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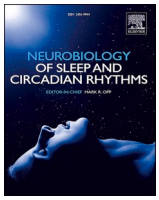

Challenging sleep homeostasis

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ABSTRACT

In this commentary, I play the Devil's advocate and assume the title of High Contrarian. I intend to be provocative to challenge long-standing ideas about sleep. I blame all on Professor Craig Heller, who taught me to think this way as a graduate student in his laboratory. Scientists should fearlessly jump into the foaming edge of what we know, but also consider how safe are their intellectual harbors. There are many ideas we accept as 'known': that sleep is ubiquitous in the animal kingdom, that it serves vital functions, that it plays an essential role in brain plasticity. All of this could be wrong. As one example, I reexamine the idea that sleep is regulated by a mysterious 'homeostat' that determines sleep need based on prior wake time.

1. Introduction

In this commentary, I play the Devil's advocate and assume the title of High Contrarian. I intend to be provocative to challenge long-standing ideas about sleep. I blame all on Professor Craig Heller, who taught me to think this way as a graduate student in his laboratory. Scientists should fearlessly jump into the foaming edge of what we know, but also consider how safe are their intellectual harbors. There are many ideas we accept as 'known': that sleep is ubiquitous in the animal kingdom, that it serves vital functions, that it plays an essential role in brain plasticity. All of this could be wrong. As one example, I reexamine the idea that sleep is regulated by a mysterious 'homeostat' that determines sleep need based on prior wake time.

2. What if there is no such thing as sleep homeostasis?

A central tenet about sleep is that it is controlled by at least two regulatory mechanisms. A circadian mechanism (Process C) determines the timing of sleep and wakefulness and a homeostatic mechanism (Process S) determines sleep propensity based on prior wake time (or possibly the absence of sleep). Only one of these mechanisms has been irrefutably demonstrated to exist on a molecular, anatomical, cellular, electrophysiological and behavioral level (Saper, 2013; Hardin and Panda, 2013; Allada et al., 2017).

Let us first consider the behavioral and electrophysiological evidence for a distinct Process S. Currently the strongest evidence is changes in mammalian non(N)REM EEG slow wave activity (SWA: a metric of sleep intensity). It is an accepted tenet that mammalian NREM SWA rises and falls in proportion to sleep propensity. A 2 Process model based on NREM SWA dynamics (Process S) and interactions with a Process C has proven highly predictive of sleep propensity under a range of experimental manipulations in humans and other mammals (Dijk and Kronauer, 1999). No other sleep metric (across mammalian species) changes in response to prior wake time (or sleep deprivation: SD) in similar, proportional, and compensatory ways (Borbely et al., 1982; Borbely and Achermann, 1992; Franken et al., 1991a, 1991b; Borbély, 2001). For example, sleep time can be increased by factors other than prior wake time. This has been shown in acute stress paradigms (such as restraint stress), which increase sleep time but in a manner unrelated to the amount of preceding wakefulness (Cespuglio et al., 1995). Sleep time lost during deprivation in vertebrates is not consistently recovered during the post-SD period, nor can it be modeled as a saturating function, as is true for NREM SWA (Horne, 1985; Beersma and Daan, 2015). Other changes observed after SD (e.g. alertness, decreased latency to sleep) are heavily influenced by biological clocks (Jewett and Kronauer, 1999), and are not used as primary indices of Process S.

Nevertheless, there have always been troubling findings with NREM SWA and a presumed Process S. NREM SWA can undershoot baseline values during recovery from SD or increase during extended sleep time. These findings do not easily comport with a homeostatic mechanism that maintains a set-point for sleep based on prior wake time (Franken et al., 1991b; De Koninck et al., 1996; Gagnon et al., 1985; Feinberg and March 1995). If decreases in NREM SWA reflect a discharge of sleep pressure (Dijk and Kronauer, 1999), then one would predict that interfering with its expression should delay wake time. This does not appear to be the case (Dijk and Kronauer, 1999). NREM SWA can also be

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disconnected from prior wake time under certain conditions. One example is early in life, as precocial mammalian species show large amounts of NREM SWA in utero at ages when wake time in miniscule (Davis et al., 1999) (and see (Davis et al., 2011) for additional examples). This does not fit a simple 2 process model by which sleep propensity is determined by prior wake time. Although Process S should be connected to sleep function (Benington, 2001), reductions in NREM SWA do not always result in negative effects on restorative or functional effects of sleep (Greene and Frank, 2010; Seibt et al., 2008). More recently, the entire relationship between NREM SWA and Process S has been questioned. The portion of SWA responsive to sleep loss resolves itself within 60 min and may be influenced by physiological variables unrelated to Process S. This challenges previous mathematical models describing changes in NREM SWA proportionate to prior wake time (Hubbard et al., 2020). All other electrophysiological measures of Process S (e.g., neuronal firing rates (Vyazovskiy et al., 2009)) must also now be reconsidered, as they are interpreted in terms of changes in NREM SWA.

