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Ameliorating antipsychotic-induced weight gain by betahistine: mechanisms and clinical implications

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Abstract
Second generation antipsychotic drugs (SGAs) cause substantial body weight gain/obesity and other metabolic side-effects such as dyslipidaemia. Their antagonistic affinity to the histaminergic H1 receptor (H1R) has been identified as one of the main contributors to weight gain/obesity side-effects. The effects and mechanisms of betahistine (a histaminergic H1R agonist and H3 receptor antagonist) have been investigated for ameliorating SGA-induced weight gain/obesity in both animal models and clinical trials. It has been demonstrated that co-treatment with betahistine is effective in reducing weight gain, associated with olanzapine in drug-naïve patients with schizophrenia, as well as in the animal models of both drug-naïve rats and rats with chronic, repeated exposure to olanzapine. Betahistine co-treatment can reduce food intake and increase the effect of thermogenesis in brown adipose tissue by modulating hypothalamic H1R-NPY-AMPKα (NPY: neuropeptide Y; AMPKα: AMP-activated protein kinase α) pathways, and ameliorate olanzapine-induced dyslipidaemia through modulation of AMPKα-SREBP-1-PPARα-dependent pathways (SREBP-1: Sterol regulatory element binding protein 1; PPARα: Peroxisome proliferator-activated receptor-α) in the liver. Although reduced locomotor activity was observed from antipsychotic treatment in rats, betahistine did not affect locomotor activity. Importantly, betahistine co-treatment did not influence the effects of antipsychotics on serotonergic receptors in the key brain regions for antipsychotic therapeutic efficacy. However, betahistine co-treatment reverses the upregulated dopamine D2 binding caused by chronic olanzapine administration, which may be beneficial in reducing D2 supersensitivity often observed in chronic antipsychotic treatment. Therefore, these results provide solid evidence supporting further clinical trials in treating antipsychotics-induced weight gain using betahistine in patients with schizophrenia and other mental disorders.

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Ameliorating Antipsychotic-Induced Weight Gain by Betahistine: mechanisms and clinical implications

Running Title: Betahistine treats antipsychotic-induced weight gain

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Table of Contents

Abstract

Second generation antipsychotic drugs (SGAs) cause substantial body weight gain/obesity and other metabolic side-effects such as dyslipidaemia. Their antagonistic affinity to the histaminergic H_1 receptor (H_1R) has been identified as one of the main contributors to weight gain/obesity side-effects. The effects and mechanisms of betahistine (a histaminergic H_1R agonist and H_3 receptor antagonist) have been investigated for ameliorating SGA-induced weight gain/obesity in both animal models and clinical trials. It has been demonstrated that co-treatment with betahistine is effective in reducing weight gain, associated with olanzapine in drug-naïve patients with schizophrenia, as well as in the animal models of both drug-naïve rats and rats with chronic, repeated exposure to olanzapine. Betahistine co-treatment can reduce food intake and increase the effect of thermogenesis in brown adipose tissue by modulating hypothalamic H_1R-NPY-AMPKα (NPY: neuropeptide Y; AMPKα: AMP-activated protein kinase α) pathways, and ameliorate olanzapine-induced dyslipidaemia through modulation of AMPKα-SREBP-1-PPARα-dependent pathways (SREBP-1: Sterol regulatory element binding protein 1; PPARα: Peroxisome proliferator-activated receptor-α) in the liver. Although reduced locomotor activity was observed from antipsychotic treatment in rats, betahistine did not affect locomotor activity. Importantly, betahistine co-treatment did not influence the effects of antipsychotics on serotonergic receptors in the key brain regions for antipsychotic therapeutic efficacy. However, betahistine co-treatment reverses the upregulated dopamine D_2 binding caused by chronic olanzapine administration, which may be beneficial in reducing D_2 supersensitivity often observed in chronic antipsychotic treatment. Therefore, these results provide solid evidence supporting further clinical trials in treating antipsychotics-induced weight gain using betahistine in patients with schizophrenia and other mental disorders.

Key Words: Betahistine; Antipsychotic drug; Histamine receptor; Weight gain; Locomotor activity; Therapeutic efficacy

Short Bullet Points

1. Betahistine co-treatment ameliorates olanzapine-induced weight gain through hypothalamic H_1R- AMPKα, NPY pathways.

2. Betahistine co-treatment reduces olanzapine-induced dyslipidaemia *via* AMPKα-SREBP-1-PPARα-dependent pathways in the liver.

3. Co-treatment with betahistine does not affect the therapeutic efficacy of antipsychotics.

List of Abbreviations

5-HT, Serotonin

5-HT_{1B}R, Serotonin 5-HT_{1B} receptor

5-HT_{2A}R, Serotonergic 5-HT_{2A} receptor

5-HT_{2C}R, Serotonergic 5-HT_{2C} receptor

5-HTT, Serotonergic 5-HT transporter

α-MSH, Alpha-melanocyte-stimulating hormone

ACC, Acetyl-CoA carboxylase

ACTH, Adrenocorticotrophin

AgRP, Agouti-related protein

AMPK, AMP-activated protein kinase

AMPKα, AMP-activated protein kinase α

Arc, Arcuate nucleus

BAT, Brown adipose tissue

BMI, Body mass index

CART, Cocaine-and amphetamine-regulated transcript

Cg, Cingulate cortex

CNS, Central nervous system

CPT1, Carnitine palmitoyltransferase 1

CPu, Caudate putamen

D_2R, Dopaminergic D_2 receptor

db/db, Leptin receptor mutation

DMN, Dorsal medial nucleus

DVC, Dorsal vagal complex

EPS, Extrapyramidal symptoms

FGAs, First generation antipsychotics

FMPH, 2-(3-trifluoromethylphenyl)histamine

H_1R, Histaminergic H_1 receptor

H_3R, Histaminergic H3 receptor

HDC, Histidine decarboxylase

ICV, Intracerebroventricular

KO, Knockout

LH, Lateral hypothalamus

M_3R, Muscarinic M3 receptor

MC_3R, Melanocortin 3 receptor

MC_4R, Melanocortin 4 receptor

mRNA, Messenger ribonucleic acid

NAc, Nucleus accumbens

NAcC, Nucleus accumbens core

NAcS, Nucleus accumbens shell

NEFA, Non-esterified fatty acid

NPY, Neuropeptide Y

O+B, Olanzapine and betahistine

ob/ob, Leptin deficiency

pAMPK, AMPK phosphorylation

PFC, Prefrontal cortex

POMC, Pro-opiomelanocortin

PPARα, Peroxisome proliferator-activated receptor-α

PVN, Paraventricular nucleus

SGAs, Second generation antipsychotic drugs

SN, Substantia nigra

SREBP-1, Sterol regulatory element binding protein 1

TG, Triglyceride

TMN, Tuberomammillary nucleus

UCP_1, Uncoupling protein 1

VMH, Ventromedial hypothalamic nucleus

1. Introduction

Second generation antipsychotic drugs (SGAs), also called “atypical antipsychotics”, are currently the first line of treatment for schizophrenia and other serious mental disorders, with fewer extrapyramidal symptoms (EPS) side-effects at clinically effective doses compared with first generation antipsychotics (FGAs) [1-4]. However, SGAs such as olanzapine and clozapine are associated with much more severe weight gain/obesity side-effects, and with other common metabolic disorders such as dyslipidaemia, gluco-metabolic abnormalities, insulin resistance, and even type II diabetes [5-7]. They are currently of great interest to clinicians due to their widespread use in clinics [8-10]. Besides the dopaminergic D_2 receptor (D_2R), accumulated evidence has demonstrated that SGAs affect a wide range of G-protein-coupled receptors including serotonergic 5-HT_{2A} (5-$HT_{2A}R$), histaminergic H_1 (H_1R), serotonergic 5-HT_{2C} (5-$HT_{2C}R$), and muscarinic M_3 (M_3R) receptors, contributing to weight gain/obesity and other metabolic side-effects [11]. Among them, H_1R and 5-$HT_{2C}R$ antagonism have been identified as the main indicators for predicting weight gain-induced by SGAs [12-14].

