# Role of Sleep in Neurogenesis

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**Abstract**

Genesis of the neurons in the brain is a cardinal process for brain development from the embryonic stage to throughout the human lifespan. Two major zones of the brain that are involved in neurogenesis are the subventricular (forebrain) and sub-granular zone (dentate granule cell layer). Additionally, the Hypothalamus is another region, that, acts as a smart control synchronizing center of the human body and a source of neural progenitor cells. This book chapter describes and illustrates the elements of neurogenesis, neurogenesis on mental health, hippocampal neurogenesis, and hypothalamic neurogenesis.

**Keywords**

Neurogenesis · Sleep · Stress · Neuropeptides · Hippocampus · Hypothalamus

## Insights into Neurogenesis: From Physiology to Pathophysiology

The creation of a new neuron in the brain is called Neurogenesis and it is essential for the development of an embryo, and it also persists in some parts of the brain long after birth (Catlow et al. 2016). The immutable edifice of the adult brain, once thought impervious to change, has undergone a transformative redefinition with the revelation of adult neurogenesis. This intricate process involves the emergence of nascent neurons from the chrysalis of stem cells, intricately weaving themselves into the existing circuits of the brain (Zhao and Moore 2018). Once confined to the realm of embryonic development, adult neurogenesis now bathes the mature mind in a luminescence of perpetual renewal, with a particular effervescence observed in the lush landscapes of the hippocampus. This groundbreaking discovery challenges and rewrites the script of traditional notions surrounding brain plasticity, introducing a paradigm where the adult brain is a dynamic and adaptable organ finely tuned to the symphony of experiences. The metaphorical emergence of new neurons, akin to saplings basking under a nurturing sun, encompasses the intricate ballet of sprouting, migrating, and integrating into the complex network of existing neural pathways (Zamproni et al. 2021).

As scientific exploration delves deeper into the caverns of neurogenesis, the luminescence emanating from this phenomenon illuminates potential pathways for understanding and addressing various facets of mental health, aging, and neurological disorders (Ming and Song 2011). The once-static landscape of the adult brain

now shimmers with the possibility of therapeutic interventions, whispering promises of minds not merely enduring, but flourishing with the echo of renewal. In this reimagined conception of the brain, where neurons act as sculptors and experiences serve as the chisels, the human mind emerges not as a static tableau but as a canvas perpetually primed for the masterpiece of adaptation (Zaidel 2014). The narrative of the brain transforms from a fixed entity to a dynamic and ever-evolving tapestry, inviting a deeper appreciation for the resilience and adaptability inherent in the human cognitive experience.

## The Captivating Dance of Neurogenesis: Unveiling the Physiology of Brain Renewal

The human brain, once thought to be a static organ frozen in time, now pulsates with the dynamic rhythm of neurogenesis. The fascinating process of the brain's exceptional ability to adapt and renew itself—the creation of new neurons from specialized neural stem cells—unlocks the mysteries of brain plasticity.

### The Stage for Creation: The Neurogenic Niche

The journey of a new neuron begins in a specialized haven within the brain called the neurogenic niche. Imagine this niche as a lush, verdant garden, where neural stem cells, like tiny gardeners, tend to the delicate dance of creation. Here, amid a symphony of molecular signals and genetic instructions, these special cells undergo a series of transformations (Peretto and Bonfanti 2015).

### From Seed to Sprout: The Birth and Migration of New Neurons

Like seeds bursting forth in spring, neural stem cells divide, giving rise to immature neurons. These fledgling cells, guided by a complex choreography of signals, embark on a journey of migration. They navigate the intricate pathways of the brain, seeking their place within existing neural networks (Urbán and Guillemot 2014).

### Building Bridges and Forging Connections: Integration and Maturation

Once they reach their destination, the new neurons begin the intricate task of integration. They sprout delicate tendrils, forming synapses, the bridges of communication that connect them to their neighbors. Neurotrophic factors, akin to growth hormones, nourish and guide these developing neurons, nurturing them into mature members of the brain's intricate circuitry (Doidge, 2007).

