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Chao Deng

University of Wollongong, chao@uow.edu.au

Katrina Western-Green

University of Wollongong, kweston@uow.edu.au

Xu-Feng Huang

University of Wollongong, xhuang@uow.edu.au

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Abstract

Atypical antipsychotics such as olanzapine and clozapine are effective at treating the multiple domains of schizophrenia, with a low risk of extra-pyramidal side-effects. However a major downfall to their use is metabolic side-effects particularly weight gain/obesity, which occurs by unknown mechanisms. The present paper explores the potential candidature of histaminergic neurotransmission in the mechanisms of atypical antipsychotic-induced weight gain, with a focus on the histaminergic H1 and H3 receptors. Olanzapine and clozapine have a high affinity for the H1 receptor, and meta-analyses show a strong correlation between risk of weight gain and H1 receptor affinity. In addition, olanzapine treatment decreases H1 receptor binding and mRNA expression in the rat hypothalamus. Furthermore, a complex role is emerging for the histamine H3 receptor in the control of hunger. The H3 receptor is a pre-synaptic autoreceptor that inhibits the synthesis and release of histamine, and a heteroreceptor that inhibits other neurotransmitters such as serotonin (5-HT), noradrenaline (NA) and acetylcholine (ACh), which are also implicated in the regulation of food intake. Thus, the H3 receptor is in a prime position to regulate food intake, both through its control of histamine and its influence on other feeding pathways. We proposed that a mechanism for atypical antipsychotic-induced weight gain may be partly through the H3 receptor, as a drug-induced decrease in H1 receptor activity may decrease histamine tone through the H3 autoreceptors, compounding the weight gain problem. In addition, atypical antipsychotics may affect food intake by influencing 5-HT, NA and ACh release via interactions with the H3 heteroreceptor.

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Full Title: The role of histaminergic H1 and H3 receptors in food intake: A mechanism for atypical antipsychotic-induced weight gain?

Authors: Chao Deng ^{1,2,*}, Katrina Weston-Green ^{1,2}, Xu-Feng Huang ^{1,2}

1: Centre for Translational Neuroscience, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia

2: Schizophrenia Research Institute, 384 Victoria Street, Darlinghurst, 2010, NSW, Australia

*** Corresponding author:**

Dr Chao Deng, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia

E-mail: chao@uow.edu.au, Tel: (+61 2) 4221 4934, Fax: (+61 2) 4221 4096

Abstract

Atypical antipsychotics such as olanzapine and clozapine are effective at treating the multiple domains of schizophrenia, with a low risk of extra-pyramidal side-effects. However a major downfall to their use is metabolic side-effects particularly weight gain/obesity, which occurs by unknown mechanisms. The present paper explores the potential candidature of histaminergic neurotransmission in the mechanisms of atypical antipsychotic-induced weight gain, with a focus on the histaminergic H1 and H3 receptors. Olanzapine and clozapine have a high affinity for the H1 receptor, and meta-analyses show a strong correlation between risk of weight gain and H1 receptor affinity. In addition, olanzapine treatment decreases H1 receptor binding and mRNA expression in the rat hypothalamus. Furthermore, a complex role is emerging for the histamine H3 receptor in the control of hunger. The H3 receptor is a pre-synaptic autoreceptor that inhibits the synthesis and release of histamine, and a heteroreceptor that inhibits other neurotransmitters such as serotonin (5-HT), noradrenaline (NA) and acetylcholine (ACh), which are also implicated in the regulation of food intake. Thus, the H3 receptor is in a prime position to regulate food intake, both through its control of histamine and its influence on other feeding pathways. We proposed that a mechanism for atypical antipsychotic-induced weight gain may be partly through the H3 receptor, as a drug-induced decrease in H1 receptor activity may decrease histamine tone through the H3 autoreceptors, compounding the weight gain problem. In addition, atypical antipsychotics may affect food intake by influencing 5-HT, NA and ACh release via interactions with the H3 heteroreceptor.

