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Review

Personalized approach to antipsychotic-induced weight gain prognosis

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Abstract: Antipsychotics (APs) are the base of schizophrenia pharmacotherapy. There are large individual differences in effectiveness and adverse drug reactions (ADRs) of APs. There is an urgent need for a personalized approach to the therapy. Genetic factors are predisposed to patient's response to APs therapy. Pharmacogenetic studies of APs have examined a number of single nucleotide variants (SNVs), of which only a few were associated with therapeutic efficacy and ADRs development. However, only a limited number of these results have clinical applications in psychiatry. Nowadays, it seems promising to study SNVs of leptin system genes (*LEP, LEPR*) and neuropeptide Y (*NRY*). Studying the mechanisms of APs-induced weight growth will allow their transmission to a personalized approach. It will help psychiatrists in patients' selection for the APs therapy. This will increase safety and effectiveness of the therapy, improve the quality of life and adherence to therapy in patients with schizophrenia.

Keywords: *pharmacogenetics; leptin; LEP; LEPR; NPY; antipsychotics; adverse drug reactions; weight gain; schizophrenia*

Introduction

Antipsychotics (APs) are the drugs of choice for schizophrenic spectrum disorders treatment. First-generation of APs (as known as typical) are high-affinity antagonists of dopamine receptors D2. Second-generation of APs (as known as atypical) have lower affinity for dopamine receptors and higher affinity for serotonin receptors (5-HT1A, 5-HT2A, 5-HT1C), histamine (H1) and adrenergic receptors (α1, α2). Mental disorders therapy requires long-term use of APs, which necessitates personalized assessment of the risk of developing adverse drug reactions (ADRs) [1]. The spectrum and severity of APs-induced ADRs vary significantly depending on APs types, as well as on personal characteristics of a patient with schizophrenia. Typical APs therapy is often associated with extrapyramidal ADRs development. The atypical APs therapy is connected to development of weight increase, cardiovascular and metabolic disorders [2, 3]. APs-induced weight increase has serious implications for general psychiatric practice. These patients have an increased risk of cardiovascular disease [4], which is linked to higher morbidity, mortality and reduced life expectancy [5]. In addition to that, APs-induced weight growth affects psychological well-being [6], leading to decrease in quality of life [5]. Patients with schizophrenia, while noticing a significant change in body weight, often stop taking APs. However, some patients treated by atypical APs do not gain weight, and this difference is believed to be due to genetic factors [7]. Understanding of APs-induced weight increase mechanisms will possibly prevent ADRs development and increase patient adherence to therapy.

Objective

Review of biological, biochemical and genetic biomarkers of AP-induced weight gain.

Results

Antipsychotic-induced weight increase

Weight increase while taking APs is an important factor in development of obesity in patients with schizophrenia. It is established that numbers of patients with mental disorders suffering from obesity are almost twice as high as of those among members of general population [8], which may be due to the intake of APs, as well as the high prevalence of nicotine addiction among this group of patients, a sedentary lifestyle and unbalanced diet [9].

Obesity is a risk factor for development of many cardiovascular diseases. According to the World Health Organization (WHO) definition, obesity is characterized by excessive accumulation of adipose tissue in a body and is measured by such an indicator as body mass index (BMI). BMI is defined as a person's weight in kilograms divided by the doubled height in meters (kg / m2). For adults, the WHO defines a person's weight as overweight with a BMI greater than or equal to 25, and as obesity with a BMI greater than or equal to 30 [10].

It should be noted that the change of body weight when taking different APs varies significantly. Studies show that taking olanzapine is associated with the largest weight growth during the first year of therapy. Thus, weight growth when taking olanzapine at the standard recommended dose of 15 mg / day can exceed 10 kg during the first year of treatment [11]. Therapeutic doses of risperidone and quetiapine may cause less weight increase than olanzapine within a year (2-3 kg) [12], while aripiprazole and ziprasidone are affiliated with a relatively low risk of weight gain [13]. Clinically significant increase in body weight is also observed with chlorpromazine intake in 18% of patients [14]. As a lot of studies have justified, maximum weight increase is observed within the first 12-16 weeks after the introduction of APs therapy, however, even after 6 months from the start of the treatment, some weight growth may be spotted [15,16, 1]. It has also been proven that after hospital discharge, a significant proportion of patients begin to lose weight, which may be associated with the increased physical activity or with the tendency of patients with mental disorders to self-adjust or cancel psychopharmacotherapy [17]. In general population, obesity is more common among women rather than men [18], which is also typical for patients with mental disorders. A study in which 194 patients with mental disorders participated, shows that 15% of men and 38% of women had a weight growth for 20% above the upper limit [19].

