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Sleep and circadian rhythms: Evolutionary entanglement and local regulation

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ABSTRACT

Circadian rhythms evolved within single cell organisms and serve to regulate rest-activity cycles in most single-cell and multiple-cell organisms. In contrast, sleep is a network emergent property found in animals with a nervous system. Rhythms and sleep are much entangled involving shared regulatory molecules such as adenosine, ATP, cytokines, neurotrophins, and nitric oxide. These molecules are activity-dependent and act locally to initiate regulatory events involved in rhythms, sleep, and plasticity.

1. Rhythms then sleep

Circadian rhythms evolved before sleep, perhaps even in the primordial soups of concentrated organic molecules. As cellular structures developed the linkage of cellular energetics to daily rhythms of temperature and light took place. As those relationships became more complex involving hundreds, if not thousands of molecules, their orchestration by internal cellular events improved cellular evolutionary fitness. These molecular symphonies became so robust that they could persist in the absence of solar ques and thereby billions of years later these arias were named circadian rhythms. Today, we recognize that the gene networks forming the basis of circadian rhythms are ancient, present in most single cell and higher order organisms, and are an integral regulatory component of rest-activity cycles.

Sleep in contrast is a multi-cellular emergent property of small local neuronal/glial networks whether *in vivo or in vitro* (Krueger and Obál, 1993; Krueger et al., 1995, 2008, 2013, 2019; Jewett et al., 2015; Hinard et al., 2012; Saberi-Moghadam et al., 2018; Bandarabadi et al., 2020; Rector et al., 2005; Vyazovskiy et al., 2011; Rattenborg et al., 2012; Corner et al., 2008; Huber et al., 2006). Although definitions of sleep at the single cell level remain unconvincing, sleep is closely linked to cellular activity whether *in vivo* (Huber et al., 2006) or *in vitro* (Hinard et al., 2012; Jewett et al., 2015). This relationship provides a logical, as well as molecular, rationale for the hypotheses that sleep evolved from rest states and has a metabolic function. Indeed, some sleep regulatory substances, e.g. ATP and adenosine, are key metabolic components providing deep associations between sleep and cellular rest-activity cycles. Further, as such molecules are released from single cell organisms and then detected by receptors on nearby cells, they provide a dynamic milieu for coordination of activity between cells. It is easy to envision how such actions could lead to coalescing of cells into multi-cellular organisms and their daily rest-activity cycles. However, the current consensus among sleep researchers is that sleep first occurs in evolution in higher order animals (not plants) with neurons such as hydra, jelly fish, C. elegans, insects and vertebrates. As these higher order animals evolved, some became nocturnal, other, diurnal, and yet others crepuscular; this separated light-driven thermo-linked metabolism, but not activity-linked metabolism, from sleep.

There are many molecules released locally by multiple cell types in response to cell stimulation and use. Several of these are well-characterized sleep regulatory molecules including ATP, adenosine, NO, prostaglandins, interleukin-1β (IL1), tumor necrosis factor α (TNF), and neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). The release of these molecules initiates local sleep and plasticity/connectivity events, in neurons and glia thus sleep and connectivity regulatory mechanisms are difficult to separate from each other (**reviewed** Krueger et al., 2016, 2019). If the stimulus/use is strong and wide spread, multiple local events will merge and synchronize eventually manifesting at higher organization levels as distinct events, e.g. memory and whole animal sleep. Viewed through this prism, it is understandable why sleep has been proposed to have plasticity/connectivity, functions. Further, because these phenomena are dependent upon cell use, they have circadian rhythms, and they are linked to core clock mechanisms, e.g. Per1, Clock, BMAL.

While it is likely that sleep serves all these functions, it is not clear why the reduced responsiveness of an organism to environmental stimuli is required, in terms of evolutionary fitness, for any of these functions except for plasticity/connectivity changes. Plasticity is a very

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local use-dependent phenomena that provides exceptional fitness. Yet, the cell activity-dependent molecules mentioned above alter the affected local circuit outputs in response to a given input. Thus before their release triggered by a bout of cell activity, the network response was adaptive as evidenced by the animal being alive. However, the activity-driven transient changes in network input – output relationships likely would alter the local network's adaptiveness, e. g. perhaps triggering a maladaptive local output in response to challenging input. Thus, while the activity-dependent molecules are altering the circuits it would be advantageous to not respond to environmental stimuli (Krueger et al., 2019, 2016). If just a few local circuits, e.g. cortical columns, were in such a use-dependent molecule-driven state performance might decrease (Van Dongen et al., 2011). However, as more and more local circuits transition, their state synchrony may trigger a higher organization level transition manifesting as sleep (Rector et al., 2005; Roy et al., 2008). As such an altered organism-level state, sleep, would ensure lower responsiveness to environmental ques and thereby provide fitness. The synchrony of the other proposed sleep functions, also driven by the same set of molecules, would likely enhance fitness because all were already connected to circadian rhythms and the simultaneous performance of those functions during circuit-associated sleep-like state would improve fitness efficiency and reduce the need for compartmentalization of those functions' mechanisms.