Previous studies have reported various intervention strategies to reduce SGA-induced weight gain [15-17]. Regarding pharmacological interventions, a number of drugs have been trialled with some success in partially ameliorating SGA-induced weight gain side-effects. A meta-analysis study examined 25 pharmacologic weight loss intervention trials (n=1221) and revealed that amantadine, metformin, reboxetine, sibutramine and topiramate were effective in partially reducing SGA-induced weight gain [18]. Another meta-analysis of 32 placebo-controlled pharmacologic intervention trials involving 1482 subjects suggested that metformin had the most promising effect on weight loss, followed by fenfluramine, sibutramine, topiramate, and reboxetine [19]. Other clinical trials also showed a similar effect of metformin in attenuating SGA-induced weight gain [18, 20-23]. A recent study reported that both metformin and berberine treatment did not affect food intake, but significantly prevented olanzapine-induced brown fat loss [24]. The same author further found that uncoupled protein-1 (UCP_1) expression was significantly increased after co-treatment of metformin and olanzapine, compared with olanzapine only treatment [24]. In addition, metformin and rosiglitazone can also reduce glucose intolerance and insulin resistance in patients treated with SGAs [25, 26]. The potential of zoisamide, sibutramine and topiramate

have also been addressed as adjuvant treatments for weight loss of schizophrenic patients treated with SGAs [27-29, 17, 30-32].

However, to date, these pharmacological intervention studies were not based on the mechanisms of SGA-induced weight gain, particularly considering H_1R and 5-$HT_{2C}R$ as the key contributors. Therefore, it is important to investigate the potential for targeting these receptors to control SGA-induced weight gain. In view that histaminergic system could be a target for preventing obesity [33], this paper reviewed recent reports from both animal and clinical studies on exploring the potential of betahistine (an H_1R agonist and H_3 receptor (H_3R) antagonist) to ameliorate SGA-induced weight gain/obesity, and more importantly summarized recent progresses in the underlying mechanisms for this preventing effects by betahistine co-treatment.

2. Materials and Methods

The systematic electronic reference search for this review paper was performed using the Medline and ScienceDirect databases (until October 2015). Key words included atypical antipsychotic, second generation antipsychotics, individual drug names such as olanzapine, risperidone, aripiprazole, quetiapine, haloperidol and ziprasidone, histamine, histamine receptor, H_1 receptor, H_3 receptor, serotonin receptor, $5HT_{2A}$ receptor, 5-HT_{2C} receptor, AMPK, betahistine, intervention, co-treatment, lipid activity, rats, mice, clinical trial, as well as their cross-references with weight gain, obesity, food intake and energy expenditure. In addition, the reference list of all papers identified was reviewed.

3. The role of histamine neurotransmission in SGA-induced weight gain

3.1 The role of histamine neurotransmission

Histamine neurons originate from the tuberomammillary nucleus (TMN) of the posterior hypothalamus (which receives very dense orexin innervations originating from the lateral hypothalamus) and project to all brain regions including the hypothalamus itself [34, 35]. Since histamine cannot cross the blood-brain barrier, it is synthesised *in situ* in the brain from

the precursor amino acid, L-histidine and catalysed by the rate-limiting enzyme histidine decarboxylase (HDC) [36]. Histamine exerts its actions *via* the specific histaminergic receptors, which have been classified into the H_1, H_2, H_3 and H_4 receptor subtypes [37, 38]. All are G-protein-coupled receptors and widely expressed throughout the body. In the central nervous system (CNS), H_1Rs are mainly located postsynaptically and are found especially in the hypothalamus, cerebral cortex and limbic system [37, 39], where they are well documented as involved in the regulation of body weight and food intake. H_2 receptors are also mainly located postsynaptically and are expressed in the hippocampus, amygdala and basal ganglia [37]. H_3 receptors are exclusively located presynaptically and found in the nucleus accumbens (NAc), striatum, basal ganglia, and hypothalamus, and regulate histamine production and release [40, 37]. H_4 receptors are expressed in the hypothalamus and spinal cord [41].

The neurotransmitter histamine plays a crucial role in the regulation of a wide range of behavioural and physiological functions in humans and animals, such as appetite, drinking, sleep, wakefulness, locomotor activity, learning and memory [37, 34, 42, 33]. In particular, histamine has been implicated in the regulation of energy homeostasis [12, 43, 44]. In other words, elevated hypothalamic histamine signalling contributed to decreased food intake and decreased body weight gain [45-47, 35], while reduction in histamine levels was associated with increased body weight gain and food intake [37, 42]. Histamine knockout mice predominantly exhibited obesity with increased visceral adiposity, hyperlipidaemia and decreased glucose tolerance [48, 36, 49]. It has also been reported that SGAs such as olanzapine can directly modulate histaminergic neurotransmission in the hypothalamus, which correlated with the regulation of feeding behaviour in rats [50]. Therefore, the histaminergic system could be a target for preventing obesity and other metabolic disorders [33].

3.2 H_1R, H_3R and SGA-induced weight gain

Histaminergic H_1Rs are highly expressed in the hypothalamic arcuate nucleus (Arc), ventromedial hypothalamic nucleus (VMH) and paraventricular nucleus (PVN) [51], and are involved in the regulation of food intake and energy expenditure [35, 52]. It has been reported that H_1R antagonists play a crucial role in increasing appetite and obesity

development [12, 53], which were also observed in H_1R knockout (KO) mice [51, 54]. Moreover, deprivation of food predominantly led to activation of H_1R expression in the hypothalamic Arc [13, 55]. It was confirmed that Intracerebroventricular (ICV) injection of the H_1R agonist, 2-(3-trifluoromethylphenyl)histamine (FMPH) inhibited food intake [56].

H_1R antagonist properties have been identified as playing a significant role in the development of SGA-induced body weight gain/obesity side-effects (approximately Clozapine = Olanzapine > Quetiapine > Risperidone > Haloperidol > Ziprasidone = Aripiprazole) [57, 58, 14, 59]. In particular, H_1R blockade is recognised as a predominant target for SGA-induced weight gain compared with other receptors [4, 60, 61]. Several animal studies found that olanzapine could modulate histaminergic neurotransmission for the regulation of food intake and weight gain in rats [62, 56, 63]. Olanzapine treatment upregulated mRNA expression and protein levels of hypothalamic H_1R, which was correlated with hyperphagia and weight gain induced by olanzapine [56, 64, 65]. Similarly, clinical studies demonstrated patients treated with antipsychotics showed a significant correlation between the genetic variants of H_1R (rs346074 – rs346070), BMI (body mass index) and obesity [66, 67].

