

## Assessment of the Ambulation-Increasing Effect of Ketamine by Coadministration with Central-Acting Drugs in Mice

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**ABSTRACT**—The coadministration of ketamine (12.5 mg/kg, but not 3.1 mg/kg, s.c.) with methamphetamine (2 mg/kg, s.c.), cocaine (10 mg/kg, s.c.), scopolamine (0.5 mg/kg, s.c.), caffeine (10 mg/kg, s.c.) and MK-801 (0.1 mg/kg, i.p.) significantly enhanced the ambulation-increasing effects. Furthermore, in the coadministration with morphine (10 mg/kg, s.c.) and GBR-12909 (10 mg/kg, i.p.), not only 12.5 mg/kg but also 3.1 mg/kg of ketamine produced a significant enhancement. On the other hand, the ambulation-increasing effect of ketamine (12.5 mg/kg, s.c.) was significantly suppressed by ceruletide (0.01 mg/kg, i.p.),  $\alpha$ -methyl-*p*-tyrosine (100 and 300 mg/kg, i.p.  $\times$  2), nimodipine (1 and 3 mg/kg, i.p.), haloperidol (0.03 and 0.1 mg/kg, s.c.), a low dose of apomorphine (0.1 mg/kg, s.c.), physostigmine (0.1 mg/kg, s.c.) and *N*6-(*L*-2-phenylisopropyl)-adenosine (0.1 mg/kg, s.c.). However, imipramine (20 mg/kg, i.p.), 6*R*-*L*-erythro-5,6,7,8-tetrahydrobiopterin (100 mg/kg, s.c.), a high dose of apomorphine (0.5 mg/kg), reserpine (0.3 and 1 mg/kg, s.c.), propranolol (0.3 and 1 mg/kg, s.c.), phenoxybenzamine (3 and 10 mg/kg, s.c.) and naloxone (0.3 and 1 mg/kg, s.c.) scarcely interacted with ketamine. These results suggest that ketamine increases the ambulatory activity in mice by facilitating dopamine release from a newly synthesized pool at the presynaptic level, which is affected by a calcium-dependent mechanism.

**Keywords:** Ketamine, Ambulation-increasing effect, Dopaminergic system

Ketamine, a potent anesthetic and analgesic agent, structurally similar to phencyclidine, often produces posthypnotic adverse psycho-reactions in humans; i.e., hallucinations, restlessness, and psychomotor agitation (1). In rodents, the behavioral stimulant effects of ketamine are manifested by rotation (2, 3), stereotypy (4) and ambulation (5–7).

It has been reported that ketamine changes the levels of brain monoamines and their metabolites in rodents (8–10), and that the ambulation-increasing effect of ketamine may be mediated by presynaptic dopamine neurons in the nucleus accumbens in mice (7). Ketamine has also been reported to interact with opioid receptors (11, 12) and cholinergic receptors (13, 14). Furthermore, recent reports have suggested that the action of ketamine is linked with antagonism to *N*-methyl-D-aspartate (NMDA) receptors (15–17).

It has been demonstrated that ketamine and the non-competitive NMDA antagonist MK-801 have similar effects on the behaviors in mice and/or rats (4, 18–

20), and that these drugs may share a common mechanism of action that is related to the phencyclidine recognition site in the brain (21). Recently, Kuribara et al. (22) showed that MK-801 increased the mouse's ambulatory activity through stimulation of the dopaminergic system, which was strongly affected by a calcium-dependent mechanism. In this study, we have intended to clarify a variety of neuropharmacological characteristics of ketamine through the coadministration with various central-acting drugs. In addition, we have compared effects of ketamine on the ambulatory activity of mice with those of MK-801 reported by Kuribara et al. (22).

### MATERIALS AND METHODS

#### Animals

Male ddY mice (Japan Laboratory Animals) at 7 weeks were used. The animals were group housed in standard breeding cages with free access to a solid diet

(MF, Oriental Yeast) and tap water except during the times of the experiments. The breeding room was controlled so that the light-dark cycle (lighting time: 6:00–18:00) and temperature ( $23 \pm 1^\circ\text{C}$ ) were almost constant.

