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Early-life Photoperiod Influences Depression-like Behavior, Prepulse Inhibition of the Acoustic Startle Response, and Hippocampal Astrogenesis in Mice

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Abstract—Environmental factors during early life stages affect behavioral and physiological phenotypes in adulthood. We examined the effect of photoperiods during development on neurogenesis and affective behaviors during adolescence/adulthood using C57BL/6J mice. Mice were born and raised until weaning under long-day conditions (LDs) or short-day conditions (SDs), followed by a 12L12D cycle until adulthood. Adult mice born under SD showed a shorter latency to first immobility in the forced swim test when compared with the mice born under LD. The mice born under SD also exhibited significantly lower prepulse inhibition, which is a characteristic of schizophrenia. However, the mice exposed to SD and LD during the prenatal period only did not show differences in prepulse inhibition. At 4 weeks of age, there were less 5-bromo-2′-deoxyuridine (BrdU)-positive cells in the dentate gyrus (DG) of the hippocampus of mice born under SD when compared with mice born under LD. Double immunostaining showed that the mice born under SD showed less BrdU/glial fibrillary acidic protein (GFAP, an astrocyte marker) cells when compared with mice born under LD. Furthermore, expression of the glucocorticoid receptor in the DG was higher in mice born under SD, and the photoperiod-dependent changes in the number of BrdU-positive cells in the DG were abolished by administration of RU486, a glucocorticoid receptor antagonist. These results suggest that the photoperiod in early life alters astrogenesis in the hippocampus via the hypothalamic–pituitaryadrenal axis and may relate to affective behaviors in adulthood.

Key words: astrogenesis, glucocorticoid, neurogenesis, mouse, schizophrenia.

INTRODUCTION

In mammals, the season of birth or early-life photoperiod is an important regulator of behavioral and physiological phenotypes in adulthood, including reproductive maturation and activity (van Haaster et al., 1993; Butler et al., 2007) and immune functions (Weil et al., 2006). Affective behaviors in adulthood are also strongly influenced by the season of birth or early-life photoperiod (Walton et al., 2011). In Siberian hamsters, perinatal exposure to a short photoperiod increases anxiety- and depression-like behaviors (Pyter and Nelson, 2006). Similar results were observed in C3H mice, in which the neuronal activity of the serotonergic neurons in the dorsal raphe is programed by photoperiod during development in a melatonin receptor 1-dependent manner (Green et al., 2015). Mechanisms underlying the effect of perinatal photoperiods on behaviors in adults may involve the hypothalamic–pituitary–adrenocortical (HPA) axis because the negative feedback from the corticosterone response to stress and hippocampal levels of glucocorticoid receptor (*GR*) mRNA were low in adult rats postnatally exposed to a short photoperiod (Toki et al., 2007).

It is widely known that the season of birth correlates with affective disorders in humans, including schizophrenia,

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Abbreviations: BDNF, brain-derived neurotrophic factor; BrdU, 5-bromo-2′-deoxyuridine; CA1, cornu ammonis-1; DCX, doublecortin; DG, dentate gyrus; EPMT, elevated plus maze test; FST, forced swim test; GFAP, glial fibrillary acidic protein; *GR*, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenocortical; LDs, long-day conditions; *MR*, mineralocorticoid receptor; NOS, nitric oxide synthase; OFT, open field test; PFA, paraformaldehyde; PPIT, prepulse inhibition test; SDs, short-day conditions; SSC, saline sodium citrate; SVZ, subventricular zone; ZT, Zeitgeber time.

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bipolar disorder, major depression, autism, and seasonal affective disorder (Torrey et al., 1997; Pjrek et al., 2004). Among them, the most studied is the relationship between season of birth and schizophrenia. Epidemiological studies revealed that individuals born from late winter to early spring have a roughly 10% increased risk of schizophrenia compared to those born in other seasons of the year (Torrey et al., 1997; Mortensen et al., 1999; Schwartz, 2011), and this disorder is associated with the duration of perinatal sunshine in males (McGrath et al., 2002). Several hypotheses have been proposed to explain the relationship between birth season and schizophrenia risk, including dysregulation of the chronobiological relationship between mother and fetus during winter (Schwartz, 2011), maternal lack of vitamin D due to less sunshine in winter (McGrath, 1999), and the high risk of infection in mothers during the winter (Brown and Derkits, 2010). However, these hypotheses have not been proven due to the complexity of these situations. Mechanisms linking birth season and schizophrenia likely relates to the impact of season of birth on brain development because birth season is associated with neurocognitive variables in the general population (McGrath et al., 2006). Notably, abnormal neurodevelopment, neural stem cell proliferation, and neurogenesis are suggested as the pathophysiology behind schizophrenia (Reif et al., 2006; Toro and Deakin, 2007; Rapoport et al., 2012).

