Medical Hypotheses 80 (2013) 486–489

Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Crosstalk between 5-HT2cR and PTEN signaling pathway in atypical antipsychotic-induced metabolic syndrome and cognitive dysfunction

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ARTICLE INFO

Article history:
Received 5 December 2012
Accepted 9 January 2013

ABSTRACT

Accumulating evidence indicates that chronic treatment with atypical antipsychotics (AAPs) leads to metabolic syndrome (MetS) and cognitive dysfunction. It has been found that patients receiving antipsychotic treatment with MetS have significantly worse cognitive function when compared to those without the MetS, suggesting an intrinsic relationship between MetS and cognitive dysfunction. Thus, investigating the reasons for the side effects induced by AAPs is an important step in the effort to understand the pathophysiology of this condition. The 5-HT2c receptor (5-HT2cR) antagonist properties of AAPs are likely to contribute to AAP-induced MetS. There is crosstalk between phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and 5-HT2cR. PTEN negatively regulates the activity of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, which plays an important role in obesity-induced insulin resistance in peripheral tissue. In the central nervous system, PI3K/AKT signaling modulates synaptic plasticity, a mechanism underlying learning and memory processes. This suggests that PI3K/AKT signaling contributes to both metabolic and cognitive activities. Since PTEN negatively regulates PI3K/AKT signaling and has crosstalk with 5-HT2cR, we hypothesized that the 5-HT2cR antagonism of AAPs may disrupt its crosstalk with PTEN and then trigger the PI3K/AKT signaling, and AAP-induced MetS and cognitive impairments may occur via this analogous signaling pathway.

Introduction

Antipsychotic drugs have been widely used to treat psychiatric disorders since typical antipsychotics (TAPs) were found to have specific therapeutic action against positive symptoms in the 1950s. Based on receptor binding and neuroimaging data, it seems as though TAPs exert an antipsychotic effect by inhibiting brain dopamine transmission, primarily by blocking the dopamine D2 receptor [1]. However, accumulating evidence has demonstrated that TAPs can cause a number of motor-related side effects that are collectively termed extrapyramidal syndromes (EPS), as well as detrimental effects on cognition. In the past decade, atypical antipsychotics (AAPs) have been approved by the US Food and Drug Administration (FDA) and are more frequently prescribed for patients with psychiatric disorders than TAPs. Compared with TAPs, AAPs are associated with a lower risk of EPS, and greater benefits for neurocognitive abilities. From a pharmacological perspective, the beneficial therapeutic efficacy of AAPs may be attributed to a combined lower affinity for dopamine receptors and greater affinity for serotonin (5-hydroxytryptamine, 5-HT) receptors [2]. However, on the other side of the coin, the adverse metabolic effects of AAPs have aroused physicians' attention, especially in the cases of clozapine, olanzapine and quetiapine [3]. Metabolic syndrome (MetS) identifies a group of obesity-related risk factors for chronic metabolic and cardiovascular diseases [4]. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia in the US showed that the prevalence of MetS in patients with schizophrenia was 40.9%, according to the National Cholesterol Education Program (NCEP) criteria [5]. The relationship between MetS and cognition impairments has received more and more attention. Recently, Lindenmayer et al. [6] have found that schizophrenia patients receiving antipsychotic treatment with MetS have significantly worse cognitive functions in the domains

Abbreviations: TAPs, typical antipsychotics; EPS, extrapyramidal syndromes; AAPs, atypical antipsychotics; FDA, US Food and Drug Administration; 5-HT, 5-hydroxytryptamine; MetS, metabolic syndrome; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; NCEP, National Cholesterol Education Program; CATIE-AD, Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; 5-HT2cR, 5-HT2c receptor; IR, insulin resistance; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Glut, glucose transporter; InsR, insulin receptor; IRS, insulin receptor substrate; SH2, src homology 2; PIP2, phosphorylate phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10; LTP, long-term potential; mPFC, medial prefrontal cortex; GST, glutathione-S-transferase.

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http://dx.doi.org/10.1016/j.mehy.2013.01.012

of processing speed, attention/vigilance, and reasoning/problem solving as compared to those without the MetS. This suggests that there may be a link between MetS and cognitive dysfunction in patients receiving antipsychotic treatment. The CATIE-Alzheimer's Disease (CATIE-AD) study indicated that AAPs are associated with worsening cognition at a magnitude consistent with 1 years deterioration compared with placebo in patients with AD [7]. These data indicate that chronic treatment with AAPs may result in MetS and cognitive impairments. However, the biological mechanism underlying MetS and cognitive impairments induced by AAPs is still unclear.

The hypothesis

Based on the findings from above mentioned studies, we have developed the hypothesis that AAP-induced MetS and cognitive impairments may occur via an analogous signaling pathway. The 5-HT2cR antagonism of the AAPs may present crosstalk with PTEN and then trigger the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, which plays an important role in both insulin resistance and synaptic plasticity (Fig. 1).

