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Importance of Initial Environments in the Development of Ambulatory Sensitization to Methamphetamine and Cocaine in Mice

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Abstract

Repeated administration of CNS stimulants such as amphetamines and cocaine induces behavioural sensitization which can be influenced by the animal's environment. This study has evaluated the effect of restraint on the development and maintenance of ambulatory sensitization to methamphetamine and cocaine in mice.

Subcutaneous administration of the CNS stimulants methamphetamine (2 mg kg^{-1}) and cocaine (20 mg kg^{-1}) seven times at three-day intervals resulted in ambulatory sensitization when the mice were placed in 20-cm diameter activity cages after each dose of the drug. However, if methamphetamine or cocaine was administered when the mice were in small jars (6-cm diameter) in which expression of ambulation, but not of circling and rearing, was completely restricted, the development of ambulatory sensitization was retarded or inhibited, with circling behaviour concurrently increased, when subsequent repeated doses of the drug were administered in the activity cage. Subsequent repeated treatment of ambulatory-sensitized mice with the drug or saline when the mice were in the jars did not change the levels of the ambulatory sensitization or the circling behaviour.

These results suggest that the mice are sensitized to the behavioural effect of CNS stimulants which can be expressed in the environment in which the drug is administered. It is also considered that the established sensitization is strongly retained and is responsible for retardation or suppression of the development of sensitization to other behavioural stimulant effects.

Repeated administration of CNS stimulants such as amphetamines and cocaine can induce behavioural sensitization (Kuribara & Hirabayashi 1985; Robinson & Becker 1986; Kuribara 1996a) including changes in neurotransmission, in particular an increase in dopamine release from presynaptic terminals (Robinson et al 1988; Akimoto et al 1989; Kazahaya et al 1989; Segal & Kuczenski 1992; Wolf et al 1993).

Occasionally, when animals are given comparatively high doses of amphetamine or cocaine, the extent of behavioural sensitization is almost independent of the environment (Browne & Segal 1977; Robinson 1984). However, it is frequently observed that behavioural sensitization to CNS stimulants is greater for animals that have been given the amphetamines or cocaine in the testing environment than for those that have been given the same drug dose in other environments, e.g. the home cage (Tilson & Rech 1973; Hinson & Poulos 1981; Post et al 1981; Weiss et al 1989; Pert et al 1990; Stewart & Vesina 1991). Hayashi et al (1980) showed that when the stimulant effect of D-amphetamine was still active exposure to a flickering light enhanced the development of sensitization to the ambulation-increasing effect. These reports suggest that an external cue in the environment, denoted 'context-dependent sensitization', is an important factor in the induction of behavioural sensitization to CNS stimulants.

It has also been suggested that repeated experience both of the CNS stimulant effect of amphetamines or cocaine and the resultant expression of a specific behaviour is an important factor in the induction of behavioural sensitization. Thus, the sensitization to the CNS stimulant is manifested as behaviour which can be expressed in the environment in which the experiment is performed (Segal 1975; Willner et al 1992; Martin-Iverson & Fawcett 1996). Hirabayashi & Alam (1981), Hirabayashi et

al (1991) and Kuribara (1995, 1996b, 1997) demonstrated that mice did not show ambulatory sensitization when they were kept in a small jar (less than 9 cm in diameter) for 3 and 2 h after each administration of methamphetamine and cocaine, respectively, to restrict the expression of ambulation without inhibiting either vertical movement or turning. These results suggest two possibilities: either the mice acquire sensitization to behaviour other than ambulation during the repeated administration of the CNS stimulant when in the jars, or the established sensitization might be retained for a long period and can act to inhibit or retard the induction of sensitization to other behaviour during subsequent repeated administration.

The aims of this study were to evaluate the effect of restraint on the development and maintenance of ambulatory sensitization to methamphetamine and cocaine in mice.

Materials and Methods

Animals

Experiments were performed with six-week-old ddY strain male mice (Japan Laboratory Animals, Tokyo, Japan), 25–28 g. Groups of 10 mice were housed in 20 cm × 25 cm × 15 cm (height) polycarbonate cages with free access to a solid diet (MF; Oriental Yeast, Tokyo, Japan) and tap-water. Conditions in the breeding room were carefully controlled (temperature, 23 ± 1°C; relative humidity, 55 ± 3%; and a 12 h light–dark cycle (lights on between 0600 and 1800 h).

