Pharmacology Biochemistry & Behavior, Vol. 11, pp. 725–728. Printed in the U.S.A.

Effects of Imipramine on Schedule Dependent and Schedule Induced Behavior[1]

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Received 20 September 1979

LOULLIS, C. C. AND M. J. WAYNER. *Effects of imipramine on schedule dependent and schedule induced behavior.* PHARMAC. BIOCHEM. BEHAV. 11(6) 725–728, 1979.—Rats were reduced to 80% body weight and were exposed to an FI 1 min reinforcement schedule for 60 min daily until lever presses, licks, and water consumption stabilized for at least 10 days. In Experiment 1, animals were injected with 0.9% saline, 2, 4, 8 and 16 mg/kg of imipramine in a counterbalanced design. In Experiment 2, following the return of all three measures to pre-injection baseline, the same animals were injected with 16 mg/kg of imipramine daily for 8 days. On Days 9 through 11 animals continued to be tested under the same conditions but imipramine was not administered. Results of Experiment 1 revealed a significant decrease in lever presses at 8 mg/kg and a decrease in lever presses and water intake at 16 mg/kg. Licks were not significantly different from saline baseline at any of the doses used. In Experiment 2, repeated administration of imipramine resulted in a significant decrease in lever presses from saline baseline on all days. Water intake was significantly depressed on Day 2 through 8. Licks were depressed on Days 2, 3, 4, 5 and 8. Animals did not show any tolerance to the repeated administration of the drug. Licks and water consumption were not significantly different from saline baseline on Days 9, 10 and 11. Lever presses returned to baseline on Day 10. These data indicate that imipramine produces differential and dose dependent effects on schedule dependent and schedule induced behavior.

Imipramine Schedule induced behavior Schedule dependent behavior Schedule induced polydipsia Adjunctive behavior

WHEN rats are subjected to intermittent schedules of food reinforcement at reduced body weight and are given the opportunity to drink, persistent post pellet licking and drinking develops. This phenomenon has been referred to as schedule induced polydipsia and has been reviewed extensively [3, 4, 12, 13]. It has been previously demonstrated that certain drugs have different effects when measured by schedule dependent and schedule induced behavior [14,15]. Therefore, the schedule induced polydipsia experiment can provide a more complete assessment of the effects of drugs on behavior and it is preferable to the more commonly used methods which only employ schedule dependent measures.

Imipramine is a tricyclic antidepressant which blocks the reuptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) by nerve terminals [2, 5, 7, 8]. The effects of imipramine on schedule dependent behavior have previously been reported [1,6]. The possible effects of this drug on schedule induced behavior, however, have not been studied. The purpose of the present study was to investigate the effects of this drug on schedule dependent and schedule induced behavior. In Experiment 1 different doses of imipramine were used in order to establish a dose effect curve for the dependent variables. In Experiment 2 animals were injected repeatedly with a single dose of the same drug in order to investigate tolerance effects.

EXPERIMENT 1

The purpose of Experiment 1 was to measure the effects of four doses of imipramine—2, 4, 8, and 16 mg/kg—on schedule dependent lever pressing, schedule induced licking, and water consumption in a one hour test session. Doses of imipramine were chosen on the basis of previously reported data on schedule dependent behavior [1].

METHOD

Animals

Four male hooded rats with an average body weight of 277 ± 12.3 (SD) g were selected from our colony and allowed to adapt to individual home cages for 10 days.

Procedure

Following adaption to home cages, animals were handled daily and records were kept of food and water intake and body weights. Body weights recorded on the eighth day were considered to be the 100% ad lib feeding weight for each animal. Animals were gradually reduced to 80% of this weight over a 7 day period by restricting daily food rations. For the next 3 days animals were trained in an experimental chamber to press a lever for 45 mg Noyes food pellets. Fol-

[1]This research was supported in part by a grant from NINCDS USPHS No. MH-13543.

