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The 5-HT_{2C} receptor and antipsychotic-induced weight gain – mechanisms and genetics

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Abstract

The mechanisms underlying weight gain resulting from antipsychotic drugs are not fully understood, although antagonism of the 5-HT_{2C} receptor is likely to contribute. Animal studies indicate that the drugs most likely to cause weight gain, clozapine and olanzapine, have direct effects on the NPY-containing neurons of the hypothalamus; these neurons mediate the effects of the circulating anorexigenic hormone leptin on the control of food intake.

The substantial differences between individuals in the extent of antipsychotic-induced weight gain suggest that genetic factors may be important. We have been studying pharmacogenetic correlates and find that a common 5-HT_{2C} receptor promoter region polymorphisms demonstrates strong associations with weight gain in two first episode psychotic samples. In both series, we have found further association of antipsychotic drug-induced weight gain with a common and functional polymorphism of the gene for leptin. Along with initial BMI, these two pharmacogenetic factors account for almost 30% of the variance in drug-induced weight gain. Interestingly, the 5-HT_{2C} polymorphism appears to determine levels of circulating leptin, providing a potential mechanism underlying the genetic association of the 5-HT_{2C} receptor with weight gain. We have undertaken functional studies of haplotypes of the 5-HT_{2C} promoter region and find the allele associated with protection from weight gain results in reduced promoter activity.

These findings demonstrate the value of pharmacogenetics in determining liability to a major side effect of antipsychotic treatment, and indicate both the molecular and physiological mechanisms underlying this side effect.

Keywords

antipsychotic drugs, pharmacogenetics, weight gain, 5-HT_{2C} receptor, side effects

Introduction – pharmacological mechanisms of antipsychotic-induced weight gain

The extrapyramidal side effects have in the past been considered to be the most troublesome consequences of antipsychotic drug treatment. However, with the introduction of newer 'atypical' drugs that may minimize these problems, other side effects have become more apparent. One of these, weight gain, will not only influence compliance with drug treatment but is inevitably associated with substantial morbidity. This includes diabetes, hypertension and cardiovascular disease, consequences of obesity that make up the metabolic syndrome.

The mechanism of antipsychotic-induced weight gain is unclear at present, however drugs which produce weight gain have high affinities at several receptors such as the 5-HT_{2C}, 5-HT_{1A}, dopamine D2 and histamine H1 receptors. Certainly, 5-HT systems are important in food and body weight regulation: 5-HT is a potent satiety signal; administration of 5-HT to rodents decreases food intake (Blundell and Leshem, 1975). Agonists at the 5-HT_{1A} and 5-HT_{2C} receptors have opposing effects on food intake with 5-HT_{1A} agonists increasing food intake (Dourish *et al*., 1985) and 5-HT_{2C} agonists decreasing food intake (Vickers *et al*., 2000). 5-HT_{2C} antagonists have been shown to increase food intake (Bonhaus *et al*., 1997) and also attenuate the decrease in food intake which is produced by 5-HT_{2C} agonists (Jackson *et al*., 1997; Clifton *et al*., 2000; Hayashi *et al*., 2005) or sibutramine, a 5-HT and noradrenaline reuptake inhibitor (Hayashi *et al*., 2004). Knock-out of the 5-HT_{2C} receptor in mice can result in obesity and increased feeding (Tecott *et al*., 1995). The antipsychotics causing the greatest weight gain are clozapine and olanzapine (Allison *et al*., 1999); they are also high-affinity 5-HT_{2C} antagonists.

However, ziprasidone, another antipsychotic which also has an

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affinity for 5-HT$_{2C}$ receptors, does not produce increased body weight. One explanation may be that ziprasidone acts as a partial agonist/antagonist at 5-HT$_{1A}$ receptors and this may provide a protective mechanism against increases in body weight and/or food intake. Our finding that co-administration of ziprasidone and olanzapine to rats prevents the hyperphagic effect produced by olanzapine alone is certainly consistent with such a protective mechanism (Kirk *et al*., 2004).

Histamine H1 receptors are also implicated in antipsychotic-induced weight gain. The mechanism by which histamine H1 receptor blockade may induce weight gain is unknown; however activation of central histamine H1 receptors decreases food intake in rats and histamine H1 antagonists attenuate the reduction in food intake produced by histamine (Lecklin *et al*., 1998). Histamine H1 antagonists have also been shown to dose-dependently induce feeding in rats (Sakata *et al*., 1988).