## The Orchestra of Influences: Modulating the Dance of Neurogenesis

The exquisite dance of neurogenesis is not a solitary performance. A multitude of factors, like the rhythm of exercise, the vibrant tapestry of enriched environments, and even the delicate interplay of neurotransmitters, can influence and modulate this process (Grońska-Pęski et al. 2021). Understanding these influences holds immense promise for the future of brain health.

### A Symphony of Renewal: Implications for Brain Health and Beyond

As we delve deeper into the physiology of neurogenesis, we open the door to the possibility of therapeutic approaches for a variety of illnesses, from neurological abnormalities to the inevitable aging-related cognitive loss. By understanding how to nurture the birth and integration of new neurons, we may 1 day be able to help brains stay resilient and adaptable throughout life (Sailor et al. 2006). In essence, the physiology of neurogenesis is not merely a biological process, but a testament to the brain's remarkable capacity for self-renewal. It is a story of resilience, of adaptation, and of the enduring potential for the human mind to create, learn, and grow, even in the face of time's relentless march (Gu et al. 2020).

## Sleep-Wake Cycle Modulation

Circadian rhythms regulate the rhythmic activities of sleeping and waking. Wakefulness is a condition in which perceptual-sensory and voluntary motor activity are fully manifested. Sleep is distinguished by quick reversibility, decreased motor activity, responsiveness, and metabolism, and is separated into two different, cyclically repeated stages: The two types of sleep are non-REM and rapid eye movement (REMS) (Schwartz and Roth 2008). Sleep is essential for learning, memory, neurogenesis, oxidative stress reversal, immunological regulation, and neurogenesis, according to research. The regulation of sleep-wake cycles can be explained by the two-process model, in which the output of a circadian pacemaker is linked to one process, which represents homeostatic sleep drive. When the two processes are integrated, they establish the beginning and conclusion of the sleep phase: sleep is initiated when homeostasis rises over a particular threshold, and awakening takes place when it falls below a particular threshold (Abhilash and Shafer 2023). It is assumed that the two thresholds are oscillated by the circadian rhythm daily.

An internal circadian clock found in the anterior hypothalamic suprachiasmatic nucleus (SCN) controls the pattern of sleep and wakefulness. The SCN neurons function as functional pacemakers because they are circadian oscillators. According to Welsh et al. (2009), these oscillations are regulated by an intrinsic cellular rhythmicity that lasts for a full day, even in the absence of external stimuli like light, dietary patterns, and social surroundings.

### Action of Neuronal Assemblies in Sleep

Despite the presence of an SCN biological clock, the global coordination of the NREMS seems to be the product of an emergent characteristic of locally coupled processes in neural networks. Cortical columns or neuronal assemblies are terms used to describe anatomically defined neural networks. According to Fernandes et al. (2015), neural assemblies are believed to represent the fundamental building blocks of the brain's processing during alertness, oscillating between functional states like wakefulness and sleep. While most neural assemblies are in a wake-like state while they are awake, most are in a sleep-like state when they are sleeping. In contrast, neuronal assemblies in a wake-like state can happen during the whole alertness period, whereas neuronal assemblies in a sleep-like state can happen during the whole sleep phase. The brain assembly paradigm states that electrical and hormonal interactions between assemblies are what generate synchronization (Krueger et al. 2008).

According to this model, states evolve throughout time as a result of threshold-based transitions, interactions with other assemblies, and the distinctive behavior of individual networks. Neural assemblies are quickly forced into sleep after achieving a sleep-like state within individual neural networks (Nowak et al. 2017). The degree of this response is correlated with each neural assembly's connectivity. Concurrently, neuronal assemblies react more quickly to signals from the circadian clock that indicate the body should be sleeping, which induces sleep. According to computer silico experiments, overstimulated neural assemblies will eventually enter a sleep-like condition (Deolindo et al. 2018). This will cause neighboring neuronal assemblies to follow suit, ultimately leading to whole-animal slumber. Thus, our model accounts for both the global sleep state's genesis and the expanding characteristics of specific networks.

