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Juvenile Desipramine Reduces Adult Sensitivity to Imipramine in Two Behavioral Tests

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DWYER, K. D. AND E. J. ROY. *Juvenile desipramine reduces adult sensitivity to imipramine in two behavioral tests.* PHARMACOL BIOCHEM BEHAV 45(1) 201–207, 1993.—The behavioral effects of adult imipramine administration were examined in female rats treated with desipramine as juveniles (JDES), treated with saline as juveniles (JSAL), and untreated as juveniles (JUNT). In the forced swimming test, the juvenile groups displayed similar behavioral effects of imipramine when administered short term following a pretest forced swimming exposure. Similar effects of imipramine were observed when administered long term prior to the only test exposure. When rats were not given a pretest forced swimming test exposure, short-term imipramine had no effect on JDES rats but did influence JSAL and JUNT rats. In the open-field test, short- and long-term imipramine treatment affected the behavior of JUNT and JSAL rats. Short-term imipramine treatment influenced open-field behavior of JDES animals, but long-term imipramine treatment had no effect. These results suggest that JDES treatment may permanently alter the neural mechanism underlying the behavioral effects of antidepressant treatment.

Depression Animal depression model Desipramine Rat Open-field behavior Forced swimming test Imipramine

JUVENILE treatment of rats with monoamine uptake inhibitors has been reported to produce alterations in adult sleep, motivation, sex behavior, alcohol consumption, aggression, and activity [(8,10–12,19–21,28,30,31); however, see (7)]. Similarity between these alterations and depressive symptomology has led to the proposal of administering monoamine uptake inhibitors to juvenile rats to produce an adult animal model of depression (9,32). Such a model was deemed potentially useful because the behavioral alterations are likely to reflect fairly permanent central disturbances.

A major use of animal models of depression is to study the mechanism by which established antidepressant treatments act to develop new antidepressant treatments. Fully characterizing an animal model of depression includes assessing responses to therapeutic manipulations. Preliminary evidence suggested that the sexual, aggressive, and activity abnormalities associated with juvenile treatment of the monoamine uptake inhibitor clomipramine may be reversed with the antidepressant imipramine (29). In that report, control rats and rats treated as juveniles were not directly compared, so sensitivity to antidepressant treatment could not be assessed.

Depressed humans may differ from normal individuals in their behavioral and biochemical responses to antidepressant drugs. Although a valid animal model does not necessarily require enhanced sensitivity to antidepressant treatments, a procedure that alters sensitivity to antidepressant drugs may provide insights into mechanisms of drug action.

In previous published studies of this proposed animal model of depression, juvenile monoamine uptake inhibitor treatment was only compared with juvenile saline (JSAL) treatment. While JSAL treatment is the appropriate comparison group for studying the effect of juvenile treatment with monoamine uptake inhibitors, JSAL treatment necessitates handling during development. Because handling during development has persistent behavioral and physiological effects (4,17), we hypothesized that JSAL treatment itself may influence both baseline behavior and behavior following adult antidepressant administration. Juvenile monoamine uptake inhibitor treatment would be a more useful model of depression if it is different from both JSAL treatment and no juvenile treatment.

In the present study, female rats treated with desipramine as juveniles (JDES) were compared with JSAL rats and rats that were untreated as juveniles (JUNT) in the Porsolt forced swimming test and in the open field. The Porsolt forced swimming test is used as a behavioral test of antidepressant efficacy (3). Animals treated with monoamine uptake inhibitors as juveniles have been found to display increased immobility on their first exposure to a swim tank (9,13) but the effect of adult antidepressant administration was not examined. Be-

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cause JDES treatment has been shown to produce adult alterations in neurochemical systems thought to be involved in antidepressant action (9), we hypothesized that JDES animals would display an altered sensitivity to the effect of the antidepressant imipramine in both the forced swimming and open-field tests.

METHOD

Experiment 1

In this experiment, animals were given a pretest succeeded by a test exposure to the forced swimming test, following Porsolt's original procedure (22).

