

Acta Medica Okayama

Volume 52, Issue 3

1998

Article 8

JUNE 1998

Repeated Mazindol and Methamphetamine Administration Produces Cross-Sensitization to Stereotyped Behavior Induced by these Agents in Rats

Yasuhiro Kawakami*

Katsuya Suemaru[†]

Hiroaki Araki[‡]

Hiromu Kawasaki**

Yutaka Gomita^{††}

Yoshiro Tanizaki^{‡‡}

*Okayama University,

[†]Okayama University,

[‡]Okayama University,

**Okayama University, kawasaki@pheasant.pharm.okayama-u.ac.jp

^{††}Okayama University,

^{‡‡}Okayama University,

Repeated Mazindol and Methamphetamine Administration Produces Cross-Sensitization to Stereotyped Behavior Induced by these Agents in Rats*

Yasuhiro Kawakami, Katsuya Suemaru, Hiroaki Araki, Hiromu Kawasaki, Yutaka Gomita, and Yoshiro Tanizaki

Abstract

The cross-sensitization to stereotyped behavior between mazindol (MZD) and methamphetamine (MAP) was investigated in rats. MZD (5 and 10 mg/kg/day, p.o.), MAP (5 and 10 mg/kg/day, p.o.) and saline (1 ml/kg, p.o.) were administered once daily for a week. Challenge with MZD (10 mg/kg, p.o.) on the 8th day caused markedly stereotyped behavior in MAP-pretreated group compared with the saline-pretreated control group. MAP (10 mg/kg, p.o.)-induced stereotyped behavior on the 8th day was also greater in MZD-pretreated group rather than the saline-pretreated control group. These results suggest that repeated MZD and MAP administration cross-sensitizes to their stereotype-producing effects.

KEYWORDS: mazindol, methamphetamine, cross-sensitization, stereotyped behavior

*PMID: 9661745 [PubMed - indexed for MEDLINE]

Copyright ©OKAYAMA UNIVERSITY MEDICAL SCHOOL

Brief Note

Repeated Mazindol and Methamphetamine Administration Produces Cross-Sensitization to Stereotyped Behavior Induced by these Agents in Rats

Yasuhiro KAWAKAMI^a, Katsuya SUEMARU^a, Hiroaki ARAKI^b, Hiromu KAWASAKI^b, Yutaka GOMITA^{b*} and Yoshiro TANIZAKI^c

Divisions of ^aPharmacy and ^cMedicine, Misasa Medical Branch, Okayama University Medical School, Tottori 682-0122, Japan and ^bDepartment of Hospital Pharmacy, Okayama University Medical School, Okayama 700-8558, Japan

The cross-sensitization to stereotyped behavior between mazindol (MZD) and methamphetamine (MAP) was investigated in rats. MZD (5 and 10 mg/kg/day, p.o.), MAP (5 and 10 mg/kg/day, p.o.) and saline (1 ml/kg, p.o.) were administered once daily for a week. Challenge with MZD (10 mg/kg, p.o.) on the 8th day caused markedly stereotyped behavior in MAP-pretreated group compared with the saline-pretreated control group. MAP (10 mg/kg, p.o.)-induced stereotyped behavior on the 8th day was also greater in MZD-pretreated group rather than the saline-pretreated control group. These results suggest that repeated MZD and MAP administration cross-sensitizes to their stereotype-producing effects.

Key words: mazindol, methamphetamine, cross-sensitization, stereotyped behavior

Mazindol (MZD), an imidazoisoindol derivative, is an effective anorectic agent in humans. The anorectic effect of MZD has been suggested to be elicited by augmented synaptic action of catecholaminergic transmitters via its uptake inhibition in the central nervous system (1). In behavioral studies of animals, a single administration of MZD causes locomotor hyperactivity and stereotyped behavior in rodents (2). Repeated MZD treatment has been reported to cause sensitization to its locomotor stimulant effect and stereotyped behavior in rats (3). Methamphetamine (MAP), which has the stimulating

effect of dopamine release and its uptake inhibition, also produces locomotor hyperactivity and stereotyped behavior, and repeated administration of MAP also causes sensitization to these behavioral effects (4). The MAP-induced behaviors have been suggested to be a useful experimental model for schizophrenia and for examination of central dopaminergic system (5). However, there are few reports related to cross behavioral responses in rats chronically treated with MZD or MAP. It is important to show many facts in order to understand the neuronal mechanisms of sensitization in rodents. In the present study, we examined MZD-induced stereotyped behavior in MAP-treated rats, and compared it to the effect of MAP in MZD-treated rats.

