Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the *DRD2*A1* allele

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Background Hyperprolactinaemia induced by D_2 dopamine receptor antagonist antipsychotic medication can result in significant health problems.

Aims To examine the role of *DRD2* polymorphism on prolactin levels in patients treated with antipsychotic medication.

Method Antipsychotic drugs with different degrees of D_2 receptor binding were given to 144 patients with schizophrenia. Serum prolactin levels were obtained and *Taq*IA *DRD2* alleles were determined.

Results Prolactin levels increased across medication groups reflecting increasingly tight D_2 receptor binding (clozapine, olanzapine, typical antipsychotics and risperidone). In the combined medication group, patients with the *DRD2*A1* allele had 40% higher prolactin levels than patients without this allele. In patients treated with clozapine (the loosest D_2 receptor binding agent), patients with the *DRD2*A1* allele had prolactin levels twice those of patients without this allele.

Conclusions Patients with the *DRD2A1* allele receiving antipsychotic medications had higher prolactin levels and were overrepresented among those with hyperprolactinaemia, suggesting greater functional D_2 receptor binding in this group.

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Hyperprolactinaemia is a frequent adverse effect of antipsychotic medication (Petty, 1999), and is the result of D_2 dopamine receptor drug binding (Markianos *et al*, 2001). Hyperprolactinaemia may result in depression, sexual dysfunction, amenorrhoea, galactorrhoea, breast cancer and osteoporosis (Maguire, 2002; Halbreich *et al*, 2003). Antipsychotic drugs vary widely in their binding affinity for the D_2 receptor. Clozapine and quetiapine, with a lower binding affinity than dopamine (Remington *et al*, 2000), have not been associated with hyperprolactinaemia (Markianos *et al*, 2002). Hyperprolactinaemia is typically associated with tighter-binding agents such as risperidone, an atypical antipsychotic, whereas olanzapine, an antipsychotic with intermediate binding, is associated with a modest increase in prolactin levels (David *et al*, 2000). The *A1* allele of the D_2 dopamine receptor gene (*DRD2*) is associated with significantly reduced density of D_2 receptors (Noble *et al*, 1991) and thus may influence D_2 receptor antagonism. This study reports the effect of *DRD2* polymorphism on prolactin response to a variety of antipsychotic medications.

METHOD

Sample

Patients were recruited at the Fortitude Valley Community Mental Health Centre, the Royal Brisbane Mental Health Unit and the Park Psychiatric Hospital. Inclusion criteria were age 18–65 years and meeting DSM–IV criteria for schizophrenia (American Psychiatric Association, 1994). Potential participants were excluded if they had schizoaffective disorder, bipolar disorder, dementia, organic brain syndrome, major depressive disorder with delusions or epilepsy. Those who were pregnant were excluded. As a range of psychoactive agents can influence prolactin levels (Jarvinen *et al*, 1992; Hugues *et al*, 2000; Basturk *et al*, 2001; Keltner *et al*, 2002), patients regularly taking antidepressant, opiate, anxiolytic or mood-stabilising medication were excluded from the study. Potential participants who nursing or medical staff believed were not adhering to their medication regimen were also excluded. All participants provided informed consent and were able to terminate participation without prejudice. Institutional ethics approval was obtained from the clinics and hospitals involved.

Assessments

A total of 144 unrelated White patients (123 men, 21 women), attending various psychiatric units for the treatment of their schizophrenia, were enrolled in the study. Their average age was 36.4 years (s.d.=12.0); 61 participants were in-patients and 83 were out-patients. A clinical history was taken by either a psychiatrist (S.B., B.L., M.B., W.W.) or a clinical psychologist (R.Y.). Demographic details including ethnic background data were obtained. The Positive and Negative Syndrome Scale (PANSS; Kay, 1990) was used to assess psychotic symptoms. All raters were trained to a criterion of 90% agreement using PANSS training videos. Interrater reliability was obtained through random checks of the PANSS by independent raters of the same patient. These reliabilities were sound.

