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Constriction of Environmental Space and the Behavioral Response to the Dopamine Agonist Quinpirole

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SULLIVAN, R., C. DOGARU AND H. SZECHTMAN. *Constriction of environmental space and the behavioral response to the dopamine agonist quinpirole.* PHARMACOL BIOCHEM BEHAV 43(4) 1217–1219, 1992.—The present study examines the influence of size of testing environment on the behavioral profile seen following injection of the dopamine D_2 receptor agonist quinpirole (0.5 mg/kg, $n = 16$) or saline ($n = 16$). All rats were tested in a counterbalanced order in both a small and large environment. Oral (licking) behaviors were observed exclusively in the small environment and only in drug-treated rats; moreover, quinpirole increased rearing in the small but not large environment. Other behaviors—sniffing, face and body grooming—were affected by quinpirole but not in an environment-dependent manner. It is concluded that limiting environmental space promotes emergence of oral responding under quinpirole. The self-directed nature of this licking (paw- and tail-licking) may reflect a hierarchical transformation of quinpirole-induced hyperactivity from exploration of space to investigation of body parts.

Dopamine D_2 receptor Stereotyped behavior Hyperactivity Environment size Licking Oral stereotypy Quinpirole

THE contrast between the behavioral effects of apomorphine (a D_1/D_2 agonist) and quinpirole a D_2 agonist) is an interesting one. Under apomorphine, the explored space shrinks progressively until eventually rats do not locomote through the environment but scan in ever greater detail the area in the immediate vicinity of their body; some may even lick or bite at their own body parts (16,17,19). Under quinpirole, the explored space shrinks, too, but differently because locomotion never ceases and rats continue to move through the environment. They do so, however, only in a limited portion of a large open field, traveling repeatedly along a few paths (6,7). Moreover, they show little if any oral investigation of environmental surfaces or body parts (1,2,4,8–10,12,13). Thus, under both drugs behavior is stereotyped but under apomorphine it is dominated by incessant tactile/olfactory and oral investigation of proximal stimuli while under quinpirole it is marked by an inflexible spatial organization of routes. The role of D_1 and D_2 receptors in the mediation of these effects is discussed elsewhere (6,10).

Contrary to this general picture, there are reports suggesting that quinpirole increases investigation of proximal stimuli, as evidenced by increased grooming (4,21) paw-nibbling, and sniffing (3). Considering that in those studies animals were tested in a relatively small environment, and size of the testing cage may alter the form of stereotyped behavior (5,11,14, 15,18,20), the present experiment examined how size of the testing apparatus affects the behavioral response to quinpirole. Our results indicate that decreasing the size of the environment does indeed favor the appearance of oral behaviors under quinpirole.

METHOD

Subjects

Thirty-two male Long-Evans hooded rats (Charles River, Canada), weighing 200–250 g at the start of the experiment, were used. They were housed in a temperature-controlled colony room with a 12 L : 12 D cycle (lights on at 7:00 a.m.). Food and water were available ad lib. Subjects were handled daily for at least 1 week before the start of the study.

Drugs

Quinpirole HCl (LY171555; Research Biochemicals Inc., Natick, MA) was dissolved in saline (0.5 mg/kg) and injected SC in the nape of the neck in a volume of 1 ml/kg. Control rats received an equal volume of physiological saline. The chosen dose of quinpirole has been shown to increase locomo-

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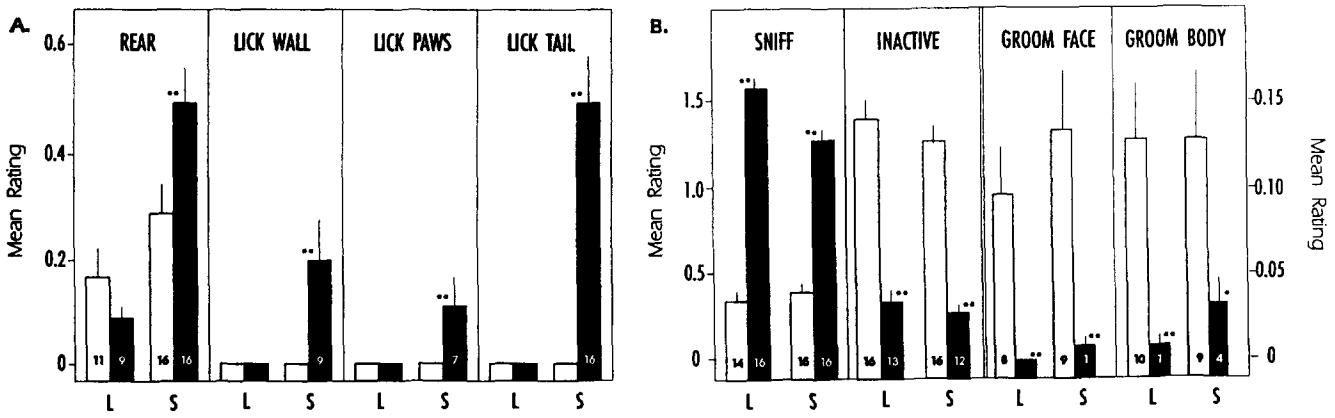