Drug-induced weight gain – leptin and hypothalamic processes

The effects of weight-inducing antipsychotic drugs may be mediated through the hypothalamus; this is an important area of the brain which is involved in food intake and body weight regulation. A number of hormones provide satiety signals to the central nervous system; one of these hormones is leptin. Leptin is a circulating hormone that is released by adipocytes in response to increased fat deposition to regulate body weight. Serotonergic and catecholamineric neurons that have inputs to the hypothalamus often contain leptin receptors (Hay-Schmidt *et al*., 2001). Several neuropeptides act in the hypothalamus to influence food intake and related processes; these include neuropeptide Y (NPY), agouti-related peptide (AGRP), pro-opiomelanocortin (POMC), ghrelin and orexin. NPY is one of the most abundant neuropeptides in the brain with high levels in several brain areas including the arcuate nucleus (ARC) and the paraventricular nucleus (PVN) of the hypothalamus (Adrian *et al*., 1983) where it plays a major role in the stimulation of food intake (Levine and Morley, 1984). These neuropeptides respond to changes in leptin levels to ultimately maintain body weight. Central leptin administration in rats decreases NPY levels in the rat hypothalamus (Wang *et al*., 1997). It is believed that leptin acts directly on NPY neurons within the arcuate nucleus of the hypothalamus as a subset of these neurons express leptin receptors (Hakansson *et al*., 1996; Baskin *et al*., 1999). The normal inhibitory effect of leptin on NPY is interrupted in genetic models of obesity leading to increased NPY expression (Wilding *et al*., 1993). NPY is also regulated by serotonin; the 5-HT$_{1B/2C}$ agonist mCPP produced decreases in food intake and NPY levels in the PVN (Dryden *et al*., 1996).

The rat hypothalamus contains 5-HT$_{2C}$ receptors (Abramowski *et al*., 1995; Clemett *et al*., 2000). Furthermore, there is evidence suggesting an interaction between 5-HT$_{2C}$ and leptin; 5-HT$_{2C}$ antagonists attenuate the reduction in food intake produced by leptin thus suggesting that the 5-HT$_{2C}$ receptors are involved in the mechanism of leptin-induced anorexia (von Meyenburg *et al*., 2003). The orexins are present in high levels in the lateral hypothalamus and the perifornical area (de Lecea *et al*., 1998; Sakurai *et al*., 1998); these peptides stimulate food intake (Edwards *et al*., 1999). Drugs which produce weight gain clinically also produce an increase in the activation of hypothalamic orexin neurons (Fadel *et al*., 2002).

Work carried out in our laboratory suggests that NPY is also involved in antipsychotic-induced weight gain. Chronic administration of clozapine, but not haloperidol, produced an increase in NPY-immunoreactive cell density in the rat arcuate nucleus (Kirk *et al*., 2005). Furthermore, we also found that acute olanzapine also produced an increase in NPY (Kirk and Reynolds, 2005). This increase could, at least in part, be due to antagonism of the 5-HT$_{2C}$ receptor resulting in disinhibition of the NPY neurons.

Pharmacogenetic associations with drug-induced weight gain

That the 5-HT$_{2C}$ receptor is directly involved in antipsychotic-induced weight gain is also demonstrated by pharmacogenetic observations. Yuan *et al*. (2000) identified several haplotypes of the promoter region of the 5-HT$_{2C}$ receptor gene – involving three single nucleotide polymorphisms (SNPs) and a variable length GT repeat sequence, all in linkage dysequilibrium – which are associated with obesity and diabetes. This finding prompted us to determine whether one 5-HT$_{2C}$ promoter polymorphism, *-759 C/T*, might be associated with weight gain in a sample of initially drug-naive Chinese patients. We found that this was indeed the case; the 22% of subjects carrying the *-759T* allele had substantially lower weight gain following 10 weeks of treatment with antipsychotic drugs (Reynolds *et al*., 2002). We have recently replicated this in a group of Caucasian first-episode patients, finding that the genetic association remains after long-term (9 months) treatment (Templeman *et al*., 2005). In this study we also observed an effect of the 5-HT$_{2C}$ receptor genotype on blood leptin prior to drug treatment, in which the protective *-759T* allele is associated with higher concentrations of leptin.

