Weight gain, antipsychotic drug treatment and pharmacogenomics

Gavin P Reynolds

Department of Biomedical Science, University of Sheffield, Western Bank, Sheffield, S10 2TN, UK
Tel: +44 (0)114 222 4662; Fax: +44 (0)114 276 5413; E-mail: G.P.Reynolds@sheffield.ac.uk

'It would be surprising and disappointing, if in a few years' time genetic testing for weight gain susceptibility was not a routine procedure prior to drug treatment of psychiatric patients.'

Pharmacotherapy is almost inevitably associated with unwanted side effects. This is particularly true for psychiatric drugs, which are notably associated with a wide variety of common, often severe and limiting, side effects including sedation, lethargy, hypotension, autonomic effects, both acute and chronic motor symptoms and weight gain.

The tolerability of such side effects relates to a variety of factors, which include social attitudes as well as perceptions of risk and benefit. There are often substantial individual and occasionally ethnic differences in the susceptibility to side effects, pointing to pharmacogenomic influences. Minimizing the incidence of such side effects has been a major target of drug development, although as yet little attention has been paid to the potential that pharmacogenomics may offer to understanding treatment-induced side effects.

Classically, the extrapyramidal side effects (EPS) have been considered to be the most troublesome of those induced by antipsychotics and include:

- parkinsonism
- akathisia (motor restlessness)
- dyskinesias

As freedom from EPS has been a major target in the development of new drugs, there are now several antipsychotic treatments available that have a lower incidence of these side effects. These 'atypical' drugs have proven invaluable for many patients, although they have yet to entirely replace cheaper classical antipsychotic drugs.

However, with increasing use of newer atypical antipsychotics and diminishing incidence of EPS, other problematic side effects have become more apparent. One of the most disabling of these, weight gain, will not only influence tolerance of and hence compliance with, drug treatment but is inevitably associated with substantial morbidity. This includes diabetes, hypertension and cardiovascular disease, along with other consequences of obesity, such as joint disease. Two atypical antipsychotic drugs, clozapine and olanzapine, may induce particularly profound weight gain although few of the other antipsychotics are free of this effect [1]. However, drug induced weight gain is not unique to the antipsychotics. A variety of other drugs can induce this side effect including some antidepressants and mood stabilizers and the antimigraine 5-HT_{1D} agonists.

The underlying mechanisms are far from understood. The pharmacological profile of the antipsychotic drugs has provided clues, with effects at a variety of neurotransmitter receptors being implicated [2]. 5-HT systems have long been known to be associated with feeding and appetite, primarily via influences at the hypothalamus. Almost all the newer atypical antipsychotics have high affinities for the 5-HT_{2A} receptor and several also affect the 5-HT_{2C} receptor site. This latter receptor has been particularly implicated in weight gain since the finding that gene knockout of the 5-HT_{2C} receptor in mice can result in obesity and increased feeding [3]. Clozapine and olanzapine are high-affinity 5-HT_{2C} antagonists likely to block this receptor site at normal clinical doses, and this action could certainly contribute to their propensity to induce weight gain.

The strong, if circumstantial, evidence for the involvement of 5-HT in feeding behavior has provided a valuable source for candidate gene hypotheses. The importance of 5-HT systems in the treatment of psychiatric disorders has stimulated the investigation of 5-HT-related candidate genes in other aspects of neuropsychiatry. The polymorphisms investigated in these candidate genes are often functional. For example, the common insertion/deletion polymorphism of the promoter region of the 5-HT transporter gene has been associated with affective disorder [4], while the structural coding region and promoter polymorphisms of the 5-HT_{2A} receptor gene are associated with schizophrenia and antipsychotic drug response [5].

Ashley Publications Ltd
www.ashley-pub.com

 ISSN 1462-2416

There have been some recent attempts to apply such pharmacogenetic hypotheses to understanding individual variability in drug-induced weight gain. A study of several polymorphisms of genes relating to 5-HT neurotransmission, including those of the 5-HT transporter and several 5-HT receptors failed to identify any association with weight gain induced by clozapine [6]. Another investigation of nine candidate genes, including three 5-HT receptors, also failed to identify any association with clozapine-induced weight gain [7].

'Some preliminary studies using reporter gene assays suggested that the likely mechanisms relate to differences in promoter activity, resulting in differences in levels of receptor expression.'

Previous genetic studies of the 5-HT_{2C} receptor in schizophrenia and its treatment have concentrated primarily on the Cys23Ser (68C/G) polymorphism. This has also been implicated as a genetic factor in antipsychotic drug response [8], although it is not associated with abnormal body weight [9], nor is there a significant association with clozapine-induced weight gain [7]. Its very low frequency in a Chinese population certainly rules it out as important in the genetic control of drug-induced weight gain in this ethnic group. However, a recent pharmacogenetic study [10] identified several haplotypes of the promoter region of the 5-HT_{2C} receptor gene; these comprised four polymorphisms: a variable length tandem repeat (VLTR) in linkage disequilibrium with three SNPs. Interestingly, these were found to be associated with obesity and diabetes in a Japanese population [10]. Some preliminary studies using reporter gene assays suggested that the likely mechanisms relate to differences in promoter activity, resulting in differences in levels of receptor expression. This was an exciting observation in that it provided strong evidence for the 5-HT_{2C} receptor as a candidate for the genetic control of drug-induced weight gain.

