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New neurons in the adult brain: The role of sleep and consequences of sleep loss

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Abstract

Research over the last few decades has firmly established that new neurons are generated in selected areas of the adult mammalian brain, particularly the dentate gyrus of the hippocampal formation and the subventricular zone of the lateral ventricles. The function of adult-born neurons is still a matter of debate. In the case of the hippocampus, integration of new cells in to the existing neuronal circuitry may be involved in memory processes and the regulation of emotionality. In recent years, various studies have examined how the production of new cells and their development into neurons is affected by sleep and sleep loss. While disruption of sleep for a period shorter than one day appears to have little effect on the basal rate of cell proliferation, prolonged restriction or disruption of sleep may have cumulative effects leading to a major decrease in hippocampal cell proliferation, cell survival and neurogenesis. Importantly, while short sleep deprivation may not affect the basal rate of cell proliferation, one study in rats shows that even mild sleep restriction may interfere with the increase in neurogenesis that normally occurs with hippocampus-dependent learning. Since sleep deprivation also disturbs memory formation, these data suggest that promoting survival, maturation and integration of new cells may be an unexplored mechanism by which sleep supports learning and memory processes. Most methods of sleep deprivation that have been employed affect both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Available data favor the hypothesis that decreases in cell proliferation are related to a reduction in REM sleep, whereas decreases in the number of cells that subsequently develop into adult neurons may be related to reductions in both NREM and REM sleep. The mechanisms by which sleep loss affects different aspects of adult neurogenesis are unknown. It has been proposed that adverse effects of sleep disruption may be mediated by stress and glucocorticoids. However, a number of studies clearly show that prolonged sleep loss can inhibit hippocampal neurogenesis independent of adrenal stress hormones. In conclusion, while modest sleep restriction may interfere with the enhancement of neurogenesis associated with learning processes, prolonged sleep disruption may even affect the basal rates of cell proliferation and neurogenesis. These effects of sleep loss may endanger hippocampal integrity, thereby leading to cognitive dysfunction and contributing to the development of mood disorders.

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Neurogenesis in the adult brain

It has long been a central dogma in neuroscience that the mammalian brain can no longer generate new neurons once it reaches adulthood. However, contrary to this dogma, research over the last few decades has now firmly established that even the adult brain contains undifferentiated progenitor cells that give rise to new neurons.[1–3] While much of our current knowledge on neurogenesis in the adult mammalian brain is based on studies in laboratory rodents, the production of new neurons in adulthood has been confirmed in a variety of other species, including humans[4] and other primates.[5]

The term neurogenesis usually refers to the combined processes of cell proliferation, survival, maturation and differentiation into a neuronal cell type. A majority of recent studies on neurogenesis is based on the administration of BrdU (5-bromo-2′-deoxyuridine), a synthetic thymidine analogue that is taken up by dividing cells and incorporated into the DNA during the S-phase of the cell cycle.[6] Newborn cells that are labeled with BrdU can be visualized in brain sections by immunohistochemical techniques. In animal studies, subjects often receive one or multiple injections of BrdU and collection of their brains is timed and adjusted, depending on the phase of neurogenesis one aims to investigate. To examine the rate of cell proliferation, animals are often killed within hours after BrdU injections. To study survival of newborn labeled cells, the brains are collected with a longer delay from several days up to weeks. Maturation and differentiation of new cells can be studied by combining immunohistochemistry for BrdU with a variety of available endogenous, cell-type specific markers.[2,3,7]

Neurogenesis in the adult brain is clearly established in at least two regions: the dentate gyrus (DG) of the hippocampal formation and the subventricular zone (SVZ) lining the wall of the lateral cerebral ventricles.[8] A number of studies have reported adult neurogenesis in additional brain areas, including the neocortex, but this has been difficult to replicate and is still a matter of debate.[8,9] The new cells that are generated in the SVZ migrate in a rostral direction to the olfactory bulb, where they differentiate mainly into GABA-ergic interneurons.[10,11] In the DG, the proliferating cells are located in the subgranular zone, the interface between the granule cell layer and the hilus. Most of the new cells that survive and reach maturity integrate with the granular cell layer and differentiate into glutamatergic neurons.[12,13] There is evidence that at least some of these newborn DG neurons fully integrate in the hippocampal network and become functionally active.[14,15]

Importantly, the rate of neurogenesis in the adult brain is not constant. Every aspect of the neurogenesis process, from proliferation to survival and differentiation, can be regulated and modulated. In the DG of young adult rats, an estimated number of 4000–9000 new cells are generated each day.[13,16] Under standard laboratory conditions, about 60% of the new cells die within a few weeks after their generation. However, various experimental conditions have been shown to affect proliferation and/or survival rate, either positively (e.g., enriched environment, exercise, and learning) or negatively (e.g., stress and glucocorticoids).[2] These findings may suggest that proliferation and survival of new neurons plays a role in the adaptation of animals to specific environmental demands and physiological conditions.