Keywords: antipsychotic; olanzapine; clozapine; body weight gain; obesity; histamine receptor

Abbreviations: 5-HT, serotonin; α -MH, *R*- α -methyl-histamine; ACh, acetylcholine; Arc, hypothalamic arcuate nucleus; CCK, cholecystokinin; DMN, dorsal motor nucleus of the vagal nerve; DVC, dorsal vagal complex; H1RKO, H1 receptor knockout; NA, noradrenaline; NTS, nucleus of the solitary tract; VMH, ventromedial hypothalamic nucleus.

1. Introduction

Antipsychotic drugs play a key role in the treatment of schizophrenia and are increasingly prescribed for other health issues such as bipolar disorder, major depression, dementia and substance abuse (Centorrino et al., 2002). In addition, these drugs are utilized in hospital emergency departments to assist patients presenting with acute psychosis (Ballerini et al., 2003).

Atypical antipsychotic drugs (such as olanzapine and clozapine) are considered to possess superior efficacy in treating the positive, negative and cognitive domains of schizophrenia compared to conventional ‘typical’ antipsychotics, particularly in schizophrenia patients that are non-responsive to conventional drug therapy (Matza et al., 2005, Keefe et al., 2006). Differing to the typical profile, atypical antipsychotic drugs generally affect a range of receptors, including adrenergic, histaminergic, serotonergic and muscarinic, with less antagonistic effects on D2 receptors than typical antipsychotic drugs and therefore a lower propensity to cause extrapyramidal side-effects (Richelson and Souder, 2000, Roth et al., 2004). However, a significant side-effect of atypical antipsychotic drug-use is weight gain/obesity, which is of social and clinical importance as it may lead to further complications such as non-compliance of medication, diabetes and cardiovascular disease. Despite this significance, the mechanisms behind atypical antipsychotic-induced weight gain remain unclear, perhaps because these drugs differ markedly in their pharmacological profiles, and because of the complex and well-preserved interactions between the systems involved in energy balance regulation. Understanding the mechanisms causing this side-effect will help to improve future pharmacotherapies for schizophrenia, as patients commonly undergo many years of drug treatment due to the

chronicity of the disease. The present paper explores the potential candidature of histaminergic neurotransmission in the mechanisms of atypical antipsychotic-induced weight gain, with a focus on the histaminergic H1 and H3 receptors. We propose that the H3 receptor may impact histaminergic H1 signaling, as well as other neurotransmitter systems such as the serotonergic, noradrenaline and acetylcholine pathways, to influence body energy balance regulation.

2. Methods

A reference search was performed across the Medline (January 1996-May 2009) and ScienceDirect (January 1995-May 2009) databases. Key words included atypical antipsychotic, individual drug names (clozapine, olanzapine, risperidone, aripiprazole, quetiapine, and ziprasidone), histamine, and histamine receptor, cross-referenced with weight gain, obesity, and food intake. In addition, the reference list of all papers identified was reviewed.

3. Weight Gain Side-Effect of Olanzapine and Clozapine treatment

Olanzapine is an atypical antipsychotic drug commonly used in the clinical setting due to its efficacy and tolerability in the treatment of the multiple domains of schizophrenia (Keefe et al., 2006, Haro et al., 2009). However, olanzapine and other atypical antipsychotic drugs such as clozapine can induce significant weight gain and further metabolic disorders including insulin resistance, diabetes and lipid metabolism dysfunction. Among antipsychotics, olanzapine has a higher risk for weight gain than the conventional antipsychotics haloperidol, chlorpromazine and fluphenazine, and its atypical counterparts risperidone, aripiprazole, sertindole, thioridazine, quetiapine, amisulpride, zotepine and ziprasidone (Allison et al., 1999, Nasrallah, 2008).

