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Caffeine enhances the stimulant effect of methamphetamine, but may not affect induction of methamphetamine sensitization of ambulation in mice

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Abstract. Methamphetamine (MAP: 1 and 2 mg/kg SC) and caffeine (CAF: 1, 3, 10 and 30 mg/kg SC) dose-dependently increased ambulation in mice. Repeated administration (5 times at 3 to 4-day intervals) of MAP, but not CAF, induced sensitization to its effect. Furthermore, the mice repeatedly receiving CAF showed no significant change in the sensitivity to MAP. Combined administration of MAP with CAF increased the effect. In the combinations of MAP (1 mg/kg) with CAF (3, 10 and 30 mg/kg), and MAP (2 mg/kg) with CAF (1 and 3 mg/kg), the effect was enhanced by the repeated administration. However, MAP sensitization was not modified by the combination with CAF in the repeated administration schedule, except in the combination of MAP (1 mg/kg) with CAF (30 mg/kg). The ambulation-increasing effects of MAP (1 mg/kg), CAF (10 mg/kg) and combination of MAP with CAF were almost equivalently inhibited by SCH 23390 (0.01 and 0.1 mg/kg SC) and YM-09151-2 (0.01 and 0.1 mg/kg SC). However, the inhibitory effects of apomorphine (0.05 mg/kg SC) and N^6-(L-phenylisopropyl)-adenosine (0.1 and 0.2 mg/kg SC) were stronger for CAF than for MAP and the combination, and those of α-methyl-*p*-tyrosine (200 mg/kg IP, 4 h before) and reserpine (1 mg/kg SC, 4 h before) were stronger for MAP and CAF alone than for the combination. The present results suggest that, although the combination of MAP and CAF enhances the ambulation-increasing effect through an interaction at dopaminergic system, CAF may not significantly modify the induction of MAP sensitization in mice.

Key words: Methamphetamine – Caffeine – Ambulation – Repeated administration – Sensitization – Mice

Psychotropic effects of CNS stimulant drugs sometimes change after repeated administration, with serious consequences such as sensitization to psychopathological effects of amphetamine (Connell 1958; Snyder 1975). In rats and/or mice, repeated administration of amphetamine elicits a sensitization to the CNS stimulant actions expressed as increase in ambulation and stereotypy (see reviews, Kuribara and Hirabayashi 1985; Robinson and Becker 1986; Tadokoro and Kuribara 1986, 1990). Such behavioral sensitization in animals induced by repeated administration may be closely related to amphetamine-psychosis (Ellinwood et al. 1973; Tadokoro and Kuribara 1986, 1990).

On the other hand, caffeine (CAF) is a commonly used CNS stimulant drug with weak dependence liability (Deneau et al. 1969; Yanagita 1992). Moreover, it is also well known that CAF is a frequent contaminant of drugs sold on the street in Japan, such as methamphetamine (Kuribara, unpublished data), partly to increase the weight and volume, but also probably to enhance the drug's action, particularly its reinforcing effect. Thus, it is important to assess whether CAF modifies the effects of MAP in the repeated administration schedule. Very few studies have focused on this issue.

In this study, the modification by CAF of the sensitization to ambulation-increasing effect of MAP was evaluated. Furthermore, the effects of some drugs, which affect dopaminergic and adenosinergic transmission, on the ambulation-increasing effects of CAF and MAP alone, and their combination were also evaluated.

Materials and methods

Animals

The experimental animals used were male mice of dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine). Groups of ten mice had been housed in standard aluminum cages (20 × 25 × 10 cm) under the controlled room-condition (temperature; 23 ± 2 °C, relative humidity; 50 ± 2%, and light period; 0600–1800 hours) with free access to solid diet (MF: Oriental Yeast, Tokyo) and tap water except during times of the experiment. When these mice were 7 weeks of the age and weighed 26–30 g, the experiment was started. All experimental procedures used were conducted in accordance with the Japanese Guideline for the Care and Use of Laboratory Animals.

