SLEEPJ, 2021, 1–16

doi: 10.1093/sleep/zsaa173
Advance Access Publication Date: 17 November 2020
Review

REVIEW

Adult hypothalamic neurogenesis and sleep–wake dysfunction in aging

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Abstract

In the mammalian brain, adult neurogenesis has been extensively studied in the hippocampal sub-granular zone and the sub-ventricular zone of the anterolateral ventricles. However, growing evidence suggests that new cells are not only "born" constitutively in the adult hypothalamus, but many of these cells also differentiate into neurons and glia and serve specific functions. The preoptic-hypothalamic area plays a central role in the regulation of many critical functions, including sleep–wakefulness and circadian rhythms. While a role for adult hippocampal neurogenesis in regulating hippocampus-dependent functions, including cognition, has been extensively studied, adult hypothalamic neurogenic process and its contributions to various hypothalamic functions, including sleep–wake regulation are just beginning to unravel. This review is aimed at providing the current understanding of the hypothalamic adult neurogenic processes and the extent to which it affects hypothalamic functions, including sleep–wake regulation. We propose that hypothalamic neurogenic processes are vital for maintaining the proper functioning of the hypothalamic sleep–wake and circadian systems in the face of regulatory challenges. Sleep–wake disturbance is a frequent and challenging problem of aging and age-related neurodegenerative diseases. Aging is also associated with a decline in the neurogenic process. We discuss a hypothesis that a decrease in the hypothalamic neurogenic process underlies the aging of its sleep–wake and circadian systems and associated sleep–wake disturbance. We further discuss whether neuro-regenerative approaches, including pharmacological and non-pharmacological stimulation of endogenous neural stem and progenitor cells in hypothalamic neurogenic niches, can be used for mitigating sleep–wake and other hypothalamic dysfunctions in aging.

Statement of Significance

In recent years, the hypothalamus has emerged as a novel neurogenic niche in the adult brain. A significant number of cells are not only "born" constitutively in the adult hypothalamus, but many of these cells differentiate into neurons, integrate into pre-existing neural circuitries, and support specific hypothalamic functions, including control of metabolism and energy balance. This review provides the current understanding of the biology and mechanisms of adult hypothalamic neurogenic processes and its contributions to hypothalamic functions, especially sleep–wake regulation. A hypothesis that a decline in hypothalamic neurogenic processes may be a contributor to the sleep–wake disruption in aging, and thus, strategies aimed at improving neurogenesis may help slow down or alleviate aging-associated sleep–wake disturbance is discussed.

Key words: cell proliferation; neurogenesis; hypothalamus; sleep–wake regulatory systems; aging

Submitted: 10 March, 2020; **Revised:** 22 July, 2020
Published by Oxford University Press on behalf of Sleep Research Society (SRS) 2020.

Introduction

Neural stem (NSCs) and progenitor cells (NPCs) constitute a diverse population of specialized cells that have the ability to generate new neurons and glia in the nervous system. In the adult mammalian brain, NSCs were first identified in the sub-granular zone (SGZ) in the dentate gyrus of the hippocampus and the sub-ventricular zone (SVZ) of the lateral ventricles (LV). Adult neurogenic processes have been extensively studied in these two classic zones [1–5]. However, neural precursors are distributed throughout the brain. In recent years, hypothalamic 3rd ventricular (3V) wall and its vicinity, including paraventricular, ventromedial, and arcuate nuclei and median eminence (ME) have emerged as novel neurogenic niches in the adult brain. Evidence suggests that a significant number of new cells are not only "born" constitutively in the adult hypothalamus, but also that many of these cells differentiate into neurons and glia and serve hypothalamic functions, including control of metabolism and energy balance, heat tolerance, and neuroendocrine regulation [6–16].

The preoptic-hypothalamic area (POAH) is a physiologically and anatomically complex region, which plays a central role in many critical functions, including sleep–wakefulness, thermoregulation, circadian rhythms, feeding, energy metabolism, and neuroendocrine functions [17–30]. The dysfunction or loss of hypothalamic neurons has been linked to common diseases, including obesity, hypertension, mood disorders, and sleep disorders [22, 31–33]. The hypothalamic sub-regions involved in these functions overlap anatomically or are located in close proximity, and many of these functions are coupled, including sleep and thermoregulation, sleep and fluid regulation, and sleep–wake, circadian rhythms, and feeding. Therefore, it is plausible that these interactive hypothalamic regulatory systems are subject to the same neurogenic processes.

A role of adult hippocampal neurogenesis in regulating hippocampus-dependent functions, including cognition, has been extensively studied and reviewed [34–36]. However, we are only beginning to understand postnatal and adult hypothalamic neurogenic processes and its contributions to various hypothalamic functions, including sleep–wake regulation. This is evident from the fact that our PubMed search with the keyword "hypothalamic neurogenesis" yield 122 research papers and 22 reviews between 1985 and 2005 and 762 articles and 238 reviews between 2006 and 2020, while a search with the keyword "hippocampal neurogenesis" yield thousands of papers and reviews during the same period. Of those articles, we narrowed searches to include studies on hypothalamic neurogenesis (process); hypothalamic neurogenesis and hypothalamic functions, including sleep–wakefulness, feeding, metabolism/energy balance, and thermoregulation; hypothalamic neurogenesis and hypothalamic sleep–wake structures, and suprachiasmatic nucleus; neurogenesis, inflammation, and aging; aging and sleep disruption; and combination of those keywords to systematically appraise the literature on the hypothalamic neurogenic process, its interactions with inflammation and aging, and its relation to various hypothalamic functions including sleep–wake control.

This review is aimed at providing a general overview of the current understanding of the adult hypothalamic proliferative and neurogenic processes and the extent to which these processes affect hypothalamic functions, including sleep–wake regulation. We propose that hypothalamic cell proliferation and neurogenesis are vital for maintaining hypothalamic neural plasticity and functions in the face of regulatory challenges. While this review is focused on hypothalamic neurogenesis, the contributions of gliogenesis cannot be ignored. Glial cells constitute nearly half of the cellular population in the CNS. They have been increasingly recognized as important regulators of nervous system development, synaptic communication, and brain functions, including sleep homeostasis [37–41].