Clozapine, which is also effective for use against treatment-resistant schizophrenia, may induce more weight than olanzapine (4.45kg and 4.15kg, respectively over 10-weeks) (Allison et al., 1999), however a recent study found that high dosages of olanzapine (mean dosage 34mg/day) induced significantly higher weight gain than clozapine (+5.6 \pm 2.0 kg olanzapine vs clozapine, mean dosage 564mg/day, after 6-months treatment) in patients with treatment-resistant schizophrenia (Meltzer et al., 2008). Another study found that patients gained 9.2kg within the first 12 weeks of olanzapine treatment (dosage range 5-20mg/day), and 15.5kg after 52 weeks, plateauing to 15.4kg after 2 years (Zipursky et al., 2005).

The broad receptor binding profile exhibited by olanzapine, clozapine and other atypical antipsychotic drugs may underlie the cause of this weight-gain side-effect, as evidence suggests a role for some of these signaling pathways in obesity. In particular, the histaminergic system is well-documented for its importance in the control of food intake (Yoshimatsu, 2006). However, there appears to be a limited understanding of the effects of weight-inducing atypical antipsychotics on central histaminergic signaling, despite evidence identifying these neurotransmitter pathways as potential targets to assist the current understanding of the mechanisms of atypical antipsychotic-induced weight gain.

4. Histamine and Body Weight Regulation

A vast body of evidence shows the importance of central histamine signaling in the control of food intake and energy regulation (Yoshimatsu et al., 2002, Yoshimatsu, 2006). Histamine neurons are located in the tuberomamillary nucleus of the posterior hypothalamus and project axons throughout most of the brain, with particularly strong

innervation in the hypothalamus (Brown et al., 2001). Histamine depolarises select brainstem neurons in the nucleus of the solitary tract (NTS) and dorsal motor nucleus of the vagal nerve (DMN) in the dorsal vagal complex (DVC) (Poole et al., 2008), which together with the hypothalamus, have a fundamental role in the control and regulation of food intake (Arora and Anubhuti, 2006, Jelsing et al., 2009).

5. Histamine H1 and H3 Receptors and Body Weight Regulation

Histamine exerts its effects through histamine H1, H2, H3 and H4 receptors (Masaki and Yoshimatsu, 2006). The histamine H1 receptor has long been target of interest in the regulation of food intake. Intracerebroventricular application of a histamine H1 receptor agonist (2-(3-trifluoromethylphenyl)histamine) potently suppresses food intake, whilst hypothalamic H1 receptor antagonism results in food intake (Sakata et al., 1997, Han et al., 2008). H1 receptor knockout (H1RKO) mice develop obesity accompanied by increased food intake, altered diurnal feeding patterns, and a decrease in uncoupling protein-1 mRNA expression (Masaki et al., 2004).

In addition to the H1 receptor, the histamine H3 receptor is implicated in the control of food intake. For example, H3 receptor antagonism in the hypothalamus reduces food intake and induces weight loss in diet-induced obese rodents, as well as rhesus monkeys and pigs (Hancock et al., 2004, Malmlof et al., 2005, Malmlof et al., 2007), whilst the H3 agonist, immpip enhances feeding in rats (Chiba et al., 2009). In addition, H3 receptor knock-out mice (H3RKO) exhibit increased body weight gain, food intake and adiposity, coupled with decreased energy expenditure, insulin and leptin resistance, as well as increased histamine turnover therefore decreased hypothalamic histamine levels (Takahashi et al., 2002). Furthermore, the H3

receptor's localisation in the hypothalamus and NTS of the DVC is supportive of its potential role in the regulation of food intake (Poole et al., 2008).

