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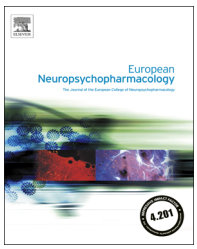

Vitamin D deficiency exacerbates atypical antipsychotic-induced metabolic side effects in rats: Involvement of the INSIG/SREBP pathway

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Abstract
Metabolic syndrome is a major concern in psychotic patients receiving atypical antipsychotics. Recent evidence suggests that sterol regulatory element-binding proteins (SREBPs) and insulin-induced genes (INSIGs) are implicated in the antipsychotic-induced metabolic side-effects. Vitamin D (VD) deficiency, a highly prevalent phenomenon among patients with psychosis, might also predispose individuals to metabolic syndrome Considering that VD has modulating effects on the INSIG/SREBP pathway, it is possible that VD may have a role in the antipsychotic-induced metabolic disturbances involving its effects on the INSIG/SREBP system. Thus, the present study aimed to evaluate the effects of VD deficiency and VD supplementation on antipsychotic-induced metabolic changes in rats. After 4-week administration, clozapine (10 mg/kg/d) and risperidone (1 mg/kg/d) both caused glucose intolerance and insulin resistance in VD deficient rats, but not in rats with sufficient VD status. Antipsychotic treatments, especially clozapine, elevated serum lipid levels, which were most apparent in VD deficient rats, but alleviated in VD-supplemented rats. Additionally, antipsychotic treatments down-regulated INSIGs and up-regulated SREBPs expression in VD deficient rats, and these effects were attenuated when VD status was more sufficient. Collectively, this study disclose the novel findings that antipsychotic-induced metabolic disturbances is exacerbated by VD deficiency and can be

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alleviated by VD supplementation, providing new evidence for the promising role of VD in prevention and treatment of metabolic disorders caused by antipsychotic medications. Furthermore, our data also suggest the involvement of INSIG/SREBP pathway in the antipsychotic-induced hyperlipidemia and beneficial effects of VD on lipid profile.

1. Introduction

Atypical antipsychotic medications are the mainstays for treating psychotic disorders, particularly in schizophrenia and bipolar disorder (Leucht et al., 2009). Unfortunately, many atypical antipsychotics are associated with metabolic disturbances such as weight gain, diabetes and dyslipidemia, which could result in increased cardiovascular risk and decreased medication adherence, and may eventually lead to clinical deterioration and decreased life expectancy (De Hert et al., 2012; Haupt, 2006).

It should be noted that patients with psychotic disorders are prone to have deficient or insufficient vitamin D (VD) status (Belvederi Murri et al., 2013; Valipour et al., 2014) and concomitant metabolic syndrome during the chronic hospitalization and antipsychotic therapy. VD, which was traditionally associated with musculo-skeletal system, now is implicated as a pleiotropic secosteroid affecting multiple aspects of human physiology. Hypovitaminosis D has been linked to a range of medical conditions including obesity, diabetes mellitus, insulin resistance, dyslipidemia, and worse cardiovascular outcomes (Christakos et al., 2013). Our previous study showed that the genetic variations of VD receptor could affect the metabolic profiles in schizophrenia patients and are associated with the susceptibility of risperidone-treated patients to metabolic abnormalities, indicating that VD signaling might be involved in the antipsychotic-induced metabolic disorders (Jiang et al., 2014). This hypothesis is further supported by a recent clinical study showing that adjunctive use of VD can significantly attenuate the antipsychotic-induced elevation of serum cholesterol levels (Thakurathi et al., 2013). Therefore, based on these observations, it is tempting to hypothesize that VD deficiency might exacerbate atypical antipsychotic-induced metabolic side effects.

Previous evidence from in vitro studies has shown that antipsychotic exposure can induce proteolytic activation of the sterol regulatory element-binding proteins (SREBPs) and upregulate SREBP-associated target lipogenesis genes in human liver cells (Raeder et al., 2006) and primary rat hepatocytes (Lauressergues et al., 2010), accompanied by increased fatty acids and cholesterol biosynthesis. These results were supported by in vivo studies, in which clozapine and risperidone were shown to activate the SREBPs with subsequent up-regulation of downstream genes and lipid accumulation (Ferno et al., 2009; Lauressergues et al., 2011). These data suggest that SREBPs, which are known as the major activators of lipogenesis (Eberle et al., 2004), are involved in the antipsychotic-induced increase of lipogenesis. The SREBPs are synthesized as inactive precursors located in the endoplasmic reticulum (ER) membrane and activated through the action of SREBP cleavage-activating protein (SCAP) by ER-to-Golgi transport followed by limited proteolytic cleavage (Raghow et al., 2008). In addition, the activation of the SREBPs is suppressed by sterol by a feedback mechanism (Bengoechea-Alonso and Ericsson, 2007). Insulin-induced gene proteins (INSIGs, including INSIG-1 and INSIG-2) are the key negative regulators of SREBPs function, which enhance the response to cholesterol by promoting the binding of cholesterol to SCAP when cholesterol is abundant, thereby retaining the SREBPs in the ER and preventing its activation processing (Dong and Tang, 2010). Moreover, clinical studies reported a strong association between the INSIG-2 polymorphisms and antipsychotic-induced metabolic disturbances, indicating that INSIGs may be implicated in the pathogenesis of metabolic abnormalities in patients treated with antipsychotics (Le Hellard et al., 2009; Liou et al., 2012). Nevertheless, the mechanisms by which the antipsychotics induce the SREBPs activation are still unknown and there is limited information about the effects of antipsychotics on the expressions of INSIGs and SCAP. Interestingly, there is evidence that VD treatment or activation of VDR can inhibit the expression of SREBPs and their target enzymes that mediate lipid synthesis, suggesting that VD is implicated in the regulation of the SREBP system (Wang et al., 2011; Yin et al., 2012). Considering the involvement of VD in the metabolic disorders, it is possible that the suboptimal VD status may contribute to the antipsychotic-induced metabolic disturbances involving its effects on the SREBP system.

To further understand the mechanisms of antipsychotic-induced metabolic side effects and clarify the potential link between VD and antipsychotic-induced metabolic disturbances, we evaluated the effects of VD and antipsychotics on metabolic-related parameters and hepatic INSIG/SREBP pathway in rats. Clozapine (CLO) and risperidone (RIS) were selected as antipsychotics with the highest and intermediate risk for metabolic disturbances, respectively (Haupt, 2006). Given the importance of peripherally-released peptide hormones in the energy homeostasis (Jin et al., 2008), the circulating levels of leptin, ghrelin, and adiponectin were also analyzed.

2. Experimental procedures

2.1. Animals, diet and experimental protocols

Fig. 1 presents a timeline of the experimental procedures. Male Sprague-Dawley rats (initially weighing 170–190 g) were maintained under controlled conditions (12/12 light/dark cycle; ambient temperature 22–25 °C; humidity 55 ± 5%), and provided ad libitum access to assigned diet and water except when they were submitted to glucose tolerance test (GTT). Rats were assigned into three dietary regimen groups, which were subjected to VD deficient diet