Apparatus

A tilting-type 'ambulometer' (SMA-10; O'Hara, Tokyo, Japan) with ten 20-cm diameter × 15 cm height bucket-like Plexiglas activity cages was used to measure the ambulation of 10 mice individually and simultaneously. The apparatus detected slight tilts of the activity cage generated by horizontal movements (positional change, i.e. ambulation) of the mouse. Vertical movements such as rearing and circling (small-diameter rotation) did not tilt the activity cage.

Glass jars (6 cm diam. × 15 cm height) were used for selective restriction of the ambulation of mice. In the jar the mouse could express vertical movements and circling almost freely.

Drugs

Methamphetamine HCl (Dainippon, Osaka, Japan) and cocaine HCl (Takeda, Osaka, Japan) were dissolved in physiological saline and administered subcutaneously in a constant volume of 0·1 mL per 10 g. The doses of methamphetamine (2 mg kg^{-1} in the salt form) and cocaine (20 mg kg^{-1} in the salt form) were optimum for induction of the ambulatory sensitization without producing strong stereotypies (Kuribara 1996b).

Experimental procedures

All experiments were performed between 0900 and 1600 h.

Methamphetamine study

Eight groups of 10 mice were treated with methamphetamine seven times at three-day intervals. The mice in group M1 were placed in the activity cages for 3 h after each administration. The mice in groups M2–M4 were placed in the jars for 3 h after the first, first and second, and first-third administrations, respectively, and in the activity cages after subsequent administrations (second, third and fourth administrations, respectively). Before the start of repeated administration of methamphetamine, the mice in groups M5, M6 and M7 were given saline one, two and three times, respectively, in the jars, at three-day intervals. The mice in group M8 were treated with saline in the activity cages three times before repeated administration of methamphetamine. After administration for the fourth and seventh times the circling behaviour, defined as comparatively small-diameter rotation without tilting of the activity cage, was measured for 1 min, starting 30 min after administration of methamphetamine.

The other two groups of 10 mice were treated with methamphetamine in the activity cages five times at three-day intervals to induce ambulatory sensitization. Subsequently, these two groups of mice were treated with either saline or methamphetamine in the jars three times at three-day intervals, followed by the challenge administration of methamphetamine three days after the last treatment. Thirty minutes after the challenge administration of methamphetamine circling was measured for 1 min.

Cocaine study

The experimental schedules were similar to those used to study methamphetamine except that the duration of the measurement of ambulatory activity or exposure of mice in the jar was 2 h, and observation of circling behaviour was conducted 20 min after administration, because the duration of action of cocaine was less than that of methamphetamine.

Statistical analysis

The mean overall ambulatory activity counts during observation periods of 3 and 2 h after administration of methamphetamine and cocaine, respectively, were analysed by one-way or two-way analysis of variance. Post-hoc analyses were per-

formed by the Bonferroni test. Values of $P < 0.05$ were considered indicative of significance.

Results

Methamphetamine study

Table 1 shows the 3-h overall ambulatory activity counts after repeated administration of methamphetamine. For group M1, activity counts increased progressively up to the fourth administration ($F(6,63) = 39.1$, $P < 0.001$) with almost constant activity counts thereafter. For groups M2, M3 and M4, activity counts after administration for the second, third and fourth times, respectively, i.e. the first exposure of the mice to the activity cages, were similar to each other and to that after the first administration to group M1. After subsequent repeated administration of methamphetamine, significant sensitization was observed for groups M2 and M3 ($F(5,54) = 18.5$, $P < 0.001$ and $F(4,45) = 4.9$, $P < 0.01$, respectively), although the development of sensitization was delayed. However, significant sensitization to the ambulation-increasing effect of methamphetamine by the seventh administration was not observed for the mice of group M4 ($F(3,36) = 1.3$, $P > 0.05$). For groups M5, M6 and M7, which were treated with saline in the jars one, two and three times, respectively, the sensitization response to methamphetamine was almost the same as that shown by group M1 ($F(6,63) = 36.0$, 44.6 and 40.3, respectively, $P < 0.001$). Group M8, receiving saline three times in the activity cages, also developed sensitization to methamphetamine ($F(6,63) = 49.3$, $P < 0.001$) as high as that observed for group M1.