### Drugs

The drugs used in this study were ketamine HCl (Ketalar Inj.<sup>®</sup>; Sankyo), methamphetamine HCl (Philopon<sup>®</sup>; Dainippon Pharm.), cocaine HCl (Takeda Chem.), morphine HCl (Takeda Chem.), scopolamine HBr (Sigma Chem.), anhydrous caffeine (Kanto Chem.), MK-801 hydromaleate (Merck/Banyu), GBR-12909 (Gist-Brocades), imipramine HCl (Tofranil Inj.<sup>®</sup>; Ciba-Geigy Japan), 6*R*-L-erythro-5,6,7,8-tetrahydrobiopterin (R-THBP; Suntory), apomorphine HCl (Sigma Chem.), ceruletide diethylamine (Shionogi Pharm.), reserpine (Apoplon Inj.<sup>®</sup>; Daiichi Pharm.),  $\alpha$ -methyl-*p*-tyrosine (AMPT; Sigma Chem.), nimodipine (Bayer AG), haloperidol (Serenace Inj.<sup>®</sup>; Dainippon Pharm.), propranolol HCl (Inderal Inj.<sup>®</sup>; Sumitomo Pharm.), phenoxybenzamine HCl (Tokyo Chem.), naloxone HCl (Sigma Chem.), physostigmine sulfate (Sigma Chem.) and *N*6-(1-2-phenylisopropyl)-adenosine (PIA; Sigma Chem.). These drugs were dissolved or suspended in or diluted by physiological saline immediately before the administration. Each drug administration volume was fixed to 0.1 ml/10 g body weight.

### Experimental procedure

The ambulatory activity of the mouse was measured with a tilting-type ambulometer (AMB-10, O'hara & Co.), which has 10 Plexiglas activity cages with a diameter of 20 cm each. Mice were individually placed in the cages and adapted to the cage for 30 min prior to the drug administration, and then the ambulatory activities were measured for 3 hr.

**Single administration of ketamine:** Ketamine (0: saline, 3.1 and 12.5 mg/kg, s.c.) was administered.

**Coadministration:** In the first series experiments, ketamine (0, 3.1 and 12.5 mg/kg, s.c.) was coadministered with methamphetamine (2 mg/kg, s.c.), cocaine (10 mg/kg, s.c.), morphine (10 mg/kg, s.c.), scopolamine (0.5 mg/kg, s.c.), caffeine (10 mg/kg, s.c.), MK-801 (0.1 mg/kg, i.p.), GBR-12909 (10 mg/kg, i.p.), imipramine (20 mg/kg, i.p.), R-THBP (100 mg/kg, s.c.) and apomorphine (0.5 mg/kg, s.c.). In the second series experiments, ketamine (12.5 mg/kg, s.c.) was coadministered with ceruletide (0.001 and 0.01 mg/kg, i.p.), reserpine (0.3 and 1 mg/kg, s.c.; pretreatment, 3.5 hr before), AMPT (100 and 300 mg/kg, i.p.  $\times$  2; pretreatment, 24 and 4 hr before), nimodipine (1 and 3 mg/kg, i.p.; pretreatment, 30 min before), haloperidol

(0.03 and 0.1 mg/kg, s.c.; pretreatment 30 min before), apomorphine (0.1 mg/kg, s.c.), propranolol (0.3 and 1 mg/kg, s.c.), phenoxybenzamine (3 and 10 mg/kg, s.c.), naloxone (0.3 and 1 mg/kg, s.c.), physostigmine (0.03 and 0.1 mg/kg, s.c.) and PIA (0.03 and 0.1 mg/kg, s.c.).

In each drug test, 10–20 mice were used. All of these experiments were carried out between 9:00–15:00.

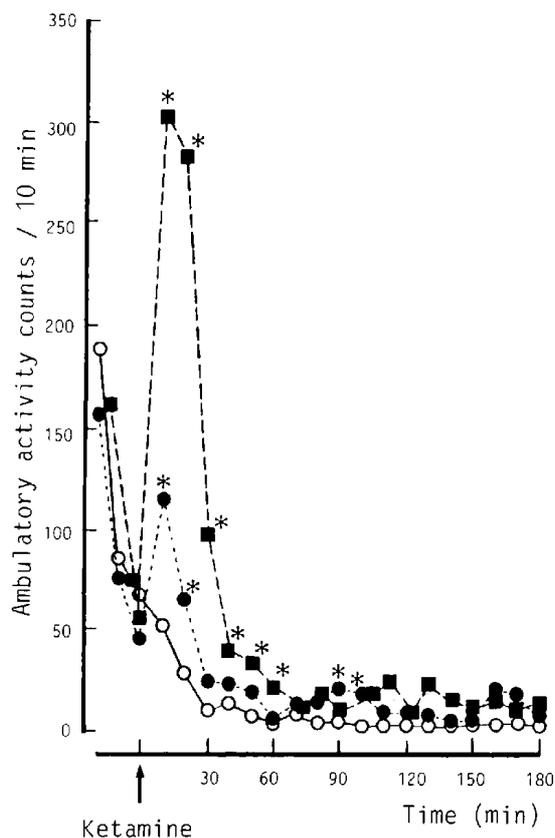
### Statistical analysis

The data were analyzed by one-way analysis of variance (ANOVA) and Student's *t*-test. These results were considered to be significantly different when *P* values were less than 0.05.