Drugs

The drugs used were methamphetamine HCl (MAP: Dainippon Pharmaceuticals, Osaka), caffeine anhydrous (CAF: Kanto Chemicals, Tokyo), SCH 23390; *R*-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl (Research Biochemicals, Natick, Mass.), YM-09151-2; *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (Yamanouchi Pharmaceuticals, Tokyo), apomorphine HCl (Sigma, St Louis, Mo.), α-methyl-*p*-tyrosine (AMPT: Sigma), reserpine (Apoplon Inj., Daiichi Pharmaceuticals, Tokyo) and N^6-(L-phenylisopropyl)-adenosine (PIA: Sigma). YM-09151-2 was first dissolved with very small amount of 1 N HCl solution, and then diluted with physiological saline. AMPT was suspended in the saline with Tween-80 (1 drop/5 ml). The other drugs were dissolved with the saline. Each injection volume was always constant at 0.1 ml/10 g body weight of the mouse regardless of the drug doses.

Procedure

The apparatus for measurement of ambulatory activity of the mouse was a tilting-type ambulometer having ten bucket-like Plexiglas activity cages of 20 cm in diameter (SMA-10; O'Hara & Co., Tokyo). The apparatus detected a slight tilt of the activity cage generated only by ambulation (locomotion) of mouse so that the horizontal movement of the mouse could be selectively assessed. Mice were individually put into the activity cages, and after an adaptation period of 30 min, drugs were administered. Then, the ambulatory activity of each mouse was measured for 3 h.

All the experiments were carried out between 0900 and 1600 hours.

Repeated drug administration and challenge administration of methamphetamine. According to the experimental schedules shown in Table 1, the 20 groups of 20 mice each were given five repeated administrations of CAF (0: saline, 1, 3, 10 and 30 mg/kg, two groups each), and combinations of MAP (1 and 2 mg/kg) with CAF (0, 1, 3, 10 and 30 mg/kg) at 3 to 4-day intervals. Seven days after the final (fifth) administration, the caffeine alone experienced mice were challenge-administered MAP (1 or 2 mg/kg). The mice that experienced the combination of MAP with CAF were challenge administered the corresponding doses of MAP.

Effects of drugs on the ambulation increasing effects of MAP, CAF and their combination. Thirty-six groups of ten drug-naive mice each were used, and modifications by SCH 23390 (0.01 and 0.1 mg/kg SC), YM-09151-2 (0.01 and 0.1 mg/kg SC), apomorphine (0.05 mg/kg SC), AMPT (200 mg/kg IP), reserpine (1 mg/kg SC) and PIA (0.1 and 0.2 mg/kg SC) of the ambulation-increasing effects of MAP (1 mg/kg), CAF (10 mg/kg) and their combination were evaluated. SCH 23390, YM-09151-2, apomorphine and PIA were simultaneously administered MAP, CAF and their combination, and AMPT and reserpine were treated 4 h before.

Statistical analyses

The mean overall ambulatory activity counts for 3 h were first analyzed using ANOVA. The factors in the former experiment were doses of CAF (five levels including saline) and number of administrations (five levels), and those in the latter experiment were doses of the test drugs (two or three levels including saline) and administrations of CAF, MAP alone and their combination (three levels). In the cases of significant overall variance, comparisons between individual mean values were conducted using Dunnett's test. When P values were equal to or less than 0.05, they were defined as statistically significant.

Results

Repeated drug administration

Figure 1 shows the mean 3-h ambulatory activity counts after repeated administration of CAF alone (0: saline control, 1, 3, 10 and 30 mg/kg), MAP (1 and 2 mg/kg)

Table 1. Experimental schedules of the repeated drug administration and the challenge of methamphetamine