## Sleep Deprivation Investigations

### Degrees of Insufficient Sleep

Sleep deprivation causes psychological and physiological alterations, affecting a variety of cognitive areas including attention and working memory. In order to evaluate the effects of sleep deprivation on neurogenesis, a number of studies used experimental paradigms to disturb rodent sleep for varied lengths of time (Alhola and Polo-Kantola 2007). Wakefulness is pushed in situations of whole or partial sleep deprivation using a number of approaches, including gentle handling, forced mobility in a gently spinning wheel, and putting rats on water-covered platforms. The diversity of extra groups or experimental conditions accounted for effects unassociated with sleep deprivation (like exercise or stress) (Alhola and Polo-Kantola 2007).

## Potential Mechanism

It is yet unknown what the underlying mechanisms are that cause sleep deprivation to negatively affect different stages of adult neurogenesis. Stress and related hormones, particularly glucocorticoids, have been suggested to act as an independent mediator of these effects (Meerlo et al. 2009). For instance, utilizing the small-platform technique, rats who got too little sleep had significantly higher corticosterone levels while experiencing slower cell proliferation. The decrease in dentate gyrus cell growth was completely eliminated in adrenalectomized rats, which produce low levels of corticosterone (Guzmán-Marín et al. 2003).

These results are controversial because they go against previous studies that found low levels of corticosterone to be necessary to maintain the anti-neurogenic effects of sleep deprivation on the hippocampus. Moreover, low corticosterone levels promote cell proliferation while high corticosterone levels limit cell development (Egeland et al. 2017). Adult neurogenesis is influenced by a number of molecular components, including cytokines, hormones, neurotransmitters, and trophic factors. Many of these parameters are influenced by sleep deprivation, suggesting a relationship between inadequate sleep and decreased hippocampus neurogenesis (Fig. 1) (Alkadhi et al. 2013).

Serotonin, for example, stimulates hippocampus neurogenesis via the serotonin-1A receptor. Serotonergic action is generally reduced during sleep, which may explain why sleep deprivation has a suppressive effect on neurogenesis. However, it's possible that this decreased serotonergic activity during sleep (Negro et al. 2020) is necessary for optimal serotonergic activity during wakefulness and, thus, could be

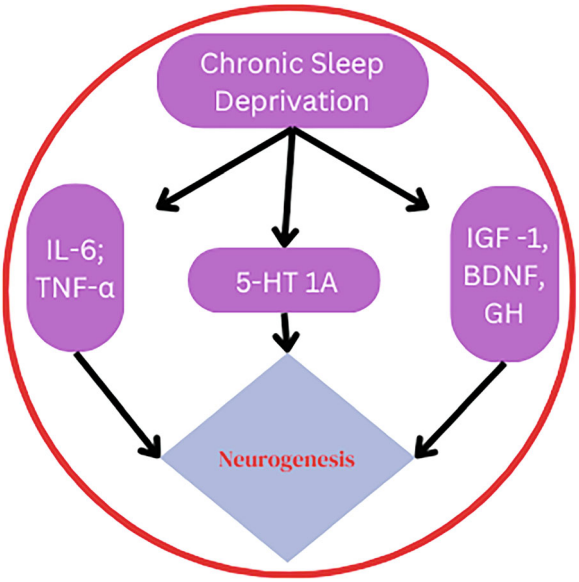


**Fig. 1** A potential mechanism of neurogenesis

essential for the impacts of waking experiences on neurogenesis. In rats, serotonin-1A receptor system sensitivity is decreased by chronic sleep deprivation but not by short-term sleep deprivation. Similar to this, a number of studies show that while protracted sleep deprivation decreases hippocampal cell proliferation, acute sleep deprivation has no influence on it (Novati et al. 2008).

