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Maternal immune activation differentially impacts mature and adult-born hippocampal neurons in male mice

Zhi Zhang, Henriette van Praag *

Neuroplasticity and Behavior Unit, Laboratory of Neurosciences, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA

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ABSTRACT

Schizophrenia is associated with deficits in the hippocampus, a brain area important for learning and memory. The dentate gyrus (DG) of the hippocampus develops both before and after birth. To study the relative contribution of mature and adult-born DG granule cells to disease etiology, we compared both cell populations in a mouse model of psychiatric illness resulting from maternal immune activation. Polyriboinosinic–polyribocytidilic acid (PolyIC, 5 mg/kg) or saline was given on gestation day 15 to pregnant female C57Bl/6 mice. Male offspring ($n = 105$), was administered systemic bromodeoxyuridine (BrdU, 50 mg/kg) ($n = 52$) or intracerebral retroviral injection into the DG ($n = 53$), to label dividing cells at one month of age. Two months later behavioral tests were performed to evaluate disease phenotype. Immunohistochemistry and whole-cell patch clamping were used to assess morphological and physiological characteristics of DG cells. Three-month-old PolyIC exposed male offspring exhibited deficient pre-pulse inhibition, spatial maze performance and motor coordination, as well as increased depression-like behavior. Histological analysis showed reduced DG volume and parvalbumin positive interneuron number. Both mature and new hippocampal neurons showed modifications in intrinsic properties such as increased input resistance and lower current threshold, and decreased action potential number. Reduced GABAergic inhibitory transmission was observed only in mature DG neurons. Differential impairments in mature DG cells and adult-born new neurons may have implications for behavioral deficits associated with maternal immune activation.

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1. Introduction

Schizophrenia is a disabling psychiatric condition whose symptoms appear in young adults. This disorder is considered to be caused by prenatal genetic (Millar et al., 2000) and/or environmental factors, such as maternal infection (Mortensen et al., 1999; Brown, 2011; Meyer, 2013), that disrupt brain development (Kannan et al., 2013; Arrode-Bruses and Bruses, 2012). Schizophrenia generally presents with positive symptoms (e.g. hallucinations), negative symptoms (e.g. flat affect) and cognitive deficits (Weinberger, 1987, 1999). In particular, hippocampal structural abnormalities and dysfunction have been documented in schizophrenia patients (Csernansky et al., 1998; Heckers et al., 1998; Nelson et al., 1998; Weinberger, 1999; Heckers, 2001; Harrison, 2004; Wexler et al., 2009; Schobel et al., 2013) and animal models (Lipska and Weinberger, 2000). In rodent models prenatal treatment with the viral mimetic PolyIC induces long-term cognitive deficits (Zuckerman and Weiner, 2005; Meyer et al., 2006; Ozawa et al., 2006), reduced hippocampal volume (Piontkewitz et al., 2012), and disturbances in neurotransmission (Ducharme et al., 2012) in the offspring.

A subfield of the hippocampus, the dentate gyrus (DG), can generate new neurons in adulthood (Altman and Das, 1965; Spalding et al., 2013). The postnatally-born cells comprise the inner one-third of the granule cell layer, whereas cells born during embryonic development contribute preferentially to the outer granule cell layer (Rakic and Nowakowski, 1981; Esposito et al., 2005; Mathews et al., 2010), and are considered 'mature' granule cells. Postnatal DG cell proliferation is reduced in schizophrenia patients (Reif et al., 2006). Adult neurogenesis is compromised in genetic (Duan et al., 2007; Kvajo et al., 2008; Manning et al., 2012), neurodevelopmental (Meyer et al., 2010; Wolf et al., 2011), and drug-induced animal models (Liu et al., 2006). Furthermore, knockdown of disrupted-in-schizophrenia1 (DISC1), a schizophrenia susceptibility gene (Millar et al., 2000), in newborn granule cells, caused an increased neuronal excitability and behavioral deficits (Zhou et al., 2013). Conversely, pharmacological treatment with risperidone

* Corresponding author at: Neuroplasticity and Behavior Unit, Laboratory of Neurosciences, NIA/NIH, Biomedical Research Center, Suite 100, 251 Bayview Blvd., Baltimore, MD 21224, USA. Tel.: +1 410 558 8064.
E-mail address: vanpraagh@mail.nih.gov (H. van Praag).

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(Piontkewitz et al., 2012) or physical activity enhanced adult neurogenesis and improved sensorimotor gating responses (Wolf et al., 2011) in rodents that sustained maternal immune challenge. These studies support the hypothesis that adult hippocampal neurogenesis may play a role in the etiology of psychiatric disorders (Ouchi et al., 2013).

Pathophysiological changes associated with maternal immune activation may impact mature and/or adult-born neurons. However, the functional properties of individual newborn and mature DG granule cells in this model are unknown. In particular, we evaluated new neurons two months after retroviral labeling. At this time-point the transiently enhanced plasticity of new neurons is deemed to have passed, and they are generally considered identical to mature neurons (Laplagne et al., 2006). Electrophysiological recordings in acute hippocampal slices derived from PolyIC exposed mice, showed that mature and new hippocampal neurons have changes in their intrinsic properties, such as increased input resistance and lower current threshold as well as decreased action potential firing. Reduced GABAergic inhibitory transmission was observed only in mature DG neurons. Altogether, our findings suggest a long-lasting differential response in mature neurons and adult-born granule cells to maternal immune inflammation.