Evaluation of hypothesis

5-HT2cR: a target of AAP-induced side effects

Some pharmacological evidence suggests that the HTR2C gene, encoding for the 5-HT2c receptor (5-HT2cR) protein, could be a candidate gene for AAP-induced MetS [8]. First, AAPs are high-affinity 5-HT2cR antagonists; second, 5-HT2cR antagonists increase food intake and weight gain in rats [9] and 5-HT2cR deficient mice are overweight as a result of increasing feeding [10]. Recently, several pharmacogenetic studies have identified the genetic association between the HTR2C gene and MetS [8,11–13]. Thus, the 5-HT2cR is believed to be a promising target for exploring the biological mechanisms of AAP-induced MetS.

Insulin resistance, the central component of MetS induced by AAPs

Clinical and preclinical studies have both documented that AAPs (e.g. olanzapine and clozapine) can result in marked insulin resistance (IR) [14,15]. It has been proposed that IR is the central component of MetS [16]. The IR state is defined by reduced sensitivity of insulin responsive tissues to insulin, which results in increased levels of glucose in the blood [17].

IR and PI3K/AKT signaling pathway

Insulin is a major anabolic hormone that plays an essential role in glucose homeostasis, by regulating the balance between hepatic glucose production and glucose uptake by muscle and adipose tissue [18]. Insulin regulates glucose transport in adipocytes and myocytes by controlling the translocation of glucose transporter (Glut) 4 between intracellular pools and the plasma membrane [19]. Insulin binds to the extracellular α-subunit of the insulin receptor (InsR), which results in the autophosphorylation and activation of the intracellular β-subunit [20]. This activates insulin receptor substrate family members (IRS1-IRS4) and Shc, which subsequently recruits downstream signaling molecules containing Src homology 2 (SH2) domains including the p85 subunit of PI3K [21]. Activated PI3K phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) generates phosphatidylinositol 3,4,5-trisphosphate (PIP3). Increased PIP3 stimulates phosphoinositide-dependent protein kinase (PDK), resulting in the activation of AKT [18].

In normal conditions, insulin stimulates Glut 4 activity in skeletal muscle via IRS tyrosine phosphorylation and downstream PI3K activation. Glut 4 is the major insulin-mediated glucose transporter in muscle and adipocytes [19]. Precise translocation of Glut 4 from intracellular stores to the plasma membrane is crucial for insulin-regulated glucose transport. The PI3K-dependent signaling pathway is critical for the metabolic effects of insulin. It has been reported that the activation of PI3K by insulin is mediated by the p85 regulatory subunit binding to IRS [22]. In genetically obese and high-fat fed animals, decreased expression of IRS and activation of PI3K are also prominent [23]. AKT is a serine/threonine kinase activated by PI3K and responsible for glycogen, lipid and protein synthesis, cell survival and anti-inflammatory response [20]. AKT contributes to IR by regulating insulin-stimulated transport of Glut 4 in peripheral tissues, and variations on AKT activity are found in various cells in diabetes and IR [20]. AKT phosphorylation is reduced in adipocytes and skeletal muscle of type 2 diabetes patients [24], and AKT2 activation is closely correlated to Glut 4 translocation though insulin-activated PI3K signals in adipocytes

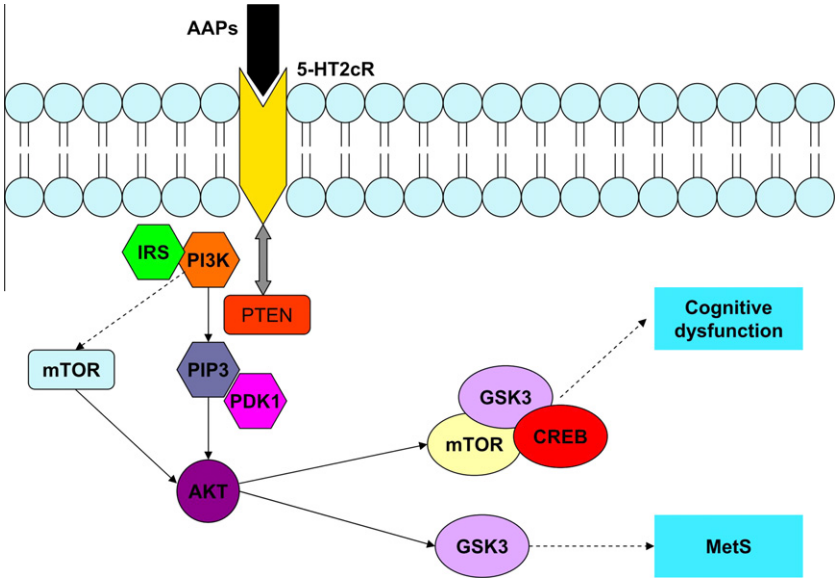

Fig. 1. Schematic representation of crosstalk between 5-HT2cR and PTEN, as well as PTEN/PI3K/AKT signaling pathway. Examples of molecules known to act on glucose metabolism and synaptic plasticity.