EJN European Journal of Neuroscience
FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, Vol. 40, pp. 2674–2679, 2014
doi:10.1111/ejn.12626

BEHAVIORAL NEUROSCIENCE

Photoperiodic regulation of hippocampal neurogenesis in adult male white-footed mice (*Peromyscus leucopus*)

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Keywords: BrdU, gliogenesis, hippocampus, photoperiod, seasonal

Abstract

Photoperiodic organisms monitor environmental day length to engage in seasonally appropriate adaptions in physiology and behavior. Among these adaptations are changes in brain volume and neurogenesis, which have been well described in multiple species of birds, yet few studies have described such changes in the brains of adult mammals. White-footed mice (*Peromyscus leucopus*) are an excellent species in which to investigate the effects of day length on adult hippocampal neurogenesis, as males, in addition to having reduced hippocampal volume in short days (SD) with concomitant impairments in hippocampus-mediated behaviors, have photoperiod-dependent changes in olfactory bulb neurogenesis. We performed the current experiment to assess the effects of photoperiod on hippocampal neurogenesis longitudinally, using the thymidine analog bromodeoxyuridine at multiple time points across 10 weeks of SD exposure. Compared with counterparts held in long day (LD) lengths, across the first 8 weeks of SD exposure hippocampal neurogenesis was reduced. However, at 10 weeks in SD lengths neurogenic levels in the hippocampus were elevated above those levels in mice held in LD lengths. The current findings are consistent with the natural photoperiodic cycle of hippocampal function in male white-footed mice, and may help to inform research on photoperiodic plasticity in neurogenesis and provide insight into how the complex interplay among the environment, genes and adaptive responses to changing day lengths affects brain structure, function and behavior at multiple levels.

Introduction

Neurogenesis in discrete areas of the mammalian brain is an ongoing process that continues throughout adulthood. Neurogenic niches have been identified in multiple areas of adult mammalian brains (Gould, 2007), however, the subgranular zone (SGZ) of the dentate gyrus (DG) represents one of the most active neurogenic niches. Nascent progenitor cells arise in the SGZ of the DG of the hippocampus, and generally are subsequently incorporated into the DG as granule cells (reviewed in Zhao *et al.*, 2008). However, proliferating cells in the SGZ have several fates: they can die, become neurons (neurogenesis), become glia (gliogenesis), or remain undifferentiated and quiescent (reviewed in Gage, 2000). Functionally, neurogenesis in the hippocampus supports the formation of new memories, and can affect cognition, affective behaviors, and spatial learning and memory, and there are many factors that regulate proliferation, differentiation, and maturation of the progenitor cells (reviewed in Zhao *et al.*, 2008).

Although initially identified earlier (Altman, 1962), the definitive functional characterization of neurogenesis in adult vertebrate brains in a naturalistic context was reported nearly two decades later (Nottebohm, 1981). Nottebohm, seeking an explanation for seasonal changes in the volumes of various brain nuclei of canaries (*Serinus canarius*), injected birds with [^{3}H]thymidine to label dividing cells. He discovered that new neurons were being produced and integrated into functional song circuits (Goldman & Nottebohm, 1983; Paton & Nottebohm, 1984). In addition to identifying neurogenesis in adult vertebrates, altered neurogenesis was associated with the observed changes in brain volume that were dependent upon breeding status (Nottebohm, 1981; Paton & Nottebohm, 1984). This pattern has been reported in other bird species (Sherry & Hoshooley, 2010), and changes in breeding status in birds are driven by changes in photoperiod; thus, photoperiod can regulate neurogenesis in adult vertebrate brains. Photoperiodic changes in brain volume have also been documented in some adults of rodent species such as voles (*Clethrionomys glareolus*), shrews (*Sorex araneus, Sorex minutus*), and white-footed mice (*Peromyscus leucopus*; Yaskin, 1994, 2009; Pyter *et al.*, 2005b; Bartkowska *et al.*, 2008). However, the role of neurogenesis in photoperiodic mammalian hippocampal volume fluctuation remains unclear. Some rodent species, such as meadow voles (*Microtus pennsylvanicus*), have seasonally altered neurogenesis independent of hippocampal volume changes (Galea & McEwen, 1999; Ormerod & Galea, 2003), whereas other species, such as Eastern grey squirrels (*Sciurus carolinensis*), *Sorex* shrews (*S. araneus, S. minutus*), and Richardson's ground squirrels (*Urocitellus richardsonii*), have seasonally altered brain or hippocampal volume changes that are not associated with any changes in hippocampal neurogenesis (Lavenex *et al.*, 2000b;