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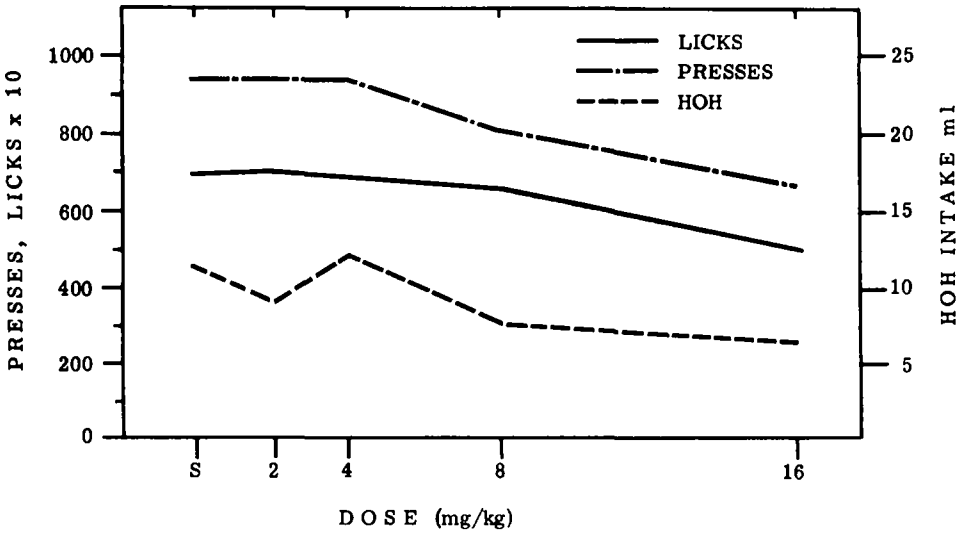

FIG. 1. Mean number of lever presses, licks, and water consumed in ml for the four animals in Experiment 1 presented as a function of saline baseline and the four doses of imipramine administered.

lowing the 3 days on continuous reinforcement, animals were placed on a FI 1 min reinforcement schedule for the duration of the experiment. All animals were tested daily for 1 hr.

The experimental chamber consisted of a standard LVE 1469 medium size test cage and matching sound attenuating cubicle with a lever and pellet dispensing mechanism. A stainless steel ball point drinking spout was mounted in the center of the back wall of the chamber, 4.0 cm above the grid floor, and protruded 1.5 cm into the cage. The drinking spout was attached to a graduated eudiometer tube for measuring water consumption. A standard food cup was mounted on the adjacent wall as close as possible to the back wall and 1.0 cm above the floor. The lever was mounted on the same wall as the food cup, 3.0 cm above the floor and 2.5 cm from the front of the cage. Licks were recorded by means of a contact resistance sensitive lickometer. During the experimental session, the number of licks and presses were recorded on individual counters and displayed on a cumulative recorder.

When licks, lever presses, and water intakes appeared to be stable over a 10 day period, animals were injected intraperitonealy with 0.9% saline, 2, 4, 8, and 16 mg/kg of imipramine in a counterbalanced design. The injections were given immediately prior to the beginning of each test session and were separated by two days of testing when no injections were given.

RESULTS

Data were analyzed by means of a single factor ANOVA with repeated measures. One analysis was carried out for each of the three dependent variables; total number of lever presses, licks, and water consumed in ml during the one hour test sessions. Five levels of the factor were included in each analysis, saline baseline and each of the four doses of imipramine.

The analysis of lever presses indicated that the main effect was significant, $F(4,12)=6.92$, $p<0.01$. A post hoc Dunnett test using the saline baseline as the control treatment revealed that lever presses were significantly decreased at 8 mg/kg ($p<0.05$) and 16 mg/kg ($p<0.01$). The analysis of licks indicated that the main effect was not significant, $F(4,12)=1.51$, $p>0.05$. The analysis of water intakes indicated that the main effect was significant, $F(4,12)=3.93$, $p<0.05$. A post hoc Dunnett test indicated that water intake was decreased at 16 mg/kg ($p<0.05$). These effects of imipramine are illustrated in Fig. 1 where the mean number of lever presses, mean number of licks, and mean water consumed in ml are presented as a function of the saline baseline and the four doses of imipramine administered.

EXPERIMENT 2

In Experiment 2, the effects of repeated administration of imipramine (16 mg/kg) on schedule dependent lever pressing and schedule induced licking and water consumption were investigated.

METHOD

Animals

Following the completion of Experiment 2, the same four animals were used in this experiment.

