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Ketamine-Induced Hyperlocomotion Associated With Alteration of Presynaptic Components of Dopamine Neurons in the Nucleus Accumbens of Mice

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IRIFUNE, M., T. SHIMIZU AND M. NOMOTO. *Ketamine-induced hyperlocomotion associated with alteration of presynaptic components of dopamine neurons in the nucleus accumbens of mice.* PHARMACOL BIOCHEM BEHAV **40**(2) 399–407, 1991.—The underlying mechanisms of ketamine-induced hyperlocomotion were examined in mice. An intraperitoneal (IP) injection of ketamine (3–150 mg/kg) increased locomotor activity in a dose-dependent fashion. A low dose of ketamine (30 mg/kg) produced peak locomotion within the first 10 min followed by a rapid decline. In contrast, a high dose (150 mg/kg) inhibited locomotor activity to the control level during the first 30 min. Thereafter the activity gradually increased and reached a peak at approximately 2 h followed by a gradual decline. The hyperactivities induced by both low and high doses of ketamine were inhibited by a low dose of haloperidol (0.10 mg/kg, IP), a dopamine (DA) receptor antagonist. However, neither a high dose of phenoxybenzamine (10 mg/kg, IP), an α-blocker nor a high dose of propranolol (20 mg/kg, IP), a β-blocker inhibited the hyperactivities. Destruction of catecholaminergic terminals by 6-hydroxydopamine suppressed ketamine-induced hyperlocomotion. Regional brain monoamine assays revealed that, at peak locomotion, a low dose of ketamine (30 mg/kg) selectively increased DA turnover in the nucleus accumbens which is a forebrain region believed to be involved in the initiation and regulation of locomotor activity, while a high dose (150 mg/kg) increased not only DA but also norepinephrine and serotonin turnover in many regions of the brain. In vitro, ketamine slightly provoked [^{3}H]DA release from nucleus accumbens and striatal slices to a similar extent, but inhibited synaptosomal uptake of [^{3}H]DA in the nucleus accumbens to a greater degree than in the striatum. These results suggest that ketamine may have indirect DA agonist action and that ketamine-induced hyperlocomotion may be mediated by presynaptic DA neurons in the nucleus accumbens rather than in the striatum.

Ketamine Locomotor activity Mouse Haloperidol Propranolol Phenoxybenzamine 6-Hydroxydopamine Dopamine turnover Dopamine uptake Dopamine release Nucleus accumbens Corpus striatum

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KETAMINE 2-(o-chlorophenyl)-2-methylaminocyclohexanone hydrochloride is a useful anesthetic agent which is characterized by rapid onset of action, remarkable analgesic properties, lack of cardiorespiratory depression and wide margin of safety. However, emergence from ketamine anesthesia is often accompanied by restlessness, mood changes, psychomotor agitation and hallucination in humans (12). The high incidence of such emergence phenomena has limited its clinical widespread acceptance (41). In rodents, ketamine produces a variety of stimulant effects including hyperlocomotion (8,18). Although it has been reported that ketamine stimulates locomotor activity and schedule-controlled responding via different neuropharmacologic mechanisms (23) and that ketamine-induced hyperlocomotion does not appear to be mediated by opiate receptors (42), the mechanisms of ketamine-induced hyperactivity are still unknown.

Dopaminergic mechanisms within the cortex, striatum and nucleus accumbens play an important role in the control of locomotor activity. It is thought that the nucleus accumbens is especially involved in the initiation and regulation of locomotor activity (1). The articulation and prolongation of locomotor activity involves norepinephrine (NE), although NE may act as a neuromodulator rather than as an action-pathway of locomotion (14). Ketamine is known to change the levels of brain monoamines and their metabolites in rats (32, 38, 43) and in primates (2) in vivo, to increase dopamine (DA) and NE release from striatal and cortical slices, respectively (33,35), and to inhibit DA uptake into striatal synaptosomes (19) and NE uptake into cortical synaptosomes (34) in vitro. It has been suggested that during recovery from ketamine anesthesia the increased NE content in the whole brain and the increased DA turnover in the striatum may be associated with the postanesthetic excitement of rats (43). However, it has been reported that the nucleus accumbens is more involved than the striatum in inducing hyperlocomotion (1). Ketamine has been reported to produce rotation (26) and stereotypy (20) in addition to hyperlocomotion. Therefore, in the present study, we focused on hyperlocomotion induced by ketamine and catecholamine turnover in discrete brain regions including the nucleus accumbens.

METHOD

Animals

Male ddY mice (Kuroda Junkei Dohbutu, Ltd., Japan), weighing 33–55 g, were used. The animals were housed with free access to standard food (Clea Japan Inc.) in an air-conditioned room with a temperature of 22–24°C and humidity of 60–70% and maintained under a constant 12-h light-dark cycle (light on 7:00 a.m.). All behavioral experiments were carried out between 10:00 and 17:00.

Drugs

Ketamine hydrochloride was purchased from Research Biochemicals Inc. (Wayland, MA); 6-hydroxydopamine (6-OHDA) hydrobromide and DL-propranolol hydrochloride were from Sigma Chemical Co. (St. Louis, MO); haloperidol was from Yoshitomi Pharmaceutical Co. (Osaka); phenoxybenzamine hydrochloride was from Tokyokasai Co. (Tokyo).

Ketamine, haloperidol and propranolol were dissolved in 0.9% saline solution. Phenoxybenzamine was suspended in 0.1% carboxymethyl cellulose sodium salt solution.

All drugs except 6-OHDA were injected intraperitoneally (IP) in a volume of 10 ml/kg. Haloperidol, phenoxybenzamine or propranolol was injected 30 min prior to IP administration of ketamine.

Locomotor Activity

Locomotor activity was measured with four circular activity cages (49.0 cm diameter × 26.5 cm high). Each cage was equipped with photocell sensor units mounted on the outer wall at equal distances 2.0 cm above the floor. Interruptions of the infrared light beams were recorded on electromechanical counters located at a distance from the activity cages and automatically printed every 10 min. Mice were individually placed in their cages and acclimatized to the cage for 30 min, injected with ketamine or 0.9% saline and then returned for an additional 3-h test period.