FIG. 1. Behaviors influenced by quinpirole in an environment-dependent (A) or environment-independent (B) manner. Each bar represents the mean (±SEM) score for the indicated behavior from 30 to 120 min after injection of saline (open bars) or quinpirole (filled bars) in the large (L) or small (S) test environment. Numerals indicate the number of animals (of possible 16) for which the intensity of the behavioral category was 1 or greater in at least one time sample; absence of a numeral indicates that no animal showed a score greater than 0. Decreased inactivity score in animals injected with quinpirole reflects a greater level of general activity. Bars marked by one or two asterisks are significantly different from saline means in the same environment ($p < 0.05$ and $p < 0.003$, respectively, Mann–Whitney U-test).

tor activity and route perseveration without inducing oral stereotypies, and is representative of the dose range from 0.125 to 8 mg/kg (6,8,10).

Apparatus

Two environments of different dimensions were employed for behavioral testing. The large environment was a Plexiglas cylinder of diameter 44 cm and height 50 cm, resting on an acrylic base covered with sawdust. The small environment was a Plexiglas rectangle (14 × 11 × 34.5 cm), resting on a plastic grid with 1.3 × 1.3-cm holes that permitted most feces to fall out of the cage.

Procedure

Subjects were randomly assigned to one of four groups (n = 8/group) comprising a 2 × 2 matrix, where one of the factors was environment size (large vs. small) and the other drug (saline vs. quinpirole). Rats were retested 3 days later but in the alternate environment. Immediately following injection, rats were placed into their respective test environment and observed from 30–120 min postinjection. A checklist of behaviors was used by a single observer to rate each rat for 30 s every 10 min, for a total of 10 samples per rat. Subjects were visually separated from one another during testing; eight were run in parallel at any one time with two being from each group. Testing was conducted from 2:00–4:00 p.m. (during the light cycle).

Behavior

The following scale was used to rate the intensity of various behaviors during each 30-s sample period: 0 = absence of the behavior in question, 1 = behavior performed for 1–15 s, 2 = behavior performed for 15–30 s of observation. Eight behaviors were rated: a) *rearing*—the rat has both forepaws off the ground, either against a wall or away from walls; b) *sniffing* of either walls or floors; c) *grooming face*; d) *grooming body*; e) *licking tail*; f) *licking paws* (the latter two are distinct from normal grooming by virtue of the licking being prolonged and focused on a restricted area of the body; g) *licking wall*. The eighth category of behavior rated was *inactivity*, characterized as lack of motion, although not necessarily sleeping, and was scored to assess the general level of activity. The mean score across the 10 time samples for each behavior was used in statistical analysis.

Statistical Analysis

Because of inhomogeneity of variance, the nonparametric Mann–Whitney U-test (two tailed) was used to compare the saline and quinpirole groups in the small testing cage and similarly in the large testing cage.

RESULTS

The response to quinpirole was affected by size of the testing environment as follows: In the small, but not the large, testing cage, rearing, licking of walls, licking of paws, and licking of the tail were more pronounced under quinpirole than saline (Fig. 1A). This was evident for the mean rating score of each behavior as well as for the number of animals showing a licking response (Fig. 1A). Interestingly, in the large environment none of the animals showed licking.

Quinpirole affected the four other behaviors scored but not in an environment-dependent manner. In both the large and small cages, quinpirole increased the ratings of sniffing but decreased inactivity and the appearance of face and body grooming compared to saline (Fig. 1B), consistent with our previous findings (8,10).

DISCUSSION

The present study shows that a constriction of environmental space favors the appearance of licking in animals injected with quinpirole. None of the animals show licking in a large testing cage, but in a small environment rats injected with quinpirole lick their paws, tail, and cage walls. Licking of paws is repetitive and directed at the backs of the forepaws for prolonged periods. Tail-licking (approximately five times more common than paw-licking) is restricted almost entirely to the tip of the tail, is performed holding the tail in the forepaws, and may last continuously through several consecu-

tive time samples. Licking of walls is much less prolonged and repetitive although clearly elevated in the small cage. Thus, when the animal's exploratory space is artificially reduced oral investigation of body parts and environmental surfaces emerges under quinpirole. Remarkably, without an externally imposed restriction, the animal by itself limits the range of explored space. However, in that instance the animal does not engage in pronounced oral investigation of surfaces or body parts but, instead, locomotes repetitively along fixed routes (6,7).

In contrast to most reports, in at least one study the reported occurrence of oral responding under quinpirole is high (3). The size of the testing apparatus employed in that study is relatively small (3). The present findings strongly suggest that this may have contributed to the observed emergence of oral responding.

The observation that limiting environmental space changes the form of behavior under quinpirole suggests that the primary effect of quinpirole is the induction of hyperactivity (7) and not of any particular responses. However, it seems that the expression of this hyperactivity follows a hierarchy: When possible, it is expressed as exaggerated locomotion through the environment; when locomotion is not physically possible, hyperactivity becomes self-directed and manifests itself as exaggerated licking of body parts. These different expressions may reflect differences in the balance of stimulation of D_1 and D_2 receptors, considering the patterns of typical responses to apomorphine (16,17,19), quinpirole (6,7,10), and quinpirole plus the D_1 agonist SK&F38393 (6,10).

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