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Association between tryptophan hydroxylase-2 genotype and the antidepressant effect of citalopram and paroxetine on immobility time in the forced swim test in mice

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ABSTRACT

Tryptophan hydroxylase-2 (TPH2) is the rate limiting enzyme of serotonin synthesis in the brain. The 1473G allele of the C1473G polymorphism in m*TPH2* gene is associated with reduced enzyme activity and serotonin synthesis rate in the mouse brain. Here, the influence of the 1473G allele on the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs), citalopram (2.5 or 5.0 mg/kg) and paroxetine (5.0 or 10.0 mg/kg), in the forced swim test was studied using B6-1473G and B6-1473C congenic mouse lines with the 1473G (decreased TPH2 activity) or 1473C (normal TPH2 activity) alleles, respectively, transferred to the genome of C57BL/6 mouse strain. Paroxetine (5.0 or 10.0 mg/kg) and citalopram (2.5 or 5.0 mg/kg) decreased immobility time in B6-1473C mice, while both doses of paroxetine and 2.5 mg/kg of citaloprame did not alter immobility time in B6-1473G mice. However, 5.0 mg/kg of citalopram reduced immobility in B6-1473G mice. The results provided genetic evidence of moderate association between 1473G allele and reduced sensitivity to SSRIs in mice.

1. Introduction

Depressive disorders are among the most disabling medical illnesses. As much as 12% of men and 21% of women have a lifetime risk of depression (Dudek, 2003). Depressive illnesses are associated with increased risk of disability and suicide (Remick, 2002). There is the great progress in the pharmacotherapy of depression, and over 30 antidepressants are present on the market, among them the selective serotonin (5-HT) reuptake inhibitors (SSRIs) prevail. The SSRIs inhibit the 5-HT reuptake and, thereby, increase 5-HT concentration in synaptic cleft and prolong its effect on the postsynaptic receptors. At the same time, about 20–40% of depressive patients are resistant to SSRI treatment (Remick, 2002; Fava, 2003).

Tryptophan hydroxylase-2 (TPH2) is the rate-limiting enzyme of 5-HT synthesis in the brain (Walther et al., 2003; Walther and Bader, 2003) and its inhibition (Koe and Weissman, 1966; Mehta et al., 2003; Dailly et al., 2006; Kornum et al., 2006) or *TPH2* gene knockout (Gutknecht et al., 2008; Savelieva et al., 2008; Alenina et al., 2009) dramatically decreases of 5-HT level in the brain. Some authors reported an association between human TPH2 gene (*hTPH2*) and therapeutic response to SSRIs (Peters et al., 2004; 2009; Tzvetkov et al., 2008; Tsai et al., 2009; Schosser and Kasper, 2009). The 1463A allele of the G1463A polymorphism in the 11th exon of *hTPH2* gene reduced TPH2 activity and antidepressant effect of SSRIs (Zhang et al., 2005).

A mouse analog of the G1463A polymorphism in the *hTPH2* gene is the C1473G polymorphism in the 11th exon of the mouse TPH2 gene (m*TPH2*) (Zhang et al., 2004; 2006). This polymorphism results in the Pro447Arg substitution in TPH2 molecule and reduction of the enzyme activity in vitro (Zhang et al., 2004; Sakowski et al., 2006) and in the mouse brain (Zhang et al., 2004; Kulikov et al., 2005; 2007; Osipova et al., 2009; Siesser et al., 2010).

The forced swim test (FST) is the most widely and most frequently used test for antidepressant activity (Borsini and Meli, 1988; Willner, 1990; Borsini, 1995; Lucki, 1997; Willner and Mitchell, 2002; Tecott, 2003; Cryan and Mombereau, 2004; Petit-Demouliere et al., 2005; Yacoubi and Vaugeois, 2007). The test is based on the observation that mice or rats following initial escape-oriented movements (swimming and climbing), develop an immobility posture in an inescapable vessel filled with water. The majority of clinically effective antidepressants, given prior to the test, decreased immobility time (Porsolt et al., 1977; 1978; Borsini and Meli, 1988; Willner, 1990; Willner and Mitchell, 2002). Genetic factors alter drug effect on immobility time in the FST (Lucki et al., 2001; David et al., 2003; Petit-Demouliere et al., 2005).

Abbreviations: TPH2, tryptophan hydroxylase-2; 5-HT, serotonin; SSRIs, selective serotonin reuptake inhibitors; FST, forced swim test.