Behavioral Observation

Mice were examined individually in a circular glass beaker (13.5 cm diameter × 19.0 cm high). After administration of ketamine, the beaker was inclined and the animal was placed on its back three times. Righting reflex and ataxia (anesthetic effects) were recorded and scored every 2 min up to 10 min after the injection, and then every 3 min for 2 h. These behavioral changes were evaluated according to the rating scale of Boast et al. (6) with minor modifications: a score of 0 indicates no obvious ataxia; +1 indicates staggering gait during locomotion but a normal righting reflex; +2 indicates that the mouse righted itself within 2 s on all 3 trials but that the hindlimb was raised; +3 indicates that the latency to righting was more than 2 s but less than 10 s at the best response in 3 trials; +4 corresponds to the absence of this reflex (no righting within 10 s on all 3 trials).

6-OHDA Treatment

Mice were anesthetized with ether. 6-OHDA at a dose of 50 μg in 2.5 μl of 0.9% saline containing 0.1% ascorbic acid was injected into both lateral ventricles at a rate of 5.0 μl/min. Control mice received the same volume of vehicle solution as 6-OHDA-treated animals. The position of the injection was 2.0 mm rostral and 1.0 mm lateral from the bregma and 3 mm in from the surface of the skull. The studies were carried out on the 3rd day after the injection, before the occurrence of behavioral supersensitivity (24).

Monoamine Assay

Mice were decapitated 10 or 20 min after the administration of 30 mg/kg ketamine and 120 min after 150 mg/kg ketamine, when ketamine-induced locomotor activity was approximately at a peak. Control animals were treated with 0.9% saline and sacrificed on a similar time-schedule. The brain was quickly removed and dissected on an ice-cold glass plate into the frontal cortex, nucleus accumbens (including olfactory tubercule), striatum, hippocampus and brainstem according to the method of Heffner et al. (17), which was slightly modified. The brain parts were weighed and frozen on dry ice and stored at −40°C until assayed. The tissue sample was smashed in 0.1 M perchloric acid containing 5 mM EDTA and 3,4-dihydroxybenzylamine 25 pg/μl, using an ultrasonic cell disruptor (40% pulsed power for 30 s; Model 185, Branson), and centrifuged at 28,000 × g for 20 min at 4°C (Kubota KR-20000T). The supernatant was filtered through a 0.45 μm membrane filter (LC3A, Gelman Sciences) and a 20 μl aliquot of the filtered solution was injected into a high performance liquid chromatography (HPLC) system. The HPLC system consisted of a delivery pump (Waters 510, Waters Associates Inc.), a sample injector (WISP 710B, Waters Associates Inc.), a reverse phase column (250 mm length × 4.6 mm i.d., Eicompak MA-ODS, Eicom Co.), an electrochemical detector (LC-4B, Bioanalytical Systems Inc.) set at a potential of +0.8V versus an Ag/AgCl reference electrode and a computing integrator-printer (Waters 740, Waters Associates Inc.). The analytical column temperature was controlled at 40°C. The mobile phase consisted of 12% (v/v) methanol containing 0.1 M sodium acetate, 0.1 M citric acid, 0.23 mM sodium octydyl sulfate and 1.6 mM EDTA adjusted to pH 3.90, and was pumped through the column at a rate of 1 ml/min.

Release Study

The nucleus accumbens or striatum was dissected as described above and the tissue chopped into slices (approximately 1.0 mm thick, 0.4 × 0.4 mm) using a McIlwain tissue chopper. The slices were immediately transferred into an incubation medium containing a cold Krebs-Ringer bicarbonate (KRB) solution. The KRB solution had the following composition (in mM): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 10; and pargyline, 0.01. Following a 10-min preincubation at 37°C, the slices were incubated for 20 min at 37°C in a water-bath in an atmosphere of 95% O_2 and 5% CO_2, with a final concentration of 0.1 μM [^{3}H]DA (dihydroxyphenylethylamine, 3,4-[7-^{3}H]-; 36.9 Ci/mmol; New England Nuclear; Boston, MA) and 60 μM ascorbic acid. Following the incubation, the slices were gently washed three times with a warm KRB solution, and then three particles of the slice were mounted on a superfusion chamber. The preparation was superfused with oxygenated KRB solution (95% O_2 and 5% CO_2) at a rate of 0.12 ml/min by means of a peristaltic pump (Pharmacia, Sweden). The superfusate was collected at 2-min intervals. At 40 and 80 min after the initiation of superfusion when the basal efflux was equilibrated, the slices were stimulated for 2 min with a high K^+ solution or 100, 250 or 400 μM ketamine solution or 250 μM ketamine solution without $CaCl_2$. The high K^+ solution (25 mM KCl) was obtained by equimolar replacement of NaCl by KCl. For Ca^{++}-free solution with 250 μM

ketamine, $CaCl_2$ was omitted from the KRB solution and an identical volume of 10 μM EGTA was added. At the end of superfusion the slices were solubilized and the radioactivity in the slices and in the collected superfusate was measured in a liquid scintillation spectrometer (LSC-900, Aloka) after vigorous shaking following the addition of 2.5 ml of scintillation fluid (3.0 g Permablend® in a mixed solution of 333 ml Triton X-100 and 667 ml toluene). The amount of radioactivity released into each fraction was expressed as a percentage of the total tritium taken up into the tissue. The total tritium content remaining in the tissue at the time of sampling was determined in each experiment by adding the radioactivity collected to the [^{3}H] content at the end of the superfusion.

