Review

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Molecular pathophysiology of metabolic effects of antipsychotic medications

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Antipsychotic medications are associated with major metabolic changes that contribute to medical morbidity and a significantly shortened life span. The mechanisms for these changes provide us with a broader understanding of central nervous and peripheral organ-mediated metabolic regulation. This paper reviews an extensive literature regarding putative mechanisms for effects of antipsychotic medications on weight regulation and glucose homeostasis as well as potential inherent metabolic risks of schizophrenia itself. We present a model suggesting that peripheral antipsychotic targets play a critical role in drug-induced weight gain and diabetes. We propose that a better understanding of these mechanisms will be crucial to developing improved treatments for serious mental illnesses as well as providing potentially novel therapeutic targets of metabolic disorders including diabetes.

Introduction

Schizophrenia affects 1% of the world's population. It is manifest by positive, negative, and cognitive symptoms that typically emerge in adolescence and early adulthood. People with schizophrenia have a 20% shorter life expectancy than the general population, with cardiovascular disease as the leading cause of death [1]. Schizophrenia-induced cardiovascular disease is in part attributable to higher rates of smoking but is likely to be further exacerbated by glucose and lipid abnormalities inherent to the pathophysiology of schizophrenia [2]. Antipsychotic drugs (APDs) are the primary medications used to treat schizophrenia and are increasingly used as adjunctive treatments for mood disorders. Second-generation APDs, often termed atypical antipsychotics (AAPs), are the current standard-of-care for treatment of schizophrenia because they are generally better tolerated than earlier medications (Box 1) [3]. Improved tolerability, however, comes with significant metabolic side effects, including obesity, type 2 diabetes (T2D), and dyslipidemia, that contribute to overall morbidity and mortality [4]. Nevertheless, no specific mechanisms have yet been identified to account for the relationship between schizophrenia and its metabolic comorbidities, nor the effects/interactions of antipsychotic medications in this regard. Although APD-induced adiposity may lead to insulin resistance, there is emerging evidence that weight gain and T2D may also be independent consequences of APD therapy [5].

Schizophrenia and abnormal glucose metabolism

For decades, there has been literature documenting an association between metabolic disease and schizophrenia [6] suggesting a metabolic phenotype intrinsic to schizophrenia. Before the APD era, cohort studies noted increased incidence of abnormal glucose metabolism in people with schizophrenia [7]. These observations corroborated cross-sectional results demonstrating that the prevalence of diabetes was greater in schizophrenic patients compared to the general population [8]. More recent studies confirmed these findings, and have shown impaired glucose tolerance in drug-naïve schizophrenic patients, as compared to healthy controls [9]. Impaired glucose tolerance has also been demonstrated in nonpsychotic, first-degree relatives of schizophrenic patients, further indicating a heritable phenotype that tracks with the risk of psychosis but is independent of the actual development of a psychotic disorder [10]. The risk of metabolic abnormalities further increases significantly with duration of illness with those who have chronic illness showing increased rates of metabolic dysfunction compared to first-episode and drug-naïve patients [11].

Recent genome-wide association studies (GWASs) have provided candidates for the association between schizophrenia and T2D [12]. *AKT1*, the gene encoding for the serine–threonine protein kinase AKT1, has been identified as a candidate gene for schizophrenia susceptibility in several global communities, across multiple studies [13].

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Box 1. Antipsychotic drugs (APDs)

Antipsychotic medications have been available for use in the United States since the FDA approval of chlorpromazine in 1954. As these new medications came to the market, they were initially categorized based on the potency of antagonism of the D2 dopamine receptor. High-potency agents, such as haloperidol and fluphenazine, and low-potency agents, like chlorpromazine and thioridazine, were in wide usage until the release of the second-generation drugs, or AAPs, which became available in the 1990s. The neuropsychiatric mechanism of action of AAPs is also through antagonism of D2 receptors, although adjunctive neurotransmitter effects, including serotonergic and histaminergic, have been related to differentiation in side effect profiles and efficacy between the two classes [67].

The primary side effect concern for the first-generation or conventional antipsychotics focused on neurological problems. Blocking D2 receptors in the nigrostriatal pathway of the brain is associated with Parkinsonian movements (pill-rolling tremor, bradykinesia, masked facies). Tardive dyskinesia, a permanent tremor which may present after several months of antipsychotic exposure, is also seen in greater numbers in high-potency conventional agents [68]. The higher the potency of the D2 blockade, the greater the likelihood of these neurological side effects [69]. Like the newer medications, low-potency conventional antipsychotics, particularly chlorpromazine, were associated with weight gain and insulin resistance [70]. The risk for weight gain from antipsychotic medications is inversely related to the potency at D2 [71]. Despite the purported differences between conventional and atypical antipsychotics, all antipsychotic medications have been associated with both neurological and metabolic side effects [72].