Subjects and subject preparation. At 6–7 days postnatal, female Long-Evans hooded pups were cross-fostered and culled into nursing groups containing 7–10 pups. Nursing groups containing JUNT controls were handled only for cage cleaning until weaning. Animals in the other nursing groups were divided into two groups. JDES animals were administered 5 mg/kg desipramine each day between postnatal days 6–7 and 20–21. JSAL controls were injected with saline at the same time. Dams of both JUNT pups and injected pups were removed from their home cages during injections (less than 15 min a day). Due to the small number of females born in the first set of litters, two sets of female pups born at separate times were used. Both sets contained 25 animals (50 total) with 7 or 8 animals in each juvenile condition. Animals were weaned at 4 weeks old and caged in groups of two or three animals of the same condition under a 12 L : 12 D photoperiod.

Procedure. Animals were tested on 2 successive days at 2.0 months old (set 1) or 2.5 months old (set 2). On day 1, animals were placed in a swim tank (Plexiglas cylinder 40 cm high, 18 cm in diameter) filled 19 cm high with room temperature water (19–22°C) for 15 min (pretest). On day 2, animals were placed in the swim tank for 5 min (test). Imipramine (20 mg/kg, IP) or saline were injected three times: 15 min after the 15-min pretest and 5 and 1 h prior to the 5-min swim test. The behavior, as recorded on videotape, was scored in mseconds using a computer with an event recorder program (Eventlog version 2.0, designed by R. Hendersen, programming by N. Sampson) by an observer blind to the experimental condition. Struggling was recorded when the rat was in a vertical position and vigorously moving all four limbs. Swimming was recorded when the rat was in a horizontal position paddling in the tank. Immobility was recorded only when the rat was not moving any limb.

Experiment 2

In Experiment 2, animals were administered saline or imipramine short term, then tested in the forced swimming test, with no prior pretest exposure. The effect of short-term saline or imipramine on open-field behavior was also examined.

Subjects. The postnatal treatment was as described in Experiment 1. Subjects included 15 JDES, 15 JSAL control, and 14 JUNT control females.

Procedure. At 10 weeks of age, animals were tested in the forced swimming test. Animals were injected with 20 mg/kg imipramine or saline 24, 5, and 1 h prior to this test. In an attempt to increase the sensitivity of this test, the forced swimming exposure was increased to 10 min. Animals were tested for 10 min in an open-field test 2 weeks after the swim test. Animals were injected with 20 mg/kg imipramine, or saline, 1 h prior to testing. Animals received the same treatment that they received in the swim test.

Open-field test. The apparatus was a 90 × 90 cm square with 40-cm high walls and a floor divided into 36 squares by white lines. Rats were placed in the corner of the open field and observed for 10 min. Between animals, the open field was cleaned with alcohol. The frequency of three behaviors—ambulation, rearing, and defecation—were measured. Ambulation was scored whenever rats moved from one square to a

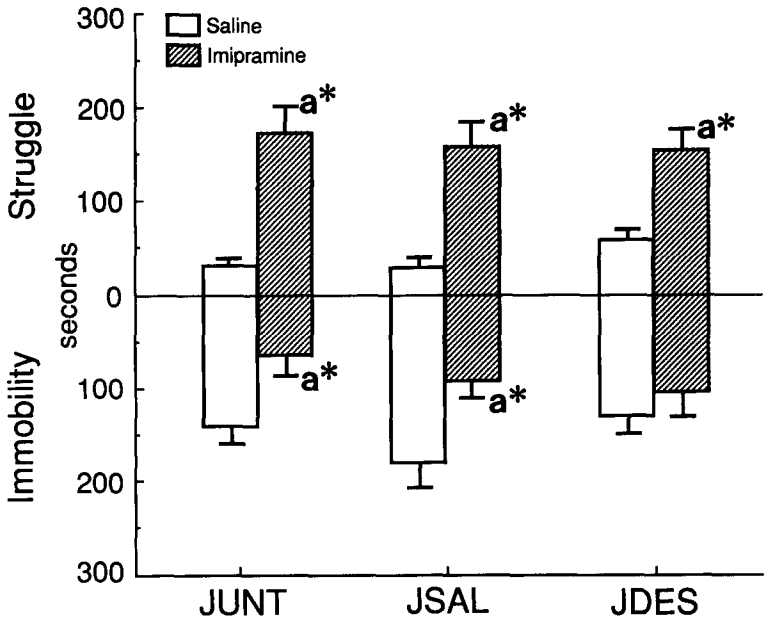

FIG. 1. Behavior (mean ± SEM) in a 5-min swimming test following a pretest and short-term saline or imipramine. a, different from saline-treated group. *$p < 0.05$