Repeated administration (5 times at 3 to 4-day intervals)	Challenge
Saline (caffeine dose = 0)	Methamphetamine 1 mg/kg
Caffeine 1 mg/kg	Methamphetamine 1 mg/kg
3	Methamphetamine 1 mg/kg
10	Methamphetamine 1 mg/kg
30	Methamphetamine 1 mg/kg
Saline (caffeine dose = 0)	Methamphetamine 2 mg/kg
Caffeine 1 mg/kg	Methamphetamine 2 mg/kg
3	Methamphetamine 2 mg/kg
10	Methamphetamine 2 mg/kg
30	Methamphetamine 2 mg/kg
Methamphetamine 1 mg/kg alone (caffeine dose = 0)	Methamphetamine 1 mg/kg
Methamphetamine 1 mg/kg + caffeine 1 mg/kg	Methamphetamine 1 mg/kg
1 + 3	Methamphetamine 1 mg/kg
1 + 10	Methamphetamine 1 mg/kg
1 + 30	Methamphetamine 1 mg/kg
Methamphetamine 2 mg/kg alone (caffeine dose = 0)	Methamphetamine 2 mg/kg
Methamphetamine 2 mg/kg + caffeine 1 mg/kg	Methamphetamine 2 mg/kg
2 + 3	Methamphetamine 2 mg/kg
2 + 10	Methamphetamine 2 mg/kg
2 + 30	Methamphetamine 2 mg/kg

In the combined administration, two drugs were administered SC simultaneously. The challenge with methamphetamine (SC) was carried out 7 days after the fifth administration. $n = 20$ in each group

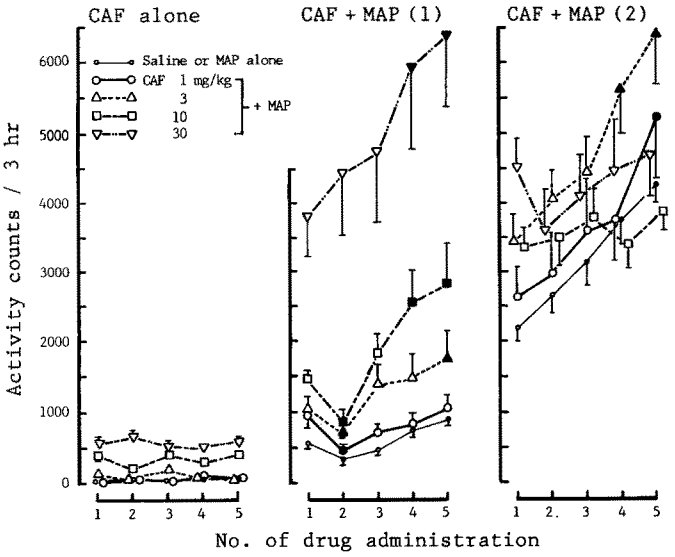

Fig. 1. Mean 3-h ambulatory activity counts with SEMs after the repeated (5×) administration at 3 to 4-day intervals of caffeine (*CAF*; 0: saline, 1, 3, 10 and 30 mg/kg) alone, combination of methamphetamine (*MAP*; 1 and 2 mg/kg) with caffeine. *Closed symbols* indicate significant difference from the value in the first administration within the group. $n = 20$ in each experiment

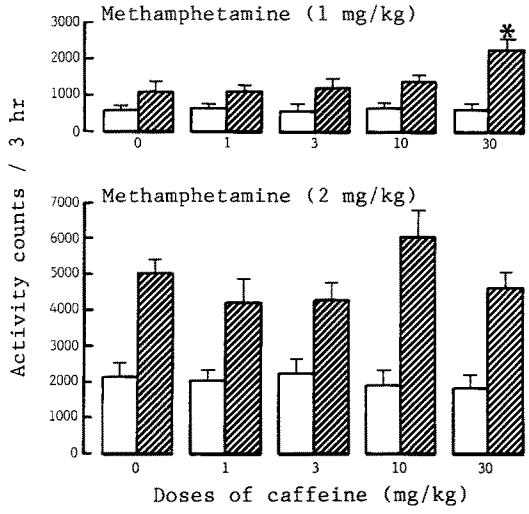

Fig. 2. Mean 3-h ambulatory activity counts with SEMs after the challenge with methamphetamine 1 mg/kg (*upper panel*) and 2 mg/kg (*lower panel*) to the mice that were injected 5 times with caffeine alone (0: saline, 1, 3, 10 and 30 mg/kg) (*open columns*), and combination of methamphetamine (1 and 2 mg/kg) with caffeine (*hatched columns*). The challenge administration was carried out 7 days after the fifth drug injection. * $P < 0.05$ vs the value of the mice injected saline or methamphetamine alone (caffeine dose = 0). $n = 20$ in each experiment

alone and the combination of MAP (1 and 2 mg/kg) with CAF (1, 3, 10 and 30 mg/kg).