## RESULTS

### Single administration of ketamine

Figure 1 shows time course changes in the ambulatory activity counts after the administration of ketamine



**Fig. 1.** Time course changes in mean ambulatory activity counts after the administration of ketamine (●—●: 3.1 mg/kg, s.c. and ■—■: 12.5 mg/kg, s.c.) and saline (○—○) in mice. \*: Significantly different from the saline-administered control value ( $P < 0.05$ ).  $N = 20$  in each experiment.

alone. The ambulation-increasing effects of ketamine were observed for 60–90 min in a dose-dependent manner, with a maximal increase at 10 min after the administration and a rapid decline thereafter. The mice exhibited a slight ataxia during the ambulation-increment.

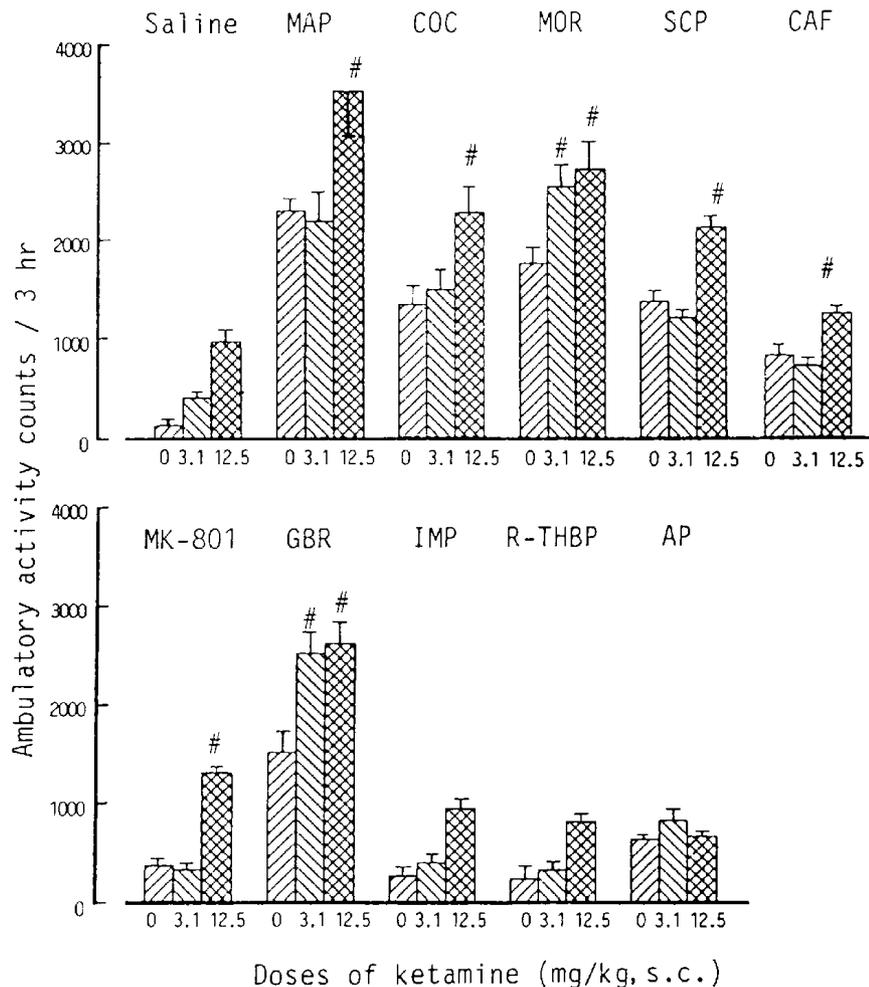
The overall ambulatory activity counts for 3 hr after the administration of ketamine at 3.1 or 12.5 mg/kg were significantly higher than the value of saline administration (data not shown, but see left, upper 3 columns of Fig. 2).