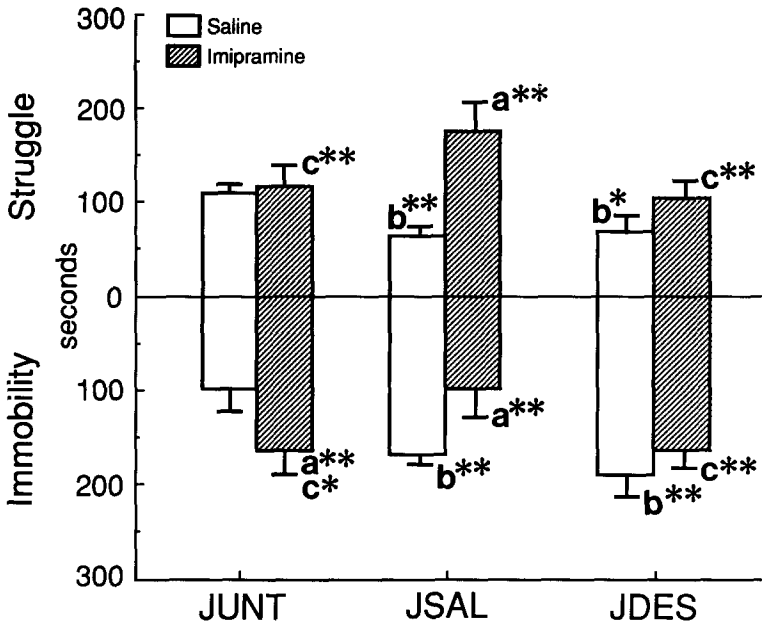

FIG. 2. Behavior (mean ± SEM) in the first 5 min of an initial 10-min swimming test following short-term saline or imipramine. a, different from saline-treated group; b, different from saline-treated JUNT; c, different from imipramine-treated JSAL. *$p > 0.05 < 0.10$, **$p < 0.05$.

neighboring one. It was also noted if the square entered was in the periphery of the open field or in the center of the open field. Rearing was scored whenever the rat lifted both forelegs in air or against the wall. Defecation was measured by number of boluses released during the test.

Experiment 3

In Experiment 3, the possible interactive effects of juvenile condition and long-term imipramine on behavior in an initial forced swimming test and open-field test were examined.

Subjects. Subjects included 16 JDES, 16 JSAL control, and 15 JUNT control female rats.

Procedure. At 9 weeks of age, animals were injected daily with 10 mg/kg imipramine or saline for 11 days. One hour following the last injection, animals were placed in a swim tank for 10 min.

At 2.5 months old, approximately 2.5 weeks after the forced swimming test, animals were injected with saline or imipramine (10 mg/kg) for 11 days. Animals received the same treatment that they received in the forced swimming test. Animals were tested for 10 min in an open field 1 h following the last injection.

RESULTS

Experiment 1

In the pretest, set 1 was less active (less struggling, more immobility) than set 2 ($p < 0.05$). Juvenile condition had no significant effect on behavior in the pretest.

In the subsequent 5-min test, the first and second groups tested displayed similar behavior. As shown in Fig. 1, imipramine increased struggling among all juvenile groups, $F(1, 38) = 43.184$, $p < 0.001$, and reduced immobility among JUNT and JSAL controls, $F(1, 38) = 9.436$, $p < 0.005$. Imipramine also reduced swimming among JUNT controls and JDES animals, $F(1, 38) = 18.467$, $p < 0.001$. There were no significant main or interactive effects of juvenile condition on behavior in the 5-min test.

Experiment 2

Forced swimming test. There were both main and interactive effects of short-term imipramine and juvenile condition on behavior in the initial 10-min forced swimming test. The interactive effects of imipramine and juvenile condition on struggling and immobility in the first 5 min of the initial 10-min test is shown in Fig. 2, $F(2, 35) = 4.562$, $p < 0.05$, $F(2, 35) = 4.946$, $p < 0.05$, respectively. JSAL controls responded to short-term imipramine with enhanced struggling and reduced immobility. In contrast, among JUNT controls short-term imipramine increased immobility. Both JSAL and JUNT controls responded to short-term imipramine administration with decreased time spent in the state of swimming [imipramine × juvenile condition interaction, $F(2, 35) = 3.475$, $p < 0.05$]. JDES animals showed no statistically significant response to short-term imipramine. A similar pattern of results was observed in the second 5 min of the swim test (data not shown).

