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Sleep homeostasis

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Research on sleep homeostasis aims to answer the question: how does the brain measure the duration and intensity of previous wakefulness in order to increase the duration and intensity of subsequent sleep? The search of regulatory factors has identified a number of potential molecules that increase their concentration in waking and decrease it during sleep. These factors regulate many physiological functions, including energy metabolism, neural plasticity and immune functions and one molecule may participate in the regulation of all these functions. The method to study regulation of sleep homeostasis is experimental prolongation of waking, which is used also to address the question of physiological purpose of sleep: prolonging wakefulness provokes symptoms that tell us what goes wrong during lack of sleep. The interpretation of the role of each identified factor in the regulation of sleep/sleep homeostasis reflects the theoretical background concept of the research. Presently three main concepts are being actively studied: the energy (depletion) hypothesis, the neural plasticity hypothesis and the (immune) defense hypothesis.

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Introduction

Sleep homeostasis means that a prolonged period of wakefulness is followed by a prolonged period of sleep. Sleep in mammals and birds sleep consists of two main phases: non-REM (NREM) sleep and REM sleep. These phases are regulated by separate mechanisms but both are under homeostatic control, as evidenced by an increase in both NREM and REM sleep after total sleep deprivation and in REM sleep only after a specific REM sleep deprivation. However, the mechanisms of REM sleep homeostasis are poorly understood, and accordingly, this presentation will concentrate on NREM sleep homeostasis, and use the term 'sleep homeostasis' also when actually speaking of NREM sleep homeostasis.

After a prolonged period of wakefulness, the subsequent sleep period is enriched with slow wave activity (SWA or SWS). On the basis of EEG recordings in both humans and animals, the regulation of sleep homeostasis has been modeled in the two-process model of sleep regulation by Borbély [1]. The model describes the increase in sleep propensity ('sleep pressure'), starting from the moment of awakening and continuing till the moment of falling asleep: the longer the waking period, the more sleep pressure is accumulated in brain and the longer it takes to dissipate it in sleep (recovery sleep).

Experimentally sleep homeostasis is addressed by sleep deprivation: the period of spontaneous waking is prolonged, usually by increasing sensory stimulation or motor activity, and its effects on (sleep) EEG as well as many physiological parameters are recorded during and after the prolonged waking period. Restriction of sleep induces a large amount of physiological changes from gene expression to metabolism and behavior [2], and it is not trivial to conclude which of these changes are directly related to regulation of sleep homeostasis and which are coincidental, related to, for example, changes of energy consumption or stress. Criteria for a sleep/homeostatic factor have been created to overcome this problem [3]. This article will introduce a selection of factors that fulfill all or most of these criteria (Table 1).

Key questions of sleep homeostasis are: first, is recovery sleep produced by the same factors that regulate spontaneous sleep–wake cycle, or are additional mechanisms initiated during prolonged wakefulness?; second, what are the molecular correlates of sleep propensity?; and third, what anatomical sites participate in the regulation of sleep homeostasis?

Sleep deprivation is often used also to clarify the purpose of sleep, and the interpretations of the results reflect the many theories about this purpose. Interestingly, many of the relevant molecules (fulfilling the criteria of a sleep factor) have multiple physiological functions, and thus not only one but several theories find support from the same results. The theories of sleep function fall to three main functional categories: energy metabolism, neural plasticity, and (cellular) defense (Table 2).

Sleep propensity

The core of the sleep homeostasis is sleep propensity, or sleep pressure that arises from waking. While SWA is the

Table 1

Humoral substances that have been shown to regulate sleep homeostasis

Substance	Molecule type	Known functions	Produced	Species studied for sleep	Mechanism in sleep SWA increase	Site of action in sleep regulation
ADE	Energy carrier, co-neurotransmitter	Signals for energy depletion Inhibits neuronal activity through A1 receptors and activates it through A2a receptors	In all cells	Cat, rat, mouse, Djungarian hamster, human, *Drosophila*, Zebra fish	Inhibition of wake-promoting cells, activation of sleep-promoting cells	Basal forebrain, VLPOA, subarachnoidal space, cortex (?)
NO	Gaseous neuromodulator	Vasodilatation, energy metabolism, through iNOS also immune function	Glia, BF cholinergic neurons	Rat, mice, rabbit	Release of adenosine	Basal forebrain, cortex?
BDNF	Neural growth factor	Synapse formation	Neurons	Rat, rabbit, *Drosophila*	Synaptic function, other???	Cortex
TNFα	Cytokine	Immune function, synapse formation	Glia (astorocytes)	Rat, rabbit, mice, human	Increase in adenosine, Direct synaptic function?	Cortex, monoamine neurons
IL-1	Cytokine	Immune function	Glia	Rat, rabbit, mice, human		
PGD2	Prostaglandin	Vasodilatation, bronchoconstriction	Microglia, leptomeninges?	Rat, mice, rabbit	Increase in adenosine	Leptomeninges below basal forebrain
GHRH	Peptide hormone	Growth hormone secretion	Hypothalamus	Rat, mice, rabbit, human	GABA, direct effect on synaptic function?	Hypothalamus

Table 2

Connection of sleep factors to physiological functions

Function	ADE	NO	BDNF	TNFα	IL-1β	PGD2	GHRH
Neural plasticity	++	+	+++	+++	+	?	?
Energy metabolism	+++	+++	++	–	–	+ (?)	+
Cellular defense	+	+++	+	+++	+++	+++	–

+++ = strong connection, ++ = connection established, + = some indication of connection.

best marker of sleep homeostasis during sleep [1], the increase in sleep propensity can be measured as increase in theta activity during waking, both in humans and animals [4•,5,6]. But what are the molecular correlates of sleep pressure? Or, in other words, what is the physiological variable or entity that is regulated for maintaining stability? On the basis of an assumption that the information of the duration of wakefulness is mediated by humoral substances, the earliest attempts to identify such molecules were made in the beginning of the 19th century. These experiments also established sleep deprivation as the key method to study sleep homeostasis.

What (in the brain) is homeostatically regulated by sleep?

There is a general agreement that neuronal activity during waking is the driving force of sleep homeostasis: there is direct experimental evidence from both humans [7] and animals [8••,9] showing that those areas of brain that are actively used during waking will produce more SWA during the subsequent sleep period. The intensity of the waking period, described as high-frequency theta activity, is an important denominator of the recovery sleep, to the extent that if a prolonged period of waking lacks high frequency theta, it will not induce sleep recovery [4•,9].

However, there is not a consensus of what aspects of this activity/what molecules are responsible for the generation of the sleep homeostasis. Is the excessive neuronal activity consuming too much energy, or other molecular resources, and initiates a defense response, which decreases neuronal activity and produces SWA? Or is the neuronal activity *per se* able to produce molecules