Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 3, pp. 427–435, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in the USA. All rights reserved
0091-3057/94 $6.00 + .00

Effects of Chronic Imipramine on Exploration, Locomotion, and Food/Water Intake in Rats

JESPER MOGENSEN,[1] THOMAS KIRK PEDERSEN AND SØREN HOLM

Laboratory of Neuropsychiatry, Department of Pharmacology, University of Copenhagen, Denmark

Received 23 March 1993

MOGENSEN, J., T. K. PEDERSEN AND S. HOLM. *Effects of chronic imipramine on exploration, locomotion, and food/water intake in rats.* PHARMACOL BIOCHEM BEHAV **47**(3) 427–435, 1994.—Three groups of rats were subjected to 15 daily injections of imipramine (10 or 20 mg/kg) or vehicle control injections, respectively. During the treatment period, both imipramine groups failed to grow while the control group gained weight normally. Both dosages of imipramine suppressed food intake significantly, while water intake was only reduced by 20 mg/kg of imipramine and only during the first 5 days of treatment. Twenty-four hours after the last imipramine injection, the animals were subjected to a test battery designed to demonstrate potential changes in locomotion and/or exploration. While locomotion appeared unaffected by both dosages of imipramine, the group receiving 20 mg/kg of imipramine demonstrated a significantly reduced exploration. The exploration of the group receiving imipramine in the concentration of 10 mg/kg was only marginally changed. The temporal pattern of exploration of the animals receiving 20 mg/kg of imipramine revealed that chronic imipramine treatment was associated with an initial "hyperexploration" followed by an "overhabituation," resulting in an overall reduction of exploration during a 15-min period.

Imipramine Food intake Water intake Body weight Exploration Locomotion Rat Habituation Chronic drug administration

THE tricyclic antidepressant imipramine blocks the reuptake of serotonin and norepinephrine (18). Long-lasting or chronic administration of imipramine has, in the rat, been found to be associated with decreased (1,3,4,9,15) or unchanged (7,13,14) locomotion if the behavioural test is performed within the first few hours following the last injection. Studies in which locomotion has been tested at least 12 h after the last imipramine injection demonstrate locomotion to be unaffected (12,17) or increased (15) by chronic imipramine administration. Based on a review of the effects of chronically administered antidepressant drugs, Vogel et al. (19) suggested that while each individual dose of tricyclic antidepressants inhibits motor activity for a few hours after injection, chronically administered antidepressants, such as imipramine, increase motor activity 12–24 h after each administration. When tested immediately upon the last imipramine injection, measures believed to reflect exploration have been found to be increased (13), reduced (9), or unaffected (8) by chronic administration of imipramine to the rat. When tested 48 h upon the last imipramine injection, measures of exploration appeared unaffected by chronic imipramine administration (17).

As argued by Hughes and Pither (9), the observations that seem to indicate an association between chronic imipramine treatment and reduced exploration may be secondary to imipramine-induced reduction of locomotion and general activity. Consequently, to study the degree to which exploration is influenced by chronic administration of imipramine, it is necessary to measure the exploration of imipramine-treated rats using apparatuses and procedures able to reflect exploratory behaviour without being significantly influenced by changes in locomotion. Using an exploration test believed to be rather unaffected by changed locomotor behaviour, Hughes and Pitcher (9) found chronic imipramine treatment to have no influence on exploratory behaviour 30 min after the last imipramine injection.

In an attempt to further clarify the effects of chronic imip-

[1] Requests for reprints should be addressed to Jesper Mogensen, Laboratory of Neuropsychiatry, Rigshospitalet-6102, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.

ramine treatment on the locomotion and exploration of the rat, we decided to subject rats that had received 15 injections of imipramine in the dosages of either 10 or 20 mg/kg body weight per day to a battery of three tests 24 h after the last injection. These tests are believed to provide a behavioural profile from which the relative contributions of locomotion and exploration can be estimated. The three tests selected were: an activity cage test that primarily is expected to reflect locomotion (J. Mogensen, S. Holm, J. Ulrichsen, H. Laursen, and R. Hemmingsen, in preparation); an analysis of open field behaviour, which includes measures of locomotion and some species-specific behaviours (e.g., grooming); and a vertical hole-board exploration test (11). The vertical hole-board test appears to belong to a category of exploration tests that are able to reflect exploratory behaviours in a manner that is relatively independent of changes in locomotion (J. Mogensen and S. Holm, in preparation). In previous experiments, the vertical hole-board exploration test has been found able to reflect the behavioural consequences of the recovery following a single, high dosage of reserpine (6), IP injection of reserpine in a dose-dependent manner (J. Mogensen and S. Holm, in preparation), SC injection of *d*-amphetamine (10,11), and IP injection of diazepam (J. Mogensen and S. Holm, in preparation). Furthermore, following a 35-day period of thiamine deficiency, rats demonstrated normal exploration of the vertical hole-board, although the same animals appeared to have severely impaired locomotion as seen in both activity cage and open field (J. Mogensen, S. Holm, J. Ulrichsen, H. Laursen, and R. Hemmingsen, in preparation).

Chronic imipramine treatment in rats has been reported to reduce body weight (1,8,9) and the intake of food and water (1). Consequently, we decided to take daily measures of body weight as well as food and water consumption during the imipramine treatment.

METHOD

Subjects

The subjects were 24 experimentally naive, male Wistar albino rats (PAN : WIST obtained from the animal quarters of the Panum Institute, Copenhagen, Denmark), weighing approximately 260 g at the beginning of the experiment (approximate age at the beginning of the experiment: 65 days). They were housed individually with rat chow and water always available. The animals' living quarters were kept on a 12 L : 12 D cycle (on 0600 h). The rats were divided into eight "sets," each made of three animals of approximately equal initial body weight. Within each set the rats were randomly assigned to one of the three treatment groups (eight animals per group). While one group only received vehicle (saline) control injections, the two other groups received daily IP injections of imipramine (imipramine hydrochloride) (Tofranil, Ciba-Geigy, Switzerland) in the dosages of 10 and 20 mg/kg body weight per day, respectively.

