DRD1 AND DRD2 POLYMORPHISMS AND LONG TERM ANTIPSYCHOTIC TREATMENT

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Introduction

Disturbances of dopamine mediated transmission are involved in the pathogenesis of schizophrenia and dopamine receptors are important targets of the antipsychotic treatment. As the density of the D_2 receptor is influenced by the genetic polymorphism of the dopamine D_2-receptor gene (DRD2) the effects of the antipsychotic drugs that are antagonists of this receptor may be modulated by its polymorphisms (1). DRD2 311 Ser/Cys variant was associated both with the clinical symptoms of schizophrenia, in particular with delusions and symptoms of disorganization (2) and with the efficacy of the antipsychotic treatments, but not with the extrapyramidal side effects (3). Studies with other polymorphisms were not so conclusive.
To assess the complex interaction between genetic and clinical factors, we studied the possible cross-interactions between DRD1 and DRD2 dopamine receptor gene polymorphisms, symptomatology of schizophrenia and schizoaffective disorders and the occurrence of treatment induced side effects taking into consideration possible clinical confounding variables.

Methods

One hundred and thirty one outpatients in stable remission meeting the DSMIV criteria for schizophrenia spectrum disorders and receiving long-term maintenance therapy with haloperidol, fluphenazine, zuclopethixole or risperidone (4) were genotyped for DRD1 A-48G, DRD2 Ins-141CDel and DRD2 Ser311Cys polymorphisms. Psychopathological symptoms were assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). Regarding extrapyramidal side effects, tardive dyskinesia was assessed with the Abnormal Involuntary Movement Scale (AIMS), akathisia with the Barnes Akathisia Scale (BARS) and parkinsonism with the Simpson-Angus Extrapyramidal Side Effects (SAS). For the statistical analysis χ^2 test, t-test, one-way analysis of variance (ANOVA), analysis of covariants (ANCOVA) and Spearman R test were used.

Results

Drug dosage was included as covariant for the genetic analyses because a cross correlation was observed between drug dose, symptomatology and extrapyramidal side effects ($p < 0.001$). In our sample, all genotypes were in Hardy-Weinberg equilibrium. Genetic variants did not differentiate patients regarding symptomatology, except DRD1 -48GG genotype, which showed a trend towards a positive effect on delusions ($p = 0.043$) and DRD2 –141C Del allele, which showed an effect on the negative symptom of stereotypy ($p = 0.0011$). The DRD2 311 Ser/Cys genotype showed a non significant association with tardive dyskinesia ($p = 0.05$). All three 311 Ser/Cys subjects showed an overall higher rate of side effects, independent from the drug used (typical versus atypical). The DRD1 showed a marginal effect on abnormal involuntary movement of the trunk ($p = 0.028$).

Conclusions

Only some marginal associations were observed between DRD1 and DRD2 polymorphisms and symptomatology. A non signifficant association was observed between DRD2 311 Ser/Cys genotype and tardive dyskinesia, but this finding was due to only 3 subjects. Our study evidenced that DRD1 and DRD2 variants are not influencing liability to tardive dyskinesia independently from the other clinical variables we included in the model.

References

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