Both human and animal aging is associated with (1) heightened inflammatory signaling in the CNS [42–44]; (2) a decline in neurogenesis, including the hypothalamic neurogenic process [31, 45–48]; and (3) sleep disruption by frequent awakenings during rest-phase and waking disruption by sleep intrusions during active-phase, decreased non-rapid eye movement (nonREM) sleep slow-wave activity, and poor homeostatic response to sleep loss [49–53]. We discuss a hypothesis that a decline in neurogenic processes, caused by chronic inflammation, contributes to the aging/dysfunction of hypothalamic sleep–wake and circadian systems and consequent sleep–wake disturbance. We further discuss the prospect of stimulating neural stem and progenitor cells in the hypothalamic neurogenic niches as a tool for mitigating sleep–wake disruption in aging.

Hypothalamic neurogenesis in the adult brain

The hypothalamus is a small structure, which is localized below the thalamus and above the pituitary gland. It is organized into multiple subregions, including some distinct nuclei around the 3V [54]. Although it represents less than 1% of the total volume of the brain, it serves as a central regulator of various vital processes including sleep–wakefulness, energy balance, osmoregulation, body temperature, hormonal balance, sexual behavior, and reproduction [17–19, 22, 25].

Recent evidence confirms the existence of hypothalamic stem/progenitor cell niches and the occurrence of postnatal and adult hypothalamic neurogenic and gliogenic processes. This evidence mostly comes from animal studies that have used tagging of proliferating cells by 5-bromo-2′-deoxyuridine (BrdU) or 5′-iodo-2′-deoxyuridine, and from cell lineage analysis of inducible mouse Cre lines [9, 55, 56]. Some genes, transcription factors, and proteins typically expressed in NSCs and NPCs such as nestin, doublecortin (DCX), doublecortin-like protein, and sex-determining region-Y (SRY-BOX2 or SOX2) have also been used as endogenous markers. Evidence indicates that NPCs from neurogenic niches can migrate deep into the parenchyma, differentiate into glia and/or neurons, and integrate into neural circuitries [6–14].

Some of the markers of proliferative or immature cells have been reported in the POAH sleep–wake regulatory regions and neuronal groups as well as in the suprachiasmatic nucleus (SCN) under normal conditions and in response to various stimuli or physiological challenges [13, 16, 57–61]. Interestingly, although SCN exhibits a low expression of the neuronal differentiation marker NeuN, the expression of stem cell markers and many genes that have been implicated in the maintenance of stem states and stages of neurogenesis have been reported in adult SCN.

In humans, adult neurogenic processes have been widely reported in the hippocampus, striatum, and SVZ [4, 5, 62–68].

Although there are only a few studies on adult hypothalamic neurogenesis in humans, DCX-labeled cells, resembling immature and developing neurons, have been reported in the adult human arcuate nucleus, median eminence, and in the ventromedial hypothalamus(VMH) [69].

Hypothalamic neuronal stem/progenitor cells: distribution and characteristics

In the hypothalamus, NSCs and NPCs are localized in organum vasculosum of the lamina terminalis (OVLT), the bottom of the 3V in the ME, cellular layers of the lateral walls of the 3V at the level of paraventricular and arcuate nuclei, and in the parenchyma [6–14]. Of these regions, because of their proximity, OVLT, 3V walls, and to a lesser extent, ME are likely sources of precursors for neural and glial cells of the POAH, including median preoptic nucleus (MnPO), medial and lateral POA, medial and lateral hypothalamus, and SCN (Figure 1).

Hypothalamic NSCs are represented by tanycytes or radial glial-like cells in the ependymal layer of ventricular walls, and astrocyte-like NSCs in the parenchyma [70–73]. Tanycytes express markers of stem or progenitor cells, including nestin, glial fibrillary acidic protein, vimentin, insulin-like growth factor-1, ciliary neurotrophic factor (CNTF), SOX2, SOX9, Hes 1 and 5, Notch 1 and 2, and LIM/homeobox protein [13, 55, 56, 69, 70, 74–81]. Proliferating cells residing in hypothalamic parenchyma [7–11, 55, 56, 82, 83] are likely to be the descendants of tanycytes [77, 84, 85]. Based on the anatomical localization of their cell bodies along the ependymal wall, the projection pattern of their basal processes, and their gene expression profiles, tanycytes have been classified into α1 and α2 and β1 and β2 sub-types [81, 86–88]. Only α2 tanycytes display the hallmarks of NSCs [56] and exhibit unlimited self-renewal, whereas α1 and β tanycytes have limited self-renewal capacity.

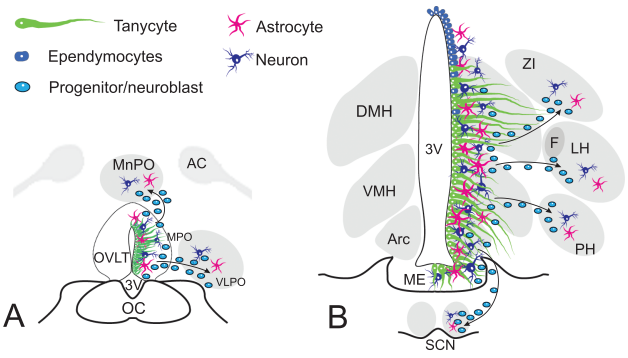

Figure 1. Schematic diagrams, based on the findings in rats and mice, showing hypothalamic neurogenic zones, including OVLT (A) and the wall of 3V, ME, and its vicinity (B) that potentially support the hypothalamic sleep–wake and circadian systems. Hypothalamic NSCs are represented by tanycytes, a subtype of ependymal cells that lines the 3V wall, and astrocyte-like NSCs in the parenchyma. NPCs from neurogenic zones migrate to (hypothetical representation) and differentiate into glia and sleep–wake and circadian neuronal phenotypes. 3V, third ventricle; AC, anterior commissure; Arc, arcuate nucleus; DMH, dorsomedial hypothalamus; F, fornix; LH, lateral hypothalamus; ME, median eminence; MnPO, median preoptic nucleus; MPO, medial preoptic area; OC, optic chiasm; OVLT, organum vasculosum of the laminae terminalis; PH, posterior hypothalamus; SCN, suprachiasmatic nucleus; VLPO, ventrolateral preoptic area; ZI, zona incerta.

Regulation of hypothalamic neurogenesis

A number of neuromediators, signaling pathways, and molecules have been implicated in the regulation of each step of the neurogenic process (Figure 2). While most of these regulatory molecules have been studied in relation to classic neurogenic zones, they likely play similar roles in the hypothalamic neurogenic process as well [89–91]. There are excellent reviews on these regulatory molecules and pathways [15, 47, 92, 93]. Here we describe some of the more extensively studied regulatory molecules and pathways.