Medications

All participants received their prescribed antipsychotic medication for at least 1 month at a stable dosage. Thirty-one patients were prescribed clozapine, 31 olanzapine, 33 typical antipsychotics (12 flupentixol, 2 fluphenazine decanoate, 13 zuclopenthixol, 3 haloperidol decanoate, 1 thioridazine, 1 thiothixene and 1 trifluoperazine) and 49 risperidone. Antipsychotic dosage was transformed to chlorpromazine equivalents per kilogram. The mean chlorpromazine equivalent dosages in the four medication groups were clozapine 5.14 mg/kg (s.d.=2.94), olanzapine 5.37 mg/kg (s.d.=2.62), typicals 5.60 mg/kg (s.d.=3.70) and risperidone 4.82 mg/kg (s.d.=2.00). There was no significant difference in dosage among the four drug groups ($F(3,128)=0.51$, $P=0.67$). Adherence by the in-patients was sound as all medication was administered by nursing staff; outpatient adherence was estimated by self-report and assessment by the treating psychiatrist. Thirty of the 33 patients receiving

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typical medication were treated with nurse-administered depot preparations.

Prolactin levels and DRD2 *alleles*

A 10 ml blood sample was drawn from each participant for DNA extraction and prolactin determination. The DNA was sent to the University of California Los Angeles for genotyping, and prolactin determination was conducted at the Royal Brisbane Hospital. Serum prolactin level was determined by a heterogeneous sandwich magnetic separation assay (Immuno 1 system; Bayer Diagnostics, Newbury, Berkshire, UK) which was standardised against the World Health Organization 3rd IRP 84/500 Reference Manual.

DNA was extracted from leucocytes using standard techniques and subsequently used as a template for determination of *Taq*1A *DRD2* alleles by the polymerase chain reaction (Grandy *et al*, 1993). As previously described (Noble *et al*, 1994), the amplification of DNA was carried out using a Perkin Elmer GeneAmp 9600 thermocycler (Perkin Elmer, Boston, MA, USA). Approximately 500 ng of amplified DNA was then digested with 5 units of *Taq*1 restriction enzyme (Gibco/BRL, Grand Island, NY, USA) at 65°C overnight. The resulting products were analysed by electrophoresis in a 2.5% agarose gel containing ethidium bromide and visualised under ultraviolet light. The *A1/A2* genotype is revealed by three fragments (310 bp, 180 bp and 130 bp) and the *A2/A2* genotype by two fragments (180 bp and 130 bp); the *A1/A1* genotype is shown by the uncleaved 310 bp fragment. Participants with *A1/A1* and *A1/A2* genotypes were considered to have $A1^+$allelic status and those with the *A2/A2* genotype were considered to have $A1^-$ allelic status.

Data analysis

Information coded from interview proformas was entered into a computer database along with prolactin results. The *Taq*1A *DRD2* allelic data were entered last. Chi-squared tests (Yates' corrected) were employed to compare differences in categorical variables between $A1^+$ and $A1^-$ allelic groups. Analysis of variance (ANOVA) was used to compare differences in prolactin levels among the various drug groups. Similarly, one-way ANOVA was employed to examine differences in prolactin levels between the $A1^+$ and $A1^-$ allelic groups. A P value of $\leqslant 0.05$ was considered to be statistically significant.

RESULTS

The results confirmed a significant gender effect in prolactin levels of patients treated with antipsychotic medications. Female participants had significantly higher prolactin levels than males ($F(1,142)=25.19$, $P<0.0001$), with the mean prolactin level for females being 1146 mIU/l (s.d.=1136) and for males being 420 mIU/l (s.d.=374). Men and women were equally represented across the four medication groups.

Analysis of variance revealed significant differences in prolactin levels among the four medication groups ($F(3,140)=19.0$, $P<0.0001$). Figure 1 shows prolactin levels in each of the treatment groups. *Post hoc* pairwise comparisons were undertaken to test differences between groups. Olanzapine compared with clozapine treatment resulted in significantly higher prolactin levels ($F(1,60)=4.76$, $P=0.033$). Patients treated with typical antipsychotics had significantly higher prolactin levels than their olanzapine-treated counterparts ($F(1,62)=7.60$, $P=0.007$). Finally, significantly higher levels of prolactin were evident in patients treated with risperidone compared with those treated with typical antipsychotics ($F(1,80)=8.97$, $P=0.004$).

