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BRIEF COMMUNICATION

Ketamine-Induced Locomotion in Rats in an Open-Field

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HETZLER, B. E. AND B. S. WAUTLET. *Ketamine-induced locomotion in rats in an open-field.* PHARMACOL BIOCHEM BEHAV 22(4) 653–655, 1985.—The effects of ketamine on locomotion in an open-field were determined in hooded rats. Animals were given intraperitoneal injections of saline, or of 1, 10, 50 or 100 mg ketamine/kg body weight on separate days. Open-field behavior was examined for 60 min following injection. The 50 mg/kg dose of ketamine produced an increase in locomotion which peaked approximately 30 min after injection. A cataleptic immobility produced by the 100 mg/kg dose was followed by postanesthetic locomotion. The ketamine-induced locomotion consisted largely of ambulation about the perimeter of the field and was accompanied by ataxia, but included relatively little tight circling (rotation) during the peak of activity. Comparisons with the results of past research suggests that test-chamber design influences the type of locomotion induced by ketamine.

Ketamine Open-field Rotation Locomotion Rats

KETAMINE hydrochloride is a phenylcyclohexylamine which produces a rapidly acting analgesia and anesthesia in both humans and animals. However, emergence from anesthesia is often accompanied by restlessness, hallucinations, mood changes, and psychomotor agitation in humans [1,6]. In rats, an anesthetic dose of ketamine produces a cataleptic immobility which is both preceded and followed by ataxia and locomotor activity [8]. This ketamine-induced locomotion has been variously described as aimless walking in wide circles [12], rotation [4, 10, 11], excitation [8] and hyperactivity [5,14].

The present experiment was designed to more completely describe the behavioral effects of ketamine in the rat. An open-field was employed as the testing environment, allowing both quantitative and qualitative evaluations of behavior. Unfortunately, the testing environment has often not been described in past studies. The main exceptions involve those studies reporting postanesthetic rotation, which have employed either rotometer bowls [10,11] or small electrophysiological recording chambers [4]. While increased spontaneous locomotor activity was reported in an experiment which measured photocell interruptions with a motility meter, qualitative descriptions of the animals' behavior were not included [9]. Using an open-field in the present experiment, we observed a great deal of post-anesthetic locomotion, but relatively little of this involved tight circling (rotation) during the peak of activity.

METHOD

Six male Long-Evans hooded rats, approximately 4 months old and weighing 420–470 g, were used. Prior to and during the experiment the animals were maintained on food and water ad lib. The animals were tested in a 0.92 meter-square open-field, with walls 46 cm high. The field was constructed of standard plywood, and was painted grey. The floor of the apparatus was divided into 36 equal squares, 15 cm on each side.

Prior to testing, the animals were handled briefly each day for about 1 week, and were placed in the apparatus once during this time for about 20 min in order to acclimate them to the field. During testing, animals were given intraperitoneal injections of physiologic saline, 1, 10, or 50 mg ketamine hydrochloride/kg body weight on separate days, according to a randomized schedule. The dosing sequence for each animal was determined from a table of random numbers, subject to the constraint that each dose appear at least once on each testing day across animals. This precaution was necessary in order to control for possible effects of prior drug experience on ketamine-induced locomotion [9]. Injections were separated by 48–96 hours, and each animal was tested at approximately the same time on each testing day. Five days after the last of these injections each animal received a ketamine dose of 100 mg/kg. The smaller ketamine doses were prepared from a standard concentration of 100 mg/ml (Ketaset,

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Bristol Labs.) by dilution with saline to a volume of 1 ml/kg. The large dose of ketamine was administered undiluted.

One minute after injection, each animal was placed in a middle square of the open-field, and allowed to explore for 59 min. Line crossings per 30 sec interval were recorded by an observer who was not blind to the dosing conditions. A line crossing was scored when all four limbs of the rat crossed a line. In addition, general qualitative observations were made of each animal's behavior.

Statistical analyses were performed on the line crossing data. Data were first averaged within successive 5-min intervals (with the exception of the first interval, which included data from only 4 min). The line crossing data were then subjected to two factor analyses of variance [3], involving repeated measures on both factors, (i.e., ketamine dose and time). When a significant main effect was found, individual means were compared with Dunnett's test. For the Dunnett tests on the effects of ketamine, individual ketamine doses were compared to the saline treatment. For the Dunnett tests on the effects of time, the first time interval was used as the basis for comparison. In all of the analyses, statistical significance was assumed when p was ≤ 0.05 for two-tailed comparisons.