Apparatuses

Activity cage. The activity cage was a wooden, gray box with no top. The floor, measuring 40 × 25 cm, was free to tilt around the midpoint of the longer axis, thereby activating two microswitches situated immediately below floor level. The pressure required to activate a microswitch (when applied at either end of the longer axis) was 8 g. The walls were 43 cm high. The cage was situated in a dark, sound-shielded chamber, and solid state equipment recorded the activity of the microswitches.

Open field. The open field, measuring 100 × 100 cm, was surrounded by 30-cm-high metal walls. The area was divided into 16 23 × 23-cm fields by a grid of 3 × 3 2.6-cm-broad tape stripes that were glued directly to the metal floor of the open field apparatus. The open field sessions were videotaped through an overhead TV camera situated directly above the open field floor. The open field was placed in the middle of a well-lit, sound-shielded room in which no other activities took place during testing.

Vertical hole-board. One semiopaque 8-mm-thick wall in a 25.6-cm-wide, 26.5-cm-deep, and 22.5-cm-high opaque chamber had 54 1.7-cm (diameter) holes (arranged in six horizontal and nine vertical lines). The center-to-center distance between holes was horizontally and vertically 2.5 cm and diagonally 3.5 cm. The top of the box also served as door to the chamber. The floor of the chamber consisted of a wire grid. The wall containing the holes had a grid of 3-mm-wide channels imbedded in it. Each channel had an infrared LED (light emitting diode) at one end and a photocell at the other end. The grid was arranged in such a way that each hole contained the crossing of one horizontal and one vertical line at its center. Nose poking would break the infrared light beams of the two channels. The photocells were connected to an interface card through which the data were collected by a DIGITAL PDP 11-computer. A detailed description of this apparatus has been published separately (11). The hole-board apparatus was placed in a sound-shielded enclosure and all testing was performed in complete darkness.

Behavioural Procedures

General procedure. On the day prior to first injection the animals were weighed, and predetermined but ample amounts of food and water were offered in the animal's home cage. Twenty-four hours later, body weight and remaining food and water were measured, the first injection was given, and preweighed amounts of food and water were offered for the next 24-h period. The body weight at the time of first injection, and food and water intakes for the 24 h preceding first injection were designated day 1 (even offering knowledge of body weights 24 h prior to day 1). The procedures related to body weight, food and water intake, and injections were repeated on days 2-16; on day 16, however, no injections were given. On day 16 all animals were subjected to the activity cage, open field, and vertical hole-board tests. The order in which the animals were exposed to the three tests was completely balanced within each group. All apparatuses were thoroughly cleaned between all individual test sessions. The behavioural testing was conducted between 0900 and 1800 h.

During all behavioural procedures (including the analysis of videotapes of open field behaviour), the experimenter was kept ignorant about the group to which an individual rat belonged.

Food and water intake. The animals lived in cages in which the floor was covered with paper only. They had ad lib access to a known amount of water in a bottle offered in the usual position (protruding from the ceiling of the cage) and likewise ad lib access to a preweighed amount of food that was scattered around on the floor of the cage. Daily measures were taken of the body weight of the animal and the amount of water and food consumed during each 24-h period, corrected for all food remains, including powdered, which were collected and weighed.

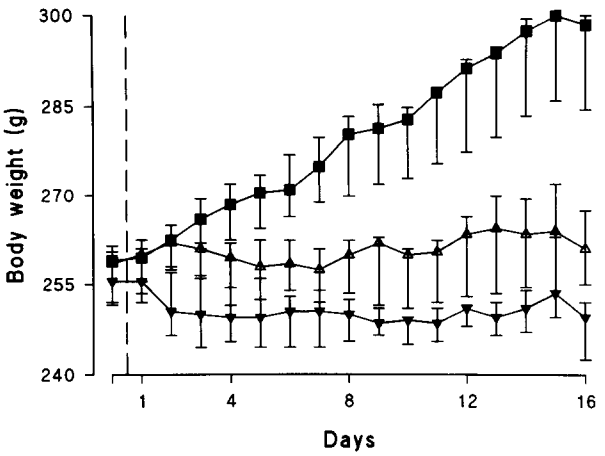

FIG. 1. Body weights for the three dosage-defined experimental groups (■: vehicle-injected control group; △: imipramine in the concentration of 10 mg/kg body weight; ▼: imipramine in the concentration of 20 mg/kg body weight) during the experimental period. Day 1 marks the measurement at the time of the first imipramine injection and day 16 marks the measurement 24 h after the last imipramine injection, which is the day on which tests of locomotion and exploration were performed. The values shown to the left of the dashed line (before day 1) are the body weights 24 h prior to the first injection. Values are given as medians with the 25% and 75% fractiles.

Activity cage. The animal was placed in the activity cage by the experimenter and the 15-min recording session was immediately started (and the door of the sound-shielded chamber closed). The only parameter considered in this test was the number of microswitch activations—the number of "counts."

Open field. At the beginning of the session, the animal was placed in the middle of the open field area and the experimenter immediately left the room, allowing the animal 10 min of undisturbed activity in the open field area. The timing started the moment the experimenter let the animal go, thereby allowing it to move freely. After the session, the videotape of the animal's open field activities was analysed to obtain the following scores: latency from the start of the session to the first body movement; the number of locomotion episodes; the total duration of locomotion episodes; the number of line crossings; the number of rearing episodes; the total duration of rearing episodes; the number of grooming episodes; and the total duration of grooming episodes. Additionally, the following parameters were calculated: the mean duration of locomotion episodes; the mean duration of rearing episodes; and the mean duration of grooming episodes.