Methods

Animals. Male Wistar rats (supplied by Charles River Lab., Kanagawa, Japan) weighing 140-160 g were used as subjects. They were housed in individual cages (20 × 15 × 15 cm) in a room with a 12L: 12D cycle (light on 0800-2000) at 22 ± 1 °C and with 40 % relative humidity. Rats were allowed free access to food and water throughout the experiment.

Drugs and administration. Drugs used were MZD (Sandz Pharmaceutical Co., Basel, Switzerland) and methamphetamine hydrochloride (Dainipon Pharmaceutical Co., Osaka, Japan). MZD was suspended in 0.5 % carboxymethyl cellulose-Na. MAP was

* To whom correspondence should be addressed.

dissolved in physiological saline. All drugs were orally administered in a volume of 0.1 ml per 100 g body weight.

Stereotyped behavior observation. Rats were orally administered MZD (5 and 10 mg/kg), MAP (5 and 10 mg/kg) or saline (1 ml/kg) once daily for a week. Challenge with MAP (10 mg/kg) and MZD (10 mg/kg) for the behavioral test was orally given 24 h after the last administration. Stereotyped behavior induced by MZD and MAP was observed in the individual wire mesh cage and scored. The stereotyped behavior was measured for 3 min at 30, 60 and 90 min after the administration. The degree of stereotyped behavior was based on the method of Nishikawa *et al.* (6) with slight modifications: 0, no stereotypy; 1, discontinuous sniffing and head movement; 2, continuous sniffing; 3, continuous sniffing and discontinuous licking or biting; 4, continuous licking or biting.

Statistical analysis. Data were analyzed by the Williams-Wilcoxon analysis.

Results

Figs. 1 and 2 show stereotyped behavior induced by MZD (10 mg/kg, *p.o.*) and MAP (10 mg/kg, *p.o.*) in rats, respectively. When respectively administered of

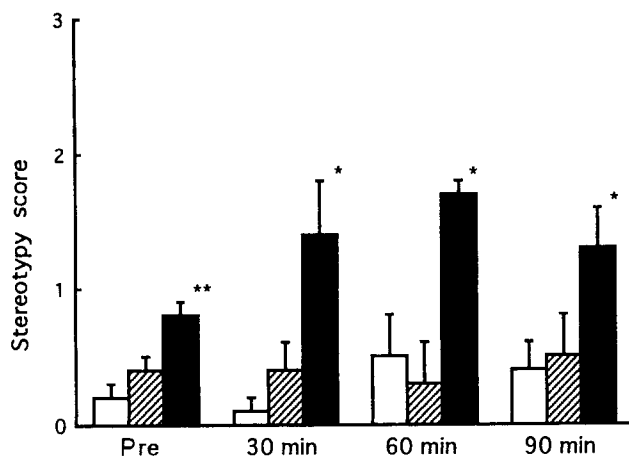


Fig. 1 Stereotyped behavior induced by acute treatment of mazin-dol (MZD) in rats repeated administration with methamphetamine (MAP) or saline. Animals were orally administered MAP at doses of 5 (▨) and 10 mg/kg (■) or saline (□) once daily for a week. MZD was orally administered 24 h after the last administration of MAP or saline. Each column represents the mean score of stereotyped behavior with SEM (n = 5). **P* < 0.05, ***P* < 0.01 vs saline control.

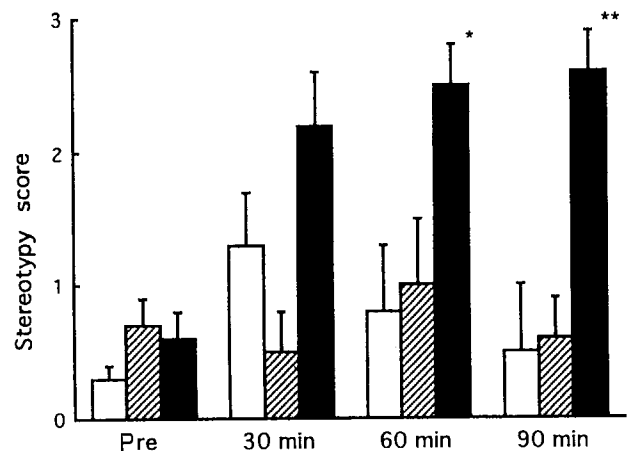


Fig. 2 Stereotyped behavior induced by acute treatment of meth-amphetamine (MAP) in rats repeated administration with mazindol (MZD) or saline. Animals were orally administered MZD at doses of 5 (▨) and 10 mg/kg (■) or saline (□) once daily for a week. MAP was orally administered 24 h after the last administration of MZD or saline. Each column represents the mean score of stereotyped behavior with SEM (n = 5). **P* < 0.05, ***P* < 0.01 vs saline control.