The function of newborn neurons in the adult brain remains a topic of intense investigation and discussion.[17–21] Since neurogenesis only occurs in significant amounts in a few brain

regions, it is often assumed that newborn neurons support a function that is rather specific for these regions. Most studies have focused on new neurons in the DG and their possible role in hippocampus function. The hippocampus is an important part of the limbic–cognitive system that plays a central role in the regulation of cognitive function and emotions.[22–25] Decades of research have clearly established the importance of hippocampus integrity for learning and memory processes. In addition, the hippocampus maintains reciprocal connections with various brain regions that are associated with the regulation of emotionality, including the amygdala and prefrontal cortex. In agreement with a role for neurogenesis in hippocampal function are several studies showing that hippocampus-dependent learning and memory formation is associated with increased cell proliferation and neurogenesis, whereas learning impairment is associated with reduced neurogenesis.[26] Recent findings indicate that the reality is slightly more complicated but, still, support the hypothesis of a link between neurogenesis and hippocampal learning.[27,28] The effect of hippocampus-dependent learning on newly generated cells may crucially depend on the age and maturation state of these cells. Enhanced survival is found for cells that are close to maturity and, presumably, ready to be functionally incorporated. In contrast, cells that do not yet have the right age may in fact be eliminated.

Since newly generated neurons may play a role in hippocampal regulation of cognitive functions and emotional behavior, a disturbance in adult neurogenesis has been proposed as mediating factor in disturbed cognitive function and mood disorders.[29,30] While stress and stress hormones often suppress the development of new neurons, antidepressant treatments promote neurogenesis. The latter is associated with normalization of behavioral symptoms of depression, which has led to the hypothesis that disruption and reduction of neurogenesis may lead to disturbances in the hippocampal network that could ultimately play a role in the pathophysiology of depression.[29,30]

Although adult neurogenesis has been one of the most important topics in neuroscience research over the last decade, surprisingly, the relationship between neurogenesis and sleep has only received attention in recent years. A number of research groups have studied the possible role of sleep in the regulation of adult neurogenesis as well as the possible consequences of disrupted and restricted sleep. This paper provides an overview of current knowledge and discusses the role of sleep in regulating neurogenesis in relation to brain plasticity, hippocampus function, learning and memory, as well as clinically relevant issues on the consequences of disrupted sleep in the context of mood disorders. Does sleep play a role in adult neurogenesis, thereby supporting hippocampal function? Do sleep deprivation, sleep restriction, or sleep disruption lead to disturbance in neurogenesis and hippocampal function? And could it be that some of the adverse effects of sleep loss on cognitive function and emotionality are in part a consequence of disturbed hippocampal neurogenesis?

Daily rhythms in hippocampal cell proliferation

Sleep displays a clear circadian or daily rhythm that is governed by an endogenous biological clock located in the suprachiasmatic nucleus of the hypothalamus.[31,32] Therefore, if sleep plays a direct role in adult neurogenesis, one might expect to see a daily rhythm in cell proliferation and expression of neurogenic markers that parallels the sleep–wake rhythm. On the other hand, one has to bear in mind that a daily rhythm in cell proliferation would not necessarily be related to sleep per se but might also be related to other rhythms under control of the biological clock, including other behavioral rhythms (e.g., locomotor activity), rhythms in activity of neuroendocrine systems (e.g., hypothalamic–pituitary–adrenal axis activity), or rhythms in activity of neurotransmitter systems (e.g., serotonergic activity). A number of studies have dealt with the question whether a daily rhythm exists in hippocampal cell proliferation.

Two studies in male mice have reported that under baseline conditions the number of proliferating cells in the subgranular zone of the DG is independent of the time of day.[33,34] In one of these studies BrdU was administered at six equally spaced time points across the 24 h light–dark cycle and the brains were collected 2 h after the injections. The number of dividing, BrdU-labeled cells did not show significant fluctuations across the cycle.[33] The other study used the endogenous marker Ki-67 to establish rates of cell proliferation in brains that were collected at eight equally spaced time points across 24 h. The number of proliferating Ki-67 positive cells did not vary across the day.[34] However, when animals were provided with a running wheel, the number of proliferating cells at the end of the active phase was significantly increased. This finding is supported and extended by another study in mice showing that restricted access to a running wheel for 3 h at different times of day increased cell proliferation, cell survival, and the total number of new neurons only in animals that had wheel access during the middle of the active phase.[35] In contrast to the stimulatory effect of running wheel activity, short sleep deprivation during the normal circadian resting phase did not affect cell proliferation in mice.[34] Taken together, these mouse studies suggest that cell proliferation in the DG may display a daily rhythm under certain conditions, but such a rhythm is more likely related to the level of activity than to the occurrence of sleep.