The results from a study of one of these SNPs (–759C/T) in a series of 123 Chinese first-episode patients with schizophrenia have recently been published [11]. It was found that this genetic marker differentiated effects on body weight following antipsychotic drug treatment, whereby presence of the variant –759T allele appeared to be protective. This was best illustrated by using the standard Food and Drug Administration (FDA) criterion of a 7% increase as indicative of a clinically significant weight gain. After 6 weeks of treatment with antipsychotic drugs, 28% of the 96 patients with the –759C allele, but none of those carrying the T allele, met this criterion; after 10 weeks of treatment the corresponding proportions were 51% and 15%, yielding an odds ratio of 6.0. The effect was apparent whether the patients received either chlorpromazine, a classical antipsychotic, or the atypical risperidone. A further analysis (unpublished) of a subgroup of these first-episode patients switched to clozapine, one of the two worst offenders in inducing weight gain, showed that with this drug too the –759 SNP was strongly associated with weight gain.

These data yielded some further interesting observations relating to the X-linkage of the 5-HT_{2C} receptor gene. While homozygous C/C females and hemizygous C allele males both demonstrated substantial weight gain, female (C/T) patients carrying the variant allele appeared to show a greater weight gain than their male (hemizygous T) counterparts. This is likely to reflect the contributions from both the C and T alleles to the female phenotype.

These findings clearly implicate neurotransmitter action through the 5-HT_{2C} receptor in the pathophysiological mechanisms underlying weight gain following initial antipsychotic drug treatment. However, what exactly those mechanisms might be remains elusive. Although the drugs that are most problematic demonstrate substantial 5-HT_{2C} antagonism, some with relatively weak effects at this receptor still induce weight gain. An example of such a drug is risperidone, where the weight gain is nevertheless still apparently under the control of the 5-HT_{2C} promoter polymorphism.

Thus, the pharmacology underlying antipsychotic drug-induced weight gain may involve a variety of effects, not necessarily always including 5-HT_{2C} antagonism, and these pharmacological mechanisms can be differentiated from the pharmacogenomic control provided by the 5-HT_{2C} promoter polymorphism. How exactly might this control be exerted? The fact that the promoter SNPs contribute to haplotypes with functional differences provides a strong indication of what might be the mediating 'endophenotype'. The variant form reportedly has a higher promoter activity, presumably leading to higher receptor expression [10], although it

should be mentioned that a recent report failed to find an effect of the VLTR polymorphism on promoter activity [12]. Whether or not the genotypic differences related to differences in receptor density (which would need to be established in brain tissue) and hence to differences in 5-HT_{2C}-mediated neurotransmission, it is still hard to explain differential effects on weight gain in patients receiving clozapine, which would fully occupy 5-HT_{2C} receptors. Thus, more complex effects than genotypes producing differences in numbers of receptors need to be invoked. One explanation might be that the 5-HT_{2C} receptor-mediated control of weight gain is relatively less important in subjects carrying the –759T allele, presumably as a result of development differences consequent upon the immediate effects of the promoter polymorphisms. This certainly provides some testable working hypotheses relating to, for example, measures of hypothalamic 5-HT_{2C} function.

Nevertheless, whatever the underlying mechanism of the differences in weight gain between genotyes, the observation provides a potential test for the propensity to weight gain in patients being prescribed antipsychotic drugs. It is likely, although yet to be shown, that the finding will generalize to the weight gain observed with a range of other drug treatments. These include:

- the antidepressant mirtazepine, which is a 5-HT_{2C} antagonist
- the serotonin re-uptake inhibitors
- other drugs with effects on 5-HT systems, such as lithium and the 5-HT_{1D} agonists

Of course there are many influences on drug-induced weight gain, and the 5-HT_{2C} receptor gene polymorphism is only one of a variety of genetic factors that may have effects on appetite, satiety, fat metabolism and disposition, thirst, activity and so on. The behavioral mechanism behind weight gain induced by antipsychotic drugs is not understood, although evidence points to a supression of satiety, at least with olanzapine [13]. This suggests in turn an effect on hypothalamic function, possibly through the action of 5-HT_{2C} receptors on the satiety response.

'Weight gain is not solely under genetic control; environmental factors inevitably interact with genomic influences to modify their effects on the organism.'