Next, let us consider the physiological basis for a presumed Process S. For comparison it is useful to start with what we know about biological clocks. In mammals, there is a comprehensive body of work that identifies the anatomical location of the master clock (the suprachiasmatic nucleus: SCN), the molecular mechanisms that generate timekeeping in the clock, and circuits that connect the clock to other regions of the central and peripheral nervous system that result in 24-h rhythms in behavior, hormone release, and autonomic function (Saper, 2013; Hardin and Panda, 2013). In contrast, there is no consensus as to where the mammalian 'sleep homeostat' exists in the brain, no accepted molecular model that explains the biological basis of Process S, and no accepted explanation for how such a process influences (and is informed by) sleep.

To expand on this point, several brain regions have been proposed as the mammalian sleep homeostat, but what is often described are circuits necessary for switching between brain states. These circuits do not display electrophysiological activity or molecular patterns indicative of a process sensing prior wake time and adjusting sleep intensity accordingly. For the most part, they are either 'wake' active or 'sleep active' (Saper et al., 2001; Porkka-Heiskanen, 2013; Donlea et al., 2017). The basal forebrain, for example, has been proposed as housing the mammalian sleep homeostat. Indeed, activation/inhibition of different types of basal forebrain neurons can increase/decrease sleep time or intensity. Unfortunately, the basal forebrain is comprised of many different cell types and it is unclear which cells (if any) sense sleep propensity, and which are involved in state-switching vs. homeostasis (Strecker et al., 2000; Porkka-Heiskanen et al., 1997; Peng et al., 2020; Zant et al., 2016; Kalinchuk et al., 2008). There is some consensus concerning a mammalian mediator of Process S (i.e. adenosine), but less agreement about how adenosine is released (and by which cells) and the primary sites of action necessary and sufficient for Process S (Donlea et al., 2017; Benington and Heller, 1995; Huang et al., 2007; Lazarus et al., 2019).

In contrast to mammals, an increasingly well-defined set of circuits, inputs and outputs necessary for a putative sleep homeostat have been identified in *Drosophila melanogaster* (Allada et al., 2017; Donlea et al., 2017). On the other hand, it is not clear if what is being measured is a true homolog to mammalian Process S. There is no intensity dimension in insect sleep (based on electrophysiology or brain imaging) comparable to NREM SWA (Bushey et al., 2015; Nitz et al., 2002; Yap et al., 2017), therefore changes in sleep time are principally used to determine homeostasis. Yet, as discussed above, sleep time is not an accurate metric of mammalian Process S, which should make one cautious in accepting this metric in non-mammalian species. In fact, compensatory increases in Drosophila sleep after SD do not make up for lost sleep time (as is also true in mammals) and may be more under the control of clocks rather than a separate homeostat (Shaw et al., 2000; Hendricks et al., 2000; Geissmann et al., 2019; Huber et al., 2004). Other putative measures of invertebrate sleep homeostasis (Huber et al., 2004) (e.g. changes in arousal thresholds, latency to sleep) are not considered reliable indices of mammalian Process S and have not led to mathematical and predictive models of invertebrate sleep propensity.

In summary, it is possible that sleep homeostasis is a mirage. It represents yet another switch in sleep/wake mechanisms that when a certain threshold of waking is exceeded, it engages other switches that trigger sleep onset. This would explain why mammalian sleep propensity appears to discharge within 60 min (Hubbard et al., 2020). This might also be entirely explained in mundane ways as increasing refractory periods in waking circuits (based on known principles of synaptic transmission) that release sleep-inducing circuits from inhibition. In other words, no special separate Process S need exist.

3. Counterpoint

As an exercise, I took a contrarian position in my discussion of the rarely challenged idea that sleep is homeostatically regulated. But of course, things are not so simple, and a discussion of some counterpoints is necessary.