One study performed in rats is in agreement with the mouse studies under baseline conditions and showed no significant daily variation in DG cell proliferation.[36] In contrast, another recent study in rats reported a rather pronounced daily rhythm in hippocampal cell proliferation with a peak at the end of the light phase, i.e., the major sleep phase in this nocturnal species.[37] Adult male rats were injected with BrdU to label proliferating cells at four time points during the daily cycle, and brains were collected 2 h later, that is, early and late in the light phase/resting phase, as well as early and late in the dark phase/active phase. Immunohistochemical analysis showed that the number of BrdU-labeled cells in the subgranular zone and the granular cell layer of the DG was about twice as high at the end of the daily light phase as it was at the other time points. This pattern, with a peak at the end of the light phase or resting phase, would be in agreement with a sleep-related enhancement of cell proliferation but might reflect other rhythms in the brain or body as well. To test if this peak in cell proliferation indeed is dependent on sleep, one would need to subject rats to sleep deprivation during the resting phase, ending around the time of the peak, and then establish whether the number of proliferating cells is lower than that in normally sleeping control rats. Various studies in rats have applied short sleep deprivation or sleep disruption of less than a day, including the light phase or main resting phase, and most of them do not find a reduction in cell proliferation.[38–40] However, in none of these studies did the end of sleep deprivation and the timing of brain collection coincide with the reported peak in cell proliferation. Therefore, these data are not conclusive. The only study that performed a short sleep deprivation during the normal resting phase, terminating around the end of the light phase, is the mouse study discussed earlier in this section.[34] That study did not find an effect of short sleep deprivation either, but the studies in mice did not report a rhythm of cell proliferation in the first place and, therefore, a species difference cannot be excluded.

Together, the results of studies that examined daily variation in the rate of hippocampal cell proliferation do not yet provide a clear picture and have to be viewed with care. A majority of the studies in rodents found no significant rhythm in cell proliferation in the subgranular zone of the DG under standard housing conditions. However, studies in mice suggest that a rhythm with a peak in the active phase may appear as a consequence of increased activity levels, whereas one study in rats suggests a rhythm with a peak during the major sleep phase. It is unclear at this point whether this peak is really dependent on sleep and it is also unclear what might explain the different results of the studies in mice versus rats.

Although the subgranular zone is the major site of cell proliferation within the DG, a smaller number of dividing cells is found in the hilus as well. It is generally believed that these scattered cells in the hilus give rise primarily to glia rather than neurons. Intriguingly, one of the studies in mice that did not find a rhythm in cell proliferation in the subgranular zone of the DG did report significantly higher levels of cell proliferation in the hilus during the light phase compared to the dark phase.[33] Also, one rat study reported a daily rhythm in cell proliferation in the hilus with higher levels in the light phase.[37] Since rats and mice are nocturnal animals, proliferation rates in the hilus were higher in the major sleep phase. This finding is in agreement with a study in rats reporting a significant decrease in cell proliferation after 20 h of sleep deprivation in the hilus but not in the subgranular zone.[38] Together, these findings suggest a circadian influence, possibly sleep-related, on gliogenesis rather than neurogenesis. The functional meaning of such a rhythm in gliogenesis remains to be established.

Effects of sleep deprivation and sleep disruption

To examine the role of sleep in neurogenesis, various studies have experimentally deprived or disrupted sleep in rodents for different durations, ranging from one to several days. While some of these studies applied prolonged total sleep deprivation for several days as a first approach to explore the relationship between sleep and neurogenesis, a number of experiments were specifically designed to better mimic sleep restriction or sleep disorders as they occur in humans, albeit in a severe form. For example, instead of total sleep deprivation, some rat studies applied chronic partial sleep deprivation[38] or chronic sleep fragmentation.[40] Across the various studies, enforcing wakefulness is achieved by a variety of different methods, including gentle handling, forced locomotion in a slowly rotating drum, forced locomotion on a treadmill, or placing animals on small platforms over water. Each of these methods may have their own non-specific effects that are unrelated to sleep loss per se, but most of the studies included additional groups and experiments that aimed to control for such non-specific effects. Importantly, while differences in methodology may be the cause of some variation in the results, overall, the effects of sleep loss appear to be fairly consistent across studies, independent of the approach that was used.

