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Catechol-*O*-methyltransferase gene variants may associate with negative symptom response and plasma concentrations of prolactin in schizophrenia after amisulpride treatment

Chun-Yen Chen[a,b], Yi-Wei Yeh[b], Shin-Chang Kuo[a,b], Pei-Shen Ho[c], Chih-Sung Liang[a,c], Che-Hung Yen[a,d], Ru-Band Lu[e], San-Yuan Huang[a,b,*]

[a] *Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan*
[b] *Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[c] *Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[d] *Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[e] *Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

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ABSTRACT

Catechol-*O*-methyltransferase (COMT) enzyme is involved in the pathogenesis of psychotic symptoms and may be associated with a therapeutic response to antipsychotic drugs. The aim of this study was to examine the relationship between *COMT* variants, plasma prolactin level, and the therapeutic effectiveness of amisulpride treatment in patients with schizophrenia. A 12-week naturalistic study of amisulpride treatment was carried out in 185 Han Chinese patients with schizophrenia. The patients were screened for 14 single-nucleotide polymorphisms of the *COMT* gene. The Positive and Negative Syndrome Scale (PANSS) was used to assess the improvement of psychopathological symptoms from the baseline to the end point in each subject. For better presentation of time-course changes in response status, a mixed model for repeated-measures (MMRM) analysis of symptom improvement during the 12-week treatment period was conducted. The change in plasma prolactin level after amisulpride treatment was also examined ($n = 51$). No significant differences in the genotype frequencies of the *COMT* variants investigated were observed between responders and non-responders. Moreover, an MMRM analysis of psychopathological symptom improvement during the 12-week treatment course showed that it depended significantly on *COMT* variants (rs4680, rs4633, and rs6267), particularly regarding changes in negative symptoms. The increase in plasma prolactin levels observed was influenced by the *COMT* rs4680 variant and was positively correlated with a reduction in PANSS negative scores. Our results suggest that variation of the *COMT* gene is associated with treatment response regarding negative symptoms and prolactin changes after amisulpride treatment in patients with schizophrenia.

1. Introduction

Genetic variations in the catechol-*O*-methyltransferase (*COMT*) gene may influence the susceptibility to schizophrenia and the response to neuroleptic treatment, because COMT is a catabolic enzyme that is involved in the regulation of central dopamine neurotransmission, which plays a key role in the pathogenesis of schizophrenia (Davis et al., 1991; Howes et al., 2009; Tunbridge et al., 2006).

The human *COMT* gene is located on chromosome 22q11.2 and consists of six exons that span ~35 kb. The Val158/108Met (rs4680) polymorphism is the variant of this gene that has been studied most widely in psychiatry, because of its functional relevance. The Val allele has higher enzymatic activity than does the Met

Abbreviations: AR1, autoregression of an order-1; COMT, catechol-*O*-methyltransferase; DSM-IV-TR, diagnostic and statistical manual of mental disorders, fourth edition, text revision; LD, linkage disequilibrium; MMRM, mixed model for repeated-measures; PANSS, positive and negative syndrome scale; PFC, prefrontal cortex; SADS-L, schedule of affective disorder and schizophrenia-lifetime; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

* Corresponding author at: Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, No. 325, Cheng-Kung Road, Sec. 2, Nei-Hu District, Taipei 114, Taiwan. Fax: +886 2 8792 6715.
E-mail address: hsy@ndmctsgh.edu.tw (S.-Y. Huang).

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allele, thereby leading to a more efficient degradation of dopamine and lower-than-normal dopamine levels in the brain (Chen et al., 2004). Previous studies found that a *COMT* functional polymorphism (rs4680) influenced individual response to antipsychotic medication (Bertolino et al., 2007; Gupta et al., 2009; Molero et al., 2007). Gupta et al. (2009) and Molero et al. (2007) demonstrated that A-allele (Met) carriers for rs4680 showed a better response to the antipsychotic treatment. Bertolino et al. (2007) showed that patients who were homozygous for the Met allele have a faster response time regarding negative symptoms after olanzapine treatment. Interestingly, the *COMT* polymorphism also affects executive cognition, which is strongly correlated with negative symptoms in schizophrenia patients (Neuhaus et al., 2009; Tunbridge et al., 2006). Advanced studies showed that *COMT* variants on the functional polymorphism rs4680 (Bosia et al., 2014; Gao et al., 2012; Weickert et al., 2004) or 3′ end SNPs (Meyer-Lindenberg et al., 2006; Panizzutti et al., 2013) may influence performance on, and neurophysiological response to, a task entailing prefrontal functions after antipsychotic treatment or computerized cognitive training. However, these studies showed that selected atypical antipsychotics with 5-HT_{2A} antagonism may confound the clinical efficacy of the dopamine effect on cognitive function and negative symptoms.

