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Mouse strain differences in immobility and sensitivity to fluvoxamine and desipramine in the forced swimming test: Analysis of serotonin and noradrenaline transporter binding

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ABSTRACT

Strain differences in immobility time in the forced swimming test were investigated in five strains of mice, namely, ICR, ddY, C57BL/6, DBA/2 and BALB/c mice. There were significant strain differences. The immobility times of ICR, ddY and C57BL/6 mice were longer than those of DBA/2 and BALB/c mice. Immobility times were not significantly related to locomotor activity in these strains. There were also differences in sensitivity to the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. In ICR, ddY and C57BL/6 mice, fluvoxamine did not affect immobility time, while it reduced the immobility time of DBA/2 and BALB/c mice dose-dependently. The noradrenaline reuptake inhibitor desipramine decreased immobility time in all strains of mice. Serotonin (5-HT) transporter binding in the brains of all five strains of mice was also investigated. Analysis of 5-HT transporter binding revealed significant strain differences, being lower in DBA/2 and BALB/c mice than in other strains of mice. The amount of 5-HT transporter binding was correlated to baseline immobility time. However, there was no significant relation between noradrenaline transporter binding and immobility time. These results suggest that the duration of baseline immobility depends on the levels of 5-HT transporter binding, leading to apparent strain differences in immobility time in the forced swimming test. Furthermore, differences in 5-HT transporter binding may cause variations in responses to fluvoxamine.

1. Introduction

It is well known that serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline have important roles in emotion and are implicated in several psychiatric disorders, including depression and anxiety in humans (Briley and Moret, 1993; Wong et al., 1995). Recently, depression has been recognized as a common disease and many antidepressants are used to treat it. Neurotransmitters, especially 5-HT and noradrenaline, are closely related to depression, and many antidepressants act on serotonergic or noradrenergic neurons. Inhibition of 5-HT or noradrenaline reuptake improves depression by elevating the levels of these amines in the synaptic cleft (Briley and Moret, 1993). In addition, selective serotonin reuptake inhibitors (SSRIs) have very low affinities for adrenergic, dopaminergic, muscarinic, histaminergic H_1, opiate, GABAergic, and benzodiazepine receptors, thereby avoiding any side effects based on these receptors (Figgitt and McClellan, 2000; Hyttel, 1994; Owens et al., 1997).

The forced swimming test in mice is widely used for the evaluation of antidepressants, as it is a simple, reliable and useful test (Porsolt et al., 1977). Many previous reports indicate that immobility (termed behavioral despair by Porsolt) in the forced swimming test is decreased by treatment with various antidepressants (Porsolt et al., 1977). We also reported that tricyclic antidepressants, including imipramine and clomipramine, and noradrenaline reuptake inhibitors like maprotiline or desipramine, reduce immobility time in mice (Yamada and Sugimoto, 2002).

SSRIs are available for the treatment of several psychiatric diseases, such as panic disorder, obsessive compulsive disorder and depression (Figgitt and McClellan, 2000; Wagstaff et al., 2002). Although the forced swimming test has been used to evaluate the efficacy of antidepressants, SSRIs have a weak effect on the immobility time of mice in this test. By contrast, drugs that can inhibit reuptake of noradrenaline, apparently induce anti-immobility effects (Detke et al., 1995; Sanchez and Meier, 1997; Yamada and Sugimoto, 2002). It was reported that imipramine,

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which inhibits both 5-HT and noradrenaline reuptake, reduces immobility time more potently than SSRIs (Sanchez and Meier, 1997).

Recent reports suggest that there are mouse strain differences in immobility time and responses to antidepressants in the forced swimming test (David et al., 2003; Lucki et al., 2001). Mouse strain differences in the efficacy of antidepressants in the tail suspension test, another behavioral test for the evaluation of antidepressants, have been reported (Ripoll et al., 2003). Therefore, genetic differences in behavioral tests of depression have been demonstrated in mice. However, it is not yet clear why there are strain differences in these behavioral tests and why differences in immobility time in the forced swimming test occur in mice.

SSRIs and noradrenaline reuptake inhibitors strongly bind the 5-HT and noradrenaline transporters, respectively, leading to accumulation of 5-HT and noradrenaline, and improvement of depression (Briley and Moret, 1993). Therefore, mouse strain differences in immobility time and responses to antidepressants may be related to differences in 5-HT and noradrenaline transporter binding. However, there has been no report examining 5-HT and noradrenaline transporter binding in various mouse strains. In the present study, we examined immobility time and locomotor activity in five strains of mice, namely, ICR, ddY, C57BL/6, DBA/2 and Balb/c mice, and the effects of the SSRI fluvoxamine and the noradrenaline reuptake inhibitor desipramine in these mice. Furthermore, we analyzed 5-HT and noradrenaline transporter binding in all five strains of mice and studied the relationship between immobility, locomotor activity, responses to fluvoxamine and desipramine, and 5-HT and noradrenaline transporter binding.