When higher doses of ketamine (25 and 50 mg/kg) were administered in our preliminary experiment, the mice showed a moderate ataxia and obstruction of their ambulation for 10–20 min in a dose-dependent man-

ner, but scarcely lost their righting reflex. With the recovery from the ataxia, the re-increment of their ambulatory activity was observed, and then the activity continued for 60–90 min after the administration (Y. Uchihashi, unpublished data). From these data, more than 25 mg/kg of ketamine could be considered as overdoses; and 3.1 and 12.5 mg/kg were selected as the minimum and maximum doses, respectively, to adequately increase the ambulatory activity in mice.

*Coadministration*

As shown in Fig. 2, the coadministration of ketamine at 12.5 mg/kg with methamphetamine, cocaine, scopolamine, caffeine or MK-801 and ketamine at 3.1 or 12.5 mg/kg with morphine and GBR-12909 significantly en-



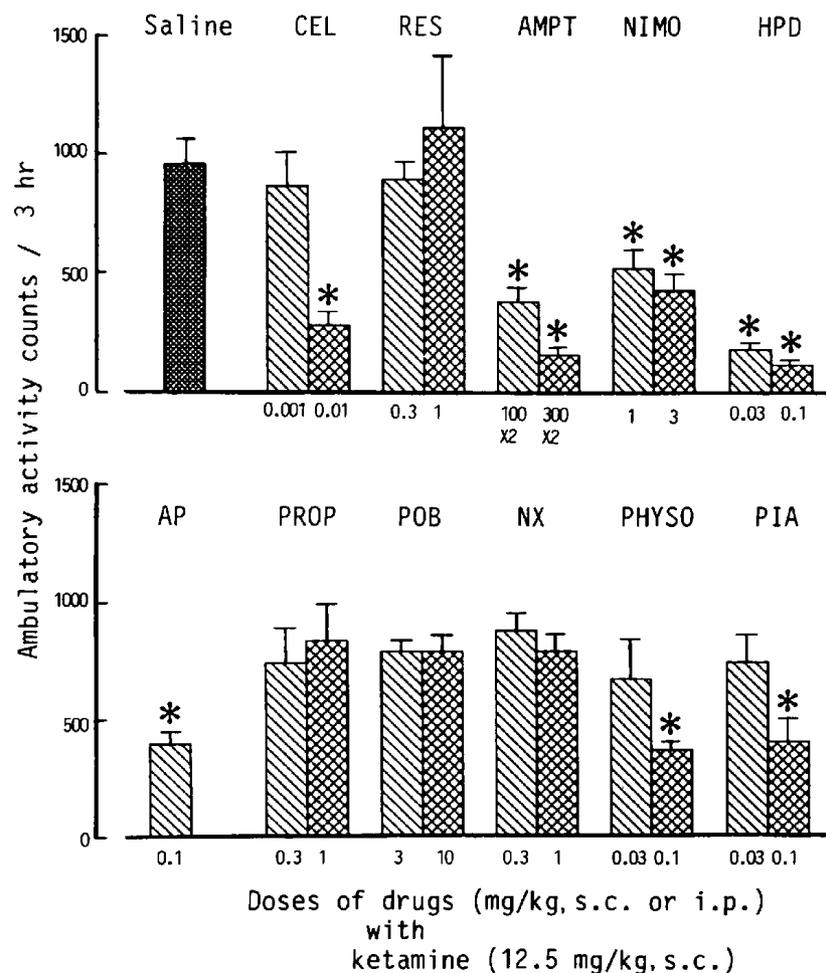
**Fig. 2.** Mean overall ambulatory activity counts for 3 hr after the coadministration of ketamine (0: saline, 3.1 and 12.5 mg/kg, s.c.) with methamphetamine (MAP: 2 mg/kg, s.c.), cocaine (COC: 10 mg/kg, s.c.), morphine (MOR: 10 mg/kg, s.c.), scopolamine (SCP: 0.5 mg/kg, s.c.), caffeine (CAF: 10 mg/kg, s.c.), MK-801 (0.1 mg/kg, i.p.), GBR-12909 (GBR: 10 mg/kg, i.p.), imipramine (IMP: 20 mg/kg, i.p.), 6R-L-erythro-5,6,7,8-tetrahydrobiopterin (R-THBP: 100 mg/kg, s.c.) and apomorphine (AP: 0.5 mg/kg, s.c.) in mice. #: Significantly different from both the values after the single administration of ketamine and the test drug ( $P < 0.05$ ).  $N = 10-20$  in each experiment.

hanced the ambulation-increasing effects; i.e., the activity counts for 3 hr were significantly higher than those after both ketamine alone and the test drug alone. In contrast, imipramine, R-THBP and a high dose of apomorphine (0.5 mg/kg) scarcely interacted with ketamine.