Open-field test. The effect of imipramine and juvenile condition on open-field ambulation is shown in Fig. 3. Imipramine administration reduced the total number of squares entered, $F(1, 37) = 13.213$, $p < 0.005$, and the number of outer squares entered, $F(1, 37) = 19.045$, $p < 0.001$. Similar effects of imipramine on total and outer squares entered were observed in the first 5 min of the test, $F(1, 37) = 7.507$, $p < 0.01$, $F(1, 37) = 13.035$, $p < 0.005$, respectively. There was no main or interactive effect of juvenile condition on total or

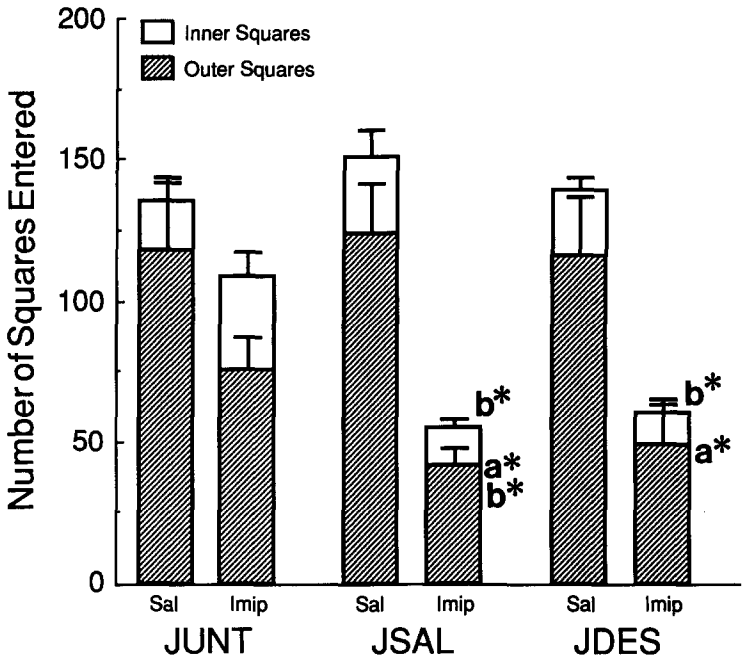

FIG. 3. Ambulation (mean) in a 10-min open-field test following short-term saline (Sal) or imipramine (Imip). SEM bars represent SEMs of inner- and outer-field ambulation. SEM of total (inner- + outer-field squares) ambulation not shown. a, different from saline-treated group; b, different from imipramine-treated JUNT. *$p < 0.05$.

outer squares entered. However, the smaller effect of imipramine among JUNT controls was not statistically significant.

There were no main effects of imipramine or juvenile condition on inner squares entered. However, there was a nonsignificant trend for an imipramine × juvenile condition interaction, $F(2, 37) = 3.175, p > 0.05 < 0.055$, which was also observed in the first 5 min of the test, $F(2, 37) = 3.198, p > 0.05 < 0.055$. Posthoc analyses indicate that imipramine-treated JUNT animals ambulated more in the inner field than the other imipramine-treated animals. In the first 5 min of the test, imipramine-treated JUNT animals also ambulated more in the inner field than saline-treated JUNT animals ($p < 0.05$).

Rearing was reduced with imipramine among all juvenile groups, $F(1, 37) = 23.823, p < 0.001$. There were no significant main or interactive effects of juvenile condition on rearing. Imipramine also tended to be associated with reduced defecation, but this effect was not statistically significant, $F(1, 37) = 3.442, p > 0.05 < 0.10$.