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The SSRIs citalopram (Cervo et al., 2005) and paroxetine (Guzzetti et al., 2008) reduced significantly immobility time in the FST in mice homozygous for 1473C allele (C57BL/6 and 129/Sv), but not in mice homozygous for 1473G allele (DBA2 and BALB/c). Activation of 5-HT synthesis in DBA2 and BALB/c mice with L-tryptophan increased, while inhibition of TPH2 in C57BL/6 and 129/Sv mice with p-chlorophenylalanine reduced the antidepressant effect of these drugs in the FST (Cervo et al., 2005; Guzzetti et al., 2008). These results were considered as pharmacological evidence of the association between the C1473G polymorphism and the antidepressant effect of SSRIs in the FST in mice (Invernizzi, 2007). However, besides the 1473G allele of *mTPH2* gene, DBA2 and BALB/c strains differ from C57BL/6 and 129/Sv strains in a great number of other genes potentially implicated in the resistance to SSRIs and these studies have not rule out the possibility that these strain differences result from variation in other genes. This problem could be solved using congenic mouse lines with the 1473C and 1473G alleles transferred to the same genetic ground (Zhang et al., 2006).

Recently, the 1473G allele was transferred to the genome of C57BL/6 mice, and two mouse lines B6-1473G and B6-1473C were created. B6-1473G mice had decreased TPH2 activity in the brain and immobility in the FST compared with B6-1473C mice (Osipova et al., 2009).

The aim of the present study was to test the hypothesis on genetic association between the C1473G polymorphism and response to SSRIs. It was intended to compare the effect of citalopram and paroxetine on behavior of B6-1473G and B6-1473C mice in the FST.

2. Materials and methods

2.1. Experimental animals

Experiments were carried out on adult mouse males (10–14 weeks old, weighing 25 ± 2 g) of the B6-1473C (n = 59) and B6-1473G (n = 60) lines. The partially congenic B6-1473G and B6-1473C lines were bred from F_1 hybrids between C57BL/6J (C/C) and CC57BR/Mv (G/G) strains using three successive crossings of heterozygous males with females of C57BL/6J strain. The heterozygous backcrosses of the third generation were intercrossed to generate B6-1473C and B6-1473G progeny with C/C and G/G genotypes, respectively, and the same genetic background consisting of 94% of C57BL/6-derived alleles and 6% of CC57BR-derived alleles of other genes that do not link to the *mTPH2* gene (Osipova et al., 2009).

After weaning mice were separated by sex and kept by 10 per cage (40 × 25 × 15 cm) until age of 3–4 months under standard conditions (temperature: 18–22 °C, relative humidity: 50–60%, standard food and water ad libitum). Two days before the experiment animals were isolated in cages of the same size to eliminate group effects.

All experimental procedures were in compliance with European Communities Council Directive of 24 November 1986 (86/609/EEC). All efforts were made to minimize the number of animals used and their suffering.

2.2. Drugs and treatments

Citalopram (2.5 or 5.0 mg/kg, Sigma-Aldrich, St Louis, MO, USA) and paroxetine (5.0 or 10.0 mg/kg, Sigma-Aldrich, St Louis, MO, USA) were diluted in saline and injected i.p. 40 min prior to the FST. The choice of these doses was based on the papers of Cervo et al. (2005) and Guzzetti et al. (2008) who showed that these doses decreased immobility time in C57BL/6 and 129/Sv mice, but not in BALB/c and DBA/2 mice. Saline was injected as a control. Each experimental group contained 9–10 animals.

2.3. The FST procedure

The FST immobility was assayed in a plastic box 15 × 15 × 25 cm containing 20 cm water at 25 °C. The box was illuminated through the semitransparent bottom with a halogen lamp of 12 W. The light from the lamp diffused by semitransparent floor was transmitted through water to the objective of a digital camera (Sony) placed at 80 cm above the box. The transmitted lighting provides the maximal possible contrast between animal and water and reduces the glares of light reflecting from water surface. The camera was connected to an IBM compatible computer with CPU clock speed of 2 GHz through IEEE1394 interface. The video stream from the camera was analyzed frame-by-frame using original EthoStudio software (http://www.EthoStudio.com). We used the same FST protocol as Cervo et al. (2005) and Guzzetti et al. (2008) and the time of immobility was recorded during the last 4 min of the 6-min testing period, after 2 min of habituation. The tests were performed by the same well-trained rater blind to the genotype and the treatment. A mouse was judged to be immobile when it floated and made only small movements to keep its head above water. Struggling was defined as vigorous climbing movements. Immobility and struggling time (s) were calculated with EthoStudio software. Swimming time (s) was calculated as the difference between total test time (240 s) and the sum of immobility time and struggling time (Mason et al., 2009). In addition to the visual procedure the immobility time of each animal was re-evaluated with original automated procedure providing the objective and precise measurement of immobility time using alterations of mouse silhouette (Kulikov et al., 2010).