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Received 7 November 2013, revised 2 April 2014, accepted 21 April 2014

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Bartkowska *et al.*, 2008; Burger *et al.*, 2013), or the association remains uninvestigated, as is the case with white-footed mice (Pyter *et al.*, 2005b). Thus, the uncoupling or coupling of neurogenesis to photoperiodic changes in hippocampal volume and function are likely species specific and dependent upon specific photoperiodic adaptations.

As mentioned, white-footed mice undergo photoperiodic changes in hippocampal morphology and function (Pyter *et al.*, 2005b; Walton *et al.*, 2011). However, the role of hippocampal neurogenesis in these photoperiod-mediated brain changes remains undescribed. As previously reported (Walton *et al.*, 2012), when compared with long day (LD) counterparts, neurogenesis in the olfactory bulbs (the other main neurogenic niche in adult mammals) is increased after 10 weeks of exposure to short days (SD), a time point during which hippocampal structure is already altered (Pyter *et al.*, 2005b). A shortcoming of this study was that it only assessed a single time point during SD exposure; thus, it remains possible that the contributions of altered neurogenesis to SD alterations in brain structure and function may occur earlier during exposure to SD. To answer this specific question, we designed the following experiment to assess hippocampal neurogenesis longitudinally at multiple time points across 10 weeks of SD exposure in adult male white-footed mice.

Materials and methods

Animals

A total of 59 male white-footed mice (*P. leucopus*) were used in this study. Mice were bred in our colony maintained at The Ohio State University, which was derived from wild-caught stock obtained through the *Peromyscus* Genetic Stock Center at the University of South Carolina. All mice were housed in cages (32 × 18 × 14 cm), maintained at constant temperature and humidity (21 ± 4 °C, 50 ± 5%), and given *ad libitum* access to food (Harlan Teklad 8640, Indianapolis, IN, USA) and filtered tap water. After weaning, mice were group housed with same-sex littermates until reaching adulthood (60–90 days of age), and thereafter housed singly once assigned to experimental groups. All husbandry was provided by Ohio State University Laboratory Animal Resources staff. All animal procedures were approved by the Ohio State University Institutional Animal Care and Use Committee, and were in compliance with guidelines established by the National Institutes of Health and the United States Department of Agriculture (Institute for Laboratory Animal Research (US), 2011).

Longitudinal assessment of neurogenesis using bromodeoxyuridine (BrdU)

To label cells undergoing mitosis in the SGZ of the DG, mice were injected intraperitoneally (i.p.) with 100 mg/kg BrdU once a day for 5 days during the middle of the light phase. Immediately prior to injection, BrdU (Sigma-Aldrich) was dissolved in 0.9% sterile saline to a final concentration of 10 mg/mL, 0.2 μm filtered, and protected from light until injection.

All mice were housed in LD conditions (16 h light: 8 h dark), and then pseudo-randomly assigned to either remain in LD lighting or be transferred to SD lighting (8 h light: 16 h dark). For both photoperiods, lights were extinguished at 15:00 h EST. To assess neurogenesis longitudinally across 10 weeks of exposure to SD, mice were pulsed with BrdU to label mitotic cells at the following time points in relation to SD exposure: 0, 2, 4, 8 and 10 weeks (Fig. 1). Mice were maintained in their respective photoperiods for 4 weeks after the final BrdU injection, and then were killed to assess progenitor cell survival (BrdU+ cells) in the hippocampus. To control for the potential effects of altered vivarium environment across different durations of photoperiod treatment, each time point group consisted of a SD cohort and a separate LD counterpart.