Experiment 3

Forced swimming test. As shown in Fig. 4, long-term imipramine enhanced struggling in the first 5 min of a an initial swim test among all juvenile conditions, $F(1, 41) = 22.651, p < 0.001$. Imipramine also reduced time spent in the state of swimming among all juvenile conditions in the first 5 min of the swim test, $F(1, 41) = 20.737, p < 0.001$. In the second 5 min of the test, imipramine administration was no longer associated with enhanced struggling but was still associated with reduced time spent swimming among all juvenile conditions, $F(1, 41) = 25.079, p < 0.001$. In the second 5 min of the test, long-term imipramine was also associated with increased immobility, $F(1, 41) = 9.345, p < 0.005$, but this only approached statistical significance ($p > 0.05 < 0.10$) among JUNT controls. There were no significant imipramine × juvenile condition interactions in this test.

Open-field test. The effect of imipramine and juvenile condition on open-field ambulation is shown in Fig. 5. There were no statistically significant effects of imipramine or juvenile condition on total squares entered, but there was a nonsignificant trend for a main effect of imipramine, $F(1, 41) = 3.072, p > 0.05 < 0.10$, and an imipramine × juvenile condition interaction, $F(2, 41) = 3.022, p > 0.05 < 0.10$. Imipramine administration was associated with a reduction in the number of outer squares entered. This effect failed to reach statistical significance in the entire 10-min test, $F(1, 41) = 3.491, p > 0.05 < 0.10$, but was significant in the second 5 min of the test, $F(1, 41) = 4.579, p < 0.05$. In both the entire 10-min test and in the second 5 min of the test, the effect of imipramine was only significant among JSAL controls.

Inner squares entered was influenced by an imipramine × juvenile condition interaction in the entire 10-min test, $F(2, 41) = 5.009, p < 0.05$, and in the first 5 min of the test, $F(2, 41) = 5.027, p < 0.05$. Posthoc analyses indicate that imipramine decreased inner-field ambulation among JSAL controls. In the first 5 min of the test, imipramine also tended ($p > 0.05 < 0.10$) to increase inner-field ambulation among JUNT controls.

Rearing in the 10-min test was influenced by a main effect of imipramine, $F(1, 41) = 6.687, p < 0.05$, and an imipramine × juvenile condition interaction, $F(2, 41) = 2.847, p > 0.05 < 0.10$ (data not shown). Similar main and interactive effects were observed in the first and second 5 min of

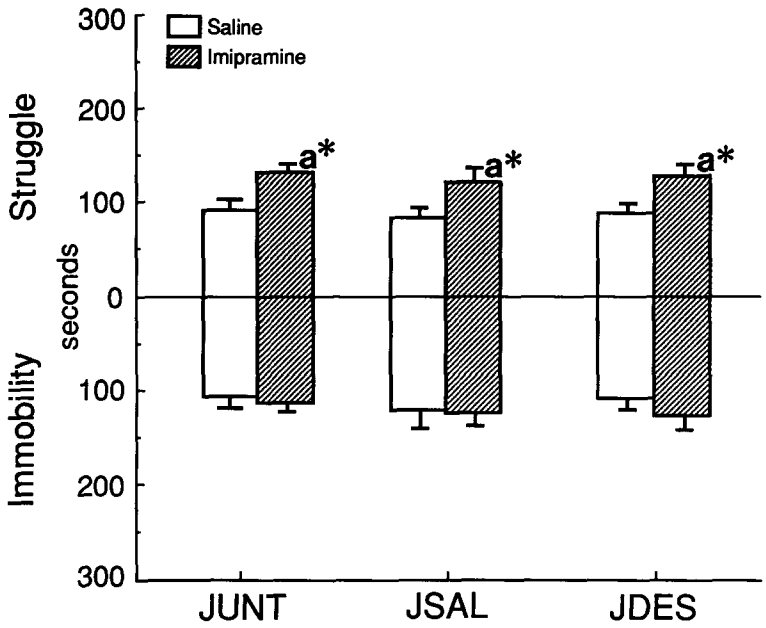

FIG. 4. Behavior (mean ± SEM) in the first 5 min of an initial 10-min swimming test following 11 daily injections of saline or imipramine. a, different from saline-treated group. *$p < 0.05$.

