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Research Report

Adolescent olanzapine sensitization is correlated with hippocampal stem cell proliferation in a maternal immune activation rat model of schizophrenia

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ABSTRACT

Previous work established that repeated olanzapine (OLZ) administration in normal adolescent rats induces a sensitization effect (i.e. increased behavioral responsiveness to drug re-exposure) in the conditioned avoidance response (CAR) model. However, it is unclear whether the same phenomenon can be detected in animal models of schizophrenia. The present study explored the generalizability of OLZ sensitization from healthy animals to a preclinical neuroinflammatory model of schizophrenia in the CAR. Maternal immune activation (MIA) was induced via polyinosinic:polycytidylic acid (PolyI:C) administration into pregnant dams. Behavioral assessments of offspring first identified decreased maternal separation-induced pup ultrasonic vocalizations and increased amphetamine-induced hyperlocomotion in animals prenatally exposed to PolyI:C. In addition, repeated adolescent OLZ administration confirmed the generalizability of the sensitization phenomenon. Using the CAR test, adolescent MIA animals displayed a similar increase in behavioral responsiveness after repeated OLZ exposure during both the repeated drug test days as well as a subsequent challenge test. Neurobiologically, few studies examining the relationship between hippocampal cell proliferation and survival and either antipsychotic exposure or MIA have incorporated concurrent behavioral changes. Thus, the current study also sought to reveal the correlation between OLZ behavioral sensitization in the CAR and hippocampal cell proliferation and survival. 5′-bromodeoxyuridine immunohistochemistry identified a positive correlation between the magnitude of OLZ sensitization (i.e. change in avoidance suppression induced by OLZ across days) and hippocampal cell proliferation. The implications of the relationship between behavioral and neurobiological results are discussed.

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1. Introduction

The use of antipsychotic drugs (APD) in children and adolescents has increased dramatically worldwide in recent years (Aparasu and Bhatara, 2007; Kalverdijk et al., 2008; Rani et al., 2008; Wong et al., 2004). APD use for patients under the age of 18 now accounts for about 15% of total usage in the U.S., not only for the management of psychosis, but also for bipolar disorder, depression, disruptive behavior, and anxiety (Domino and Swartz, 2008). Clinical studies have established that children and adolescents tend to be more susceptible than adults to the adverse consequences of APD use, including prolactin elevation and motor side effects (Haddad and Sharma, 2007; Wudarsky et al., 1999). Preclinical studies in animal models suggest that this may be due to the differential biological effects APD have on adolescents versus adults (Choi et al., 2010; Spear et al., 1980). For instance, chronic treatment of various APD for 21 days significantly reduced the number of dopamine (DA) D_1 receptors in both the medial prefrontal (mPFC) and dorsolateral frontal cortices of adolescent rats, but not adult rats. In contrast, DA D_2 receptor levels were elevated in the mPFCs of adult rats after chronic APD infusion, but not in adolescent rats (Moran-Gates et al., 2006).

Animal studies have also illustrated that application of APD during adolescence, a critical period for neurodevelopment, can stimulate neuronal and behavioral functional changes that are reflected in adulthood (Vinish et al., 2013). Adolescent rats chronically exposed to the atypical APD olanzapine (OLZ) therapy released significantly less DA upon stimulation during adulthood than vehicle treated rats. Interestingly, our group has also shown that adolescent APD exposure (postnatal days [P] 35–60, Andersen et al., 2000) can increase APD response in adulthood, a phenomenon known as "antipsychotic sensitization" (Qiao et al., 2013a, 2013b, 2014). Although not well understood, APD behavioral sensitization due to chronic treatment is well documented. For example, the exponential curve of psychotic symptoms improvement over the first 4 weeks of treatment; the antipsychotic effect growing with the passage of time (i.e. time-dependent sensitization), and the worsening of extrapyramidal side effects after years of medication are all well-known demonstrations of APD sensitization (Agid et al., 2003; Fallon and Dursun, 2011; Kapur et al., 2006). Clinically, APD sensitization may play an important implication in prescription considerations, especially after drug abstinence. Furthermore, concerning the adolescent patient population, APD sensitization may interact with developmental trajectories to alter adulthood behavior and brain functions.

In a previous study, we showed that OLZ, an APD widely prescribed in the adolescent population, induces an increased behavioral sensitivity over repeated treatment during adolescence (Pakyurek et al., 2013). This increase in sensitivity remains evident when rats are re-exposed to OLZ in adulthood (Qiao et al., 2013a). The study employed the rat conditioned avoidance response (CAR) test to measure APD response. This test is widely used and well-validated for assessing APD activity in rodents, and numerous studies have verified that clinically relevant doses of APD suppress avoidance behavior in animals (Wadenberg and Hicks, 1999; Wadenberg, 2010; Wadenberg et al., 1997). The model is commonly used to predict the clinical potency of APD, and thus an ideal measure of behavioral sensitization over repeated exposure (Arnt, 1982; Wadenberg et al., 2001).

One mechanism that may be associated with long term APD sensitization is drug-induced changes in cell proliferation and survival. While the effects of APD on cell growth are still inconsistent across studies, long-term administration of APD has been reported by some to increase cell proliferation in the subventricular zone as well as the subgranular zone of the hippocampus in adult animals (Halim et al., 2004; Keilhoff et al., 2010; Maeda et al., 2007; Wakade et al., 2002; Wang et al., 2004). However, no prior study has considered this effect of APD as a potential mechanism of APD sensitization in adolescence. Also, much of our APD sensitization work has used otherwise healthy rats, and it remains to be elucidated whether APD sensitization is generalizable and can also be demonstrated in preclinical disease models. In the present study, we addressed this issue by testing OLZ in a rat maternal immune activation (MIA) model of schizophrenia, a well-studied model that gained much popularity in the recent decade (Meyer and Feldon, 2010). Adult rodent offspring born to infected mothers displayed specific histological and behavioral abnormalities relevant to those seen in human patients with schizophrenia, including increased prefrontal cortical pyramidal cell density (Fatemi et al., 1999), deficits in learning (Shi et al., 2003), sensorimotor gating (Wolff and Bilkey, 2008), latent inhibition (Zuckerman and Weiner, 2003), and working memory (Ozawa et al., 2006).

Examination of hippocampal cellular changes associated with OLZ sensitization using a preclinical model is relevant to the treatment of schizophrenia. First, impaired hippocampal cell proliferation is thought to contribute to cognitive deficits in schizophrenia, and induction of hippocampal cell growth has been suggested as a possible therapeutic mechanism of APD treatment (Kempermann et al., 2008; Reif et al., 2006, 2007; Toro and Deakin, 2007). However, it is unclear whether the induction of cell proliferation by antipsychotics is related to behavioral phenotypes that are representative of drug efficacy. Secondly, MIA as a preclinical model of schizophrenia has been shown to reduce neurogenesis in some studies, and one previous study suggested that APD treatment may reverse this dysfunction (Cui et al., 2009; Piontkewitz et al., 2012b; Vuillermot et al., 2010; Wolf et al., 2011). However, no study has connected this cellular change in MIA animals with behavioral effects, which warrants the current idea of examining the relationship between cell proliferation and survival associated with APD treatment and the CAR behavior observed in a preclinical model.

In this study, we investigated the potential connection between the induction and expression of OLZ sensitization in adolescent rats and OLZ-induced cell proliferation and survival in the dentate gyrus (DG) of rat hippocampi, using the CAR task for behavioral assessment and 5′-bromodeoxyuridine (BrdU) immunohistochemistry for cellular examination.