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BRIEF COMMUNICATION

Chronic Imipramine Effects on Exploratory Behavior in Rats

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HUGHES, R. N. AND J. M. PITHER. *Chronic imipramine effects on exploratory behavior in rats.* PHARMACOL BIOCHEM BEHAV 27(2) 359–362, 1987.—Approximately 100 days old hooded rats, socially isolated or group-housed since weaning, received 15 daily IP injections of isotonic saline, 10 mg/kg or 20 mg/kg of imipramine HCl. Following their last injection, the rats' active choices of a novel environment, frequencies of rearing and grooming, and cells entered in an exploration box were recorded. The drug treatment reduced rearing, ambulation and (for isolated rats only) grooming, but had no effect on novelty choices. There was a significant weight loss with the higher dose and (for males only) with social isolation during the drug treatment period. While imipramine reduced grooming in isolated but not group-housed rats, there were no other interactions between the two forms of treatment. It was concluded that, in spite of its sedative action on motor activity, chronic imipramine did not alter curiosity about a novel environment.

Chronic imipramine Exploratory behavior Grooming Social isolation Rearing Body weight Ambulation Rats

IN a recent review File and Tucker [6] concluded that neither acute nor chronic administration of tricyclic antidepressant drugs produces consistent effects on rodent exploratory behavior. Since they possess motor sedative properties [24], it is problematic to assume an exploratory-motivated basis for the effects of tricyclics on measures which rely heavily on locomotor activity [6]. While non-selectively blocking the re-uptake of noradrenaline and serotonin [24], acute imipramine decreases exploration defined as tunnel entries [22] or time spent in a novel Y-maze arm [4]. Both of these effects could arise from the drug's non-specific sedative action [6].

Apart from studies of locomotor or rearing activity, there have been few assessments of chronic imipramine effects on exploratory choice responses which are relatively free from contamination by activity changes. The present study therefore investigated the effects of chronic imipramine on an earlier devised choice measure [11] which appears less affected by drug-modified locomotor activity than many other indices of exploration. The test procedure enables distinctions to be drawn between drug effects on free choices of a novel environment and locomotor activity with little likelihood of the former being systematically contaminated by the latter since, at one time or other, most combinations of changes in the two responses have been observed i.e., decreased novelty choices and increased [10], unchanged [15] or decreased locomotor activity [20]; unchanged novelty choices and increased [13], unchanged [12] or decreased locomotor activity [14]; increased novelty choices and increased [25] or unchanged locomotor activity [17]. Even when covarying in a very similar manner, the two responses do not significantly correlate [16].

Since, in addition to its influence on the effects of several other drugs [2,18], social isolation has been proposed as a means of detecting antidepressant properties [7,8], half the subjects in the present study were socially isolated from weaning until testing.

METHOD

Subjects

The subjects were 36 male and 36 female hooded rats of a strain (NZBW) originally developed at the University of Otago, New Zealand. They were weaned when 25 days old and assigned in equal numbers to a socially isolated or group-housed condition. Isolated rats were individually kept in metal 17×17×20 cm high cages. Group-housed subjects were kept in groups of 6 same-sexed animals in metal 30×30×50 cm high cages. All cages had wire mesh lids and their floors were covered with wood shavings that were replaced once a week. The rats were kept in reversed 12 hr light-dark conditions at an ambient temperature of 20–22°C with ad lib food and water.

Apparatus

For each rat, the apparatus comprised one of four Perspex exploration boxes described in detail elsewhere [10,17]. Briefly, each box consisted of four 20×20×20 cm cells and could be divided in half by inserting opaque slides

TABLE 1

MEAN (±SEM) BODY WEIGHT DIFFERENCES IN GRAMS BETWEEN DAYS 1 AND 15 OF CHRONIC IMIPRAMINE TREATMENT AND DIFFERENCES FOR MALE AND FEMALE ISOLATED AND GROUP-HOUSED RATS

Imipramine			Males		Females	
Saline	10 mg/kg	20 mg/kg	Isolated	Grouped	Isolated	Grouped
9.67 ± 2.25	2.38 ± 1.81	−18.10 ± 4.54*	−10.67 ± 4.76	3.44 ± 6.47†	0.05 ± 3.07	−0.88 ± 2.00

*Significantly different from saline group, $p<0.01$ Dunnett's test.
†Significantly different from same-sexed isolated group, $p<0.01$, t-test.