Uptake Study

The nucleus accumbens and striatum from 10 to 15 mice were dissected and homogenized in 20 volumes (tissue wet weight) of ice-cold 0.32 M sucrose using 10 up and down strokes of a motor driven glass-teflon homogenizer (0.15 mm clearance). The combined homogenates were centrifuged at 1,000 × g for 10 min at 4°C. The supernatant was decanted and centrifuged at 30,000 × g for 20 min at 4°C. The pellet was resuspended in 15 volumes (original tissue wet weight) of 0.32 M sucrose. Protein concentration was determined according to the method of Lowry et al. (21). One hundred μl of this suspension (0.3 mg protein/ml) was preincubated with 610 μl of KRB solution and 200 μl of H_2O/test compound solution for 10 min at 37°C. The uptake was started by adding 40 μl of [^{3}H]DA (final concentration 10 nM) and 50 μl of ascorbic acid (60 μM). After incubation for 10 min at 37°C, the reaction was stopped by the addition of 4 ml ice-cold KRB solution and the diluted synaptosomal suspensions were immediately filtered through glass microfiber filters (Whatman GF/B). The filters were washed twice with 4 ml of ice-cold KRB solution and placed in scintillation vials. After the addition of 10 ml of scintillation fluid (Toluene Scintillator, Packard), the vials were shaken vigorously. After at least 24 h, the radioactivity was measured as above. The active uptake of [^{3}H]DA was obtained by subtraction of uptake values at 0°C from those at 37°C. Using standard linear regression analysis, the values for the percentage uptake activity were then plotted against the log of the concentration of the test compound, and IC_{50} values were calculated. The average IC_{50} (S.E.M.) values were taken from the averages of four independent IC_{50} determinations, each performed in duplicate and calculated from six inhibitor concentrations.

Statistical Analysis

The data were analyzed by one-way analysis of variance (ANOVA) with wholly significant-difference (WSD) test or Student's t-test. The results were considered statistically significant when p values were less than 0.05.

RESULTS

Effects of Ketamine on Locomotor Activity

An IP injection of ketamine in mice increased total locomotor counts over 3 h in a dose-dependent manner, $F(7,76) = 17.33$, $p<0.001$, and the effects were significant at doses of 20–150 mg/kg (Fig. 1). Figure 2 shows the time-course effects on locomotor activity. The peak effect of low doses of ketamine (10–30 mg/kg) occurred within the first 10 min with a rapid decline thereafter (Fig. 2A). In contrast, locomotor activity induced by 50 and 100 mg/kg ketamine gradually increased after the injection reaching a peak at 20 and 80 min, respectively. At the highest dose (150 mg/kg), locomotor activity was inhibited to the control level during the first 30 min, after which activity gradually increased reaching a peak at 110 min followed by a gradual decline but sustained hyperactivity throughout the remaining 70 min of recording (Fig. 2B).

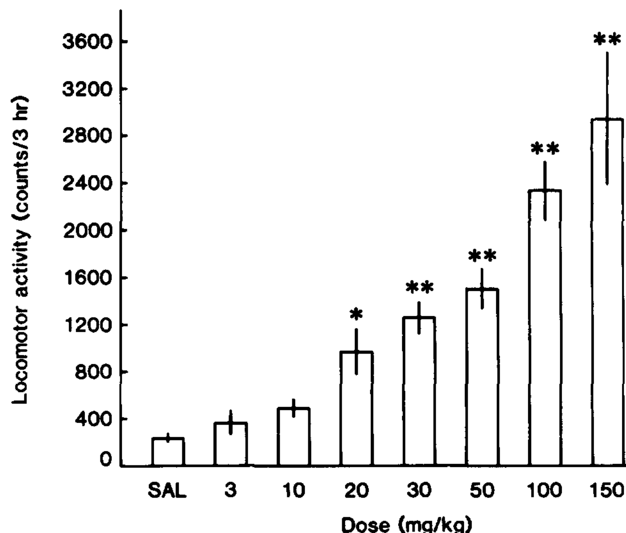

FIG. 1. Effects of ketamine on locomotor activity in mice. Animals were injected IP with various doses of ketamine or saline (SAL) 30 min after mice were placed in the test cage for acclimatization. The cumulative locomotor counts were determined as the total of each 10-min count over 3 h. Each bar represents the mean ± S.E.M. (n = 10–14). *$p<0.05$, **$p<0.01$ as compared to saline-treated mice, one-way ANOVA with WSD test.

Effects of Ketamine on Anesthesia

Figure 3 demonstrates the time-course effects of ketamine-induced anesthesia in mice. Ketamine produced anesthetic effects in a dose-dependent fashion. The peak effect of 30 mg/kg occurred at 4 min postinjection followed by a rapid decline; the mice returned to a normal condition within 10 min. At the peak, the mice showed anesthetic scores of 1.9 ± 0.1 (mean ± S.E.M., n = 10), which indicate slight and continuous staggering gate but almost normal righting reflex. Ketamine at 150 mg/kg also produced a peak at 6 min but thereafter the effect declined gradually and the mice did not return to normal until 90 min following the injection. At the peak, the mice completely lost their righting reflex (shown as a score of +4). A score of +4 was considered sleeping. The sleeping time from 150 mg/kg ketamine was 16.3 ± 1.8 min (n = 10). This caused inhibition of locomotion to control level during the first 30 min after injection. The peak effect on locomotor activity occurred approximately 20 min after mice returned to normal from the anesthetic effects of ketamine (Figs. 2 and 3).

Effects of Various Drugs on Ketamine-Induced Hyperlocomotion

Figure 4 shows the effects of the DA antagonist, haloperidol, the α-blocker, phenoxybenzamine and the β-blocker, propranolol on ketamine-induced hyperlocomotion in mice. The locomotor stimulatory effects produced by 30 and 150 mg/kg ketamine were suppressed by pretreatment with haloperidol (0.05–0.20