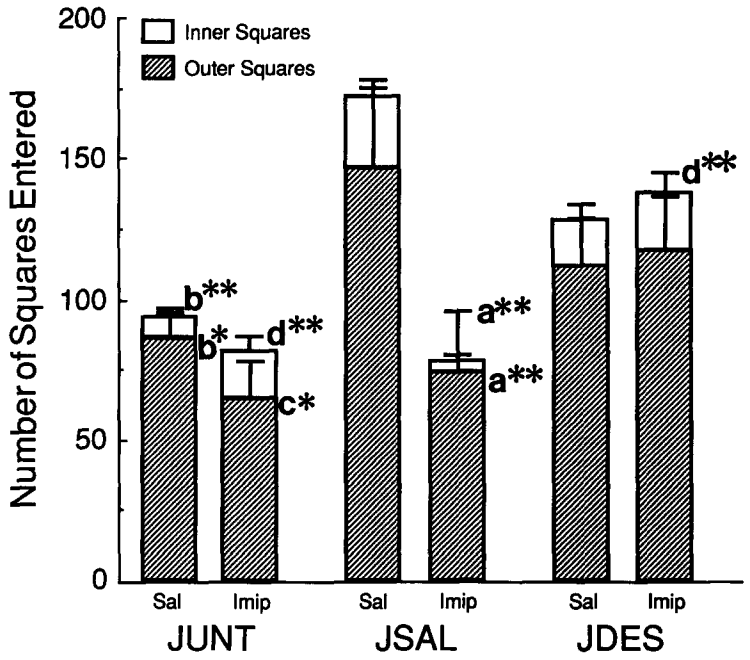

FIG. 5. Ambulation (mean) in a 10-min open-field test following 11 daily injections of saline (Sal) or imipramine (Imip). SEM bars represent SEMs of inner- and outer-field ambulation. SEM of total (inner- + outer-field squares) ambulation not shown. a, different from saline-treated group; b, different from saline-treated JSAL; c, different from imipramine-treated JDES; d, different from imipramine-treated JSAL. *$p > 0.05 < 0.10$, **$p < 0.05$.

the test. Posthoc analyses indicate that imipramine reduced rearing among JSAL controls in the first and second 5 min of the test ($p < 0.05$) and tended to reduce rearing among JUNT controls in the second 5 min of the test ($p > 0.05 < 0.10$). Long-term imipramine had no effect on the rearing of JDES animals.

There were no main effects of imipramine or juvenile condition on defecation in the open field, but there was a nonsignificant trend for an imipramine × juvenile condition interaction, $F(2, 41) = 3.088$, $p > 0.05 < 0.10$, whereby only JUNT animals showed a significant decrease in defecation with imipramine.

DISCUSSION

Contrary to our hypothesis, the behavior of untreated or saline-treated JDES animals in the forced swimming and open-field tests was fairly similar to that of JSAL controls. Further, there was no evidence of enhanced sensitivity to imipramine among JDES animals.

In two prior reports (9,13) of enhanced immobility among animals treated as juveniles with desipramine, nomifensine, or zimeldine, animals were tested in a swim tank larger than that used in the original forced swim procedure (22) and that used in the present studies (51 cm high, 40 cm in diameter vs. 40 cm high, 18 cm in diameter). Previously, we also found that JDES females, but not JDES males, showed more immobility than JSAL controls when tested in a large swim tank (6). Differences in strain, sex, and water temperature may also account for these discrepancies.

In the open-field tests, saline-treated JDES animals behaved similar to saline-treated JSAL controls. This is consistent with reports of no effect of juvenile clomipramine treatment on ambulation on initial exposures to the open field (7,19,20) but contrasts with the increased ambulation associated with juvenile clomipramine, desipramine, or zimeldine treatment reported by others (11,12). Recently, an age-dependent effect of juvenile clomipramine treatment in male rats on open-field ambulation was reported (8). We found a similar age-dependent effect of JDES treatment on ambulation among female rats such that 6.5-month-old JDES animals, but not 2.5-month-old JDES animals, ambulated more than age-matched JSAL controls (5). These findings suggest that JDES treatment may have long-term effects that only emerge gradually, perhaps with aging. This gradual onset of open-field hyperactivity and other changes associated with juvenile monoamine uptake inhibitor treatment has also been compared to the usual course of depression (29).

For the most part, the behavioral effects of imipramine are consistent with previous reports. Increased struggling and decreased immobility in the forced swimming test following a pretest and imipramine administration has been found by many investigators (3). Decreased swimming with imipramine is consistent with previous observations in this laboratory (unpublished observations) and with a report of decreased swimming with desipramine (1). The reduced ambulation in the open field with imipramine is consistent with previous studies (24).