As shown in Table 2, after administration of methamphetamine for the fourth and seventh times the amount of circling was significantly dependent on the treatment ($F(7,72) = 14.9$ and 7.5, respectively, $P < 0.001$). Compared with group M1, significant increases in the circling were observed for groups M2, M3 and M4 after the fourth administration and for groups M3 and M4 after the seventh administration. Significant changes in circling behaviour were not observed with the other groups after repeated administration of methamphetamine.

As shown in Table 3, in methamphetamine-sensitized mice administration of saline or methamphetamine on three subsequent occasions when

Table 1. Effects of restraint on the development of sensitization to ambulatory stimulation caused by repeated subcutaneous administration of methamphetamine (2 mg kg^{-1}) at three-day intervals.

Group	Treatment	Methamphetamine administration						
		1	2	3	4	5	6	7
M1	Methamphetamine (cage) × 7	**2091 ± 269**	2382 ± 327	3797 ± 519*	4602 ± 406*	4950 ± 453*	4663 ± 320*	4707 ± 657*
M2	Methamphetamine (jar) × 1 and methamphetamine (cage) × 6	Methamphetamine (jar)	**1857 ± 314**	2401 ± 174†	2775 ± 325*†	3862 ± 562*	4294 ± 583*	5020 ± 739*
M3	Methamphetamine (jar) × 2 and methamphetamine (cage) × 5	Methamphetamine (jar)	Methamphetamine (jar)	**2057 ± 413**†	2250 ± 506†	3633 ± 699*†	3873 ± 531*	4156 ± 620*
M4	Methamphetamine (jar) × 3 and methamphetamine (cage) × 4	Methamphetamine (jar)	Methamphetamine (jar)	Methamphetamine (jar)	**2143 ± 441**†	2392 ± 438†	2828 ± 479†	2860 ± 618†
M5	Saline (jar) × 1 and methamphetamine (cage) × 7	**2130 ± 390**	2962 ± 600	3840 ± 694*	4340 ± 652*	4840 ± 794*	5012 ± 898*	4946 ± 591*
M6	Saline (jar) × 2 and methamphetamine (cage) × 7	**2114 ± 536**	2811 ± 462	3826 ± 420*	4692 ± 648*	4936 ± 421*	4890 ± 711*	5113 ± 609*
M7	Saline (jar) × 3 and methamphetamine (cage) × 7	**2005 ± 251**	2704 ± 437	3886 ± 485*	4797 ± 610*	5007 ± 561*	4910 ± 697*	5078 ± 638*
M8	Saline (cage) × 3 and methamphetamine (cage) × 7	**1926 ± 292**	2306 ± 330	4051 ± 372*	4883 ± 401*	4901 ± 507*	4950 ± 615*	5051 ± 592*

Each datum is the mean 3-h activity count ± s.e.m. for 10 mice after administration of methamphetamine. *$P < 0.05$, significantly different from the count at the first behavioural observation in the activity cage after administration of methamphetamine (indicated in bold). †$P < 0.05$, significantly different from result for group 1.

Table 2. Amount of circling after repeated subcutaneous administration of methamphetamine (2 mg kg^{-1}) at three-day intervals.

Group	Treatment	Methamphetamine administration	
		Fourth	Seventh
M1	Methamphetamine (cage) × 7	2·6 ± 0·7	1·0 ± 0·2
M2	Methamphetamine (jar) × 1 and methamphetamine (cage) × 6	8·6 ± 1·1*	1·1 ± 0·4
M3	Methamphetamine (jar) × 2 and methamphetamine (cage) × 5	10·7 ± 1·3*	3·7 ± 0·8*
M4	Methamphetamine (jar) × 3 and methamphetamine (cage) × 4	13·1 ± 2·1*	11·9 ± 2·3*
M5	Saline (jar) × 1 and methamphetamine (cage) × 7	2·1 ± 0·3	0·8 ± 0·2
M6	Saline (jar) × 2 and methamphetamine (cage) × 7	1·9 ± 0·5	1·4 ± 0·4
M7	Saline (jar) × 3 and methamphetamine (cage) × 7	1·6 ± 0·5	1·3 ± 0·3
M8	Saline (cage) × 3 and methamphetamine (cage) × 7	2·1 ± 0·6	1·1 ± 0·3