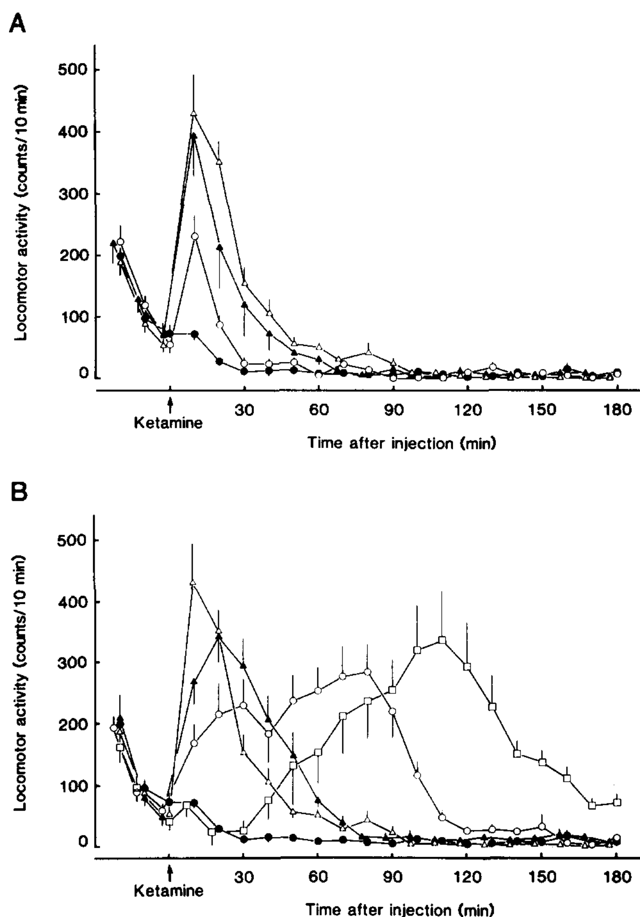

FIG. 2. Time-course effects of ketamine on locomotor activity in mice. Animals were injected IP with various doses of ketamine [○, 10 mg/kg; ▲, 20 mg/kg; and △, 30 mg/kg; (A); ▲, 50 mg/kg; ○, 100 mg/kg; and □, 150 mg/kg; (B)] or saline (●) 30 min after mice were placed in the test cage for acclimatization. Each point represents the mean ± S.E.M. (n = 10–14). In cases of points without vertical bar, S.E.M. is within the symbol.

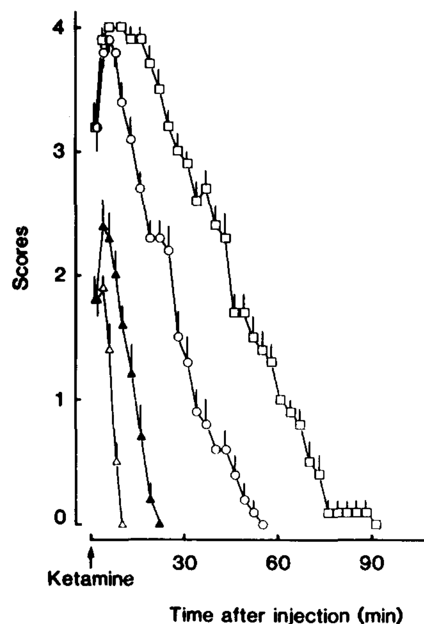

FIG. 3. Time-course effects of ketamine-induced anesthesia in mice. Animals were injected IP with various doses of ketamine (△, 30 mg/kg; ▲, 50 mg/kg; ○, 100 mg/kg; and □, 150 mg/kg). Each point represents the mean ± S.E.M. (n = 10).

mg/kg) in a dose-dependent manner, $F(3,56) = 14.21$, $p<0.001$, and $F(3,56) = 14.29$, $p<0.001$, respectively. Low doses (0.05 and 0.10 mg/kg) of haloperidol did not, on their own, interfere with the animals' spontaneous locomotor activity, although the medium dose (0.20 mg/kg) did decrease the activity, $F(3,56) = 4.53$, $p<0.01$ (Fig. 4A). Furthermore, the sleeping time and the recovery time (needed to return to normal) for 150 mg/kg ketamine were not potentiated by pretreatment with low doses of haloperidol (data not shown). However, neither a relatively high dose of phenoxybenzamine (10 mg/kg) nor a high dose of propranolol (20 mg/kg) inhibited ketamine-induced hyperlocomotion (Fig. 4B).

Effects of 6-OHDA Lesions on Ketamine-Induced Hyperlocomotion

To ascertain whether ketamine acts on presynaptic or postsynaptic DA neurons, we examined behavioral responses to ketamine in animals which had 6-OHDA lesions in the presynaptic neurons but which did not have behavioral supersensitivity. Figure 5 demonstrates the effect of 6-OHDA lesions on ketamine-induced hyperlocomotion in mice on the 3rd day following intracerebroventricular (ICV) injection of 50 μg of 6-OHDA. The locomotor hyperactivity induced by ketamine (30 and 150 mg/kg) was blocked by 6-OHDA lesions (Fig. 5A, B). The cumulative locomotor counts over 3 h induced by ketamine at a dose of 30 mg/kg in 6-OHDA-lesioned mice were 47% fewer than that in control animals which had been pretreated with vehicle solution (1493 ± 173 vs. 789 ± 165 counts/3 h, n = 10 for each group, $p<0.01$). DA contents of the nucleus accumbens and striatum were examined in all mice tested at least 7 days following behavioral experiments. DA content within the nucleus accumbens of the lesioned groups was reduced to 55% of the control value (4830 ± 427 vs. 2680 ± 516 ng/g wet tissue, n = 10 for each group, $p<0.01$), and that within the striatum was also reduced to 61% of control (12113 ± 480 vs. 7445 ± 703 ng/g wet tissue, n = 10 for each group, $p<0.01$). The 3-h locomotor counts induced by 150 mg/kg ketamine in 6-OHDA-lesioned groups were 59% fewer than in the control groups (2973 ± 404 vs. 1214 ± 243 counts/3 h, n = 10 for each group, $p<0.01$). DA content within the nucleus accumbens of the lesioned groups was 57% of control (4830 ± 427 vs. 2754 ± 404 ng/g wet tissue, n = 10 for each group, $p<0.01$), and that within the striatum was also 69% of control (12113 ± 480 vs. 8397 ± 505 ng/g wet tissue, n = 10 for each group, $p<0.01$). Since the cumulative counts following saline injections were virtually identical in the 6-OHDA- (241 ± 47 counts/3 h) and vehicle- (253 ± 57) pretreated animals, it seems that the lesion per se did not interfere with the animals' ability to move about the test cage. Furthermore, the sleeping time and the recovery time with 150 mg/kg ketamine were unchanged by 6-OHDA lesions (data not shown).

