

Polymorphism of the Promoter Region of the Serotonin 5-HT_{2C} Receptor Gene and Clozapine-Induced Weight Gain

Gavin P. Reynolds, Ph.D.

Zhijun Zhang, M.D., Ph.D.

XiaoBin Zhang, M.D.

Objective: Weight gain, leading to further morbidity and poor treatment adherence, is a common consequence of treatment with antipsychotic drugs. A recent study showed that a polymorphism of the promoter region of the serotonin 5-HT_{2C} receptor gene is associated with antipsychotic-induced weight gain. The authors determined whether this association held true for weight gain after clozapine treatment.

Method: Thirty-two Chinese Han patients with first-episode schizophrenia were genotyped for the -759C/T polymorphism and

had weight changes monitored after 6 weeks of clozapine treatment.

Results: The authors found that the 10 patients with the -759T variant allele showed significantly less weight gain than those without this allele. The effect was strongest in the male patients and not apparent in the female patients.

Conclusions: These findings identify an important genetic factor associated with clozapine-induced weight increases in schizophrenia.

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One major side effect of treatment with antipsychotic drugs is weight gain. This problem has become more apparent with increasing use of the newer atypical antipsychotics. Two of these drugs, clozapine and olanzapine, may induce particularly profound weight gain, although of the other classical and atypical antipsychotics, few are free of this effect (1). Inevitably, drug-induced weight gain has consequences on both treatment adherence and morbidity.

The underlying mechanisms remain unclear, although there are some pharmacological clues, with effects proposed at, e.g., histamine, serotonin (5-HT), and adrenergic receptors (2). The 5-HT_{2C} receptor has been particularly implicated; knockout of this receptor in mice can result in obesity and increased feeding (3). Clozapine and olanzapine are high-affinity 5-HT_{2C} antagonists, which could contribute to their propensity to induce weight gain.

The substantial interindividual and interracial differences in drug-induced weight gain suggest that genetic factors may be important (4). Genetic studies of the 5-HT_{2C} receptor have concentrated on the cys23ser polymorphism, reportedly associated with clozapine response (5) and tardive dyskinesia (6). This polymorphism, however, is not associated with abnormal body weight (7), and a recent study (4) showed no significant association with clozapine-induced weight gain. Nevertheless, Yuan et al. (8) identified several polymorphisms of the promoter region of the 5-HT_{2C} receptor gene associated with obesity and diabetes. These authors proposed that these likely functional mechanisms relate to the effects of observed differences in promoter activity on levels of receptor ex-

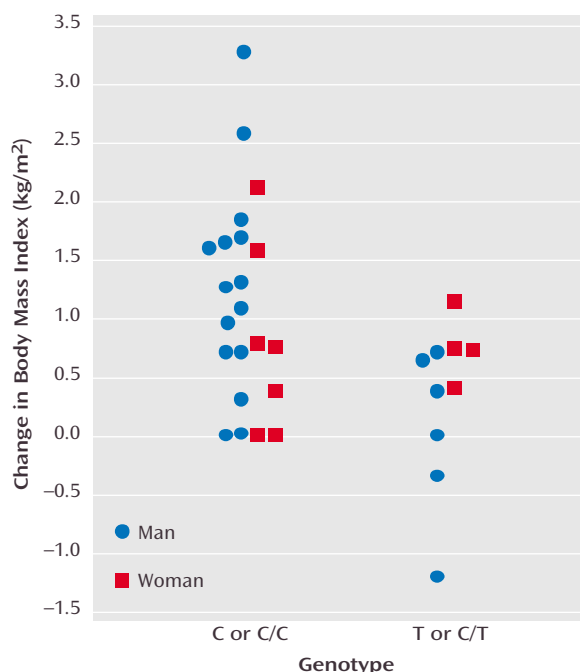
pression. Their finding prompted us to determine whether one of their identified polymorphisms, -759C/T, might differentiate effects on body weight in patients being treated with antipsychotic drugs. In a study of 123 drug-naïve patients, we found that this was indeed the case; 22% of subjects carrying the -759T allele had substantially lower weight gain after treatment with antipsychotic drugs (9).

The patients received mainly risperidone or chlorpromazine, which has moderate effect on weight gain (1). It was unclear whether the more profound weight gain occurring with clozapine and olanzapine, both likely to induce substantial 5-HT_{2C} receptor blockade at normal clinical doses, would also demonstrate a genetic association with the -759C/T polymorphism. Thus, we investigated whether weight gain with clozapine treatment was also associated with this polymorphism of the promoter sequence of the 5-HT_{2C} receptor gene.