Circling was defined as rotation of comparatively small diameter which did not tilt the activity cage. Observation was conducted for 1 min, 30 min after administration of methamphetamine. Each datum is the mean ± s.e.m. of results from 10 mice. *$P < 0·05$ significantly different from result for group 1.

the mice were in the jars induced no significant changes in either methamphetamine-induced ambulation (saline, $F(1,18) = 0·3$, $P > 0·05$; methamphetamine, $F = 0·2$, $P > 0·05$) or in methamphetamine-induced circling behaviour (saline, $F(1,18) = 0·2$, $P > 0·05$; methamphetamine, $F = 0·6$, $P > 0·05$).

Cocaine study

Table 4 shows the 2-h overall ambulatory activity counts after repeated administration of cocaine. For group C1, the activity counts increased progressively as far as the fourth administration and were almost constant thereafter ($F(6,63) = 25·3$, $P < 0·001$). For groups C2, C3 and C4 the activity counts after the first exposure of mice to the activity cage, i.e. after administration of cocaine for the second, third and fourth times, respectively, were similar to each other and to that after the first administration to group C1. After subsequent repeated administrations of cocaine significant sensitization ($F(5,54) = 8·3$, $P < 0·001$) was observed for the mice in group C2. However, significant sensitization to the ambulation-increasing effect of cocaine by the seventh administration ($F(4,45) = 1·6$ and $F(3,36) = 1·2$, $P > 0·05$) was not observed for groups C4 and C5. When mice in jars were pretreated with saline one, two and three times (C5, C6 and C7, respectively) or when those in the activity cages were pre-treated three times (group C8) there was no effect on the development of ambulatory sensitization to cocaine ($F(6,63) = 30·1$, 34·9, 31·6 and 27·4, respectively, $P < 0·001$).

As shown in Table 5, after administration of cocaine for the fourth and seventh times the amounts of circling were significant depending on the treatment ($F(7,72) = 17·0$ and 13·1, respectively, $P < 0·001$). Compared with group C1, significant increases in circling were observed for groups C2, C3 and C4 after the fourth administration, and for groups C3 and C4 after the seventh administration. Significant changes in circling behaviour were not observed for the other groups after repeated administration of cocaine.

As shown in Table 6, when cocaine-sensitized mice in the jars were subsequently treated three times with saline or cocaine no significant changes were observed in cocaine-induced ambulation

Table 3. Effect of restraint on ambulation and circling mice sensitized to the ambulation-increasing affect of subcutaneous methamphetamine (2 mg kg^{-1}).

Treatment	Before		After	
	Ambulation	Circling	Ambulation	Circling
Saline (jar) × 3	5019 ± 537	1·9 ± 0·3	5230 ± 676	1·9 ± 0·4
Methamphetamine (jar) × 3	4955 ± 575	1·7 ± 0·3	5016 ± 404	2·2 ± 0·5

Methamphetamine-sensitization was induced by administration of five doses of methamphetamine at three-day intervals. The treatment (injection of methamphetamine or saline when the mouse was in a 6-cm diameter jar) was performed three times at three-day intervals. Methamphetamine was administered three days after the end of treatment. Ambulation is the 3-h overall activity count. Circling was observed for 1 min, 30 min after the administration of methamphetamine. Each datum is the mean ± s.e.m. of results from 10 mice.

Table 4. Effects of restraint on the development of sensitization to ambulatory stimulation caused by repeated subcutaneous administration of cocaine (20 mg kg^{-1}) at three-day intervals.

