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Associations between MDR1 gene polymorphisms and schizophrenia and therapeutic response to olanzapine in female schizophrenic patients

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Abstract

Multidrug resistant protein (MDR1) gene, which codes for P-glycoprotein and functions as an efflux transporter in different cells, is widely localized in normal tissues including the gastrointestinal tract, blood cells, biliary tract, kidney and brain and plays a major role in absorption, distribution and elimination of various xenobiotics. Therefore, MDR1 gene variants were proposed as potential susceptibility factors for diseases and as determinants of treatment response to various drugs. We investigated the relationships between exon 21 G2677T and exon 26 C3435T genetic variants of MDR1 gene with susceptibility and treatment response in female schizophrenic patients. The study was conducted in two steps. We first compared allele, genotype and haplotype distributions between 117 female schizophrenic patients and 123 control female subjects. Afterwards, we studied treatment response to olanzapine, in 87 out of 117 previously unmedicated female patients. Overall, we found lower representation of G2677/C3435 haplotype in schizophrenic female patients compared to controls. Test result for linkage disequilibrium between loci was found to be significant. Furthermore, we found significant associations between MDR1 exon 21 G2677T genotypes and treatment response measured with positive PANSS percentage changes, with T allele and TT genotype being associated with significantly better treatment response. A borderline, non-significant statistical association was found between MDR1 exon 26 C3435T genotypes and treatment response, with TT genotype being associated with better treatment response. Our data support functional importance of the MDR1 mutations for the susceptibility and treatment response in female schizophrenic patients.

Keywords: Schizophrenia; MDR1; Olanzapine; P-glycoprotein; Treatment response; Genetic polymorphism

1. Introduction

Antipsychotic drugs are considered the core treatment in a variety of schizophrenic spectrum disorders (American Psychiatric Association, 2004). Compared to typical antipsychotics, second generation antipsychotics (SDAs) have more acceptable side effect profiles and possibly broader symptom efficacy, especially concerning negative symptoms, thus bringing considerable progress in the treatment of schizophrenic patients (Bagnall et al., 2003). Still, obvious interindividual differences in treatment response to SDAs indicate that genetic factors may be relevant.

Amongst the best understood mediators of drug resistance is the multi drug resistant (MDR1 or ABCB1) P-glycoprotein (P-gp) (Ling, 1997). The transmembrane efflux transporter P-gp is widely localized in normal tissues including the apical membrane of the gastrointestinal tract, blood cells, the biliary canalicular membrane of hepatocytes, the luminal membranes of proximal tubular epithelial cells in the kidney and the luminal membranes of

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endothelial cells in cerebral capillaries forming the blood-brain barrier (Cordon-Cardo et al., 1989; Hitzl et al., 2001), and thus limits cellular uptake of xenobiotics by excreting these compounds into bile, urine and intestinal lumen, and limits accumulation in the brain. Therefore it plays a major role in absorption, distribution and elimination of drugs (Lin and Yamazaki, 2003). P-gp is highly polymorphic and its expression in endothelial cells in cerebral capillaries forming the blood–brain barrier limits substrate access to the brain (Thompson et al., 2000; El Ela et al., 2004). Studies using mice models showed the impact of P-gp on blood–brain barrier; olanzapine penetration into brain was greater in transgenic abcb1a (mdr1), P-glycoprotein-deficient mice than in FVB1 (wild-type) animals (Wang et al., 2004). P-glycoprotein-deficient mice were also reported to have 10 times higher drug concentrations (Uhr and Grauer, 2003; Uhr et al., 2006). Reports using in vitro methods suggest that risperidon, sertraline and paroxetine may be P-gp substrate, unlike clozapine, haloperidol, chlorpromazine, citalopram and venlafaxine (Schinkel et al., 1997; Mahar Doan et al., 2002; Weiss et al., 2003). Using ATP-ase activity as a marker of P-gp binding affinity, the authors demonstrated that P-gp may in various degrees influence the access of antipsychotics to the brain, where olanzapine was ranked as an intermediate P-gp substrate (Boulton et al., 2002). According to data from animal studies using knock-out mice, olanzapine is an intermediate P-pg substrate (Wang et al., 2004).