I presented two arguments against Process S. The first essentially deals with how sleep homeostasis is defined, based on the current best metric of Process S (NREM SWA). The second deals with the absence of a central 'master' sleep homeostat comparable to the mammalian SCN. Addressing the first argument, as originally conceived, NREM SWA is an *index* of a deeper brain process that requires sleep and is not necessarily the process itself (Horne, 1985; Beersma and Daan, 2015). Therefore, disconnections between NREM SWA and neural outcome measures (e.g., cognition, brain metabolism) are to be expected. The distance from this measure (NREM SWA) from that function (whatever it is) introduces variability. For example, NREM SWA has been hypothesized to decrease synaptic strength (Tononi, 2009). But there is no convincing direct evidence *in vivo* demonstrating that the accumulation and discharge of NREM SWA is driven by or drives changes in synapses (Frank, 2012). The mere presence of NREM SWA could be conducive to synaptic remodeling, but its build up and discharge may reflect some other, unrelated process. This may explain why no clear picture has emerged concerning the role of NREM SWA in synaptic plasticity (Seibt and Frank, 2019; Klinzing et al., 2019; Steriade and Timofeev, 2003; Timofeev and Chauvette, 2017). Therefore, an important challenge is to test direct links between this measure of sleep propensity and proposed sleep functions. Recent findings showing that sleep propensity dissipates within 60 min are more difficult to explain (Hubbard et al., 2020), but it would be premature to disregard hundreds of studies based on a single report. It is important that these findings be replicated and subjected to further tests using subjects with variable time courses of Process S (Franken et al., 2001) as well as mutants that show increases and decreases in the compensatory response to SD (Shaw and Franken, 2003).

Turning to the second argument, let us consider that the sleep homeostat is not a centralized nucleus but is instead an emergent property of a more diffuse matrix of brain cells. Astrocytes form a dense cell matrix throughout the brain, which allows them to sample surrounding neuronal activity and provide feedback. This provides a simple means of adjusting set-points in neural metabolism, neuronal energy supply, or synaptic transmission (Benington and Heller, 1995; Frank, 2013). Astrocyte homeostats could mediate 'local' sleep (via feedback onto subsets of neurons) as well as global changes in sleep architecture and EEG activity (via direct influence on state-switches). These 'peripheral' and 'central' sleep homeostats may be synchronized by global changes in neuromodulators (Frank, 2013). This view is supported by findings in mammals and invertebrates, where astrocytes have been shown to track sleep propensity and influence compensatory changes in sleep after SD (Frank, 2013; Ingiosi et al., 2020; Liu et al., 2016; Blum et al., 2021; Halassa et al., 2009). Therefore, perhaps we haven't found the 'sleep homeostat' because we have been looking in the wrong place.

4. Concluding remarks

This commentary is not intended to be an exhaustive pro and con on the seminal idea that is sleep homeostasis. It is rather presented as a provocative prod for further investigation of this and other central topics in sleep. Scientists have made extraordinary progress, but many of our most accepted ideas should be periodically revisited with an inquisitive eye. I chose one idea, but many more could be (should be) subjected to similar interrogation.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

Allada, R., Cirelli, C., Sehgal, A., 2017. Molecular mechanisms of sleep homeostasis in flies and mammals. Cold Spring Harb Perspect Biol 9.

Beersma, D.G.M., Daan, S., 2015. On the role of sleep intensity in a model of sleep regulation. Sleep 38, 661–662.

Benington, J., 2001. Sleep homeostasis and the function of sleep. Sleep 23, 959–966.

Benington, J., Heller, H.C., 1995. Restoration of brain energy metabolism as the function of sleep. Prog. Neurobiol. 45, 347–360.

Borbély, A.A., 2001. From slow waves to sleep homeostasis: new perspectives. Arch. Ital. Biol. 139, 53–61.

Borbely, A.A., Achermann, P., 1992. Concepts and models of sleep regulation: an overview. J. Sleep Res. 1, 63–79.

Blum, I.D., Keleş, M.F., Baz, E.-S., Han, E., Park, K., Luu, S., Issa, H., Brown, M., Ho, M.C. W., Tabuchi, M., et al., 2021. Astroglial calcium signaling encodes sleep need in Drosophila. Curr. Biol. 31 (1), 150–162.

Borbely, A.A., 1982. Sleep regulation: circadian rhythm and homeostasis. Current topics in neuroendocrinology. In: Ganten, D., Pfaff, D. (Eds.), Sleep: Clinical and Experimental Aspects. Springer-Verlag), Berlin, pp. 82–103.

Bushey, D., Tononi, G., Cirelli, C., 2015. Sleep- and wake-dependent changes in neuronal activity and reactivity demonstrated in fly neurons using in vivo calcium imaging. Proc. Natl. Acad. Sci. Unit. States Am. 112, 4785.