The data on dose-dependent weight gain while taking APs is quite contradictory, which may be linked to nosological affiliation and a course of mental disorder, which itself, as suggested by some authors, may affect the change in BMI [20, 21]. It has been shown that decrease in appetite and weight loss distinguishes depressive states, while increase in appetite and, as a consequence, weight gain is typical for manic states [21]. Padmavati R. et al. (2010) were focused on two groups of schizophrenic patients, who had never received drug therapy, being treated with APs. The paper shows that the prevalence of obesity and metabolic disorders was lower in the group of patients who never took APs than in the group who regularly receive medical treatment [22]. The results of a multicenter study, conducted on 1796 patients taking olanzapine, show

correlation between the dose of the drug and the degree of weight gain – large doses of olanzapine provoke greater body weight gain [23].

Pathogenesis of antipsychotic-induced weight gain

Obesity is a multifactorial disease, mechanisms of the development of which are yet to be understood. The accumulation of fat in the subcutaneous and especially the abdominal region is accompanied by changes in expression of a number of genes encoding proteins that regulate energy metabolism [24]. The mechanisms underlying APs-induced weight gain remain unknown, although there is some evidence of serotonergic, histaminergic, and adrenergic neurotransmitter systems been involved in the pathogenesis of obesity [25]. As it is known, the second-generation of APs introduces an imbalance in central mechanisms of food behavior control due to its interaction with 5-HT2C serotonin receptors and H1-histamine receptors [26]. There is also evidence of an interaction between the serotonergic system and leptin. It has been proven that mice knocked out with the 5-HT2C gene exhibit hyperleptinemia and leptin insensitivity [27]. Antagonists of the 5-HT2C receptor slow down the onset of satiety, which is mediated by inhibition of POMC (proopiomelanocortin) neurons, as well as decrease in the activity of neuropeptide Y [27]. It has been justified that possessors of SNV -759T of the *HTR2C* gene are prone to gain less weight than carriers of the wild-type C allele [26]. Possessing of the T allele is associated with lower gene expression, which may affect the level of circulating leptin [28].

Histamine, produced in the tuberomamillary nucleus of hypothalamus, affects the H1-histamine receptors. Alongside with that histamine also suppresses the feeling of hunger, which intensifies lipolysis process. Histamine and the signaling pathway, in which H1 receptors are involved, appear to be essential for the functioning of the leptin system. The conclusion is based on the fact that the effects of leptin are attenuated in mice knocked out with the H1 receptor [29].

It is assumed that genetic factors may also be important in development of APs-induced weight gain [7]. Stimulation of appetite and inhibition of satiety can provoke development of dyslipidemia and cause body weight increase in patients receiving atypical APs. Genes encoding leptin (*LEP*), leptin receptor (*LEPR*), and neuropeptide Y (*NPY*) appear to be promising candidate genes for studying APs-induced weight gain. The above mentioned genes can potentially be related to APs-induced ADRs due to the proven effects of leptin [30], ghrelin [31] and adiponectin [32] on food intake control, body weight and other metabolic parameters.

Since the sequencing of the *LEP* (ob) gene in 1994, leptin has attracted a widespread attention as a metabolic regulatory hormone [33]. Leptin is secreted mainly by adipocytes in white adipose tissue, decreasing food intake and increasing energy expenditure [34] through the central control of appetite and peripheral regulation of metabolic activity, and is encoded by the *LEP* gene (Figure 1).

Leptin binds to the membrane receptor both in ventromedial (central) parts of hypothalamus and peripheral areas, including liver, skeletal muscles, and β-cells of pancreas [35]. Stimulation of leptin receptors in the nucleus of hypothalamus reduces the effects of appetite-stimulating hormones such as melanin-concentrating hormone (MCH) and neuropeptide Y, while increasing the activity of appetite suppressing hormones such as α-melanocyte-stimulating hormone (α-MSH) and corticotropin -releasing factor [35]. Peripheral leptin agonism stimulates metabolic activity in skeletal muscles by increasing consumption of fatty acids and enhancing the effects of insulin. Evidence for metabolic activity of leptin has been demonstrated on mice, in which the genetic inability to

produce leptin is phenotypically manifested in the form of overeating and, as a result, obesity. Injecting mice with the recombinant leptin leads to decreased appetite and subsequent weight loss [36]. People who carry mutations in both copies of the *LEP* gene suffer from obesity and respond to exogenous leptin, while this effect is less prominent in heterozygotes. In humans, leptin predominantly circulates in a bound form with the soluble leptin receptor (sOB-R). SOB-R levels increase alongside with weight loss, as well as with concomitant decrease of leptin levels.