## Sleep-Induced Neurogenesis in Hippocampus: An Independent Modulator for the Hippocampal Neuronal Network

Sleep has a pivotal role in maintaining the quality of life for the life span. It is associated with various health benefits and maintaining good health including mental health. Nerve cell longevity including increased cell proliferation and cell survival is linked with sleep. On the contrary, sleeplessness including sleep deprivation, and sleep diminution is linked with the impediment of neuron proliferation and survival (Mueller et al. 2015). Sleep has been demonstrated to trigger neurogenesis in the subcortical area, where the neural stem and progenitor cells give rise to new neurons from the early to adult stages of brain development (Malykhin et al. 2010). Many extrinsic and intrinsic variables that impact the maturation, specialization, and integration of the nerve population in the hippocampal dentate gyrus influence the hippocampal neurogenesis (Toda et al. 2019). In both adult humans and rodents, a reciprocal association has been shown between hippocampus neurogenesis and adequate sleep. In rat hippocampus dentate gyrus neurogenesis, new proliferating neurons are present within the sub-granular zone (SGZ) where it gets mature and transmutes into glutamatergic neurons (Cameron and McKay 2001; Jiang et al. 2023). According to Navarro-Sanchis et al. (2017), adult humans share the same neurogenesis pathway, and clinical data indicates that mature neurons migrate into the striatum while overlapping neurogenic proliferation occurs in the hippocampus SGZ. The typical physiological adaptations that include learning and memory, cognitive function, and emotion regulation are therefore influenced by the integration of mature neurons with other subcortical locations (Tyng et al. 2017).

## Mechanism of Neurogenesis in the Hippocampus and DG

The hippocampal dentate gyrus is a specific subcortical area for neurogenesis. In the SGZ, a thin layer situated between the granular cell layer and the hilus of the hippocampus formation, progenitor cells are actively converted into neurons, astrocytes, or oligodendrocytes (Kempermann et al. 2015). These progenitor cells are transiently active in SGZ and proliferate to produce clusters of new cells in the neurogenic area (Llorente et al. 2022). According to estimates, the dentate gyrus produces 5000–9000 new cells every day. Rats using a variety of experimental procedures have shown that hippocampus neurogenesis is up- and down-regulated during the sleep-wake cycle (Van der Borght et al. 2009). Human growth hormone is

one substance that shows sleep-facilitated release, and in certain species, lack of sleep has a detrimental effect on neurogenesis. The formation of spines and functional synapses in newly formed neurons is stimulated by neuron connections from cortical and subcortical gateways (Leproult and Van Cauter 2009). The inhibitory neurotransmitter gamma amino butyric acid (GABA) depolarizes immature neurons, and this synaptic input is crucial for differentiation in neuronal proliferation and differentiation.

## Hypothalamic Neurogenesis

The hypothalamus is a deep and small structure that covers 1% volume of the brain and is positioned under the thalamus. It is systematically divided into multiple sub-regions, including some distinct nuclei and it participates in many central regulations such as energy equilibrium, alertness, sleep, osmoregulation, hormonal balance, temperature, and sexual behaviors (Stachenfeld 2008). Recent studies proved that the hypothalamic progenitor/stem cell is principally involved in the adult hypothalamic neurogenesis fabrication of neural circuits. Also, the neuropeptides secreted in the hypothalamus during the new neuron generation facilitate embryonic and adult brain development (Fig. 2) (Plakkot et al. 2023).

Neoteric neuro-research evidence illustrates that newly generated hypothalamic neurons pointedly play a role in the homeostasis of our body, specifically, controlling body mass, metabolism, energy steadiness as well as social behaviors (Plakkot et al. 2023).