Brain histology

Four weeks after the conclusion of BrdU injections, mice were transcardially perfused with 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS), reproductive tissues were collected to measure photoperiodic responsiveness, and brains were postfixed at 4 °C overnight in the same solution. Brains were cryoprotected in 30% sucrose: 0.1 M PBS solution, then frozen on dry ice and held at −80 °C until cryostat sectioning. Every sixth coronal section (40 μm) throughout the dorsal hippocampus was collected onto positively charged slides and processed immunohistochemically for BrdU. For assessment of progenitor cell survival and progenitor cell phenotype, tissues were processed using a modified protocol adapted from Leuner *et al.* (2009). For all staining, antigen retrieval was performed by microwaving tissues at medium power for 5 min in boiling 0.1 M citric acid (pH 6.0). Tissues were then allowed to cool to room temperature (RT) in citric acid, rinsed 3 × in 0.1 M PBS, denatured in 2 N HCl for 30 min at 37 °C, and then immediately placed in 0.1 M sodium borate decahydrate (pH 8.5) for 10 min. After 3 × PBS rinses, tissues were blocked for 30 min in a solution of 1% Tween, 0.1 M PBS and 10% normal donkey serum.

For BrdU+ cell visualization, tissues were then incubated overnight at 4 °C in primary antibody (rat anti-BrdU; Accurate Chemical OBT0030) at 1 : 200 in 1% Tween in 0.1 M PBS, then in biotinylated donkey anti-rat secondary (1 : 200), and developed with ABC/DAB (Vector Labs) following the manufacturer's instructions. To quantify progenitor cell survival, all BrdU+ cells from three areas (SGZ, granule cell layer, hilus) of the two-blade DG in the dorsal hippocampus, corresponding to figs 42–52 in the mouse brain atlas (Paxinos & Franklin, 2004), were then counted at 200 × magnification. For each brain, cell counts across treatment groups were normalized by dividing the number of cells by the mean of their respective LD group, and then each area of the DG was analysed separately. No differences were found in progenitor cell survival among LD cohorts, so these data were combined for comparative analysis against the SD exposed groups.

To assess the phenotype of the BrdU+ cells, tissues were processed to label the mitotic marker BrdU, the neuronal marker NeuN (neuronal nuclei), and the glial marker GFAP (glial fibrillary acidic protein). Following the antigen retrieval and blocking steps described above, tissues were then incubated in the following primary antibodies: rat anti-BrdU (Accurate Chemical OBT0030) 1 : 200, mouse anti-NeuN (Chemicon MAB377) 1 : 1000, and rabbit-anti GFAP (Abcam AB7260) 1 : 2500 dissolved in the blocking solution described above. Tissues were incubated in primary antibodies at RT for 24 h, rinsed 3 × in PBS, re-blocked in blocking solution, and then incubated in the following secondary antibodies at 1 : 500 dilution for 2 h at RT in 1% Tween in 0.1 M PBS: donkey anti-rat 488 (712-485-150), donkey anti-mouse (715-515-150), and donkey anti-rabbit (711-605-152, all from Jackson ImmunoResearch). Following staining, 25 randomly selected BrdU+ cells from the dorsal two-blade DG of each brain were assessed for co-labeling with neuronal and glial markers by examining them in orthogonal planes via collection of stacks of 1-μm-thick optical sections using the 40 × objective on a Nikon Eclipse C1 Plus confocal fluorescent