As indicated in the previous section, a number of reports suggest that the basal rate of cell proliferation in the subgranular cell layer of the DG is not strongly affected by short sleep deprivation lasting less than one day.[34,38–40] However, cell proliferation is significantly suppressed when deprivation or disruption of sleep is prolonged and lasts for several days or more.[38–45] A number of experiments have directly compared the effect of acute, short sleep deprivation (<1 day) with effects of prolonged sleep restriction or disruption (>3 days) and indeed confirm that a reduction in hippocampal cell proliferation is only found with prolonged sleep restriction or disruption.[38–40] The effects of prolonged sleep deprivation or disruption on the rate of cell proliferation are substantial, ranging from 30 to 80% across studies. Also, this effect may be rather persistent as one study showed no evidence of recovery for at least 8 h following a 48 h sleep deprivation. After 2 days of sleep deprivation and after a subsequent 8 h recovery period, there was a reduction in cell proliferation of 36 and 39%, respectively.[42]

Sleep deprivation or sleep disruption may not only have a negative impact on cell proliferation but, perhaps more relevant, also on subsequent survival, maturation and differentiation of these cells. Several studies in rats show that prolonged sleep disruption reduces the fraction of new cells later expressing a neuronal phenotype.[40,43,44] Thus, sleep deprivation may affect the newly born cells' capacity to subsequently develop mature neuronal properties. Importantly, whereas proliferation of progenitor cells in the DG is generally not affected by short sleep deprivation, one study showed a reduction in the number of new cells developing into neuron after only a single day of sleep fragmentation.[40] Also, a relatively mild sleep restriction interfered with the increase in neurogenesis associated with learning.[46] Rats trained in a water

maze for 4 days showed an increase in the number of new neurons, which was abolished by sleep deprivation during the first half of the resting phase following each of the training sessions. It might thus be that the processes of cell survival and differentiation are more sensitive to sleep loss than cell proliferation. On the other hand, the data on this issue are rather limited and a number of other papers reported no effect of sleep deprivation on cell survival and maturation.[38,45]

It does not require *total* deprivation of sleep to suppress hippocampal cell proliferation and neurogenesis. A study in rats applied an intermittent treadmill system to examine the effects of prolonged sleep fragmentation.[40] Rats were placed on a treadmill that was on and off for 3 and 30 s, respectively. This may seem like a strenuous schedule but continuous EEG recordings showed that the animals adapted and still acquired a significant amount of sleep, albeit highly fragmented. In fact, the total amount of NREM sleep was not significantly different from that in control animals but consisted of shorter and less consolidated bouts. The amount of REM sleep on the other hand was strongly suppressed, but this reduction became smaller over time, presumable with an increase in REM sleep pressure. Sleep fragmentation was conducted for 1, 4 or 7 days and the rats received BrdU injections 2 h prior to the end of the experiment. The rate of cell proliferation in the DG was established by immunohistochemical analysis of cells positive for BrdU as well as cells positive for the endogenous proliferation marker Ki-67. The number of proliferating BrdU positive and Ki-67 positive cells in the DG was not yet affected after 1 day of sleep fragmentation but it was reduced by about 70% after 4 and 7 days. In separate groups of animals, the fate of new cells was determined 3 weeks after the end of the sleep fragmentation period by immunofluorescent double labeling for BrdU and the neuronal marker NeuN or the glial marker S100β. In the previously sleep disrupted rats, the fraction of BrdU positive cells expressing a neuronal phenotype was significantly reduced by about 20–30%. Thus, sleep fragmentation not only reduced the production of new cells but, for a given pool of new cells, fewer developed into adult neurons. This pronounced reduction in cell proliferation and neurogenesis after 4–7 days of sleep fragmentation is in the same range as the effects that have been reported after several days of near total sleep deprivation.[41,43] Importantly, the effects of sleep fragmentation by treadmill walking were compared to a procedure that involved similar treadmills which were on and off for 15 and 150 min, respectively. In other words, the control rats were housed under identical conditions and were forced to walk for a similar time and distance but had longer periods of uninterrupted sleep. This approach strongly favors the interpretation that effects were the result of sleep disruption per se rather than a non-specific side effect of the procedure. An important question remained whether the reduction in cell proliferation and neurogenesis was the result of NREM sleep fragmentation or the result of REM sleep reduction.

The majority of studies in rats validated the consequences of sleep deprivation with EEG sleep recordings. In many cases, sleep deprivation affected both NREM and REM sleep, although some of the methods cause a particularly strong reduction in REM sleep, e.g., the platform over water method.[45] One study aimed at a selective suppression of REM sleep by providing a waking stimulus only when animals entered REM sleep but not when they entered NREM sleep.[44] The experimental animals were subjected to 4 days of REM sleep deprivation while yoked control animals received the same amount of stimulation, but independent of sleep phase. REM sleep in the sleep deprived rats was reduced by 79% compared to the yoked control animals and by 83% compared to undisturbed home cage controls. The amount of NREM sleep was only reduced by 17% compared to home cage control animals and did not significantly differ from the amount of NREM sleep in the yoked controls. Also, the amount of EEG slow-wave activity during NREM sleep, which is generally considered as an indicator of sleep intensity, did not differ in sleep deprived rats and yoked controls. Thus, despite a similar amount of stimulation, experimental animals and yoked controls only differed in the amount of REM sleep. Hippocampal cell proliferation was reduced by 63% in the REM sleep deprived animals

compared to the yoked controls. This reduction of cell proliferation is in the range of what has been found after 4 days of near of total sleep deprivation.[43] In other words, the effect of sleep deprivation or sleep disruption on hippocampal cell proliferation that has been reported in various studies can be fully explained by a reduction in REM sleep, although this does not exclude an additional effect of NREM sleep deprivation. Selective REM sleep deprivation also reduced the percentage of new cells that later expressed mature neuronal markers. However, this effect seemed to be somewhat smaller than previously reported for a similar period of total sleep deprivation.[43] Thus, the reduction in the percentage of cells that mature and develop into adult neurons as reported after various protocols and methods of sleep deprivation may be related to a reduction in both NREM and REM sleep.