Method

We analyzed a subgroup of patients from our original study of weight gain in Chinese Han patients admitted after a first episode of schizophrenia (9). Exclusion criteria included evidence of other medical or neurological illness and family history of diabetes or eating disorder. Genomic DNA was isolated from blood taken on admission after we obtained written informed consent; ethical approval for the study was obtained from the Nanjing Brain Hospital. A total of 32 subjects were studied over a period of 6 weeks after initiation of clozapine treatment; the mean dose was 273 mg/day (SD=31). Of these subjects, four received clozapine from the time of admission, while 28 were switched to clozapine after review of their first 6 weeks of treatment, according to local clinical

FIGURE 1. Association of the -759C/T Genotype With Weight Gain After 6 Weeks of Clozapine Treatment in 32 Chinese Subjects With First-Episode Schizophrenia



cal practice. Their weights were recorded, and changes in body mass index (kg/m^2) were calculated.

Genotypes were identified from *FauI*-digested fragments of two-primer products amplified by polymerase chain reaction corresponding to -885 to -634 of the 5-HT_{2C} receptor gene regulatory region on chromosome X (GenBank accession number U49648) (8, 9). Male patients showed hemizygosity, with six (28.6%) of 21 carrying the variant allele, while four (36.4%) of 11 female patients were heterozygous. The association of genotype (presence or absence of the -759T allele) to weight gain was tested with univariate analysis of variance (ANOVA), which also provided correlation coefficients. All statistical analyses employed SPSS version 10.0 (SPSS, Inc., Chicago); data are expressed as means and standard deviations.

Results

Substantial weight gain was observed in the 6 weeks after initiation of clozapine treatment, with an increase of 2.4 kg ($\text{SD}=2.7$). Figure 1 shows that this weight gain, expressed as change in body mass index, was substantially and significantly less in the patients with the -759T allele (mean=0.32 kg/m^2 , $\text{SD}=0.68$, versus mean=1.12 kg/m^2 , $\text{SD}=0.88$) ($F=6.49$, $\text{df}=1$, 30, $p<0.02$, $r^2=0.18$). This association held true after exclusion of the four patients receiving clozapine at admission ($F=4.31$, $\text{df}=1$, 26, $p<0.05$) and after exclusion of two subjects with body mass indexes <18 and one with a body mass index >28 ($F=4.29$, $\text{df}=1$, 27, $p<0.05$). Stepwise linear regression established that there were no significant confounding effects of initial body mass index, age, duration of illness, or drug dose on weight gain.

Although after inclusion of sex as a fixed factor in ANOVA, the sex-by-genotype interaction did not reach significance

($F=3.49$, $\text{df}=1$, 28, $p<0.08$); the results suggested differential effects between male and female patients. Separate analysis showed a strong effect of genotype on weight gain in male patients (-759C: mean=1.26 kg/m^2 , $\text{SD}=0.90$; for -759T: mean=0.03 kg/m^2 , $\text{SD}=0.72$) ($F=6.55$, $\text{df}=1$, 19, $p=0.008$, $r^2=0.32$) but not in female patients (C/C: mean=0.80 kg/m^2 , $\text{SD}=0.79$; C/T: mean=0.75 kg/m^2 , $\text{SD}=0.31$).

Discussion

Our results show that the -759C/T polymorphism of the 5HT_{2C} receptor regulatory region influences initial weight gain after clozapine treatment of schizophrenia patients. The correlation coefficients suggest that this polymorphism accounts for approximately 18% of the variance in weight gain in this study group. It is notable that the association was stronger in the male patients, explaining approximately 32% of the weight gain, but was not apparent in the female patients. This finding is based on a small group of female patients and needs replication before definitive conclusions can be drawn. However, the effect may be related to the X linkage of the 5-HT_{2C} receptor gene; the heterozygous female phenotype results from contributions from both the common (-759C) and variant (-759T) alleles.

Clozapine-induced weight gain depends on several factors not addressed here. These may include effects at other receptors; functional polymorphisms in such candidate genes may contribute to individual differences, as will several nongenetic factors. Replication of our results in non-Chinese racial groups would confirm the potential of pharmacogenetics in predicting patient susceptibility to a major side effect limiting antipsychotic drug use.

Received July 25, 2002; revision received Dec. 7, 2002; accepted Dec. 13, 2002. From the Department of Biomedical Science, University of Sheffield; and the Department of Psychiatry, Nanjing Brain Hospital and Nanjing Medical University, Nanjing, China. Address reprint requests to Dr. Reynolds, Department of Biomedical Science, University of Sheffield, Sheffield S10 2TN, UK; g.p.reynolds@sheffield.ac.uk (e-mail).

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