Cespuglio, R., Marinesco, S., Baubet, V., Bonnet, C., El Kafi, B., 1995. Evidence for a sleep-promoting influence of stress. Adv. Neuroimmunol. 5, 145–154.

Davis, F.C., Frank, M.G., Heller, H.C., 1999. Ontogeny of sleep and circadian rhythms. In: Zee, P.C., Turek, F.W. (Eds.), Regulation of Sleep and Circadian Rhythms, vol. 133. Marcel Dekker, Inc., New York, pp. 19–80.

Davis, C.J., Clinton, J.M., Jewett, K.A., Zielinski, M.R., Krueger, J.M., 2011. Delta wave power: an independent sleep phenotype or epiphenomenon? J Clin Sleep Med 7, S16–S18.

De Koninck, G.C., Hébert, M., Carrier, J., Lamarche, C., Dufour, S., 1996. Body temperature and the return of slow wave activity in extended sleep. Electroencephalogr. Clin. Neurophysiol. 98, 42–50.

Dijk, D.J., Kronauer, R.E., 1999. Commentary: models of sleep regulation: successes and continuing challenges. J. Biol. Rhythm. 14, 569–573.

Donlea, J.M., Alam, M.N., Szymusiak, R., 2017. Neuronal substrates of sleep homeostasis; lessons from flies, rats and mice. Curr. Opin. Neurobiol. 44, 228–235.

Feinberg, I., March, J.D., 1995. Observations on delta homeostasis, the one-stimulus model of NREM-REM alternation and the neurobiologic implications of experimental dream studies. Behav. Brain Res. 69, 97–108.

Frank, M.G., 2012. Erasing synapses in sleep: is it time to be SHY? Neural Plast. 2012.

Frank, M.G., 2013. Astroglial regulation of sleep homeostasis. Curr. Opin. Neurobiol. 23, 812–818.

Franken, P., Dijk, D.J., Tobler, I., Borbely, A.A., 1991a. Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. Am. J. Physiol. 261, R198–R208.

Franken, P., Tobler, I., Borbely, A.A., 1991b. Sleep homeostasis in the rat: simulation of the time course of EEG slow-wave activity. Neurosci. Lett. 130, 141–144.

Franken, P., Chollet, D., Tafti, M., 2001. The homeostatic regulation of sleep need is under genetic control. J. Neurosci. 21, 2610–2621.

Gagnon, P., De Koninck, J., Broughton, R., 1985. Reappearance of electroencephalogram slow waves in extended sleep with delayed bedtime. Sleep 8, 118–128.

Geissmann, Q., Beckwith, E.J., Gilestro, G.F., 2019. Most sleep does not serve a vital function: evidence from Drosophila melanogaster. Science advances 5 eaau9253-eaau9253.

Greene, R.W., Frank, M.G., 2010. Slow wave activity during sleep: functional and therapeutic implications. Neuroscientist 17, 618–633.

Halassa, M.M., Florian, C., Fellin, T., Munoz, J.R., Lee, S.Y., Abel, T., Haydon, P.G., Frank, M.G., 2009. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61, 213–219.

Hardin, P.E., Panda, S., 2013. Circadian timekeeping and output mechanisms in animals. Curr. Opin. Neurobiol. 23, 724–731.

Hendricks, J.C., Finn, S.M., Panckeri, K.A., Chavkin, J., Williams, J.A., Sehgal, A., Pack, A.I., 2000. Rest in drosophila is a sleep-like state. Neuron 25, 129–138.

Horne, J.A., 1985. Sleep function, with particular reference to sleep deprivation. Ann. Clin. Res. 17, 199–208.

Huang, Z.-L., Urade, Y., Hayaishi, O., 2007. Prostaglandins and adenosine in the regulation of sleep and wakefulness. Current Opinion in Pharmacology Neurosciences 7, 33–38.

Hubbard, J., Gent, T.C., Hoekstra, M.M.B., Emmenegger, Y., Mongrain, V., Landolt, H.P., Adamantidis, A.R., Franken, P., 2020. Rapid fast-delta decay following prolonged wakefulness marks a phase of wake-inertia in NREM sleep. Nat. Commun. 11, 3130.

Huber, R., Hill, S.L., Holladay, C., Biesiadecki, M., Tononi, G., Cirelli, C., 2004. Sleep homeostasis in Drosophila melanogaster. Sleep 27, 628–639.

Ingiosi, A.M., Hayworth, C.R., Harvey, D.O., Singletary, K.G., Rempe, M.J., Wisor, J.P., Frank, M.G., 2020. A role for astroglial calcium in mammalian sleep and sleep regulation. Curr. Biol. : CB 30, 4373-4383 e4377.

