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Review

The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity

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ABSTRACT

Sleep deprivation is a common feature in modern society, and one of the consequences of sleep loss is the impairment of cognitive function. Although it has been widely accepted that sleep deprivation affects learning and memory, only recently has research begun to address which molecular signaling pathways are altered by sleep loss and, more importantly, which pathways can be targeted to reverse the memory impairments resulting from sleep deprivation. In this review, we discuss the different methods used to sleep deprive animals and the effects of different durations of sleep deprivation on learning and memory with an emphasis on hippocampus-dependent memory. We then review the molecular signaling pathways that are sensitive to sleep loss, with a focus on those thought to play a critical role in the memory and synaptic plasticity deficits observed after sleep deprivation. Finally, we highlight several recent attempts to reverse the effects of sleep deprivation on memory and synaptic plasticity. Future research building on these studies promises to contribute to the development of novel strategies to ameliorate the effects of sleep loss on cognition.

Contents

1. Introduction

Millions of people worldwide experience sleep deprivation on a daily basis [1]. The pressure to stay up longer in our modern 24/7 society impacts a growing percentage of the population [2,3]. A population-based study indicated that, over the past 50 years, sleep duration in adult and adolescent Americans has decreased by 1.5–2 h per night in adults and adolescents, with 30% reporting sleep of 6 h per night or less [4].

One of the first indications that sleep might be beneficial for the formation of memories came from a study by Jenkins and Dallenbach

Abbreviations: AMPAr, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptors; CREB, cAMP response element binding protein; ERK, extracellular signal-regulated kinase; GABAr, gamma-aminobutyric acid receptor; LTP, long-term potentiation; mAChr, muscarinic cholinergic receptor; nAChr, nicotinic acetylcholine receptor; NMDAr, N-methyl-D-aspartate receptor; PDE, phosphodiesterase; PDE4, cyclic AMP specific phosphodiesterase-4; PKA, cyclic AMP-dependent protein kinase A; REM sleep, rapid eye movement sleep; Rolipram, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone; SNARE, *N*-ethylmaleimide-sensitive factor attachment protein receptor.

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[5] that showed that sleep attenuated the rate of forgetting. In the 1960s, Morris and colleagues found that sleep deprivation impaired memory processing [6]. In the decades thereafter, it became apparent in both humans and animal models that specific forms of memory are affected by sleep deprivation [7–10]. To combat the effects of sleep deprivation, it is critical to understand the molecular and cellular mechanisms by which sleep deprivation leads to cognitive deficits. Here, we review current knowledge of the intracellular signaling pathways that are affected by sleep deprivation, with an emphasis on the impact of sleep deprivation on hippocampal function (see Fig. 1 for a schematic summary). In addition, we discuss the different approaches that have been developed to reverse memory and plasticity deficits induced by sleep deprivation.

2. Methods for sleep deprivation in rodents: advantages and drawbacks

To elucidate which cellular and molecular effects of sleep deprivation lead to memory impairments, many research laboratories have utilized rodents as study objects. Three primary techniques have been used to deprive laboratory rodents of sleep. Each of these methods has particular advantages and drawbacks, as discussed below.

The first is the platform-over-water, pedestal, or "flower pot" method, which is the best method to selectively deprive animals of rapid eye movement (REM) sleep for one or multiple days with only intermittent monitoring by the researcher [11]. Animals are placed in a chamber with one or multiple small platforms surrounded by water. When the animals enter REM sleep, their muscle tone diminishes and the animals fall into the water, waking them up and preventing them from going into REM sleep. For control animals, the small platforms are replaced with larger ones, allowing them to enter REM sleep without falling into the water [12]. The concern with this particular method is that large-platform control animals, which obtain normal amounts of REM sleep, also show some alterations in neuronal function (see Section 4 of this review). This suggests that aspects of the method other than the loss of REM sleep are responsible for some of the phenotypes observed after using the platform-over-water method [13].