Vertical hole-board. The animal was placed in the hole-board apparatus; the top of the hole-board chamber and the sound-shielded enclosure were closed and the animal was allowed 15 min of undisturbed exploration. The apparatus automatically recorded all hole visits, storing the information about duration and position of the visit. A hole visit would be

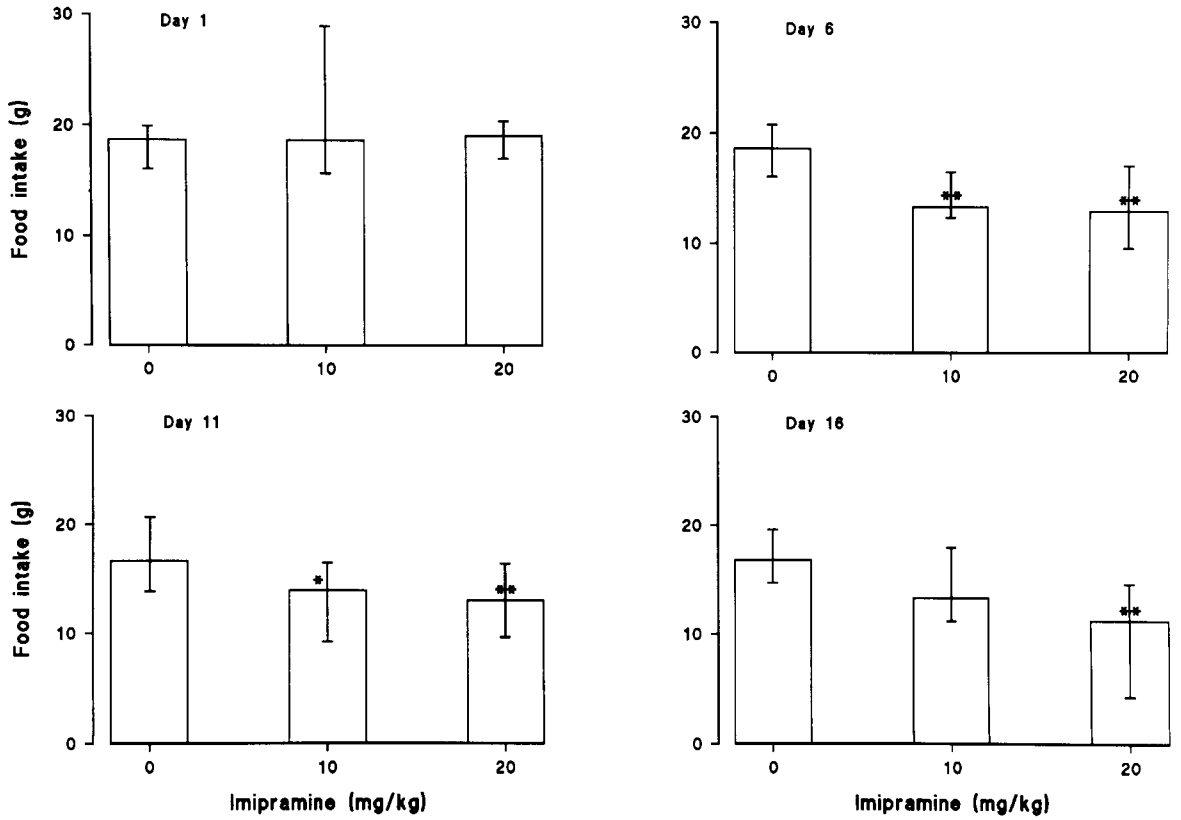

FIG. 2. Food intake of the three dosage-defined experimental groups during the experimental period (days of the experiment are defined as described in Fig. 1). Values are given as medians with ranges. *Significantly ($p < 0.05$) different from the vehicle-injected control group. **Significantly ($p < 0.01$) different from the vehicle-injected control group.

registered if the animal simultaneously broke both a horizontal and a vertical infrared line, thereby also indicating the position at which the visit occurred. Previous experience indicates that almost all such visits are performed by passing the nose and in some instances also the mouth through a hole. From the computer files containing the data, the following parameters were calculated: the latency from initiation of the session (defined as the closure of the door of the sound-shielded enclosure) to the occurrence of the first hole visit; the total number of individual visits; the total time spent visiting holes; the mean duration of individual visits; the number of different holes visited; the mean number of visits per visited hole; the number of visits to the sixth (lowermost) row of holes as percentage of the total number of visits (a parameter that might reflect motoric impairments via the animal's inability to reach to higher rows); the number of visits during the first, second, and third 5-min period; the number of short (duration < 0.5 s) visits as percentage of the total number of visits; and the number of clusters of individual visits (a cluster of visits is defined by the temporal proximity of consecutive visits; if the intervisit time exceeds 10.0 s, the following visit constitutes the first visit of the next cluster).

RESULTS

The results are shown in Figs. 1-6 and Tables 1-2. The daily measures of body weights from the individual dosage-defined groups were subjected to the Spearman Rank Order Correlation Test (16). If the body weight exhibited a gradual increase (as seen with normal animals) across days, this would be reflected in a significant "day" effect. For the vehicle-treated control group, the Spearman Rank Order Correlation Test demonstrated a significant ($p < 0.01$) day-to-day difference between body weights, while no significant correlations between body weights and days were found for the two imipramine-treated groups.

Kruskal-Wallis analysis of variance (ANOVA) (16) revealed that the body weights of the three groups did not differ significantly when first measured (on the day prior to first injection), while on day 16 (when last measured) the groups differed significantly ($p < 0.01$). Further analysis of the body weights on day 16 [using the Mann-Whitney *U*-test, two-tailed (16)] revealed that on this day both imipramine-treated groups differed significantly ($p < 0.01$) from the vehicle-treated controls, while the difference between the two imipramine-treated groups was nonsignificant.