2.4. Statistics

All values were presented as means ± SEM. The visually evaluated time of immobility, struggling and swimming were compared with two-way ANOVA followed by Newman–Keuls post-hoc comparisons. The automatically evaluated data were compared with the distribution-free permutation test to decrease risk of false positives (Kulikov et al., 2010).

3. Results

3.1. Effect on immobility time

In the experiment with citalopram, a significant effect of a dose ($F_{2,54} = 10.7$, $p < 0.001$) on immobility time was shown. Both 2.5 mg/kg ($p < 0.01$) and 5.0 mg/kg ($p < 0.05$) doses of citalopram significantly decreased immobility time in B6-1473C mice, but the drug attenuated immobility time in B6-1473G mice only at the dose of 5.0 mg/kg ($p < 0.05$), but not at the dose of 2.5 mg/kg (Fig. 1A). No effect of genotype ($F_{1,54} < 1$, $p > 0.05$) and genotype × dose interaction ($F_{2,54} = 1.5$, $p > 0.05$) on immobility time was revealed.

In the experiment with paroxetine, a significant effect of a dose ($F_{2,53} = 8.0$, $p < 0.001$) on immobility time was shown. Both 5.0 mg/kg ($p < 0.01$) and 10.0 mg/kg ($p < 0.01$) doses of paroxetine significantly decreased immobility time in B6-1473C mice, but these doses of paroxetine did not alter immobility time in B6-1473G mice (Fig. 2A). No effect of genotype ($F_{1,53} < 1$, $p > 0.05$) and genotype × dose interaction ($F_{2,53} = 1.3$, $p > 0.05$) on immobility time was revealed.

The results of visual registration were confirmed by automated registration. Both citalopram (Fig. 1B) and paroxetine (Fig. 2B) significantly reduced automatically evaluated immobility time in B6-1473C mice ($p = 0.03$ for citalopram and $p = 0.01$ for paroxetine), but not in B6-1473G mice ($p > 0.05$).

3.2. Effect on struggling and swimming

Control mice of both genotypes seldom showed struggling behavior. Time of struggling in four control groups of animals did not differ significantly from zero. Citalopram at the dose of 2.5 mg/kg ($F_{2,54} = 4.2$, $p < 0.02$), but not paroxetine ($F_{2,53} = 1.7$, $p > 0.05$) increased significantly the time of struggling in B6-1473C mice (Table 1).

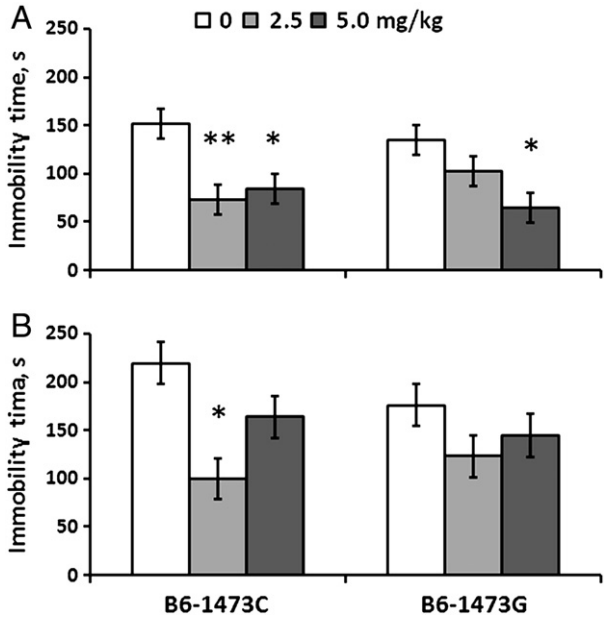

Fig. 1. Visually (A) and automatically (B) evaluated immobility time (s) in the FST in B6-1473G and B6-1473C mice treated with saline, 2.5 mg/kg or 5.0 mg/kg of citalopram. Saline or citalopram was injected i.p. 40 min prior the test. Immobility time was recorded for 240 s after 120 s of adaptation period. Each bar presents mean ± SEM of 10 animals. *p<0.05, **p<0.01 vs. corresponding saline-treated control.