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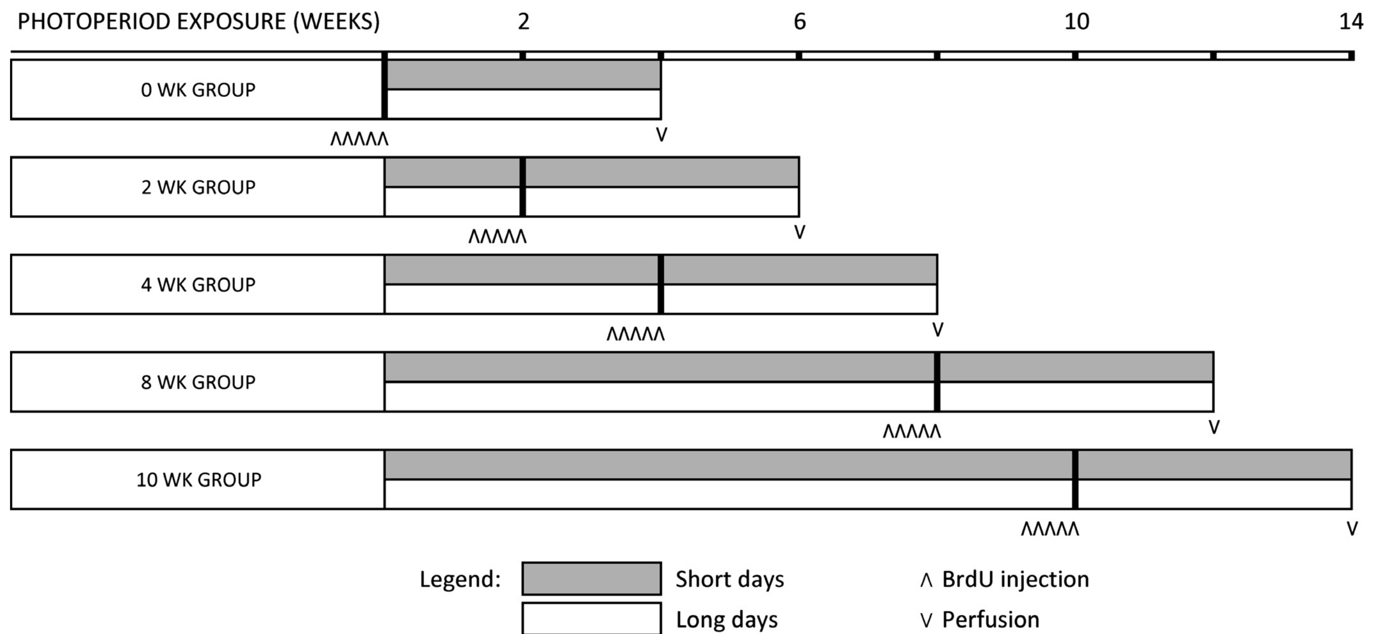

FIG. 1. Schematic of the longitudinal assessment of neurogenesis experimental design. Mice were pulsed with bromodeoxyuridine (BrdU) for 5 days and survived 4 weeks prior to being killed to assess neurogenesis. To label mitotic cells at specific times across photoperiod exposure, BrdU was given at five time points: 0 weeks [i.e. mice were all injected in long day (LD) conditions, then placed into short day (SD) or remained in LD for 4 weeks]; 2 weeks (i.e. mice were placed into SD or remained in LD for 2 weeks, then were pulsed with BrdU and allowed to survive for 4 weeks), 4 weeks, 8 weeks, and 10 weeks.

microscope (Epp *et al.*, 2007; Leuner *et al.*, 2009; Gibson *et al.*, 2010). Due to a technical issue, sections from the group that spent 10 weeks in SD could not be processed or analysed for progenitor cell phenotype.

Statistics

All neurogenesis data were analysed using one-way ANOVA, with time point as the main factor, and DG layer as the dependent variables for progenitor cell survival data or co-label of BrdU+ cells as the dependent variables for cell phenotype data. Significant differences were followed up by LSD *post hoc* tests. For assessing photoperiodic responsiveness via reproductive tissue mass, the gonadosomatic index (GSI) was calculated using the following formula: GSI = ((paired testes mass/body mass)*100), and data were analysed using one-way ANOVA as above. Correlation analyses were then performed between GSI and relative progenitor cell survival for each region of the dorsal DG. Statistical analyses were performed using SPSS (v.19, IBM). Correlations and mean differences were considered significant if $P \leq 0.05$.

Results

Progenitor cell survival

In the SGZ, there was a main effect of time in photoperiod on progenitor cell survival ($F_{5,53} = 2.543$, $P < 0.05$; Fig. 2B). Follow-up analyses revealed that, compared with all other groups, the group that spent 10 weeks in SD had the highest numbers of BrdU+ cells (Fig. 2B). Additionally, both the LD and 10-week groups had significantly greater numbers of BrdU+ cells in the SGZ than all other groups exposed to SD (Fig. 2B). Photoperiod did not affect progenitor cell survival in the granule cell layer ($F_{5,53} = 0.942$, $P > 0.05$; Fig. 2C) or in the hilus ($F_{5,53} = 1.986$, $P > 0.05$; Fig. 2D).

Correlation between reproductive status and progenitor cell survival

Time in SD altered GSI as expected in photoperiodic rodents ($F_{5,49} = 12.824$, $P < 0.05$; Fig. 3A). Reproductive status, as measured by GSI (Fig. 3A), was not correlated with progenitor cell survival in the SGZ ($r_{53} = 0.07$, $P > 0.05$; Fig. 3B), granule cell layer ($r_{53} = -0.067$, $P > 0.05$; Fig. 3C) or hilus ($r_{53} = 0.215$, $P > 0.05$; Fig. 3D) of the dorsal hippocampus.

