Sleep Medicine Reviews (2006) **10**, 307–321

SLEEP MEDICINE reviews

www.elsevier.com/locate/smrv

PHYSIOLOGICAL REVIEW

Cellular consequences of sleep deprivation in the brain ☆

Chiara Cirelli*

Department of Psychiatry, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI 53719, USA

KEYWORDS
Sleep loss;
Cerebral cortex;
Synaptic plasticity;
Rat;
Microarray

Summary Several recent studies have used transcriptomics approaches to characterize the molecular correlates of sleep, waking, and sleep deprivation. This analysis may help in understanding the benefits that sleep brings to the brain at the cellular level. The studies are still limited in number and focus on a few brain regions, but some consistent findings are emerging. Sleep, spontaneous wakefulness, short-term, and long-term sleep deprivation are each associated with the upregulation of hundreds of genes in the cerebral cortex and other brain areas. In fruit flies as well as in mammals, three categories of genes are consistently upregulated during waking and short-term sleep deprivation relative to sleep. They include genes involved in energy metabolism, synaptic potentiation, and the response to cellular stress. In the rat cerebral cortex, transcriptional changes associated with prolonged sleep loss differ significantly from those observed during short-term sleep deprivation. However, it is too early to draw firm conclusions relative to the molecular consequences of sleep deprivation, and more extensive studies using DNA and protein arrays are needed in different species and in different brain regions.

A cellular function for sleep?

All animal species studied so far sleep[1] and sleep may have multiple functions, which may differ in different species.[2] It is quite possible, however, that sleep also has a core function that is conserved from invertebrates to mammals. If this is the case, that function is most likely a cellular one, because flies and humans share most pathways for intercellular and intracellular signaling, from membrane receptors and ion channels to nuclear transcription factors, but differ significantly in the number, anatomy, and complexity of brain circuits. One way to understand the benefits that sleep may bring at the cellular level is to perform an extensive analysis of its molecular correlates. More specifically, the identification of the genes whose expression changes in the brain between sleep and wakefulness may clarify if, and why, brain cells need sleep and why their functions are impaired if

☆This work was supported by NIMH and NIGMS.
*Tel.: +1 608 263 9236.
E-mail address: ccirelli@wisc.edu.

1087-0792/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smrv.2006.04.001

they are prevented from doing so during sleep deprivation. In the last 15 years subtractive hybridization, mRNA differential display, and cDNA microarrays have emerged as new powerful methods in transcriptomics, the study of the complete set of RNA transcripts produced by the genome at any one time. Microarrays, in particular, are now the most popular tool to perform whole-genome expression profiling of different tissues in different species, from *Drosophila* to humans. This review summarizes the results of the transcriptomics studies that have identified functional categories of genes whose expression varies during sleep, wakefulness, and sleep deprivation. At least some of these gene categories are conserved from invertebrates to mammals.

Transcriptomics and targeted approaches

Table 1 lists the studies that used transcriptomics approaches to identify state-dependent genes, i.e. genes whose transcript (mRNA) levels vary as a function of sleep, wakefulness, and/or sleep deprivation. Most state-dependent genes have been identified using microarrays, which allow the analysis of thousands of transcripts in a single experiment. Early studies, however, used subtractive hybridization and mRNA differential display, other methods that allow an extensive and unbiased analysis of gene expression changes. A discussion of the advantages and limitations of the different techniques is beyond the scope of this review. Suffice to say, however, that microarrays are currently the most effective, comprehensive, and sensitive method to detect genome-wide expression changes. Other state-dependent transcripts have been identified using more targeted approaches, such as in situ hybridization, northern blot analysis, and polymerase chain reaction (PCR). These studies, not listed in Table 1, have targeted single genes because of prior evidence suggesting the involvement of these genes in sleep regulation. Using these approaches it was found, for instance, that tyrosine hydroxylase mRNA levels increase in the locus coeruleus after 3–5 days of REM sleep deprivation,[3,4] and that changes in mRNA levels of growth hormone releasing hormone,[5–7] somatostatin,[6] interleukin-1β,[7,8] and cortistatin[9] occur in the rat or mouse brain across the light/dark cycle and/or after sleep deprivation. It was also found that the mRNA levels of the canonical circadian genes *per1* and *per2* increase in the cerebral cortex during sleep deprivation, while those of *dbp*, another circadian gene, decrease.[10] Genes related to glycogen metabolism,[11] uncoupling proteins,[12] and peptidoglycan recognition protein[13] were also shown to change their expression in the brain due to sleep loss. Finally, it was found that brain-derived neurotrophic factor (BDNF) is induced by sleep deprivation and spontaneous wakefulness,[14,15] while basic fibroblast growth factor mRNA levels increase during the recovery sleep following sleep deprivation.[15] Several of these transcripts have also been identified using microarrray analysis, as discussed below.

As indicated in Table 1, several transcriptomics studies have focused on the cerebral cortex, but other brain regions are now being considered, including cerebellum, hypothalamus, and brainstem. Most published studies have been performed in rats and mice, but flies, hamsters, sparrows, and humans are also currently being investigated.

The first important conclusion from transcriptomics studies is that gene expression in the brain changes extensively as a function of sleep, spontaneous wakefulness, and short term (a few hours) sleep deprivation. This is perhaps not surprising, because the typical duration of sleep–waking states and the time constants of their regulation is not in milliseconds but in minutes and hours, a time frame perfectly compatible with changes in neural gene expression. Also, previous studies had already identified changes in the content or synthesis of brain RNA,[16–19] as well as overall changes in brain protein synthesis,[20–23] as a function of sleep, waking, or sleep deprivation. In the array studies published so far, 5% or more of the transcripts tested show changes in gene expression according to behavioral state. Interestingly, a similar percentage of genes (from 1% to 10%) changes because of differences in circadian time.[24–32] In the cerebral cortex of rats, out of the 15,459 transcripts we tested, 808 (5.2%) were affected by time of day, independently of behavioral state, and 752 (4.9%) were affected by sleep and wakefulness independently of time of day.[33] These data indicate that, at least in the rat, day/night time and sleep/wakefulness influence gene expression in the cerebral cortex to a similar extent. Peripheral tissues such as liver and heart also show significant changes in gene expression as a function of circadian time. Whether this is also true for sleep-dependent and wakefulness-dependent genes is currently unknown, because none of the array studies published so far has focused on peripheral tissues.

The second important conclusion is that there are not only "wakefulness" or "wakefulness-related" genes, i.e. genes whose brain transcript levels are higher during waking and short-term