Group	Treatment	Cocaine administration						
		1	2	3	4	5	6	7
C1	Cocaine (cage) × 7	**1432 ± 293**	1940 ± 239	2536 ± 357*	2892 ± 397*	3016 ± 439*	2843 ± 511*	3051 ± 534*
C2	Cocaine (jar) × 1 and cocaine (cage) × 6	Cocaine (jar)	**1366 ± 286**	1576 ± 210†	2307 ± 395*	2651 ± 356*	2635 ± 387*	2843 ± 587*
C3	Cocaine (jar) × 2 and cocaine (cage) × 5	Cocaine (jar)	Cocaine (jar)	**1493 ± 395**†	1687 ± 417†	1844 ± 409†	1777 ± 529†	1959 ± 608†
C4	Cocaine (jar) × 3 and cocaine (cage) × 4	Cocaine (jar)	Cocaine (jar)	Cocaine (jar)	**1217 ± 256**†	1468 ± 258†	1342 ± 207†	1652 ± 387†
C5	Saline (jar) × 1 and cocaine (cage) × 7	**1294 ± 186**	1760 ± 251	2601 ± 289*	2811 ± 341*	2973 ± 378*	3115 ± 524*	3094 ± 501*
C6	Saline (jar) × 2 and cocaine (cage) × 7	**1239 ± 159**	1972 ± 301	2574 ± 360*	2957 ± 395*	2894 ± 380*	2917 ± 480*	3159 ± 538*
C7	Saline (jar) × 3 and cocaine (cage) × 7	**1174 ± 156**	2005 ± 281	2423 ± 274*	2965 ± 377*	2913 ± 351*	3088 ± 404*	3051 ± 459*
C8	Saline (cage) × 3 and cocaine (cage) × 7	**1399 ± 250**	1862 ± 203	2446 ± 317*	2912 ± 330*	2895 ± 320*	2982 ± 372*	3002 ± 387*

Each datum is the mean 2-h activity count ± s.e.m. for 10 mice after administration of cocaine. *$P < 0.05$, significantly different from the count at the first behavioural observation in the activity cage after administration of cocaine (indicated in bold). †$P < 0.05$, significantly different from result for group 1.

Table 5. Amount of circling after repeated subcutaneous administration of cocaine (20 mg kg^{-1}) at three-day intervals.

Group	Treatment	Cocaine administration	
		Fourth	Seventh
C1	Cocaine (cage) × 7	2·2 ± 0·5	3·1 ± 0·6
C2	Cocaine (jar) × 1 and cocaine (cage) × 6	4·0 ± 1·1*	4·9 ± 1·6
C3	Cocaine (jar) × 2 and cocaine (cage) × 5	13·7 ± 2·1*	14·2 ± 1·7*
C4	Cocaine (jar) × 3 and cocaine (cage) × 4	13·9 ± 2·6*	14·6 ± 2·5*
C5	Saline (jar) × 1 and cocaine (cage) × 7	2·6 ± 0·6	2·3 ± 0·4
C6	Saline (jar) × 2 and cocaine (cage) × 7	2·2 ± 0·4	3·1 ± 0·6
C7	Saline (jar) × 3 and cocaine (cage) × 7	1·9 ± 0·5	1·9 ± 0·4
C8	Saline (cage) × 3 and cocaine (cage) × 7	1·7 ± 0·4	2·7 ± 0·5

Circling was defined as rotation of comparatively small diameter which did not tilt the activity cage. Observation was conducted for 1 min, 20 min after administration of cocaine. Each datum is the mean ± s.e.m. of results from 10 mice. *$P < 0.05$ significantly different from result for group 1.

Table 6. Effect of restraint on ambulation and circling by mice sensitized to the ambulation-increasing effect of subcutaneous cocaine (20 mg kg^{-1}).

Treatment	Before		After	
	Ambulation	Circling	Ambulation	Circling
Saline (jar) × 3	2902 ± 351	2·5 ± 0·6	2994 ± 340	2·7 ± 0·6
Cocaine (jar) × 3	2948 ± 316	2·9 ± 0·7	3022 ± 351	2·4 ± 0·5

Cocaine-sensitization was induced by administration of five doses of cocaine at three-day intervals. The treatment (injection of cocaine or saline when the mouse was in a 6-cm diameter jar) was performed three times at three-day intervals. Cocaine was administered three days after the end of treatment. Ambulation is the 2-h overall activity count. Circling was observed for 1 min, 20 min after the administration of cocaine. Each datum is the mean ± s.e.m. of results from 10 mice.

(saline, $F(1,18)=0{\cdot}1$, $P>0{\cdot}05$; cocaine, $F=0{\cdot}3$, $P>0{\cdot}05$) or circling (saline, $F(1,18)=0{\cdot}3$, $P>0{\cdot}05$; cocaine; $F=0{\cdot}5$, $P>0{\cdot}05$).

