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PREVENTIVE EFFECT OF α-LIPOIC ACID ON PREPULSE INHIBITION DEFICITS IN A JUVENILE TWO-HIT MODEL OF SCHIZOPHRENIA

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Abstract—Some pathophysiological models of schizophrenia posit that prenatal inflammation sensitizes the developing brain to second insults in early life and enhances brain vulnerability, thereby increasing the risk of developing the disorder during adulthood. We previously developed a two-hit animal model, based on the well-established prenatal immune challenge with poly-inosinic/cytidylic acid (polyI:C), followed by juvenile restraint stress (RS). We observed an additive disruption of prepulse inhibition (PPI) of acoustic startle in juvenile mice submitted to both insults. Previous studies have also reported that oxidative stress is associated with pathophysiological mechanisms of psychiatric disorders, including schizophrenia. We report here that PPI disruption in our two-hit animal model of schizophrenia is associated with an increase in oxidative stress. These findings led us to assess whether α-lipoic acid, an antioxidant, can prevent both increase in oxidative status and PPI deficits in our juvenile *in vivo* model of schizophrenia. In the offspring submitted to prenatal injection of polyI:C and to RS, treatment with α-lipoic acid prevented the development of PPI deficits 24 h after the last period of RS. α-Lipoic acid also improved PPI performance in control mice. The reversal effect of α-lipoic acid pretreatment on these behavioral alterations was further accompanied by a normalization of the associated oxidative status and dopaminergic and GABAergic abnormalities in the prefrontal cortex. Based on our double insult paradigm, these results support the hypothesis that oxidative stress plays an important role in the development of PPI deficits, a well-known behavior associated with schizophrenia. These findings form the basis of future studies aiming to unravel mechanistic insights of the putative role of antioxidants in the treatment of schizophrenia, especially during the prodromal stage. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: lipoic acid, prepulse inhibition, dopamine D2 receptor, GAD67, schizophrenia.

INTRODUCTION

Schizophrenia is a neuropsychiatric disease that affects 1% of the general population and is characterized by three core features: positive (delusions, hallucinations, disturbances of thoughts and paranoia), negative (lack of motivation, alogia and social withdrawal) and cognitive symptoms (attention and memory deficits) (Flaum and Andreasen, 1991). Additionally, the risk of developing schizophrenia-like symptoms is enhanced by environmental factors occurring at prenatal or early postnatal periods, two critical stages during brain development (McDonald and Murray, 2000; Opler and Susser, 2005). Indeed, since the last 25 years, the neurodevelopmental hypothesis of schizophrenia has proposed that a cerebral insult during early (prenatal/perinatal) brain development increases the vulnerability to the subsequent emergence of clinical symptoms during adolescence and early adulthood (Murray and Lewis, 1987; Weinberger, 1987; Rapoport et al., 2012). Among environmental factors, maternal viral infection during the second trimester of pregnancy has been associated with early brain development disruption and increased risk of schizophrenia (O'Callaghan et al., 1994; Suvisaari et al., 1999; Brown et al., 2000; Brown et al., 2004). Accordingly, prenatal injection of poly-inosinic/cytidylic acid (polyI:C), an agonist of Toll-like receptor 3 (TLR3) that mimics the acute inflammatory response to viral infection (Shi et al., 2003), elicits features reminiscent of schizophrenia in adult offspring. Consequently, prenatal immune challenge with polyI:C has been proposed as a neurodevelopmental model of schizophrenia (Boksa, 2008). Beyond this one-hit hypothesis, it has also been proposed, that maternal infection creates a long-term and latent vulnerability to the development of schizophrenic symptoms, that are only unmasked by insults occurring later in life, such as physical injury or environmental stressors (Maynard et al., 2001). This ''two-hit'' hypothesis of schizophrenia has gained increasing attention to explain the late adolescent/early adulthood onset of schizophrenia (Maynard et al., 2001).

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Abbreviations: ANOVA, analysis of variance; D2R, D2 receptor; DNPH, 2,4-dinitrophenylhydrazine; EDTA, ethylenediaminetetraacetic acid; G12, gestational day 12; GAD67, glutamic acid decarboxylase 67; GSH, glutathione; IgG-HRP, immunoglobulin G horseradish peroxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PFC, prefrontal cortex; polyI:C, poly-inosinic/cytidylic acid; PPI, prepulse inhibition; RS, restraint stress; TBST, Tris-buffered saline with 0.2% Tween-20.

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Our group has previously developed and characterized a two-hit model with behavioral and mechanistic features relevant to schizophrenia in juvenile mice, based upon the well-established prenatal immune challenge with polyI:C followed by juvenile restraint stress (RS). The combination of both insults was associated with deficits in sensorimotor gating, as evaluated by prepulse inhibition (PPI) of acoustic startle response (Deslauriers et al., 2013). This PPI impairment was also associated with cortical and striatal changes in mRNA and protein levels of the dopamine D2 receptor (D2R) and the rate-limiting enzyme glutamic acid decarboxylase (GAD67) (Deslauriers et al., 2013), reminiscent of the pathophysiology of schizophrenia (Maynard et al., 2001). Likewise, changes in D2R levels have consistently been shown to be affected by antipsychotic treatments in schizophrenic patients (Goldsmith et al., 1997; Laruelle, 1998; Howes et al., 2012) and decreased GAD67 expression in the hippocampus (Benes et al., 2007) and the prefrontal cortex (PFC) (Mirnics et al., 2000; Reynolds and Beasley, 2001; Hashimoto et al., 2003; Torrey et al., 2005) is one of the most consistent findings in schizophrenia patients.

