1-1-2013

The role of hypothalamic H1 receptor antagonism in antipsychotic-induced weight gain

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Abstract

Treatment with second generation antipsychotics (SGAs), notably olanzapine and clozapine, causes severe obesity side effects. Antagonism of histamine H1 receptors has been identified as a main cause of SGA-induced obesity, but the molecular mechanisms associated with this antagonism in different stages of SGA-induced weight gain remain unclear. This review aims to explore the potential role of hypothalamic histamine H1 receptors in different stages of SGA-induced weight gain/obesity and the molecular pathways related to SGA-induced antagonism of these receptors. Initial data have demonstrated the importance of hypothalamic H1 receptors in both short- and long-term SGA-induced obesity. Blocking hypothalamic H1 receptors by SGAs activates AMP-activated protein kinase (AMPK), a well-known feeding regulator. During short-term treatment, hypothalamic H1 receptor antagonism by SGAs may activate the AMPK—carnitine palmitoyltransferase 1 signaling to rapidly increase caloric intake and result in weight gain. During long-term SGA treatment, hypothalamic H1 receptor antagonism can reduce thermogenesis, possibly by inhibiting the sympathetic outflows to the brainstem rostral raphe pallidus and rostral ventrolateral medulla, therefore decreasing brown adipose tissue thermogenesis. Additionally, blocking of hypothalamic H1 receptors by SGAs may also contribute to fat accumulation by decreasing lipolysis but increasing lipogenesis in white adipose tissue. In summary, antagonism of hypothalamic H1 receptors by SGAs may time-dependently affect the hypothalamus-brainstem circuits to cause weight gain by stimulating appetite and fat accumulation but reducing energy expenditure. The H1 receptor and its downstream signaling molecules could be valuable targets for the design of new compounds for treating SGA-induced weight gain/obesity.

Keywords

H1, hypothalamic, role, gain, induced, weight, antipsychotic, antagonism, receptor, CMMB

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

He, M., Deng, C. & Huang, X. (2013). The role of hypothalamic H1 receptor antagonism in antipsychotic-induced weight gain. CNS Drugs, 27 (6), 423-434.

The Role of Hypothalamic H1 Receptor Antagonism in Antipsychotic-Induced Weight Gain

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Running title: H1 receptor antagonism and antipsychotic-induced weight gain

Word count: words 4742 (text only)

Characters (no space): 28595

Characters (with space): 33315

Paragraphs: 34

Lines: 413

Acknowledgments: The study is supported by an Australian National Health and Medical Research Council (NHMRC) grant to Xu-Feng Huang and Chao Deng (ID 635231). Meng He is supported by the China Scholarship Council—University of Wollongong Joint Postgraduate Scholarship. Prof. Huang, Ms. He and A/Prof. Deng have no conflicts of interest.

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Figure captions:

Fig. 1 Possible neural pathways of SGA-induced weight gain by H1 receptor antagonism.

Neuronal histamine regulates body weight by decreasing feeding but increasing energy expenditure and WAT lipolysis **(A) In normal conditions:** histamine regulates food intake via acting on H1 receptors in the ARC, PVN and VMH, in which AMPK may act as a downstream pathway (1). Histaminergic neurons also project to the NTS, which can receive descending projections from most hypothalamic regions and control food intake (2). Activation of H1 receptors in the POA and PVN increases energy expenditure, possibly by increasing the sympathetic nervous activity in the rVLM and rRPa (3), therefore increasing BAT thermogenesis (4). Central histamine and H1 receptors may also increase WAT lipolysis but decrease lipogenesis, possibly by activating the sympathetic neurons, decreasing fat accumulation and body weight (5). **(B) Proposed role of H1 receptors in SGA-induced weight gain:** Central H1 receptor antagonism contributes to SGA-induced obesity, by increasing food intake, WAT lipogenesis and fat accumulation but decreasing energy expenditure and lipolysis. During short-term treatment, H1 receptor antagonism by SGAs activates AMPK-CPT1 signaling in the hypothalamic regions (ARC, PVN and VMH),

possibly also the brainstem NTS, leading to hyperphagia and weight gain (1 and 2). During long-term treatment, H1 receptor antagonism in the PVN and POA decreases sympathetic nervous activity (3), which thus decreases BAT thermogenesis (4). Hypothalamic H1 receptor antagonism by SGAs may inhibit sympathetic nervous activity, leading to increased lipogenesis but decreased lipolysis. This effect may lead to increased fat accumulation and weight gain (5). AMPK AMP-activated protein kinase, ARC arcuate nucleus, BAT brown adipose tissue, CPT1 carnitine palmitoyltransferase 1, EE energy expenditure, FI food intake, GLUT glutamatergic neuron, HA neuron histamine neuron, H1R histamine H1 receptor, NTS nucleus of solitary tract, POA preoptic area, PVN paraventricular nucleus, rRPa rostral raphe pallidus, rVLM rostral ventrolateral medulla, SGAs second generation antipsychotics, SNS sympathetic nervous system, TM tuberomammillary nucleus, VMH ventromedial hypothalamus, WAT white adipose tissue