The genotypes of the 144 patients were as follows: *A1/A1* ($n=7$), *A1/A2* ($n=55$) and *A2/A2* ($n=82$). The mean age of the $A1^+$ group (35.5 years, s.d.=12.7) was not significantly different from that of the $A1^-$ group (37.1 years, s.d.=11.5) ($F(1,141)=0.66$, $P=0.42$). There was no significant difference between the $A1^+$ and $A1^-$ groups according to gender ($\chi^2(1)=0.048$, $P=0.83$), in-patient or outpatient status ($\chi^2(1)=0.00$, $P>0.99$), family history of schizophrenia ($\chi^2(1)=0.00$, $P>0.99$), criminality ($\chi^2(1)=0.02$, $P=0.90$), binge drinking ($\chi^2(1)=0.08$, $P=0.78$) or suicide attempts ($\chi^2(1)=2.03$, $P=0.16$). There was also no significant difference in markers of psychosis severity, as measured by number of admissions ($F(1,140)=1.45$, $P=0.23$), PANSS positive symptoms ($F(1,140)=0.06$, $P=0.81$) and PANSS negative symptoms ($F(1,139)=2.60$, $P=0.11$). There was no difference in antipsychotic chlorpromazine equivalent dosage between $A1^+$ and $A1^-$ patients taking clozapine ($F(1,128)=2.36$, $P=0.14$), olanzapine ($F(1,27)=1.0$, $P=0.33$), typical antipsychotics ($F(1,24)=0.33$, $P=0.57$) and risperidone ($F(1,45)=0.47$, $P=0.50$).

Table 1 shows the serum prolactin levels of $A1^+$ and $A1^-$ group patients treated with antipsychotic medications. Analysis of variance of the total sample of patients indicated that those carrying the *A1* allele had about a 40% higher prolactin level than patients without this allele ($F(1,142)=4.50$, $P=0.04$).

Clozapine, the loosest-binding antipsychotic drug, showed a significant difference across allelic groups, with a

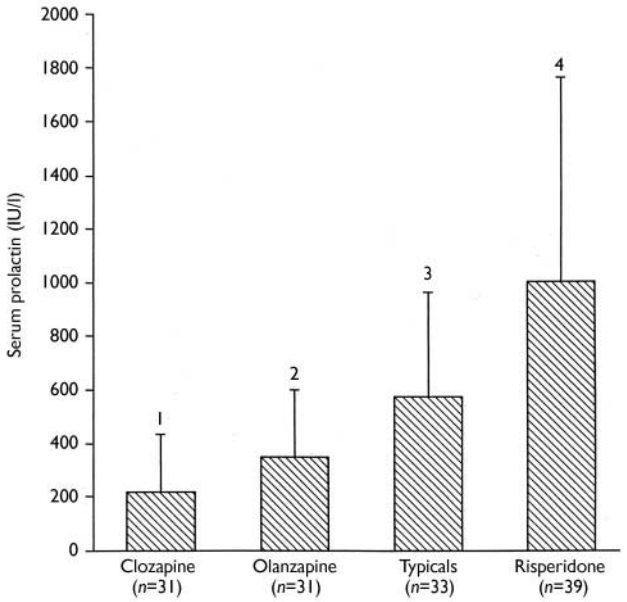

Fig. 1 Serum prolactin levels in patients with schizophrenia treated with different antipsychotic medications. 1 v. 2, $P=0.033$; 2 v. 3, $P=0.007$; 3 v. 4, $P=0.004$.

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Table 1 Serum prolactin levels in patients with or without the *DRD2**A1* allele receiving antipsychotic medication for schizophrenia

Antipsychotic group	*A1* allele present		*A1* allele absent		*P*
	Prolactin level, IU/l mean (s.d.)	*n*	Prolactin level, IU/l mean (s.d.)	*n*	
All antipsychotics (n=144)	708 (622)	62	499 (561)	82	0.04
Clozapine (n=31)	310 (318)	12	147 (78)	19	0.04
Olanzapine (n=31)	327 (107)	9	346 (293)	22	0.85
Typical antipsychotics (n=33)	622 (350)	14	530 (422)	19	0.52
Risperidone (n=49)	1058 (736)	27	928 (800)	22	0.56

prolactin level that was twice as high in *A1*$^+$ patients compared with *A1*$^-$ patients (F(1,29)=4.63, P=0.04). When the analysis was conducted for male patients only (there were too few women patients for analysis), significance remained (F(1,26)4.58, P=0.04). There was no significant difference in prolactin levels between *A1*$^+$ and *A1*$^-$ patients in the other antipsychotic drug groups.