Cell proliferation

Most adult NSCs are quiescent. The balance between their quiescent and proliferative states is tightly regulated [93–95]. Dysregulation and/or loss of quiescence may result in a premature proliferation of NSCs ultimately leading to the depletion of neural stem and progenitor cells [96–100]. Stem cells undergo both symmetric and asymmetric divisions. In symmetric division, both daughter cells remain in stem condition, whereas in the asymmetric division, one of the daughter cells remains in stem state, while the other continues to divide (Figure 2). Some notable factors that have been implicated in cell proliferation are described below.

i) The proneural factors are critical regulators of cell proliferation and neurogenesis. They also contribute to the neuronal subtype identity of cells. Achaete-scute complex homolog 1 (ASCL1) and neurogenin-2 are the two important proneural transcription factors. They are expressed in neural precursors and have been implicated in the initiation and regulation of neurogenesis in the vertebrate nervous systems [101–103].

ii) The maintenance of most NSCs requires Notch signaling molecules [104]. The core of the Notch signaling includes four proteins (Notch1–Notch4). Notch proteins can activate the transcription of several genes in the host cells. Some of those genes are involved in the regulation of stem cell activity and neurogenesis. While Notch-1 maintains actively proliferating NSCs, Notch-2 maintains its quiescence [105].

iii) Cytokines and growth factors act independently or synergistically to regulate different steps of neurogenesis from cell proliferation and survival of progenitor/immature cells to differentiation and neuronal and glial maturation [91, 106]. Growth and trophic factors like CNTF, fibroblast growth factor, nerve growth factor, vascular endothelial growth factor, and brain-derived growth factor, are known to increase cell proliferation, neurogenesis, and gliogenesis [6–8, 11–14, 77, 91, 106–108].

iv) Many neurotransmitters, including, gamma-aminobutyric acid (GABA), glutamate, and dopamine, and signaling molecules like nitric oxide, also act as regulators of stem cell activities [81, 96, 109–116]

v) Neuronal afferents innervate both ventricular and parenchymal areas of the hypothalamus [117–121]. These afferents may selectively affect distinct pools of adult NSCs and change their proliferative status [122]. Such afferents are likely to influence the neurogenic processes near and within sleep–wake regulatory hypothalamic structures and SCN.

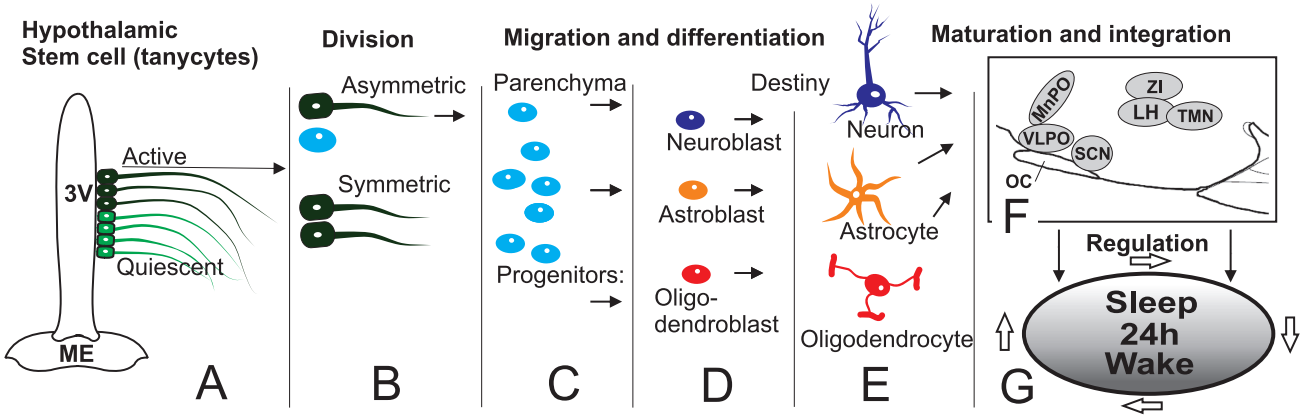

Figure 2. Schematic representation of hypothalamic neurogenesis and gliogenesis. (A) Hypothalamic quiescent stem cells do not divide but retain the capacity to proliferate in certain conditions, while active stem cells have the ability to proliferate. (B) The stem cell can divide into two new identical stem cells (symmetric division) or one progenitor cell and another stem cell (asymmetric division). (C) Progenitor cell migrates to parenchyma and remain there or continue proliferating; then (D) progenitor cells start differentiating and migrating to the destination site; (E) differentiates into neurons, astrocytes, or oligodendrocytes; and (F–G) integrate into neural circuits to participate in the regulation of physiological activities including sleep–wake regulation.

vi) Several neuropeptides and metabolic hormones, including thyroid hormone, melanocortin, orexin-A, neuropeptide Y, insulin, leptin, oxytocin, and ghrelin, have also been reported to induce neurogenesis [89, 123–125]. The gonadotropin-releasing hormone has been shown to stimulate cell proliferation in the hypothalamus of old mice and also ameliorate aging-related cognitive decline [126]. It is hypothesized that sex steroids, specifically estrogens, act in conjunction with neurotrophins to induce classic growth factor responses, including increased cellular proliferation, differentiation, and survival [127].

vii) Various brain insults, including mechanical and ischemic injuries, seizure, stroke, and excitotoxic lesions acutely enhance NSC proliferation, migration, and differentiation [128–138]. This increased neurogenesis seems to be a protective and self-repair response [139, 140]. However, chronic insults, including chronic inflammation [141, 142], sleep-fragmentation, and sleep deprivation [143–147], are known to suppress neurogenesis (see further section).

Cell migration and differentiation

After proliferation, the fate of new cells is determined by various endogenous factors and cytokines that direct their migration and differentiation into neuronal or glial lineage (Figure 2) or their death. A deficit in the migration of newly generated cells to destination sites might result in improper neural circuitry maintenance and dysfunction [90]. It may also accelerate aging processes (see further section). Here, we describe some of the well-studied mechanisms which regulate the migration and differentiation of neural precursors in the SGZ and SVZ [90, 108, 148, 149]. Similar mechanisms may regulate neurogenic processes in the hypothalamus.

The migration of neuroblasts is guided chemotactically along gradients of various transcription and growth factors, and chemokines that can attract or repulse the cells to keep them in the migratory path [108, 149]. The list of these factors includes neurogenin-2, glial cell-derived neurotrophic factor (GDNF), epidermal growth factor (EGF), hepatocyte growth factor, netrin, and chemo-repellents, such as SLIT-2. GDNF and EGF increase the migratory potential of newborn neuroblasts. Hepatocyte growth factor keeps neuroblasts on the path. Chemo-repellents, for example, SLIT-2, may regulate the long-distance directional migration of neuroblasts [108].