Fig. 2 Potential role of hypothalamic H1 receptor and AMPK-CPT1 signaling in SGA-induced hyperphagia Histamine, synthesised by the oxidative decarboxylation of histidine by the enzyme histidine decarboxylase (HDC) (1), mediates feeding by acting at postsynaptic H1 receptors. In addition, the synthesis and release of histamine is controlled by pre-synaptic H3 receptors. SGAs such as olanzapine and clozapine competitively bind to H1 receptors in the hypothalamus, and reduce H1 receptors expression in the ARC and VMH (2). Post-synaptic H1 receptor antagonism by SGAs leads to AMPK activation (pAMPK) (3). Activated AMPK directly inhibits ACC activity (pACC), which results in decreased malonyl-CoA levels. The decrease in malonyl-CoA, which is an inhibitor of CPT1, disinhibits CPT1 activity, and therefore increases food intake and causes weight gain. ACC Acetyl-CoA carboxylase, AMPK AMP-activated protein kinase, CPT1 carnitine palmitoyltransferase 1, FAS fatty acid synthase, FI food intake, HA neuron histamine neuron, HDC histidine

decarboxylase, H1R histamine H1 receptor, H3R histamine H3 receptor, SGAs second generation antipsychotics

Abstract

Treatment with second generation antipsychotics (SGAs), notably olanzapine and clozapine, causes severe obesity side effects. Antagonism of histamine H1 receptors has been identified as a main cause of SGAinduced obesity, but the molecular mechanisms associated with this antagonism in different stages of SGA-induced weight gain remain unclear. This review aims to explore the potential role of hypothalamic histamine H1 receptors in different stages of SGA-induced weight gain/obesity and the molecular pathways related to SGA-induced antagonism of these receptors.

Initial data have demonstrated the importance of hypothalamic H1 receptors in both short and long-term SGA-induced obesity. Blocking hypothalamic H1 receptors by SGAs activates AMP-activated protein kinase (AMPK), a well-known feeding regulator. During short-term treatment, hypothalamic H1 receptor antagonism by SGAs may activate the AMPK—carnitine palmitoyltransferase 1 signaling to rapidly increase caloric intake and result in weight gain. During long-term SGA treatment, hypothalamic H1 receptor antagonism can reduce thermogenesis, possibly by inhibiting the sympathetic outflows to the brainstem rostral raphe pallidus and rostral ventrolateral medulla, therefore decreasing brown adipose tissue thermogenesis. Additionally, blocking of hypothalamic H1 receptors by SGAs may also contribute to fat accumulation by decreasing lipolysis but increasing lipogenesis in white adipose tissue.

In summary, antagonism of hypothalamic H1 receptors by SGAs may timedependently affect the hypothalamus-brainstem circuits to cause weight gain by stimulating appetite and fat accumulation but reducing energy expenditure. The H1 receptor and its downstream signaling molecules could be valuable targets for the design of new compounds for treating SGA-induced weight gain/obesity.

1. Introduction

Antipsychotic medication is commonly used in the clinic to treat schizophrenia, bipolar disorder and other psychotic disorders. Unfortunately, prescription of antipsychotic drugs, particularly the second generation antipsychotics (SGAs) such as olanzapine and clozapine, is associated with dramatic weight gain/obesity (reviewed in [1-3]). This weight gain induced by SGAs is a significant factor for patient noncompliance and causes severe co-morbidities including dyslipidaemia, type II diabetes, cardiovascular disease and stroke (reviewed in [1-4]). These issues highlight the urgency of understanding the mechanisms underlying SGA-induced weight gain/obesity. Previous studies have indicated that numerous factors in the brain and peripheral tissues regulating appetite, metabolism and body weight are involved in SGA-induced obesity (reviewed in [2, 5]). SGAs directly interact with a range of neurotransmitter receptors that are involved in energy homeostasis, such as histaminergic H1, serotoninergic 2A and 2C, adrenergic α, muscarinic M3 and dopaminergic D2 receptors (reviewed in [3, 5-6]). Notably, the antagonistic effect on histamine H1 receptors has been identified as a primary contributor of SGA-induced obesity, particularly with the use of olanzapine and clozapine.[7-8] This review focuses on exploring the role of central H1 receptor antagonism and its related molecular pathways in SGA-induced weight gain/obesity.

Our review is based on a literature search that was performed using the MEDLINE (January 1996–September 2012) and ScienceDirect (January 1995–September 2012) databases. The search was limited to articles in English. Key words included antipsychotic, second generation antipsychotic, individual drug names such as olanzapine, clozapine, quetiapine, risperidone, aripiprazole and haloperidol, histamine, histamine receptor, AMPK, CPT1 as well as their cross-references with food intake, energy expenditure, lipid metabolism, weight gain and obesity. Additionally, the reference lists of all papers selected were reviewed.