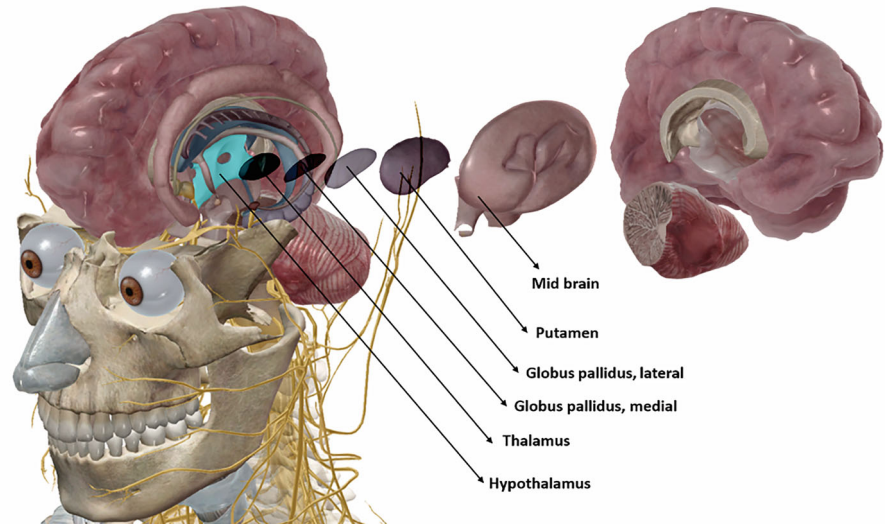


**Fig. 2** Position of the thalamus, the hypothalamus of the brain

## Hypothalamic Neuropeptides, Neurogenesis, and Regulation

Numerous peptides, including those involved in sexual control, are secreted by the neuron population in several areas of the hypothalamus (Table 1). Important neuronal function regulators include brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). A study found that BDNF infusion in adult rat lateral ventricles stimulates the development of new neurons in the hypothalamus (Bathina and Das 2015). Analogous research demonstrated that the formation of neural progenitor and neural stem cells in the adult rodent brain is regulated by the proteins BDNF, transforming growth factor α, VEGF (vascular endothelial growth factor), neurotrophic factor (CNTF), and FGF2 (Bath and Lee 2010) (Table 2).

In the hypothalamic neurogenic cascades, Evans et al. first, reported the hypothalamic immature mitotic neurons and the hypothalamic neurogenic niche was observed in the lining of the ventral portion (third ventricle). The adult age third ventricle surface becomes a neurogenesis source and a high number of immature neuron migrations are spotted in the niche region of hypothalamic neurogenesis. These hypothalamus migrating neurons modulate the brain plasticity and web the brain's functional circuits (Hussain et al. 2024).

**Table 1** Medication and antidepressant medications that have an impact on neurogenesis

| Medication | Treatment schedule | Results |
|---|---|---|
| Hypnotic drug: Zolpidem | Twice a day; 2 days for acute experiment and 21 days for chronic experiments | Acute tests showed that the hilus was larger than the SGZ and that cell proliferation was reduced in both young people (10–15%) and the elderly (30–40%). Young mice's SGZ cell survival decreased slightly as a result of the long-term experiment, while it increased slightly in older mice (Methippara et al. 2010) |
| Psychostimulant drugs: Modafinil or Caffeine | Given to rats which were completely sleep deprived for 2 days | Barred waning in neuronal proliferation and differentiation later sleep deficit (Bishir et al. 2020) |
| Medications that treat depression Tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), and monoamine oxidase inhibitors (MAOI) | Electroconvulsive seizures have been investigated on adult male Sprague-Dawley (SD) rats | While several kinds of antidepressants enhance proliferating cells by 20–40%, chronic treatment for electroconvulsive seizures boosts cell proliferation by 50% (Malberg et al. 2000) |
| Haloperidol is a non-antidepressant psychotropic medication | Adult male *SD* rats test | The long-term use of the medications did not substantially alter the quantity of BrdU-positive cells (Gilbert et al. 2005) |

**Table 2** Neuropeptide synthesized in different hypothalamus parts and its function

| Hypothalamus regions/neurons | Neuropeptide | Function |
|---|---|---|
| The arcuate nucleus of the hypothalamus | NPY[a], AgRP, and anorexigenic peptides, POMC (Huang et al. 2021) | Food intake |
| Ventromedial nucleus, Medio basal (MB) hypothalamus | Substance P, enkephalins, and NPY | Sexual behaviors and analgesia |
| The periventricular part and supraoptic nuclei | producing corticotrophin-releasing hormone (CRH), TRH, oxytocin, and vasopressin (Ferguson et al. 2008) | Blood circulation |
| Lateral hypothalamic area (LHA) | Orexin, Melanin-concentrating hormone (MCH) (Skrapits et al. 2015) | Regulation of sleep/wakefulness |
| Hypothalamic $Crh^{+}$ neurons | Galanin | Primarily responsible for regulating the body's reactions to stress, including eating (Corradi et al. 2022) |