Effects of Ketamine on Monoamine Contents

The levels of monoamines and their metabolites were examined in discrete brain regions 10 or 20 min after 30 mg/kg ket-

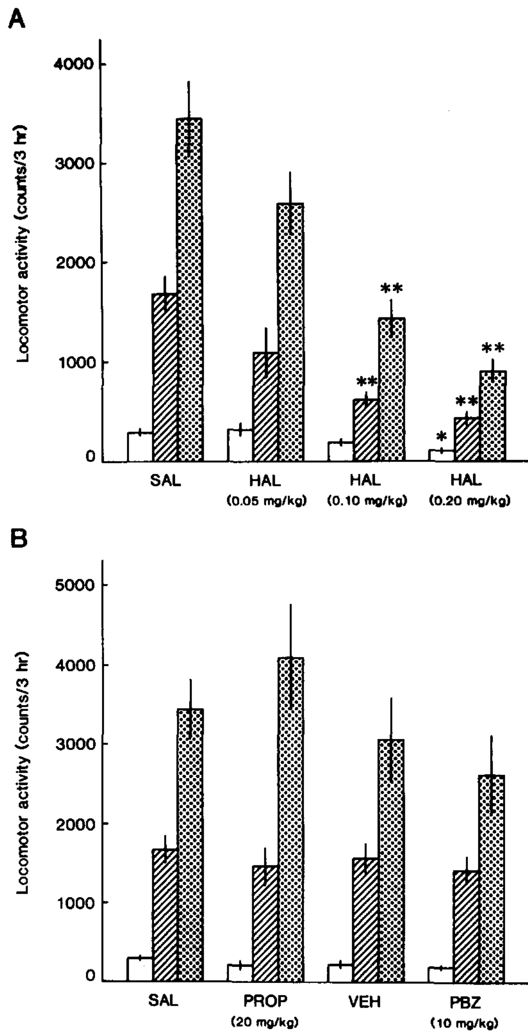

FIG. 4. Effects of haloperidol (HAL) (A), phenoxybenzamine (PBZ) and propranolol (PROP) (B) on ketamine-induced hyperlocomotion in mice. All drugs, saline (SAL) or vehicle (VEH) were given 30 min prior to ketamine (hatched bars, 30 mg/kg or dotted bars, 150 mg/kg) or saline (open bars) injection. The cumulative locomotor counts were determined as the total of each 10-min count over 3 h. Each bar represents the mean ± S.E.M. (n = 10–20). $*p<0.05$, $**p<0.01$ as compared to saline- or vehicle-pretreated mice, one-way ANOVA with WSD test.

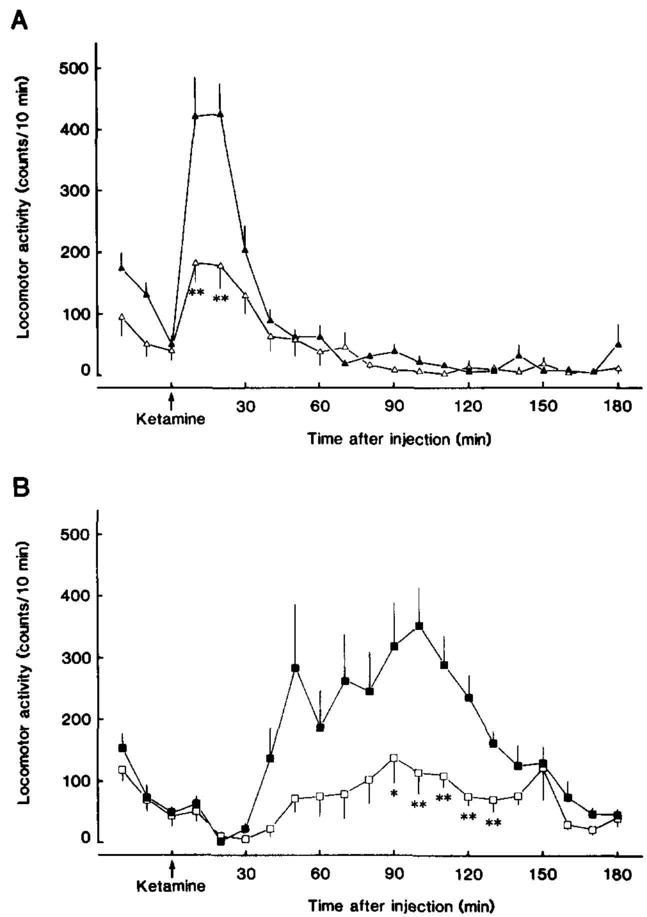

FIG. 5. Effects of 6-OHDA lesions on ketamine-induced hyperlocomotion in mice. Animals were pretreated ICV with 50 μg of 6-OHDA or vehicle and 3 days later injected IP with ketamine at a dose of 30 mg/kg [△, 6-OHDA and ▲, vehicle; (A)] or 150 mg/kg [□, 6-OHDA and ■, vehicle; (B)]. Each point represents the mean ± S.E.M. (n = 10). In cases of points without vertical bar, S.E.M. is within the symbol. $*p<0.05$, $**p<0.01$ as compared to vehicle-pretreated mice at the same time, Student's *t*-test.

amine injection and 120 min after 150 mg/kg, when ketamine-induced locomotor activity was approximately at a peak. The results are summarized in Tables 1 and 2. Ten minutes after 30 mg/kg ketamine injection, the level of homovanillic acid (HVA) was slightly but significantly increased in the nucleus accumbens and frontal cortex by 21% and 30%, respectively, but not in the striatum. Twenty minutes after the injection, both 3,4-dihydroxyphenylacetic acid (DOPAC) and HVA levels in the nucleus accumbens were increased by 12% and 20%, respectively. HVA was also increased in the striatum by 25%. The contents of NE, 5-hydroxytryptamine (5-HT) and their metabolites were unaltered at a dose of 30 mg/kg. Two hours after the high dose (150 mg/kg) of ketamine, the concentration of HVA was significantly increased by 60% to 139% in all regions, without alteration of DA content. The level of 3-methoxy-4-hydroxy-phenylglycol (MHPG) in the brainstem was also significantly increased by 53%. A similar tendency toward increasing MHPG was noted in the nucleus accumbens. The content of 5-hydroxyindoleacetic acid (5-HIAA) was significantly increased in the striatum, hippocampus and brainstem by 34%, 31% and 38%, respectively. DA, NE and 5-HT levels were not modified in any brain region at any time following the administration of any dose of ketamine.