Discussion

These experiments have revealed that sensitization to the ambulation-increasing effect of methamphetamine and cocaine was established by the fourth administration and that almost the same level of ambulatory sensitization was reproduced thereafter when the mice were exposed to the activity cages after each administration of the drug. These results are consistent with those obtained from previous studies (Kuribara 1995, 1996b, 1997).

However, when mice were first exposed to small jars, in which the expression of ambulation was selectively restricted, two to three times after administration of methamphetamine or cocaine, ambulatory sensitization was significantly retarded or reduced during subsequent repeated administration of drug in the activity cages, despite administration a sufficient number of times (4-6) for the development of maximum ambulatory sensitization (as demonstrated for groups M1 and C1). It is also interesting to note that a significant increase in circling behaviour was observed for the mice for which ambulatory sensitization was retarded or inhibited. Because the mice in the jars were completely restricted from expressing ambulation but almost completely free to express circling and rearing, it is considered that the selective restriction of ambulation resulted in an increase in the expression of circling behaviour after repeated administration of the drugs. This supposition might be supported by the observation that mice exposed three times in the jars after each administration of methamphetamine or cocaine, which might be sufficient to establish sensitization to circling behaviour, showed no significant ambulatory sensitization. These results suggest that establishment of sensitization to the circling behaviour tends to retard or inhibit the development of ambulatory sensitization.

In contrast, repeated exposure of mice in the jars after the administration of saline did not affect the development of ambulatory sensitization to methamphetamine or cocaine, and did not induce any increase in circling behaviour during subsequent administration of the drugs in the activity cages, indicating that the combination of saline and restraint did not affect the process of development of sensitization to the ambulatory stimulating or circling-increasing effects of methamphetamine and cocaine. These results are in agreement with the report by Beck et al (1986) that the initial environment influenced the development of sensitization to amphetamine-induced stereotypy. Thus, it is highly probable that the mice acquire sensitization to the behavioural stimulant effect which can be expressed in the environment during the presence of the acute effect of the drug.

Initial restraint of mice in jars after administration of methamphetamine or cocaine acted to inhibit or retard the development of sensitization to increased ambulation. However, the established ambulatory sensitization and the amount of circling behaviour were not changed by repeated treatment with saline, methamphetamine or cocaine when the mice were in the jars. These results suggest that once sensitization to the ambulatory stimulant effect of methamphetamine or cocaine has been established, the mice retained the behavioural pattern even after treatment with saline or the drug in the jars, suggesting long-lasting retention of the conditioned drug effect; this has been reported by many researchers (Beck et al 1986; Kuribara 1995, 1996a, 1997; Martin-Iverson & Fawcett 1996).

Although it is widely accepted that increased dopamine release from the presynaptic terminal plays an important role in behavioural sensitization (Robinson et al 1988; Wolf et al 1993), the correlation between the environment-dependent behavioural sensitization and neurochemical changes remains unclear (Ohmori et al 1995a). However, many reports suggest that induction of behavioural sensitization is one of the phenomena of learning and memory, i.e. conditioning, because of the inhibition of behavioural sensitization to amphetamines and cocaine by anti-cholinergic, NMDA-receptor blockers, NO-synthase inhibitors and protein-synthesis inhibitors, etc. (Karler et al 1993; Pudiak & Bozarth 1993; Ohmori et al 1995b; Ohno & Watanabe 1995; Heidbreder & Snippenberg 1996). The establishment of sensitization to the ambulatory stimulant effect in the activity cage and the circling-increasing effect in the jar after repeated administration of both methamphetamine and cocaine strongly suggest environment-dependent conditioning of the expression of specific behaviour.

The results of this study suggest the following conclusions: behavioural sensitization to methamphetamine and cocaine in mice is established by administration three or four times; the sensitization developed to the behavioural stimulant effect is that which can be expressed in the environment during the acute drug effect, i.e. the ambulatory stimulant effect in the activity cage, and the circling–increasing effect in the jar; development of sensitization to one behavioural stimulant effect might

inhibit or retard the development of sensitization to other behavioural stimulant effects; the established sensitization is retained even after repeated operations which are responsible for inhibition or retardation of the development of the behavioural sensitization; and conditioning to (or learning of) the specific behavioural stimulant effect is one of the main factors in environment-dependent behavioural sensitization to methamphetamine and cocaine.

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