So far, most of the studies on adult neurogenesis in relation to sleep were focused on the DG and did not include the SVZ lining the lateral ventricles; perhaps because the hippocampus is considered by many as a more interesting brain region than the olfactory bulb, which is the final destination of most newly generated SVZ cells. One study, however, did include the SVZ and found no changes in cell proliferation after 3 days of sleep deprivation whereas proliferation in the granular cell layer of the DG was significantly decreased; suggesting that sleep deprivation affects adult cell proliferation with some regional specificity.[39] Even within the DG, there may be regional variation in the effect of sleep deprivation. Although sleep deprivation appears to suppress cell proliferation throughout the DG, there is some indication that the effects may be stronger in the ventral or posterior region, compared to the dorsal or anterior region.[42] This is an issue of potential interest given the evidence of functional differentiation between different hippocampal subregions. Selective lesion studies show that in rodents the dorsal hippocampus has a preferential role in certain forms of learning and memory, particularly spatial learning, whereas the ventral hippocampus is more strongly associated with regulation of emotional behavior and anxiety.[22,24]

Sleep deprivation, the role of stress and other mechanisms

The finding of reductions in cell proliferation and neurogenesis after sleep deprivation or sleep disruption suggest that sleep itself promotes the production of new cells and neurons. However, the mechanisms by which sleep affects different aspects of neurogenesis are unknown. The fact that cell proliferation does not appear to be diminished by short sleep deprivation of less than a day,[34,38–40] and the finding that reduced proliferation after prolonged sleep deprivation does not normalize after 8 h of recovery sleep,[42] seem to suggest that the relationship between sleep and neurogenesis is indirect. In other words, sleep may not promote cell proliferation and maturation directly but, instead, sleep may be essential for normal functioning of other processes and systems that, in turn, regulate neurogenesis. Prolonged sleep deprivation might affect these other processes and by that have cumulative adverse effects that gradually diminish cell proliferation and neurogenesis over the course of several days.

Decreases in the production and survival of new DG granule cells have been found in response to a variety of harmful factors including chronic stress and glucocorticoids.[47,48] It has been proposed that effects of prolonged sleep deprivation might be an indirect result of stress and increased levels of stress hormones, particularly glucocorticoids.[39] Indeed, sleep loss may be mildly stressful by itself and, on top of that, some methods of sleep deprivation that are applied in animal studies involve a certain degree of stress that may not be related to sleep loss per se.[49] Often, studies include additional groups to control for the non-specific effects of the sleep deprivation method. For example, the studies that achieved sleep deprivation by enforced treadmill walking included control animals that were subjected to the same amount of treadmill movement but with longer periods of rest to allow sleep[40,41,43] and studies that applied sleep deprivation by a small platform surrounded by water included control animals that were exposed to larger platforms that allowed them to rest without the risk of falling in the water.

[39,45] While such additional groups may control for many non-specific aspects of the sleep deprivation method, they may not always exclude the possibility that sleep deprived animals have elevated stress hormone levels compared to the procedural controls.

