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Effects of the DRD3 Ser9Gly polymorphism on aripiprazole efficacy in schizophrenic patients as modified by clinical factors

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ABSTRACT

Aripiprazole, a novel antipsychotic agent, has a unique pharmacological action (partial agonist) on the dopamine neurotransmission system. Aripiprazole has high affinity for dopamine D2 and D3 receptors (DRD2 and DRD3). We investigated whether the efficacy of aripiprazole can be predicted by a functional DRD3 gene polymorphism Ser9Gly (rs6280) as modified by clinical factors in Han Chinese hospitalized patients with acutely exacerbated schizophrenia. After hospitalization, the patients ($n = 128$) were given aripiprazole for up to four weeks. Patients were genotyped for DRD3 Ser9Gly polymorphism by Restriction Fragment Length Polymorphism (RFLP) method. Clinical factors such as gender, age, duration of illness, education level, diagnostic subtype and medication dosage were recorded. Psychopathology was measured biweekly with the Positive and Negative Syndrome Scale (PANSS). The effects of genetic and clinical factors on PANSS performance after aripiprazole treatment were analyzed by a mixed model regression approach (SAS Proc MIXED). We found that, although the Ser carriers have numerically larger score reductions when compared with non-carriers in almost all PANSS dimensions, the difference of their effects are statically not significant. However, the clinical factors, including dosage of aripiprazole, age, duration of illness, and diagnostic subtype could influence PANSS performance after aripiprazole treatment. This study suggests that DRD3 Ser9Gly polymorphism may not contribute significantly to inter-individual differences in therapeutic efficacy of aripiprazole, but some clinical factors may predict treatment efficacy.

1. Introduction

Inter-individual differences in response to antipsychotic drug treatment remain a critical problem in the management of schizophrenic patients. The time period before a clinician can determine whether a drug is ineffective and subsequently consider alternative pharmacotherapy can be lengthy when the predictors of antipsychotic drug response are unclear (Conley et al., 1997). In the past years, genetic variations in drug receptors and clinical factors (gender, age, duration of illness) have been recognized to contribute to the variations in individual responses to antipsychotic drugs (Lane et al., 2005b). Although the results remain preliminary, these efforts represent a valuable approach for understanding the mechanism of antipsychotic agents and for future individualization of clinical treatment.

Aripiprazole, a novel antipsychotic drug, has a unique pharmacological characteristic (partial agonist) on the dopamine neurotransmission system. This drug has high affinity for dopamine D2 and D3 receptors (DRD2 and DRD3) (Ki = 0.8 and 13 nM, respectively), a lower affinity for the D4 receptor (Ki = 200 nM), and negligible affinity for D1-like dopamine receptors (Kikuchi et al., 1995; Yokoi et al., 2002). Clinically, the partial agonist property may worsen psychotic or mood symptoms in some schizophrenic patients (Raja, 2006; Reeves and Mack, 2004). Therefore, it is important to clarify the underlying causes or factors that may affect inter-individual variation in response to aripiprazole.

The correlation of aripiprazole treatment response in schizophrenic patients with some DRD2 genetic variants has been studied in our previous investigation (Shen et al., 2008). We found that A1 carriers of DRD2 TaqIA polymorphism (rs1800497) are associated with superior therapeutic response on positive symptoms after 4-week aripiprazole treatment. In addition, the T carriers of DRD2 C957T polymorphism (rs6277) were associated with superior treatment response for excitement symptoms when compared with non-carriers. Since aripiprazole also has high affinity for DRD3, genetic variant(s) which influence density and function of these receptors may be important in explaining variability in response to aripiprazole.

Abbreviations: DRD2, dopamine D2 receptors; DRD3, dopamine D3 receptors; PANSS, positive and negative syndrome scale; RFLP, restriction fragment length polymorphism.

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DRD3 gene, located at chromosome 3q13.3, contains 5 exons and has a missense polymorphism in the exon 1 leading to a serine–glycine substitution (Ser9Gly, rs6280) in the extracellular N-terminal domain (Sokoloff et al., 1992). Previous research suggests this polymorphism is associated with altered dopamine binding affinity, indicating a possible functional effect (Jeanneteau et al., 2006; Lundstrom and Turpin, 1996). When expressing the Ser9Gly mutant with the Semliki Forest virus system, the Ser/Gly and Gly/Gly mutant showed significantly higher dopamine binding activity compared to Ser/Ser wildtype (Lundstrom and Turpin, 1996). In human embryonic kidney (HEK 293) transfected cells, dopamine-mediated cyclic adenosine monophosphate (cAMP) response was increased and mitogen-associated protein kinase signal was prolonged for the Gly9 variant when compared with the Ser9 variant (Jeanneteau et al., 2006). In combination, the gain of function of Gly9 variant may increase DRD3 densities in some brain areas and decrease aripiprazole efficacy in schizophrenic patients.