2. Histamine and histamine H1 receptors in body weight control and obesity

2.1 The role of histamine and H1 receptors in food intake regulation

In both humans and animals, histaminergic fibers are extensively distributed in the central nervous system (CNS) and hold a key position in brain homeostatic regulation such as feeding rhythms, energy metabolism, the sleep–waking cycle, and learning (reviewed in [9-11]). Histaminergic neurons originating from the tuberomammillary nucleus (TM) of the hypothalamus project to many brain areas including the structures within the hypothalamus (reviewed in [9-11]). Increased histamine signaling in the hypothalamus contributes to reductions in food intake and body weight in cats,[12] rats[13-14] and mice[15-16]. Histamine-deficiency mice (histidine decarboxylase (HDC) deficient mice) exhibit obesity, increased visceral adiposity, hyperleptinemia and hyperinsulinemia, and are predominantly obesity prone when fed a high-fat diet.[17-18] To date, four histamine receptors (H1-H4) have been found in mammals, in which the H1 receptor is the most well-documented in feeding and body weight regulation.[11] In H1 receptor knock-out (KO) mice, mature-onset obesity

accompanied by hyperphagia and increased visceral adiposity have been found,[19] while in humans, prescription of H1 antihistamine medicines (blocking H1 receptors) is also associated with increased body weight[20-22] and body mass index (BMI), according to the National Health and Nutrition Examination Survey (NHANES)[23]. A number of studies have shown that histamine suppresses food intake though H1 receptors in the hypothalamic ventromedial nucleus (VMN) and paraventricular nucleus (PVN).[24-27] Previous studies in rats found that food deprivation under scheduled feeding significantly activated the neurons that express H1 receptors in the caudal arcuate nucleus (ARC).[28-29] These findings revealed that the ARC H1 receptors also play a role in feeding regulation. Additionally, the synthesis and release of histamine are regulated by pre-synaptic H3 autoreceptors.[30-31] Therefore, central histamine regulation of food intake may also be modulated by H3 receptors. Treatment with an H3 receptor antagonist induced hypophagia, which could be attenuated by H1 receptor antagonist.[32] Furthermore, H3 heteroreceptors are located on non-histaminergic neurons, regulating release of neurotransmitters such as acetylcholine, serotonin and dopamine, which may also be involved in food intake regulation.[6, 33-36]

2.2 The role of histamine and H1 receptors in energy expenditure

The hypothalamic histamine and H1 receptors have long been known for their involvement in energy expenditure regulation, by regulating sympathetic outflow to brown adipose tissue (BAT).[19, 37-39] Microinjection of histamine into the PVN or preoptic area (POA), which are important regions controlling BAT thermoregulation via the sympathetic nervous system, significantly activated BAT sympathetic activity and increased BAT uncoupling protein 1 (UCP-1) mRNA expression in rats.[38] The POA, which is a main region for histamine regulating body temperature, sends outflows to the rostral raphe pallidus (rRPa) that contains sympathetic premotor neurons to regulate BAT thermogenesis (reviewed in[40]). Intra-MnPO

(median preoptic nucleus) injection of histamine and an H1 receptor agonist, 2-pyridylethylamine, significantly induced hyperthermia without increasing motor activity in mice.[39] Studies also suggest that activation of H1 receptors expressed on glutamatergic neurons in the MnPO activates BAT thermogenesis by stimulating sympathetic neurons in the rRPa.[39, 41] Additionally, in the medial preoptic nucleus (MPON), H1 receptor activation on the glutamatergic neurons also significantly regulates body temperature, although H2 receptors may play a predominant role in this region.[42] Furthermore, a body of evidence has shown the importance of the PVN in central regulation of BAT sympathetic activity and energy expenditure (reviewed in [43]). The PVN contains thermoregulatory neurons which project to the rRPa and rostral ventrolateral medulla (rVLM), important autonomic regions, to regulate sympathetic outflows to BAT and contributes to BAT thermoregulation.[43-46] Possibly, activation of H1 receptors in the PVN may stimulate the sympathetic outflow to rRPa and rVLM, which thus increases BAT thermogenesis. Collectively, this evidence suggests that histamine may increase energy expenditure via its action on H1 receptors in the PVN and POA and stimulate the sympathetic outflows to the rRPa and rVLM, therefore increasing BAT sympathetic activity and thermogenesis (Fig. 1A). To test this hypothesis, future studies may examine the effect of histamine or H1 receptor agonists on BAT thermogenesis by directly injecting histamine or H1 receptor agonists into the PVN and POA, and test whether this effect could be blocked by H1 receptor antagonists.