BrdU+ cell phenotype

Four weeks after being pulsed with BrdU, there were no differences among photoperiod groups in dentate neurogenesis ($F_{4,41} = 0.532$, $P > 0.05$), gliogenesis ($F_{4,41} = 0.490$, $P > 0.05$), or in undifferentiated BrdU+ progenitor cells ($F_{4,41} = 0.550$, $P > 0.05$; Fig. 4B).

Discussion

Photoperiod significantly altered the number of newly born cells surviving for 4 weeks after BrdU injections in the SGZ of the DG. Additionally, almost all of these newly born cells that survived for 4 weeks following BrdU injections expressed neuronal markers (Fig. 4) regardless of photoperiod. When compared with LD lengths, the number of BrdU-labeled cells was reduced across the first 8 weeks of SD exposure; however, this photoperiod-dependent reduction in neurogenesis was completely reversed by 10 weeks in SD (Fig. 2). The current data provide further evidence that a single environmental signal, day length, can alter neurogenesis in adult mammals. Although we did not directly assess proliferation in this study, we have previously reported that photoperiod alters neurogenesis without affecting proliferation rates in the subventricular zone and olfactory bulb (Walton *et al.*, 2012). Additionally, the experimental design incorporated a control for proliferation rates in the 0-week group, as they were all pulsed with BrdU in LD, and then randomly

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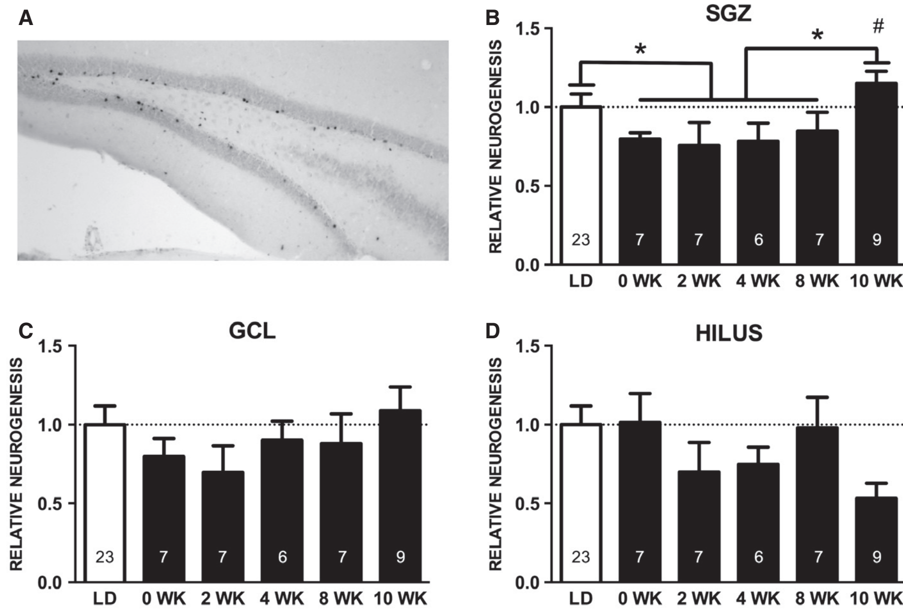

FIG. 2. Progenitor cell survival in the dentate gyrus (DG) across exposure to short day (SD) lengths. Representative photomicrograph of a hippocampal section immunostained for bromodeoxyuridine (BrdU) used to quantify progenitor cell survival in the DG (A). In the subgranular zone (SGZ) where the majority of BrdU+ cells were found, BrdU+ progenitor cell survival was impaired across the first 8 weeks of SD exposure; however, by 10 weeks in SD progenitor cell survival rebounded and was increased compared with long day (LD) mice (B). Day length did not affect dentate progenitor cell survival in the granule cell layer (C) or in the hilus (D). $^{*}P \leq 0.05$ compared with 0, 2, 4 and 8 week groups; $^{\#}P \leq 0.05$ compared with LD mice, LSD *post hoc* test. LD = long day control group, other labels on the abscissa indicate time in the photoperiod when mice were pulsed with BrdU (see Fig. 1). Numbers within bars indicate the *N* of animals within each group.

