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REVIEW

REGULATION OF NEURON–ASTROCYTE METABOLIC COUPLING ACROSS THE SLEEP–WAKE CYCLE

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Abstract—Over the last thirty years, a growing number of studies showed that astrocytes play a pivotal role in the energy support to synapses. More precisely, astrocytes adjust energy production to neuronal energy needs through different mechanisms grouped under the term "neurometabolic coupling" (NMC). In this review we describe these mechanisms of coupling and how they involve astrocytes. From a physiological point of view, these mechanisms of coupling are particularly important to ensure normal synaptic functioning when neurons undergo rapid and repetitive changes in the firing rate such as during the sleep/wake transitions. Investigations into brain energy metabolism during the sleep/wake cycle have been mainly focused on glucose (Gluc) consumption and on glycogen metabolism. However, the recent development of substrate-specific biosensors allowed measurements of the variation in extracellular levels of glutamate, Gluc and lactate (Lac) with a time resolution compatible with sleep stage duration. Together with gene expression data these experiments allowed to better define the variations of energy metabolite regulation across the sleep/wake cycle. The aim of this review is to bring into perspective the role of astrocytes and NMC in the regulation of the sleep/wake cycle. The data reviewed also suggest an important role of the astrocytic network. In addition, the role of astrocytes in NMC mechanisms is consistent with the "local and use dependent" sleep hypothesis.

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Key words: lactate, glucose, glutamate, adenosine, locus coeruleus, gap-junctions.

Contents

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Abbreviations: Ade, adenosine; ADP, adenosine di-phosphate; ANLS, astrocyte–neuron lactate shuttle; ATP, adenosine tri-phosphate; DAB, 1,4-dideoxy-1,4-imino-D-arabinitol; EEG, electro-encephalogram; EMG, electro-myogram; EOG, electrooculogram; FDG, fluoro-deoxy glucose; GLAST, glutamate–aspartate transporter; Gln, glutamine; GLT1, glutamate transporter type-1; Glu, glutamate; Gluc, glucose; GLUT, glucose transporter; GPhos, glycogen phosphorylase; GS, glutamine synthase; GSynt, glycogen synthase; Lac, lactate; LDH, lactate dehydrogenase; LGCU, local glucose uptake; MCT, monocarboxylate transporter; NA, noradrenaline; NMC, neuro-metabolic coupling; NREM, Non-Rapid Eye Movement sleep; PET, positron emission tomography; PFK, phospho-fructo kinase; PPP1, protein phosphatase 1; PS, Paradoxical Sleep; PTG, protein targeting to glycogen; SWA, slow wave activity; SWS, slow-wave sleep; SF, sleep fragmentation; TSD, total sleep deprivation; VIP, vasoactive intestinal peptide; W, waking.

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INTRODUCTION

Since we spent one third of our life asleep, everyone has an intimate knowledge of sleep and its capacity to improve our cognitive and physical functions but also its great fragility regarding life stressors. However, even if great progress has been made since the 60s in the understanding of its mechanisms and in the description of its neuronal substrates, the exact regulation and functions of sleep remain unknown and constitute one of the most stimulating enigmas in neuroscience.

Until recently, sleep research was mainly dominated by a "neurocentric" approach, likely because the different sleep stages have been initially characterized through the electroencephalographic method that reflects cortical neuronal activity; furthermore glial cells were only considered as the "anatomic support" of the neuronal network. However, over the last twenty years, a growing number of studies showing the direct involvement of astrocytes in synaptic functions and in neuronal energy support, led researchers to hypothesize an active involvement of glial cells in sleep mechanisms and functions.

The aim of this review is to present results showing how glial cells ensure energy support to neurons throughout the sleep–wake cycle. Since most of the studies have interrogated astrocyte functions we only considered this type of glial cell in the present review.