After the first administration to the drug-naive mice, CAF dose-dependently increased the ambulatory activity [$F(4,95) = 8.37$, $P < 0.001$]. The ambulation increments after doses of 3 mg/kg and higher of CAF were significantly higher than after control treatment. The combination of MAP with CAF produced a dose-dependent enhancement in the effect; for 1 mg/kg MAP [$F(4,95) = 19.38$, $P < 0.001$], and for 2 mg/kg MAP [$F(4,95) = 22.71$, $P < 0.001$]. In the combination of MAP with CAF 3 mg/kg and more, the activity counts were significantly higher than those after the administration of the corresponding doses of MAP alone.

The ambulation increasing effect of CAF was dose dependent, but not significantly changed by the repeated five times administration [$F(4,475) = 19.79$, $P < 0.001$ for CAF doses, $F(4,475) = 0.32$, ns for administration, and $F(16,475) = 0.11$, ns for the interaction]. However, there were significant CAF dose, administration and the dose × administration dependent variations in the effect after repeated administration of the combination of MAP with CAF; for MAP (1 mg/kg) with CAF [$F(4,475) = 40.89$, $P < 0.001$ for CAF doses, $F(4,475) = 37.91$, $P < 0.001$ for administration, and $F(16,475) = 9.06$, $P < 0.001$ for the interaction], and for MAP (2 mg/kg) with CAF [$F(4,475) = 24.61$ for CAF doses, $P < 0.001$, $F(4,475) = 27.13$, $P < 0.001$ for administration, and $F(16,475) = 5.93$, $P < 0.01$ for the interaction]. Individual comparisons revealed that, although a significant decrease in the effect was observed in the second administration of MAP (1 mg/kg), the repeated administration of MAP alone produced enhancement in the effect, and the activity counts in the fifth administration were 1.6 and 1.9 times as high as those in the first administration of MAP 1 and 2 mg/kg, respectively. Following the repeated administration of MAP (1 mg/kg) with CAF (1, 3 and 10 mg/kg), the activity counts in the second administration were significantly lower than those in the first administration. However, after repeated administration of MAP (1 mg/kg) with CAF (3, 10 and 30 mg/kg), significant enhancement in effects was produced. A progressive enhancement in the effect was produced by the repeated administration of MAP (2 mg/kg) with CAF (1 and 3 mg/kg). The other combinations induced neither enhancement nor decrease in the effect following the repeated administration.

Challenge with methamphetamine

Figure 2 shows the mean 3-h activity counts after a challenge administration of MAP (1 mg/kg: upper panel, and 2 mg/kg: lower panel) to the mice that were treated with repeated administration of CAF alone (open columns) and combination of MAP with CAF (hatched columns). ANOVA revealed that the repeated treatment with CAF (1–30 mg/kg) did not significantly modify the sensitivities to MAP in both the single and combined administration schedules; for MAP (1 mg/kg) [$F(4,95) = 0.27$, ns for the single treatment, and $F(4,95) = 2.18$, ns for the combined treatment], and for MAP (2 mg/kg) [$F(4,95) = 0.54$, ns for the single treatment, and $F(4,95) = 1.93$, ns for the combined treatment]. However, individual comparisons showed that repeated administration of MAP (1 mg/kg) with CAF (30 mg/kg) produced a significant enhancement in the sensitivity to challenge MAP (1 mg/kg).