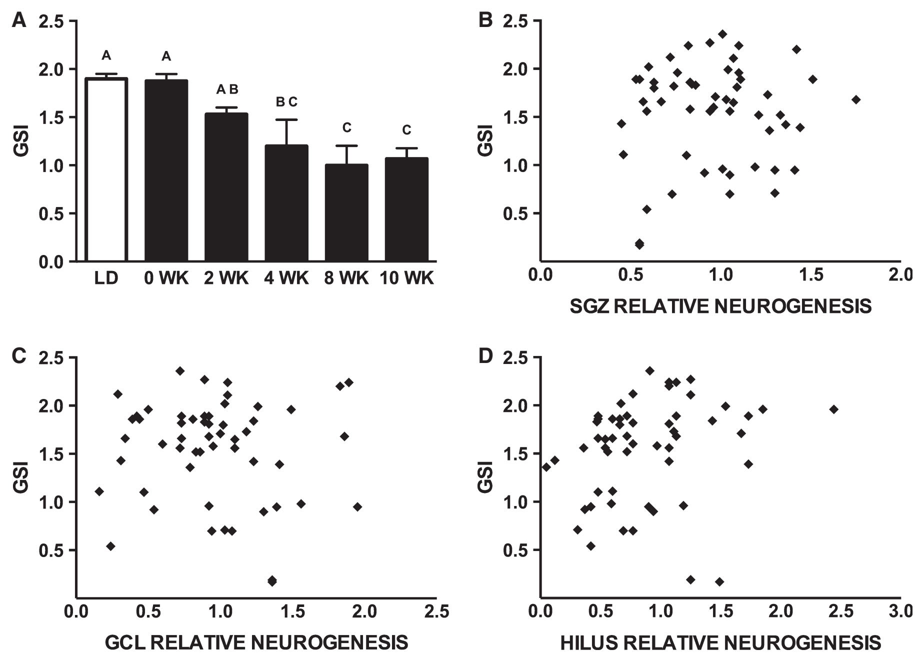

FIG. 3. Correlation between reproductive status and progenitor cell survival. Consistent with photoperiodic reproductive responses in this species, gonadosomatic index (GSI) was reduced across exposure to short day (SD) lengths (A). There was no correlation between GSI and relative neurogenesis in the subgranular zone (SGZ) (B), granule cell layer (GCL) (C), or hilus (D) of the dentate gyrus (DG). Means with different letters are significantly different in (A).

assigned to photoperiod (Fig. 1). Therefore, although this group had equal proliferation rates to its LD counterpart, SD exposure for 4 weeks decreased the survival of those newly born cells arising from pools proliferating at the same rate (Fig. 2B). This pattern has also been observed in male meadow voles where photoperiod impaired cell survival without altering proliferation rate (Ormerod & Galea, 2003). Nonetheless, a follow-up study assessing proliferation rates longitudinally across exposure to photoperiod will be necessary to definitively assess whether proliferation rates affect the photoperiodic differences in DG neurogenesis in this species found in this study.