2.3 The role of histamine and H1 receptors in lipolysis

In addition to energy expenditure regulation, central histamine and H1 receptors can also regulate body weight by modulating white adipose tissue (WAT) lipid metabolism and fat accumulation. Intracerebroventricular (ICV) injection of histamine or an H3 receptor antagonist (thioperamide: increases histamine synthesis and release) into the 3rd ventricle

(which easily accesses the H1 or H3 receptors in the hypothalamus) in rats accelerated WAT lipolysis and decreased visceral adiposity accumulation.[47] Central administration of histamine in rats increased the lipolytic response, which could be blocked by the H1 receptor antagonists, mepyramine and chloropyramine.[48] In humans, histamine also stimulates lipolysis in subcutaneous fat cells, but this effect is weak.[49] Additionally, histamine H1 receptor KO mice exhibit hypertrophy of WAT adipocytes, increased visceral adiposity and obesity, which suggests that H1 receptors have an important effect on WAT lipogenesis.[19, 50] A previous electrophysiological study suggests that activation of the efferent sympathetic nervous system in the hypothalamus and brainstem regions that innervate WAT largely contributes to hypothalamic neuronal histamine-regulated WAT lipolysis (Fig. 1A).[47] Orexin-A-induced sympathetic nervous activity in WAT of rats can be blocked by the H1 receptor antagonist, diphenhydramine.[51] These findings suggest that brain histamine might partly regulate WAT lipid metabolism through the H1 receptors via activating the sympathetic neurons that innervate WAT. Additionally, studies in animal model found that neural populations in the PVN project indirectly to the WAT through multisynaptic pathways, which may modulate autonomic outflow and WAT lipid metabolism.[52-53] This could be another mechanism by which central histamine regulates WAT lipolysis.

3. The role of histamine and histamine H1 receptors in second-generation antipsychotic (SGA)-induced weight gain

Emerging data have shown that histamine H1 receptors play an important role in SGA-induced weight gain/obesity (reviewed in [6-7]). Based on the data from the literature, the weight gain liability of different SGAs is clozapine = olanzapine > quetiapine≥ risperidone > ziprasidone = aripiprazole (reviewed in [7, 54-56]). The exact values of binding affinity of

antipsychotics on the H1 receptor can vary from study to study. Overall, the affinity of SGAs for the H1 receptors is approximately clozapine > olanzapine > quetiapine > risperidone > ziprasidone > aripiprazole.[57-58] A previous study which screened 17 antipsychotics to test the relationship between weight gain and their affinities for 12 neurotransmitter receptors found that the antagonism of the H1 receptor is a strong predictor for short-term antipsychotic-induced weight gain.[57] It was also revealed that H1 receptor occupancy is strongly correlated with SGA-induced weight gain both in clinic trials and estimated by meta-analysis.[8] Recently, studies in patients treated with antipsychotics showed a significant association of interaction between the genetic variants of H1 receptors (rs346074−rs346070) and BMI and obesity when comparing patients treated with high H1 receptor affinity antipsychotics (olanzapine, clozapine and quetiapine) with those treated with lower H1 receptor affinity antipsychotics (such as aripiprazole).[59] However, earlier studies also reported no relationship between other H1 receptor variants and clozapine-induced weight gain.[60-61] Additionally, in a rat model, both short- (1 week) and long-term (12 weeks) treatment of olanzapine (1.5mg/kg/day, oral), but not haloperidol (0.3mg/kg/day, oral) or aripiprazole (2.25 mg/kg/day, oral), reduced H1 receptor expression in the hypothalamic ARC and VMH, in which the mRNA expression of ARC H1 receptor is significantly correlated with body weight gain and feeding efficiency.[62] These findings show that blockade of H1 receptors largely contributes to SGA-induced obesity in both short- and long-term treatment. However, another study also suggested that the antagonism of serotonin 2C (5-HT2C) receptors but not H1 receptors in the presence of dopamine D2 receptor antagonism contributes to olanzapine-induced obesity, since co-treatment of haloperidol (D2 receptor antagonist) with either SB 243213 (5-HT2C receptor antagonist) or SB 243213+mepyramine (H1 receptor antagonist), but not mepyramine alone, mimicked an olanzapine-like increase in body weight in rats.[63] On the other hand, activation of H1 receptors can attenuate SGA-induced weight gain. For

example, in both schizophrenia patients and animal models, co-treatment of olanzapine and betahistine, an H1 receptor agonist and H3 receptor antagonist, significantly reduced olanzapine-induced weight gain.[64-65] A recent clinical study[66] demonstrates that co-treatment of betahistine and reboxetine (a norepinephrine reuptake inhibitor) with olanzapine for 6 weeks in patients significantly attenuated olanzapine-induced weight gain, and the attenuating effect of betahistine+reboxetine was two-fold larger than the reboxetine-only treatment reported in a previous study[67].

