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REVIEW

The role of ghrelin signalling in second-generation antipsychotic-induced weight gain

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Summary Based on clinical and animal studies, this review suggests a tri-phasic effect of second-generation antipsychotics (SGAs) on circulating ghrelin levels: an initial increase exerted by the acute effect of SGAs; followed by a secondary decrease possibly due to the negative feedback from the SGA-induced body weight gain or hyperphagia; and a final re-increase to reach the new equilibrium. Moreover, the results can also vary depending on individual SGAs, other hormonal states, dietary choices, and other confounding factors including medical history, co-treatments, age, gender, and ghrelin measurement techniques. Interestingly, rats treated with olanzapine, an SGA with high weight gain liabilities, are associated with increased hypothalamic ghrelin receptor (GHS-R1a) levels. In addition, expressions of downstream ghrelin signalling parameters at the hypothalamus, including neuropeptide Y (NPY)/agouti-related peptide (AgRP) and proopiomelanocortin (POMC) are also altered under SGA treatments. Thus, understanding the role of ghrelin signalling in antipsychotic drug-induced weight gain should offer potential novel pharmacological targets for tackling the obesity side-effect of SGAs and its associated metabolic syndrome.

Contents

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1. Introduction

Schizophrenia is a complex mental disorder affecting approximately 1.5% of the adult population worldwide (Bhugra, 2005). Second-generation antipsychotics (SGAs) have become the primary treatment for schizophrenia and other psychotic disorders due to their claimed superior efficacy and induction of fewer extrapyramidal side-effects compared to the first-generation antipsychotics (Kane et al., 2009; Leucht et al., 2009a,b). However, metabolic side-effects, in particular body weight gain, have emerged as an increasing concern for SGAs in light of their accompanying complications and deterioration in drug compliance (Lieberman et al., 2005). Although some valuable insights have been achieved, the mechanism of SGA-induced weight gain remains unclear.

Ghrelin is a 28-amino-acid orexigenic hormone secreted mainly from the X/A-like cells (rodent equivalent of the human P/D1 cells) at the fundus of the stomach (Kojima et al., 1999; Nakazato et al., 2001; Tschop et al., 2000). Ghrelin could increase food intake and lead to body weight gain in humans (Adachi et al., 2010; Druce et al., 2005), which coincides with clinical observations that patients on antipsychotics often experience increased appetite and food intake. In addition, clinical (Basoglu et al., 2010; Chen et al., 2011; Esen-Danaci et al., 2008; Hosojima et al., 2006; Kim et al., 2008; Murashita et al., 2005, 2007a; Palik et al., 2005; Perez-Iglesias et al., 2008; Roerig et al., 2008; Tanaka et al., 2008; Togo et al., 2004; Vidarsdottir et al., 2010) and animal studies (Albaugh et al., 2006; Davey et al., 2012; Weston-Green et al., 2011) suggest that SGA treatments modulate circulating ghrelin levels. Moreover, rats treated with olanzapine, an SGA with significant weight gain liabilities, have elevated hypothalamic ghrelin receptor (also called growth hormone secretagogue receptor 1a; GHS-R1a) expression (Davey et al., 2012; Zhang et al., 2012), indicating that ghrelin signalling may play a role in antipsychotic-induced obesity.

Multiple factors, such as the antagonism of the histaminergic H1 receptor and serotoninergic 5-HT2c receptors have been suggested as important factors contributing to the weight gain side-effect induced by SGAs (Kroeze et al., 2003; Nasrallah, 2008; Reynolds and Kirk, 2008); and the role of α-adrenergic (Nasrallah, 2008), muscarinic M3 (Weston-Green et al., 2012b), and histaminergic H3 (Deng et al., 2010) antagonism has also been suggested. However, we have very limited understanding of the role of ghrelin signalling in SGA-induced body weight gain. Considering the fact that ghrelin is an important orexigenic circulating hormone, as well as the presence of GHS-R1a and ghrelin at the hypothalamic arcuate nucleus (Arc), the energy homeostasis regulatory centre, elucidating the molecular mechanisms of ghrelin signalling under SGA treatments may assist in exploring pharmacological targets for tackling the weight gain side-effects of SGAs.

2. The ghrelin signalling system

2.1. Ghrelin and the ghrelin receptor

The biochemical features and orexigenic actions of ghrelin and the ghrelin receptor have been reviewed previously (Andrews, 2011a; Castaneda et al., 2010; Schellekens et al., 2010). Ghrelin is posttranslationally acylated by the enzyme ghrelin O-acyltransferase (GOAT) on Ser3 of the ghrelin peptide, which is essential for binding ghrelin to the GHS-R1a receptor (Andrews, 2011b; Bednarek et al., 2000; Schellekens et al., 2010; Yang et al., 2008). The GHS-R1a receptor is highly expressed in the Arc, where food intake and energy homeostasis are regulated (Harrold et al., 2008).

Recent findings of the heterodimerization between the GHS-R1a receptor and other G protein-coupled receptors, including the dopaminergic D1 and D2, the serotoninergic 5-HT2c, and the melanocortinergic MC4 receptors (Jiang et al., 2006; Kern et al., 2012; Rediger et al., 2011; Schellekens et al., 2013), have shed light on novel mechanisms of food intake and body weight regulation via the ghrelinergic system. Further, SGAs such as olanzapine and clozapine are antagonists of the D2 and 5-HT2c receptors, which induces weight gain (Nasrallah, 2008). Hence the weight gain liabilities of these SGAs can also be due to the functional interactions between these receptors and the GHS-R1a receptor.

2.2. Transduction of ghrelin signals from the peripheral to the brain

Several lines of evidence support the role of the vagus-nucleus of the solitary tract (NTS)-Arc pathway in ghrelin signal transduction from the peripheral to the brain