The histamine H3 receptor has a distinct role in numerous appetite signalling pathways. For example, the H3 receptor inverse agonist, thioperamide, inhibits food intake induced by the potent orexigen neuropeptide Y and its structural relative, peptide YY (Itoh et al., 1999), whilst H3 receptor agonists, *R*- α -methyl-histamine (α -MH) and Imetit, decrease bombesin-induced satiety in rats (Kent et al., 1997). In addition, H3 receptor activation reduces the anorexigenic effects of amylin in fasted rats (Lutz et al., 1996). Similarly, a study by Attoub and colleagues (2001) found that α -MH dose-dependently inhibited the satiating effects of cholecystokinin (CCK), whilst thioperamide enhanced CCK-induced satiety. They also found that pre-treatment with pyrilamine, a post-synaptic H1 receptor antagonist, inhibited CCK-induced satiety (Attoub et al., 2001), indicating that whilst H3 controls pre-synaptic histamine concentrations, CCK-induced satiation is also dependent upon the post-synaptic activation of the H1 receptor. Although it is clear that the H3 receptor plays an important role in regulating food intake, the question of how weight-inducing atypical antipsychotic drugs affect H3 receptor neurotransmission appears to be largely unanswered.

6. Histaminergic mechanisms for atypical antipsychotic-induced weight gain

6.1 A role for the H1 receptor

The severity of weight gain induced by an antipsychotic drug may be predicted by its H1 antagonistic properties. In fact, a meta-analysis by two groups, (Kroeze et al., 2003, Matsui-Sakata et al., 2005) found significant strong correlations between

antipsychotic H1 receptor affinity and antipsychotic-induced weight gain. For example, olanzapine is a potent H1 receptor antagonist, whereas haloperidol, an antipsychotic with a low propensity to increase body weight, has a low affinity for H1 receptors (Richelson and Souder, 2000). A recent study from our laboratory found that acute (1-week) and chronic (12-weeks) olanzapine treatment significantly down-regulated H1 receptor mRNA expression in the hypothalamic arcuate (Arc) and ventromedial nucleus (VMH), but not haloperidol or aripiprazole, antipsychotics with a lower risk of weight gain side-effect (Han et al., 2008). In addition, olanzapine decreased H1 receptor binding density in the VMH. This altered H1 signaling was accompanied by an increase in food intake and weight gain in olanzapine-treated rats compared to those treated with aripiprazole or haloperidol (Han et al., 2008). Coinciding with the findings from our laboratory, a study by Kim and colleagues (2007) found that olanzapine and clozapine activate hypothalamic AMP-protein kinase (AMPK), which increases food intake and weight gain (Minokoshi et al., 2004), via H1 receptor antagonism. Taken together, these findings suggest that a possible mechanism for atypical antipsychotic-induced weight gain is through a drug-induced decrease in the hypothalamic expression of the H1 receptor, blockade of which is linked to downstream AMPK activation, resulting in increased food intake (Figure 1) that, when coupled with an insufficient increase in locomotor activity, contributes to weight gain (Kim et al., 2007, Han et al., 2008).

6.2 A possible role for the H3 receptor

The effect of weight-inducing atypical antipsychotic drugs on H3 receptors in the brain appears to be unknown. It is possible that the olanzapine-induced decrease in post-synaptic H1 receptors observed by our early study (Han et al., 2008) would result