Hyperprolactinaemia is defined using community sample cut-off levels set at a 95% reference range: $\geqslant$430 mU/l in men and $\geqslant$560 mU/l in women (Vanderpump *et al*, 1998). In total, 64 patients, 44% of the sample, exceeded these levels. Only 7 of these patients were prescribed lower-binding agents (clozapine and olanzapine) confirming that these medications are rarely associated with hyperprolactinaemia (5% of the sample). Forty of the patients on risperidone exceeded these prolactin levels, indicating that 81% of patients on this medication were in the hyperprolactinaemic range. A Yates'-corrected χ^2 analysis conducted to compare allelic status in the group with prolactin levels in the normal range and those with hyperprolactinaemia was significant (χ^2(1)=5.52, P=0.02). Those with *A1*$^+$ allelic status were significantly overrepresented in the group of patients with clinical hyperprolactinaemia.

DISCUSSION

Prolactin response to antipsychotic medication was greatest in patients prescribed risperidone. Prolactin response was successively lower in patients administered typical antipsychotics, olanzapine and clozapine. This order across medications has also been found in positron emission tomography binding studies (e.g. Markianos *et al*, 2001) where D_2 dopamine receptor occupancy corresponded to serum prolactin levels. Prolactin levels were higher in women than in men.

Individuals with the *A1* allele and higher prolactin levels when treated with antipsychotic medication and were over-represented among patients with clinical hyperprolactinaemia. The *A1*$^+$ participants also had significantly higher prolactin levels than *A1*$^-$ participants when treated with the loosely binding agent clozapine. The greater prolactin response to antipsychotics observed in *A1*$^+$ patients with schizophrenia in this and other studies (Mihara *et al*, 2000, 2001) may be the result of *A1*$^+$ individuals having fewer unbound dopamine receptors at any given antipsychotic dose. Our results indicate that in addition to the D_2 receptor binding dissociation constant of antipsychotic medications, individual D_2 receptor density is also important in determining prolactin response to antipsychotic agents.

Individuals with the *A1* allele have a reduced density of brain D_2 receptors (Noble *et al*, 1991; Thompson *et al*, 1997; Phjalainen *et al*, 1998; Jonsson *et al*, 1999). An early brain autopsy study (Noble *et al*, 1991) found a significant reduction of approximately 30% in the number of D_2 dopamine receptors (B_{max}) in the caudate nucleus of *A1*$^+$ compared with *A1*$^-$ subjects; there was no difference in D_2 binding affinity (K_d) between the two allelic groups. Thompson *et al* (1997) also reported a 30–40% reduction in D_2 receptor density in the striatum of *A1*$^+$ compared with *A1*$^-$ individuals. An *in vivo* study of healthy Finnish volunteers (Pohjalainen *et al*, 1998) showed significantly decreased D_2 receptor density in the striatum of *A1*$^+$ compared with *A1*$^-$ individuals, with no difference in K_d between the two groups. In another positron emission tomography study of healthy humans using [^{11}C]-labelled raclopride (Jonsson *et al*, 1999), a significant association of the *A1* allele was found with low D_2 receptor density. *Taq*1A *DRD2* variants are now known to be in linkage disequilibrium with C957T, a synonymous mutation in the human *DRD2* (Duan *et al*, 2003). Furthermore, C957T affects messenger ribonucleic acid (mRNA) folding, leading to a decrease in mRNA stability and a 50% decrease in D_2 dopamine receptor proteins. These effects dramatically diminish dopamine-induced upregulation of D_2 receptors. As a result of fewer D_2 receptors at any dose of antipsychotic medication, *A1*$^+$ individuals may have a lower density of free, unbound D_2 receptors, and consequently an enhanced prolactin response.