Amisulpride (Solian®), a substituted benzamide derivative, is a second-generation antipsychotic drug that is a highly selective and potent antagonist of the dopamine D_2/D_3 receptors, with little affinity for D_1, serotonin, histamine H_1, muscarinic, or alpha-adrenergic receptors, and that binds preferentially to the limbic cortical dopamine D_2/D_3 receptors rather than those of striatal structures. High dosages preferentially antagonize postsynaptic D_2/D_3 receptors, resulting in reduced dopamine transmission, and low dosages preferentially block presynaptic D_2/D_3 receptors, resulting in enhanced dopamine transmission (Miyamoto et al., 2005). This medication showed better efficacy and tolerability than did other antipsychotic agents, including a lower discontinuation rate and fewer adverse effects regarding weight gain, extrapyramidal symptoms, and sedation (Leucht et al., 2013). A recent meta-analysis delineated the high efficacy of amisulpride for treating negative symptoms in schizophrenia patients (Furukawa et al., 2015). This highly specific receptor profile renders it ideally suited to examining whether antipsychotic efficacy regarding psychopathological symptoms and cognitive function may be achieved purely by selective action at the limbic cortical dopamine function, and to assessing the relationship with the variants of the *COMT* gene (Bressan et al., 2003).

Although amisulpride is an effective and safe antipsychotic drug, it leads to prolactin increase, as shown by clinical observation (Kotan et al., 2011). Prolactin is an anterior pituitary peptide hormone that is under tonic dopaminergic control in the tuberoinfundibular tract. Thus, the plasma level of prolactin may be regarded as a measurable biomarker of central dopamine function and a useful correlate of clinical response to antipsychotic drugs (Zhang et al., 2002). Several studies have addressed the association between *COMT* polymorphisms and prolactin concentration during risperidone treatment; however, their results were controversial (Gao et al., 2012; Yasui-Furukori et al., 2008). Gao et al. (2012) showed that the mean plasma concentration of prolactin in subjects with the A allele of rs4680 was significantly higher than in carriers of the G/G genotype, contrarily Yasui-Furukori et al. (2008) found no differences in prolactin concentration between A and G-allele carriers after risperidone treatment. This discrepancy may be explained by the relative complexity of the pharmacological profile of risperidone.

To the best of our knowledge, no previous study has investigated the association between *COMT* gene polymorphism and the treatment efficacy of amisulpride. The aim of this study was to specify whether *COMT* polymorphisms influence the outcome of amisulpride monotherapy in patients with schizophrenia. The promoter, two functional SNPs (rs4680 and rs6267), some exonic and intronic variants, and 3′ end SNPs of the *COMT* gene were tested in a 12-week naturalistic treatment cohort study using amisulpride. Furthermore, we explored whether *COMT* variants affect plasma prolactin level, and the relationship between plasma prolactin level and the therapeutic effectiveness after amisulpride treatment.

2. Materials and methods

2.1. Participants

Participants were recruited from an inpatient population, and all gave written informed consent after the procedures of the study were explained completely. To minimize the effect of ethnic differences on gene frequencies, all participants were unrelated Han Chinese who were born and living in Taiwan, and all their biological grandparents were of Han Chinese ancestry. Each patient was assessed initially by an experienced attending psychiatrist and subsequently interviewed by a well-trained psychologist using the Chinese version of the modified Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (Endicott and Spitzer, 1978; Merikangas et al., 1998). The inter-rater reliability κ values of the SADS-L were good to excellent for major depression, bipolar disorder, anxiety disorder, schizophrenia, and substance abuse/dependence (Huang et al., 2004). A family history of schizophrenia was defined as the presence of one or more first-degree relatives with a history of schizophrenia.

The inclusion criteria were as follows: (1) diagnosis of schizophrenia according to the DSM-IV-TR (American Psychiatric Association, 2000); (2) a severity rating on the Positive and Negative Syndrome Scale (PANSS) score of at least $\geq$70; (3) a drug-naïve or drug-free for 1 month of antipsychotic and other psychotropic medications; (4) absence of other psychiatric axis I disorder; and (5) age between 20 and 65 years. The exclusion criteria were: (1) significant active physical illness; (2) organic brain disease; (3) current or past epilepsy; (4) any concomitant major psychiatric disorder; (5) history of substance abuse/dependence (with the exception of nicotine dependence); (6) receiving prolactin-influencing medication; or (7) pregnancy or lactation. A 12-week, open-label, flexible-dose amisulpride regimen with an initial dose of 200 mg/day was instituted, and dosage was adjusted according to the patient's symptoms. Patients with schizophrenia who started using antipsychotic drugs other than amisulpride, or mood stabilizers or antidepressants, were dropped from the naturalistic follow-up study.

This study was performed in accordance with the 1994 Declaration of Helsinki and ethical laws pertaining to the medical profession, and its design was approved by the Institutional Review Board for the Protection of Human Subjects of the Tri-Service General Hospital (TSGH), which is a medical teaching hospital that belongs to the National Defense Medical Center, Taipei, Taiwan.

2.2. Genotyping methods for the COMT gene

On the basis of the human *COMT* polymorphisms listed in the NCBI SNP database (www.ncbi.nlm.nih.gov/projects/SNP/), the Human HapMap Project database (www.hapmap.org), the SZgene database (http://www.szgene.org/geneoverview.asp?geneid=420), and a review of the literature, we selected 13 single nucleotide polymorphisms (SNPs) with minor allele frequencies (MAFs) >0.1 that covered a region of 30 kb of the *COMT* gene. Besides, we examined one potentially functional polymorphism (rs6267) (Lee et al., 2005) though its MAF <0.1. Genomic DNA was extracted from peripheral