3.1 Intracellular mechanisms for SGA-induced weight gain by H1 receptor antagonism

3.1.1 Potential role of hypothalamic H1 receptor-AMPK signaling in feeding regulation.

It is well-known that hypothalamic AMP-activated protein kinase (AMPK) links energy metabolic status and neurotransmitter/neuropeptides systems to regulate energy balance and body weight (reviewed in [68-70]). Previous evidence revealed that AMPK may be key in H1 receptor-involved food intake regulation. Kim et al.,[58] reported that histamine significantly inhibited AMPK activity in hypothalamic slices; in contrast, the H1 receptor antagonist, triprolidine, stimulated AMPK activity in both hypothalamic slices and the mouse hypothalamus. Recently, a study on the hypothalamic GT1-1 cell line also found similar results; the H1 receptor antagonist, chlorpheniramine, increased the protein level of phosphor-AMPK (pAMPK: activated AMPK), which could be blocked by histamine.[73] A range of evidence has demonstrated that activation of hypothalamic AMPK increases food intake and body weight, while inhibition of hypothalamic AMPK decreases feeding and body weight.[51, 53, 55, 60]

Hypothalamic AMPK regulates fatty acid metabolism pathways in the CNS and plays an important role in feeding regulation and energy homeostasis, although the CNS does not use fatty acids as a primary energy source (reviewed in [68, 74]). Both genetic and pharmacological modifications of the key steps of AMPK-regulated fatty acid metabolism affect food intake and body weight (AMPK-ACC—Malonyl- CoA—CPT1 axis; ACC: acetyl-CoA carboxylase; CPT1: carnitine palmitoyltransferase 1) (reviewed in [68, 72]). Briefly, AMPK activation by phosphorylation directly inhibit acetyl-CoA carboxylase (ACC) activity, which is an important enzyme that converts acetyl-CoA to malonyl-CoA. This effect results in a decrease in malonyl-CoA, which is an allosteric inhibitor of carnitine palmitoyltransferase 1 (CPT1), and inhibits fatty acid synthesis. Decreased malonyl-CoA levels disinhibits CPT1 activity which up-regulates food intake partly by increasing fatty acid oxidation (reviewed in [68, 72]). To date, two types of CPT1, that is, CPT1a and CPT1c, have been implicated in CNS feeding regulation.[75-76] CPT1a (CPT1 liver form) is an outer mitochondrial membrane enzyme, transferring fatty acids into mitochondria for β-oxidation, which regulates food intake and body weight.[75, 77] CPT1c is a brain-specific CPT1 highly expressed in the hypothalamus (reviewed in [78]). Overexpression of CPT1c in the hypothalamic ARC significantly increases food intake after overnight fasting in rats.[79] In addition, CPT1c KO mice exhibit reduced food intake and weight gain under normal diet, but rapidly gain weight when fed a high fat diet, suggesting that CPT1c may also play a role in protecting against high fat diet-induced obesity.[80] However, in contrast to CPT1a, CPT1c is not located at the outer membrane of mitochondria but at the endoplasmic reticulum (ER) of neurons.[81] Although it shows high sequence similarity with CPT1a and has been identified as a target of malonyl-CoA in controlling energy homeostasis, CPT1c does not stimulate fatty acid oxidation.[80] These findings suggest that CPT1c may have a unique mechanism in feeding and body weight

regulation compared to CPT1a. However, the mechanisms of CPT1c in feeding and body weight regulation remain elusive.

Within the hypothalamus, the ARC, PVN and VMH are key regions for AMPK regulating food intake, and also play important roles in H1 receptor-involved food intake regulation we already discussed.[26-28, 68, 71-72, 82-83] It is possible that AMPK may act as a downstream signaling target of H1 receptors in the ARC, PVN and VMH in food intake regulation (Fig. 1A). To test this hypothesis, further studies may examine whether the H1 receptor antagonist-induced hyperphagia and weight gain could be reduced by blocking AMPK in the ARC, PVN or VMH.

3.1.2 Intracellular mechanisms for SGA-induced weight gain associated with H1 receptor antagonism

Although the intracellular downstream signaling pathway of H1 receptors in SGA-induced weight gain is not fully understood, studies have indicated that hypothalamic AMPK signaling is significantly involved. Both in vitro and in vivo studies have found that clozapine, olanzapine, and quetiapine, with high affinities for H1 receptors and a high risk of inducing weight gain, significantly increased hypothalamic AMPK.[58, 84-85] Importantly, the stimulatory effect of clozapine on hypothalamic AMPK was attenuated by histamine administration, and was abolished in H1 receptor KO mice.[58] In contrast, SGAs with lower obesogenic effect and lower H1 receptor affinities such as ziprasidone are less effective at increasing hypothalamic AMPK activity.[58] However, a study in rats also reported that acute treatment of olanzapine (50 μg) or clozapine (25 mg/kg) did not significantly increase the hypothalamic AMPK phosphorylation and its directly downstream ACC, although there was an increasing trend.[86] Subchronic olanzapine treatment (6mg/kg/day, 5 days) reduced

hypothalamic pAMPK and pACC levels compared with vehicle.[86] It is suggested that in this study, the lack of AMPK activation by the SGAs may also have been caused by other factors, such as the drug doses used (high doses caused sedation), time after the last drug injection (20 hours) and whether the rats were fasted or not.

