DRD2/ANKK1 Taq1A (rs 1800497 C>T) genotypes are associated with susceptibility to second generation antipsychotic-induced akathisia

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Abstract

Although the advent of atypical, second-generation antipsychotics (SGAs) has resulted in reduced likelihood of akathisia, this adverse effect remains a problem. It is known that extrapyramidal adverse effects are associated with increased drug occupancy of the dopamine 2 receptors (DRD2). The A1 allele of the DRD2/ANKK1, rs1800497, is associated with decreased striatal DRD2 density. The aim of this study was to identify whether the A1(T) allele of DRD2/ANKK1 was associated with akathisia (as measured by Barnes Akathisia Rating Scale) in a clinical sample of 234 patients who were treated with antipsychotic drugs.
Definite akathisia (a score ≥ 2 in the global clinical assessment of akathisia) was significantly less common in subjects who were prescribed SGAs (16.8%) than those prescribed FGAs (47.6%), p < 0.0001. Overall, 24.1% of A1+ patients (A1A2/A1A1) who were treated with SGAs had akathisia, compared to 10.8% of A1 (thus, A2A2) patients. A1+ patients who were administered SGAs also had higher global clinical assessment of akathisia scores than the A1 subjects (p = 0.01). SGAs maintained their advantage over FGAs regarding akathisia, even in A1+ patients who were treated with SGAs. These results strongly suggested that A1+ variants of the DRD2/ANKK1 Taq1A allele do confer an associated risk for akathisia in patients who were treated with SGAs, and these variants may explain inconsistencies found across prior studies, when comparing FGAs and SGAs.

Introduction

The advent of second-generation antipsychotics (SGAs) marked a significant change in the pharmacotherapy of schizophrenia. The introduction of SGAs allowed many patients to receive antipsychotic treatment without experiencing extrapyramidal symptoms (EPS). The lower rate of EPS associated with SGAs resulted in the term atypical antipsychotic and a new class of medication was established (Kendall, 2011); however, not all patients treated with SGAs are free of EPS (Rummel-Kluge et al., 2010). Although these effects are often less pronounced (Mihanovic et al., 2010), they include: parkinsonism, tardive dyskinesia, dystonia and akathisia.

Akathisia is characterised by motor restlessness and accompanying subjective distress. It thus has both objective and subjective components and it has been associated with suicidal ideation (Hansen and Kingdom, 2006; Mihanovic et al., 2010), homicidal ideation (Schulte, 1985), diminished subjective well-being (Kim and Kim, 2009), medication non-adherence (Markkula et al., 2007; Perkins et al., 2002), dysphoria (Halstead et al., 1994), cognitive impairment (Kim and Byun, 2007) and anxiety (Hodge, 1959). Akathisia also increases the risk of tardive dyskinesia (Sachdev, 2004). Furthermore, worsening akathisia, anxiety and depression are robust predictors of antipsychotic switching (Nyhuis et al., 2010).

The pathophysiological mechanisms underlying akathisia are not fully defined; however, low activity of dopaminergic projections from the midbrain to the ventral striatum may be involved (Stahl and Lonnen, 2011). Depletion of dopamine using alphamethyl-para-tyrosine (AMPT) (4–5 g/day) induces dysphoria and akathisia in medication-free patients with schizophrenia (Vorunganti and Awad, 2006).

Positron emission tomography (PET) studies have confirmed the role of dopamine D2 receptors (DRD2) in akathisia. Selective blockade of DRD2 by radioactive carbon-labeled [11C] raclopride shows induction of akathisia in both control participants and those with
schizophrenia. The most severe symptoms occur with maximal binding of basal ganglia DRD2 (Farde, 1992). Individuals vary in their susceptibility for getting symptoms of akathisia, but hereditary factors are likely to confer risk for this disorder (Eichhammer, et al., 2000) and other key adverse events (Barnes et al., 2011). Because DRD2 are involved in the pathophysiology of akathisia, then DRD2 polymorphisms were reasonable candidates for possible genetic risk. Interestingly, the DRD2/ANKK 1 polymorphism was first described as associated with alcohol dependence disorder (Blum et al., 1990). Next, it was found that the carriers of the A1 allele of the DRD2/ANKK 1 Taq1A polymorphism (thus: A1/A1, A1/A2 and A1+) have a 30% lower DRD2 density than the non-carriers (i.e. A2/A2, A1-) (Noble, 2003). In vivo PET reveals that although the DRD2 availability (Bmax) is decreased in A1+ healthy individuals, the affinity for dopamine (Kd) is unaffected (Pohjalainen, 1998).