2. Entanglement of sleep, rhythms, and plasticity

Although there are some studies suggesting a clear independence of sleep and circadian rhythm regulations (Mistlberger et al., 1983) there are today many examples linking sleep, time-of-day, and activity to the sleep regulatory set of molecules mentioned above. Thus, one of the earlier studies of the somnogenic properties of interleukin-1β (IL1), now a well-characterized sleep regulatory substance (**reviewed** Krueger et al., 2008; Imeri and Opp 2009), showed that at certain doses, IL1 induces sleep in rats if administered during dark hours, but the same dose enhances wakefulness if given during the daylight hours (Opp et al., 1991). In the same study, low doses of IL1 enhanced non-rapid eye movement sleep at both times of the day while high IL1 doses promoted wakefulness regardless of when it was given. Such findings suggest a very delicate balance between pro-vs anti-somnogenic activities of the IL1 family. We now know that many members of the IL1 family, e.g. the IL1 receptor antagonist, the brain-specific IL1 receptor accessory protein (AcPb) and another isoform of AcP, the soluble AcP, the IL1 type II receptor, the soluble IL1 receptor are all anti-inflammatory while IL1, the IL1 type I receptor, and AcP are pro-inflammatory. Both *IL1* and *AcPb* mRNAs have distinct diurnal variations in brain with highest levels occurring at zeitgeber time zero (ZT0), the beginning of the rat sleep cycle (Taishi et al., 2012). Further, *AcPb* mRNA increases during sleep deprivation but *AcP* mRNA does not. AcPb is required for sleep rebound after sleep deprivation and AcP and AcPb alter sleep and development of burstiness, synchrony and slow wave power in neuronal/glial cultures (Nguyen et al., 2019a, 2019b). Regardless, the Opp study was published before many of these family members were characterized, and before Fontana's group showed a direct interaction of IL1 with clock molecular components (Cavadini et al., 2007) yet it strongly hinted that a richer more complex set of molecular reactions linked sleep regulation to clock rhythms.

The rat somatosensory cortex receives afferent input from mystacial whiskers. If the whiskers are cut, the contralateral cortical columns receiving input from the cut whisker rapidly reorganize; this is a well-characterized model used to investigate synaptic plasticity. This model was used to determine the influence of sleep loss on the expression of nerve growth factor (NGF), a somnogenic activity-dependent substance (Takahashi and Krueger, 1999; Brandt et al., 2001) and on *Homer 1a* mRNA, a sleep- and synaptic scaling-linked use-dependent molecule (Nelson et al., 2004; Maret et al., 2007). Sleep loss from ZT0 – ZT6 enhances somatosensory NGF-immunoreactive pyramidal neurons in layer V. In contrast, unilateral mystacial whisker cuts do not affect somatosensory NGF immunoreactivity in the contralateral or ipsilateral sides in undisturbed rats. A unilateral whisker cut at light onset, combined with sleep deprivation increases NGF-immunoreactive neurons only on the side that received input from the remaining intact whiskers. In contrast, NGF immunoreactivity on the side contralateral to the cut whiskers decreases in sleep-deprived rats to levels below those observed in undisturbed control animals. Thus, NGF expression is influenced by the interaction of sleep, afferent input and the nature of ongoing synaptic reorganization. The same rat whisker-somatosensory model was used to characterize *Homer 1a* mRNA somatosensory expression comparing nighttime to daytime and in combination with sleep deprivation plus a unilateral whisker cut. *Homer 1a* mRNA is greater at night (active period) than during the day (sleep period). The whisker cut alone increases *Homer 1a* mRNA about 2-fold at ZT6 while decreases it about 60% at ZT18. Sleep deprivation alone has larger effects, *Homer 1a* mRNA at ZT6 increases 11-fold while at ZT18, it decreases about 50%. The combination of sleep loss plus whisker had about the same effect as sleep deprivation alone at ZT6 but at ZT18 there was an interactive effect with *Homer 1a* mRNA increasing after these treatments; either treatment alone decreases expression at ZT18.

The studies mentioned showing interactions of sleep regulatory molecules with rhythms and the interactive effects on plasticity emphasize how difficult it will be to separate mechanisms from function for either sleep or circadian rhythms. These molecules, including others mentioned, e.g. ATP, adenosine, BDNF, and TNF, are synthesized in response to local signals, often even localized to subcellular sites, and act locally. One of their actions is to alter local circuit outputs in response to standardized inputs. That has been interpreted as “local sleep”. Regardless, sleep, inflammation, cerebral blood flow, neuroplasticity, and brain metabolism are all initiated locally, yet their emergent whole animal properties manifest in myriad ways including interactions with circadian rhythms. This emergence is not understood, nor is the compartmentalization of molecular mechanisms providing specificity of function for the emergent property, nor is how the disturbance of emergence or compartmentalization leads to pathology understood. These issues will challenge us for many years but are beginning to become tractable.

Credit author statement

James M. Krueger is the sole author and wrote the article alone.

Declaration of competing interest

The author has no conflicts of interests nor do the contents of the manuscript contain information with conflicts of interest.

James M. Krueger.

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