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Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: A meta analysis

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Abstract

Background: A polymorphic site in the gene encoding the dopamine 3 receptor (DRD3) resulting in a serine (Ser) into glycine (Gly) substitution has been shown to affect dopamine binding affinity, and may contribute to individual differences in susceptibility to antipsychotic-induced tardive dyskinesia (TD).
Methods: A Medline, EMBASE and PsychINFO search of literature published between 1976 and March 2005 yielded 11 studies from which data were extracted for calculation of pooled estimates using meta-analytic techniques.
Results: The Gly allele increased the risk relative to the Ser allele (OR = 1.17; 95% CI: 1.01–1.37) with evidence of publication bias. No significant genotype effects were apparent.
Conclusions: TD may be associated with functional variation in the DRD3 allele. However, caution is required in interpreting this finding, as there is evidence of publication bias, genetic methodology has shortcomings, and the relation between antipsychotics, schizophrenia and TD is complex.

Keywords: (Genetic) polymorphism; Extrapyramidal (syndrome/disorder); Tardive dyskinesia; Drug-induced; Antipsychotic; Dopamine 3 receptor

1. Introduction

Treatment with antipsychotic drugs is associated with tardive dyskinesia (TD), a potentially irreversible side effect that can be very distressing for patients due to motor performance difficulties, social stigmatization and poorer quality of life (Marsalek, 2000). TD is characterized by hyperkinetic involuntary movements

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of the choreoathetoid type with a fluctuating intensity in time (Sachdev, 2005). Most common are oro-facial and limb–truncal dyskinesia (Muller et al., 2004).

Since not all patients exposed to antipsychotics develop TD, research of risk factors is important. Although a lower incidence of TD is observed with the second generation antipsychotics (SGAs), they still carry a risk of movement disorder (Tenback et al., 2005; Correll et al., 2004). In addition, many patients continue to take first generation antipsychotics (FGAs) in combination with SGAs (Procyshyn et al., 2001).

Reported prevalence rates of TD vary widely with a median rate of 24% (Yassa and Jeste, 1992). The cumulative incidence rates are around 3–5% in the first years, reaching a plateau at about 20–25% (Sachdev, 2005; Jeste et al., 1995). Dosage, cumulative amount of antipsychotic treatment and drug-intervals correlate positively with the prevalence and severity of TD (Friedman, 2004; Marsalek, 2000; van Harten et al., 1998).

Older age is the most important risk factor with a five to six times higher incidence of TD compared to younger patients (Jeste et al., 1995). Similarly, cognitive impairment also increases the risk (Waddington and Youssef, 1996), as does female sex in older age groups (>50 years) and male sex in younger age groups (van Os et al., 1999). There is some evidence of a higher risk of TD in African-Caribbean and African-American populations and a lower risk in Chinese and other Asian populations (Sachdev, 2005; Glazer et al., 1994). Patients with affective disorders may be more susceptible to (more severe) TD compared to patients with other diagnoses (Kane et al., 1985), as are patients with diabetes mellitus or patients with a family member suffering from diabetes (Mukherjee and Mahadik, 1997). Furthermore, negative symptoms may be associated with a higher risk (van Os et al., 2000), as are the use of drugs and alcohol (Sachdev, 2005).

Some studies support familiality of the TD phenotype in that untreated siblings of schizophrenic patients may have a higher rate of abnormal movements (Lencer et al., 2004; McCreadie et al., 2003; Muller et al., 2001), but this evidence cannot be considered conclusive. However, as drug-related factors predict only a minor part of the variance in the development of TD, an important role for pharmacogenetic interactions can be hypothesized (Lerer, 2002).

Different candidate genes have been investigated that may be related to increased liability for TD, such as i) genes coding for the cytochrome P 450 2D6, 1A2 and 3A4 that are involved in the metabolism of antipsychotics (Patsopoulos et al., 2005; Tiwari et al., 2005a,b), ii) genes coding for free radical scavenging enzymes like manganese super oxide dismutase (Zhang et al., 2003), iii) genes coding for the dopamine 2 and 3 receptors as well 5-HT2A and -2C receptors (Lattuada et al., 2004; Basile et al., 2002; Kaiser et al., 2002).

Data from pharmacological and neuroimaging studies suggest dysregulation of the dopamine system in schizophrenia. This provides a rationale for the study of genes involved in dopamine signalling (Hoogendoorn et al., 2005). Several dopamine receptors have been examined and the D_2-like dopamine 3 receptor (DRD3) is of particular interest because of its high density in areas thought to be implicated in schizophrenia (Lerer, 2002). Furthermore, the gene encoding DRD3 has one polymorphic site, resulting in a serine (Ser) to glycine (Gly) substitution causing significantly higher dopamine binding affinity (Lundstrom and Turpin, 1996). Various meta-analyses indeed showed a small but significant association between this DRD3 polymorphism and schizophrenia. Other polymorphisms in or near DRD3 did not result in significant associations with schizophrenia although haplotype-based association studies showed a trend among Japanese and UK patients (Jonsson et al., 2003).

The relation between DRD3 and TD is biologically plausible because DRD3 is selectively expressed in the ventral striatum and pallidum, a brain region implicated in motor function (Suzuki et al., 1998). DRD3 agonists inhibit locomotor brain activity, whereas DRD3 antagonists exert opposite effects (Accili et al., 1996). Although these conclusions are obtained from in vitro studies, they nevertheless provide an attractive hypothesis for genetic sources of variability in susceptibility to TD (Lerer et al., 2002; Basile et al., 1999). Given the fact that part of the risk for TD is thought to be associated with the illness itself (van Os et al., 1997), the Ser to Gly substitution polymorphism in DRD3 is an attractive candidate for study in the context of TD.

The DRD3 Ser9Gly polymorphism to date remains the only site within DRD3 that has been studied in relation to the risk of TD. Steen et al. (1997) showed a significant excess of Gly-allele and Gly–Gly homo-