These effects can be observed even within a 72-hour fasting [37]. Leptin levels are positively correlated with adipose tissue, but the fact that obese people may have chronically elevated levels of leptin suggests a certain level of leptin's insensitivity [35].

It has been shown that the level of circulating leptin positively correlates with a body mass index. For instance, in patients with anorexia nervosa, a low leptin level increases alongside with weight growth during the treatment [38]. Leptin has multiple effects on energy homeostasis by activating key hypothalamic nuclei and peptides-energy balance regulators such as neuropeptide Y, proopiomelanocortin (POMC) and its product, α-melanocyte-stimulating hormone. Neuropeptide Y is a low molecular weight neuropeptide expressible in the cortical and hypothalamic areas of the brain, which, in turn, stimulates increased food intake, decreased energy expenditure and changes in peripheral metabolic activity [39, 40]. It is assumed that excessive secretion of neuropeptide Y in the arcuate nucleus of hypothalamus may be one of the most probable causes of hypothalamic obesity development [41].

Pharmacogenetic aspects of antipsychotic-induced weight gain

It has been proven that taking clozapine and a number of other APs increases serum leptin levels [42], which may cause APs-induced weight gain. It has been found that carriage of a SNV rs7799039 (G2548A) in the promoter area of *LEP* gene is associated with the general obesity phenotype [43]. Carriage of this SNV affects the expression of leptin, possibly at the level of transcription, and increases the level of leptin secretion by adipocytes of adipose tissue. Zhang et al. (2003) report that carriage of SNV rs7799039 (G2548A) in the promoter area of the *LEP* gene is associated with APs-induced weight gain after 10 weeks of the treatment with risperidone or chlorpromazine in the group of Chinese patients with schizophrenia [33]. In addition to that, carriage of the AA genotype for this SNV may be a genetic risk factor for development of weight gain while taking APs [44, 33]. However, another study shows that although carriage of the rs7799039 of *LEP* gene is not linked to weight gain after a short-term (6 weeks) treatment with risperidone, olanzapine, haloperidol, quetiapine, ziprasidone, and amisulpride, it is significantly associated with APs-induced weight gain in a long term (3 months). Moreover, carriage of the G allele, rather than the A allele, is affiliated with weight gain in this group of patients [28]. Brandl E.J et al. (2012) shown an association of carriage of the rs7799039G - rs10954173G - rs3828942G haplotype (Figure 2) of the *LEP* gene with weight gain in schizophrenic patients taking APs [45]. In a recent study, the association between to carriage of the allele A SNV rs3828942 of *LEP* gene and disorders of carbohydrate metabolism development (an increase of the glucose concentration in a blood plasma for an empty stomach to a value above 6.1 mmol / L) in patients taking APs has also been presented [46].

Puangpetch A. et al. (2019) investigated association between SNVs of candidate genes, in particular the SNVs rs7799039 of *LEP* gene and rs1137101 of *LEPR* gene, with metabolic disorders development in Thai schizophrenic patients receiving risperidone or clozapine. The authors discover that the prevalence of hyperglycemia is higher among patients treated with clozapine (64.0%) than among patients treated with risperidone (30.8%). SNV (rs7799039) of *LEP* gene demonstrated a significant association with hyperglycemia development ($\chi 2 = 9.879$, $p = 0.008$) among patients receiving risperidone;

patients with genotype AA have the highest risk of hyperglycemia developing (41.1%), and genotypes AG and GG - 20.8% and 0%, respectively. None of SNV researched genes is associated with the risk of hyperglycemia developing in patients taking clozapine [47].

Klemettilä J.P. et al. (2015) studied the role of leptin, adiponectin, and inflammatory cytokine levels in serum as possible biochemical markers of APs-induce weight gain. It is worth mentioning that the researchers hypothesize correlation between SNVs rs7799039 (-2548 A / G) of *LEP* gene, rs1501299 of *ADIPOQ* gene, and rs1414334 of *HTR2C* gene and weight increase in schizophrenic patients receiving clozapine therapy. The authors reveal connection between increased body weight and the level of the following indicators: leptin, cytokines, adipokine in blood serum of patients with metabolic disorders. However, the results of this study do not confirm a significant effect of SNV rs7799039 of *LEP* gene on the control of APs-induced weight gain among patients with schizophrenia [48].