Effects of Ketamine on Release of [^{3}H]DA

When added to the superfusion medium for 2 min, ketamine produced a slight but concentration-dependent increase of tritium overflow from accumbens slices preloaded with [^{3}H]DA, $F(4,42) = 6.39$, $p<0.001$ (Table 3). This effect returned to basal efflux level within 10 min when ketamine was removed from superfusion buffer. Ketamine (250 μM) caused a weak but significant increase of [^{3}H]DA release from the striatum, $F(2,19) = 34.49$, $p<0.001$, as well as from the nucleus accumbens. The release from the nucleus accumbens and striatum was not modified by a

TABLE 1

EFFECTS OF KETAMINE ON LEVELS OF DA, DOPAC AND HVA IN DISCRETE MOUSE BRAIN REGIONS

Region Dose (mg/kg)	Time	DA (ng/g tissue) Control	DA (ng/g tissue) Ketamine	DOPAC (ng/g tissue) Control	DOPAC (ng/g tissue) Ketamine	HVA (ng/g tissue) Control	HVA (ng/g tissue) Ketamine
Cortex							
30	10 min	75 ± 8	68 ± 8	58 ± 10	70 ± 8	108 ± 8	140 ± 13*
30	20 min	59 ± 5	63 ± 5	55 ± 8	61 ± 9	125 ± 9	150 ± 13
150	120 min	56 ± 8	62 ± 6	71 ± 6	67 ± 9	165 ± 29	293 ± 28†
Accumbens							
30	10 min	5044 ± 119	4982 ± 219	2225 ± 109	2435 ± 136	1047 ± 40	1263 ± 43†
30	20 min	5384 ± 107	5303 ± 149	1342 ± 32	1500 ± 48*	914 ± 29	1099 ± 35†
150	120 min	5781 ± 110	5321 ± 237	1829 ± 98	1913 ± 86	833 ± 44	1470 ± 75†
Striatum							
30	10 min	10768 ± 162	11031 ± 364	2342 ± 138	2379 ± 116	1661 ± 87	1840 ± 40
30	20 min	9219 ± 278	9346 ± 115	1888 ± 152	1749 ± 97	1400 ± 77	1753 ± 90†
150	120 min	9636 ± 256	9191 ± 175	1728 ± 122	1775 ± 89	1468 ± 51	2496 ± 94†
Hippocampus							
30	10 min	69 ± 19	85 ± 10	152 ± 14	125 ± 22	193 ± 36	249 ± 40
30	20 min	35 ± 5	59 ± 16	30 ± 3	42 ± 5	78 ± 10	87 ± 9
150	120 min	27 ± 5	48 ± 8*	46 ± 4	53 ± 8	101 ± 10	162 ± 17*
Brainstem							
30	10 min	40 ± 4	39 ± 2	47 ± 5	40 ± 3	38 ± 4	44 ± 5
30	20 min	40 ± 2	44 ± 2	33 ± 2	45 ± 3†	40 ± 4	55 ± 6
150	120 min	42 ± 1	53 ± 2†	31 ± 2	53 ± 2†	44 ± 4	105 ± 5†

Mice were decapitated 10 or 20 min after IP injection of 30 mg/kg ketamine and 120 min after 150 mg/kg ketamine. Values are expressed as the mean ± S.E.M. (n = 6–10). *$p<0.05$, †$p<0.01$, as compared to each control, Student's *t*-test.

Ca^{++}-free medium. The stimulation with 25 mM KCl for 2 min potently increased [^{3}H]DA release from both the nucleus accumbens and striatum (Table 3). This effect was reversed within 15 min after removal of the solution. The release induced by the high K^+ was Ca^{++}-dependent (data not shown).

Effects of Ketamine on [^{3}H]DA Uptake

Ketamine inhibited synaptosomal uptake of [^{3}H]DA in the nucleus accumbens to a greater degree than in the striatum. The IC_{50} of 21 ± 7 μM (n = 4) in the nucleus accumbens was significantly lower than the IC_{50} of 58 ± 13 μM (n = 4) in the striatum ($p<0.05$). GBR 12909 [1-(2-(bis (4-fluorophenyl) methoxy)-ethyl)- 4-(3-phenylpropyl)piperazine; Research Biochemicals Inc., Wayland, MA], which is a potent and selective DA uptake inhibitor, inhibited [^{3}H]DA uptake with equal potency in the nucleus accumbens and striatum. The IC_{50} for GBR 12909 was 2.6 ± 0.6 nM (n = 4) in the nucleus accumbens and 2.5 ± 0.9 nM (n = 4) in the striatum.

DISCUSSION

The present study demonstrated that ketamine increased locomotor activity in a dose-dependent fashion in mice. As shown in Fig. 2, ketamine produced a distinctive time-course pattern of motor activity changes, typified by the difference of locomotor pattern between low and high doses. Low doses of ketamine (10–30 mg/kg) produced the peak effect within the first 10-min time period with a rapid decline. In contrast, at the highest anesthetic dose (150 mg/kg), locomotor activity was inhibited to the level of control during the first 30-min postinjection because of impaired motor activity. Figure 3 shows this inhibition of locomotor activity due to the high doses of ketamine. Thereafter the activity gradually increased and reached a peak at approximately 2 h postinjection with a gradual decline. These time-course results are similar to the data of Hetzler and Wautlet (18) who examined ketamine-induced locomotion in rats in an open-field. The hyperlocomotion induced by both a low (30 mg/kg) and a high (150 mg/kg) dose of ketamine was inhibited by a low dose of haloperidol (0.10 mg/kg), a DA receptor antagonist. This dose of haloperidol did not affect spontaneous locomotor activity. However, neither a high dose of α-blocker nor a high dose of β-blocker inhibited ketamine-induced hyperactivity (Fig. 4). These results indicate that the hyperlocomotion induced by ketamine may be mediated by DAergic neurons rather than by noradrenergic neurons.