In the experiment with citalopram a significant effect of a dose on swimming time ($F_{2,54}=5.6$, $p<0.01$) was demonstrated. Citalopram at the doses of 2.5 mg/kg ($p<0.01$) and 5.0 mg/kg ($p<0.05$) significantly increased swimming time in B6-1473C mice. At the same time, the drug increased swimming time in B6-1473G mice only at the dose of 5.0 mg/kg ($p<0.05$), but not at the dose of 2.5 mg/kg ($p>0.05$) (Table 1). No significant effect of genotype ($F_{1,54}<1$, $p>0.05$) and genotype × dose interaction ($F_{2,54}<1$, $p>0.05$) on swimming in the FST was shown.

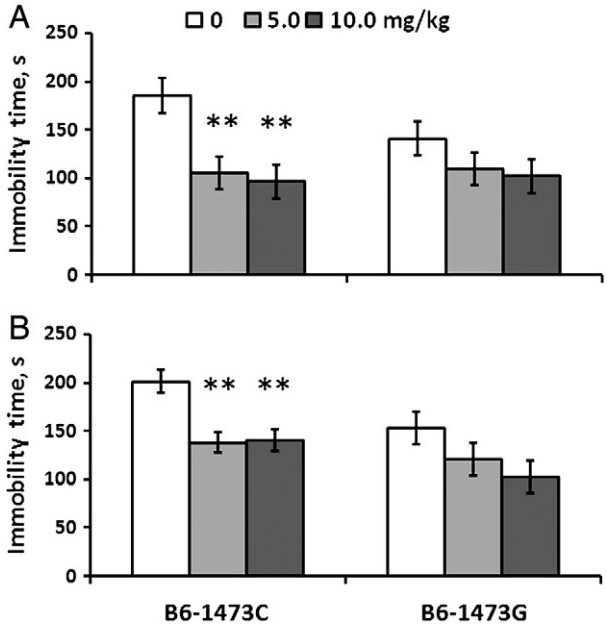

Fig. 2. Visually (A) and automatically (B) evaluated immobility time (s) in the FST in B6-1473G and B6-1473C mice treated with saline, 5.0 mg/kg or 10.0 mg/kg of paroxetine. Saline or paroxetine was injected i.p. 40 min prior the test. Immobility time was recorded for 240 s after 120 s of adaptation period. Each bar, except for the B6-1473C control, presents mean ± SEM of 10 animals. The bar of the B6-1473C control presents mean ± SEM of 9 animals. **p<0.01 vs. saline-treated B6-1473C mice.

Table 1
Effect of citalopram or paroxetine on struggling time (s) and swimming time (s) in the FST in B6-1473C and B6-1473G mice.

Doses (mg/kg, ip)	B6-1473C		B6-1473G	
	Struggling, s	Swimming, s	Struggling, s	Swimming, s
Citalopram				
0	2.7 ± 10.0	85.9 ± 13.3	11.5 ± 10.0	93.2 ± 13.3
2.5	40.0 ± 10.0**	126.8 ± 13.3*	24.6 ± 10.0	112.7 ± 13.3
5.0	28.1 ± 10.0	127.3 ± 13.3*	36.6 ± 10.0	138.4 ± 13.3*
Paroxetine				
0	7.4 ± 11.0	46.5 ± 14.6	8.1 ± 10.4	90.7 ± 13.8
5.0	21.6 ± 10.4	112.6 ± 13.8*	18.3 ± 10.4	112.1 ± 13.8
10.0	17.8 ± 10.4	125.6 ± 13.8**	35.9 ± 10.4	102.0 ± 13.8

*p<0.05, **p<0.01 vs corresponding control (0 mg/kg).

In the experiment with paroxetine a significant effect of a dose on swimming ($F_{2,53}=6.6$, $p<0.01$) was demonstrated. Both doses of paroxetine significantly increased swimming time ($p<0.01$) in B6-1473C, but not in B6-1473G mice (Table 1). No effect of genotype ($F_{1,53}<1$, $p>0.05$) and genotype × dose interaction ($F_{2,53}=3.0$, $p>0.05$) on swimming was revealed.

Significant negative correlations between immobility and struggling ($r=-0.63$, $p<0.01$ for citalopram and $r=-0.59$, $p<0.01$ for paroxetine) and immobility and swimming ($r=-0.82$, $p<0.001$ for citalopram and $r=-0.84$, $p<0.001$ for paroxetine) were shown. At the same time, correlation between struggling and swimming was not significant ($r=0.07$, $p>0.05$ for citalopram and $r=0.05$, $p>0.05$ for paroxetine).