As shown in Fig. 3, ceruletide, AMPT, nimodipine, haloperidol, physostigmine and PIA dose-dependently suppressed the ambulation-increasing effect of ketamine at 12.5 mg/kg. Furthermore, a low dose of apomorphine (0.1 mg/kg), which selectively stimulates the pre-synaptic autoreceptors and reduces motor activity in mice (23), significantly suppressed the effect of keta-

mine. Propranolol, phenoxybenzamine and naloxone did not markedly change the effect of ketamine. Although reserpinized mice did not show ambulation for 10–20 min after the administration of ketamine, a successive increase in the activity appeared; thereby, the overall activity counts were not significantly different from those after ketamine alone.

The changes in ambulation-increasing effects after the coadministration of ketamine and MK-801 with various central-acting drugs are compared in Table 1. The data of MK-801 were taken from those reported by Kuribara et al. (22).



**Fig. 3.** Mean overall ambulatory activity counts for 3 hr after the coadministration of ketamine (12.5 mg/kg, s.c.) with ceruletide (CEL: 0.001 and 0.01 mg/kg, i.p.), reserpine (RES: 0.3 and 1 mg/kg, s.c.; pretreatment, 3.5 hr before), *α*-methyl-*p*-tyrosine (AMPT: 100 and 300 mg/kg, i.p. × 2; pretreatment, 24 and 4 hr), nimodipine (NIMO: 1 and 3 mg/kg, i.p.; pretreatment, 30 min before), haloperidol (HPD: 0.03 and 0.1 mg/kg, s.c.; pretreatment, 30 min before), apomorphine (AP: 0.1 mg/kg, s.c.), propranolol (PROP: 0.3 and 1 mg/kg, s.c.), phenoxybenzamine (POB: 3 and 10 mg/kg, s.c.), naloxone (NX: 0.3 and 1 mg/kg, s.c.), physostigmine (PHYSO: 0.03 and 0.1 mg/kg, s.c.) and *N*6-(*l*-2-phenylisopropyl)-adenosine (PIA: 0.03 and 0.1 mg/kg, s.c.) in mice. \*: Significantly different from the value after the administration of ketamine with saline ( $P < 0.05$ ).  $N = 10-20$  in each experiment.

**Table 1.** Comparison between interactions of ketamine and MK-801 with various central-acting drugs by means of ambulatory activity in mice

	Ketamine	MK-801
Methamphetamine	+	+
Cocaine	+	+
Morphine	+	+
Scopolamine	+	+
Caffeine	+	+
GBR-12909	+	+
Imipramine	NC	NC
Apomorphine (high dose)	NC	NC
Ceruletide	-	-
Reserpine	NC	-
$\alpha$ -Methyl- <i>p</i> -tyrosine	-	NC
Nimodipine	-	-
Haloperidol	-	-
Apomorphine (low dose)	-	NC
Propranolol	NC	?
Phenoxybenzamine	NC	?
Naloxone	NC	NC
Physostigmine	-	?
Pilocarpine	?	NC
N6-( <i>L</i> -2-Phenylisopropyl)-adenosine	-	NC

+: Enhanced. -: Suppressed. NC: No significant change. ?: Not evaluated. The data of MK-801 are taken from the experiment by Kuribara et al. (ref. 22).

## DISCUSSION

Ketamine was reported to produce an ambulation-increasing effect in mice through an activation of dopaminergic transmission (7). In agreement with this result, the present experiment showed that the ambulation-increasing effect of ketamine was significantly enhanced after the coadministration of ketamine with the test drugs which increased the mouse's ambulatory activity through the activation of dopamine neurons. These drugs are considered to directly activate the dopaminergic systems by releasing and/or inhibiting the uptake of catecholamines in methamphetamine-, cocaine- and GBR-12909-treated animals (24–26) and indirectly activate those by stimulating the opioid receptors in morphine-treated animals (27), by blocking the muscarinic cholinergic receptors in scopolamine-treated animals (28) and by blocking the adenosine receptors in caffeine-treated animals (29). On the contrary, ketamine did not interact with imipramine, R-THBP and high doses of apomorphine (0.5 mg/kg), which were catecholamine uptake inhibitors (24), coenzyme of tyrosine hydroxylase (30) and postsynaptic dopamine receptor agonist (23), respectively. These results were almost consistent with those of the non-competitive NMDA antagonist MK-801 demonstrated by Kuribara et al.