During and after migration, the new cells undergo differentiation into glia or specific neuronal phenotypes under the control of various regulatory molecules. For example, chronic administration of amylin increases the number of newly proliferated cells in the area postrema and promotes their differentiation predominantly into neurons rather than astrocytes [150]. The transcription factor, neurogenic differentiation-1 (NeuroD1), induces the differentiation of adult hippocampal neural progenitors into neurons. Its deletion in neurogenic niches results in a significant reduction of new neurons [151, 152]. Molecules that direct the proliferated cell to differentiate into specific phenotypes may be of particular therapeutic interest.

The timeline of cell differentiation may vary for different cell types. Electrophysiological maturation of new hippocampal granule cells progresses over 2–7 weeks after cell division [153–157]. In the hypothalamus, neurons involved in feeding/metabolism and thermoregulation exhibit mature phenotypes in about 5 weeks [7, 16]. Thus, neuronal maturation in the hypothalamus may take several weeks in rodents. Interneurons or small neurons with short projections are likely generated faster and more successfully than large neurons with long projecting axons. It also remains to be seen if hypothalamic neurons generated in the adult brain can grow long axons.

Hypothalamic regulation of sleep–wake and circadian functions

The neural circuitry involved in the regulation of sleep and arousal is complex. It consists of a complex network of sleep-active or sleep-regulatory and wake-active or wake-regulatory neuronal groups that are distributed at several levels of the neuraxis [20, 22, 29, 158]. These sleep- and wake-active neuronal groups/systems interact with each other and the circadian pacemaker for the timely expression and maintenance of sleep-wakefulness. Here, we briefly describe notable sleep–wake regulatory and circadian systems in the POAH that are potentially subjected to its neurogenic processes (Figure 3).

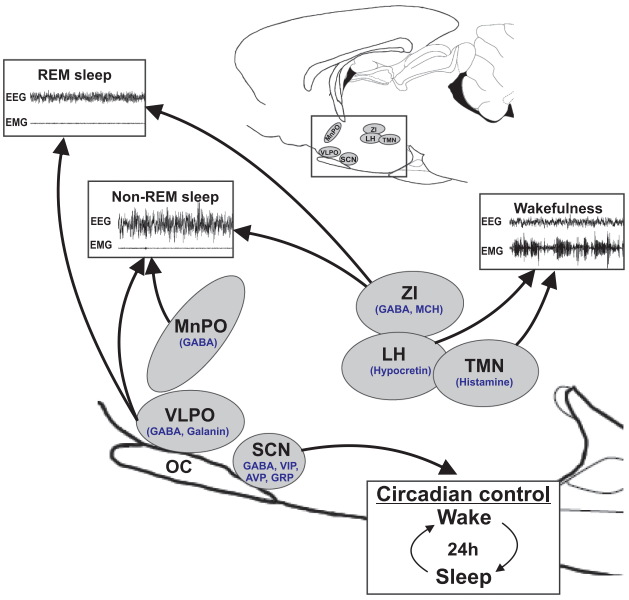

Figure 3. Schematic representation of critical hypothalamic areas controlling sleep, wakefulness, and circadian activity in rodents. SCN is the master circadian pacemaker that controls the timing of the sleep–wake cycle. Almost all SCN neurons are GABAergic. These neurons also express neuropeptides, including VIP, AVP, and GRP. While sleep-active neurons are diffusely distributed throughout the POAH, a higher concentration of these neurons are localized in the MnPO and VLPO. MCH and GABA neurons in the ZI/LH are also involved in the regulation of both nonREM and REM sleep. Perifornical (PF)-LH and TMN contain hypocretin and histamine neurons, respectively, that are involved in the control of arousal and wakefulness. The MnPO and VLPO via sleep-active GABA and galanin neurons exert inhibitory effects on wake-promoting hypocretin and histamine neurons in PF-LH and TMN. VIP, vasoactive intestinal peptide; AVP; arginine vasopressin; GRP, gastrin-releasing peptide.

The POAH plays a central role in the regulation of sleep–wakefulness and circadian activity. In the POAH, concentrations of sleep-active neurons are localized in the ventrolateral preoptic area (VLPO) and median preoptic nucleus (MnPO) [22, 159–162]. These neurons express the inhibitory neurotransmitters GABA and galanin [20, 27, 163–165]. These neurons exhibit increased discharge during nonREM/REM sleep and also express the neuronal excitation marker c-Fos during sleep [27, 159–161, 163, 166]. MnPO and VLPO sleep-active neurons project to and inhibit major wake-promoting systems in the brainstem and hypothalamus, including hypocretin (also called orexin) and histamine systems [22, 167–172]. Evidence suggests that MnPO and VLPO neurons are also involved in the homeostatic regulation of sleep, as during sleep deprivation, their sleep-promoting activity increases with accumulating sleep debt [173, 174]. Sleep-active neurons expressing melanin-concentrating hormone (MCH) and GABA in the zona incerta (ZI) and lateral hypothalamus (LH) also contribute to the regulation of nonREM and REM sleep [175–177]. Of course, the POA region also controls several other functions, including temperature control, drinking behavior, and cardiovascular regulation [25, 118, 178, 179].

The hypothalamic wake-regulatory systems most notably include the hypocretin and histamine systems [22, 23, 180, 181]. Hypocretin expressing neurons are localized in the perifornical-lateral hypothalamic area and are wake-active [182–184]. The hypocretin system has been implicated in the promotion and stabilization of waking and muscle tone regulation [22, 180]. A loss of hypocretin signaling is linked to the pathogenesis of narcolepsy [33, 185], which is marked by increased sleepiness and a higher propensity for REM sleep. Histaminergic neurons are localized in the tuberomammillary nucleus, are wake-active, and promote arousal [22, 23, 181].

The SCN is localized just above the optic chiasm and is the primary circadian pacemaker in mammals [186]. SCN neurons generate autonomous circadian rhythms and drive circadian rhythms in other brain areas and tissues through several outputs [24, 187]. Almost all SCN neurons are GABAergic. SCN neurons also express several neuropeptides including vasoactive intestinal peptide, calbindin, neurotensin, and gastrin-releasing peptide in the SCN core and arginine vasopressin, in the SCN shell [188–192]. Several non-neuronal cell types are also present in the SCN that play less defined roles [193, 194]. A recent study suggests that astrocytes in the SCN can autonomously encode circadian information and instruct their neuronal partners to initiate and sustain circadian patterns of complex mammalian behaviors [195]. Light–dark rhythms, in part, control SCN output through a direct photic-driven pathway from the retina.