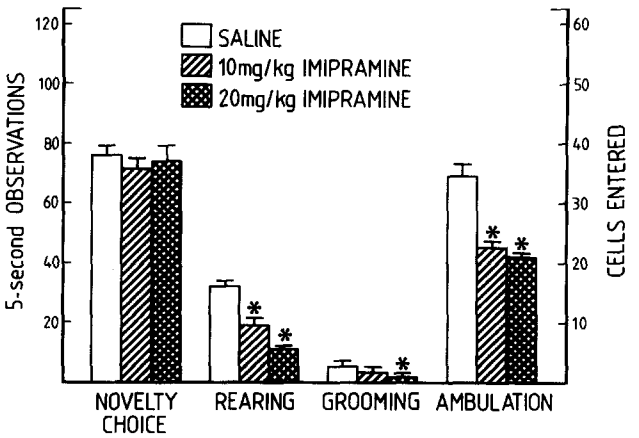

FIG. 1. Mean (±SEM) 5-sec observations of novelty choice, rearing and grooming, and mean (±SEM) cells entered following chronic treatment with isotonic saline, 10 mg/kg or 20 mg/kg of imipramine HCl. *Significantly different from saline group ($p<0.01$, Dunnett's test).

into two gaps in an opaque Perspex wall. The boxes were enclosed in sound-attenuated ventilated chambers and were illuminated by 8 W fluorescent tubes. Observations of the rats were made through a one-way window in the front wall of each chamber.

Procedure

Seventy to eighty days after weaning, equal numbers of male and female isolated and group-housed rats were weighed and received fifteen daily IP injections of either isotonic saline or 10 or 20 mg/kg of imipramine HCl ('Tofranil,' Ciba Geigy) in a volume of 2 ml/kg. These doses were within the range known to be effective after 10–20 days of chronic treatment [24]. On the fifteenth day, each rat was confined to one half of an exploration box for 60 min. (Equal numbers of rats from each group were confined to the two halves.) It was then weighed for the last time, given its final injection and, 30 min later, returned to the same half of the box from which slides separating the two halves had been removed. Twenty sec later it was observed for 10 min during which time it was noted every fifth second whether or not the rat was in the previously inaccessible novel half (novelty choice), and if it was rearing up on its hind legs or grooming. The total number of cells entered was also recorded (ambulation). All observations were conducted blind by J.M.P.

RESULTS

Behavioral Measures

Effects of the drug treatment on all behavioral measures can be seen in Fig. 1. Separate three-way ANOVAs (drug dose × isolation × sex) revealed a significant imipramine effect for rearing, $F(2,60)=49.58$, $p<0.001$, grooming, $F(2,60)=3.43$, $p<0.05$, and ambulation, $F(2,60)=48.34$, $p<0.001$. Although there was no significant main effect of housing on grooming, $F(1,60)=2.99$, a significant interaction occurred between the drug and housing conditions for this measure, $F(2,60)=5.29$, $p<0.01$. In isolated rats, mean levels (±SEM) of grooming were 7.67±1.90 for saline, 4.08±1.03 for 10 mg/kg and 1.25±0.35 for 20 mg/kg imipramine groups. For group-housed animals these values were 2.58±0.54 (saline), 2.42±1.26 (10 mg/kg) and 3.33±0.64 (20 mg/kg).