Table 2. Effects of drugs on the ambulation-increasing effects of SC administration of methamphetamine (1 mg/kg), caffeine (10 mg/kg), and their combination

Test drugs	Methamphetamine (1 mg/kg)	Caffeine (10 mg/kg)	Methamphetamine + Caffeine (1 mg/kg) (10 mg/kg)
Drug alone	476 ± 44(100)	481 ± 65(100)	1764 ± 276(100)
SCH 23390 0.01 mg/kg SC	278 ± 47(58.4)*	291 ± 31(60.4)*	740 ± 194(42.0)*
0.1	64 ± 10(13.4)*	51 ± 5(10.6)*	367 ± 85(20.8)*
YM-9151-2 0.01 mg/kg SC	137 ± 26(28.7)*	172 ± 20(35.7)*	731 ± 174(41.5)*
0.1	51 ± 7(10.6)*	52 ± 5(10.7)*	209 ± 20(11.9)*
APOMOR 0.05 mg/kg SC	353 ± 68(74.1)*	250 ± 47(51.9)*	1680 ± 219(84.4)
PIA 0.1 mg/kg SC	416 ± 74(87.4)	398 ± 46(82.7)	1687 ± 166(95.6)
0.2 mg/kg SC	466 ± 149(97.8)	184 ± 35(38.2)*	1489 ± 219(84.4)
Saline (IP, 4 h)	558 ± 66(100)	406 ± 39(100)	1657 ± 133(100)
AMPT 200 mg/kg (IP, 4 h)	37 ± 6(6.6)*2	40 ± 5(9.9)*	261 ± 54(15.8)*
Saline (SC, 4 h)	536 ± 41(100)	459 ± 51(100)	1712 ± 158(100)
RES 1 mg/kg (SC, 4 h)	84 ± 17(15.7)*	3 ± 2(0.7)*	745 ± 79(43.5)*

SCH 23390, YM-09151-2, apomorphine (APOMOR) and N^6-(*L*-phenylisopropyl)-adenosine (PIA) were administered simultaneously, and α-methyl-*p*-tyrosine (AMPT) and reserpine (RES) were administered 4 h before the administration of methamphetamine, caffeine and the combination. Figure in each parenthesis indicates the % of each control value

* $P < 0.05$ vs the corresponding control values (Dunnett's test). $n = 10$ in each experiment

Effects of drugs on the ambulation-increasing effects of MAP, CAF and their combination

As shown in Table 2, all of the test drugs reduced the ambulation-increasing effects of CAF, MAP and their combination. Hereafter, the administrations of MAP, CAF and their combination are called as drug condition. ANOVA revealed that there were sometimes significant effects of the test drugs, drug condition and their interactions; for SCH 23390 [$F(2, 81) = 41.95$, $P < 0.001$ for the doses and $F(2, 81) = 12.50$, $P < 0.001$ for the drug condition, with no interaction $F(4, 81) = 0.86$, ns], YM-09151-2 [$F(2, 81) = 48.12$, $P < 0.001$ for the doses and $F(2, 81) = 21.08$, $P < 0.001$ for the drug condition, with no interaction $F(4, 81) = 0.37$, ns], apomorphine [$F(1, 54) = 9.35$, $P < 0.001$ for the doses, $F(2, 54) = 7.81$, $P < 0.01$ for the drug condition and $F(2, 54) = 6.99$, $P < 0.01$ for the interaction], PIA [$F(2, 81) = 12.09$, $P < 0.001$ for the doses, $F(2, 81) = 10.64$, $P < 0.001$ for the drug condition and $F(4, 81) = 12.07$, $P < 0.001$ for the interaction], AMPT [$F(1, 54) = 59.97$, $P < 0.001$ for the doses, and $F(2, 54) = 11.30$, $P < 0.001$ for the drug condition, with no interaction $F(2, 54) = 2.09$ ns], and reserpine [$F(1, 54) = 45.15$, $P < 0.001$ for the doses, $F(2, 54) = 14.92$, $P < 0.001$ for the drug condition and $F(2, 54) = 10.70$, $P < 0.001$ for the interaction]. Individual comparison revealed that, except for the effects of apomorphine on the combination of MAP with CAF, and PIA (0.1 mg/kg) on the MAP and CAF alone, the ambulation-increasing effects of all the drug conditions were significantly reduced by the test drugs.

