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SHORT COMMUNICATION

Serotonin transporter promoter region polymorphisms do not influence treatment response to escitalopram in patients with major depression

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Abstract

Several studies and meta-analyses have implicated a polymorphism in the promoter region of the serotonin transporter (5-HTT) gene, 5-HTTLPR in treatment outcomes of selective serotonin re-uptake inhibitors in patients with major depression. In this study we investigated the impact of 5-HTTLPR and a functional SNP rs25531 on the treatment outcomes to escitalopram in depressive patients. The study sample consisted of 135 outpatients with major depressive disorder (mean age 31.1 ± 11.6 years, 68% females) treated with escitalopram 10–20 mg/day for 12 weeks. There were no significant associations between 5-HTT promoter region polymorphisms and response rate or mean change of depressive symptoms during escitalopram treatment. However we showed that patients carrying S allele of 5-HTTLPR may have increased risk for some side effects, including headache, induced by escitalopram medication.

1. Introduction

It is difficult in clinical practice to predict which patients will respond well to any particular pharmacological treatment despite such predictions having the potential to help clinicians avoid lengthy ineffective medication trials and to reduce patients' exposure to drug side effects (Malhotra

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et al., 2007). The serotonin transporter (5-HTT) gene has become a main target for pharmacogenetic studies in affective disorders due to its being the target of therapeutic effects of many antidepressants. Several studies have implicated a polymorphism in the promoter region of the 5-HTT gene, 5-HTTLPR, in therapeutic outcomes to treatment with selective serotonin re-uptake inhibitors (SSRIs). In particularly there was reported that the more highly expressed variant, the long allele (L), of this polymorphism was associated with better clinical response in Caucasian subjects, although the opposite finding has been observed in Asian populations (for review Serretti et al., 2008). These findings were not replicated in the largest sample of depressive patients, those from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, where no association between response to citalopram and 5-HTTLPR was found (Kraft et al., 2007). Recently, Serretti et al. (2007) performed a meta-analysis of 5-HTTLPR effect on the antidepressant treatment based on 15 available studies including data of 1435 subjects. The results of this meta-analysis confirmed the significant, and independent from ethnic differences, association of the L variant of 5-HTTLPR with a better response to SSRIs whereas the subjects with SS genotype had difficulties to reach remission. Additionally, the meta-analysis of 5-HTTLPR on the SSRIs-induced side effects in 2323 patients showed significantly reduced risk of adverse effects for the L allele (Kato and Serretti, 2008). Taken together these mentioned studies indicated 5-HTTLPR polymorphism as possible predictor for both treatment response and intolerance to SSRIs.

More recently, two subtypes of the L allele have been described, whereas L variant with an adenosine at SNP rs25531 (La) has been reported to have higher activity than the long variant with a guanine at rs25531 (Lg) (Hu et al., 2006). Earlier, rs25531 SNP has been associated with treatment outcomes to SSRI fluoxetine (Kraft et al., 2005; Peters et al., 2004). However, no evidence of association between genotype at the rs25531 SNP and remission to SSRI citalopram was found in depressive patients derived from STAR*D trial (Mrazek et al., 2008). Nevertheless, the side effect burden analyzing in STAR*D sample showed that subjects carrying the low-expression S or Lg alleles were more likely to experience citalopram adverse effects (Hu et al., 2007).

Escitalopram, the S-enantiomer of citalopram, is a SSRI that binds to both the primary site on the 5-HTT as well as to an allosteric site that greatly augments the efficacy of the inhibition of serotonin reuptake (Sanchez et al., 2004). It has been shown to be significantly superior yet with improved tolerability compared with conventional SSRIs (Kennedy et al., 2006). Moreover higher 5-HTT occupancy in midbrain was found after multiple dose administration of 10 mg/day escitalopram compared with 20 mg/day citalopram despite similar plasma concentrations of the S-enantiomer (Klein et al., 2007). These results can also be explained by an attenuating effect of R-citalopram on the occupancy of S-citalopram at the 5-HTT. Considering this unique action mechanism of escitalopram we aimed in current study to investigate the possible impact of 5-HTT promoter region polymorphisms on its treatment response and side effects in patients with major depression who were participated in our recent clinical trial (Maron et al., in press).

2. Methods

2.1. Subjects

The study sample consisted of 135 outpatients with Major Depressive Disorder, MDD (mean age 31.1 ± 11.6 years, 68% females) recruited at the Psychiatry Clinic of the Tartu University Hospital in Tartu, Estonia. The diagnosis according to DSM-IV criteria was verified using Mini International Neuropsychiatric Interview (M.I.N.I. 5.0.0) and substantiated by psychiatric history and medical records. At least moderate severity of depression was required for inclusion as indicated by a Montgomery–Asberg Depression Rating Scale (MADRS) total score of 22 or higher. MDD patients with a secondary current comorbid anxiety disorder were included in this study, except for obsessive–compulsive disorder, posttraumatic stress disorder, or panic disorder, and these comprised 51% of the sample. Patients were excluded if they met diagnostic criteria for any of the following: bipolar disorder, psychotic disorder or features, current eating disorders, mental retardation, any pervasive developmental disorder or cognitive disorder, or alcohol or drug abuse-related disorders within 12 months prior to baseline. Additional exclusion criteria were acute infections, neurological or any other unstable general disorders, serious suicide risk, formal behaviour therapy, or systematic psychotherapy, pregnancy or breastfeeding. None of patients was known to have history of hypersensitivity or non-response to escitalopram or other SSRIs. The majority of the patients were of Estonian ethnicity (96%), exclude ethnic stratification in our study. The Human Studies Ethics Committee of the University of Tartu and State Agency of Medicines had approved the study protocol, and all participants provided written informed consent.

2.2. Treatment and clinical assessment

The patients were treated with escitalopram 10–20 mg/day for 12 weeks using open-label, placebo non-controlled study design as was described earlier (Maron et al., in press). No other medications, including anti-inflammatory drugs, were allowed during the study, except of hormonal contraceptives and zolpidem or zopiclone for insomnia. Clinical severity and treatment response were assessed bi-weekly using the MADRS and Clinical Global Impression scale (CGI). Hamilton Depression Scale (HAM-D) was also used as secondary scale for clinical assessments. Additionally, the patients were asked to evaluate the depressive symptoms on the Beck Depression Inventory (BDI) and possible side effects on the Toronto Side-effect Scale (TSES; Vanderkooy et al., 2002) each time of visits. All patients started treatment with escitalopram in a dose of 10 mg/day for the first 4 weeks. The patients showing at least 50% decline in the MADRS total score at week 4 continued taking 10 mg of escitalopram until the end of study. The dose of escitalopram was increased and kept at 20 mg in patients who demonstrated less than 50% decrease in MADRS total score at week 4 or who showed exacerbation of depressive symptoms in any of following visits. At the end of week 12 the patients were defined as responders if the decrease in both MADRS and HAM-D total scores was at least 50% and score on the CGI improvement scale was 2 or less. The remitters were defined if the scores were less than 12 on the MADRS and less than 8 on the HAM-D accordingly to earlier clinical trials (Kennedy et al., 2006). Patients who did not meet these criteria were defined as non-responders and non-remitters respectively. The severity of depressive symptoms and treatment response were rated blindly to genotypes by one psychiatrist. Each visit the patients were also asked to report about their regularity of taking the medication.

2.3. Genotyping

Genomic DNA was extracted from whole blood using the standard salt precipitation method. 5-HTT gene linked polymorphic region was