The Kruskal-Wallis ANOVA (16) demonstrated significant ($p < 0.01$) group differences on the daily food intake of the three studied groups on all days but day 1. As illustrated in Fig. 2, further analysis by the Mann-Whitney *U*-test (two-tailed), indicated that chronic treatment with both studied imipramine dosages was associated with significantly reduced food intake (while significant differences between the two imipramine-treated groups were never demonstrated on this

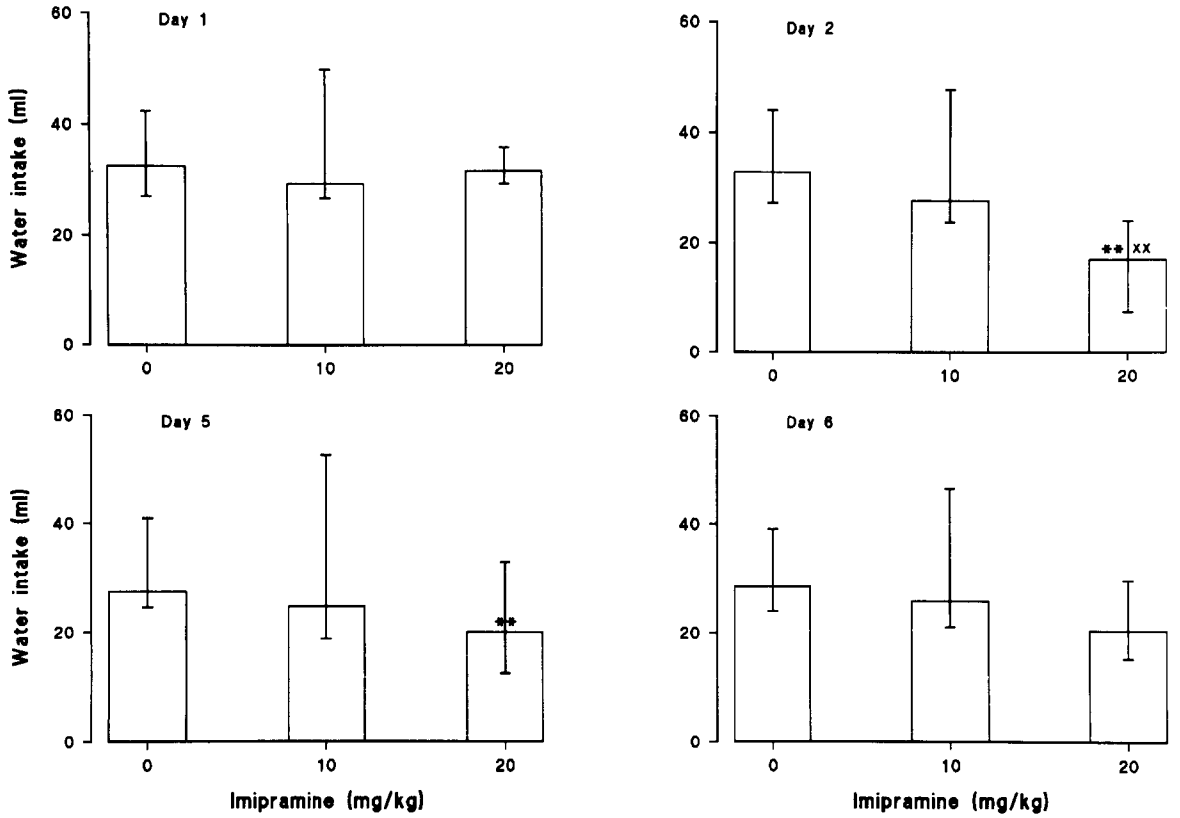

FIG. 3. Water intake of the three dosage-defined experimental groups during initial part of the experimental period (days of the experiment are defined as described in Fig. 1). Values are given as medians with ranges. **Significantly ($p < 0.01$) different from the vehicle-injected control group. xxSignificantly ($p < 0.01$) different from the group receiving imipramine in the concentration of 10 mg/kg.

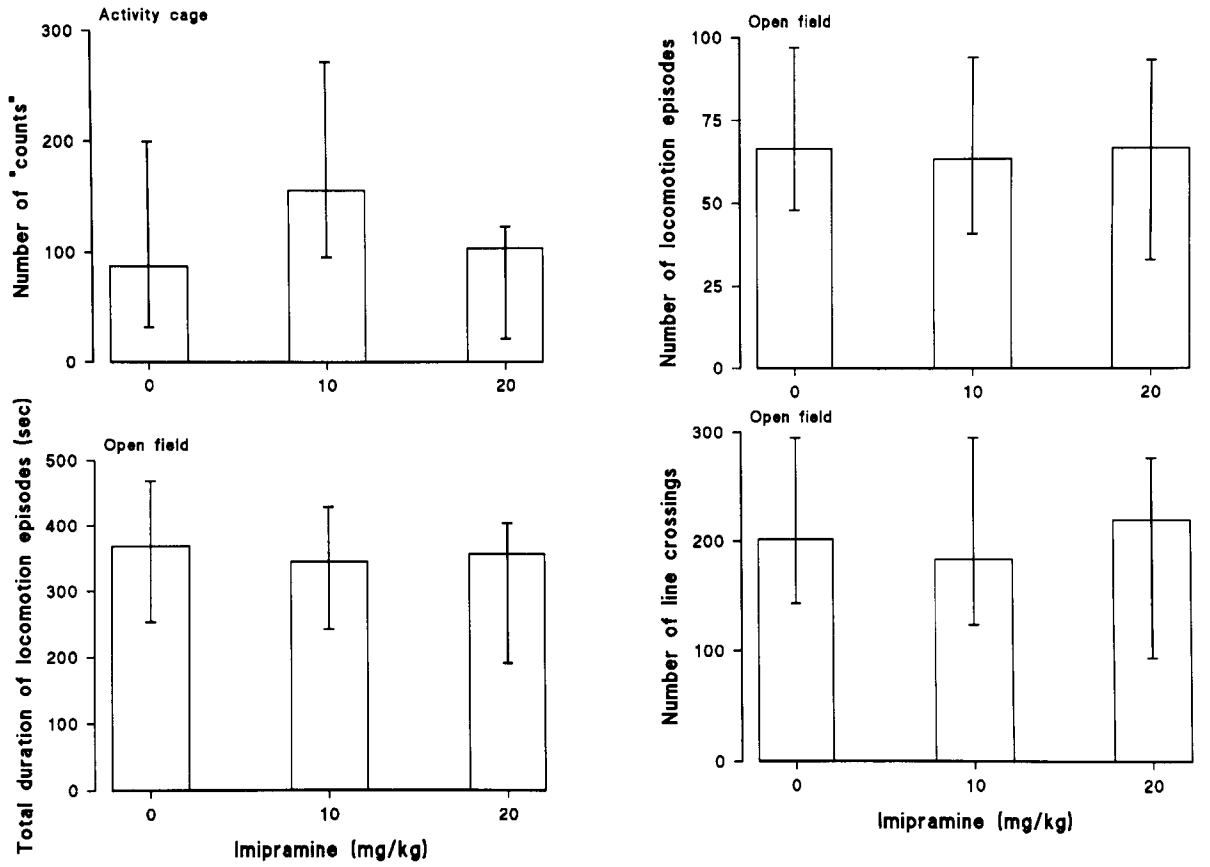

FIG. 4. Aspects of the performance of the three dosage-defined experimental groups in the activity cage and open field tests. The number of counts in the activity cage, locomotion episodes in the open field, and line crossings in the open field, as well as the total duration of locomotion episodes in the open field, are shown. Values are given as medians with ranges.