Taking the importance of AMPK in SGA-induced hyperphagia and the key role of hypothalamic AMPK-CPT1 signaling in feeding and body weight regulation together, it is conceivable that by blocking H1 receptors in the hypothalamus, SGAs may activate AMPK-CPT1 signaling, leading to hyperphagia and weight gain (Fig. 2). Moreover, as has been discussed, H1 receptors in the ARC, PVN and VMH play a key role in feeding regulation, in which AMPK signaling may act as a downstream pathway (Fig. 1A). SGAs may activate the AMPK-CPT1 signaling in the ARC, PVN and VMH following H1 receptor antagonism to up-regulate food intake and weight gain (Fig. 1B). To date, the role of hypothalamic AMPK-CPT1 signaling in SGA-induced obesity has not been investigated. However, a study in rats has reported that a single intraperitoneal injection of clozapine (5-20mg/kg) significantly activated AMPK-CPT1 signaling in the prefrontal cortex, suggesting that clozapine affects lipid metabolism in the brain.[87]

In addition to the hypothalamus, H1 receptors and AMPK-CPT1 signaling in the nucleus of solitary tract (NTS) in the brainstem may also play a role in feeding regulation and contribute to SGA-induced weight gain. Previous studies in rats found that the brainstem dorsal vagal complex (DVC) is significantly involved in mediating olanzapine-induced weight gain.[88-89] The NTS, within the DVC, not only receives ascending projections about energy status from the gut, but also receives descending projections from most hypothalamic regions including the ARC, PVN and VMH to regulate food intake (reviewed in [90-91]). Histamine neurons

originating from the TM send projections to the NTS.[92-93] A recent study in rats found that in the NTS, the H1 receptors are extensively co-localized with the neuronal marker (NeuN) but not the glial cell marker (glial fibrillary acidic protein), suggesting that the H1 receptors are predominantly located on neurons but not on glial cells.[93] Activation of H1 receptors in the NTS is associated with cardiovascular homeostasis regulation in rats, which increases arterial pressure and heart rate.[93] However, the role of NTS H1 receptors in feeding and body weight regulation is unknown (Fig. 1A). Additionally, AMPK in the NTS has been reported to respond to energy status and mediate food intake. AMPK activity in the NTS was increased in food deprived rats, which was abolished by refeeding.[94] Both 4th icv and medial NTS injection of an AMPK inhibitor, compound C, significantly reduced food intake [94], but the functional significance of AMPK-CPT1 signaling in the NTS has not been well established in appetite and body weight regulation. Taken together, it is important to investigate the role of NTS H1 receptors and AMPK-CPT1 signaling in feeding regulation and their relationship with the hypothalamus to better understand the hypothalamus-brainstem circuits in feeding and body weight control, as well as their role in SGA-induced hyperphagia and obesity (Fig. 1B).

3.2 Does AMPK-CPT1 signaling play a different role in the three stages of SGA-induced obesity?

In both schizophrenia patients and animal models, recent research has indicated that antipsychotic-induced weight gain occurs in distinct phases. It has been reviewed that in the clinic, weight gain induced by SGAs such as olanzapine and clozapine can be demonstrated as occurring in 3 stages. In stage 1 (the first 3 months), SGAs rapidly increase body weight; in stage 2 (3-18 months) SGAs cause a steadier but lower rate of increasing body weight; while in stage 3 (> 18 months) the weight gain reaches a plateau and increased body weight is

maintained during SGA treatment.[95] In rats, a similar effect has also been reported, although the period of every stage is shorter.[96] Interestingly, a number of studies found that olanzapine (1-8mg/kg/day) causes dramatic increase of daily food intake particularly during short-term treatment (<2 weeks) in rats.[96-99] During long-term treatment, the olanzapine treatment group showed no significant difference in food intake from week 3-5, but maintained a higher body weight compared to the vehicle-treated control rats.[96-97, 99] In addition, pair-fed rats which were given the same amount of food did not increase weight gain during short-term olanzapine treatment (6mg/kg/day, oral, 5days).[86] Patients treated with SGAs exert significantly decreased energy expenditure especially after chronic treatment (6-12 months).[95, 100-102] In the animal model, olanzapine, clozapine and quetiapine have been found to decrease energy expenditure.[99, 103-104] These findings support the hypothesis that during short-term SGA treatment, the rapid increase in body weight may be primarily caused by hyperphagia, while during long-term treatment, in which period food intake is no different from the control, decreases in energy expenditure may play the main role in SGA-induced obesity at least in animal models.