Sleep–wake and circadian activities are important determinants of successful adaptation, survival, and performance in a diverse and challenging environment. Therefore it is vital to maintain the normal functioning of hypothalamic structures and involved cell types that regulate those functions. Many factors related to lifestyle, diet, environment, and aging are known to affect these systems adversely. We propose that hypothalamic neurogenesis helps maintain hypothalamic function in the face of regulatory challenges.

Hypothalamic neurogenesis and hypothalamic functions

Growing evidence shows that adult hypothalamic cell proliferation/neurogenesis plays a vital role in maintaining adaptive plasticity and functionality. It is thought that the reorganization or successful remodeling of neural circuits includes two balanced processes; the apoptosis or phagocytosis of existing potentially dysfunctional and damaged neurons by microglia, and their replenishment and support by neurogenic processes [10, 196, 197].

Recent studies suggest that newly formed cells can integrate into neuronal circuitry and synthesize and release neurotransmitter/neuropeptides and thus support hypothalamic functions, including regulation of energy homeostasis, heat acclimation, body weight, and sleep–wakefulness [7, 51, 61, 82, 198, 199]. For example:

i) Patch-clamp recording of newly formed hypothalamic cells indicates that although immature, these neurons receive synaptic inputs, indicating their integration into the local hypothalamic circuitry [56].
ii) Newly formed neurons in arcuate nuclei respond to acute fasting as well as exogenous leptin by increased expression of the c-fos protein, a marker of neuronal activation [55].
iii) Chronic and selective impairment of hypothalamic neural stem/progenitor cell proliferation, survival, and/or neuronal differentiation adversely affects hypothalamic functions leading to the onset of metabolic disorders [55].
iv) Chronic blockade of hypothalamic neurogenesis and gliogenesis by intracerebro-ventricular (ICV) infusion of cytosine-β-D-arabinofuranoside (AraC), an antimitotic agent, for 5–40 days impairs several hypothalamic regulatory processes including energy-metabolic control, heat

tolerance, an estrous-related surge in luteinizing hormone, and sleep–wake function [7, 61, 200–202].

v) Functional improvement in hypothalamic physiology has been reported after restoring impaired cell proliferation and neurogenesis. Chronic infusion of CNTF increases hypothalamic neurogenesis and normalizes metabolic regulation, and decreases weight in obese mice [7].

vi) A lack of stem/progenitor cells accelerates hypothalamic senescence and dysfunction and shortens life span. In contrast, central treatment with healthy hypothalamic stem/progenitor cells causes slowing of the aging-related processes and extends the life span [45].

Neurogenesis in sleep–wake and circadian regulatory hypothalamic areas

Recently, we found BrdU+ cells, a marker of cell proliferation, in several hypothalamic sleep–wake regulatory regions, including MnPO, POA, dorsomedial hypothalamus (DMH), VMH, and LH, and SCN after 4 weeks of continuous ICV infusion of BrdU (Figure 4) [200]. Many of those cells were observed in these sites even 6–8 weeks after treatment (unpublished observation). Evidence suggests that NSCs/NPCs can migrate considerable distances from the neurogenic zones into deep hypothalamic parenchyma and differentiate into neurons or glia [7, 11, 55, 71, 75]. Therefore, given the proximity of 3V wall, OVLT, and ME, to the POAH sleep–wake and circadian systems, it is likely that progenitor cells generated in these neurogenic zones migrate to the POAH sleep–wake structures and the SCN.

The roles of adult hypothalamic neuro- and glio-genesis in sleep–wake functions were studied only recently [200]. We found that chronic ICV infusion of AraC suppressed cell proliferation around the 3V wall and adjacent POAH sleep–wake and circadian regulatory regions by 96% in young adult mice (Figure 4). The AraC-treated young mice also exhibited sleep–wake features similar to those observed in aged mice (discussed below), including sleep fragmentation, decreases in nonREM and REM sleep amounts, and decreased delta activity in nonREM recovery sleep (Figure 4). These mice also exhibited increased waking disruption in the dark phase and a decreased circadian amplitude of sleep–wake expression [200].

In our study, the stages of differentiating cells and phenotypes of BrdU+ cells in the POAH were not determined [200]. The time from BrdU infusion to the end of the experiment was 4–8 weeks. Therefore, these BrdU+ cells could be at any stage from progenitor to different stages of maturating glia, neuron, or oligodendrocyte. Several studies have reported that neurogenesis also occurs in the hypothalamic parenchyma [7, 8, 10, 11, 56, 82], very close to the area of final differentiation. Thus, these newborn cells in the medial preoptic area (MPO), MnPO, VLPO, medial and LH, and SCN could be neuroblasts, immature, or mature neurons (Figure 2). Also, these newborn cells may differentiate into any of the sleep-, wake-, and SCN neuronal phenotypes and affect specific function(s).

Hypothalamic neurogenesis and sleep–wake dysregulation in aging

Sleep disruption is one of the most frequent and challenging problems of advancing age. In an epidemiological study,