The destruction of presynaptic DA neurons by 6-OHDA resulted in the suppression of ketamine-induced locomotor activity in mice examined on the 3rd day, when denervation supersensitivity had not yet occurred (24), suggesting that the presence of intact presynaptic DA neuron was indispensable for the full response to ketamine. It is well known that 6-OHDA destroys not only DAergic terminals but also noradrenergic terminals. We actually confirmed in this study that NE within the cortex, nucleus accumbens and striatum of 6-OHDA-lesioned mice was reduced to 8–32% of control (data not shown). To protect NE neurons and destroy DA neurons selectively, a specific NE uptake inhibitor, e.g., desipramine, may be used. However, a NE uptake inhibitor was not used in the present study because it might have affected the behavior of animals examined on the 3rd day after ICV injection of 6-OHDA (7). We demonstrated that α- and β-noradrenergic antagonists did not inhibit ketamine-induced hyperlocomotion, and that a low dose of ketamine did not change NE turnover. These results suggest that the destruction of presynaptic NE neurons by 6-OHDA would not affect the suppression of ketamine-induced hyperactivity.

N-Methyl-D-aspartate (NMDA) is an excitatory amino acid (EAA) agonist that acts as an NMDA-preferring EAA receptor subtype. Ketamine is known to be a noncompetitive NMDA an-

TABLE 2

EFFECTS OF KETAMINE ON LEVELS OF NE, MHPG, 5-HT AND 5-HIAA IN DISCRETE MOUSE BRAIN REGIONS

Region		NE (ng/g tissue)		MHPG (ng/g tissue)		5-HT (ng/g tissue)		5-HIAA (ng/g tissue)	
Dose (mg/kg)	Time	Control	Ketamine	Control	Ketamine	Control	Ketamine	Control	Ketamine
Cortex									
30	10 min	414 ± 14	447 ± 26	74 ± 19	85 ± 5	503 ± 38	623 ± 49	351 ± 23	370 ± 28
30	20 min	374 ± 27	377 ± 16	120 ± 19	122 ± 7	627 ± 29	644 ± 23	348 ± 18	350 ± 14
150	120 min	245 ± 10	260 ± 19	122 ± 14	147 ± 30	462 ± 35	482 ± 29	567 ± 24	608 ± 26
Accumbens									
30	10 min	752 ± 35	666 ± 50	116 ± 9	95 ± 7	1001 ± 64	925 ± 36	833 ± 38	878 ± 52
30	20 min	514 ± 19	551 ± 21	125 ± 13	111 ± 8	1016 ± 38	1040 ± 24	568 ± 18	589 ± 23
150	120 min	725 ± 45	690 ± 46	108 ± 9	133 ± 9	1002 ± 44	963 ± 16	861 ± 47	1013 ± 55
Striatum									
30	10 min	205 ± 22	207 ± 10	127 ± 43	85 ± 34	598 ± 28	635 ± 19	589 ± 32	600 ± 27
30	20 min	164 ± 12	155 ± 8	89 ± 10	107 ± 7	500 ± 29	505 ± 8	457 ± 16	450 ± 15
150	120 min	245 ± 31	263 ± 14	126 ± 12	139 ± 12	572 ± 24	576 ± 15	521 ± 26	699 ± 34†
Hippocampus									
30	10 min	447 ± 23	506 ± 41	n.d.	n.d.	640 ± 50	694 ± 52	699 ± 39	663 ± 22
30	20 min	510 ± 18	488 ± 34	n.d.	n.d.	598 ± 30	541 ± 27	787 ± 28	740 ± 34
150	120 min	502 ± 22	530 ± 43	n.d.	n.d.	680 ± 13	698 ± 60	663 ± 36	867 ± 53†
Brainstem									
30	10 min	772 ± 32	699 ± 24	136 ± 2	129 ± 7	845 ± 50	746 ± 17	522 ± 27	455 ± 24
30	20 min	694 ± 19	696 ± 11	170 ± 6	188 ± 6	721 ± 22	764 ± 21	521 ± 17	502 ± 19
150	120 min	620 ± 16	603 ± 24	96 ± 2	147 ± 11†	704 ± 67	708 ± 33	512 ± 17	709 ± 35†

n.d. = not detectable.

Mice were decapitated 10 or 20 min after IP injection of 30 mg/kg ketamine and 120 min after 150 mg/kg ketamine. Values are expressed as the mean ± S.E.M. (n = 6–10). †$p<0.01$, as compared to control, Student's t-test.

tagonist which has been identified through iontophoretic (22), electrophysiological (36) and behavioral (4) techniques. It has been reported that competitive NMDA antagonists as well as noncompetitive NMDA antagonists produce an increase of locomotor activity (37), and that nerve terminals for EAAs are located in the nucleus accumbens (9). These findings suggest that ketamine-induced hyperlocomotion may be mediated by a reduction of NMDA-mediated neurotransmission. However, intra-accumbens injections of NMDA also produce a dose-related increase in locomotor activity (13,27). This discrepancy suggests that the role of the NMDA-receptor system in locomotor activity has not been clarified. Furthermore, the interaction between EAAs and DA in the nucleus accumbens is still unknown. Therefore, it is not possible to conclude at present that ketamine-induced hyperactivity is responsible for NMDA antagonism.

Our study of the effects of ketamine on regional monoamine metabolism in the brain has shown rather specific action on the DAergic system. Ten minutes after injection a low dose of ketamine increased the level of DA metabolite in the nucleus accumbens and frontal cortex without changing the DA level, but not in the striatum. At 20 min after the injection, this dose of ketamine increased DA turnover not only in the nucleus accumbens but also in the striatum. This finding is interesting because the more rapid onset of action occurred in the nucleus accumbens which contains a high density of DA nerve terminals associated with the initiation and regulation of spontaneous locomotor activity. Similar results on DA metabolism in the nucleus accumbens and striatum have been demonstrated for phencyclidine, a derivative of ketamine (11). The frontal cortex may also contribute to the increase in locomotor activity induced by ketamine. However, the level of DA in the frontal cortex was much lower than in the nucleus accumbens. Moreover, at 20 min after the administration of a low dose of ketamine, the DA metabolites did not increase in the frontal cortex, although locomotor activity still increased and the DA metabolites did increase in the nucleus accumbens at that time (Table 1, Fig. 2A). This may imply that ketamine-induced hyperlocomotion occurs in association with increased DA turnover in the nucleus accumbens rather than in the striatum or the frontal cortex.