It is suggested that the AMPK-CPT1 signaling pathway may play a different role in the different stages of SGA-induced obesity. During short-term olanzapine treatment (2mg/kg/day, oral, 14 days) daily food intake significantly increased, accompanied by increased hypothalamic AMPK.[85] Our study in rats found that hypothalamic pAMPK tended to increase after 8-days olanzapine treatment (3mg/kg/day, oral), returned to normal level after 15-days treatment, but significantly reduced after 36-days treatment.[105] These findings illustrate time-dependent changes of hypothalamic AMPK signaling in SGA-induced obesity. Possibly, the activation of hypothalamic AMPK signaling following H1 receptor antagonism may be responsible for the rapid increase of food intake and body weight during short-term

SGA treatment. Following prolonged SGA treatment, the hypothalamic AMPK signaling declines, reducing the stimulatory effect on food intake. After long-term SGA treatment, the reduction of pAMPK may be a compensation response induced by energy overload and high body weight.

3.3 The role of H1 receptors in SGA-induced decreased energy expenditure and obesity

SGAs may also decrease energy expenditure through central H1 receptor antagonism, leading to weight gain and obesity. As has been reviewed, both clinical and preclinical studies found that treatment with obesogenic SGAs such as olanzapine, clozapine and quetiapine are associated with decreased energy expenditure.[95, 99-104] In the animal model, olanzapine, clozapine and quetiapine have been found to decrease energy expenditure by inhibiting sympathetic activity and BAT thermogenesis.[98, 102-103] A number of studies suggest that BAT thermoregulation is important in both humans and rodents in regulating body temperature and body weight, although some early studies found a wider distribution of BAT and less relevance to thermoregulation in humans than in rodents.[99, 106-111] However, the central mechanism by which SGAs decrease BAT thermogenesis remains unclear. An immunohistochemistry study in rats found that subcutaneous injection of olanzapine (10 mg/kg) decreased BAT temperature, and largely stimulated Fos protein expression in the PVN, lateral hypothalamic area (LHA), and brainstem locus coeruleus (LC) and rVLM, which play important roles in BAT thermoregulation.[99] The study showed that the LHA orexin neurons are activated by olanzapine. This evidence suggests that olanzapine treatment may affect the hypothalamic - brainstem pathways which regulate energy expenditure, resulting in a reduced sympathetic nerve activity and BAT thermogenesis.[99] Central histamine infusion increased energy expenditure, while disruption of H1 receptor signaling

(H1 receptor KO) led to decreased energy expenditure and obesity.[15, 19] As has been reviewed, activation of H1 receptors in the POA and PVN may increase energy expenditure by regulating sympathetic input into the rRPa and rVLM to increase BAT thermogenesis. It is conceivable that during long-term SGA treatment, central H1 receptor antagonism may contribute to SGA-induced decreased energy expenditure and weight gain. Possibly, disruption of central H1 receptors by SGAs in the POA and PVN may inhibit sympathetic nerve activity through rRPa and rVLM, which then reduces BAT thermogenesis and energy expenditure (Fig. 1B).

Additionally, SGA-induced decreased energy expenditure could also be partly caused by sedation. Both clinical (reviewed in [112-114]) and preclinical [86, 115] studies reported dosage-related effects of sedation of some SGAs such as olanzapine and clozapine. It has been suggested that SGA-induced sedation is largely related to the binding affinity of SGAs for the H1 receptors (reviewed in [7, 113]).

3.4 The role of H1 receptors in SGA-induced impaired white adipose tissue lipogenesis and lipolysis, and obesity

Recent studies indicate that SGAs such as olanzapine, clozapine and quetiapine can also induce disequilibrium between subcutaneous WAT lipogenesis and lipolysis, which contributes to SGA-induced weight gain.[116-118] An in vitro study in adipocytes showed that olanzapine, clozapine and quetiapine can stimulate lipogenesis rate but reduce lipolysis rate, suggesting that “obesogenic” SGAs may directly induce fat synthesis in WAT.[118] Another study also found similar results; olanzapine increased the expression of sterol regulatory element binding protein (SREBP-1) in 3T3-L1 cells, an important modulator of

lipogenesis.[119] In female rats, olanzapine treatment (6mg/kg/day, oral, 2-week) increased WAT lipogenic gene expression such as fatty acid synthase and acetyl-CoA carboxylase 1, and these changes were positively correlated with weight gain induced by olanzapine.[117] In addition, the changes of these lipogenic genes also existed in pair-fed rats, suggesting that the effect was directly caused by olanzapine treatment but not a secondary effect of weight gain.[117] Furthermore, a study in male rats showed that olanzapine treatment (10mg/kg/day, oral) increased fat accumulation by stimulating adipose tissue lipogenesis while attenuating lipolysis.[120] As discussed above, activation of hypothalamic histamine-H1 receptor signaling increases sympathetic nerve activity to increase WAT lipolysis.[47] The blocking of hypothalamic H1 receptors by SGAs may be able to attenuate WAT lipolysis, leading to increased fat accumulation and weight gain. In addition, H1 receptors signaling can affect WAT lipogenesis,[19] but the mechanism is not well understood. WAT lipogenesis is significantly regulated by hypothalamic neurons through modulating sympathetic outflow to WAT.[121] Therefore, disruption of central H1 receptor signaling by SGAs may also play a role in enhancing WAT lipogenesis, thus increasing fat accumulation and weight gain during SGA treatment.