MZD and MAP once daily for a week, acute treatment with MAP in a dose of 10 mg/kg resulted in a more remarkable degree of stereotyped behavior than that resulting from acute treatment with MZD in a dose of 10 mg/kg (Figs. 1 and 2). The values of pre in Figs. 1 and 2 show the degree of stereotyped behavior before challenge with MZD and MAP, respectively administered on the 8th day. The scores of stereotyped behavior in MAP-pretreated group (10 mg/kg) were significantly higher than in the saline-pretreated control group (*P* < 0.01).

The scores of stereotyped behavior in rats given a single administration of MZD (10 mg/kg) on the 8th day were also markedly higher in the MAP-pretreated group (10 mg/kg) compared than in the saline-pretreated group (Fig. 1). The scores of stereotyped behavior in rats given a single administration of MAP (10 mg/kg) on the 8th day were markedly higher in the MZD-pretreated group (10 mg/kg) compared with the saline-pretreated group (Fig. 2).

Discussion

The present study showed that repeated MZD and MAP administration cross-sensitizes to their stereotype-producing effects. MZD decreases catecholamine uptake,

and MAP accelerates the release of catecholamine and decreases its uptake. MZD and MAP have been demonstrated to produce various behavioral and physiological responses via its their effect to augment synaptic action on the central catecholaminergic systems. We have already reported that repeated administration of MZD (5 and 10 mg/kg) and MAP (5 and 10 mg/kg) significantly suppresses food intake and increase of body weight, and that these agents cause locomotor hyperactivity and stereotyped behavior. Furthermore, we found that the repeated administration of MZD causes sensitization to its locomotor stimulating and stereotype-producing effects, and that the increased locomotor activity and stereotyped behaviors caused by MZD are dose-dependently reduced by pimozide, a dopamine receptor antagonist (3). These findings indicate that locomotor hyperactivity and stereotyped behavior induced by MZD are mediated by the central dopaminergic system.

Administration of MAP to rodents produces locomotor hyperactivity followed by stereotyped behavior at high doses. In the present study, daily doses of MAP (10 mg/kg) caused markedly stereotyped behavior rather than locomotor hyperactivity. In addition, when rats were measured for stereotyped behavior before challenge with MZD on the 8th day, the score of stereotyped behavior in MAP-pretreated group was significantly higher than saline-pretreated control group. The enhancement of stereotyped behavior may be due to accumulation of MAP by repeated administration with high doses.

In the present study, repeated treatment with MZD, a potent dopamine uptake inhibitor, showed sensitization to the stereotype-producing effect of MAP. Furthermore, repeated MAP treatment also showed sensitization to the effect of MZD. Therefore, these results suggest that MZD and MAP cross-sensitize to their stereotype-producing effects, and that the cross-sensitized effects may be associated with central dopaminergic systems.

References

1. Engstrom RG, Kelly LA and Gogerty JH: The effects of 5-hydroxy-5-(4'-chlorophenyl)-2, 3-dihydro-5H-imidazo (2, 1-a) isoindol (mazindol, SaH 42-548) on the metabolism of brain norepinephrine. *Arch Int Pharmacodyn Ther* (1975) **214**, 308-321.
2. Zambotti F, Carruba MO, Barzagli F, Vicentini L, Groppetti A and Mantegazza P: Behavioural effects of a new non-phenylethylamine anorexigenic agents: Mazindol. *Eur J Pharmacol* (1976) **36**, 405-412.
3. Kawakami Y, Suemaru K, Kawasaki H and Gomita Y: Behavioral changes induced by repeated administration of mazindol, an anorexiant, in rats. *Jpn J Psychopharmacol* (1996) **16**, 139-143.
4. Hirabayashi M and Alan MR: Enhancing effect of methamphetamine on ambulatory activity produced by repeated administration in mice. *Pharmacol Biochem Behav* (1981) **15**, 925-932.
5. Angrist BM, Shopsin B and Gershon S: The comparative psychotomimetic effects of stereoisomers of amphetamine. *Nature* (1971) **234**, 152-153.
6. Nishikawa T, Magata N, Takashima M and Toru M: Behavioral sensitization and hyperresponsiveness of striatal and limbic dopaminergic neurons after repeated methamphetamine treatment. *Eur J Pharmacol* (1983) **88**, 195-203.

Received October 14, 1997; accepted February 9, 1998.