Dopamine receptor drug occupancy and consequent receptor blockade are necessary for both clinical antipsychotic action (Kapur & Remington, 2001) and a variety of other effects. Studies with conventional antipsychotic drugs report that approximately 70% occupancy results in maximal therapeutic efficacy (Nordstrom *et al*, 1993). A trend towards improved efficacy in patients with treatment-resistant schizophrenia was found when doses of olanzapine were increased to an average of 30.4 mg (Volavka *et al*, 2002). Preliminary investigations have been undertaken to increase the efficacy of clozapine, an agent with a high D_2 receptor dissociation constant or loose binding, by adding haloperidol, an agent with a low dissociation constant (Kapur *et al*, 2001). Individuals lacking the *A1* allele may be more likely to benefit from these approaches to improve drug D_2 receptor occupancy given that they may have relatively more free, unbound, D_2 receptors. Conversely, *A1*$^+$ individuals are unlikely to derive as much improvement from this approach, with optimal therapeutic effect being likely at lower dosages in these patients. Patients lacking the *A1* allele may require higher doses for maximal antipsychotic effect, particularly when prescribed a loosely binding antipsychotic such as clozapine or quetiapine.

According to the rapid dissociation model (Kapur & Seeman, 2001), loose-binding atypical agents are hypothesised to have an antipsychotic action without causing other effects of dopamine blockade such as raised prolactin levels or extrapyramidal side-effects (Kapur & Seeman, 2001). Our data are not consistent with this,

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because clozapine has definite effects on serum prolactin levels, with *A1*+ individuals having significantly raised prolactin levels compared with *A1*− patients. The D_2 blockade effect of clozapine in *A1*+ patients is not limited to an antipsychotic effect alone.

Other clinical parameters influenced by D_2 receptors require investigation. For example, D_2 receptor occupancy correlates with liability to extrapyramidal adverse effects in patients treated with risperidone (Yamada *et al*, 2002) and a variety of antipsychotic drugs, including clozapine (Broich *et al*, 1998), haloperidol (Kapur *et al*, 2000) and olanzapine (Jauss *et al*, 1998). Individuals with the *A1* allele treated with antipsychotic medication may experience extrapyramidal adverse effects at lower dose than *A1*− patients, as these patients have decreased nigrostriatal D_2 receptor density (Thompson *et al*, 1997).

Limitations of the study

Although the total number of patients investigated is adequate, one of the limitations of this study is the relatively small number of patients in each medication subgroup. Further research involving larger numbers of patients with each individual medication is indicated in order to ascertain whether or not this association occurs with specific antipsychotic agents. Prospective studies examining the changes in prolactin levels over time are also recommended.

Implications of the study

Our study implicates the D_2 receptor dissociation constant of the antipsychotic agent as well as DRD_2 variants as important determinants of D_2 receptor blockade induced by antipsychotic medications. Patients carrying the *A1* allele generally display higher prolactin levels, probably as a result of lower density of free, unbound, D_2 receptors, and may be at increased risk of adverse effects associated with hyperprolactinaemia. The results demonstrate that this association is most evident with the loose D_2 receptor binding antipsychotic agent, clozapine. Future research should employ this pharmacogenetic approach to investigate clinical parameters other than prolactin response. This may result in clinicians being able to optimise antipsychotic treatment with regard to drug selection, dose and possible adverse effects.

CLINICAL IMPLICATIONS

- In patients with schizophrenia, serum prolactin levels increased in proportion to tightness of antipsychotic medication D_2 dopamine receptor binding.
- Patients with the *DRD2*A1* allele treated with antipsychotic medications had higher prolactin levels than patients without this allele, and a higher percentage of patients with the *DRD2*A1* allele compared with patients without this allele had hyperprolactinaemia.
- The *A1* allele of *DRD2* may be a useful clinical marker for identification for those at risk of hyperprolactinaemia and associated adverse effects.

LIMITATIONS

- Studies with a larger number of people with schizophrenia in each medication subgroup are recommended.
- Prospective studies examining changes in prolactin levels over time are indicated.
- Clinical correlation of hyperprolactinaemia in patients with the *DRD2*A1* allele were not assessed.

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