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Maturation- and sex-sensitive depression of hippocampal excitatory transmission in a rat schizophrenia model

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ABSTRACT

Schizophrenia is associated with behavioral and brain structural abnormalities, of which the hippocampus appears to be one of the most consistent region affected. Previous studies performed on the poly I:C model of schizophrenia suggest that alterations in hippocampal synaptic transmission and plasticity take place in the offspring. However, these investigations yielded conflicting results and the neurophysiological alterations responsible for these deficits are still unclear. Here we performed for the first time a longitudinal study examining the impact of prenatal poly I:C treatment and of gender on hippocampal excitatory neurotransmission. In addition, we examined the potential preventive/curative effects of risperidone (RIS) treatment during the peri-adolescence period. Excitatory synaptic transmission was determined by stimulating Schaffer collaterals and monitoring fiber volley amplitude and slope of field-EPSP (fEPSP) in CA1 pyramidal neurons in male and female offspring hippocampal slices from postnatal days (PNDs) 18–20, 34, 70 and 90. Depression of hippocampal excitatory transmission appeared at juvenile age in male offspring of the poly I:C group, while it expressed with a delay in female, manifesting at adulthood. In addition, a reduced hippocampal size was found in both adult male and female offspring of poly I:C treated dams. Treatment with RIS at the peri-adolescence period fully restored in males but partly repaired in females these deficiencies. A maturation- and sex-dependent decrease in hippocampal excitatory transmission occurs in the offspring of poly I:C treated pregnant mothers. Pharmacological intervention with RIS during peri-adolescence can cure in a gender-sensitive fashion early occurring hippocampal synaptic deficits.

1. Introduction

Schizophrenia is a severe and chronic psychotic illness affecting almost 1% of the population worldwide. In the hippocampus of schizophrenic patients, anomalies like pyramidal neuron loss, asymmetric alterations in hippocampal neuronal size and shape, were described, possibly resulting in aberrant functional connectivity of hippocampal network (Benes et al., 1991; Boyer et al., 2007; Harrison, 1999; Harrison and Eastwood, 2001; Jonsson et al., 1999). Postmortem and magnetic resonance imaging (MRI) studies showed altered hippocampal size and shape in first episode subjects as well as in the prodromal stage, before expression of the full clinical phenotype (Harrison, 1999, 2004; DeLisi, 2008; Lawrie et al., 2008; Nelson et al., 1998). At the neurophysiological level, many lines of evidence support dopaminergic and glutamatergic dysregulations as a major pathogenic mechanism of schizophrenia (Coyle, 2006; Javitt et al., 2011; Moghaddam and Javitt, 2012).

Converging evidence from epidemiological, brain imaging and neuropathological studies suggest that schizophrenia is a neurodevelopmental disorder, whereby brain abnormalities occur early in life and where genetic, epigenetic and environmental factors provide substantial triggers for the disease to manifest clinically at early adulthood (Arnold, 1999; Beckmann, 1999; Murray et al., 1992; Murray and Lewis, 1987; Weinberger, 1987; Bilbo and Schwarz, 2012). One of the major environmental risk factors for schizophrenia is maternal immune activation (MIA) subsequent to maternal viral or bacterial infections during pregnancy (Brown et al., 2000; Fatemi et al., 2012; Hultman et al., 1999; Mednick et al., 1988; Yolken et al., 2000). Immune activation of pregnant rodents by injection of a synthetic analog of double-stranded

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RNA, polyriboinosinic polyribocytidilic acid (poly I:C), which mimics viral infection, leads to a broad range of schizophrenia-relevant behavioral and neuroanatomical deficits that exhibit a characteristic emergence at adulthood (Meyer et al., 2005; Ozawa et al., 2006; Shi et al., 2003; Zuckerman et al., 2003; Zuckerman and Weiner, 2003, 2005; Piontkewitz et al., 2012a).

Electrophysiological studies on the poly I:C model of schizophrenia suggest that one of the consequences of MIA may be an alteration of hippocampal synaptic transmission and long-term plasticity in the offspring (Boksa, 2010). However, these studies yielded conflicting results, with an increase or decrease of the glutamatergic or GABAergic neurotransmission (Hellstrom et al., 2005; Ducharme et al., 2012; Escobar et al., 2011; Lante et al., 2007; Lowe et al., 2008; Oh-Nishi et al., 2010; Roumier et al., 2008).

It has been shown that anti-psychotic drugs (APDs) can treat the behavioral abnormalities in the poly I:C model and in other models of MIA (Shi et al., 2003; Zuckerman et al., 2003; Zuckerman and Weiner, 2005; Piontkewitz et al., 2009, 2011a; Romero et al., 2007). Furthermore, treatment with APDs during peri-adolescence prior to the emergence of schizophrenia-like abnormal behavior was shown to prevent the emergence of neuroanatomical and behavioral symptoms in adults of various animal model of schizophrenia (Piontkewitz et al., 2009, 2011a, 2012b; Meyer et al., 2010; Richtand et al., 2006, 2011).