ANKK1 may also influence dopaminergic neurotransmission, by affecting the phosphorylation of amino acid residues within the key proteins involved in dopaminergic activity (Munafò et al., 2007). The DRD2/ANKK 1 Taq1A polymorphism is located in a putative substrate binding domain of the ANNK1 gene, which results in a Glu713Lys substitution. This polymorphism may alter substrate-binding specificity (Neville, 2004). Most studies that have investigated genetic variants of the DRD2/ANKK 1 Taq1A polymorphism find that there is no association with EPS, in patients who were treated with first generation antipsychotics (FGAs) (Kaiser et al., 2002; Wu et al., 2006). Only one single study reports a positive association (Güzey et al., 2007). To date, any genetic studies investigating whether akathisia is associated with SGAs have not included the DRD2 Taq1A ANKK 1 (Dolzan et al., 2007). Yet patients receiving antipsychotic medications do have higher prolactin levels, which suggests greater functional DRD2 binding in this group (Young et al., 2004).

As the condition of akathisia is associated with maximal binding of DRD2 (Farde, 1992), our current study investigated whether or not A1+ patients who were treated with first or second generation antipsychotics were at an increased risk for akathisia.

Materials and methods

Participants

We made a cross-sectional study using 234 patients between 18–65 years of age whom had a DSM IV diagnosis of schizophrenia and were already undergoing treatment. Because affective disorder diagnoses are associated with akathisia (Bratti et al., 2007) we excluded any participants with a current or past history of bipolar disorder, major depressive disorder or schizoaffective disorder. Because cognitive dysfunction is also a risk factor for akathisia (Bratti et al., 2007), the participants with an organic brain syndrome, dementia or epilepsy were excluded.
Participants were recruited from a major community mental health centre, plus two inpatient units that were housed in tertiary referral teaching hospitals. Because various psychoactive agents can also induce akathisia (Peitl et al., 2010), we excluded patients taking antidepressant, opiate, anxiolytic or mood-stabilising medications. In addition, we excluded those taking antiemetic and antihistamine medications from our study. All included patients were treated with antipsychotic monotherapy, at a stable dose, for a minimum of 4 weeks. Participants provided informed consent prior to inclusion and were able to withdraw from the study at any time, without prejudice. The institutional ethics approvals were obtained from the clinics and hospitals involved, as well as the Queensland University of Technology (QUT). We followed all procedures in accordance with the ethical standards of these institutional ethics committees and the Declaration of Helsinki 1975, revised Hong Kong 1989.

Assessments

A total of 234 unrelated patients were recruited (189 males, 45 females). Of these, 191 patients were treated with SGAs, which were prescribed as follows: 58 patients were taking olanzapine, 55 risperidone, 53 clozapine, 12 depot risperidone (risperdal consta), 10 quetiapine, two were given amisulpride and one, aripiprazole. Also, 43 patients were treated with FGAs: 15 patients were prescribed flupenthixol decanoate, 16 zuclopenthixol acetate, eight received fluphenazine decanoate and four patients, haloperidol decanoate. For our statistical analysis, the dose of these antipsychotics was transformed to ‘mg chlorpromazine equivalents per kilogram’ (CPZEK).

The average age of the study participants was 40.16 years (SD = 13.80). Ninety participants were inpatients and 144 were outpatients: These subjects had been diagnosed with schizophrenia for an average of 16.76 years (SD = 12.58).