The results of prior studies on antipsychotic treatment outcome (such as clozapine and risperidone) and DRD3 Ser9Gly polymorphism were conflicting. There were four studies focusing on responses to clozapine treatment and the Ser9Gly polymorphism. Shaikh et al. (1996) showed that the Ser/Ser genotype was more frequent in patients who did not respond to clozapine. Scharfetter and co-workers reported higher Gly/Gly frequencies in responders (Scharfetter et al., 1999). Malhotra et al. (1998) and Barlas et al. (2008) suggested the association between this polymorphism and response to clozapine was unlikely to exist. There were also four studies focusing on this polymorphism and antipsychotic response to risperidone. Szekeres et al. (2004) showed that Ser/Ser genotype was associated with poor therapeutic response and severe executive dysfunction. Lane and co-workers reported that Ser/Ser or Ser/Gly had better performance on negative symptoms than those with Gly/Gly (Lane et al., 2005a). Reynolds et al. (2005) suggested a better response in the heterozygotes than the homozygote Gly/Gly or Ser/Ser groups. Xuan et al. (2008) showed no association between this polymorphism and inter-individual differences in the therapeutic efficacy of risperidone.

Most of the previous genetic-response pharmacogenetic studies on the correlation of genetic factors with neurotransmitter receptors or transporters cannot be replicated (Malhotra et al., 2004). These studies do not usually take into account clinical factors such as gender, age, duration of illness, level of education, diagnostic subtype and medication dosage (Malhotra and Goldman, 1999; Staddon et al., 2002). The current study objective was to explore whether aripiprazole efficacy is affected by the Ser9Gly polymorphisms in the DRD3 gene as modified by clinical factors in Han Chinese hospitalized patients with acutely exacerbated schizophrenia.

2. Materials and methods

2.1. Patient population

This study was conducted in the inpatient unit of Tzu-Chi General Hospital, Hualien, Taiwan from 2006 to 2008. The Structured Clinical Interview for DSM IV (American Psychiatric Association, 2000) was used for the diagnosis. Newly hospitalized schizophrenic patients with acute exacerbation were screened and evaluated by experienced psychiatrists. Patients entering into this study were Han Chinese from Taiwan and satisfied the following criteria: physically healthy with all laboratory parameters within normal limits; aged 18 to 60 years; had a minimum baseline total score of 60 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); had neither current nor past DSM IV diagnosis of mood disorders or substance (including alcohol) abuse; had not received depot antipsychotics for the preceding 6 months; had no history suggesting that antipsychotic treatment would be contraindicated. After complete description of the study to the participants, written informed consent was obtained in line with the Institution's Review Board guidelines (IRB094-11).

2.2. Study design and assessments

During the study period, clinical factors such as gender, age, duration of illness, level of education, diagnostic subtype and medication dosage were recorded. The dosage of aripiprazole was gradually titrated to the target dose within 2 weeks according to the clinicians' judgments. In patients where clinical responses were inadequate, dosage of aripiprazole was titrated up to 30 mg per day or to the highest tolerable dose. Nursing staff closely monitored the patient's compliance. Anticholinergic drugs for extrapyramidal symptoms or diazepam for sedation could be administered as needed.

Drug efficacy and safety assessments were conducted at baseline and every two weeks after initiating drug treatment. Four clinical dimensions of schizophrenia (positive, negative, general psychopathology and excitement) on PANSS were used to assess drug efficacy (Kay et al., 1987). Drug safety was evaluated by routine physical and neurological examinations, laboratory tests, the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005) and the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU) (Lingjaerde et al., 1987). The ESRS was designed to evaluate three types of extrapyramidal symptoms: parkinsonism, dystonia, and dyskinesia. Other side-effect profiles were determined by the UKU.

2.3. Genotyping for DRD3 Ser9Gly polymorphism

Genomic DNA was extracted from peripheral blood samples. Polymerase chain reaction (PCR) amplification of the DRD3 Ser9Gly polymorphism was conducted with the following primers: 5′-GCTCTATCTCCAACTCTCACA-3′ and 5′-AAGTCTACTCACCTCCAGGTA-3′ (Ebstein et al., 1997). The PCR products were then digested overnight with 1.5 units of MscI restriction enzyme at 37 °C. DNA fragments were visualized by 3% agarose gel electrophoresis and stained with ethidium bromide. An experienced researcher, blinded to patients' antipsychotic responses, conducted the genotyping and interpreted the genotype data.

2.4. Data analysis

Patient characteristics data stratified by each genotype were compared using Chi-square test, ANOVA, and Fisher's exact test depending on data distribution. Baseline PANSS scores and scores change with treatment duration of each genotype were compared using a mixed model approach (SAS Proc MIXED, SAS Version 9.0, SAS Institute, Cary, NC) and significance level was <0.05. SAS Proc MIXED accommodated the correlated nature of repeated measurements over time on the same individual and allowed the incorporation of covariates without adjusting P values. When genetic and clinical factors were combined, their effects on PANSS performance were also analyzed using SAS Proc MIXED with a significance level of <0.05. Post-hoc power analysis was implemented using the computer program GPower (Buchner et al., 1996).

3. Results

3.1. Patient characteristics

A total of 172 newly hospitalized schizophrenic patients with acute exacerbation were screened and evaluated by experienced psychiatrists. Of these patients, 128 who had completed three assessments (weeks 0, 2, and 4) were eligible for data analysis. The reasons for premature discontinuation included: patients withdrew informed consent ($n=4$), family members disagreed ($n=7$), concurrent physical illness ($n=11$), diagnosis changed ($n=6$), patient were using long-