Since histamine cannot pass the blood-brain barrier, direct peripheral H_1R antagonism by SGA treatment may also contribute to the obesity side-effects [13, 56, 64]. The H_1R antagonistic affinity of SGAs is significantly correlated not only with increased body weight and adiposity, but also with insulin-resistance in schizophrenia patients [68, 60, 69]. Other antihistamine drugs such as loratadine and cyproheptadine are also associated with increased body weight and hyperplasia [70-73]. Furthermore, the H_1R antagonistic affinity of SGAs contributes to fat accumulation *via* downregulation of lipolysis, while upregulating lipogenesis in white adipose tissue [74-77].

In addition to H_1R, the histaminergic H_3R is another significant target for regulating food intake and is highly expressed in the TMN of the hypothalamus [12, 78, 79]. Furthermore, H_3 heteroreceptors are also located on non-histaminergic neurons, regulating release of neurotransmitters such as acetylcholine, serotonin and dopamine, and may also be involved in food intake regulation [78, 42, 80, 81]. However, SGAs maintain a very weak antagonistic potency at histaminergic H_3Rs in the brain [82, 83]. As a result, H_3R may play an indirect role in regulating the weight gain/obesity side-effects induced by SGAs. For example, it is

possible that SGAs can block postsynaptic H_1Rs, which may then lead to accumulation of histamine in the synaptic cleft [12] (summarised in Figure 1). Since the release and synthesis of histamine are regulated by presynaptic H_3 autoreceptors [84, 78], the accumulated histamine then activates the pre-synaptic H_3R slowing the synthesis and secretion of histamine and heightening feeding behaviour [85, 12, 78, 80]. On the other hand, it was found that intraperitoneal injection of risperidone immediately increased hypothalamic histamine release, that was regulated by H_3R [86].

3.3 The role of hypothalamic H_1R-AMPK signalling in SGA-induced weight gain

Hypothalamic AMP-activated protein kinase (AMPK) is highly expressed in the Arc, PVN, VMH and Lateral hypothalamus (LH) of the hypothalamus [63, 87, 88]. It has been suggested that AMPK activity could be inhibited by histamine in hypothalamic tissue slices, while it is activated by H_1R antagonist triprolidine in both hypothalamic tissue slices and the hypothalamus of knock-out mice [63]. In addition, it is important to note that hyperphagia in diet-induced obese animals is attributed to the effect of hypothalamic AMPK signalling [89]. Kahn and colleagues showed that AMPK activity in the hypothalamic Arc and PVN was inhibited by anorexigenic leptin and augmented by orexigenic Agouti-related protein (AgRP) [90]. Hypothalamic AMPK is also involved in feeding regulation and food intake by regulating the AMPK-ACC-Malonyl-CoA-CPT1 axis (ACC: acetyl-CoA carboxylase; CPT1: carnitine palmitoyltransferase 1) [91-94]. A study using the CT1-1 cell line reported that the protein level of phosphor-AMPK (pAMPK) is activated by the H_1R antagonist chlorpheniramine, while it is blocked by histamine [95].

It has been found that olanzapine and clozapine activated hypothalamic AMPK by blocking H_1Rs to increase food intake and body weight gain [63, 96, 97]. In hypothalamic tissue slices, the level of pAMPK can be enhanced markedly by olanzapine, which indicates that the weight gain/obesity side-effects associated with olanzapine is mediated by activation of hypothalamic AMPK linked to blockade of the histaminergic H_1R [63]. Further *in vivo* studies in a rat model showed that the pAMPK level was upregulated by olanzapine administration correlated with changes in weight gain [56, 64, 65]. Additionally, administration of olanzapine by acute ICV infusion increased hypothalamic pAMPK expression [98, 99]. Therefore, besides H_1R itself, its downstream AMPK signals are also

valuable targets for treating SGA-induced weight gain/obesity side-effects [12, 13] (summarized in Figure 1).

4. The role of hypothalamic neuropeptide and regulation of energy homeostasis in SGA-induced weight gain

SGA-induced weight gain is associated with alterations to the neuroendocrine network that controls appetite, food intake and satiety [7, 67]. As mentioned above, the hypothalamic Arc plays a crucial role in appetite and energy homeostasis *via* activation of 2 distinct neural populations: (1) anabolic/orexigenic neurons expressing Neuropeptide Y (NPY) and AgRP, and (2) catabolic/anorexigenic neurons expressing pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript (CART) [100-102], which are involved in the regulation of SGA-induced weight gain.

4.1 The role of NPY and AgRP in SGA-induced weight gain

In the CNS, NPY is mainly synthesized in the hypothalamus, brainstem and anterior pituitary [103]. As the biomarker for obesity, NPY is a major mediator in promoting energy storage [104], which regulates food intake, fat deposition and metabolism *via* various G-protein-coupled NPY receptors including NPY receptor subtype 1, 2, and 5 [105, 106]. For example, the NPY receptor sub-type 5 antagonist, Velneperit, has been identified in clinical tests as a potential anti-obesity drug [107, 108]. It has been reported that injection of NPY into the PVN repeatedly led to sustained hyperphagia, body weight gain and fat mass accumulation [109, 110]. In addition, synthesis and secretion of Arc NPY resulted in response to energy deficiency and greater metabolic need such as increased exercise, cold and pregnancy [111-113]. Moreover, the Arc NPY neurons play a role in integrating peripheral energy signals, such as blood glucose concentration, ghrelin, leptin and insulin [114, 115]. AgRP is synthesised exclusively in the Arc that projects to adjacent hypothalamic regions such as the PVN, DMN and LH [116, 110]. The major function of AgRP is to stimulate feeding by antagonising melanocortins at the MC_3R (melanocortin 3 receptor) and MC_4R (melanocortin 4 receptor) in the hypothalamus [117-120] (summarised in Figure 1). Polymorphism of the AgRP gene is associated with inherited leanness in humans [121]. Similar to NPY, both leptin deficiency (*ob/ob*) and leptin receptor mutation (*db/db*) resulted in overexpression of

AgRP in the Arc of mice [122, 118, 123], which has also arisen from fasting in rats and mice [124]. AgRP is sustained for up to a week after a single ICV injection, compared with the effects of NPY which are sustained over hours [125, 126]. Selective ablation of NPY/AgRP-expressing nuclei in adult mice resulted in acute reduction of feeding [127].