in an increase in synaptic histamine, which may slowdown histamine synthesis and secretion through the H3 autoreceptor, compounding the enhancement of feeding behaviour (Figure 1) (Takahashi et al., 2002, Chiba et al., 2009). Supporting this hypothesis, Lozeva and colleagues (2003) found that acute (1-week) enhanced central histamine concentrations, induced by L-histidine loading, increased H3 receptor expression in some regions of the rat brain, excluding the hypothalamus. However, the absence of an increase in hypothalamic H3 receptor binding following L-histidine loading after 1-week may be attributed to the short treatment period, as chronic over-exposure to an agonist can significantly alter the intracellular distribution of these G-protein-coupled receptors (Koenig and Edwardson, 1997). Coinciding with this idea, Poyurovsky and colleagues (2005) evaluated the weight-attenuating effects of β -histidine (a potent H3 antagonist and weak H1 agonist) on olanzapine-induced weight gain in a small group of schizophrenia patients. β -histidine has been shown with an effect to inhibit food intake in rats (Szelag et al., 2001). Through co-administration of olanzapine with β -histidine for 6-weeks, schizophrenia patients showed a weight increase during the initial 2 weeks of the trial with no additional weight gain or a minor reduction of body weight from weeks 3 to 6. This delayed response of β -histidine on curbing and controlling olanzapine-induced weight gain suggests its marked antagonist effect on pre-synaptic H3 receptors, rather than the direct but weak agonist effect on post-synaptic H1 receptor (Poyurovsky et al., 2005). In addition, a study by Lacour and Sterkers (2001) found that 1-week treatment with β -histidine decreased the binding density of the H3 receptor, whilst 3-weeks treatment resulted in an increase in H3 binding in the cat brain. Taken together, these studies provide evidence that examination of H3 binding alterations in a chronic setting may be more representative of the clinical application of weight-inducing antipsychotic drugs.

It is also important to consider that H3 heteroreceptor activity may also play a role in atypical antipsychotic-induced weight gain. The H3 heteroreceptors are located on pre-synaptic axon terminals of serotonin (5-HT), noradrenaline (NA), and acetylcholine (ACh) neurons, where they regulate neurotransmitter release (Pollard et al., 1993, Arrang et al., 1995, Leurs et al., 1998). It has been reported that the H3 heteroreceptors inhibits serotonin release (5-HT), which results in an increase in food intake (Cole et al., 1998). In fact, the clinical efficacy of the anti-obesity drugs, fenfluramine and sibutramine, can be attributed to their ability to enhance 5-HT availability (Cole et al., 1998, Tallett et al., 2009). Also, the antihistamines cyproheptadine and promethazine are non-selective 5-HT receptor antagonists, in addition to their potency as histamine receptor blockers, that induce food-intake and weight gain in humans and rats (Yoshimatsu et al., 2002).

Clozapine has been shown to possess moderately low H3 receptor antagonistic properties (Schlicker and Marr, 1996), which may be contrary to its weight-gain liability in an acute treatment setting. However, antagonism of the H3 heteroreceptor has been shown to disinhibit neurotransmitter release (Arrang et al., 1995), which in the case of H3 heteroreceptors located on NA and ACh neurons, may account for the side-effect of atypical antipsychotic-induced food intake (Figure 1), as studies show that NA and ACh can act as orexigens to increase food intake (Kurose and Terashima, 1999, Pratt and Blackstone, 2009). Furthermore, secretion of these neurotransmitters is inhibited by the activation of H3 receptors (Arrang et al., 1995), whilst H3 antagonism disinhibits the release of these neurotransmitters.

7. Conclusion:

Atypical antipsychotic drugs, such as olanzapine and clozapine, are commonly used in the clinical setting due to their efficacy in treating the multiple domains of schizophrenia. However, these drugs cause weight gain/obesity and other metabolic side-effects such as diabetes and dyslipidaemia, which occur by unknown mechanisms. The histaminergic system is well-documented for its involvement in reducing food intake through the histamine-induced activation of the H1 receptor. Olanzapine and clozapine have a high affinity for the H1 receptor and olanzapine treatment has been shown to decrease H1 receptor binding density and mRNA expression in the hypothalamus. The histamine H3 receptor also plays an important role in food intake and body weight. It acts as a pre-synaptic autoregulator of histamine synthesis and release, as well as a heteroreceptor for numerous other neurotransmitter signalling pathways, some of which are implicated in the regulation of feeding behaviour. However, the effect of weight-inducing antipsychotic drugs on the H3 receptor is unknown. In the present review, we proposed that the weight gain side-effect of some atypical antipsychotic drugs may be partly through an effect on the H3 receptor, compounding the weight gain side-effect. In addition, weight-inducing antipsychotic drugs may increase food intake by affecting the H3 heteroreceptor, which influences 5-HT, NA and ACh release.