A number of studies directly addressed the issue of stress and glucocorticoids by performing experiments on sleep deprivation and neurogenesis in animals with surgically removed adrenals.[39,40,45] In the first of these studies, rats were sleep deprived for 3 days by the small-platform method, which was associated with a strong increase in corticosterone levels and a highly significant reduction in DG cell proliferation, compared to both large-platform controls and home cage controls.[39] The experiment was repeated in sham-operated animals and adrenalectomized animals receiving a low dose of corticosterone in their drinking water, necessary to maintain normal physiology. The sham-operated rats exposed to extended sleep deprivation displayed the characteristic reduction in cell proliferation. Yet, this effect of sleep deprivation was completely eliminated in the adrenalectomized animals. These results suggested that the effects of prolonged sleep deprivation on hippocampal cell proliferation are mediated by elevated levels of glucocorticoids.[39] This is in sharp contrast with two more recent studies, both of which demonstrate that the suppression of hippocampal cell proliferation following sleep deprivation or sleep fragmentation largely persists in adrenalectomized rats.[40,45] The discrepancy may be related to methodological differences, particularly the way corticosterone supplementation was performed. As pointed out by one of the recent studies, the finding that adrenalectomy blocked the effect of sleep deprivation may have been the result of a methodological flaw.[45] Supplementing corticosterone via a water bottle may lead to erroneous findings when sleep deprivation is performed using a platform that is surrounded by water as well. Instead of drinking exclusively from the bottle, rats in that condition may also drink directly from the pool, and thereby ingest less corticosterone than control rats. Importantly, whereas stress and high levels of corticosterone suppress cell proliferation, below-normal levels of corticosterone such as in the case of adrenalectomy without glucocorticoid replacement can promote cell proliferation.[50] Consequently, the adrenalectomized, sleep-deprived rats drinking from the pool may have had chronically lowered levels of corticosterone that upregulated cell proliferation and thereby compensated for the adverse effect of sleep deprivation. To test this hypothesis, Mueller and colleagues[45] measured fluid intake in adrenalectomized rats receiving replacement corticosterone via water bottles, and confirmed a 60% reduction in corticosterone ingestion during a 4-day sleep deprivation, and no difference in cell proliferation between sleep deprived and control rats. In contrast, cell proliferation was reduced by 25–40% across replicate experiments in sleep deprived rats when replacement corticosterone was clamped at the same level as in control rats, using subcutaneous minipumps. Collectively, these studies suggest that elevated glucocorticoids are not required for the reduction in cell proliferation following prolonged sleep deprivation or sleep disruption. Note that none of the adrenalectomy studies examined cell survival and differentiation. Therefore, it is currently unknown whether or not glucocorticoids are involved in the reported reductions in neuronal differentiation following sleep deprivation.

In conclusion, while stress associated with sleep deprivation may contribute to the suppression of cell proliferation and neurogenesis, a number of studies clearly show that prolonged restriction or disruption of sleep have a suppressive effect on hippocampal cell proliferation that is independent of adrenal stress hormones.

There are various factors other than stress and glucocorticoids that could account for the reduction in cell proliferation and neurogenesis following sleep deprivation. The generation of new cells and neurons in the adult brain is regulated and affected by a wide variety of molecular factors, including trophic factors, cytokines, hormones and a range of neuromodulators and neurotransmitters.[2,3,51] Several of these factors are also affected by

deprivation or disruption of sleep and may, therefore, provide a link between insufficient sleep and reductions in hippocampal cell proliferation and/or neurogenesis.

For example, serotonin promotes hippocampal cell proliferation and neurogenesis, in part via the serotonin-1A receptor.[52,53] Serotonergic activity during sleep itself is relatively low,[54] which would not fit with a direct effect of sleep on neurogenesis. However, this quiescence of serotonergic activity may be necessary to maintain normal serotonergic activity during wakefulness, which in turn may be important for the neurogenic effect of waking experiences. Indeed, recent studies in rats show that chronic sleep restriction reduces the sensitivity of the serotonin-1A receptor system.[55,56] This reduction is not immediately evident but only develops in the course of prolonged sleep restriction, which is in agreement with the finding that suppression of hippocampal cell proliferation does not occur after short sleep deprivation but only after prolonged sleep deprivation.

One of several growth factors that is known to promote neurogenesis is insulin-like growth factor (IGF)-1[57,58] whereas sustained sleep deprivation in rats has been shown to reduce the level of IGF-1.[59] Brain-derived neurotrophic factor (BDNF) also facilitates DG cell proliferation and survival[60,61] and hippocampal expression of BDNF was found to be reduced after 48 h of sleep deprivation.[62] Interestingly, this decrement in BDNF was correlated with REM sleep loss, which may be of relevance given the suggestion that sleep deprivation-induced suppression of DG cell proliferation is largely related to loss of REM sleep.[44]

A reduction in neurogenesis following sleep deprivation might also be related to increased levels of proinflammatory cytokines such as interleukin (IL) 6 and tumor necrosis factor (TNF) α. There is evidence that both IL-6 and TNF-α are increased after sleep deprivation and after chronic sleep curtailment,[63,64] and plasma levels of IL-6 levels are also increased in patients with primary insomnia.[65] Exposure to both IL-6 and TNF-α decrease neurogenesis in vitro and these cytokines may also mediate the detrimental effects of neuroinflammation on hippocampal neurogenesis in vivo.[66]

Clearly, the mechanisms by which prolonged sleep deprivation or sleep disruption affect adult neurogenesis may involve a complex and interacting set of factors, and some of these factors may have selective effects on the different stages of the neurogenesis process, from proliferation to maturation and incorporation.

Sleep deprivation, learning and neurogenesis

One important issue concerning the relationship between sleep and neurogenesis has only reached sparse attention. Most studies so far examined effects of sleep deprivation on basal rate of cell proliferation and neurogenesis. However, the importance of sleep may not just lie in regulating basal rates of neurogenesis but, rather, mediating changes in neurogenesis associated with, for example, learning.