A clinical history was taken by one of three consultant psychiatrists, a clinical psychologist, or a clinical nurse. We collected demographic details, including ethnic background: 215 patients identified themselves as Caucasian, eight as Asian, five as Polynesian or Melanesian (New Zealand Maori or Fijian), three as Aboriginal Australian, and three provided no information. Because smoking is associated with lower levels of antipsychoticinduced akathisia (Barnes et al., 2006), we obtained data concerning cigarette consumption. In addition, we obtained data pertaining to comorbid substance use, because substance abuse is associated with akathisia (Kumar and Sachdev, 2009). These data included: milligrams of nicotine consumed daily, carbon monoxide concentration expired, Alcohol Use Disorders Identification Test (AUDIT) scores (Babor et al., 2001) and lifetime illicit drug use. The AUDIT is a reliable and valid screening instrument for alcohol use disorders in people with schizophrenia (Dawe et al., 2000).
All patients were administered the Barnes Akathisia Rating Scale (BARS) as outlined by Barnes (1989). Both the reliability and validity of this scale are well established by published studies (Barnes, 2003). All our study assessors were experienced mental health professionals with a comprehensive understanding of akathisia. All were trained in the use of the BARS, in order to maximise reliability (Tracy et al., 1997). All raters employed a standard examination procedure (Gervin and Barnes, 2000). Interrater reliability was ascertained in a random selection of patients. These tests were conducted at different times by another examiner, who was blinded to previous findings. We observed the study subjects in a sitting position for > 2 minutes and also whilst standing, engaged in neutral conversation, for at least 2 minutes as the scale instructions indicate. All ratings were performed blind to the genotyping data. Additionally, as negative symptoms, affective disorder and cognitive function are individual risk factors for akathisia, we administered the 7-item negative scale of the Positive and Negative Syndrome Scale (PANSS) used by Kay et al. (1987), the General Health Questionnaire (GHQ) used by Goldberg (1972) and the Trail Making Test, parts A and B (Reitan, 1958).

Genotyping method

We extracted DNA from blood lymphocytes, using standard techniques, and subsequently used it as a template for the determination of DRD2/ANKK1 genotypes. We performed DRD2/ ANKK1TaqIA(rs 1800479(>T)) genotyping by restriction fragment length polymorphism (RFLP) analysis of PCR products in two laboratories, at the University of California Los Angeles (UCLA) and QUT. A genomic sequence of 501 bp of the coding region of ANKK1 was amplified by PCR using the forward primer 5’-GCACGTGCCACCATACCC-3’ and the reverse primer 5′-TGCAGAGCAGTCAGGCTG -3′. A total of 5–10 ng of genomic DNA was amplified in a PCR master mix containing 0.2 μM of forward primer and 0.2 μM of reverse primer, 1x PCR buffer, 1.5 mM MgCl2, 200 μM dNTP and 1 unit of ‘Platinum Taq DNA Polymerase’ (Invitrogen) in a 25 μL volume. PCR amplification conditions were as follows: Step1, 94°C for 4 min; Step 2, 94°C for 30 s; Step 3, 68°C for 30 s andStep 4, 72°C for 30 s. Steps 2–4 were repeated in 40 cycles that were followed by 72°C for 3 min. The amplified PCR fragments were digested with Taq1 restriction enzyme (New England Biolabs) and the digested fragments were visualized by agarose gel electrophoresis. The A1/A2(CT) genotype was revealed by three fragments:

310bp, 180bp and 130bp. The A2/A2(CC) genotype was indicated by two fragments: 180bp and 130bp. The A1/A1(TT) genotype created an uncleaved 310bp fragment upon visualization, so all genotypes were readily distinguishable from each other. Any subjects with the A1/A1 and A1/A2 genotypes were considered to have the A1+ allelic status, while those with the A2/A2 homozygous genotype were considered to have the A1allelic status, consistent with previous studies (Noble, 2003) and a dominant model of inheritance.
Statistical analysis

Chi-square test (Yates corrected) and Fisher’s exact test, where appropriate, were employed to compare differences in noncontinuous variables between A1+ and A1 allelic groups. Analysis of variance (ANOVA) was used to compare differences among the various drug groups, with akathisia as a continuous variable. Similarly, one-way ANOVA was employed to examine differences in akathisia between the A1+ and A1 allelic groups. A p-value of < .05 was considered to be statistically significant.