Jewett, M.E., Kronauer, R.E., 1999. Interactive mathematical models of subjective alertness and cognitive throughput in humans. J. Biol. Rhythm. 14, 588–597.

Kalinchuk, A.V., McCarley, R.W., Stenberg, D., Porkka-Heiskanen, T., Basheer, R., 2008. The role of cholinergic basal forebrain neurons in adenosine-mediated homeostatic control of sleep: lessons from 192 IgG-saporin lesions. Neuroscience 157, 238–253.

Klinzing, J.G., Niethard, N., Born, J., 2019. Mechanisms of systems memory consolidation during sleep. Nat. Neurosci. 22, 1598–1610.

Lazarus, M., Chen, J.F., Huang, Z.L., Urade, Y., Fredholm, B.B., 2019. Adenosine and sleep. Handb. Exp. Pharmacol. 253, 359–381.

Liu, S., Liu, Q., Tabuchi, M., Wu, M.N., 2016. Sleep drive is encoded by neural plastic changes in a dedicated circuit. Cell 165, 1347–1360.

Nitz, D.A., van Swinderen, B., Tonini, G., Greenspan, R.J., 2002. Electrophysiological correlates of rest and activity in Drosophila melanogaster. Curr. Biol. : CB 19, 1934–1940.

Peng, W., Wu, Z., Song, K., Zhang, S., Li, Y., Xu, M., 2020. Regulation of sleep homeostasis mediator adenosine by basal forebrain glutamatergic neurons. Science 369, eabb0556.

Porkka-Heiskanen, T., 2013. Sleep homeostasis. Curr. Opin. Neurobiol. 23, 799–805.

Porkka-Heiskanen, T., Strecker, R.E., Thakkar, M., Bjorkum, A.A., Greene, R.W., McCarley, R.W., 1997. Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science 276, 1265–1268.

Saper, C.B., 2013. The central circadian timing system. Curr. Opin. Neurobiol. 23, 747–751.

Saper, C.B., Chou, T.C., Scammell, T.E., 2001. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 24, 726–731.

Seibt, J., Frank, M.G., 2019. Primed to sleep: the dynamics of synaptic plasticity across brain states. Front. Syst. Neurosci. 13, 2.

Seibt, J., Aton, S.J., Jha, S.K., Coleman, T., Dumoulin, M.C., Frank, M.G., 2008. The non-benzodiazepine hypnotic zolpidem impairs sleep-dependent cortical plasticity. Sleep 31, 1381–1391.

Shaw, P.J., Franken, P., 2003. Perchance to dream: solving the mystery of sleep through genetic analysis. J. Neurobiol. 54, 179–202.

Shaw, P.J., Cirelli, C., Greenspan, R.J., Tononi, G., 2000. Correlates of sleep and waking in Drosophila melanogaster. Science 287, 1834–1837.

Steriade, M., Timofeev, I., 2003. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 37, 563–576.

Strecker, R.E., Morairty, S., Thakkar, M.M., Porkka-Heiskanen, T., Basheer, R., Dauphin, L.J., Rainnie, D.G., Portas, C.M., Greene, R.W., McCarley, R.W., 2000. Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. Behav. Brain Res. 115, 183–204.

Timofeev, I., Chauvette, S., 2017. Sleep slow oscillation and plasticity. Curr. Opin. Neurobiol. 44, 116–126.

Tononi, G., 2009. Slow wave homeostasis and synaptic plasticity. J Clin Sleep Med 5, S16–S19.

Vyazovskiy, V.V., Olcese, U., Lazimy, Y.M., Faraguna, U., Esser, S.K., Williams, J.C., Cirelli, C., Tononi, G., 2009. Cortical firing and sleep homeostasis. Neuron 63, 865–878.

Yap, M.H.W., Grabowska, M.J., Rohrscheib, C., Jeans, R., Troup, M., Paulk, A.C., van Alphen, B., Shaw, P.J., van Swinderen, B., 2017. Oscillatory brain activity in spontaneous and induced sleep stages in flies. Nat. Commun. 8, 1815-1815.

Zant, J.C., Kim, T., Prokai, L., Szarka, S., McNally, J., McKenna, J.T., Shukla, C., Yang, C., Kalinchuk, A.V., McCarley, R.W., et al., 2016. Cholinergic neurons in the basal forebrain promote wakefulness by actions on neighboring non-cholinergic neurons: an opto-dialysis study. J. Neurosci. 36, 2057–2067.