[a]*NPY* Neuropeptide Y, *AgRP* Orexigenic agouti-related peptide, *POMC* Proopiomelanocortin

## Hypothalamic Neurogenesis and Sleep

The hypothalamus plays a crucial role in mammals' most important physiological function "sleep" through the neuropeptide-producing neurons. Orexin neurons produce the orexin which is responsible for sleep and lack of orexin/hypocretin-producing neurons (orexin neurons) cause narcolepsy (sleep disorder) (Singh and Biswas 2023). Orexin A peptide is composed of 33 amino acid residues (Fig. 3a), and orexin B peptide (Fig. 3b) is composed of 28 amino acids. Orexin neurons/receptor inhibition (Fig. 3c) by light or antagonist during the night causes time-of-day-dependent NREM sleep initiation. Another lateral hypothalamic area (LHA) neuron is an MCH (Melanin-concentrating hormone) producing neuron that is also linked to sleep/wakefulness management (Konadhode et al. 2015).

To be more precise, these neurons that produce MCH are dormant during awake and activate during sleep (España and Scammell 2011). The anterior hypothalamic rostral γ-aminobutyric acid (GABA)-ergic cells are less active during non-REM sleep and more active during REM sleep or wakefulness (Fig. 4) (Siegel, 2004).

## Hypothalamic Neurogenesis in Stress

Acute and chronic stress is one of the forceful environmental factors that modify brain function, neuron generation (neurogenesis), and brain structure. In

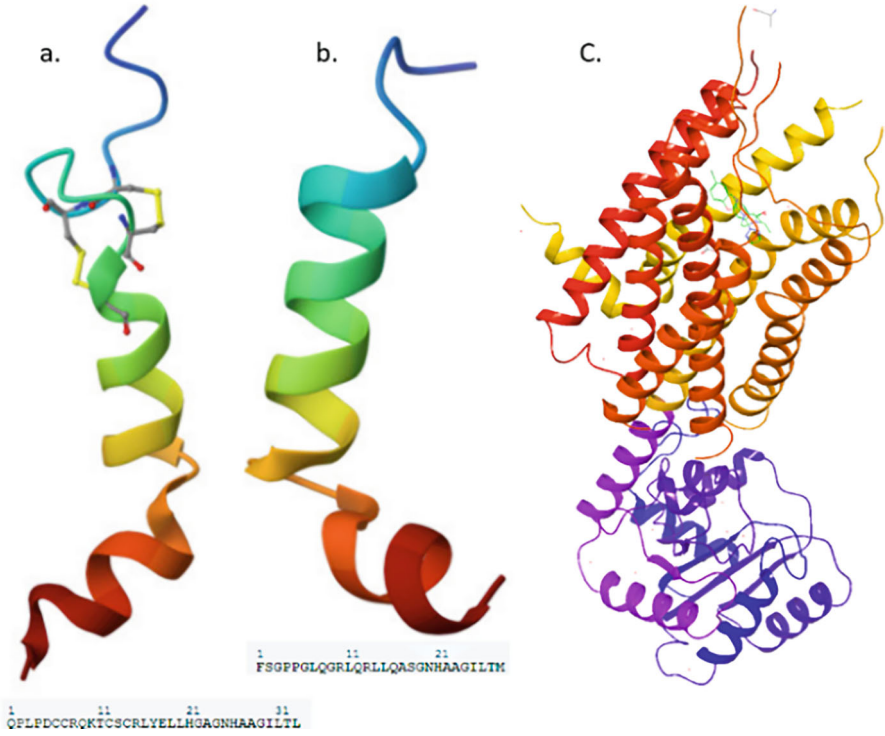


**Fig. 3** (**a**) Secondary structure of Orexin A peptide with sequence; (**b**) secondary structure of Orexin B peptide with sequence; (**c**) secondary structure of Orexin receptor