The effects of SGAs on expression of NPY and AgRP have been investigated in previous studies. Fernø and colleagues demonstrated that short-term exposure to olanzapine (6 days) resulted in upregulated NPY and AgRP expressions in the Arc of both rats fed *ad libitum* and pair-fed rats [98]. Olanzapine upregulated NPY mRNA expression in a dosage dependent manner in the hypothalamic Arc [128]. Furthermore, increased hypothalamic NPY and AgRP expression were also observed by the study using ICV administration of olanzapine [98, 99]. It has also been reported that the NPY level was upregulated in short (7 days) and mid-term (15 days) olanzapine treatment in rats [129]. Ak and colleagues also reported that the plasma NPY level was attenuated in first attack psychotic male patients treated with olanzapine [100], while quetiapine increased the NPY level in cerebrospinal fluid from schizophrenia patients [130]; these changes in NPY level were associated with SGA-induced weight gain. It has also been reported that clozapine enhanced hypothalamic NPY expression in rats [131, 60] (summarised in Figure 1). The association between AgRP, fat mass and appetite have been examined and were found to be disrupted in olanzapine-treated patients, but not in patients treated with ziprasidone [132]. Although an early study by Ruano and colleagues reported that a polymorphism (rs1468271) in the NPY gene had no association with body weight gain in patients treated with olanzapine and risperidone [133], a recent study by Tiwari and colleagues suggested a significant association between the SNPs rs16147, rs5573, and rs5574 in NPY and weight gain in clozapine and olanzapine-treated patients [134]. The same authors also revealed an association of rs6837793, near NPY_5R, with the weight gain profile in patients treated with risperidone, which supported the role of the NPY system in SGA-induced weight gain. Furthermore, it has been reported that there was significant upregulation of NPY expression in H_1R-knockout and HDC (the neuronal histamine-synthesising enzyme)-knockout mice compared to wild mice [135]. Therefore, SGAs may regulate NPY signalling through acting at H_1R directly, and this requires further investigation.

4.2 The role of POMC and CART in SGA-induced weight gain

POMC is synthesized from the 285-amino-acid-long polypeptide precursor, and produces peptide hormones including β-endorphins and melanocortin [118, 136, 137]. There are several subtypes of the melanocortin peptides, such as adrenocorticotrophin (ACTH) and alpha-melanocyte-stimulating hormone (α-MSH), which act at G-protein-coupled melanocortin receptors such as the $MC_{1\text{-}5}$ receptors [118, 138, 139]. In the brain, POMC is mainly expressed in the Arc [138, 140], and projects to various regions of the hypothalamus [118, 141]. Certain POMC gene mutations may contribute to obesity in healthy human populations [142, 143], while mouse knockout for POMC also shows the obese phenotype [138, 144]. POMC mRNA expression is reduced by food restriction, while it is increased in overfed rats [145, 146]. Importantly, activation of POMC neurons is regulated by the binding of 5-HT to $5\text{-}HT_2R$ [100, 147] (summarised in Figure 1). Additionally, POMC expression in the Arc is also regulated by the dopaminergic system *via* D_2R [148, 149]. CART is a peptide (first isolated from the ovine hypothalamus), and is widely distributed throughout the central and peripheral nervous systems [150, 151]. CART protein is encoded by the CARTPT gene, which functions in feeding, reward, stress and pain transmissions [152, 153]. Similar to POMC, CART also downregulates food intake and body weight [154, 155]; a previous study revealed that CART has an effect on neuronal activities (including the hypothalamic VMH and PVN), which are involved in the neuroplasticity of hypothalamic feeding circuits [156]. Furthermore, CART interacts with other important mediators such as the cannabinoid CB_1 receptor, insulin and leptin, involved in the regulation of feeding [157, 158, 150]. On the other hand, ICV administration of CART was accompanied by a decrease in plasma insulin and leptin levels and an increase in lipid oxidation, which limits fat storage [159].

In terms of the effect of SGAs on expression of POMC and CART, it was shown that olanzapine treatment resulted in attenuation of POMC but not CART expression in the hypothalamus of rats [98, 65, 160, 128, 129]. Ak and colleagues also reported that the plasma POMC level was elevated in first attack psychotic male patients treated with olanzapine, but no changes in plasma CART level were observed [100]. It should be noted that olanzapine suppresses POMC expression by blocking $5\text{-}HT_{2C}R$, and indirectly blocking $5\text{-}HT_{1B}$ receptors ($5\text{-}HT_{1B}R$), while that suppression is abolished by GABA (gamma-aminobutyric acid) neurons [161] (summarised in Figure 1). However, a recent genetic study reported that neither the POMC single nucleotide polymorphisms (SNPs) (rs6713532, rs1047521,

rs3754860) nor the CART SNP (rs10515115, rs3763153, rs3857384, rs11575893, rs16871471) gene variants was associated with weight gain in chronic schizophrenia patients treated with SGAs [162]. On the other hand, a genetic polymorphism study suggested that MC_4R is relevant to SGA-induced weight gain and related metabolic disorders [163].

5. Co-treatment with betahistine to control SGA-induced weight gain

5.1 Betahistine and its safety profile

As reviewed above, the antagonistic property of histaminergic H_1R is the major contributor to SGA-induced weight gain side-effects; therefore, there is great potential for controlling that weight gain by targeting H_1R. The question is therefore whether an H_1R agonist could be used to prevent and treat SGA-induced obesity. One candidate is FMPH, a selective H_1R agonist, which has been shown to reverse SGA-induced hyperphagia after ICV injection [56]. Unfortunately, it is unable to cross the blood-brain barrier [164]. In fact, over the past 30 years, a number of histaminergic ligands have been tested on their effects on food intake and body weight, however to-date there is no highly selective and orally deliverable H_1R agonist on the market [reviewed by Provensi et al. [33]]. Another candidate is betahistine (C8H12N2), which can cross the blood-brain barrier and acts centrally by enhancing histamine neurotransmission in the tuberomamillary nuclei of the posterior hypothalamus [167]. Betahistine acts as a modulator of the histaminergic system and has both H_1R-agonistic and H_3R-antagonistic properties in the brain [74,168,169]. Under normal conditions, histamine may activate H_1R on the hypothalamic neurons, leading to a decrease in food intake, while SGAs such as olanzapine block histaminergic H_1R on the hypothalamic neurons causing an increase in food intake. As an H_1R agonist, betahistine can directly activate H_1R and may compete with olanzapine for binding to H_1R, therefore reducing the H_1R antagonist property of olanzapine. On the other hand, betahistine, as an H_3R auto receptor antagonist, increases histamine release by blocking presynaptic H_3R, which may augment its direct agonistic effects on H_1R, and reduce weight gain [170].

It is worth noting that betahistine is readily available in clinics, has a high safety profile (only 1:100000 reported adverse drug reactions), and has been used to treat more than 130 million patients suffering vestibular disorders such as vertigo and dizziness since the 1970s [165,

166]. It has been trialled as an anti-obesity drug in clinical trials. A randomised, double-blind placebo-controlled trial reported that 32 mg/day treatment of betahistine in 20 obese female subjects for 28 days resulted in 1.1% weight loss, compared to 0.6% weight gain in the placebo group [167]. Barak and colleagues also reported that 12 weeks' treatment of betahistine (16-48 mg/kg) in 281 adults led to significant weight loss in the subgroup of non-Hispanic women ≤50 years old with 48 mg/day betahistine treatment [167].