Sleep–wake cycle structure and regulation

From a behavioral point of view, the sleep–wake cycle is observed across the animal kingdom, from worms to humans through insects, fish, birds and mammals. Across the phylogeny, many different species display a daily period of locomotor inactivity during which they adopt a specific body posture and display a higher threshold of sensory reactivity, three cardinal criteria of "sleep behavior" (Campbell and Tobler, 1984). Moreover the length of the rest period usually increases as a function of the length of the previous active period, a hallmark of the homeostatic regulation of sleep observed in mammals. The presence of these typical "sleep" features justified the use of drosophila and zebrafish as experimental models in sleep studies (Cirelli and Tononi, 2008; Zimmerman et al., 2008). However, in the great majority of animal sleep studies, rodents are used because their sleep displays features similar to those of other mammals including humans, particularly from an electrophysiological point of view. Sleep studies are usually performed using "polygraphic" recordings including the electroencephalogram (EEG), the electromyogram (EMG) and the electrooculogram (EOG) which respectively allow measuring cortical activity, muscle tone as well as eye movements. In addition to the polygraphic method, the Fast Fourier Transformation analysis (FFT) is classically used to assess qualitative differences in the spectral components of sleep EEG. Therefore, three vigilance stages, the Slow Wave Sleep (SWS) also called Non-Rapid Eye Movement (NREM) sleep, the Paradoxical Sleep (PS) equivalent to Rapid Eye Movement (REM) sleep and waking (W) are classically determined and display the following features:

- During SWS, the EEG signal displays oscillations of high amplitude and low frequencies while the EMG signal reveals the absence of movement and a decline in muscle tone. Power spectrum analysis of EEG indicates a large predominance of low frequencies, including sleep spindles (8–14 Hz) during the early period of the sleep period followed by an increase in delta waves (1–4.5 Hz, also defined as slow wave activity (SWA)) and slow waves (< 1 Hz). At the cellular levels, EEG slow waves corresponds to the alternation of an "UP-state" in which cortical neurons are depolarized and more excitable, and a "DOWN-state" in which the same neurons are hyperpolarized and silent (Vyazovskiy and Faraguna, 2015).
- During PS, the EEG signal is apparently closer to the waking EEG and displays oscillations of low amplitude and high frequencies. The EEG power spectrum is then shifted toward more rapid frequencies with a specific peak at 5–7 Hz (theta band). The muscle tone reaches a minimum and the density of rapid eye movements (which are almost abolished during SWS) increases considerably.
- During waking, the EEG trace displays oscillations of low amplitude and rapid frequencies which correspond to desynchronization of cortical cells ("up-state") that have a high rate of firing. The power spectrum of the waking EEG exhibits a predominance in alpha (9–12 Hz), beta (12–30 Hz) and gamma (> 30 Hz) frequency bands.

Although many factors involved in the regulation of sleep are still unknown, a large body of evidence indicates that sleep regulation results in the interaction between circadian and homeostatic mechanisms (Borbély and Achermann, 1999).

A circadian regulation of sleep propensity controls the occurrence of the sleep period over the day. Similar to total sleep time and sleep episode duration, the daily sleep distribution varies greatly across mammals (Siegel, 2001). The daily distribution of sleep and wakefulness episodes follows a circadian rhythm (i.e. centered on a 24-h period). In standard conditions, this rhythm is driven by the suprachiasmatic nucleus (SCN) of the hypothalamus which directly integrates information about light intensity from the retina (Dibner et al., 2010). Through its neuronal projections and its action on the synthesis of humoral factors (such as melatonin), the SCN synchronizes different cellular clocks present in all neurons and astrocytes of the brain as well as in most of the cells of the body. Indeed, a set of genes (known as "clock genes") encode for proteins exerting positive and negative feedback on their own synthesis and on the synthesis of other proteins with a timing close to 24 h. This constitutes the molecular mechanisms of the cellular clock (Panda et al., 2002; Ko and Takahashi, 2006).

As we already mentioned, sleep is also regulated by homeostatic mechanisms. This means that the total sleep duration varies as a function of the preceding

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