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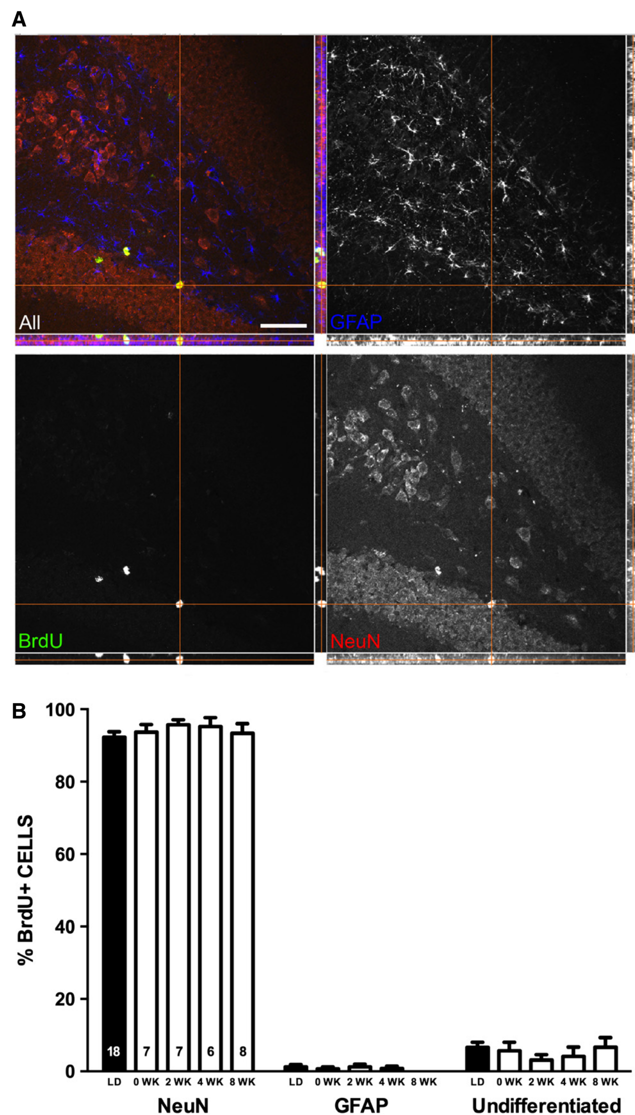

FIG. 4. Phenotype of dentate progenitor cells after 4 weeks survival. Representative confocal photomicrograph and orthogonal projection of a section of the dentate gyrus (DG) of the hippocampus showing colocalization of the mitotic marker bromodeoxyuridine (BrdU) and the neuronal marker NeuN (A). Photoperiod did not affect the phenotype of progenitor cells (B). The majority of BrdU+ cells were NeuN+, a small percentage of undifferentiated progenitor cells were present, and glial fibrillary acidic protein (GFAP)+ BrdU+ cells were very sparse (B). Scale bar: 50 μm (A). Numbers within bars indicate the *N* of animals within each group.

Among photoperiodic rodents in which neurogenesis has been assessed, the photoperiodic regulation of proliferation, cell survival, and neurogenesis may differ dependent upon species and sex. For example, photoperiod does not affect DG cell proliferation or neuron number in male or female Eastern grey squirrels (Lavenex *et al.*, 2000a), nor does it affect proliferation in male meadow voles (Ormerod & Galea, 2003), whereas proliferative rates are higher in female voles in short photoperiods (Galea & McEwen, 1999). However, in common with male meadow voles (Ormerod & Galea, 2003) and two species of photoperiodic shrews (Bartkowska *et al.*, 2008), male white-footed mice in the current study displayed decreased cell survival in the DG in SD photoperiods (Fig. 4). In common with photoperiodic shrews (Bartkowska *et al.*, 2008), male white-footed mice across the first 8 weeks of SD exposure decreased neurogenesis, whereas in common with Syrian hamsters (*Mesocricetus auratus*; Huang *et al.*, 1998), mice held in SD for 10 weeks enhanced cell survival. Taken together with the aforementioned studies, the longitudinal change in neurogenesis across SD reported in the current study highlights an issue with drawing overarching conclusions from the previous studies regarding photoperiodic regulation of neurogenesis: it is possible that the reported differences, or lack thereof, merely reflect an artifact of sampling time point in the SD group. Thus, we cannot make generalizations about the role of photoperiod or the interaction of steroids and photoperiod in the regulation of adult neurogenesis, as this needs to be addressed in a longitudinal, species-specific, and sex-specific manner.

Functionally, hippocampal neurogenesis has documented roles in supporting the formation of new memories, and can affect cognition, affective behaviors, and spatial learning and memory (reviewed in Zhao *et al.*, 2008). Nascent dentate neurons can begin to participate in learning and memory formation at 4–6 weeks old (reviewed in Zhao *et al.*, 2008; Deng *et al.*, 2010), but do not fully mature for 2–4 months (van Praag *et al.*, 2002). We have previously reported that mice exposed to SD for 10 weeks had impaired hippocampal-dependent spatial learning and memory, and impaired hippocampal long-term potentiation (Walton *et al.*, 2011, 2013). The current findings, that hippocampal neurogenesis is impaired across the first 8 weeks of SD exposure (Fig. 2), provide support for a potential role of altered neurogenesis in the SD impairment of hippocampal function in white-footed mice, as new neurons born within this time frame would be most likely to contribute to the formation of new spatial memories (Zhao *et al.*, 2008; Deng *et al.*, 2010). Although neurogenesis is increased at 10 weeks in SD, those neurons would not likely contribute to the formation of new memories for another 4–8 weeks. Thus, neurons born at 10 weeks in SD would not be functional at the time when hippocampal function has been tested in a photoperiodic context in this species (Pyter *et al.*, 2005b; Walton *et al.*, 2011).