Considering the localization of the P-pg and its role in absorption, distribution and elimination of various xenobiotics, it might act as a barrier to different exogenous noxa. Functional variants with altered gene expression might therefore constitute a susceptibility factor for complex diseases, where both genetic and environmental factors were shown to affect the disease risk (Furuno et al., 2001). As schizophrenia is a complex disease, and environmental factors are important for its expression (Kaplan and Sadock, 2003), MDR1 gene could play an important role.

Functional polymorphisms of the MDR1 gene were extensively studied through their influence on expression of MDR1 (Hoffmeyer et al., 2000; Nakamura et al., 2002), their association with pharmacokinetics and bioavailability of some drugs (Uhr et al., 2006) and their associations with clinical effects (Loscher and Potschka, 2002; Roberts et al., 2002; Yamauchi et al., 2002; Eichelbaum et al., 2004). Two single nucleotide polymorphisms (SNP), silent mutation C3435T in exon 26 and exon 21 SNP G2677T generated greatest interest, yet were found to be contradictorily associated with different changes in expression of the MDR1 protein and plasma drug concentration (Hoffmeyer et al., 2000; Sakaeda et al., 2001).

To date, linkage disequilibrium (LD) analysis of different MDR1 polymorphisms showed C3435T to be in LD with at least one other functional polymorphic locus (Kim et al., 2001; Tang et al., 2002). Considering that C3435T is a silent mutation not resulting in amino acid changes, the association found in the study suggests that it may be in linkage disequilibrium with another, functional polymorphism of MDR1 gene. The non-synonymous exon 21 SNP G2677T might seem particularly interesting. It could also explain the conflicting results.

Polymorphisms of different genes that could serve as potential gene markers in the prediction of treatment response to SDAs in schizophrenia have been extensively studied. However, to date only one study reported association of exon 26 C3435T and exon 21 G2677T with treatment response to bromperidol in schizophrenic patients (Yasui-Furukori et al., 2006), although most second generation antipsychotics were shown to be P-gp substrates (Boulton et al., 2002; El Ela et al., 2004). Considering the role of P-gp in bioavailability and its expression in endothelial cells in cerebral capillaries forming the blood–brain barrier which limits substrate access, we hypothesized that functional polymorphisms of MDR1 gene might influence treatment response. The aims of the study were to investigate the potential influence, of MDR1 polymorphisms exon 26 C3435T and exon 21 G2677T on treatment response in schizophrenic patients treated with olanzapine and on their susceptibility to schizophrenia.

2. Methods

The study was conducted in two steps. First, we compared allele, genotype and haplotype distributions between 117 female schizophrenic patients and 123 control female subjects. All patients and subjects were of Croatian descent. All patients were acutely exacerbated women aged 18–65 and meeting DSM-IV criteria for schizophrenia or schizoaffective disorder, referred to the Department of Psychiatry, Zagreb University Hospital Centre. Patients with significant abnormalities on standard laboratory tests, EEG, physical examination, significant organic or neurological disease, or history of mental disorders other than schizophrenia (alcoholism, drug addiction and epilepsy) were excluded from the study. At screening, diagnosis was made by two experienced psychiatrists (VM and LH) and each was kept blind to the diagnosis made by the other. The means $\pm$ SD age, years of education, and duration of illness were 39.4 ± 11.5 years, 11.9 ± 2.8 years and 7.8 ± 7.5 years, respectively. The control group consisted of 123 female subjects, blood donors, aged 35–65, without any history of neuropsychiatric disorders. The means $\pm$ SD age and years of education were 38.1 ± 11.3 years and 12.7 ± 1.5 years, respectively.

Second, we studied the baseline symptomatology and treatment response to olanzapine. However, 30 out of 117 patients had already failed one or two antipsychotic medications during treatment prior to the beginning of the study. Therefore, we studied baseline severity of symptoms and treatment response to olanzapine in the sample of 87 out of 117 female schizophrenic patients who had received no antipsychotic medication prior to olanzapine admission. Olanzapine was administered in open treatment, in fixed doses (olanzapine 10 mg/day ($n = 77$), or