particular, it lessens the production of fresh neural or precursor neurons in the human, sheep, and mouse hypothalamic neurogenic niche of the brain (McEwen et al. 2016). Early life stress (ELS) is a factor that has a direct correlation to changes in the population of new neurons in the hypothalamus later in life. In their study of chronic ELS, Pascal Bielefeld et al. (2021) found that mice's hypothalamus area showed suppression of neurogenesis. Reduced levels of β-tanycytes are observed in the hypothalamus, while proliferating cells are found in the parenchymal portions of the third ventricle (Bielefeld et al. 2021). Also in ME, a strong drop in Nestin-GFP+/Sox2+ cell proliferation. These results conclude that the ELS produced long-term effects in the ventral parenchymal areas of cell proliferation.

Alonso et al. 2023 reported two factors (corticotrophin-releasing factor (CRF) and vasopressin (AVP)) crucially involved in controlling the stress response through synergizing the CRF1 and V1b receptors (Fig. 5a, b). The blockade or antagonizing of these two receptors will be the specific target for the patient suffering from stress (Beurel and Nemeroff 2014).

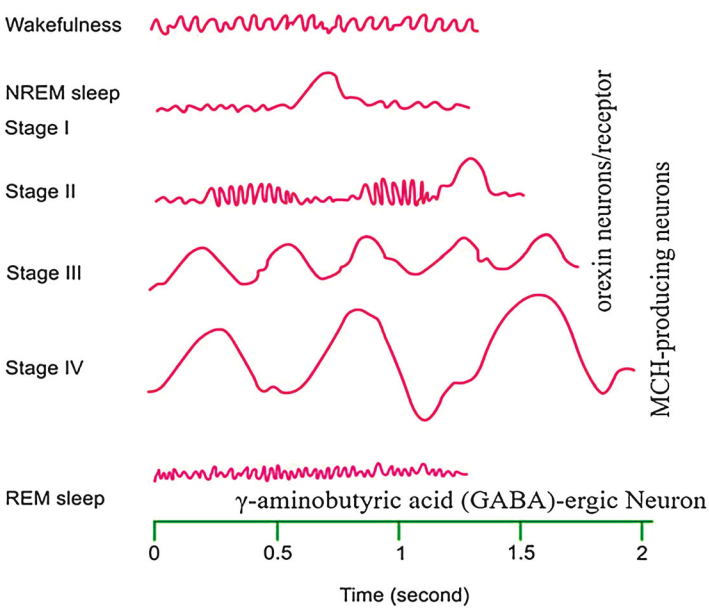


**Fig. 4** Hypothalamic neurons involved in the different stages of sleep stages. *NREM-Non–rapid eye movement, REM- Rapid eye movement

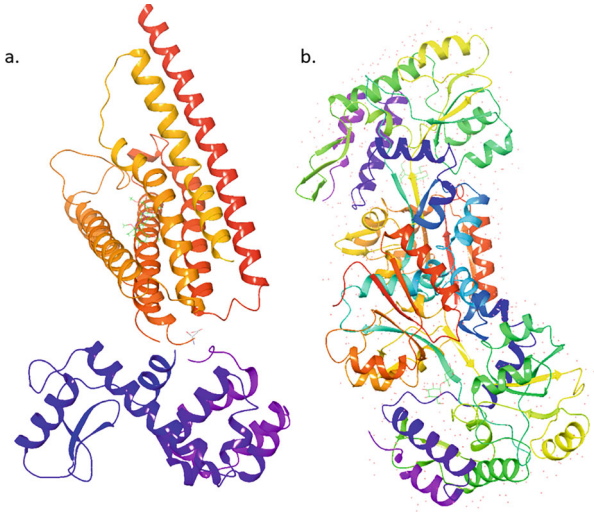


**Fig. 5** (**a**) Secondary structure of corticotropin-releasing hormone receptor 1; (**b**) Secondary structure of Vasopressin V1b Receptor

