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Aripiprazole-induced adverse metabolic alterations in polyI:C neurodevelopmental model of schizophrenia in rats

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ABSTRACT

Schizophrenia appears to be linked to higher incidence of metabolic syndrome even in the absence of antipsychotic treatment. Atypical antipsychotics substantially differ in their propensity to induce metabolic alterations. Aripiprazole is considered to represent an antipsychotic drug with low risk of metabolic syndrome development. The aim of this study was to evaluate metabolic phenotype of neurodevelopmental polyI:C rat model and assess metabolic effects of chronic aripiprazole treatment with regard to complex neuroendocrine regulations of energy homeostasis. Polyinosinic:polycytidylic acid (polyI:C) was administered subcutaneously at a dose of 8 mg/kg in 10 ml on gestational day 15 to female Wistar rats. For this study 20 polyI:C and 20 control adult male offspring were used, randomly divided into 2 groups per 10 animals for chronic aripiprazole treatment and vehicle. Aripiprazole (5 mg/kg, dissolved tablets, ABILIFY®) was administered once daily via oral gavage for a month. Altered lipid profile in polyI:C model was observed and a trend towards different dynamics of weight gain in polyI:C rats was noted in the absence of significant antipsychotic treatment effect. PolyI:C model was not associated with changes in other parameters i.e. adipokines, gastrointestinal hormones and cytokines levels. Aripiprazole did not influence body weight but it induced alterations in neurohumoral regulations. Leptin and GLP-1 serum levels were significantly reduced, while ghrelin level was elevated. Furthermore aripiprazole decreased serum levels of pro-inflammatory cytokines. Our data indicate dysregulation of adipokines and gastrointestinal hormones present after chronic treatment with aripiprazole which is considered metabolically neutral in the polyI:C model of schizophrenia.

1. Introduction

Atypical antipsychotics, drugs with indisputable benefits in the treatment of a wide spectrum of psychiatric disorders, substantially differ in their propensity to induce metabolic alterations including weight gain, dyslipidemia, impaired glucose tolerance or insulin resistance, yet the underlying pathophysiological mechanisms are complex and have not been fully elucidated (Henderson et al., 2015). Aripiprazole (ARI) is considered a metabolically neutral antipsychotic agent with low risk of metabolic syndrome development (Kasteng et al., 2011; Nasrallah et al., 2016). Switching to antipsychotics characterized by lower propensity to induce metabolic dysregulation represents one of the recommended strategies to reduce cardio-metabolic risk in patients experiencing metabolic alterations during antipsychotic treatment (American Diabetes Association et al., 2004). This approach is supported by clinical data as switching from olanzapine to ARI led to weight reduction and a decrease in cholesterol and triglyceride serum levels (Newcomer et al., 2008; Stroup et al., 2011; Takeuchi et al., 2010). However, ARI was also reported to induce significant weight gain (Malla et al., 2016).

In addition, there is evidence that antipsychotic-naïve first episode schizophrenia patients are more prone to metabolic abnormalities (Enez Darcin et al., 2015). Therefore, it seems that

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schizophrenia *per se* is linked to higher incidence of metabolic syndrome development (Kritharides et al., 2016; Kucerova et al., 2015; Malan-Müller et al., 2016) and as the common underlying pathophysiology of schizophrenia and metabolic syndrome distorted inflammatory pathways have been suggested (Leonard et al., 2012). Pro-inflammatory cytokines have been implicated in etiology of neuropsychiatric disorders, while the low-grade pro-inflammatory state is associated with obesity, diabetes mellitus and cardiovascular morbidity (Aguilar-Valles et al., 2015; Reisinger et al., 2015).

The neurodevelopmental theory of schizophrenia postulates the association between the pre- and perinatal environmental factors such as prenatal infection, subsequent maternal immune activation and later risk of schizophrenia (Canetta and Brown, 2012; Ratnayake and Hill, 2016). This provides a concept for chronic neurodevelopmental animal models of neuropsychiatric disorders such as *in utero* exposure to a viral mimetic agent polyinosinic:polycytidylic acid (polyI:C) (Meyer and Feldon, 2012; Reisinger et al., 2015). Neurodevelopmental models of schizophrenia have several advantages over other types of preclinical models as the condition of the animals is chronic and reflects several aspects of schizophrenia-related symptomatology and pathophysiology (Micale et al., 2013). The polyI:C model is widely recognized and considered suitable for basic and translational schizophrenia research (Meyer and Feldon, 2012; Ratnayake and Hill, 2016).

Similarly as in human it could be assumed that schizophrenic-like phenotype in rodent models may involve intrinsic vulnerability to metabolic disturbances and susceptibility to metabolic alterations induced by antipsychotic medication further proving the validity and translational potential of the models (Kucerova et al., 2015). So far, preclinical research has extensively addressed metabolic effects of atypical antipsychotics (AAP) (Boyda et al., 2010) but despite the high clinical relevance, there is a lack of studies assessing the relation between metabolic abnormalities and schizophrenia-like phenotype in rodents *per se*. Moreover, to the best of our knowledge, metabolic abnormalities induced by antipsychotic treatment have not been evaluated in rodent schizophrenia-like models yet.