Results

Genotyping results obtained from the two laboratories were crosschecked and found to be 100% in agreement. Definite akathisia (a score ≥ 2 in our global clinical assessment of akathisia) was present in 16.8% of subjects whom were prescribed SGAs (n = 185) and in 47.6% of those prescribed FGAs (n = 42) ($\chi^2 [1] = 18.72; p < 0.0001$). Seven patients were not assessed on this scale. The mean global clinical assessment score of those taking SGAs was 0.53 (SD = 0.87). Those prescribed FGAs had a higher mean score, of 1.29 (SD = 1.00). ANOVA revealed significantly higher global clinical assessment of akathisia scores in those patients prescribed FGAs, as compared to those taking SGAs ($F [1,225] = 24.64; p < 0.0001$). Over the entire sample, A1+ participants (n =102) had higher scores on the global clinical assessment of akathisia than the A1 participants (n = 125) ($F [1,225] = 5.58, p = 0.011$). Genotype data were missing in seven participants. A1+ individuals (n = 83) who were administered SGAs had higher global clinical assessment of akathisia scores (mean = 0.71; SD = 0.98) than A1 participants administered the same class of medication (mean = 0.38; SD = 0.73 (n = 102) ($F [1,183] = 6.790, p = 0.01$); however, among those taking FGAs, the global clinical assessment of akathisia scores on the BARS were not significantly different in A1+ (n = 19) and A1 (n = 23) patients (mean = 1.42 A1+ compared to A1 = 1.17) ($F [1, 40] = 0.64; p = 0.430$). Table 1 displays the results of global clinical assessment of akathisia on the BARS, as related to DRD2 allelic status.

Of the patients prescribed SGAs, 31 had definite akathisia (a score ≥ 2 for the global clinical assessment of akathisia). Twenty of these participants (64.5%) were found to be A1+ and 11 (35.5%) were A1-. The A1+ group was over-represented ($\chi^2 [1] = 5.82, p = 0.016$). Definite akathisia occurred in 24.1% of A1+ patients whom were treated with SGAs, as compared to 10.8% of the A1 patients. When A1+ patients treated with SGAs (n = 83) were compared to all patients treated with FGAs (n = 42), akathisia occurred more frequently in the FGA group ($\chi^2 [1] = 7.09; p = 0.008$). In order to account for possible confounders, all A1+ patients in the entire sample (n = 102) were compared with all A1 participants (n = 125). ANOVA was employed to compare the continuous variables of age, dosage of antipsychotic (CPZEK),
milligrams of nicotine consumed daily, expired carbon monoxide concentration AUDIT scores, PANSS negative scale scores and the Trail Making Test, parts A and B. These comparisons revealed no significant differences between A1+ and A1 participants. Chi-square statistics were also employed to compare categorical variables in A1+ and A1 patient groups. There were no differences in gender, presence of binge drinking, proportion of current smokers, nor prevalence of lifetime illicit drug use between A1+ and A1 participants. These results are listed in Table 2.

Discussion

In our study, the prevalence of akathisia in schizophrenic patients whom were prescribed either SGAs or FGAs was generally higher than was previously reported. Our results indicated that 16.8% of patients prescribed SGAs and 47.6% of patients prescribed FGAs exhibited akathisia. The previously-reported figures are approximately 24% for SGAs and 13% for FGAs (Miller et al., 1998). The higher point prevalence of akathisia that we describe here may be due to our systematic examination and diagnostic assessment for akathisia, which may have detected a higher number of cases. In addition, our clinical sample contained 90 inpatients who were acutely unwell, so they may have been prescribed an increased dosage of antipsychotic medication, as a result, which also could have contributed to the increased prevalence of akathisia found in this sample.

Akathisia was found more frequently in patients prescribed FGAs, than in those prescribed SGAs. Individuals carrying the A1 allele were over-represented among patients with clinical akathisia, as nearly one in four A1+ patients who were prescribed SGAs had akathisia. Recently, a controversy has developed regarding the advantages of SGAs compared to FGAs (Kendall, 2011; Girgis, 2011). SGAs were initially promoted as being free of extrapyramidal adverse effects (Leucht and Davis, 2011). The ability of these medications to produce an antipsychotic effect without producing EPS and their unique action as serotonin 2 (5-HT2) receptor antagonists provided the rationale for the drugs’ designation as ‘atypical.’ In addition, the majority of SGAs do not appear as likely as FGAs to induce increases in prolactin. Risperidone and amisulpride are exceptions to this rule (Young et al., 2004; Lee et al., 2012); however, single photon and positron emission studies show that all antipsychotics of both the first and second generation do antagonise DRD2 (Leucht and Davis, 2011).