The link with leptin is also apparent from pharmacogenetic studies of the leptin gene. We find circulating leptin increases substantially in patients receiving antipsychotic drugs (Zhang *et al*., 2004), indicating that the normal control this hormone imparts on food intake is awry in such patients. Recent reports show that genetic variants in the leptin gene promoter region are associated with obesity and influence leptin function (Mammès *et al*., 2000). We hypothesized that this may also affect drug-induced weight gain and found an association of the *-2548A/G* polymorphism with weight gain (Templeman *et al*., 2005). We find that the 5-HT$_{2C}$ and leptin promoter polymorphisms, together with age and body mass index, account for almost 30% of the variance in short-term drug-induced weight gain.

5-HT$_{2C}$ receptor pharmacogenetics – molecular mechanisms

To understand fully the mechanism(s) underlying the association of the 5-HT$_{2C}$ receptor polymorphism with drug-induced weight gain, it is necessary to understand the effect of the polymorphism

on receptor expression. There have been several gene-reporter studies investigating the effects of the 5-HT$_{2C}$ receptor gene promoter polymorphisms on levels of transcription. First, it has been reported that haplotypes containing either the *-759T* or *-697C* genotype show increased promoter activity when expressed in a mouse embryonal carcinoma cell line (Yuan *et al*., 2000). Investigations again using non-neuronal cell lines support the increased activity of the *-759T* genotype and also report functionality at the *-997* site (Buckland *et al*., 2005). In addition they demonstrate that the length of the GT repeat and the previously untested *-1165G/A* polymorphism have no discernable effects on transcription levels. Data contrary to these findings are also evident in the literature. McCarthy *et al.* (2005) applied the mouse cell model to an extended region of the promoter that incorporated six promoter polymorphisms. Despite the apparent similarities to the published methodology of Yuan *et al*. (2000) there was no reported difference in activity between the two most common haplotypes. However, a reduction in activity was observed in haplotypes containing the *-697C* genotype, which only reached significance in the haplotype containing *-759C* and *-997G* genotypes.

It is therefore unclear whether the resistance to antipsychotic-induced weight gain, conferred to carriers of haplotypes containing the *-759T* genotype, is a result of increased expression of the receptor. We undertook an investigation into the relative activities of the two most abundant haplotypes. That most strongly associated with antipsychotic-induced weight gain, *-997G*, *-759C*, *-697G* (haplotype A) and the haplotype associated with resistance to weight gain, *-997A*, *-759T*, *-697C* (haplotype B) were assessed in SH-SY5Y human neuroblastoma cells, a more physiological relevant cell line. We have reported that haplotype B shows reduced activity, 41% that of haplotype A. A similar reduction, 66% compared to haplotype A, was still apparent after differentiating the cells to produce a more neuronal, post-mitotic, phenotype (Hill and Reynolds, 2005). The apparent contradiction in effect compared to previous findings using non-neuronal cells can be understood in terms of differences in the transcription factor complement between cell types.

These data demonstrate that the 5-HT$_{2C}$ receptor genotype conferring resistance to antipsychotic-induced weight gain is likely to reflect diminished neuronal expression of the receptor. It is therefore hypothesized that underactivity of the 5-HT$_{2C}$ receptor associated with haplotype B results in adaptive changes in other systems regulating weight and food intake resulting in resistance to weight gain. We have observed possible adaptive changes in the leptin system where carriers of the *-759T* genotype, (i.e. primarily haplotype B) have increased basal levels of circulating leptin (Templeman *et al*., 2005). Although the mechanisms by which 5-HT$_{2C}$ receptor signalling regulates leptin levels is unknown it is possible that increased circulating leptin levels act on hypothalamic NPY neurones to decrease NPY release resulting in reduced feeding.

Conclusions

The 5-HT$_{2C}$ receptor is closely involved in the weight gain that occurs following treatment with many antipsychotic drugs. It is likely to contribute directly, via the 5-HT$_{2C}$ antagonist effects of these drugs, to the pharmacological mechanisms leading to increased food intake, although effects of the drugs at other receptors may also be important as additional, or modulatory, mechanisms. The receptor effects of the antipsychotics are likely to be mediated by neuronal systems in the hypothalamus and involve disruption of the normal response to leptin and possibly other hormones controlling food intake and body weight. Additional to the antagonist effect of the antipsychotic drugs at the 5-HT$_{2C}$ receptor, functional variants of the promoter region of the receptor gene also determine the severity of antipsychotic-induced weight gain. The underlying mechanisms are likely to involve effects of promoter region polymorphisms on receptor expression, with consequent effects that may include an influence on levels of circulating leptin.

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