(22). They suggested that the ambulation-increasing effect of MK-801 appeared through the stimulation of dopamine release from the presynapse, although its mechanism was different from that of amphetamines, cocaine or GBR-12909. MK-801 also enhanced the effect of ketamine.

GBR-12909 and morphine showed significant enhancements of the effect in the coadministration with ketamine at not only 12.5 mg/kg but also at 3.1 mg/kg, which slightly produced an ambulatory increment. It was reported that GBR-12909 acted on the dopaminergic system more selectively than methamphetamine and cocaine (26). The dopaminergic selectivity of GBR-12909 may contribute to the strong enhancement of the ketamine effect. However, it is curious that morphine, unlike the other indirect dopamine stimulants, i.e., scopolamine and caffeine, showed a synergic interaction with ketamine. Naloxone (opioid receptor antagonist) scarcely suppressed the effect of ketamine. Smith et al. (11) demonstrated that ketamine interacted with opioid receptors in a stereospecific manner. In our experiment, racemic ketamine was used; and because of this, the interaction with naloxone might have become weak. It is possible that the synergic effect of morphine on the ketamine-induced ambulatory increment appeared through a dopaminergic mechanism, which is related to the delicate interaction between opioid receptors. In the interaction of ketamine with GBR-12909 and morphine, further investigations are required.

On the other hand, the ambulation-increasing effect of ketamine at 12.5 mg/kg was suppressed by nimodipine (calcium blocker) (31, 32), ceruletide (CCK-like decapeptide, which suppresses the central dopaminergic systems through a modification of afferent transmission) (33) or haloperidol (dopamine receptor antagonist) (24). These results also indicate that the stimulative effect of ketamine appears through the calcium-dependent dopaminergic mechanism, like that of MK-801 (22). However, Irifune et al. (7) suggested that the dopamine release from the presynapse by ketamine was calcium-independent. This is in conflict with our result. Nimodipine was reported to reduce the synthesis as well as the release of dopamine in mouse brain (31, 32). The reduction of dopamine synthesis by nimodipine may affect the ambulatory increment by ketamine. The dopaminergic mechanism of ketamine is also supported by the results that propranolol ( $\beta$ -blocker) and phenoxybenzamine ( $\alpha$ -blocker) (24) did not modify the effect of ketamine.

In contrast with MK-801 (22), AMPT (tyrosine hydroxylase inhibitor) (24) or a low dose of apomorphine (0.1 mg/kg, presynaptic dopamine autoreceptor agonist) (23) reduced the effect of ketamine, but reserpine

(monoamine depletor) (24) had only a slight action. Thus, it is strongly suggested that newly synthesized dopamine and store site dopamine in the presynapse play an important role in the ambulation-increasing effect of ketamine and in that of MK-801, respectively. However, it is interesting that R-THBP did not enhance the ambulatory increment by ketamine. R-THBP was reported to markedly augment the effect of methamphetamine, which was intimately connected with the newly synthesized dopamine (34). It is probable that ketamine stimulates the dopamine release, but hardly affects the dopamine synthesis, unlike methamphetamine.

It is also interesting that the low dose of apomorphine reduced the effect of ketamine, but did not interact with that of MK-801 (Table 1). The stimulation of presynaptic dopamine autoreceptors suppresses the calcium-dependent dopamine release and the dopamine synthesis (35). The dose of apomorphine in our experiment (0.1 mg/kg) may not affect the dopamine release but may reduce the dopamine synthesis.

Moreover, physostigmine (cholinesterase inhibitor), which indirectly stimulates the muscarine receptors and has pilocarpine (muscarine receptors agonist)-like actions (24) and PIA (adenosine receptors agonists) (36) suppressed the ambulation-increasing effect of ketamine more intensely than that of MK-801 (22). These test drugs produced the suppression of the mouse's ambulation indirectly through the central dopamine system (24, 28, 36). The peak and the duration of ketamine action was much more rapid and shorter than those of MK-801 (Fig. 1 and ref. 22). It is probable that physostigmine and PIA, which are also short-acting drugs, non-specifically interacted with the ketamine due to their rapid action and short duration.

In conclusion, like MK-801, ketamine has an ambulation-increasing effect by facilitating the dopamine transmission. However, its mechanism is the release of newly synthesized dopamine, which is different from the release of stored dopamine by MK-801. This difference between ketamine and MK-801 in the dopaminergic mechanism suggests that the ambulation-increasing effect of ketamine may appear through a direct action on the dopaminergic system, not through an indirect action by affecting the NMDA system.

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