Procedure

Animals continued to be tested daily in the experimental chamber after the completion of Experiment 1. A series of 0.9% saline intraperitoneal injections were given to all animals over four consecutive days in order to establish a saline baseline. These saline injections were followed by injection of 16 mg/kg of imipramine on eight consecutive days. The animals were then tested in the experimental chamber for three additional days during which no injections were administered.

RESULTS

Data were analyzed by means of a single factor ANOVA with repeated measures. One analysis was carried out for each of the three dependent variables; total number of lever presses, licks, and water consumed in ml during the one hour test session. Twelve levels of the factor were included

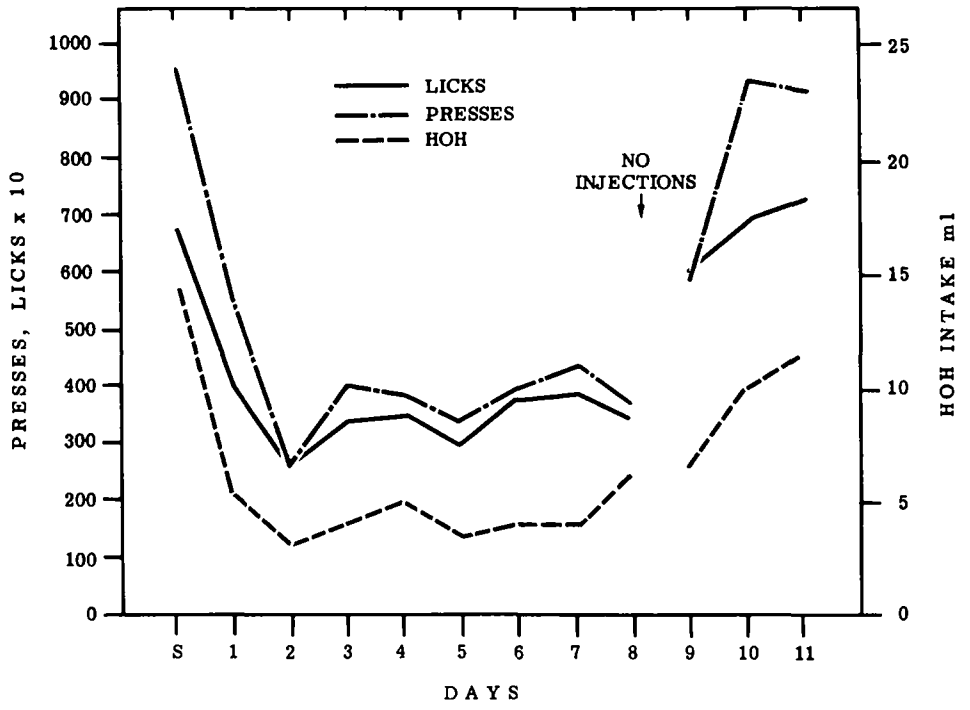

FIG. 2. Mean number of lever presses, licks, and water consumed in ml for the four animals in Experiment 2 presented as a function of saline baseline, the eight injections of 16 mg/kg imipramine and three post-drug days.

in each analysis, saline baseline (mean of four injections), each of the eight consecutive injections of 16 mg/kg imipramine, and the three post-drug days.The analysis of lever presses indicated that the main effect was significant, $F(3,11)=5.5$, $p<0.01$. A post hoc Dunnett test using the saline baseline as the control treatment revealed significant decreases in lever presses for all the imipramine days and the first postdrug day, $p<0.01$. Analysis of licks indicated that the main effect was significant, $F(3,11)=4.49$, $p<0.01$. A post hoc Dunnett test revealed significant decreases in licks for imipramine Days 2, 3, 4, 5 and 8, $p<0.05$. Analysis of water intakes indicated a significant main effect, $F(3,11)=5.85$, $p<0.01$. A post hoc Dunnett test revealed that water intakes were significantly decreased on imipramine on Days 2 through 8, $p<0.01$.

The effects of repeated imipramine administrations are illustrated in Fig. 2. where the mean number of lever presses, mean number of licks, and mean water consumed in ml are presented as a function of the saline baseline, the eight injections of 16 mg/kg of imipramine and the three post-drug days.