However, a high anesthetic dose of ketamine did not show specific action on the DAergic system and increased NE and 5-HT turnover in some regions at peak locomotion. In all regions, the concentration of DA metabolites was increased, showing that ketamine has no regional specificity at the anesthetic dose. The increased NE turnover may be corroborated by the report that ketamine had weak NE releasing properties and inhibited the uptake of NE in vitro (33). However, as shown in Fig. 4B, the action of ketamine on the noradrenergic system does not appear to play an important role in locomotor activity. All the experiments that have shown the effect of ketamine on monoamine metabolism were performed at anesthetic doses (2, 32, 38, 43). Since we examined the effects of ketamine not only at anesthetic doses but also at low doses, we were able to observe specific and sensitive effects of ketamine on the DAergic system.

In the present in vitro study, ketamine produced similar weak but significant [^{3}H]DA releases from accumbens and striatal slices. High K^+ greatly increased the release. The effect of ketamine was unaltered by the removal of extracellular Ca^{++} (Table 3). However, release of [^{3}H]DA due to high K^+ was Ca^{++}-dependent. Therefore, the mechanism of [^{3}H]DA release elicited by ketamine may be different from the Ca^{++}-dependent depolarization mechanism. It has been demonstrated that ouabain, a Na^+, K^+-ATPase inhibitor, releases cytoplasmic [^{3}H]DA by a carrier-mediated process in a Ca^{++}-independent manner (28,39). Ketamine may release [^{3}H]DA in a similar fashion to ouabain, although the precise nature of the process is unclear.

Ketamine inhibited synaptosomal uptake of [^{3}H]DA in the

TABLE 3

EFFECTS OF KETAMINE AND A HIGH K^+ ON TRITIUM OVERFLOW FROM MOUSE ACCUMBENS AND STRIATAL SLICES PRELOADED WITH [^{3}H]DA IN THE PRESENCE AND ABSENCE OF Ca^{++} IN MEDIUM

Superfusion Medium	Evoked Overflow of [^{3}H]DA (% of tissue tritium content) Accumbens	Striatum
Vehicle	1.8 ± 0.1 (n=23)	1.3 ± 0.1 (n=11)
Ketamine		
100 μM	2.3 ± 0.3 (n=7)	
250 μM	2.6 ± 0.3 (n=6)*	2.2 ± 0.2 (n=5)*
400 μM	3.2 ± 0.2 (n=5)*	
Ketamine (in Ca^{++}-free)		
250 μM	2.6 ± 0.1 (n=5)*	2.2 ± 0.1 (n=6)*
25 mM KCl	12.5 ± 1.1 (n=23)*	27.5 ± 3.2 (n=11)*

Values are shown as the mean ± S.E.M. The number of experiments in parentheses. *$p<0.01$, as compared to value of the vehicle control, one-way ANOVA with WSD test.

nucleus accumbens and striatum in a concentration-dependent manner. It is of interest that the IC_{50} of 21 μM in the nucleus accumbens was significantly lower than that of 58 μM in the striatum, showing that ketamine inhibited DA uptake in the nucleus accumbens more sensitively than in the striatum. This finding may be supported by the observation that different mechanisms are involved in the regulation of DA uptake in the nucleus accumbens and striatum (25). In contrast, GBR 12909, a potent and selective DA uptake inhibitor, inhibited DA uptake with equal potency in the nucleus accumbens and striatum. The IC_{50} values for GBR 12909 in the nucleus accumbens and striatum were 2.6 and 2.5 nM, respectively. These results are consistent with the data of Berger et al. (5). Although the exact mechanism of conflicting effects between ketamine and GBR 12909 is unclear, it is conceivable that these compounds may interact at different sites or states of the DA uptake carrier. Ketamine is about 10,000 times less effective than GBR 12909, but it is distributed extremely rapidly to the brain tissue, and brain levels during locomotion and anesthesia are within the range of 5–100 μg/g tissue (an apparent molar concentration range of 20–400 μM) in rodents (10,29). Although it is not easy to compare in vivo to in vitro results, ketamine is effective in vitro in inhibiting the synaptosomal uptake of [^{3}H]DA and releasing [^{3}H]DA from brain slices when within this concentration range. On the basis of these biochemical data, the potent site of action for ketamine may be the DA uptake system, since the effects on DA release appear to be weak. These results indicate that ketamine may have indirect DA agonist action, a notion supported by the fact that it increases DA turnover in vivo and that it inhibits DA uptake and slightly facilitates DA release in vitro.

It is considered that uptake inhibitors of DA reduce DA turnover in vivo owing to the inhibition of activity of DA neurons resulting from activation of transsynaptic feedback pathways. However, it has been shown that selective and potent DA uptake inhibitors (which do not stimulate the release of DA) have only slight effects on the metabolism of DA in the brain (16,40). Shore has reported that coadministration of certain DA uptake inhibitors and a DA antagonist induced synergistically an increase in DA metabolism and suggests that an impulse-induced facilitation of DA release may have been responsible for this synergistic effect (31). Phencyclidine produces a biphasic dose-dependent increase in firing rate on substantia nigra and ventral tegmental DA neurons, and decreases in firing rate are not observed until very high doses of phencyclidine are administered (15). Similar results have been reported for ketamine. These findings suggest that the more immediate increase of DA turnover in the nucleus accumbens induced by ketamine may reflect the inhibition of DA uptake in the nucleus accumbens to a greater degree than in the striatum, since the coexistence of an increase in impulse flow and the DA uptake inhibitor induces a synergistic increase in DA metabolism.

Clinical studies on ketamine have shown that droperidol, a DA antagonist, significantly decreased the incidence of restlessness, crying, screaming, hallucination and vomiting associated with recovery from ketamine anesthesia in men (3,30). This evidence is supported by the present in vivo and in vitro studies.

In conclusion, ketamine-induced hyperlocomotion may be mediated by presynaptic DA neurons in the nucleus accumbens rather than in the striatum, where ketamine inhibits DA uptake and slightly provokes DA release.

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