## Conclusions and Perspectives

Research reports of the last two decades concluded that the hypothalamic neurogenesis and organization of neural networks are modified periodically based on different stimuli such as sleep and stress. In this context, various hypothalamic neuropeptides and receptors are involved in the management of homeostasis of the human body, importantly, sleep and stress. In this AI era, designing and developing binding site pharmacophoric group-based inhibitors for orexin and MCH-producing receptors will be the potent treatment of various sleep disorders. Similarly, CFR and V1b receptor-based drug design will increase the neurogenesis in the hypothalamus leading to the modification of the neural circuit of stress management.

Most of our understanding of adult neurogenesis derives from studies conducted in labs using animal models. Despite the technical difficulties of measuring new neurons in live subjects, adult neurogenesis has been proven in humans. Taking into consideration all the animal model studies that are discussed in this article, there are a number of problematic and inconsistent results. Given that each species' unique characteristics, both genetic and individual, may influence neurogenesis and sleep regulation, results achieved with certain species and under particular experimental settings cannot be repeated in other species. Thus, animal model studies of neurogenesis must be expanded to obtain more strong conclusions on the underlying processes of sleep's modulatory effects on neurogenesis.

More investigation is required to determine the anti-neurogenic effects of sleep deprivation on various hippocampal regions, given the evidence of functional differentiation of diverse hippocampus subfields. In order to fully comprehend the functional implications of neurogenesis, it is also critical to look into how sleep deprivation affects neurogenesis in other parts of the brain. The effects found in the basal rate of cell development in REMS vs. NREM deprivation must also be replicated to establish more compelling results. It is imperative to comprehend the neuro-genic connection among sleep, learning, hippocampus-dependent memory, and mood disorders. Additionally, human clinical trials are necessary to explore the functional consequences of increased neurogenesis resulting from antidepressant treatment. Determining whether neurogenesis in MDD patients is linked to behavioral and molecular responses to antidepressant treatments is crucial (Boas et al., 2019; Duric and Ronald, 2013; Park, 2019). Lastly, since adult human neurogenesis may have unidentified side effects that have an impact on other cognitive and affective processes, the negative hypnotic effects of neurogenesis need to be understood and assessed in humans.

The idea that neuronal neurogenesis stops at puberty seems to be fading in light of the adult brain's flexibility and ability to change structurally in response to experience. While adult neurogenesis appears to be limited or nonexistent in other areas of the central nervous system, it is now thought to continue actively throughout life in the SVZ and SGZ of the hippocampus dentate gyrus. In non-neurogenic tissues, neurogenesis can occur after pathogenic stimulation, including brain injury. Although research on adult human neurogenesis is still in its early stages, data

from animal models suggests that hippocampus plasticity may be influenced by newly formed neurons in adulthood.

Adult neurogenesis in rats reduced by the chronic sleep disruption. Conversely, brief sleep deprivation seems to promote cell growth and survival. Prolonged sleep deprivation can damage the integrity of the hippocampal formation and ultimately cause cognitive impairment, which can exacerbate mood disorders and other medical conditions. Whether adult neurogenesis contributes to this kind of regulation is yet unknown. Therefore, addressing adult neurogenesis during sleep disorders could be a promising strategy to reverse the possible negative effects of chronic sleep disorders on emotional and cognitive functioning.

## Cross-References

- ▶ An Understanding of Different Mechanisms Leading to Neurodegenerative Diseases
- ▶ Mechanisms of Neuronal Apoptosis and Excitotoxicity
- ▶ Mitochondrial Transplantation as a Newer Therapeutic Approach for Neurodegenerative Diseases
- ▶ Neuroinflammation & Microglial Activation in Schizophrenia: An Overview
- ▶ Nutrition and Brain Neurotransmitters
- ▶ Three Neurodegenerative Diseases: A Single Hope

**Competing Interests** The authors declare that they have no known competing interests that could have appeared to influence the work reported in this paper.

**Ethics Approval** No animals were used in this work.

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