2. Materials and methods

2.1. Animals

Male ICR, ddY, C57BL/6Cr, DBA/2Cr and BALB/cCr mice, aged 5–7 weeks, were purchased from SLC Japan Inc (Japan). Mice were housed in groups of five mice under a controlled 12-h/12-h light–dark cycle (light from 7:00 a.m. to 7:00 p.m.), with the room temperature at 23±1 °C and humidity at 55±5%. The mice were given free access to food and water. Each mouse was only used once. Experiments were performed in accordance with the Guiding Principles for Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society.

2.2. Forced swimming test

The forced swimming test was performed according to the methods described by Porsolt et al. (1977) and our previous report (Yamada and Sugimoto, 2002). Each mouse was placed in a 25-cm glass cylinder (10-cm diameter) containing 10 cm of water at 23±1 °C. Immobility was recorded during a 6-min swimming test. A mouse was judged to be in immobile when it floated and its hindlimbs were immobile, and only small movements of forepaws were made to keep the head above the water level.

2.3. Drugs and treatment

Fluvoxamine maleate and desipramine HCl were purchased from Sigma and dissolved in saline. Fluvoxamine (5–20 mg/kg) and desipramine (10–40 mg/kg) were injected i.p. Mice in the control group received saline. Thirty minutes after treatment with fluvoxamine or desipramine, the forced swimming test was performed.

2.4. Measurement of locomotor activity

The locomotor activity of mice was measured using a digital counter with an infrared sensor (NS-AS01, Neuroscience Inc., Japan) following the method described in previous reports (Yamada et al., 2004). An infrared sensor was set over an open-top clear polycarbonate cage (22.5×33.8×14.0 cm) into which each mouse was placed. Locomotor activity was determined over a period of 10 min. The apparatus detects and records a digital count of the horizonal movements of animals.

2.5. Measurements of specific binding of 5-HT and noradrenaline transporters

The binding assay for 5-HT and noradrenaline transporters in brain homogenates from mice was performed using [^{3}H]paroxetine and [^{3}H]nisoxetine, respectively, as previously described (Habert et al., 1985; Tejani-Butt et al., 1990). Mice were decapitated and brains were removed and stored at −80 °C until analysis. Brain tissue was homogenized in 19 volumes of 50 mM Tris–HCl buffer (pH 7.4)

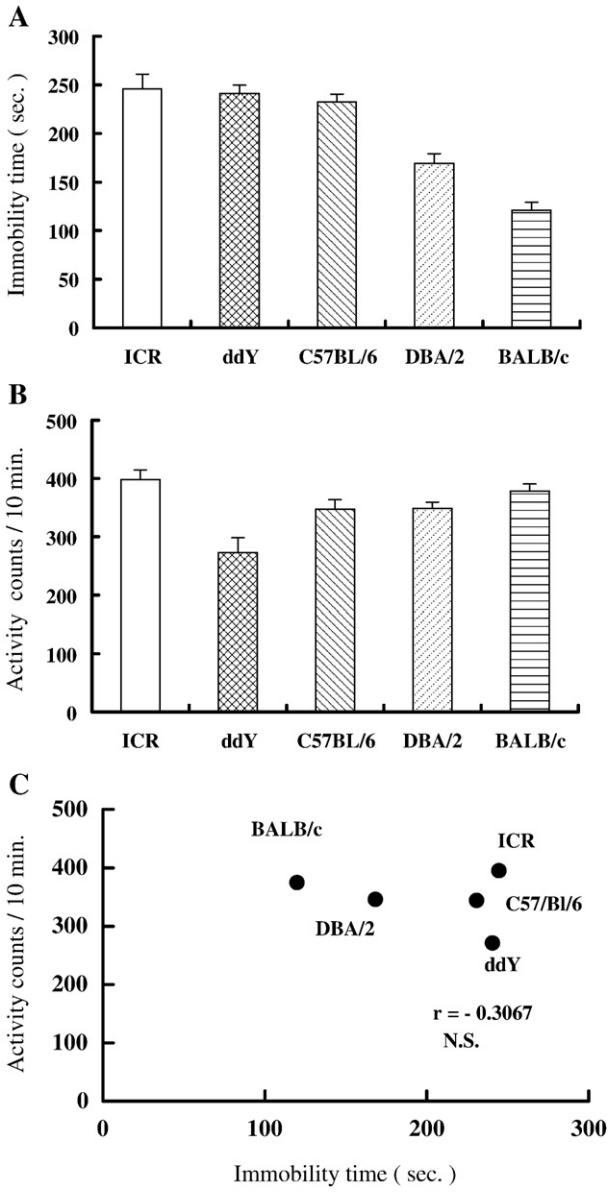

Fig. 1. Immobility time in the forced swimming test and locomotor activity in five strains of mice. (A) Immobility time in the forced swimming test. Results are shown as means±S.E.M. (N=7–9). A significant difference among the five strains of mice was revealed by ANOVA [$F(4, 34)=31.84$, $P<0.001$]. (B) Locomotor activity in five strains of mice. Results are shown as means±S.E.M. (N= 7–8). A significant difference among the five strains of mice was revealed by ANOVA [$F(4, 33)=7.67$, $P<0.001$]. (C) Correlation between immobility time and locomotor activity in five strains of mice.