DISCUSSION

These data indicate that imipramine produces differential and dose dependent effects on schedule dependent and schedule induced behavior. The results of Experiment 1 on schedule dependent behavior are in agreement with previously reported data [1]. Furthermore, the results of Experiment 2 indicate that there is no tolerance to repeated injections of the drug with respect to the three parameters measured. In general it can be stated that, both in Experiment 1 and 2, licking was affected the least, followed by water consumption, and finally lever pressing which was affected the most.

Since imipramine blocks the reuptake of both NE and 5-HT it is not possible to specify the neurotransmitter responsible for these effects. Further experiments using specific uptake blockers such as fluoxetine (preferential inhibitor of 5-HT uptake) or nisoxetine (preferential inhibitor of NE uptake) are needed in order to provide such answers. It has also been suggested that the therapeutic effects of imipramine, as well as other tricyclic antidepressants, in clinical depression is a result of changes in receptor sensitivity rather than the result of increased neurotransmitter availability at the synaptic cleft when uptake is inhibited [9, 10, 11]. Since changes in postsynaptic receptor sensitivity develop over a period of time, such a hypothesis helps explain why the clinical effects of tricyclic antidepressants are not evident for weeks. It would therefore be of interest to investigate further the effects of imipramine and other tricyclic antidepressants, on schedule dependent and schedule induced behavior in animals injected with the drug over a period of weeks.

REFERENCES

1. Ando, K. Profile of drug effects on temporally spaced responding in rats. *Pharmac. Biochem. Behav.* **3**: 833–841, 1975.
2. Carlsson, A., H. Corrodi, K. Fuxe and T. Hokfelt. Effects of some antidepressant drugs on the depletion of intraneuronal brain catecholamine stores caused by 4-α-dimethyl tyramine. *Eur. J. Pharmac.* **5**: 367–373, 1969.
3. Falk, J. L. Conditions producing psychogenic polydipsia in animals. *Ann. N.Y. Acad. Sci.* **157**: 569–593, 1969.
4. Falk, J. L. The nature and determinants of adjunctive behavior. *Physiol. Behav.* **6**: 577–588, 1971.
5. Hamberger, B. and J. Tuck. Effects of tricyclic antidepressants on the uptake of noradrenalin and 5-hydroxytryptamine by rat brain slices incubated in buffer or human plasma. *Eur. J. Clin.* **5**: 229–235, 1973.
6. Kornetsky, C. A comparison on the effects of desipramine and imipramine on two schedules of reinforcement. *Int. J. Neuropharmac.* **4**: 13, 1965.
7. Lassen, L., E. Peterson, B. Kjellberg and S. Olsson. Comparative studies of the new 5-hydroxytryptamine uptake inhibitor and some tricyclic thymoleptics. *Eur. J. Pharmac.* **3**: 108–115, 1975.
8. Meek, J., K. Fuxe and N. E. Anden. Effects of antidepressant drugs of the imipramine type on central 5-hydroxytryptamine neurotransmission. *Eur. J. Pharmac.* **9**: 325–332, 1970.
9. Riggin, S. J. and S. K. Chanda. Development of β-andrenergic receptor subsensitivity by antidepressants. *Nature* **268**: 455–456, 1977.
10. Schultz, J. Psychoactive drug effects on a system which generates cyclic AMP in brain. *Nature* **261**: 417–418, 1976.
11. Sulser, F., Vetulani, J. and P. J. Mobley. Mode of action of antidepressant drugs. *Biochem. Pharmac.* **27**: 257–261, 1978.
12. Wayner, M. J. Motor control functions of the lateral hypothalamus and adjunctive behavior. *Physiol. Behav.* **5**: 1319–1325, 1970.
13. Wayner, M. J. Specificity of behavioral regulation. *Physiol. Behav.* **12**: 851–869, 1974.
14. Wayner, M. J., I. Greenberg, S. Fraley and S. Fisher. Effects of Δ^9-tetrahydrocannabinol and ethyl alcohol on adjunctive behavior and the lateral hypothalamus. *Physiol. Behav.* **10**: 109–132, 1973.
15. Wayner, M. J., F. B. Jolicoeur, D. B. Rondeau and F. C. Barone. Effects of acute and chronic administration of caffeine on schedule dependent and schedule induced behavior. *Pharmac. Biochem. Behav.* **5**: 343–348, 1976.