Many studies suggest that sleep plays a role in learning and memory formation.[67–69] Various mechanisms have been proposed for the effect of sleep on memory but one that has not received much attention is neurogenesis. Sleep might support memory formation by promoting the survival and functional integration of new hippocampal neurons. Certainly, a possible relationship between sleep and neurogenesis in the context of learning and memory fits with a number of important findings. One, the hippocampus is an important structure for memory formation and one of the few brain areas displaying a substantial amount of adult neurogenesis. Two, both hippocampal neurogenesis and hippocampal memory processes are sensitive to sleep loss. Indeed, sleep deprivation alters molecular and electrophysiological properties of hippocampal neurons,[70] and it has a particularly disruptive effect on memory formation when this memory is hippocampus-dependent.[71,72]

So far, only one study tested whether the deleterious effects of sleep loss on hippocampus-dependent learning were associated with reduced survival of new cells.[46] Rats were trained in a water maze for 4 days, either on a hippocampus-dependent spatial task (submerged invisible platform) or a hippocampus-independent nonspatial task (visible platform). Following each of the daily training sessions, animals were kept awake for 6 h during the first half of their normal resting phase. The animals had received an injection of BrdU to label newly generated cells one week prior to the test. Presumably, by the time of learning, these new cells reached a state of maturity that made them suitable for incorporation in the hippocampal network. In agreement with other reports, rats that were trained on the hippocampus-dependent spatial learning task displayed a pronounced increase in survival of newborn cells, compared with animals that were trained on the hippocampus-independent task. However, this increase in cell survival was abolished in the sleep-restricted animals and, importantly, sleep restriction also impaired hippocampus-dependent spatial learning. It is tempting to think that the learning impairment and reduction in neurogenesis were linked, in line with the hypothesis that sleep normally promotes hippocampus-dependent memory formation by increasing the survival and integration of newborn neurons in the hippocampal network. Most models of memory formation are based on structural remodeling of synapses and adaptation of synaptic strength in existing circuits, and sleep following the initial learning is thought to contribute to this process by means of neuronal replay and reactivation of plasticity processes.[67–69] Yet, such sleep-dependent synaptic plasticity might not only involve existing neurons but might also include maturation and strengthening of synapses from new neurons that are added to the network. Further studies are required to confirm this neurogenic link between sleep and learning, yet, the first results open up a new avenue for research on the possible mechanism of sleep-related memory formation.

Sleep disturbance and the human hippocampus

Although most of the current knowledge on adult neurogenesis is derived from studies in laboratory rodents, the generation of new neurons in the adult brain has been confirmed in humans as well.[4] In elderly cancer patients that were injected with BrdU, postmortem analysis of brain tissue and immunostainings for BrdU together with specific neuronal markers unequivocally demonstrated the existence of proliferating cells and generation of new neurons in the DG of the hippocampus. Nonetheless, study of adult neurogenesis in humans has been limited, until now, by lack of methods for in vivo measurement of newly generated neurons in healthy, living subjects. Recent studies on the development of magnetic resonance imaging of neuronal progenitor cells are promising and open the possibility of investigating neurogenesis under a variety of experimental and disease-related conditions, even in human subjects.[73,74] While these methods require further refinement and validation, they may eventually provide an opportunity to study neurogenesis in relation to sleep and sleep disturbance in our own species. So far, there is no evidence for a relationship between sleep and neurogenesis in human beings; yet, the finding that prolonged sleep deprivation or sleep fragmentation reduce hippocampal cell proliferation and neurogenesis in rats raises the possibility that chronically restricted or disrupted sleep associated with, for example, life style, stress or disease may affect the generation of new neurons in the adult human brain as well.

Clearly, there is ample evidence that the structural integrity and function of the hippocampus depend in part on sleep, not only in laboratory rodents but in humans as well. Imaging studies in humans have confirmed the role of sleep in hippocampus function and formation of memory.[75,76] Also, cognitive performance, including the nocturnal consolidation of hippocampus-dependent memories is disrupted in patients suffering from chronic insomnia.[77,78] Furthermore, in vivo imaging in patients with primary insomnia revealed a significant reduction in hippocampal volume.[79] Adult neurogenesis in humans, particularly at an older age, may be too limited to explain this reduction in volume,[80] but a decrease in the production

of new neurons might still contribute to it. Independent of the reduction in volume, the functional consequences and cognitive disturbances associated with insomnia may very well be related to reductions in neurogenesis.

Along the same line, alterations in hippocampal neurogenesis may also be involved in the well established link between disrupted sleep and clinical depression. Increasing evidence suggests that disturbed sleep may not only be a symptom of depression but, instead, may be a factor that sensitizes individuals and contributes to the development of mood disorders. In agreement with this, primary insomnia often precedes and predicts the onset of a new depressive episode.[81] Also, experimental studies in rodents show that chronic sleep curtailment gradually leads to physiological and neurobiological alterations that are remarkably similar to what is found in depression.[55,56] As discussed in previous sections, chronically disrupted and restricted sleep may also lead to a reduction in hippocampal cell proliferation and neurogenesis.[38–45] On the basis of these findings one might hypothesize that chronically disrupted sleep by causing a decrease in hippocampal neurogenesis might be one of the factors contributing to the pathophysiology of depression.