In offspring, the proliferation and differentiation of neural stem cells, i.e., neurogenesis or gliogenesis, during adolescence and adulthood are affected by the nutritional status and immune activation of dams during gestation and/or lactation, as well as by maternal deprivation during lactation (Kikusui et al., 2009; Matos et al., 2011; Hoeijmakers et al., 2014; Musaelyan et al., 2014). A possible system that links perinatal environment and neuronal development is the stress-sensitive HPA axis. Indeed, the exposure of rats to chronically high levels of corticosterone reduced cell proliferation and the density of immature neurons in the dentate gyrus (DG) of the hippocampus (Brummelte and Galea, 2010), and this effect was normalized by treatment with mifepristone, a GR antagonist (Mayer et al., 2006). In contrast, an adrenalectomy increased neurogenesis (Gould et al., 1992), and this effect was normalized by restitution of diurnal or nocturnal levels of corticosterone (Rodriguez et al., 1998). It was also reported that *GR* and mineralocorticoid receptor (*MR*) expression in the hippocampus during adulthood is affected by early life stress (e.g., maternal separation) (Ladd et al., 2004). Furthermore, corticosterone suppresses the expression of neurotrophins, such as brain-derived neurotrophic factor (BDNF) (Schaaf et al., 2000), which is deeply involved in neurogenesis (Chen et al., 2007). Our previous study determined that plasma corticosterone levels in C57BL/6J mice under short-day conditions (SD) exhibited higher peaks than those under long-day conditions (LD) (Otsuka et al., 2012). Thus, early-life photoperiods may affect neurogenesis or gliogenesis and modulate affective behaviors related to neuronal construction, such as schizophrenia-like behaviors. Our current study examined the effect of pre- and post-natal photoperiod on representative characteristics of schizophrenia, prepulse inhibition deficits in the acoustic startle response (Parwani et al., 2000), and other behavioral outcomes using C57BL/6J mice. We further analyzed proliferation and differentiation of neural stem cells in the brain and the involvement of the HPA axis in early-life photoperiod-induced effects on cell proliferation in the DG.

EXPERIMENTAL PROCEDURES

Animals

Male and female six-week-old C57BL/6J mice were obtained from Japan SLC. After arrival, male and female mice were housed separately in groups of four with food (MF, Oriental Yeast, Tokyo, Japan) and drinking water provided *ad libitum*. The cages were placed in light-tight boxes in a room maintained at a temperature of 25 °C ± 1 °C. Animals were acclimated to SD (6 h light–18 h dark, 6L18D) or LD (18L6D) for more than three weeks before pairing. After the pairing of mice, pregnant dams were housed individually. Following birth, pups were housed with littermates and the dam until weaning. Pups were weaned at 3 weeks of age. On the day of weaning, the lighting conditions of mice for Experiments 1a, 2, and 3 were changed to 12L12D. After weaning, male and female mice were housed separately. These mice were designated as LD or SD mice based on the photoperiod conditions prior to weaning. The mice in Experiment 1b were exposed to 12L12D from the day of birth. The pups were reared until 8, 9, 4, or 10 weeks of age for Experiments 1a, 1b, 2, or 3, respectively. Only males were used in the experiments to avoid the effect of estrus cycle on behavior and neurogenesis. Most studies report little or no correlation between the sex of individuals with schizophrenia and their season of birth (Torrey et al., 1997). All animal experiments reported here were conducted in accordance with the Guidelines for Animal Experiments in Faculty of Agriculture in Kyushu University and the Law (No. 105) and Notification (No. 6) by the Japanese Government.

Experiments 1a and 1b: Effect of photoperiod in early life on affective behaviors. The effect of pre- and post-natal photoperiods on affective behaviors in adulthood was analyzed in Experiment 1a (Fig. 1). We analyzed spontaneous activity in a novel environment and anxiety-like behaviors in the open field test (OFT), anxiety-like behaviors in the elevated plus maze test (EPMT), prepulse inhibition of the acoustic startle response in the prepulse inhibition test (PPIT), and depression-like behavior in the forced swim test (FST). Prepulse inhibition deficits are one of the representative symptoms of schizophrenia (Braff et al., 2001), and anxiety- and depression-like behavior has been used to evaluate the negative symptoms of schizophrenia (Miyamoto and Nitta, 2014). The behavioral tests began when LD and SD mice were 8-weeks-old. We used two cohorts of LD and SD mice for behavioral tests: one cohort (n = 13) was sequentially used for OFT, EPMT, and PPIT with a 2–3-day interval between tests, and the

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