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REVIEW

Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: A meta-analysis

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Abstract
Background: People with schizophrenia are more likely than general population to suffer from metabolic abnormalities, with second-generation antipsychotics (SGAs) increasing the risk. Low plasma adiponectin levels may lead to metabolic dysregulations but evidence in people with schizophrenia, especially for the role of SGAs, is still inconclusive.
Objective: To compare plasma adiponectin levels between people with schizophrenia and healthy controls, and to estimate the relative effect of schizophrenia and SGAs on adiponectin.
Methods: We performed a systematic review and meta-analysis of observational studies published up to 13 June 2014 in main electronic databases. Pooled standardized mean differences (SMDs) between index and control groups were generated. Appropriate subanalyses and additional subgroup analyses were carried out.
Results: Data from 2735 individuals, 1013 with and 1722 without schizophrenia, respectively, were analysed. Schizophrenia was not associated with lower adiponectin levels (SMD of −0.28, 95%CI: −0.59, 0.04; $p = 0.09$). However, individuals with schizophrenia taking SGAs had plasma levels significantly lower than controls ($p = 0.002$), which was not the case of drug free/drug naïve subjects ($p = 0.52$). As regards single antipsychotic drugs clozapine ($p < 0.001$) and olanzapine ($p = 0.04$) — but not risperidone ($p = 0.88$) — were associated with adiponectin levels lower than controls.
Conclusions: People with schizophrenia per se may not have levels of adiponectin lower than controls, though treatment with SGAs is associated with this metabolic abnormality. This bears

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clinical significance because of hypoadiponectinemia involvement in cardiovascular diseases, even if mechanisms whereby SGAs affect adiponectin remain unexplained. Longitudinal studies evaluating long-term effects of SGAs on adiponectin are needed.

Contents

1. Introduction

A large body of evidence shows that people who suffer from schizophrenia are more likely than the general population to have metabolic abnormalities, such as diabetes, dyslipidemia, abdominal obesity, and metabolic syndrome (e.g., Bartoli et al., 2013a; De Hert et al., 2011a; Mitchell et al., 2013; Osborn et al., 2008). A number of potential explanations of this association have been proposed. In part, the development of metabolic abnormalities is attributable to the individual-level detrimental health behaviours common in people with schizophrenia, including unhealthy dietary habits, excessive alcohol intake, smoking, and lack of exercise (Clerici et al., 2014; De Hert et al., 2011a). However, based on unmedicated clinical populations, it has also been argued that people with schizophrenia may have a specific susceptibility to metabolic abnormalities (e.g., Cohn et al., 2006; Ryan et al., 2003; Verma et al., 2009). Furthermore, antipsychotic medications, particularly second generation antipsychotics (SGAs) such as olanzapine and clozapine, seem to raise the risk of metabolic side effects such as hyperglycaemia, dyslipidemia, and weight gain (Correll et al., 2011; Das et al., 2012; Newcomer, 2005).

Mechanisms underlying these metabolic abnormalities in people with schizophrenia are not fully understood so far, but in recent years it has been suggested that adipokines — biologically active cytokines secreted by adipose tissue — may play a major role, influencing energy and vascular homeostasis, and immune response (e.g., Klemettilä et al., 2014; Kubota et al., 2006; Maury and Brichard, 2010; Song et al., 2013). In particular, adiponectin is an adipokine which has recently attracted considerable attention because of its interactions with both genetic and environmental (e.g., food intake and exercise) factors (Imbeault, 2007; Kadowaki et al., 2008; Okamoto et al., 2006). It is synthesized by white adipose tissue (Maeda et al., 1996) and circulates at relatively high concentrations, accounting for up to 0.05% of total serum protein (Lihn et al., 2005). Although its physiological function is not entirely clear, adiponectin is certainly involved in the modulation of glucose and lipid metabolism (Liu et al., 2012), with low plasma levels associated with obesity (Kadowaki et al., 2006), insulin resistance, and, in a dose—response manner, with type 2 diabetes as shown by a rather conclusive meta-analysis (Li et al., 2009). Furthermore, plasma adiponectin levels are negatively correlated with triglycerides concentration and waist circumference, possibly explaining the associations between hypoadiponectinemia, dyslipidemia and metabolic syndrome, respectively (Gardener et al., 2013; Matsuzawa et al., 2004; Ryo et al., 2004).

Preliminary findings on adiponectin in people with schizophrenia as compared with healthy controls are contradictory (Jin et al., 2008), with research in drug free subjects showing both higher (Song et al., 2013) and lower (Cohn et al., 2006) plasma levels. In addition, atypical antipsychotics might influence adiponectin regulation independently of components of metabolic syndrome and gender (Hanssens et al., 2008), but also findings on their effect are