4. Discussion

The present study was aimed to re-examine the association between C1473G polymorphism and sensitivity to citalopram and paroxetine using B6-1473C (C/C) and B6-1473G (G/G) congenic mouse lines with similar genetic background and reduced uncontrolled genetic variation in other genes (Osipova et al., 2009).

Both doses of citalopram and paroxetine reduced immobility time in B6-1473C mice. At the same time, low dose (2.5 mg/kg) of citalopram and both doses of paroxetine failed to attenuate immobility time in B6-1473G mice. Only relatively high dose of citalopram (5.0 mg/kg) produced antidepressant effect on immobility of B6-1473G mice. The resistance of B6-1473G mice to citalopram and paroxetine shown using visual evaluation of the immobility was confirmed with objective automated evaluation of immobility time. The drug-induced alteration in swimming of B6-1473C and B6-1473G mice corresponded to the alterations in their immobility time. It was shown that all used doses of citalopram and paroxetine increased swimming time in the 1473C allele carriers, while all doses of paroxetine and low dose of citalopram failed to increase swimming in B6-1473G mice. Struggling was a minor type of behavior in the FST, seldom observed in the control mice and less sensitive to citalopram and paroxetine compared with immobility and swimming. In the present study significant negative correlations between immobility and struggling as well as between immobility and swimming were found. Therefore, struggling and swimming provided no additional information compared with immobility time. In the contrast to Cervo et al. (2005) and Guzetti et al. (2008), in the present study no effect of the genotype × dose of citalopram or paroxetine interaction on immobility or swimming time was shown and, therefore, C1473G polymorphism did not seem to be the key factor defining sensitivity to SSRIs.

The tail suspension test (TST) is another commonly used test for antidepressant activity. Many antidepressants reduce immobility time

in the TST (Cryan et al., 2005). Brain 5-HT is involved in the regulation of immobility in the TST (O'Leary et al., 2007). Recently, Siesser et al. (2010) using four congenic mouse strains with the 1473C and 1473G alleles transferred to the BALB/c and C57BL/6 genomes, respectively, did not find any association between the C1473G polymorphism and the response to 5 mg/kg of escitalopram in the TST. However, this dose of escitalopram corresponding to 10 mg/kg of citalopram was too high to show the difference in the drug effect on the 1473C and 1473G alleles carriers. In our study, we found the difference in the antidepressant effect of citalopram on FST immobility time between B6-1473G and B6-1473C mice at relatively low dose of 2.5 mg/kg, while higher dose of 5 mg/kg significantly reduced immobility in mice of both genotypes.

Although acute SSRIs administration reduced immobility time in the FST, several weeks of treatment were needed for the therapeutic effect (Blier, 2003). Recently, it was shown that in mice of BALB/cJ, BALB/cByJ and SEA/GnJ strains homozygous for the 1473G allele a chronic (four weeks) administration of citalopram was needed to decrease significantly immobility time in the FST (Jiao et al., 2011). This finding supported the idea of lowered sensitivity to citalopram in 1473G allele carriers.

It is commonly accepted that the antidepressant effect of acute SSRIs treatment results from the increase of 5-HT concentration in the synaptic cleft. Inbred mice homozygous for 1473G allele showed 20–40% reduction in the basal extracellular 5-HT concentration in the brain compared with inbred mice homozygous for 1473C allele. Citalopram produced dose-dependent increase in extracellular 5-HT in inbred mice homozygous for 1473C allele, but had significantly less effect in inbred mice homozygous for 1473G allele. A tryptophan load enhanced basal extracellular 5-HT in the brain of homozygous for 1473G allele mice but did not affect ability of citalopram to raise extracellular 5-HT (Calcagno et al., 2007). It could be hypothesized that 1473G allele decreasing 5-HT synthesis in mouse brain suppresses the SSRI-induced accumulation of 5-HT in the synaptic cleft and, therefore, attenuates the antidepressant effect of extracellular 5-HT on immobility in the FST.

Thus, the result of the present study agreed with the observations of other authors (Cervo et al., 2005; Guzzetti et al., 2008) and indicated the implication of the C1473G polymorphism in the regulation of the antidepressant-like effect of SSRIs on immobility time in the FST. At the same time, this polymorphism does not seem to be crucial for SSRI treatment and antidepressant-like effect of citalopram on the behavior in the FST in mice homozygous for 1473G allele can be achieved with increased dose of the drug and/or treatment time.

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