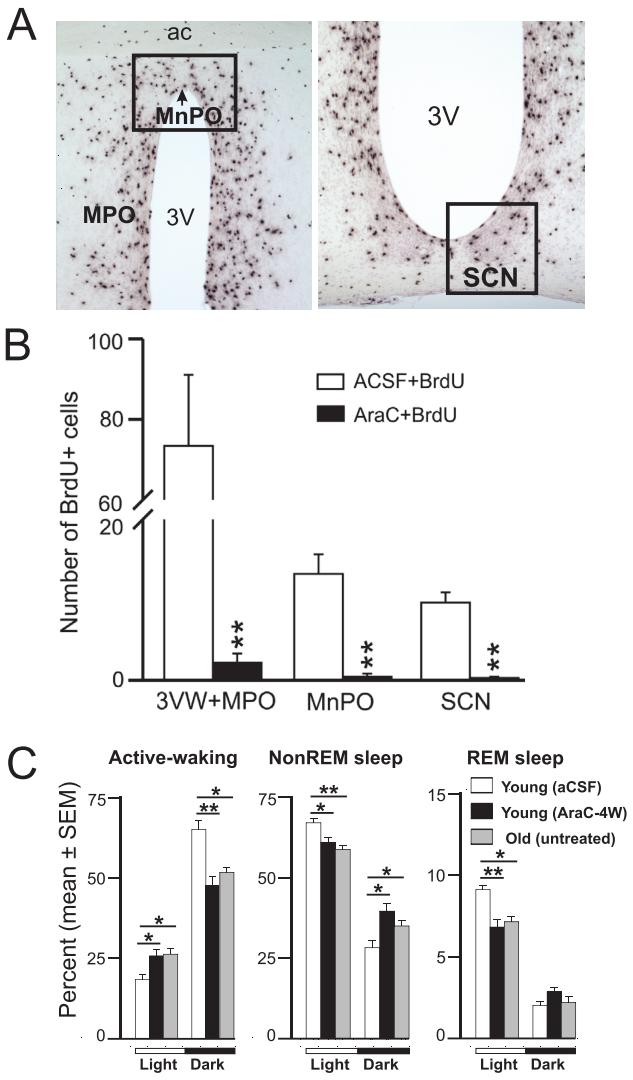

Figure 4. Hypothalamic cell proliferation/neurogenesis and its role in sleep–wake regulation. (A) Hypothalamic proliferative cells in 4-month-old mice after 4 weeks of BrdU infusion into the lateral ventricle via a mini-osmotic pump. A large number of BrdU-positive cells were observed in the MnPO, MPO, SCN, and adjacent areas. (B) BrdU-positive cells (mean ± SEM) in the MnPO, MPO, and SCN in artificial cerebrospinal fluid (aCSF)-treated control group versus AraC-treated group. AraC dramatically reduced the number of BrdU+ or proliferating cells in these regions. (C). Sleep–wake profiles of young control (aCSF treated), young AraC-treated, and old untreated mice. Note that the sleep–wake profiles of mice with chronic blockade of hypothalamic cell proliferation were similar to those exhibited by old mice (Adopted from Kostin et al. [2019]).

35%–40% of people aged 65 and older reported disorders of initiating and/or maintaining sleep on a chronic basis [50]. Sleep disruption by frequent awakenings, decreases in nonREM sleep amount, and slow-wave activity (SWA, an index of sleep need, and the restorative properties of nonREM sleep) are hallmarks of human sleep in aging [49, 53]. This attenuation of nonREM sleep and SWA occurs at all circadian phases [203]. Other features include a decline in REM sleep amount, dampening of the S–W circadian rhythm amplitudes and reduced homeostatic response to sleep loss [53, 204]. Aging is also associated with shortening of sustained waking bouts with more sleep intrusions and shortened latencies to sleep during the active period. In rodents, aging is associated with similar changes in the sleep–wake organization [51, 52, 200, 205]. We note that findings on the total

amount of nonREM sleep during the light period and recovery nonREM sleep and EEG delta activity after sleep deprivation have been inconsistent [51, 206, 207].

Aging is also associated with a decline or impaired neurogenic processes. There is a decrease in the number of hypothalamic NSCs and their proliferative activity [45, 55], although they retain the capacity to produce new neurons [6]. The number of tanycytes in hypothalamic neurogenic areas declines with aging [46]. Furthermore, tanycyte shape and the relationships among tanycytes, neural terminals, and the basal lamina of the portal capillary system undergo age-related progressive disorganization [208]. The separation between tanycytes increases, possibly compromising the blood–brain barrier [209]. The expression profile of NSCs and NPCs also change with aging. The number of cells expressing proteins related to proliferation or neurogenesis including, nestin, SOX2, Bmi1, Musashi1, also decline in the hypothalamic 3V wall with increasing age [45]. Some evidence suggests that replacing or replenishing neurons by stimulating endogenous NSCs or by transplanting healthy NSCs help restore neuronal circuitries and hypothalamic functions as well as slow down the aging, whereas suppressing neurogenesis induces hypothalamic dysfunction and accelerates aging [7, 45, 200].

We found that in young mice, short-term (less than 2 weeks) suppression of hypothalamic cell proliferation/neurogenesis by AraC did not produce significant effects on sleep–wakefulness. However, its chronic suppression caused sleep–wake disruption similar to that observed in aging, which outlasted AraC treatment [200]. Much evidence shows that sleep is associated with increased hippocampal cell proliferation and survival, while its chronic disruption adversely affects cell proliferation and neurogenesis [144, 146, 147, 210]. The findings of our study provide first direct evidence that neurogenesis plays a role in sleep–wake regulation as its chronic suppression contributes to sleep–wake disruption similar to aging. A declined hypothalamic neurogenesis, resulting in fewer newborn mature neurons in the POAH, has been implicated in attenuated acquired heat tolerance in old rats [48]. Impaired neurogenesis is also a primary risk factor for most neurodegenerative diseases that are also marked by sleep disruption [179].

We hypothesize that the differentiation of newborn hypothalamic neurons into various sleep- and wake-active and SCN neuronal phenotypes and their functional integration declines with aging. We propose that a reduction in the hypothalamic neurogenic process affects the replacement of dysfunctional or lost neurons as well as the production of trophic/growth factor(s) for supporting existing cells and their circuitries. These changes play a significant role in the aging of hypothalamic sleep–wake regulatory systems and the SCN (Figure 5).

A decreased number of sleep-regulatory galanin-containing neurons have been reported in the diagonal band of Broca in old rats [211], and in the intermediate nucleus of old humans, equivalent to the VLPO in rodents [212]. The loss of neurons was correlated with sleep fragmentation. The age-related loss of hypocretin and MCH neurons in the LH and noradrenergic and dopaminergic neurons in the brainstem have also been reported [30, 213, 214]. The reason(s) of age-related neuronal loss remains unknown. However, decreased neuronal populations in the aged brain may likely be related to declining hypothalamic neurogenesis. Also, declining support to existing neurons by pro-neurogenic cytokines, growth factors, and regulatory RNA, produced by NSCs and immature cells, may result in reduced neuroprotection, neuronal repair, increased neurodegeneration, and accelerated aging [45].

Some evidence indicates that dysfunction of hypothalamic sleep–wake and circadian regulatory neuronal groups and not necessarily their loss contribute to sleep–wake disturbances in aging. For example (1) our preliminary findings suggest that MnPO and VLPO sleep-active neurons in old rats exhibit a significantly lower nonREM/wake discharge ratios during the natural sleep–wake cycle and an attenuated response to sleep deprivation compared with young rats [215]; (2) in rodent brains, including hypothalamic areas like SCN no age-related decline in neuronal counts are found. Instead, they exhibit changes in neuronal volume [216, 217]. Similarly, old and young monkeys of both sexes exhibit no age-related difference in neuronal or glial numbers in various hypothalamic regions, including SCN [218]; (3) aging is associated with a decreased responsiveness to the phase shifting, to behavioral and pharmacological challenges, and decreasing ability to adapt to new light/dark schedule [219–224]. Those changes could be caused by alterations in morphology and gene expression within neuronal circuits of the aged SCN; and (4) age-related decline in SCN efferent and afferent signaling is also well documented [225–232].