4. Conclusions

SGAs such as clozapine and olanzapine, drugs commonly used in the clinic to treat schizophrenia, cause weight gain/obesity by several mechanisms. Accumulated data suggest that central H1 receptor antagonism plays a key role.[8, 58, 62, 65] The H1 receptor occupancy strongly predicts weight gain liability of an SGA, [8, 57] while, activation of histamine H1 receptors by betahistine, for example, is effective to block SGA-induced obesity.[65-66] Additionally, recent research has indicated that the development of SGA-induced obesity is time-dependent; increased food intake is mainly responsible for rapid increase in weight

during short-term treatment, while the weight gain is mainly driven by decreased energy expenditure during long-term treatment (reviewed in [95]). These findings suggest that different mechanisms may be involved in different stages of SGA-induced weight gain.

As has been discussed, during short-term SGA treatment, activation of AMPK-CPT1 signaling in the hypothalamic ARC, PVN and VMH, and possibly brainstem NTS, following H1 receptor antagonism may significantly contribute to SGA-induced hyperphagia and rapid increase in weight. During long-term treatment, hypothalamic H1 receptor antagonism may play a key role in SGA-induced decreased energy expenditure, possibly by inhibiting sympathetic outflow to rRPa and rVLM, reducing BAT thermogenesis. In addition, central antagonism of H1 receptors by SGAs may be largely responsible for SGA-induced decreased lipolysis and increased lipogenesis, leading to fat accumulation and weight gain (Fig. 1B). However, since histamine also exists in peripheral tissues but cannot pass the blood brain barrier, and H1 receptors are expressed in the peripheral tissues (reviewed in [11, 122]), peripheral H1 receptor antagonism by SGA treatment may also contribute to SGA-induced obesity, but the focus of this review was on the mechanisms underlying histamine action in the CNS on the regulation of food intake, energy expenditure, WAT lipid metabolism and body weight. To better understand the role of central H1 receptors and the histaminergic system in SGA-induced obesity, further studies are needed to investigate whether activation of central H1 receptors is able to reverse SGA-induced hyperphagia, decreased energy expenditure and impaired WAT lipid metabolism, as well as their relationship with the possibly related signaling pathways mentioned above.

It is worth noting that obesity and other metabolic abnormalities may lead to diabetes and cardiovascular disease (CVD) (reviewed in [123-124]). Therefore, it is important to increase the

screening and monitoring of metabolic and CVD risk in patients treated with SGAs. In fact, numerous guidelines have been developed for improving the physical health of patients treated with antipsychotics (reviewed in [125-127]). They recommend that patients on antipsychotics monitor their body weight, dietary habits, waist circumference, blood pressure and fasting plasma glucose etc during the course of their SGA treatment (reviewed in [126, 128-129]). When metabolic symptoms are obvious, one option is to switch from a high weight gain liability drug such as olanzapine to antipsychotics with a lower H1 receptor affinity and weight gain liability such as ziprasidone or aripiprazole (reviewed in [127, 130]). Additionally, besides switching medication, pharmacologiccal treatments may also be considered to reduce SGA-induced weight gain such as the co-treatment of betahistine and reboxetine.

In addition, it should be noted that current animal models for SGA-induced weight gain have several limitations. For example, current animal models only mimic olanzapine-induced weight gain in female but not in male rats. In addition, although weight gain using clozapine is well-established in humans, generally clozapine does not cause weight gain in female rats.[131] Although animal models can provide valuable information about the mechanism of antipsychotic-induced weight gain, caution must be taken to avoid simply extrapolating animal data to humans.

Taken together, the data that we have review in this article suggest that the central H1 receptor plays a key role in SGA-induced weight gain. The antagonistic effect of the H1 receptor can result in increased food intake, decreased energy expenditure, impaired regulation of WAT lipid metabolism and increased fat accumulation. AMPK signaling is affected by the antipsychotic medication via the H1 receptor contributing to body weight gain, although other systems should not be ignored in this context (eg: 5-HT2C receptor). An

improved understanding of the mechanisms underlying the H1 receptor antagonism in SGA-induced weight gain could help in designing a better treatment strategy for preventing and treating SGA-induced weight gain and its associated life-threatening diseases such as type 2 diabetes and CVDs.

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