parameter). Only on day 16 did the food intake of the group receiving 10 mg/kg imipramine not differ significantly from the control group.

Significant ($p < 0.01$) differences between the daily water intake of the three groups were only found on days 2, 3, 4, and 5 of the experiment (Kruskal-Wallis ANOVA). As illustrated in Fig. 3, further analysis by the Mann-Whitney *U*-test (two-tailed) demonstrated that only imipramine treatment at the dosage of 20 mg/kg caused a significant reduction in the daily intake of water.

All parameters measured in the activity cage, open field, and vertical hole-board (see the Method section) were first analysed using the Kruskal-Wallis ANOVA (16), and if this test demonstrated significant group differences, further analyses using the Mann-Whitney *U*-test (16) compared individual groups.

While none of the parameters of the activity cage and open field tests (some of which are illustrated in Fig. 4) revealed significant group differences, seven parameters of the vertical hole-board exploration test demonstrated significant differences between groups. The seven parameters to contain significant group differences were: the total number of visits ($p < 0.01$); the total duration of visits ($p < 0.05$); the number of different holes visited ($p < 0.05$); the mean number of visits per visited hole ($p < 0.01$); the number of visits in the first 5-min period of the test ($p < 0.01$); the number of visits in the last 5-min period of the test ($p < 0.05$); and the number of clusters ($p < 0.01$). As illustrated in Figs. 5 and 6, the subsequent Mann-Whitney *U*-tests (16) demonstrated that on all seven parameters the group receiving 20 mg/kg differed significantly from the vehicle control group and on five of the seven parameters the two imipramine groups differed significantly. The only significant ($p < 0.05$) difference between the vehicle control group and the group receiving 10 mg/kg imipramine was found on the parameter, number of clusters.

DISCUSSION

As clearly demonstrated by Fig. 1 and the statistical analysis described in the Results section, animals receiving either 10 or 20 mg/kg per day of imipramine fail to grow significantly during the 15-day treatment period, while the vehicle control group demonstrated a normal growth pattern.

Beginning 48 h after first injection (and throughout the experiment), both dosages of imipramine were associated with a significantly reduced intake of food (Fig. 2). Injections of imipramine in the concentration of 20 mg/kg were associated with a temporary reduction in water intake. The reduction of water intake began 24 h after the first imipramine injection and lasted approximately 72 h.

The arrested growth of the two imipramine-treated groups appears more likely to be a consequence of the reduced intake