Inflammation–neurogenesis–aging and sleep–wake disruption

The mechanism(s) underlying the decline or deterioration of neurogenic processes with aging is not well understood and could be induced by a combination of factors. We propose that chronic inflammatory signaling underlies the decline in neurogenic processes with aging (Figure 5). The following evidence is consistent with this hypothesis.

i) Both animal and human studies indicate that the brains from older subjects are in a native heightened inflammatory state, even in the absence of overt diseases [43, 44]. This may get further aggravated by comorbid conditions, including arthritis, diabetes mellitus, and obesity [141]. Neuroinflammation and inflammation-induced cytokine products, for example, interferon-γ, interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, nitric oxide, or decreased levels of neurotrophic factors are detrimental to endogenous adult neurogenesis and gliogenesis [233–237].

ii) Consistent with the whole brain findings, in a preliminary study, we found that sleep-regulatory MnPO and VLPO regions in rats exhibit an elevated hypothalamic inflammatory microenvironment as evident from increases in the levels of TNFα and IL-6 proteins and corresponding RNAs [238]. Our preliminary findings also suggest: (1) that neurons in these regions exhibit an accumulation of lipofuscin, a marker of cellular aging and (2) that increasing inflammation in the MnPO by chronic low-dose lipopolysaccharide infusion, which likely causes disruption of hypothalamic neurogenesis, induces aging-like sleep–wake disruption in young animals [238].

iii) Sleep disruption and high-fat diet can cause systemic and brain inflammations, even in the absence of infection and injury. Acute and chronic sleep deprivation or restriction, also produce a pro-inflammatory response in the brain, including the hypothalamus and peripheral tissues, and also decreases cell proliferation [239–254]. Increased levels

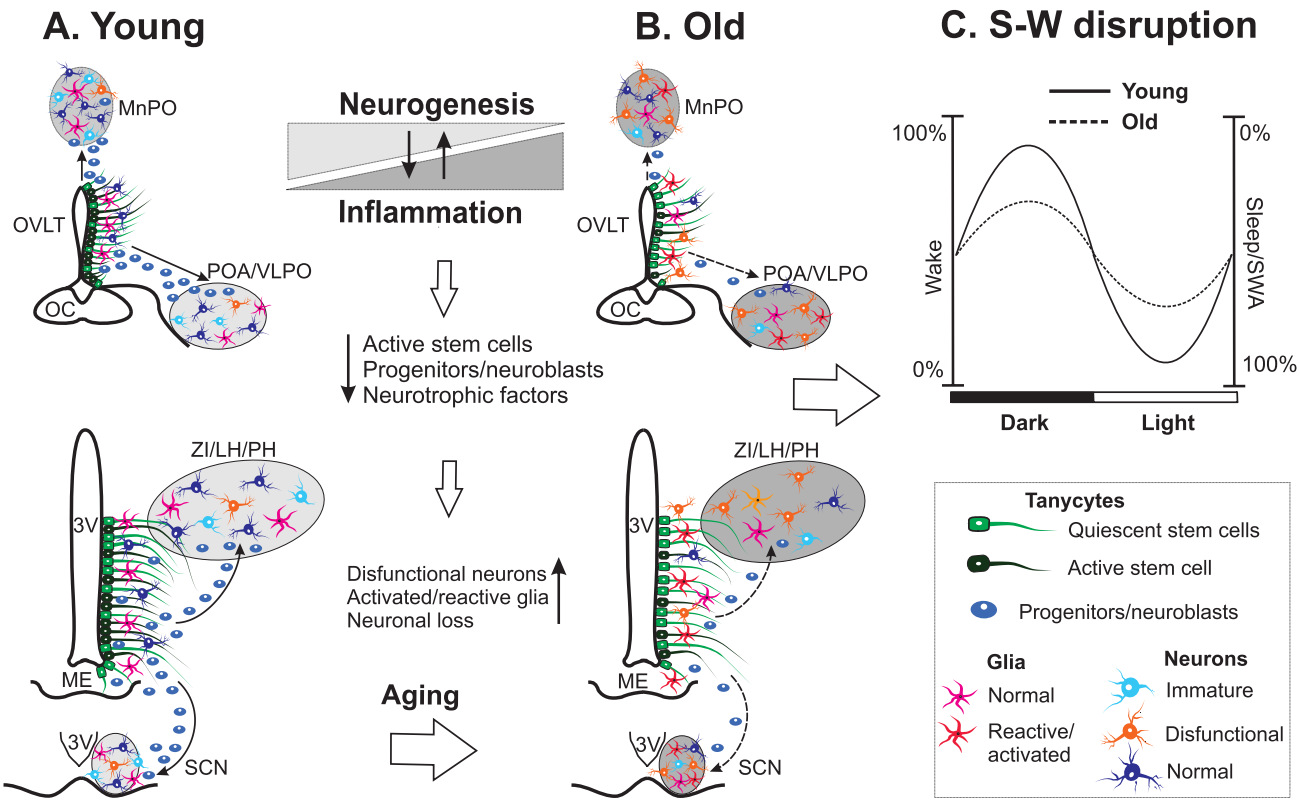

Figure 5. (A). Schematic representation of the hypothalamic neurogenic process in young subjects and the hypothesized antagonistic interactions between inflammation and neurogenesis that contribute to aging of sleep/wake and circadian systems. (B). Aging is marked by decreased neurogenesis (or fewer newborn neurons in sleep–wake regulatory structures and SCN) and increased inflammatory hypothalamic microenvironment (or increased number activated or reactive glia). These changes lead to the aging of hypothalamic sleep–wake and circadian systems, as marked by the loss of functional neurons or an increase in the number of dysfunctional neurons. (C). Old subjects with chronically suppressed neurogenesis exhibit increased sleep fragmentation by waking intrusions, reduced amount of sleep, and slow-wave activity in nonREM sleep during the rest-phase. The active-phase is marked by waking disruption by increased sleep intrusions. They also exhibit a declined homeostatic response to sleep loss.

