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Review

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 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.

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Abbreviations: 5-HT, serotonin; $5\text{-HT}_{1B}R$, serotonin 5-HT_{1B} receptor; $5\text{-HT}_{2A}R$, serotonergic 5-HT_{2A} receptor; $5\text{-HT}_{2C}R$, 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.

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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 hypotha-