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A genetic mouse model of helplessness sensitive to imipramine

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Abstract

Lines of mice were selectively bred to diverge in their spontaneous helplessness in the tail suspension test. By the second generation of selection, only mice of the helpless line were sensitive to the antidepressant imipramine. Genetic factors substantially contribute to the susceptibility to helplessness in this mouse model. These selectively bred lines may represent potentially useful animal models to investigate behavioural, neurochemical and neuroendocrine correlates of antidepressant action.

Keywords: Selective breeding; Antidepressant; Depression, animal model

Most psychotropic drugs exert their beneficial actions in mentally ill patients but not in healthy humans. Thus, antidepressant drugs, when taken by a healthy person, induce nothing more than side effects, unrelated to an action on mood, whereas they alleviate depressive symptomatology in depressed patients. For animal experimentation aimed at screening antidepressants this has the following consequences: genetically and/or environmentally manipulated models would be closer to the clinical situation than models based on standard laboratory strains.

In the tail suspension test, immobility, which probably mimics a state of helplessness, is simply induced by suspending mice by the tail for short periods, i.e., placing them in an aversive situation (Stéru et al., 1985). Marked differences exist between strains of mice in both the amount of immobility observed and effects of the reference antidepressant drug imipramine in the tail suspension test (Van der Heyden et al., 1987). Although no effect of imipramine was observed in this test when using CD1 mice (Van der Heyden et al., 1987), recent results from our laboratory showed that imipramine is indeed active, provided that a preselection procedure was carried out to retain spontaneously 'helpless' CD1 mice.

The ability of imipramine to reduce immobility in mice selectively bred for a spontaneous high immobility score in the tail suspension test was studied.

Initially, 92 male and 58 female stock (S0) CD1 mice (Charles River, Saint-Aubin lès Elbeuf, France), weighing 17 ± 1 g when purchased, were tested for spontaneous 'helplessness'. Two pairs of mice with the highest immobility scores and two other pairs with the lowest immobility scores were intermated to begin the 'helpless' and 'non-helpless' lines, respectively. Pups were weaned from their mothers at 21–22 days. All mice from the first (S1) and second (S2) selected generations were tested in the tail suspension test, and those with the most extreme and stable behaviour appropriate to their line were chosen to serve as breeders (2–6 pairs in each line). In both directions of selection, non-sibling mating was used to obtain the S2 generation and further selection is in progress. The animals used here in the imipramine experiment were from S2. At all times, they were housed under a 7 a.m. to 7 p.m. day/night cycle with food and water ad libitum. When not used in experiments, they were kept in same-sex groups in Makrolon cages. Testing was performed between 9 a.m. and 5 p.m., using the computerized device ITEMATIC-TST developed by ITEM-LABO (Le Kremlin-Bicêtre, France; Porsolt et al., 1993). Mice were suspended for 6 min by the tail, using adhesive Scotch tape, to a hook connected to a strain gauge that transmitted all movements to a central unit which calculated the total duration of immobility.

The upper panel in Fig. 1 indicates the percentage of mice scoring ≥ 115 s (helpless) or ≤ 35 s (non-helpless) in the foundation population and in the first two generations of selective breeding. After one generation of selection there was a reduction of overlap in the distribution of immobility scores. In the second generation no mice from

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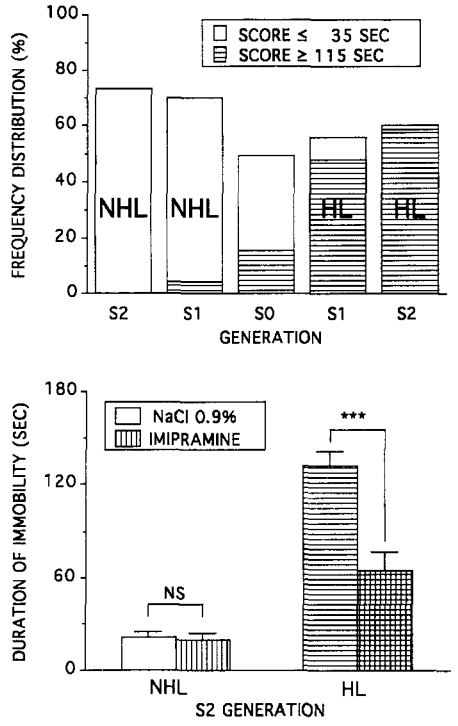

Fig. 1. Upper panel: Percentage of mice having immobility scores either ≥ 115 s (helpless) or ≤ 35 s (non-helpless) in the foundation population and in the first two generations of selective breeding of the helpless and non-helpless lines. *n* ranged from 67 to 140 mice tested under identical conditions per group. Lower panel: Effect of imipramine in mice selectively bred for their spontaneous helplessness in the tail suspension test. Mice from the two lines received in a random order either NaCl 0.9% or imipramine (30 mg/kg i.p.) 5 h and 30 min before the test in two trials performed a week apart. Data are mean ± S.E.M. values from 20 mice per group (10 males and 10 females in the helpless line and 12 males and 8 females in the non-helpless line). *** Statistically significant difference (Student *t*-test; $P < 0.001$) from saline values.

the non-helpless line but 59% of mice from the helpless line had a score ≥ 115 s.

Mice from this second generation were injected intraperitoneally 5 h and 30 min before the test with either vehicle (NaCl 0.9%) or the tricyclic antidepressant imipramine (Ciba-Geigy, France; 30 mg/kg, 0.2 ml per 20 g).

Imipramine induced a significant ($P < 0.001$) decrease in the immobility score in mice from the helpless line as compared to saline controls, whereas it was devoid of any effect ($P > 0.05$) in mice from the non-helpless line, as seen in the lower panel in Fig. 1.

In agreement with Trullas et al. (1989), who reported that significant differences in motor activity observed among inbred strains were unrelated to their immobility times in the tail suspension test, another experiment showed no significant differences in open field activity between the two selected lines.

These findings show that performance in the mouse tail suspension test is under specific genetic control. Interestingly, evidence from family and twin studies suggests that genetic factors play a role in the development of affective disorders (Kendler et al., 1994). Our results also demonstrate that animals prone to be helpless but not 'healthy' controls are sensitive to an antidepressant. Further antidepressant or non-antidepressant drugs would need to be tested before concluding that this helpless line is sensitive only to antidepressants. In that case, these selectively bred lines may provide a novel approach to investigate behavioural, neurochemical and neuroendocrine correlates of antidepressant action.

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