AKT1 is also recognized as a key mediator of insulin signaling and glucose metabolism, making it an attractive molecular interface for neuropsychiatric and metabolic consequences of schizophrenia. Loss-of-function *AKT1* mutations result in glucose intolerance, probably as a result of reduced insulin secretion and/or impaired action in liver, muscle, and hypothalamus [14]. In schizophrenia, lower levels of *AKT1* expression have been found in lymphocytes and frontal cortex of brain [13]. This reduction was associated with decreased phosphorylation of AKT1 substrates, including glycogen synthase kinase 3 beta (GSK3β), suggesting a functional defect in insulin signaling in the brain [15]. Conversely, treatment of mice with the APD haloperidol increased AKT signaling in the CNS – whether this holds true for peripheral organs, or in patients with schizophrenia, remains to be determined [15]. It is also unclear whether in schizophrenia, insulin/AKT signaling is reduced in hypothalamic regions that mediate satiety and systemic insulin sensitivity.

APDs induce metabolic dysfunction

APDs are associated with substantial risk for adverse metabolic conditions. The high prevalence and poor tolerability of these metabolic side effects frequently leads to suboptimal medication compliance and high rates of APD discontinuation, resulting in symptomatic relapse and poor long-term patient outcomes.

Concerns regarding the metabolic side effects of APDs were greatly increased following the introduction of the 'second generation' or 'atypical' drugs, which have come to dominate the APD market. Interestingly, among this group of medications, clozapine and olanzapine simultaneously cause the most metabolic dysfunction and weight gain of all the APDs, while demonstrating the greatest clinical efficacy for core psychotic symptoms [3].

Because APDs have relatively well defined nominal molecular targets through which they convey their therapeutic effects, a framework within which to study cellular mechanisms of APD action centrally and peripherally has emerged (Figure 1). In fact, the same neurotransmitter signaling networks targeted by APDs have also been implicated in metabolic dysregulation and obesity, highlighting potential shared molecular mechanisms of schizophrenia and obesity/T2D.

Antipsychotic-induced obesity is primarily the result of altered energy intake

Weight gain only occurs when energy intake exceeds expenditure, both of which can be affected by pathologic states and pharmacotherapy. When access to food is not limited, excess caloric consumption is the principal driver of positive energy balance and consequent deposition of lean tissue and fat. Additive or compensatory effects on energy expenditure may follow and affect rates of weight gain.

APDs have been hypothesized to affect both energy intake and expenditure (Figure 2); however, in humans, weight gain with APDs has been more consistently associated with increased food consumption [16]. A well-designed crossover study by Fountaine *et al.* showed that olanzapine treatment resulted in an estimated 345 kcal/day (18%) excess energy intake in 30 healthy male volunteers and 2.62 kg increased body weight (over 15 days), with greater food intake seen at all meals [17]. This acute perturbation may be an underestimate of what has long been recognized in clinical practice [16] – increased caloric intake and weight gain effects may in fact be higher in APD-treated schizophrenia patients than in healthy controls, and may be associated with increased food craving and binge eating [18]. For example, in olanzapine-naïve adolescents with schizophrenia, 4 weeks of olanzapine treatment was associated with an estimated increase of energy intake of 589 kcal/day (28%), leading to significant increases in abdominal circumference and body weight [19].

In the study by Fountaine *et al.* cited above, an excess of 345 kcal/day for 15 days would equate to approximately 5175 total excess kcal consumed over the trial length. Thus, the net weight gain cannot be accounted for solely by caloric excess, because 2.62 kg of increased body weight would equate to approximately 13 100 additional kcal (assuming 5000 kcal/kg mixed tissue). This 'back-of-the-envelope' calculation suggests two possible hypotheses – either APD-induced weight gain is a combination of increased food intake as well as decreased energy expenditure, and/or the caloric excess is accompanied by a large increase in body water, which may account for a substantial fraction (>50%) of the acute weight gain in short-term studies. The hypothesis that APDs reduce resting energy expenditure (REE) has been tested with mixed results. Although multiple groups have reported minimal to no change in energy expenditure [20,21], Fountaine *et al.* actually found that olanzapine increased REE (+113 kcal/24 h [17]. This is not a wholly unexpected result – energy intake and expenditure are not independent variables. In weight-reduced humans, energy