The second method of sleep deprivation utilizes forced locomotion, in which the animal is placed in a chamber with a revolving floor or rotating drum that forces the animal to reposition itself with each revolution [14,15]. This method can be tailored to achieve total deprivation or selective deprivation of a particular sleep stage. Control animals can be manipulated to move just as much as deprived animals, but with longer periods of rest in between, thereby preventing excessive sleep loss. For example, the schedule for rotation of the chamber for a sleep-deprived animal might be 10 s on, 30 s off, whereas the schedule for a control animal might be 10 min on, 30 min off. Thus, the control animal has repeated periods of 30 min during which it can sleep undisturbed, but the sleep-deprived animal has a maximum of 30 s to rest before it is forced to move again (see [16]). This technique is often used to model sleep fragmentation, such as which might occur due to sleep apnea, caring for an infant throughout the night, or otherwise fitful sleep. The interpretation of the effect of sleep deprivation using this technique can be challenging and depends on using the correct control groups, because locomotor activity or stress evoked using this technique may mask or reverse the effects the effects of sleep deprivation.

The third sleep deprivation method is based on gentle handling or mild stimulation. In this technique, researchers make mild noises, gently jostle the animal's home cage, disturb the animal's nesting material, and in some cases stroke the animal [17–19]. Gentle handling is very effective at inducing total sleep deprivation as determined by electroencephalography [20], and seems to be a strong model of typical sleep deprivation in humans. One downside of the gentle handling technique is that it requires constant vigilance by the researcher, with the result that gentle handling is rarely carried out for longer than 12 h.

Because the gentle handling method involves direct contact between the researcher and the cage or the animal itself, a concern is whether the memory deficits resulting from sleep deprivation by gentle handling are due to sleep loss or non-specific side effects of the technique itself. To test this issue, Hagewoud and colleagues [21] trained animals at the beginning of the resting phase (in rodents, this is the light phase) and recorded the amount of stimulation needed to keep them awake during the following 6 h. Next, the authors trained a new cohort of rats at the end of the resting phase and determined whether giving the animals the same amount of stimulation during the first 6 h of the active phase (in rodents, this is the dark phase, in which they spend only a short time sleeping) would also induce memory deficits. They found that giving the same amount of stimulation during the first 6 h of the active phase, in contrast to the resting phase, did not induce a memory deficit. These findings indicated that the memory deficits observed after sleep deprivation in the light phase were not likely a consequence of the gentle handling method used to sleep deprive animals but rather a consequence of sleep loss.

In some other sleep deprivation studies, the introduction of novel objects or new nesting material is used to keep animals awake, or animals are allowed to explore novel environments [22,23]. Although these techniques have successfully kept animals awake without elevating plasma corticosterone levels [23], they may be problematic when the goal is to study the effects of sleep deprivation on memory or synaptic plasticity. For example, it has been reported that the exploration of new environments and new objects facilitates hippocampal LTD and occludes LTP *in vivo* [24,25], increases the phosphorylation of NMDA and AMPA receptor subunits, and activates ERK1/2 signaling [26]. Furthermore, nest building behavior has been reported to accelerate REM sleep generation [27]. It would be useful, as suggested by Hagewoud and colleagues [21], to separate the effects of exposure to a novel environment, novel objects, or new nesting material from the effects of prolonged wakefulness on plasticity and memory, perhaps by applying these methods of sleep deprivation during the animals' active phase, in which they naturally sleep much less.

A recurring matter of debate in the field of sleep research is how many of the molecular and cellular changes observed after sleep deprivation can be attributed to stress, rather than to sleep loss itself. We believe that the role of stress as the major factor in the memory and plasticity deficits observed particularly after brief sleep deprivation is overstated. Two recent studies in which the activation of the stress signaling pathway is temporarily or permanently disrupted have shown that sleep deprivation leads to cognitive impairments even in the absence of stress-mediated signaling [28,29]. Also, the changes in plasma corticosterone levels during brief sleep deprivation by gentle handling in many cases do not reach levels beyond those observed during the stress hormone's natural circadian oscillation [30], during exploration of a novel environment containing novel objects [31], or due to exposure to a conspecific of the opposite sex [32]. In some cases, the mildly increased plasma corticosterone levels observed after sleep deprivation do not even reach statistical significance [18,19,21,33]. Further if brief sleep deprivation acts as a mild stressor, one might expect that this would enhance memory, as mild increases in glucocorticoids have been shown to facilitate rather than impair memory and plasticity formation [34]. Thus, although mild stress is inherent to most forms of sleep deprivation in the laboratory as in the real world, it is unlikely that this stress component can explain the effects of sleep deprivation on the molecular signaling pathways that result in impairments in memory and synaptic plasticity.

In summary, the sleep deprivation techniques described above all have particular advantages, but each also has its limitations. Because of the different characteristics of each of these sleep deprivation methods, it is important to consider the technique and duration of sleep deprivation used in each of the studies described below.