Oxidative stress has been suggested to participate in the pathophysiology of schizophrenia and other psychiatric disorders (Yao et al., 2001). An increase in lipid peroxidation has been observed in the plasma of schizophrenic patients (Mahadik et al., 1998), as well as a decrease in glutathione (GSH) levels (Do et al., 2000; Grima et al., 2003) and in total antioxidant status (TAS) (Yao et al., 1998). Likewise, an increase in cerebral oxidative stress has been reported in a rodent model submitted to RS (Kim et al., 2005). These findings led us to assess (1) whether the PPI disruption observed in our two-hit model of schizophrenia, was associated with oxidative stress and (2) whether α-lipoic acid, an antioxidant, could prevent the changes in oxidative status, PPI impairment and D2R/GAD67 alterations in this two-hit animal model.

EXPERIMENTAL PROCEDURES

Animals

Male and female C57BL/6 mice were obtained from Charles River Laboratories (Sherbrooke, QC, Canada) at age of 8–10 weeks for mating. Animals were kept at 20 °C environmental temperature on a 10-h light/14-h dark cycle. They had *ad libitum* access to food and water. Experimental protocols were approved by the institutional Animal Research Ethics Review Board at the Université de Sherbrooke, in compliance with the policies of the Canadian Council on Animal Care. Mating was done on site. Timed pregnant mice were injected intraperitoneally (i.p.) with saline or 20 mg/kg polyI:C (Sigma–Aldrich, Oackville, ON, Canada), as previously described, at gestational day 12 (G12) (Shi et al., 2003; Deslauriers et al., 2013). The timing of polyI:C exposure at G12 was chosen as it has been demonstrated that early/middle, as opposed to late, fetal development in mice is critical for polyI:C exposure (Meyer et al., 2008) and the proliferation of dopaminergic progenitor cells, in mice, peaks between G12 and G13 within the caudal region of the developing fetal brain (Bayer et al., 1995; Marti et al., 2002). Mice were weaned on postnatal day 22 (PN22) and housed in groups of two to four mice. Thus, the offspring were submitted or not, from postnatal days 33 to 35 (PN33–35), to RS for 2 h per day, for three consecutive days, as previously described (Deslauriers et al., 2013). RS was performed by placing each mouse in a 50 mL conical tube. The tube was cut to the size of a juvenile mouse. Thus, the animal could not move forward or backward. The control mice for RS were kept individually in a new home cage for the same time period, with no access to water and food. The mice were born from 16 saline-treated dams (mean: 7.33 per litter; $n = 118$) and 24 polyI:C-treated dams (mean: 5.25 per litter; $n = 126$). Mice from each litter were also divided in each group for behavioral assessment ($n = 36$) and biochemical analysis ($n = 208$). The groups for each experiment are described below. There was no significant difference in male/female ratios between saline-treated and polyI:C-treated dams' litters and all male and female offspring were divided equally (male:female distribution of 1:1 for each group in each experiment) for behavioral observations and biochemical analysis.

Experiment 1: Determination of oxidative status in two-hit model

For the analysis of oxidative stress at 3 h and 24 h after the last period of RS, the mice were randomized into four groups: (1) saline ($n = 28$), (2) saline with RS (saline + RS) ($n = 40$), (3) polyI:C (PolyIC) ($n = 36$) and (4) polyI:C with RS (PolyIC + RS) ($n = 40$). Mice were euthanized and their whole brains were kept and frozen at −80°C until use. To extract the PFC and striatal tissues, 3-mm slices from bregma +4 mm to +1 mm and from bregma +1 mm to −2 mm (Paxinos and Franklin, 2008), respectively, were cut out using a brain matrix.

Immunochemical determination of protein carbonyl groups. Oxidation of water soluble proteins can be evaluated by quantification of protein carbonyl groups (Sedlak et al., 2009). Western blotting and transfer on polyvinylidene fluoride (PVDF) membranes were done as described below (see section Western blotting). Membranes were subjected to 2,4-dinitrophenylhydrazine (DNPH) derivatization, as previously described (Deslauriers et al., 2011). Briefly, membranes were incubated sequentially in 100% methanol (MeOH) (1 min), in 20% MeOH-80% TBS (5 min) and in 2 N hydrochloric acid (HCl) (5 min) at room temperature. Then, membranes were incubated in a solution of DNPH (0.01% (w/v) in 2 N HCl) for 5 min and washed 3 times (5 min) in 2 N HCl and 7 times (5 min) in 100% MeOH. Membranes were incubated in TBS (5 min) and blocked in 5% milk powder in TBS for 1 h at room temperature. Incubation with primary rabbit antibody anti-dinitrophenyl-KLH (1:25 000) in TBS containing 5% (w/v) milk powder and 1% (v/v) Tween-20 was performed for 1 h at room temperature. After three washes (5 min) in TBS containing 5% (w/v) milk powder and 1% (v/v) Tween-20, membranes were incubated with goat anti-rabbit immunoglobulin G

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