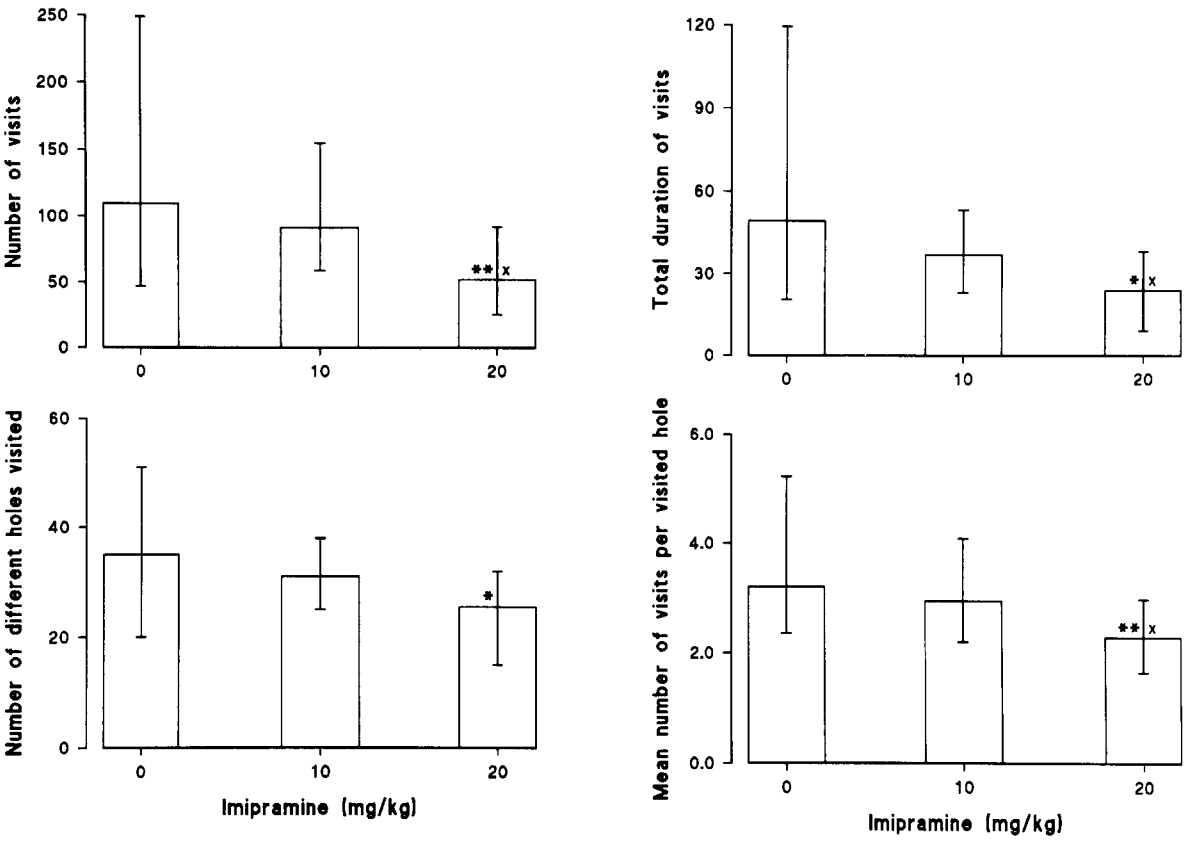

FIG. 5. Aspects of the behaviour of the three dosage-defined experimental groups in the vertical hole-board test. The number of visits, total duration of visits, number of different holes visited, and mean number of visits per visited hole are shown. Values are given as medians with ranges. *Significantly ($p < 0.05$) different from the vehicle-injected control group. **Significantly ($p < 0.01$) different from the vehicle-injected control group. ˣSignificantly ($p < 0.05$) different from the group receiving imipramine in the concentration of 10 mg/kg body weight.

of food than a reflection of metabolic changes provoked by a changed level of general activity. Whether the imipramine-associated decrease in food consumption, as suggested by File and Tucker (2), is secondary to a nonspecific sedation cannot be evaluated on the background of the present data. Our results are, however, in agreement with the outcome of previous studies (1,8,9).

The three groups of the present study did not differ significantly on any measure believed primarily to reflect locomotion and motor abilities. All measures from the activity cage and open field, as well as the one "motoric" parameter from the hole-board (the visits to sixth row of holes as percentage of total number of visits), appeared unaffected by the presently studied levels of chronic imipramine treatment (Fig. 4 and Tables 1-2). Since both the rather "exploration-independent" activity cage test and the parameters of the open field test, which may be more easily influenced by both locomotion and exploration, appear to contain no group differences, it seems safe to conclude that if chronic imipramine in dosages of 10 or 20 mg/kg influences locomotion, as presently measured, either tolerance had developed by the time of study or locomotion had normalized 24 h after the last injection.

Seven of the twelve parameters from the vertical hole-board exploration test reveal significant effects of chronic imipramine treatment. One of the five parameters not to reveal significant group differences was the locomotion-dependent variable—number of visits to sixth row as percentage of total number of visits. While only the number of clusters was able to differentiate between the vehicle-treated control group and the group receiving imipramine in the concentration of 10 mg/kg, the group receiving 20 mg/kg of imipramine demonstrated a significantly reduced number of visits, spent significantly less time visiting holes, visited a significantly lower number of different holes, had a significantly lower number of visits to each of the holes visited, had a lower number of clusters, and demonstrated a changed temporal pattern of visits. The change in temporal patterning of visits revealed itself in a significant increase in the number of visits during the first 5-min period of the 15-min test, while the number of visits during the last 5 min of the test was significantly lower than the corresponding value of both control animals and rats receiving 10 mg/kg of imipramine. In other words, the 20 mg/kg group overresponded in initial parts of the test and underresponded in the later parts of the test. Since the number of visits during the complete test was significantly reduced in this group, the initial overproduction was more than outweighed by later reductions in the number of visits. The effect of this dosage of imipramine could be interpreted as an initial hyperexploration followed by an overhabituation.

From the outcome of the vertical hole-board exploration

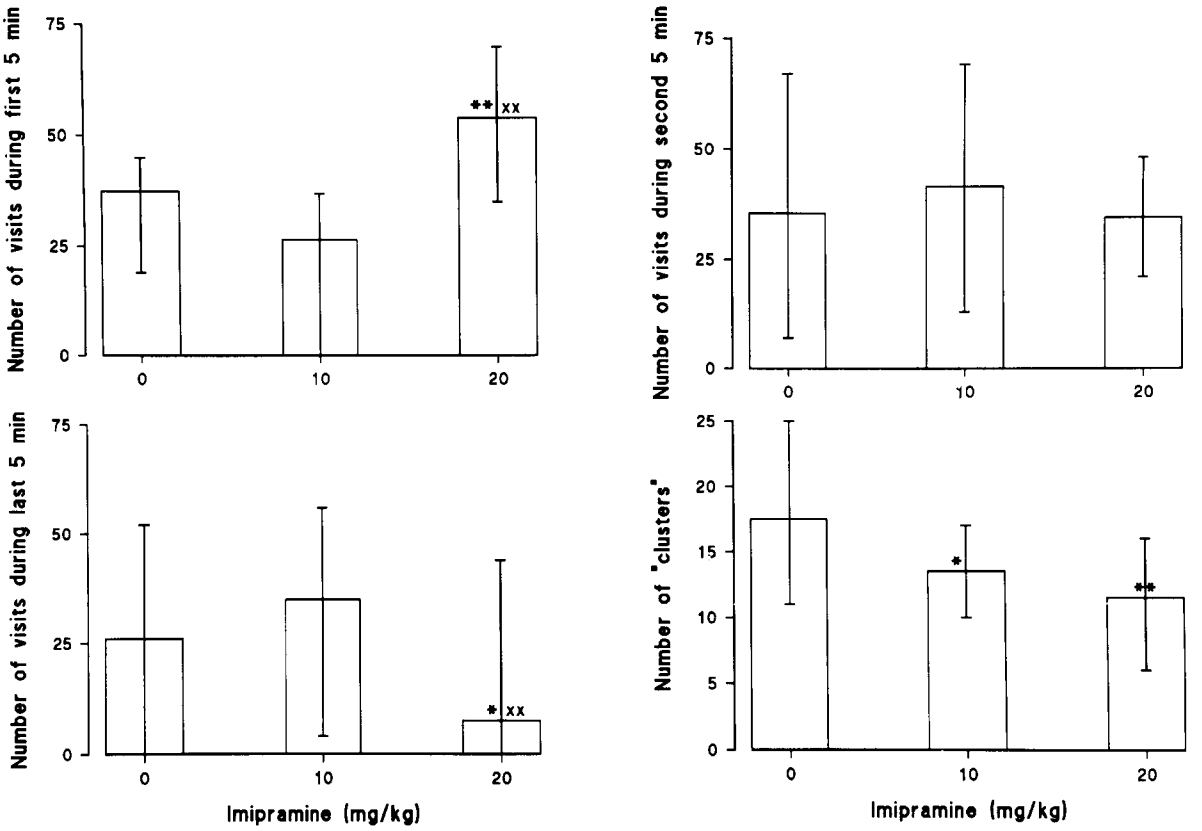

FIG. 6. Aspects of the behaviour of the three dosage-defined experimental groups in the vertical hole-board test. The number of visits during the first, second, and last 5-min period of the test, as well as the number of clusters during the entire test period, are shown. Values are given as medians with ranges. *Significantly ($p < 0.05$) different from the vehicle-injected control group. **Significantly ($p < 0.01$) different from the vehicle-injected control group. ^{xx}Significantly ($p < 0.01$) different from the group receiving imipramine in the concentration of 10 mg/kg body weight.