So far, the proposed link between neurogenesis and depression was primarily based on animal studies showing that stress and stress hormones suppress the production of new neurons whereas antidepressant treatment promotes neurogenesis.[29,30] Indeed, stress is not only a potent inhibitor of neurogenesis but is generally considered as an important causal factor in the etiology of depression.[82,83] Yet, on the basis of the well established link between disrupted sleep and the occurrence of depression[81] and the finding that prolonged sleep disruption can suppress adult hippocampal cell proliferation and neurogenesis independent of adrenal stress hormones,[40,45] we propose that the link between neurogenesis, hippocampal function and depression may be related to disrupted sleep as much as stress or glucocorticoids.

In conclusion, while studies on the relevance of neurogenesis in humans await the development of in vivo imaging techniques, data from animal experiments provide a clear framework suggesting that newly generated neurons in adulthood may be involved in hippocampal plasticity. While modest sleep restriction may interfere with enhancement of neurogenesis associated with learning processes, prolonged sleep disruption may even affect the basal rates of cell proliferation and neurogenesis. The effects of sleep loss may endanger hippocampal integrity and could ultimately lead to cognitive dysfunction and contribute to the development of mood disorders.

Practice points

- New neurons are generated in selected areas of the adult mammalian brain, particularly the dentate gyrus of the hippocampal formation and the subventricular zone of the lateral ventricles. The function of adult-born neurons is still a matter of debate but, in the case of the hippocampus, integration of new cells in to the existing circuitry may be involved in memory processes and cognitive function.
- The production of new neurons in the adult brain does not occur at a constant rate. Controlled studies in laboratory rodents have shown that various experimental conditions affect proliferation and/or survival rate, either positively (e.g., enriched environment, exercise, and learning) or negatively (e.g., stress and glucocorticoids).
- While disruption of sleep for a period shorter than one day appears to have little effect on the basal rate of cell proliferation, prolonged restriction or disruption of sleep may have cumulative effects that cause a major decrease in cell proliferation, cell survival and neurogenesis. Most methods of sleep deprivation that have been

applied affect both NREM and REM sleep. Available data favor the hypothesis that decreases in cell proliferation are related to a reduction in REM sleep, whereas a reduction in the number of cells that subsequently develop into adult neurons may be related to a reduction of both NREM and REM sleep.

- Short sleep deprivation may not affect the basal level of cell proliferation and neurogenesis; however, one study in rodents shows that even mild restriction of sleep may prevent the increase in neurogenesis that occurs with hippocampus-dependent learning. Since sleep deprivation also disturbs memory formation, these data suggest that promoting survival, maturation and integration of new cells may be an unexplored mechanism by which sleep supports learning and memory processes.
- The mechanisms by which sleep loss affects different aspects of adult neurogenesis are unknown. It has been proposed that adverse effects of sleep deprivation may be mediated by stress and glucocorticoids. However, a number of studies clearly show that prolonged sleep loss can inhibit hippocampal neurogenesis independent of adrenal stress hormones.
- Since disrupted sleep is linked to a reduction in neurogenesis and also linked to clinical depression, we propose that insufficient sleep by reducing neurogenesis endangers hippocampal integrity and thereby contributes to the pathophysiology of depression.

Research agenda

- Data on the question whether there is a daily and sleep-dependent rhythm in hippocampal cell proliferation are not consistent and, therefore, inconclusive. A comparative study with rats and mice with properly timed sleep deprivation is needed.
- While hippocampal cell proliferation may only be suppressed by prolonged sleep disruption, some studies suggest that survival and differentiation of new cells may be more sensitive to sleep loss. However, the information is limited. Also, very little is known on the recovery of changes in neurogenesis after sleep loss.
- Although various studies have shown that sleep deprivation or sleep disruption decrease hippocampal cell proliferation and neurogenesis, the underlying biochemical mechanisms are largely unknown and require further study.
- An important question regarding the link between sleep and neurogenesis concerns the functional implication. The possibility that sleep may promote hippocampus-dependent memory formation by stimulating survival and incorporation of new cells provides a new avenue of research.
- More study is required on the relationship between chronic sleep disturbance and neurogenesis in the context of mood regulation and depression. It seems relevant to test whether reductions in cell proliferation and neurogenesis induced by prolonged sleep disruption are normalized by antidepressant pharmaca.
- The further development of techniques that allow in vivo imaging of neurogenesis in living subjects is required to study relationship between sleep, sleep disturbance and neurogenesis in humans.

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