In this study, we examined the impact of prenatal poly I:C treatment on hippocampal glutamatergic neurotransmission and volume at different periods of offspring postnatal development. Sex differences are known to exist in schizophrenia (DeLisi, 1992; DeLisi et al., 1989; Gattaz et al., 1994; Grigoriadis and Seeman, 2002; Hafner and an der Heiden, 1998; Rana et al., 2012; Piontkewitz et al., 2011b). Thus, we explored whether differences in nature or timing of the hippocampal neurophysiological defects would be found between male and female offspring. Finally, based on our previous studies (Piontkewitz et al., 2009a, 2011a, 2012a,b), we investigated the potential preventive effects of risperidone (RIS) administered during peri-adolescence (postnatal days [PNDs] 34–47) on hippocampal glutamatergic transmission defects in male and female offspring. A maturation and sex dependent decrease in hippocampal glutamatergic transmission was observed in poly I:C offspring. At juvenile age (PNDs 18–20), a significant reduction in the Schaffer collateral-CA1 pyramidal neuron transmission was found exclusively in male offspring from poly I:C-treated mothers. At adult stage, both male and female offspring of poly I:C-treated mothers exhibited a depression in glutamatergic transmission and RIS treatment during peri-adolescence corrected these deficits. MRI imaging data indicated that adult male and female offspring of poly I:C treated dams exhibit reduced hippocampal size that was restored by administration of RIS at peri-adolescence.

2. Methods and materials

2.1. Animals

Adult (350–400 g) Wistar rats were housed 3–4 to a cage under reversed cycle lighting (lights on: 19:00–7:00 h) with ad lib food and water. All experimental protocols conformed to the guidelines of the Institutional Animal Care and Use Committee of Tel-Aviv University, Israel, and to the guidelines of the NIH (animal welfare assurance number A5010-01).

2.2. Prenatal poly I:C treatment

Prenatal treatment was performed as described previously (Zuckerman et al., 2003; Zuckerman and Weiner, 2003; Piontkewitz et al., 2009). At 3 months of age, Wistar rats were mated and the first day after copulation was defined as day 1 of pregnancy. On gestation day (GD) 15, pregnant dams were anesthetized with 3% isoflurane (Minrad, Bethlehem, PA) in 98% O_2 and given a single intravenous injection at the tail vein of 4 mg/kg poly I:C (Sigma, Rehovot, Israel; dissolved in saline), or an equivalent volume of saline. The volume of injection was 1 ml/kg. Poly I:C caused weight loss for about 1 day without significantly increasing miscarriage rate. On PND 21 (except where mentioned), pups were weaned and housed 2–4 to a cage by sex and litter, and maintained undisturbed until the experimental manipulation (drug injection at PND 34, hippocampal slices preparation and MRI scanning). In all experiments, each experimental group consisted of subjects derived from multiple independent litters, with no more than 1–2 rats from the same litter in any of the experimental groups. $N = 6–7$ offspring of poly I:C or saline- treated mothers that were sacrificed at each PND. 1–3 slices were recorded from each offspring.

2.3. Preventive treatment

Preventive treatment was given on PNDs 34–47. This time period is considered to represent adolescence or peri-adolescence (Spear, 2000), in which poly I:C offspring are behaviorally and neuroanatomically asymptomatic (Piontkewitz et al., 2011a). Our previous work showed that preventive treatment during PNDs 34–47 with the APD RIS, successfully prevented the behavioral and neuroanatomical abnormalities in offspring of poly I:C treated mothers (Piontkewitz et al., 2011a). Female and male offspring of poly I:C and saline injected mothers were daily injected intraperitoneally (i.p.) with 0.045 mg/kg RIS (Janssen, Beerse, Belgium) or vehicle on PNDs 34–47 (Piontkewitz et al., 2011a). RIS was dissolved in 0.1 M tartaric acid (7.5 μl/mg) and diluted with saline. The volume of injection was 1 ml/kg.

2.4. Hippocampal slice preparation

Brains were rapidly removed from both female and male offspring at PNDs 18–20, 34, 70 and 90. Coronal hippocampal slices (400 μm thick) were prepared in a cold (4 °C) storage buffer containing (in mM): sucrose, 206; KCl, 2; $MgSO_4$, 2; NaH_2PO_4, 1.25; $NaHCO_3$, 26; $CaCl_2$, 1; $MgCl_2$, 1; glucose, 10 using a Leica VT1200 vibratome. Slices were immediately transferred to a submerged recovery chamber at room temperature artificial cerebrospinal fluid (aCSF) bubbled with 95% O_2 and 5% CO_2 for at least 1 h before recording. The aCSF contained (in mM): NaCl, 125; KCl, 2.5; $CaCl_2$, 1.2; $MgCl_2$, 1.2; $NaHCO_3$, 25; NaH_2PO_4, 1.25; glucose, 25. Compared groups had always the same time of recovery in aCSF.

2.5. Field excitatory post-synaptic potentials recordings

Extracellular field excitatory post-synaptic potentials (fEPSPs) were recorded from hippocampal slices of male and female offspring of poly I:C and saline injected mothers at PNDs 18–20, 34, 70, 90. Slices were placed in the recording chamber and perfused (2 ml/min) with aCSF bubbled with 95% O_2 and 5% CO_2 at room temperature. The recording pipette (1–2 MΩ) was filled with aCSF and placed in the stratum radiatum of CA1 to record fEPSPs. Synaptic events were evoked by bipolar stimulating platinum iridium electrode in the Schaffer collateral using isolated stimulating unit (digitimer LTD). Data were acquired using pClamp 10.3 software (Molecular Devices) in conjunction with a multiclamp700B interface digitized with DigiData 1440A (Molecular Devices). At the beginning of each experiment, slices were repeatedly stimulated at 0.03 Hz in order to validate the slice's stability. For fEPSP recordings, Schaffer collaterals were stimulated with a series of increas-