TABLE 1

ASPECTS OF THE PERFORMANCE OF THE THREE DOSAGE-DEFINED EXPERIMENTAL GROUPS IN THE OPEN FIELD TEST

	Vehicle-Injected Control Group	Imipramine (10 mg/kg)	Imipramine (20 mg/kg)
Latency to first body movement (s)	3.25 (0.84–5.77)	2.71 (1.00–8.29)	1.85 (0.86–60.81)
Mean duration of locomotion episodes (s)	5.10 (4.05–6.88)	4.85 (4.14–8.52)	5.54 (4.27–9.45)
Number of rearing episodes	49 (41–81)	55 (34–62)	42 (25–64)
Total duration of rearing episodes (s)	125.925 (90.69–188.51)	111.885 (101.41–157.78)	104.990 (53.43–130.84)
Mean duration of rearing episodes (s)	2.29 (2.07–2.95)	2.24 (1.80–2.98)	2.32 (1.74–4.09)
Number of grooming episodes	8.5 (1–13)	9.0 (5–22)	7.0 (1–15)
Total duration of grooming episodes (s)	58.830 (5.77–124.32)	43.005 (23.91–122.96)	44.555 (3.02–206.51)
Mean duration of grooming episodes (s)	6.29 (2.21–9.56)	4.81 (3.42–7.69)	7.42 (3.02–13.77)

Values are given as medians with ranges. Further descriptions are given in the Method section.

TABLE 2

ASPECTS OF THE BEHAVIOUR OF THE THREE DOSAGE-DEFINED EXPERIMENTAL GROUPS IN THE VERTICAL HOLE-BOARD TEST

	Vehicle-Injected Control Group	Imipramine (10 mg/kg)	Imipramine (20 mg/kg)
Latency to first hole visit (s)	21.420 (0.23-33.63)	32.875 (7.27-171.07)	16.285 (5.02-36.47)
Mean duration of individual visits (s)	0.41 (0.20-0.57)	0.36 (0.30-0.59)	0.41 (0.33-0.56)
Number of visits to sixth "row" as percentage of total number of visits	16 (4-45)	25 (9-35)	13 (6-28)
Number of "short" visits as percentage of total number of visits	72.0 (60-87)	74.0 (61-79)	69.5 (50-82)

Values are given as medians with ranges. Further descriptions are given in the Method section.

test—which is believed to reflect exploration in a rather locomotion-independent manner (J. Mogensen and S. Holm, in preparation)—it may be concluded that at least certain types of exploration are influenced by chronic treatment with imipramine in the concentration of 20 mg/kg, even when the exploration is tested 24 h after the last injection. If such exploratory behaviours are influenced by chronic imipramine in the dosage of 10 mg/kg, such effects seem to be only marginal. Since the animals of the experimental group demonstrating an abnormal hole-board exploration had significantly lower body weights than the rats of the control group, it could be speculated that physical weakness might have contributed to the changed hole-board exploration of the animals receiving imipramine in the concentration of 20 mg/kg. Such a possibility, however, is contradicted by the fact that the animals receiving the high concentration of imipramine demonstrated an increased rather than decreased exploration during the first 5 min of the test session when compared to control animals. If physical weakness had modified the hole-board exploration of imipramine-treated animals, one would have expected reduced or at least normal exploration during the initial test phases. The fact that the temporal distribution of exploration activities appears to be the primary factor affected by imipramine treatment points to a central rather than peripheral mechanism as the most likely explanation for the phenomenon.

At least part of the mechanism behind the imipramine-associated changes in exploratory behaviour seems to be changes in the temporal distribution of exploratory activities (present data). If, at certain dosages, chronic imipramine treatment in the rat causes a pattern of change like the presently observed initial hyperexploration followed by an overhabituation, the outcome of exploration tests may be greatly influenced by the duration of the test. Had the vertical hole-board exploration test of the present experiment lasted only 5 min, the parameter total number of visits would have demonstrated that the animals receiving imipramine in the dosage of 20 mg/kg explored significantly more than vehicle-treated controls. If the question of the temporal aspects of exploration is considered, some of the discrepancies of the literature on the association between antidepressive drugs and exploration may be better understood.

Although the question has so far never been addressed directly, it could be imagined that not only exploratory behaviour but even locomotion would be affected by imipramine via an interference with the temporal distribution of behavioural activities. If the locomotion and general activity of animals subjected to chronic imipramine treatment is, indeed, found to be modified as a consequence of initial hyperactivity followed in later test phases by overhabituation, it could be imagined that even our activity cage and open field tests would have revealed the locomotion of imipramine-treated rats to differ from normal locomotion if the individual tests would have lasted shorter or longer. Direct tests of the temporal distribution of locomotion and general activity upon chronic imipramine administration should be performed to address more directly the question of potential similarities between the ways in which chronic imipramine affects exploration and locomotion. Additionally, it should be studied in which ways, if any, the imipramine-induced modifications of habituation interact with the changed circadian rhythms of animals subjected to chronic administration of imipramine (20).