This study shows that patients who were prescribed SGAs experience akathisia less commonly than those taking typical medications; however, this comparative advantage of atypical drugs regarding EPS risk is diminished in the A1+ patients. Nearly one-quarter of A1+ patients who were treated with SGAs developed akathisia. In comparison, only one-tenth of the A1 patients exhibited akathisia, when treated with SGAs. The SGAs may confer a more significant benefit for A1 patients. However, despite the fact that nearly one-quarter of
A1+ patients who were prescribed an SGA had definite akathisia, the SGAs prescribed to A1+ patients were still significantly less likely to produce akathisia than were FGAs. These results confirmed previous studies, which found that Taq1A variants were not associated with an increased liability for akathisia, in patients treated with ‘typical’ agents (Kaiser et al., 2002; Wu et al., 2006). However, the number of patients (n = 43) who were prescribed FGAs in the present study was not sufficient to demonstrate whether or not akathisia is associated with the A1+ status in this group.

A1+ subjects who were treated with serotonin specific reuptake inhibitors are also reported to have an increased risk for EPS (Hedenmalm, et al., 2006), which demonstrates that A1+ patients are at risk for akathisia across different drug groups. Furthermore, A1+ patients are at an increased risk for tardive dyskinesia (Chen, 1997). Increased serum prolactin is also found in A1+ patients who are treated with SGAs (Young et al., 2004; López-Rodríguez, 2011), illustrating that individual genetically-determined differences in DRD2 Bmax are contributory factors to the serious adverse effects that are associated with SGAs.

The increased occurrence of akathisia, tardive dyskinesia and hyperprolactinaemia in A1+ patients may have contributed to the current debate regarding the validity of previously-stated differences between FGAs and SGAs. A recent editorial by Kendall (2011) suggests that there is little difference between SGAs and FGAs, so they should all should be grouped as ‘just plain antipsychotics.’ Debate in this area has been based on the premise that individuals with DSM-IV criteria schizophrenia are physiologically homogeneous. Interactions between medication and genetically determined differences in physiology (specifically dopamine receptor polymorphisms) have not been considered so far in effectiveness trials comparing FGAs with SGAs. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) by Lieberman et al. (2005) finds no differences in the incidence of akathisia between perphenazine and three different SGAs; however, the patients’Taq1A status was not ascertained.

The present study was limited by its cross-sectional nature, although inter-rater reliability tests were conducted to ensure the accurate determination of akathisia. The genotyping system employed in this study was based on the restriction digest method, which was employed in two separate laboratories (at UCLA and QUT), but the results were identical in each case. A further limitation was the relatively small number of patients who were prescribed FGAs, so a larger study is required to demonstrate whether Taq1A is a risk factor for this group. Yet another limitation was the lack of investigation of two other putative functional polymorphisms (141C Ins/Del and Ser311Cys). As the minor allele frequency of the 141C Ins/Del is approximately 10% (Jönsson et al., 1999) and the minor allele frequency of the Ser311Cys is approximately 2% (Jönsson et al., 2003), a considerably larger study would be needed to ascertain whether or not these polymorphisms are also risk factors for akathisia.
Future research should employ a prospective methodology to examine the effects of genotype on akathisia. Examination of other parkinsonian signs and symptoms should also be performed, as it is likely that reduced striatal D2 density would probably influence parkinsonian symptoms (e.g. tremor, rigity and akinesia) as much, if not more, than akathisia. Our current data suggest that future investigations should include an examination of DRD2/ANKK1 Taq1A genotypes as a possible confounder, when adverse effects of SGAs and FGAs are compared. The current data have provided further support to the notion that antipsychotic-induced DRD2 antagonism is greater in A1+ patients, placing them at an increased risk for both EPS and raised serum prolactin. If our findings are replicated, a reduced dosage of antipsychotic medication in A1+ patients may result in a decreased likelihood of experiencing these adverse effects.

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Conflict of interest

In the last 3 years, BRL and MB received lecture fees, as well as conference expenses, from both Eli Lilly and Lundbeck. MB has been an advisory board member for Eli Lilly.

References