Although the association with the –759C/T polymorphism is a strong one, it only explains a proportion of the variance in drug-induced weight gain. Functional polymorphisms in other neurotransmitter receptors that mediate hypothalamic function may also play important roles. But weight gain is not solely under genetic control; environmental factors inevitably interact with genomic influences to modify their effects on the organism. This environmental interaction with genetics is no better illustrated than by the current obesity epidemic that, despite the strong genetic component, can be understood in terms of a variety of recent and rapid social and economic changes.

Drug-induced weight gain will also be influenced by non-genetic factors. The drug treatment itself can be modified; for example, patients can be prescribed antipsychotic drugs with fewer or minimal effects on weight. Dietary restriction and education can also be valuable. However, there is no doubt that identifying potential genetic susceptibility to weight gain in patients would provide an invaluable addition to the clinical information from which pharmacotherapeutic decisions can be made.

It is unfortunate that genetic testing is not yet an accepted and routine part of the process in determining optimal and individualized pharmacotherapy, despite the clear potential that pharmacogenomics has to offer. CYP2D6 and apolipoprotein E status are just two of many other examples of genetic measures that could provide valuable information for drug prescribing. It would be surprising and disappointing, if in a few years' time genetic testing for weight gain susceptibility was not a routine procedure prior to drug treatment of psychiatric patients. Then pharmacogenomics will truly have come of age.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Allison DB, Mentore JL, Heo M *et al.*: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am. J. Psychia.* 156, 1686-1696 (1999).

• **A comprehensive meta-analysis of the different propensities of the antipsychotic drugs to induce weight gain.**

2. Casey DE, Zorn SH: The pharmacology of weight gain with antipsychotics. *J. Clin. Psychia.* 62(Suppl. 7), 4-10 (2001).

3. Tecott LH, Sun LM, Akana SF *et al.*: Eating disorder and epilepsy in mice lacking 5-HT2C serotonin receptors. *Nature* 374, 542-546 (1995).

•• **An important receptor knockout model highlighting the role of the 5-HT_{2C} receptor in the control of body weight.**

4. Lesch KP: Variation of serotonergic gene expression: neurodevelopment and the complexity of response to psychopharmacologic drugs. *Eur. Neuropsychopharmacol.* 11, 457-474 (2001).

• **A useful review of the different genomic approaches to investigating the 5-HT system and its pharmacogenetics, including a discussion of 5-HT pharmacogenomics in a developmental context.**

5. Arranz MJ, Munro J, Owen MJ *et al.*: Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. *Mol. Psychia.* 3, 61-66 (1998).

6. Hong CJ, Lin CH, Yu YWY, Yang KH, Tsai SJ: Genetic variants of the serotonin system and weight change during clozapine treatment. *Pharmacogenetics* 11, 265-268 (2001).

7. Basile VS, Masellis M, McIntyre RS, Meltzer HY, Lieberman JA, Kennedy JL: Genetic dissection of atypical antipsychotic-induced weight gain; novel preliminary data on the pharmacogenetic puzzle. *J. Clin. Psychia.* 62(Suppl. 23), 46-66 (2001).

• **A useful and comprehensive review of the complexities of hypothalamic control of body weight, including (negative) association data testing some candidate gene hypotheses of weight gain induced by clozapine.**

8. Sodhi MS, Arranz MJ, Curtis D *et al.*: Association between clozapine response and allelic variation in the 5-HT2C receptor gene. *Neuroreport* 7, 169-172 (1995).

• **An early observation of a genetic factor contributing to antipsychotic drug response.**

9. Lentes KU, Hinney A, Ziegler A *et al.*: Evaluation of a Cys23Ser mutation within the human 5-HT2C receptor gene: no evidence for an association of the mutant allele with obesity or underweight in children, adolescents and young adults. *Life Sci.* 61, PL9-P16 (1997).

10. Yuan X, Yamada K, Ishiyama-Shigemoto S, Koyama W, Nonaka K: Identification of polymorphic loci in the promoter region of the serotonin 5HT2C receptor gene and their association with obesity and Type II diabetes. *Diabetologia* 43, 373-376 (2000).

•• **First identification of the importance of these functional polymorphisms in control of body weight.**

11. Reynolds GP, Zhang ZJ, Zhang XB: Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. *Lancet* 359, 2086-2087 (2002).

•• **Demonstration of a strong association of a polymorphism of the promoter region of the 5-HT_{2C} receptor with antipsychotic drug-induced weight gain in previously untreated schizophrenic patients.**

12. Meyer J, Saam W, Mossner R *et al.*: Evolutionary conserved microsatellites in the promoter region of the 5-hydroxytryptamine receptor 2C gene (HTR2C) are not associated with bipolar disorder in females. *J. Neural Transm.* 109, 939-946 (2002).

13. Thornton-Jones Z, Neill JC, Reynolds GP: The atypical antipsychotic olanzapine enhances ingestive behaviour in the rat. *J. Psychopharmacol.* 16, 35-37 (2002).

• **A demonstration of the acute effect of olanzapine in increasing feeding via a supression of satiety.**