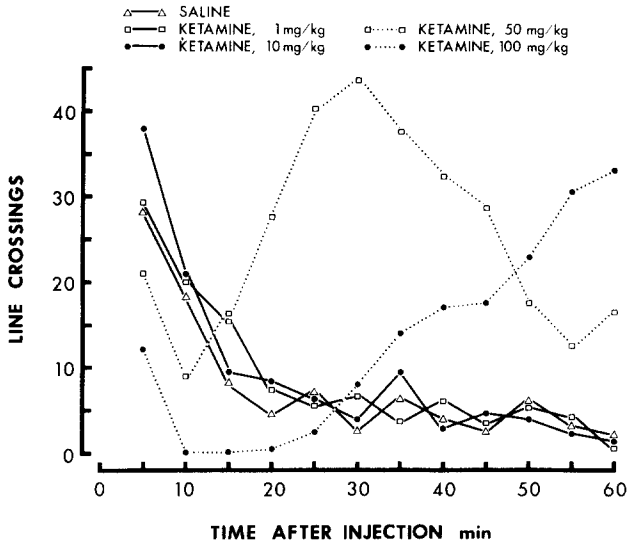

FIG. 1. Mean line crossings (per min) during a 60-min open-field test session. Data are presented for successive 5-min periods following administration of saline and 4 doses of ketamine. Data were obtained from 6 rats.

RESULTS

Figure 1 presents the mean number of line crossings per minute, for each 5-min interval during the testing session. There were significant effects of both ketamine level, $F(4,20)=5.77$, $p<0.005$, and time, $F(11,55)=4.06$, $p<0.001$, on line crossings. However, the ketamine × time interaction was also significant, $F(44,220)=5.19$, $p<0.001$.

Dunnett tests indicated that neither the 1 nor the 10 mg/kg dose of ketamine produced an effect on line crossings in comparison to the saline control. An apparent increase in line crossings at the first time interval for the 10 mg/kg dose did not reach significance. Both the 50 and 100 mg/kg ketamine doses resulted in reliable changes in line crossings, although at different time intervals. Specifically, line crossings were significantly increased at 20–45 min for the 50 mg/kg dose and at 50–60 min for the 100 mg/kg dose. The 100 mg/kg dose also significantly depressed line crossings at 5–10 min.

In regard to the effects of time, there was a general decline in the number of line crossings following the first time interval for saline and the 1 and 10 mg/kg doses of ketamine. Dunnett tests indicated that this decline was significant beginning at 15 min for saline and the 10 mg/kg ketamine dose, and beginning at 20 min for the 1 mg/kg dose. In contrast, no such significant decline was observed for the 50 and 100 mg/kg doses of ketamine. In comparison to the 5 min interval, animals receiving the 50 mg/kg ketamine dose displayed a significant increase in line crossings at the 25 and 30 min intervals, while animals receiving the 100 mg/kg dose showed an increase at the 55 and 60 min intervals.

Behavioral Observations

Following saline injection, the animals initially engaged in a variety of behaviors (e.g., standing, walking and grooming), but over the course of the hour they spent increasing time resting in a corner. A 1 mg/kg dose of ketamine produced no major behavioral change in comparison to the control condition. In contrast, within the first 5 min following injection of a 10 mg/kg ketamine dose, the animals usually demonstrated body swaying, ataxia and some circling within a small radius. Coordination improved over the next 5–10 min, and later behavior appeared normal. A 50 mg/kg dose of ketamine produced more obvious ataxia, with the animal often falling on its side. Body swaying, head movements (e.g., head swinging) and circling were also prominent. As the ataxia diminished, tight circling gave way to locomotion along the walls of the box. This locomotor activity peaked roughly 30 min after injection. Within 2 min following administration of the 100 mg/kg dose, a pronounced ataxia developed (as evidenced by the animal rolling on its side). A few circles preceded the cessation of movement (with the exception of head movements, which persisted throughout the hour). Body movements began to reappear 30–40 min after injection, mainly in the hind limbs. Initial attempts to "swim" in circles gradually changed to locomotion about the perimeter of the box, accompanied by marked ataxia. Such locomotion was, however, often interspersed with more tight circling. When returned to the home cage at the end of the hour, all animals receiving the 100 mg/kg dose displayed pronounced circling.

DISCUSSION

The present experiment provides the first account of the effects of ketamine on the behavior of rats in an open-field. Both dose-response and time-course relationships were evident. Locomotion reached a peak approximately 30 min after administration of a 50 mg/kg dose of ketamine, while locomotion was still increasing 60 min following a dose of 100 mg/kg.

In comparison to past experiments [10, 11, 12], the results of the present experiment also emphasize the role played by environmental factors in modulating the effects of ketamine on locomotor activity. Thus, in a small cage or a bowl, ketamine produces tight circling, while in an open-field the animals mainly locomote around the perimeter during the peak of activity. Test-box design has also been shown to affect behaviors induced by apomorphine [7] and phencyclidine [13].

It has been suggested that dopaminergic mechanisms are involved in ketamine-induced rotation [10,11], since rotation in the rat primarily reflects asymmetric activity in the nigrostriatal dopamine system [2]. GABA-ergic participation has also been implicated since ketamine-induced rotation can be altered by pretreatment with GABA-transaminase inhibitors [10]. However, given the apparent influence of test-box design on ketamine-induced locomotion, the underlying neural mechanisms may be more complex than previously envisioned.

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