of cytokines (e.g. IL-1β, TNFα, and IL6) may be involved in this process. A chronic high-fat diet triggers oxidative stress and several pro-inflammatory cascades, including the TNFα and IKKβ/NF-κB cascades in the hypothalamus [255–257], depletion of hypothalamic NSCs and neurogenic impairment [78, 258]. Sleep disruption and high-fat diet, when applied together, produce an additive effect on hypothalamic inflammation via microglial activation [259]. Obese subjects exhibit sleep–wake profiles resembling to that observed in aged animals [260, 261]. Sleep disruption by itself causes disturbance of metabolic regulations and weight gain [262–265]. Thus, metabolic and sleep-regulating neuronal circuitries influence each other and are adversely affected by chronic inflammation.

iv) The 3V wall regions are highly susceptible to inflammatory damage, and this has been shown to underlie a form of hypertension [266].

v) Treatments that decrease brain inflammation, for example, calorie restriction/fasting and exercise, increase neurogenesis and improve sleep–wake architecture, including EEG delta power as well as cognitive performance in adulthood and aging [44, 267–274].

In brief, growing evidence support, (1) that chronic inflammation adversely affects neurogenesis including hypothalamic neurogenesis; (2) that the brains from older subjects are in a heightened inflammatory state and exhibit a decline in neurogenic processes including in the hypothalamus; (3) that chronic suppression of hypothalamic neurogenic process produces sleep–wake disruption similar to that observed in the aging; (4) that manipulations that reduce inflammation and/or increase neurogenesis improve aging-associated sleep–wake disturbance. However, the causal interactions between inflammation–hypothalamic neurogenesis and sleep–wake changes in aging remain poorly understood.

Neurogenesis: a tool for therapeutic intervention of hypothalamic dysfunctions including sleep–wake dysfunction in aging

Several studies have explored the therapeutic potential of stimulating neurogenic processes by activating endogenous NSCs by intrinsic and extrinsic molecules, by implanting exogenous NSCs or targeting cell differentiation. Exposure to low-frequency (50 Hz) electromagnetic fields, physical activity, or rewarding experience has also been used as nonpharmacological approaches for stimulating neurogenesis [275]. In general, stimulation of the neurogenic process using pharmacological or nonpharmacological strategies has been shown to have beneficial effects on cognition, obesity, stroke, and brain trauma [7, 91, 276–278]. Behavioral manipulations, for example, exercise or low-calorie diet that is known to stimulate neurogenesis, have been shown to alleviate sleep disruption in aging [267, 273, 274].

The therapeutic potential of stimulating hypothalamic neurogenesis for treating aging-associated sleep–wake and circadian pathologies at the moment remains largely obscure. However, by targeting neurogenesis and/or differentiation of glial cells into neurons or neuroblasts, it seems possible to replace or replenish dysfunctional or lost cells or remodel hypothalamic neuronal circuitries. Some of these approaches may include the application of various growth factors, anti-inflammatory drugs or behavioral treatments (exercise, dietary interventions, controlling sleep, and circadian rhythms), application of senolytic agents, trophic neurotransmitter precursors or neuroendocrines, transcription factors, micro RNA (miRNA), a cocktail of small molecules, or combining pharmacological and behavioral approaches [108, 279, 280]. The transcription factors (NeuroD1, ASCL1, and Lmx1a) and the miRNA have been used to help cells differentiate into dopamine neurons in an in vivo animal model [281]. In recent years, astrocyte-derived neurogenesis has gained interest, given that neural progenitor cells are limited to a few neurogenic zones. The astrocyte pool is significantly large, even in the aged brain, and could be a better target for therapeutic remodeling or restoration of the hypothalamic functions, including generation of new sleep-active GABAergic or galaninergic neurons to alleviate sleep disturbance or hypocretin or histamine neurons to reduce wake-disruption in aging. Many neurons in aged brains have altered gene expression because of epigenetic changes. Thus epigenetic factors are also being explored as therapeutic targets.

Currently, the translational potential of increasing the production of neurons to alleviate hypothalamic dysfunction remains in its infancy. It is plausible that increasing the production of new neurons may have limited benefit considering the presence of old dysfunctional or senescent cells. Such situations would warrant a combination of approaches, for example, elimination of senescent neurons by stimulating apoptosis, followed by replacing those neurons by new cells via stimulating neurogenesis. Functional improvements after removal of post-mitotic senescent cells has been documented in peripheral tissue using senolitic drugs that “attacked” cells with aging markers [282–284]. In the aging brain, neurons may express aging markers and may be affected by senolitic drugs. However, such interactions in the CNS remains elusive. Furthermore, as regards remodeling of “aged” neuronal circuitry, it remains to be seen if neurogenesis replaces sleep- and wake-active neurons with longer projections.

Conclusion

There is mounting evidence that new cells are constitutively born in adult mammalian hypothalamus and that these newborn cells differentiate into neurons. New neurons integrate into pre-existing neural circuitries and support hypothalamic functions, including regulation of energy homeostasis, body weight, and acquired heat tolerance. Evidence also suggests that hypothalamic neurogenesis affects sleep–wake function and that POAH sleep–wake and circadian systems are subject to similar neurogenic processes. This review provided an update on the postnatal adult hypothalamic neurogenic processes and their contributions to hypothalamic functions. Growing evidence supports a hypothesis that a decline in the hypothalamic neurogenic process, caused by chronic neuroinflammatory signaling is a contributor to sleep–wake and other hypothalamic dysfunctions in aging. Thus strategies aimed at increasing neurogenesis may slow down or alleviate aging-associated sleep–wake disturbance or other aging-related hypothalamic dysfunctions. In recent years, while our knowledge of the hypothalamic neurogenic mechanism has expanded greatly, there remain many unanswered questions about the phenotype and functionality of newborn neurons in the hypothalamic sleep–wake circuitry, including (1) what are the phenotypes of the cells that are affected by neurogenesis; (2) to what extent aging-related sleep–wake and circadian deficits are causally related to the progression of changes in hypothalamic NSCs and NPCs in aging; (3) whether increasing hypothalamic neurogenesis could improve aging-associated sleep–wake and other hypothalamic dysfunctions; (4) and to what extent the interactions between inflammation and hypothalamic neurogenesis affects sleep–wake and circadian disorders in aging. Addressing those questions may provide mechanistic insights into aging-associated sleep–wake and other hypothalamic dysfunctions.

Funding

This work was supported by the US Department of Veterans Affairs, Merit Awards, BX000936 (Alam) and BX003520 (McGinty).

Disclosure statement

Financial disclosure: none.

Nonfinancial disclosure: none.

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