5.2 Animal trials in betahistine intervention for reducing weight gain in drug naïve or chronic/repeated olanzapine treatment rat models

Several animal studies have reported the effects of co-treatment of betahistine with olanzapine on reducing SGA-induced weight gain. Interestingly, the combined histaminergic H_1R/H_3R action of betahistine has been proven to be efficient in increasing satiety and reducing the desire to eat fatty foods in rats [168] (Table 1). Using the established rat model of olanzapine-induced weight gain, it was found that after short-term (2 weeks) treatment, drug naïve rats treated solely with olanzapine (1 mg/kg, t.i.d.) exhibited significant body weight gain and increased food intake (all $p<0.001$). However, betahistine only (2.67 mg/kg, t.i.d.) treatment had no effect on weight gain and food intake. Importantly, the O+B co-treatment group exhibited significantly reduced feeding efficiency and body weight (~50% net decrease) compared to the olanzapine only-treated group ($p=0.015$) in drug-naïve rats [169] (Figure 2A). Olanzapine treatment also increased white fat mass, but had no effect on water intake [169]. Furthermore, olanzapine reduced locomotor activity of rats, which was significantly correlated with weight gain. These results suggested that reduced activity partially contributed to the weight gain side-effect induced by olanzapine. However, co-treatment with betahistine cannot improve locomotor activities decreased by olanzapine. This finding may be one possible explanation of why betahistine can only partially improve olanzapine-induced weight gain [169] (Table 1).

It is worth noting that clinical patients suffering with schizophrenia, bipolar disease and other mental disorders often face chronic, even life-time, treatment with antipsychotic drugs [165]. Since betahistine has a high safety profile and low adverse drug reaction, it is essential to investigate the effectiveness of betahistine in prevention of weight gain and obesity following chronic antipsychotic treatment in schizophrenia and other mental disorders. On the other

hand, it is well known that antipsychotics cause a significant body weight gain not only in drug-naïve patients, but also in chronic patients who usually have already had previous antipsychotic exposure [6, 65, 170]. In order to investigate whether chronic co-treatment of O+B would have similar weight-attenuating effects, the effect of co-treatment with betahistine was trialled in a rat model with repeated and chronic exposure to olanzapine [65]. It is interesting that in a chronic rat model, the significant body weight gain induced by olanzapine-treatment could be reversed following drug withdrawal; however weight gain was resumed after re-introducing olanzapine treatment (Figure 3A). It was shown that 6 week co-treatment of olanzapine (1 mg/kg, t.i.d.) and betahistine (9.6 mg/kg, t.i.d.) significantly decreased (~51.4%) olanzapine-induced weight gain in rats with repeated SGA exposure. Furthermore, co-treatment also reduced feeding efficiency, liver and fat mass [65]. In addition, olanzapine-treated rats significantly increased inguinal fat ($p<0.001$), and periovary, mesentery fat ($p<0.05$) compared to controls (Table 1). In addition, a recent study found that chronic olanzapine treatment caused a significant upregulation of the circulating non-esterified fatty acid (NEFA), triglyceride (TG) and hepatic lipid accumulation without altering cholesterol synthesis in rats, while betahistine co-treatment significantly reversed olanzapine-induced plasma TG and circulating NEFA [75]. Overall, the studies provided solid preclinical data for preventing/treating SGA-induced weight gain/dyslipidaemia by betahistine treatment, which provides strong support for further clinical trials to improve SGA (olanzapine) induced obesity and its related metabolic disorders using betahistine co-treatment.

5.3 Clinical trials for co-treatment of betahistine and olanzapine for reducing SGA-induced weight gain/obesity

Two clinical studies investigated the effect of betahistine treatment on weight loss in obese (otherwise healthy) subjects. Barak and colleagues conducted a multicentre randomized, placebo-controlled weight loss trial using betahistine (16, 32, 48 mg/day) in 281 obese adults for a 12-week treatment [171]. The overall results revealed that betahistine did not induce significant weight loss in obese participants at the above dosages, while the prevalence of adverse events was low. However, further subgroup analysis revealed that the non-Hispanics women $\leq$ 50 years old, treated by betahistine (48 mg/day) lost ~4.24 kg body weight, compared with the placebo group (~1.65 kg) ($p=0.005$) [171] (Table 1). Another randomized

placebo-controlled double-blind trial reported that 24 hours treatment of betahistine (48, 96, or 144 mg/day) had no effect on food intake or appetites [172], suggesting that long term administration may be the essential factor to reveal the effect of betahistine on energy intake [172] (Table 1).

There have been several clinical studies investigating the effects of betahistine co-treatment in reducing SGA-induced weight gain/obesity in schizophrenia patients. A small clinical trial (in three first-episode schizophrenia patients) found that betahistine (48 mg t.i.d.) was able to prevent significant weight gain caused by olanzapine treatment (10 mg/day) in a 6 weeks' trial of co-treatment with O+B [173]. In detail, an increase in weight during the initial 2 weeks was observed, followed by no additional weight gain (2 patients) or a minor reduction of body weight (one patient) from week 3 to 6. Overall, no subject gained 7% of baseline weight (a cut-off for clinically significant weight gain) [173] (Table 1). Hence, these results indicated a possible attenuating effect of betahistine on olanzapine-induced weight gain in schizophrenia patients.

A later clinical trial with a double-blind placebo-controlled randomized design reported that co-administration with olanzapine, betahistine (48 mg/kg, t.i.d.) and reboxetine (4 mg b.i.d.) (a selective norepinephrine reuptake inhibitor) for 6 weeks in first episode schizophrenia patients resulted in significantly and clinically attenuated weight gain compared with olanzapine-only treatment (2.02±2.37 and 4.77±3.16kg, respectively, p=0.006) [174]. The corresponding increase in BMI was 0.65±0.75 in the olanzapine/reboxetine/betahistine group and 1.53±0.99 kg/m^2 in the olanzapine/placebo group (p=0.008) [174] (Table 1). Importantly, there was complementary action in the CNS pathway in combination treatment with betahistine, reboxetine and olanzapine, namely, the weight attenuating effect of this combination was two-fold larger than reboxetine only combination (2.75 kg *vs.* 1.46 kg) [175, 174].

Another double-blind study demonstrated that 48 healthy women were treated with one week of betahistine (144 mg/day) or matching placebo, followed by olanzapine administration (7.5 or 10 mg/day) for 3 weeks [176]. The result illustrated that the average weight gain in betahistine and placebo groups was 1.2 and 1.9 kg, respectively (p=0.0489), while 52% of the placebo group gained more than 2.0 kg, compared with only 23% in the treatment group (p=0.043) [176] (Table 1). The most recent clinical trial is in progress in evaluating the

effects of betahistine on reversing SGA-induced weight gain in adolescents and young adults; 40 individuals with a diagnosis of schizophrenia or other mental disorders aged from 12-18, who have been treated with clozapine, olanzapine, risperidone, or quetiapine for 6 weeks and with at least 2% weight gain will be recruited for this trial [177] (Table 1).

Overall, betahistine co-treatment has shown clinically meaningful attenuation of olanzapine-induced weight gain without changing the therapeutic effect of these antipsychotics. These clinical findings correspond with the results of animal studies, in which it was demonstrated that the co-treatment with betahistine partially reduced olanzapine-induced weight gain side-effects [169]. It is worthy to note that histaminergic modulation may counterbalance drug-induced overfeeding and weight gain, however it may be ineffective when there is no drug-dependent alteration as showed in clinical trials in obese (otherwise health) subjects [172, 171]. Therefore, it is not clear whether it could be useful as a weight-loss medication in obese non-medicated people.

6. The mechanisms underlying betahistine in reducing antipsychotic-induced weight gain

As discussed above, SGA-induced weight gain may be addressed through the upregulation of hypothalamic H_1R-AMPKα signalling, and NPY levels, accompanied by downregulation of POMC mRNA expression (summarised in Figure 1) [12, 98, 178, 63-65, 179, 160, 97, 129]. Additionally, it was also revealed that the expression of BAT UCP_1 and PGC-1α protein levels (biomarkers of thermogenesis) is reduced by chronic olanzapine treatment [65, 180]. These results both confirmed that decreased energy expenditure and increased food intake/feeding efficiency contributed to increased weight gain induced by chronic olanzapine treatment [65, 180].

