後）では、射精した動物の割合は溶媒対照群の成績に比して低い値（p < 0.05）を示し、第 5 回目の観察では全動物に射精は認められなかった（p < 0.01）。さらにイントロミッションの割合も第 5 回目で低価を示した（p < 0.05）。連続投与群の動物には観察期間中、同動行動の出現は認められなかった。以上の成績より、覚醒剤メタンフェタミンはラットの交尾行動におけるイントロミッションならびに射精の発現に対して抑制効果を示すものと推測される。