On the background of the present observations it may be of interest to note the results of Gately et al. (5), who studied the consequences of interventricular administration of 5,7-dihydroxytryptamine, which causes a substantial loss of serotonin in the brain: while habituation of both locomotion and exploratory responses in a test apparatus—which in some respects resembles the hole-board apparatus of the present experiment—appeared decreased by such a treatment when measured 3 days after the injection, the lesioned animals appeared to overhabituate if measured 11 days after administration of 5,7-dihydroxytryptamine. Both the chronic administration of imipramine, which blocks the reuptake of both serotonin and norepinephrine (18), and the long-term compensatory changes induced by global damage to the serotonergic system (5) appear to be associated with changes within aspects of habituation.

ACKNOWLEDGEMENTS

We are grateful for the financial support received from the Danish Medical Research Council, Dansk Statoil Fond, Den Danske Johanniterordens Hospitalsfond, Direktør E. Danielsen og Hustrus Fond, Direktør Ib Henriksens Fond, Direktør Jacob Madsen og hustru Olga Madsens Fond, Dr.med.vet. Axel Thomsen og hustru Martha Thomsen, f. Hagen-Johansens legat, Eli og Egon Larsens Fond, Fabrikant Albert Nielsens og Hustru Anna Nielsens Fond, Fhv. lærer Svend Aage Nielsen Wacherhausens legat, Fonden af 1870, Fonden til Forskning af Sindslidelser, Fonden til Lægevidenskabens Fremme, Founda-

tion for experimental research in neurology, Kong Christian den Tiendes Fond, Købmand i Odense Johann og Hanne Weimann, f. Seedorffs Legat, Købmand Sven Hansen og Hustru Ina Hansens Fond, Læge Eilif Trier-Hansen og hustru Ane Trier-Hansens legat, Lægeforeningens Forskningsfond, Novos Fond, P. A. Messerschmidt og Hustrus Fond, P. Carl Petersens Fond, Psykiatrisk Forskningsfond af 1967, Skizofrenifonden af 1986, Vera og Carl Johan Michaelsens Legat, and Voltens legat. We would also like to thank Ciba-Geigy for the generous gift of the Tofranil and Ulla Mogensen for secretarial assistance.

REFERENCES

1. Broitman, S. T.; Donoso, A. O. Effects of chronic imipramine and clomipramine oral administration on maternal behavior and litter development. Psychopharmacology (Berlin) 56:93–101; 1978.
2. File, S. E.; Tucker, J. C. Behavioral consequences of antidepressant treatment in rodents. Neurosci. Biobehav. Rev. 10:123–134; 1986.
3. Freund, J. L.; Freund, D.; Hoffmann, R.; Glanzmann, P.; Kahlau, F. Über das Verhalten der Ratten im Open Field ohne Belastung, unter akuter und länger andauernder Wirkung von Imipramin und Tranylcypromin sowie über Abhängigkeiten vom Reaktionstyp (emotive und nichtemotive Tiere). Arzneimittelforschung 29:1150–1154; 1979.
4. Furgiuele, A. R.; Aumente, M. H.; Horovitz, Z. P. Acute and chronic effects of imipramine and desipramine in normal rats and in rats with lesioned amygdalae. Arch. Int. Pharmacodyn. Ther. 151:170–179; 1964.
5. Gately, P. F.; Segal, D. S.; Geyer, M. A. The behavioral effects of depletions of brain serotonin induced by 5,7-dihydroxytryptamine vary with time after administration. Behav. Neural Biol. 45: 31–42; 1986.
6. Geoffroy, M.; Mogensen, J. Differential recovery in measures of exploration/locomotion after a single dosage of reserpine in the rat. Acta Neurobiol. Exp. 48:263–274; 1988.
7. Giardina, W. J.; Radek, R. J. Effects of imipramine on the nocturnal behavior of bilateral olfactory bulbectomized rats. Biol. Psychiatry 29:1200–1208; 1991.
8. Harrison-Read, P. E.; Steinberg, H. Tricyclic antidepressant drugs and individual differences in the exploratory activity of rats: Contrasting effects of tertiary and secondary amine compounds. Psychopharmacology (Berlin) 69:85–91; 1980.
9. Hughes, R. N.; Pither, J. M. Chronic imipramine effects on exploratory behavior in rats. Pharmacol. Biochem. Behav. 27:359–362; 1987.
10. Iversen, I. H.; Mogensen, J. *d*-Amphetamine affects one-trial appetitive conditioning in rats. Abstract published at Association for Behavior Analysis: Tenth Annual Convention, Nashville, TN; 1984.
11. Iversen, I. H.; Mogensen, J. A multipurpose vertical holeboard with automated recording of spatial and temporal response patterns for rodent. J. Neurosci. Methods 25:251–263; 1988.
12. Köhler, U.; Rauca, C. Effects of BCH 325 (Pro-D-Phe-Pro-Gly) on open field behavior after chronic stress procedure. Peptides 13:141–144; 1992.
13. Kulkarni, S. K.; Dandiya, P. C. Effects of antidepressant agents on open field behaviour in rats. Psychopharmacologia 33:333–338; 1973.
14. Maj, J.; Rogóz, Z.; Skuza, G.; Sowinska, H. Antidepressants given repeatedly increase the behavioural effect of dopamine D-2 agonist. J. Neural Transm. 78:1–8; 1989.
15. Meltzer, D.; Fox, P. A. Increases in spontaneous activity following intermittent imipramine administration. Psychopharmacologia 21:187–191; 1971.
16. Siegel, S. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill; 1956.
17. Smialowski, A. Repeated imipramine enhances sensitivity of the brain dopaminergic system related to exploratory behavior. J. Neural Transm. 69:201–209; 1987.
18. Tucker, J. C.; File, S. E. The effects of tricyclic and 'atypical' antidepressants on spontaneous locomotor activity in rodents. Neurosci. Biobehav. Rev. 10:115–121; 1986.
19. Vogel, G. W.; Minter, K.; Woolwine, B. Effects of chronically administered antidepressant drugs on animal behavior. Physiol. Behav. 36:659–666; 1986.
20. Wirz-Justice, A.; Campbell, I. C. Antidepressant drugs can slow or dissociate circadian rhythms. Experientia 38:1301–1309; 1982.