Several studies systematically investigated the mechanisms of olanzapine and betahistine co-treatment on attenuating olanzapine-induced weight gain in the rat brain using both drug-naïve and chronic animal models [64, 65, 75]. In detail, the study using olanzapine-naïve rats with 2 weeks' treatment found that co-treatment of O+B reversed the enhanced H_1R and AMPK expression induced by olanzapine treatment (Figure 2B) [64]. In addition, the O+B

co-treatment decreased the pAMPKα/AMPKα ratio (compared with olanzapine only treatment), which was positively correlated with total food intake and H_1R expression [64]. These findings were confirmed in the chronic repeated olanzapine-treatment rat model; the olanzapine-only treatment increased hypothalamic H_1R, pAMPKα and AMPKα expression, as well as AMPK/pAMPK changes correlated with body weight gain, hyperphagia and feeding efficiency [65] (Figure 3B). They are also confirmed by another study in which acute ICV injection of FMPH (an H_1R agonist) reduced olanzapine-induced hyperphagia [56]. Since acute ICV injection of FMPH significantly reduced the olanzapine-induced enhanced AMPKα levels [56], the effect of co-treatment with betahistine in reversing AMPKα/pAMPKα signalling is through activation of the H_1Rs (summarised in Figure 1).

It has been revealed that co-treatment with betahistine attenuates the elevated hypothalamic NPY mRNA expression induced by olanzapine in the mediobasal hypothalamus (including the Arc) (Figure 2B) [64]. Moreover, AMPK phosphorylation could be promoted by stimulating orexigenic hormones such as NPY and AgRP [181]. Since there are synaptic interactions between NPY afferents and histamine neurons, and the H_3R antagonist suppresses NPY induced feeding [182], it is possible that co-treatment with betahistine may activate histamine H_3R to inhibit olanzapine-induced hyperphagia by suppressing NPY (summarised in Figure 1).

It is very interesting that although olanzapine administration decreased the POMC mRNA level, that level was not affected by O+B co-treatment in both betahistine animal studies (Figure 2B & 3B) [64, 65], which indicated that betahistine attenuation of olanzapine-induced weight gain was not *via* the POMC pathway [64, 65]. The result was consistent with previous reports that hypothalamic H_1R is independent of the POMC-melanocortin 4 receptor pathway in regulation of food intake and body weight [183]; instead, hypothalamic POMC neurons are regulated by 5-$HT_{2C}R$ (summarised in Figure 1).

In addition, UCP_1 and PGC-1α protein levels (biomarkers for thermogenesis) in brown adipose tissue (BAT) were decreased in rats with drug treatment which indicated a decrease in thermogenesis [65] (Figure 3B). Chronic co-treatment with betahistine also reversed the attenuated BAT UCP_1 and PGC-1α expressions, which illustrated that the two biomarkers of thermogenesis were involved in the decreased energy expenditure and increased weight gain induced by chronic olanzapine treatment [65]. Furthermore, the negative correlation between

hypothalamic pAMPKα, and BAT UCP_1 and PGC-1α levels, is in line with the previous report about hypothalamic AMPK modulating BAT thermogenesis, and UCP_1 and PGC-1α expression [184-187].

Overall, the results from the acute experiment suggested that co-treatment with betahistine may reverse olanzapine induced body weight gain *via* the H_1R-NPY and H_1R-pAMPKα pathways (Figure 2B; summarised in Figure 1) [64]. The olanzapine induced changes in the hypothalamic H_1R, pAMPKα, BAT UCP_1 and PGC-1α were reversed by chronic co-treatment of O+B (Figure 3B; summarised in Figure 1) [65]. Therefore, co-treatment with betahistine may regulate BAT UCP_1 and PGC-1α *via* the hypothalamic H_1R and pAMPKα pathway.

Furthermore, olanzapine-only treatment significantly increased NEFA in plasma, sterol regulatory element binding protein 1 (SREBP-1) and its target gene expression such as peroxisome proliferator-activated receptor-α (PPARα) in the liver, while these changes could be ameliorated by O+B co-treatment [75]. The same study also revealed that co-treatment of O+B increased the hepatic AMPKα, PPARα and its responsive molecule CPT1A, but decreased the SREBP-1 protein expression compared with olanzapine treatment [75]. Therefore, the co-treatment with betahistine improvement in olanzapine-induced dyslipidaemia is attributed to alteration of the post-transcriptional process of SREBP-1 to ameliorate olanzapine-induced lipid accumulation in the liver, as well as the responses of lipid-metabolic genes, and activation of the AMPK signalling pathway *via* action at hepatic H_1R [75].

7. Co-treatment with betahistine does not affect the efficacy of antipsychotics

Serotonin receptors are G protein coupled receptors such as 5-$HT_{2A}R$ and 5-$HT_{2C}R$; they play a vital role in the therapeutic effects of SGAs and the pathophysiology of schizophrenia [188, 189]. Studies on 5-HTT gene polymorphism have revealed an association with responses to the therapeutic effects of olanzapine and other SGAs [190, 191]. The dopamine receptor, especially the D_2R, is essential for the therapeutic effect of antipsychotics [192, 193]. There

are three main dopaminergic pathways projecting dopaminergic neurons, the mesolimbic (from VTA to NAc, involved in positive symptoms of schizophrenia), the mesocortical (from VTA to cortex including the PFC and Cg, involved in the negative symptoms and cognitive deficits of schizophrenia), as well as the nigrostriatal pathways (from the SN to the CPu), also involved in the pathophysiology of schizophrenia and antipsychotic treatment [192, 194].

A key issue is whether co-treatment with betahistine has an impact on the therapeutic effects of antipsychotics. Two studies investigated the effects of olanzapine and betahistine co-treatment on the 5-HT_{2A}R, 5-HT_{2C}R, 5-HTT, and D_2R bindings in the brain regions associated with the therapeutic efficacy of antipsychotics, including the PFC, NAcC, NAcS and Cg, in both drug-naïve and chronic/repeated olanzapine-treated rats [195, 196].

It was shown that there was significant reduction of 5-HT_{2A}R binding density by olanzapine in various brain regions including the PFC, Cg, NAcC and NAcS [197, 195, 196, 189, 198]. More importantly, it was revealed that co-treatment with O+B didn't influence olanzapine's effect on 5-HT_{2A}R in both short-term/drug-naive and chronic/drug re-exposure studies [195, 196]. As another target for the therapeutic effects of antipsychotics, the 5-HT_{2C}R could be downregulated by SGA treatment including olanzapine [196, 199, 198]. Furthermore, it was revealed that O+B co-treatment didn't interfere with the downregulation effect of 5-HT_{2C}R binding density in the PFC, Cg, NAcC and NAcS induced by olanzapine-only administration [196]. Except the 5-HT_{2A}R and 5-HT_{2C}R, 5-HTT gene polymorphism studies have revealed an association with responses to the therapeutic effects of olanzapine and other SGAs [190, 191]. In the short-term treatment study, both the olanzapine-only and the O+B co-treatment studies significantly attenuated 5-HTT bindings in the SN and VTA of drug-naïve rats [195]. Additionally, the chronic study showed that reduced 5-HTT binding density was observed in the PFC, Cg, NAcC and NAcS in the olanzapine-only treatment and in the Cg, and in the Cg and NAcS by co-treatment with betahistine [196]. Thus, these studies revealed that co-treatment with betahistine had a similar effect on 5-HTT bindings compared with olanzapine-only treatment in both studies, although the effect occurred in different brain regions [195, 196].