Both H1 and H3 receptors appear to be good candidates to enhance the current understanding of the mechanisms of atypical antipsychotic-induced weight gain. In addition, obesity is a non-discriminatory and serious public problem, and understanding the mechanisms behind antipsychotic-induced weight gain may also help to unravel the pathophysiology of obesity in the general population.

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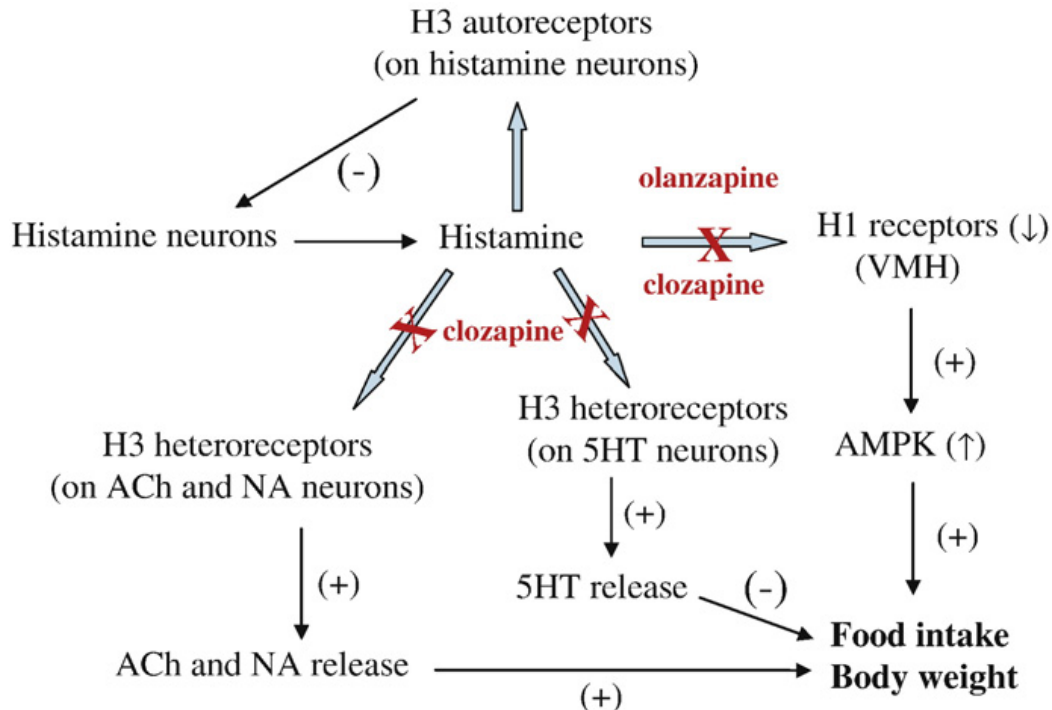


Figure 1 Proposed mechanisms of atypical antipsychotic-induced weight gain through histaminergic H1 and H3 receptors. Olanzapine and clozapine can block H1 receptors and decrease H1 receptor density in the ventromedial nucleus (VMH), activating AMP-protein kinase (AMPK), which increases food intake and weight gain. An olanzapine-induced decrease in post-synaptic H1 receptors may result in an increase in synaptic histamine, which activates the pre-synaptic H3 autoreceptor, slowing histamine synthesis and secretion and compounding hyperphagic behaviour. Clozapine (with some H3 antagonistic properties) may act on H3 heteroreceptors to disinhibit acetylcholine (ACh) and noradrenaline (NA) release, which may enhance food intake. Although antagonistic effects on H3 heteroreceptors may increase 5-HT release, which decreases food intake, these antipsychotics are also 5-HT receptor antagonists which can induce food intake and weight gain. Taken together, the H3 receptor may act as an auto- or hetero-receptor to mediate complex interactions between numerous neurotransmitter systems to induce hyperphagia and body weight gain.