Furthermore, the percent changes of activity counts showed that SCH 23390 and YM-09151-2 reduced the ambulation-increasing effects of MAP, CAF and their combination with almost the same degree. The inhibitory actions of apomorphine and PIA were stronger for CAF alone than for MAP alone and for the combination of MAP with CAF. Such effects of AMPT and reserpine were stronger for MAP and CAF alone than for the combination.

Discussion

CAF shows strong antagonist effects at adenosine receptors, and concomitantly stimulates catecholaminergic systems through this blockade of adenosine-related inhibitory systems (Cardinali 1980; Fredholm 1980; Snyder et al. 1981). The CAF-induced ambulation increment might reflect such actions. Like CAF, MAP also increases ambulation. The ambulation-increasing effect of MAP is also induced by the activation of catecholaminergic, particularly dopaminergic, systems through facilitation of the release and inhibition of reuptake of catecholamines (McMillen 1983; Mason 1984; Fischman 1987). The reductions of the ambulation-increasing effect by the D_1 antagonist SCH 23390 (Iorio et al. 1983; Mailman and Schultz 1984) and the D_2 antagonist YM-09151-2 (Terai et al. 1983) were almost the same in magnitude for the combination of MAP with CAF with those for MAP and CAF alone. At the doses administered in this experiment, both SCH 23390 and YM-09151-2 block postsynaptic dopamine D_1 and D_2 receptors, respectively. However, the reductions of ambulation-increasing effect by dopamine autoreceptor stimulation (apomorphine), dopamine synthesis inhibition (AMPT) and dopamine depletion (reserpine) (Mason 1984) at the presynaptic level were stronger for either MAP or CAF alone than for the combination of MAP with CAF. Moreover, adenosine receptor stimulation (PIA) (Snyder et al. 1981) was only effective for significant reduction of the ambulation-increasing effect of CAF alone. These results suggest that the enhancement of the ambulation-increasing effect by the combined administration of MAP with CAF is elicited through acceleration of dopaminergic transmission at presynaptic level, which is directly affected by methamphetamine rather than by indirect modification through adenosinergic system.

The repeated administration of MAP induced sensitization to the ambulation-increasing effect, while CAF produced no significant change in its effect throughout repeated administration. These results are consistent with

the data from our previous studies (Fujii et al. 1989; Kuribara and Tadokoro 1989), though there are a few reports which suggest development of tolerance to some effects of caffeine (Chou et al. 1985; Holtzman et al. 1991). From these considerations, it can be concluded that basis of the ambulation-increasing effect of MAP is different from that of CAF.

Previously, we reported that intermittent administration of several drugs with CNS stimulant actions elicits a cross-sensitization to the ambulation-increasing effect of MAP in mice (Kuribara and Hirabayashi 1985; Tadokoro and Kuribara 1990). There have also been reports that suggest a close interaction between adenosinergic and dopaminergic systems (Ferre et al. 1991a, b). Therefore, it was initially expected that CAF could significantly modify the induction of MAP sensitization. However, in the present experiment, repeated treatment with CAF alone did not produce any significant modification in the sensitivity to MAP. Holtzman (1983) also demonstrated no significant change in the sensitivity to *d*-amphetamine in the mice that were given CAF through CAF-containing drinking water. These findings suggest again that the behavioral characteristics of CAF are quite different from those of amphetamines.

The present experiment demonstrated that, although some combinations of MAP with CAF elicited significant enhancement in the effect during the repeated administration, the MAP sensitization assessed by the challenge-administration was scarcely modified, except in the case of combination of MAP (1 mg/kg) with CAF (30 mg/kg). This finding clearly indicates the differential nature of CNS stimulant action of MAP and CAF. MAP has both dopamine release-facilitating and reuptake-inhibiting actions (McMillen 1983; Mason 1984; Fischman 1987), whereas CAF has dopamine releasing action through blockade of the adenosinergic system (Cardinali 1980; Fredholm 1980; Snyder et al. 1981). It is possible that the CNS stimulant actions of MAP and CAF are separate, although more work is required to confirm this conclusion.

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