The natural history of white-footed mice may provide some insight into why, after 10 weeks in SD, neurogenesis was increased above the rate of LD mice. Male *P. leucopus* maintain breeding territories in the spring and early summer (King, 1968), and the observed attenuation of neurogenesis upon exposure to SD lengths may represent an adaptation to conserve energy during the SD of winter when territorial maintenance, and thus, elevated spatial memory is unnecessary. Upon exposure to SD, the hypothalamic–pituitary–gonadal (HPG) axis is inhibited and the mice become reproductively inactive. Maximal reproductive responses to SD occur at about 12 weeks, and then mice become refractory to SD lengths and the reproductive system spontaneously recrudesces (Pyter *et al.*, 2005a). Preceding gonadal recrudescence, the neuroendocrine axis becomes activated and there is a gonadotropin [luteinizing hormone (LH) and follicle-stimulating hormone] surge, which rises above levels found in LD, prior to gonadal increases in volume and increased secretion of testosterone (Berndtson & Desjardins, 1974). Presumably, changes within the brain precede measurable endocrine and gonadal changes. In common with the gonadotropin surge described above, the enhancement of neurogenesis in the hippocampus at 10 weeks in SD may represent ‘recrudescence’ of the hippocampus to prepare it for the enhanced spatial memory necessary to maintain breeding territories, as these neurons would need to born at minimum 4–8 weeks prior to breeding season and territory establishment to be functional in the hippocampus (Deng *et al.*, 2010). In captive male meadow voles, reproductive status is positively associated with neurogenesis (Ormerod & Galea, 2003) and testosterone is positively correlated with neurogenesis in rats (Spritzer & Galea,

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2007). Although we did not directly measure androgens or gonadal responses in the current study, androgens likely did not contribute to the enhanced neurogenesis of mice at 10 weeks in SD. At the time that the mice were killed and brains collected (14 weeks in SD; Fig. 1), the photoperiodic cycle of gonadal volume in the mice was at nadir (Fig. 3A; Pyter *et al.*, 2005a), and thus circulating androgen concentrations were also presumably low (Knotts & Glass, 1988). Additionally, reproductive status as measured via GSI was not correlated with BrdU+ cell survival in the DG (Fig. 3). However, it is possible that the enhanced neurogenesis after 10 weeks in SD may be dependent on other factors associated with HPG axis activation, such as the surge in gonadotropin-releasing hormone (Hawken *et al.*, 2009) or the LH surge (Mak *et al.*, 2007).

In conclusion, the rate of neurogenesis in the DG of male white-footed mice varied across exposure to SD. Upon exposure to SD, neurogenesis was attenuated for 8 weeks. However, by 10 weeks in SD lengths, neurogenesis was enhanced above levels of LD mice, potentially as a mechanism to recover the spatial memory function of the hippocampus in preparation for breeding season. The current findings are consistent with the natural photoperiodic cycle of hippocampal function in male white-footed mice, and may help to inform research on photoperiodic plasticity in neurogenesis and provide insight into how the complex interplay between the environment, genes, and adaptive responses to changing day lengths affects brain function and behavior at multiple levels.

Acknowledgements

The authors thank Dr Rusty Gage and Eunice Mejia for assistance with experimental design and tissue processing. The authors also thank Peter Fredericks and Shan Chen for technical assistance. This work was supported by NIH R01MH057535 to R.J.N. The authors have no competing interests to declare.

Abbreviations

BrdU, bromodeoxyuridine; DG, dentate gyrus; GFAP, glial fibrillary acidic protein; GSI, gonadosomatic index; HPG, hypothalamic–pituitary–gonadal; LD, long day; LH, luteinizing hormone; NeuN, neuronal nuclei; PBS, phosphate-buffered saline; RT, room temperature; SD, short day; SGZ, subgranular zone.

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