Both olanzapine and co-treatment of O+B did not cause any significant changes in D_2R bindings in any brain regions tested after 2 weeks' treatment [195]. However, in the chronic treatment studies, it was revealed that olanzapine administration upregulated the D_2R binding

levels in the Cg, NAcC, NAcS and CPu [196], as well as the PFC, CPu and NAc [200]. This antipsychotic-induced D_2R upregulation could cause "dopaminergic supersensitivity" in clinics [201, 193], in which long-term/chronic treatment with antipsychotics could enhance vulnerability to psychosis frequently observed after drug withdrawal [201]. Additionally, the up-regulation of D_2R in the CPu by chronic olanzapine administration is associated with the development of EPS [200]. It is interesting that chronic betahistine-only treatment at a higher dosage (9.6 mg/kg) significantly decreased D_2R binding in the NAc and CPu, while no change was observed in short-term treatment at a lower dosage (2.67 mg/kg). This difference is possibly attributable to both the difference in dosage and treatment duration (2.67 mg/kg for 2 weeks' study vs. 9.6 mg/kg for 5 weeks' study). It is important to note that olanzapine-elevated D_2R binding in the NAc was reversed by co-treatment with betahistine, which suggests that co-treatment with betahistine may improve therapeutic effects by preventing the "dopaminergic supersensitivity" (vulnerability to psychosis) and EPS caused by chronic antipsychotic treatment [196].

Importantly, clinical studies revealed that betahistine is well-tolerated and safe for co-treatment with olanzapine to schizophrenia patients, with no interference with the therapeutic effect of antipsychotic such as improvement of positive systems of schizophrenia and general psychopathology [176, 202, 173]. Therefore, betahistine is a safe drug for co-administration with olanzapine for mitigating antipsychotic-induced weight gain/obesity, without influencing their therapeutic action.

8. Conclusions

The SGAs are the first line antipsychotics prescribed to treat schizophrenia and other mental disorders. However they are associated with troublesome weight gain/obesity side-effects, and other metabolic disorders, which may lead to causes of premature death. Therefore, it is extremely important to prevent and treat weight gain/obesity induced by SGAs. It has been suggested that the histamine H_1R, its downstream pathways and associated neuropeptide are involved in the SGA-induced weight gain/obesity side-effects [6, 12, 13]. It has been reported that betahistine acts as modulator for the histaminergic system through its H_1R-agonsitic and H_3R-antagonsitic properties in the brain [167, 203]. Importantly, both animal studies and clinical trials have shown that co-treatment with betahistine is effective to ameliorate

olanzapine-induced weight gain, which acts *via* modulation of the hypothalamic H_1R-AMPKα, NPY, and BAT UCP_1-PGC-1α pathways. Furthermore, co-treatment with betahistine was effective in ameliorating olanzapine-induced dyslipidaemia *via* modulation of the AMPKα-SREBP-1 and PPARα-dependent pathways in the liver [75]. Therefore, these results not only confirm the importance of these pathways in SGA-induced weight gain/obesity side-effects, but also implicate the pathways as promising targets for pharmacological intervention to reduce the SGA-induced weight gain. On the other hand, it has been also reported that co-treatment with betahistine does not affect the key receptor binding sites for the therapeutic efficacy of olanzapine at serotonergic 5-HT_{2A}R, 5-HT_{2C}R and 5-HTT, which is consistent with clinical reports that betahistine did not influence therapeutic efficacy. In addition, chronic betahistine treatment significantly reversed D_2R binding density enhanced by olanzapine, which suggests further clinical investigations into whether co-treatment with betahistine could improve the efficacy of olanzapine by preventing "dopaminergic supersensitivity" caused by chronic antipsychotic treatment [195, 196]. Overall, in conjunction with previous preclinical and clinical trials in drug-naïve and repeated SGA administration subjects [169, 65, 174, 173], it is necessary to conduct further clinical trials to investigate the effects of co-treatment with betahistine on reducing olanzapine-induced weight gain side-effects in schizophrenia patients with chronic and repeated antipsychotic treatment. Furthermore, trials of the co-treatment of betahistine with other antipsychotics are worth conducting in the future.

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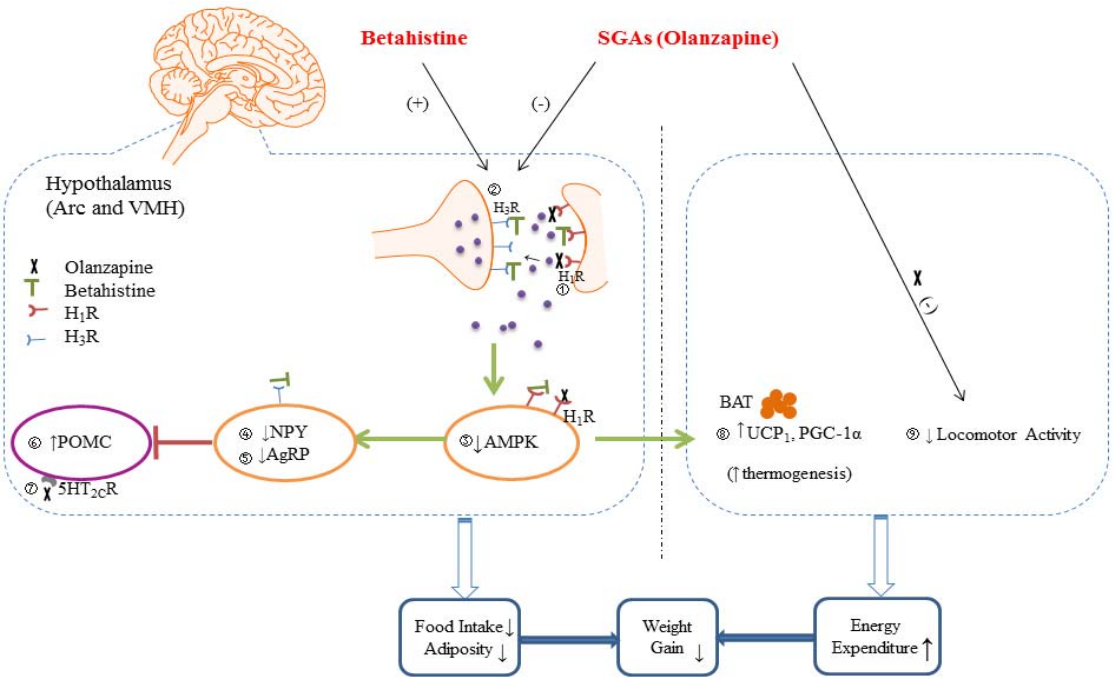

Figure 1. A proposed mechanism underlying betahistine reducing SGA-induced body weight gain/obesity side-effects through regulation of energy intake and expenditure. On the one hand, SGAs block the histamine H_1 receptors. The H_1R blockade by SGAs may cause a compensatory upregulation of H_1R density in the hypothalamus, and enhance hypothalamic AMPK, NPY and AgRP expression. SGAs may downregulate POMC levels through acting on 5-$HT_{2C}R$. On the other hand, SGAs may reduce thermogenesis by attenuating UCP_1 and PGC-$_{1\alpha}$ expression in BAT, which could also be modulated by hypothalamic H_1R-AMPK signalling. In addition, decreased energy expenditure could also be due to reduced locomotor activity caused by SGA treatment. As an H_3R antagonist, betahistine could block H_3R, and then stimulate histamine release; betahistine (as a H_1R agonist) can directly activate H_1R that may compete with and decrease the H_1R antagonist effect of olanzapine. Furthermore, as an H_3R antagonist, betahistine increases histamine release by blocking presynaptic H_3R autoreceptors which may augment its direct agonistic effects on H_1R. Therefore, betahistine may reduce food intake and weight gain caused by antipsychotics, such as olanzapine.