There were also some surprising differences between the juvenile groups in their behavioral responses to imipramine. The effect of short-term imipramine was the same for the three juvenile conditions when preceded by a pretest exposure to the forced swimming test but was different for the three juvenile conditions when there was no prior pretest. Among JUNT controls, the effect of short-term imipramine when there was no pretest was different from that observed following a prior pretest. However, the effect of short-term imipramine among JSAL controls did not seem to be influenced by the presence or absence of a prior pretest exposure to the forced swimming test. JDES animals showed no evident effect of short-term imipramine when there was no prior pretest. A previous report indicated that the antiimmobility effect of imipramine did not depend upon a prior pretest, but the antiimmobility effect of desipramine and other antidepressants did depend upon a prior pretest (2). Another group also found that in the first 5 min of an initial exposure to the forced swimming test desipramine had no apparent antiimmobility effect, but desipramine did enhance struggling and reduce swimming in the first 5 min of this test (1).

In the open-field test, there appeared to be subtle differences in the effect of short- or long-term imipramine on inner- and outer-field ambulation between JUNT and JSAL controls. Among JSAL controls, imipramine acted primarily to reduce outer-field ambulation. In contrast, among JUNT controls imipramine appeared to have less effect on the outer-field ambulation and tended to increase inner-field ambulation. The open-field behavior of JDES animals was responsive to short-term imipramine but not to long-term imipramine.

The different responses to imipramine displayed by JUNT and JSAL controls could relate to the daily handling received by JSAL controls during injections. Handling in development has been shown to increase open-field activity and influence avoidance learning, spatial memory in old age, and presumed measures of emotionality in young adulthood (4,16). Handling also increases the efficiency of the adrenocortical response to stress in adulthood (17). Behavior in both the forced swimming and open-field tests may be modified by alterations in adrenocortical functioning (14,15,23,25,26,33). While handling provides a potential explanation for the differences observed between JUNT and JSAL controls, some important procedural differences distinguish the treatment of animals in this study from that of animals in handling studies. In contrast to handling studies (16), the "unhandled" JUNT controls had their dams briefly removed each day and were handled for cross-fostering. The "handled" JSAL controls were not handled until day 6 or 7. The discrepant behavioral responses to imipramine between JUNT and JSAL controls may also be due to the fact that JSAL controls, but not JUNT controls, had saline injections and JDES animals as cage mates during development. Regardless of the source of the differences between JUNT and JSAL controls, these findings indicate that the control group plays a critical role in interpreting the effect of juvenile treatment.

Contrary to our initial hypothesis, JDES animals showed no evidence of enhanced imipramine sensitivity in the forced swimming test or in the open-field test. In fact, in an initial exposure to the forced swimming test short-term imipramine did influence behavior of JUNT and JSAL controls but had no effect on JDES animals. In the open-field test, long-term imipramine influenced the behavior of JUNT and JSAL controls but had no effect on JDES animals. This reduced behavioral sensitivity to imipramine administration suggests that JDES treatment may permanently alter the neural mechanisms underlying antidepressant action. JDES treatment has been associated with enhanced levels of limbic 3-methoxy-4-hydroxphenylethyleneglycol-sulfate and diminished hypothalamic levels of dopamine, serotonin, and 5-hydroxyindoleacetic acid in adulthood (9).

Some investigators suggest that the adult behavioral alterations seen after juvenile monoamine uptake inhibitor administration are not the result of the monoamine uptake inhibitor

administration per se but a result of the rapid eye movement (REM) sleep disturbances associated with antidepressant administration (18-20,29,32). REM sleep was not monitored in this study, but previous studies have found that desipramine also disrupts REM sleep (27). If REM sleep disruption is involved in the mechanism by which JDES treatment reduces adult sensitivity to imipramine, then other agents that disrupt REM sleep may also alter sensitivity to imipramine. Many antidepressant treatments, including both those with and those without major monoamine uptake-inhibiting properties, have been found to disrupt REM sleep (27). It is plausible that early postnatal administration of other agents that disrupt REM sleep may also reduce adult sensitivity to the behavioral effects of antidepressants such as imipramine.

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