Differences between the saline and each drug condition were significant ($p<0.05$, Dunnett's test) for isolated rats only. The novelty choice measure was unaffected by imipramine, $F(2,60)=1.43$, with the subjects maintaining a significant preference for the novel side in spite of their prior treatment i.e., overall mean (±SEM) novelty choice out of 120=71.04±2.32, one-sample $t(71)=4.76$, $p<0.001$.

While female rats reared (23.19±2.04) significantly more often than males (17.94±1.74), $F(1,60)=9.10$, $p<0.01$, no other main effect or interaction involving sex or isolation was significant.

Body Weight

On the first day of imipramine treatment, females (185.64±2.85 g) were of course much lighter than males (296.39±6.42 g), $F(1,68)=487.00$, $p<0.0001$. However there was no significant weight difference between isolated (244.28±5.35 g) and group-housed subjects (237.75±3.92 g), $F(1,68)=1.69$.

Differences were calculated between each rat's weight on the first and last days of drug treatment. The effects on these differences of imipramine and (for each sex separately) isolation can be seen in Table 1.

A significant drug effect occurred, $F(2,60)=24.99$, $p<0.001$, as well as a significant interaction between housing and sex, $F(1,60)=5.13$, $p<0.05$.

DISCUSSION

While rearing and ambulation were decreased by both doses of imipramine, active choices of the novel environment were unaffected by the treatment, with subjects still showing significant preferences for novelty. This suggests that either tolerance for the effects of chronic imipramine on

novelty choices developed more rapidly than for motor activity, or, as is more likely, that curiosity about the novel environment was uninfluenced by the drug treatment. Since little effort is required to move between the familiar and novel halves of an exploration box, novelty choices were probably less affected by imipramine's non-specific sedative properties than measures of exploratory behavior which depend more on locomotor activity.

Although the imipramine-induced decrease in rearing and ambulation were in line with the effects of chronic imipramine on general motor activity [24], they disagreed with Kulkarni and Dandiya [19] who found that chronic treatment increased the former response in an open field but had no effect on the latter. These authors also showed that acute imipramine reduced ambulation but not rearing. Discrepancies between the present results and those of Kulkarni and Dandiya [19] could be due in part to the use of different types of apparatus.

The weight loss between days 1 and 15 of chronic treatment with 20 mg/kg of imipramine replicated earlier findings [9]. This loss probably arose from lowered food consumption [3] which unfortunately was not recorded in the present study. Although Tucker and File [24] regard decreased food intake as secondary to non-specific sedation, suppression of appetite is a common clinical side-effect of imipramine [1,5].

Since social isolation is known to modify rearing and ambulation in exploration boxes and open fields [7, 8, 18, 21, 23], it is surprising that the experience was so ineffective in the present study. Apart from a significant weight loss in male rats between the beginning and end of drug treatment, its only other influence was to increase grooming in saline subjects. This effect could have arisen from attempts to increase stimulation in a relatively impoverished environment which were not evident in imipramine-treated rats because of the drug's sedative action. Although Garzon, Fuentes and del Rio [7] suggest that at least 9 months of social isolation is required for the modification of open-field locomotor activity, behavioral changes in an exploration box have been observed with periods of isolation comparable to that used in the present study [18]. It is therefore likely that the impact of isolation was lessened by the daily handling which accompanied chronic imipramine treatment. Consequently, in future research of this nature it may be useful to avoid daily injections (and thus handling) by providing drugs in the rats' drinking water.

Although, as previously observed [14, 16, 17, 18], females reared more often than males, higher grooming frequencies in males reported earlier [12] did not occur. However, significant sex differences are not a consistent feature of this latter measure [17,25].

From the main results of the present study it is concluded that, while decreasing rearing and ambulation, chronic imipramine had no effect on exploratory-motivated behavior as measured by active choices of a novel environment. It is therefore unlikely that the drug treatment interfered with curiosity tendencies but rather maintained them at non-drug levels in spite of its motor depressant action.

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