Abbreviations: 5-$HT_{2C}R$, serotonin 5-HT_{2C} receptor; AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; BAT, brown adipose tissue; H_1R, histamine H_1 receptor; NPY, neuropeptide Y; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; POMC, pro-opiomelanocortin; UCP_1, uncoupling protein 1.

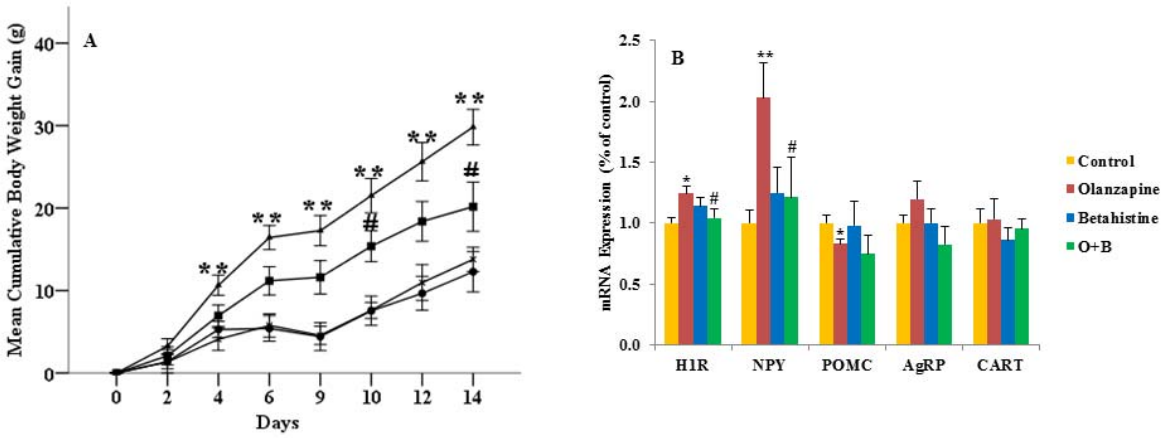

Figure 2. Effects of 2-week olanzapine and/or betahistine treatment on body weight gain and histamine H_1 receptor-AMPK, NPY signallings. (A) Cumulative body weight gain in female Sprague Dawley rats treated with olanzapine (1 mg/kg, t.i.d.; n=12), betahistine (2.67 mg/kg, t.i.d.; n=12), co-treatment (O+B; n=12 or control (vehicle; n=12) for 14 days. (Adapted from Deng et al., 2012, Journal of Psychopharmacology; 26(9):1271-9). (B) Effects of olanzapine and/or betahistine treatment on hypothalamic mRNA expression of H_1R, NPY, POMC, AgRP and CART.

Abbreviations: AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; H_1R, histaminergic H_1 receptor; NPY, neuropeptide Y; O+B: combined olanzapine and betahistine; POMC, pro-opiomelanocortin; t.i.d.: three times daily. *p<0.05, **p<0.01 vs. control, #p<0.05 *vs*. olanzapine.

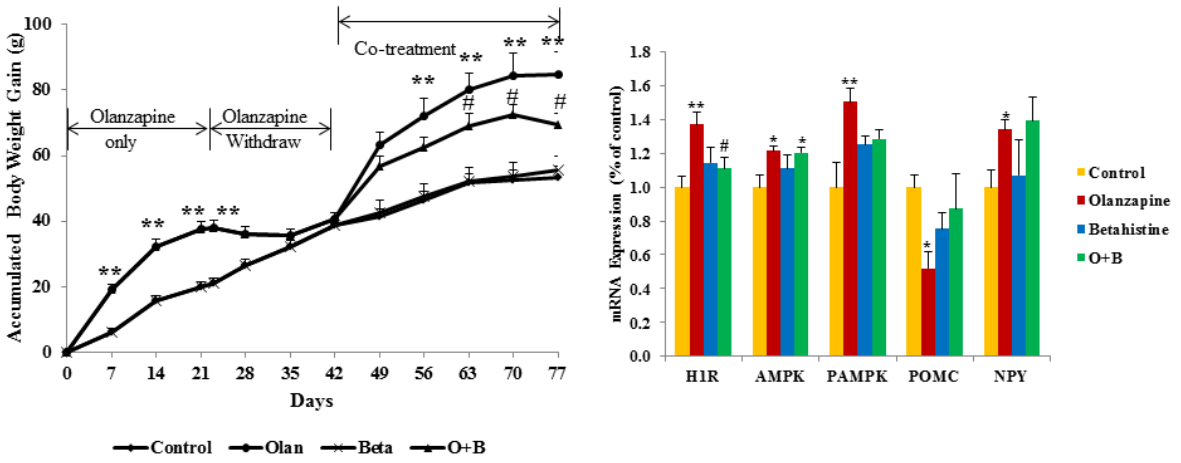

Figure 3. Effects of chronic olanzapine and/or betahistine treatment on body weight gain and histamine H_1 receptor-AMPK, NPY signallings. (A) The trend of three phases of drug administration on the accumulated body weight side-effect. Olanzapine (1 mg/kg, t.i.d.; n= 12), betahistine (9.6 mg/kg, t.i.d.; n=12), co-treatment (O+B; n=12) or control (vehicle; n=12) for 11 weeks. (¤: control, N: olanzapine, x: betahistine, m: O+B co-treatment). * p<0.05, ** p<0.01 *vs.* control, # p<0.05 *vs.* olanzapine. (Adapted from Lian et al., 2014, PLoS One; 9(8):e104160). (B) Effects of olanzapine and/or betahistine treatment on the protein expression of histamine H_1R, AMPKα, pAMPKα, POMC and NPY. Abbreviations: H_1R: H_1 receptor, AMPKa: AMPK-activated protein kinase α, pAMPKα: the AMPK phosphorylation α and POMC: pro-opiomelanocortin. * p<0.05, ** p<0.01 *vs.* control; # p<0.05, # p<0.05 *vs.* olanzapine.

Chemical compound studied in this article

Olanzapine (PubChem CID: 4585)

Betahistine (PubChem CID: 68643)

Risperidone (PubChem CID: 5073)

Clozapine (PubChem CID: 2818)

Aripiprazole (PubChem CID: 60795)

Haloperidol (PubChem CID: 3559)