2. Methods and materials

2.1. Animals

Three-month old female and male C57BL/6J breeders were obtained from the Jackson Laboratory (Bar Harbor, Maine), housed with a 12 h light/dark cycle and ad libitum access to food and water. Breeding began after 2 weeks of acclimatization. Male and female mice were co-housed for 3 consecutive days. The day a sperm plug was found was considered E0. Plug-positive females were placed in individual polycarbonate cages. Pregnancy was verified by weight gain (~8 g) and abdominal protrusion. All procedures were approved by the Animal Care and Use Committee of the NIA.

2.2. Prenatal treatment and procedures

Pregnant females on gestation day 15 (GD15) received a single injection of PolyIC (Sigma–Aldrich, St Louis, MO) or vehicle (0.9% NaCl) at a dose of 5 mg/kg (Meyer et al., 2008; Wolf et al., 2011). PolyIC was dissolved in sterile pyrogen-free 0.9% NaCl solution at a final concentration of 1 mg/ml. All solutions were administered intraperitoneally (i.p.) with an injection volume of 5 ml/kg (Wolf et al., 2011). Animals were returned to their home cage immediately after the injection and left undisturbed until offspring weaning. Mice born to PolyIC-treated and vehicle-treated dams were weaned and sexed at postnatal day 21 (P21). There was no significant difference in the litter size between control and PolyIC groups (control = 6.5 ± 0.6 *vs.* PolyIC = 7.4 ± 0.7, $p = 0.4$). To avoid potential sex difference-related changes, only male offspring ($n = 105$) were used. Mice were group housed (2–4 mice per cage). To label dividing cells, bromodeoxyuridine (BrdU) (50 mg/kg at a concentration of 10 mg/ml) was injected i.p. at one month of age for 5 consecutive days. This set of mice ($n = 52$) was used for behavioral testing and immunohistochemistry studies. The behavioral tests were performed with multiple independent litters which were not all born at the same time. During the course of the study some behavioral tests (tail-suspension test, rotarod) were added after several mice had already been taken for histology. No mouse was purposely excluded from any test. Additional animals ($n = 53$) were injected intracerebrally into the DG at one month of age with retrovirus expressing green fluorescent protein (GFP) to label proliferating cells. These mice were used for electrophysiology (Fig. 1A). Male offspring born to vehicle-treated dams are control mice; the male offspring of PolyIC-treated dams are termed PolyIC mice.

2.3. Behavioral tests

Behavioral testing started at 3 months of age. Control ($n = 25$ from 12 dams) and PolyIC ($n = 27$ from 13 dams) male mice from at least 12 independent litters were studied.

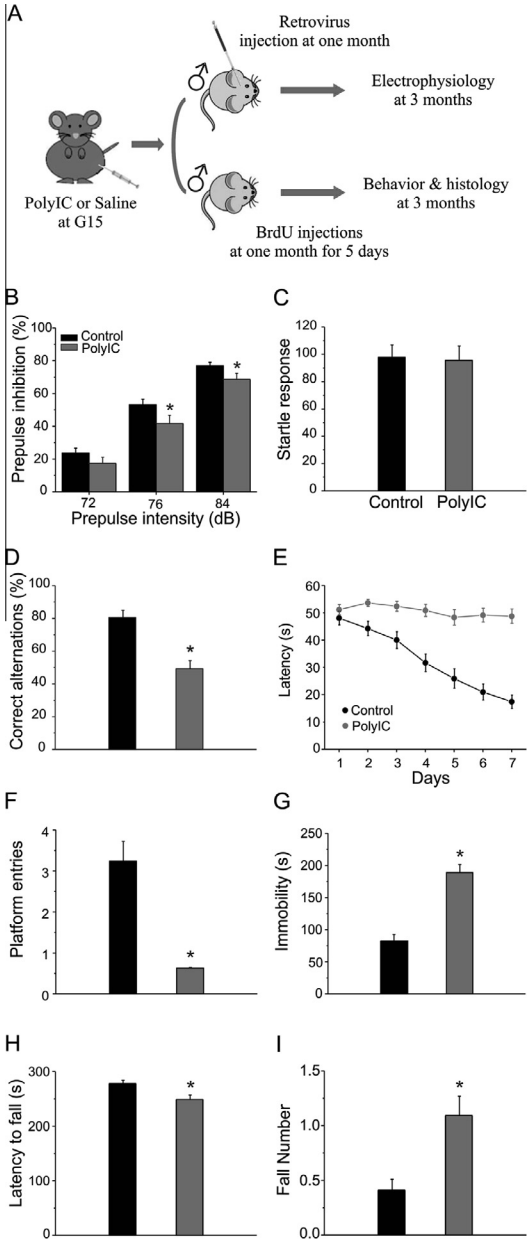

Fig. 1. Experimental design and behavioral tests. (A) Schematic diagram of experimental design. (B) The percentage of PPI in PolyIC mice ($n = 23$) was significantly reduced compared with control the group ($n = 20$) at prepulse levels of 76 dB and 84 dB. (C) The startle reactivity amplitude in pulse alone trials was similar between control and PolyIC groups. (D) Spontaneous alternation rate in T-maze was significantly higher in the control mice ($n = 12$) as compared with PolyIC ($n = 7$) mice. (E) The latency to the platform in the control group ($n = 25$) decreased significantly over training days as compared to the PolyIC mice ($n = 27$) in Morris water maze. (F) The controls displayed significantly more platform entries during the probe trial as compared to PolyIC exposed mice. (G) Immobility time in the tail suspension test was significantly higher in the PolyIC mice ($n = 12$) as compared with the control group ($n = 7$). (H, I) Rotarod performance: decreased latency to fall (H) and an increased number of falls (I) was observed in PolyIC ($n = 18$) as compared to control mice ($n = 17$). All values are means ± SEM. $^*p < 0.05$.