In another study, an association is found between carried SNV rs1137101 of *LEPR* gene with metabolic syndrome development. When examining patients with schizophrenia taking APs, it is established that carried G allele is protective against metabolic syndrome development [49]. However, this is not consistent with the data of the previous studies, in which carrying of G allele is associated with an increased risk of obesity in women with schizophrenia (n = 200) [50], also with increased ratio of common cholesterol level: HDL, which reflects the risk of developing cardiovascular diseases (n = 353) [51]. Both studies were conducted in Netherlands on patients who received atypical APs for at least 3 months, most of whom were taking clozapine and olanzapine. The inconsistency of the data presented in the studies indicates a need for further studies of leptin system genes in large samples and with a strict design.

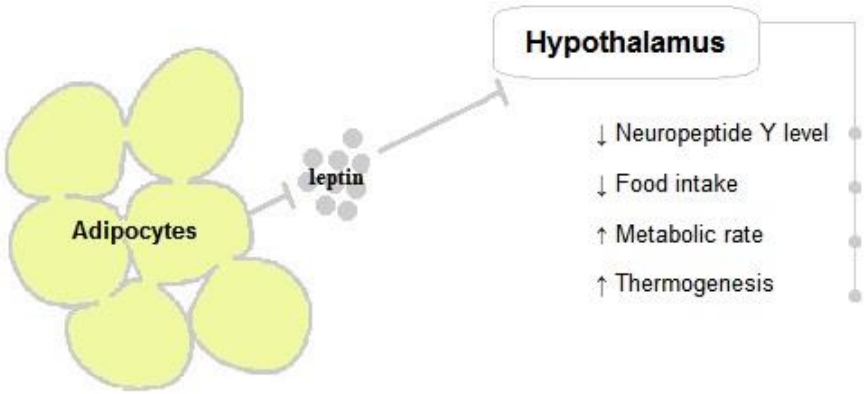

Figure 1. Leptin action in hypothalamus and adipocyte axis: leptin is secreted by adipocytes and interacts with its signaling receptor in the hypothalamus to decrease production of neuropeptide Y (↓), inhibits appetite (↓) increases metabolic rate (↑) and increases body temperature (↑).

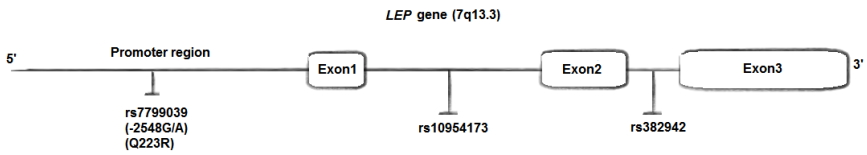

Figure 2. Localisation SNVs wich associate with APs-inducted weight gain in *LEP* gene.

The association of SNV of NRY gene with APs-induced weight gain is yet to be fully comprehended. Only a few studies are currently presented in the literature. In a sample of 226 schizophrenic patients who took clozapine and olanzapine for 14 weeks, an association of carrying C SNV allele rs16147 of NRY gene with a significant increase in weight compared with carrying of TT genotype is shown. It is also shown that carrying SNV rs5573 and rs5574 is significantly associated with changes in weight while taking atypical APs [52]. It should provide a concise and precise description of experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

Conclusions

Long-term use of APs is associated with the development of ADRs, which leads to deterioration in the life quality of patients. Development of obesity-related diseases, stigma and lack of adherence to therapy are consequences of APs-induced weight gain in patients with schizophrenia. The severity of APs-induced ADRs, in particular weight growth and metabolic disorders, varies significantly from patient to patient. To date, there are no valid predictors in clinical practice that would allow any sort of personalized approach to the selection of APs therapy [53]. In recent years, the genetic contribution to the development of APs-induced HP, weight gain in particular, has been widely studied [54]. Special attention in foreign studies is paid to the genes of leptin system and neuropeptide Y.

Identification of significant genetic predictors of the risk of APs-induced weight gain is an important task for personalized medicine. ADRs while taking APs is often the reason for therapy regime violation and significantly decreased quality of life for patients with mental disorders. The ethnic characteristics of the sample are an important factor for assessing the association of SNV possessors in genes candidates and the development of ADRs.

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