Furthermore, metabolic alterations after chronic ARI exposure in healthy rodents have been investigated less intensely compared to other antipsychotic agents (Boyda et al., 2010). Therefore, the need to focus on evaluating metabolic dysregulation also in antipsychotics carrying lower metabolic risks has been expressed (Ersland et al., 2015) and this approach may also contribute to better understanding of the underlying mechanisms. In rodent experiments, metabolic abnormalities induced by antipsychotics, specifically weight gain, glucose metabolism dysregulation and altered lipid profile have been described (Boyda et al., 2010). Nevertheless, the frequently inconsistent findings do not allow definite conclusions on the potential pathophysiological mechanisms likely due to methodological heterogeneity. More recently, the attention in this field has been drawn to complex energy homeostasis regulation and the role of adipokines, gastrointestinal hormones and other modulators, yet few preclinical studies have assessed these putative alterations with regard to antipsychotic treatment (Horska et al., 2016, 2017; Skrede et al., 2012; Zhang et al., 2013).

The aim of this study is to evaluate metabolic phenotype of polyI:C rat model and assess metabolic effects of chronic ARI treatment with regard to complex neuroendocrine regulations of energy homeostasis. Thus, in this study we analyzed apart from basic serum biochemical parameters a spectrum of gastrointestinal hormones, adipokines and markers of inflammation. This includes leptin, ghrelin, glucagon-like peptide 1 (GLP-1), glucagon, fibroblast growth factor 21 (FGF-21) and pro-inflammatory cytokines – interleukin 1 and 6 (IL-1, IL-6) and tumor necrosis factor α (TNF-α). These hormones are involved in energy homeostasis regulations and associated with obesity and insulin resistance (Blüher and Mantzoros, 2015; Quarta et al., 2016). The role of cytokines in energy homeostasis is well-described (Fontana et al., 2007; Glund and Krook, 2008) and it is highly relevant in a model based on a prenatal pro-inflammatory insult.

We hypothesized that the polyI:C model may possess intrinsic metabolic derangements as a part of the schizophrenia-like phenotype and ARI treatment may induce dysregulations in the metabolic parameters to a higher extent in the polyI:C animals even in the absence of significant changes in body weight. This study was designed to assess potential metabolic disturbances present in the polyI:C model *per se*, the effect of ARI on metabolic variables in normal rats and the possible interaction between the polyI:C model and ARI treatment.

2. Material and methods

2.1. Animals

Adult male and female Wistar rats were purchased from the Masaryk University breeding facility (Brno, Czech Republic) and time-mated. Polyinosinic:polycytidylic acid (polyI:C) was administered at a dose of 8 mg/kg in 10 ml subcutaneously on a gestational day (GD) 15 to 11 rats, while vehicle (saline) was injected to 10 control rats. The average surviving litter size was n = 10.5 in both control and polyI:C treated mothers. The average proportion of male and female offspring was 52% of males and 48% of females. No cross-fostering was used, the mothers were regularly weighed and no differences were observed between control and polyI:C treated mothers. The offspring were weaned on a postnatal day (PND) 22 and group-housed.

For this study 20 polyI:C and 20 control male offspring weighing 250–350 g were used. The polyI:C and control rats were randomly divided into 2 groups per 10 animals for chronic (28 days) ARI treatment or vehicle control. The treatment was initiated when the animals were 11 weeks old. All animals were pair-housed in standard polycarbonate housing cages. Environmental conditions during the whole study were constant: relative humidity 50–60%, temperature 23 °C ± 1 °C, normal 12-h light-dark cycle (6 a.m.–6 p.m. light). Standard rodent chow and water were available *ad libitum*. All procedures were performed in accordance with EU Directive no. 2010/63/EU and approved by the Animal Care Committee of the Faculty of Medicine, Masaryk University, Czech Republic and Czech Governmental Animal Care Committee, in compliance with Czech Animal Protection Act No. 246/1992.

2.2. Drugs and treatments

PolyI:C was purchased from Sigma-Aldrich spol. s.r.o., Prague, Czech Republic as a sodium salt and dissolved in saline to obtain a concentration of 8 mg/kg in 10 ml. Subcutaneous administration of 8 mg/kg on gestational day 15 was chosen according to validated protocol using a Wistar strain of rats (Missault et al., 2014). This protocol was validated but the complex schizophrenia-like phenotype was not assessed in this study due to concerns about non-standard energy expenditure and stress related to behavioural testing which may bias the metabolic data. However, this is a limitation of the study.

Aripiprazole (ARI) was obtained as ready-made preparation for human use in tablets (ABILIFY® non-coated tablets, 15 mg, Otsuka Pharmaceutical Europe Ltd., GB). The solution was prepared by dissolving the tablets to obtain ARI dose of 5 mg/kg in 1 ml. The