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Editorial

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TCF4's role in sleep/wake state and sleep function

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A fundamental aspect of sleep is the gating of transitions from wake to sleep and sleep to wake. The gating is influenced by arousal centers. They determine the probability that the absence or presence of stimuli, including exteroceptive and interoceptive stimuli, will result in a transition from wake to sleep or sleep to wake, respectively. Thus, on average, the duration of sleep time is a function of arousal system activity.

Sleep function depends on mechanisms engaged during time spent in sleep. It follows that sleep duration, gated by arousal center activity, constrains sleep function. Furthermore, intuitively we know that the longer we are awake, the sleepier we feel (other environmental conditions being equal). However, the changes that are mediated by sleep function cannot be equated with the changes needed to modulate arousal center activity. For example, the duration of sleep can be decreased by experimental sleep deprivation or genetically increased neuronal excitability by a loss of function of various potassium channels [1–3]. A pharmacological decrease of excitability from benzodiazepines or by enhancing K2P channel activity with anesthesia agents [4], increases sleep time. These changes in sleep time can occur independently of high or low sleep need. On the other hand, slow wave activity during NREM or slow wave sleep (SWS-SWA) correlates with previous waking duration [5–7] and is often employed as a marker for sleep need. This too, can be dissociated from wake/sleep duration by either a genetic loss of function of *Adora1* (to decrease SWS-SWA after sleep loss) or of *Ak* (to increase SWS-SWA with normal sleep time) [8, 9]. Nonetheless, an understanding of the mechanisms determining daily sleep amount can form a necessary foundation for therapeutic approach(es) to pathologies primarily affecting arousal systems and, as a result, disrupting sleep function.

A study published recently in **Sleep** [10] provides a genomic mechanism that is sufficient to reduce daily sleep amount involving the interaction of class 1, basic helix-loop-helix transcription factors, TCF 3/4/12 with CREB and HDAC4/5. Forebrain overexpression of *Tcf4* reduces NREM and REM time suggesting sufficiency of this transcription factor to increase arousal. However, a triple knockout of *Tcf3/4/12* by injection of AAV-*sgRNA*$^{TCF3/4/12}$ into constitutively expressing *Cas9* transgenic mice failed to alter sleep time. The lack of effect could either suggest that genes, *Tcf 3/4/12*, are not essential for the normal control of sleep time or, as suggested by the authors, that the knockdown of these transcription factors was not complete enough to affect arousal and sleep time.

This study also addresses how overexpression of *Tcf4* can reduce sleep time. Compared to the wild type, reduced NREM time in ABC-*Tcf4* mice (*Tcf4* overexpression) could be restored by the loss of function of *Creb1*. This was demonstrated using *Creb1flox/flox* knockin mice (with normal NREM time) and retro-orbital administration of multiple AAV-PHP.eB vectors. The vectors had the following constructs: (1) AAV-*hSyn-Tcf4* for *Tcf4* overexpression and (2) AAV-*hSyn-Cre* to generate ABC-*Tcf4/Creb1* KO. The restoration of NREM time in *Tcf4* overexpressing mice after *Creb1* knockdown demonstrates the reliance of overexpressed *Tcf4*'s sleep reduction on CREB activity [10]. The dependence of *Tcf4* overexpression effects on *Hdac4* appears to be relatively minor since, in *Hdac4* knockdown mice *Tcf4* overexpression still reduced sleep [10].

In striatum and cortex, CREB activity increases neuronal excitability [11, 12] raising the possibility of a generalized increase of forebrain excitability from overexpressed *Tcf4* and CREB interaction. Of relevance to the control of wake/sleep time, a loss of function of *Creb1* in the forebrain of mice increases sleep time and overexpression decreases sleep time [13–15] but it is less clear whether this involves interaction with TCF4 under physiological conditions. Perhaps a more complete conditional knockout of *Tcf3/4/12* using transgenic floxed animals can help answer this question.

HDAC4 localized to the nucleus also increases waking [15] whereas a loss of function of *Hdac4* decreases waking [16]. Expression of *Hdac4cn* localized to the posterior hypothalamus, a region known to positively, regulate arousal [17], is sufficient to increase wake time and this effect requires *Creb1* function. When CREB activity is locally inhibited in the posterior hypothalamus, *Hdac4cn* is no longer able to increase wake time [15]. An essential role for *Tcf3/4/12* in posterior hypothalamic *Hdac4cn* is unlikely, since the brain-wide *Tcf4* overexpression increase in wake time is only slightly affected by brain-wide *Hdac4* knockdown, suggesting independence of *Tcf4* overexpression from *Hdac4*. This would not rule out *Tcf4* overexpression localized to the posterior hypothalamus as sufficient to increase wake time.

The overexpressed *Tcf4* effects on SWS-SWA are potentially of interest, to the extent that SWS-SWA is a marker for sleep need. Under physiological conditions, SWS-SWA energy correlates with the previous duration of waking [7] but the mechanism responsible for this correlation is unclear. Thus, when SWS-SWA is reduced by *Tcf4* overexpression [10], this outcome might be due to reduced sleep need or it could be due to a more direct effect on the expression of SWS-SWA energy, independent of sleep need. Sleep does alter the transcriptome of brain tissue [18], reduce glutamatergic, cortical synaptic strength [19], both in an MEF2c-dependent manner [20], and increase metaplastic potential for LTP [21]. Toward an understanding of *Tcf4* overexpression's effects on sleep need, one may ask what its effects are on any of these sleep-dependent outputs.

In conclusion, the study by Zhou et al. [10] opens an important new line of investigation into the role of *Tcf4* in arousal and possibly in sleep function that has not been previously considered. *Tcf4* overexpression is sufficient to reduce sleep time and alter SWS-SWA, likely through different intracellular pathways involving CREB (for effects on sleep duration) and HDAC4. Further study of these TCF4-dependent pathways with respect to their roles in both arousal and sleep function is likely to provide significant advances in the field's understanding of sleep and wake.

Conflict of Interest Statement

The author has no financial or nonfinancial conflicts of interest to disclose.

References

1. Pang DS, Robledo CJ, Carr DR, *et al*. An unexpected role for TASK-3 potassium channels in network oscillations with implications for sleep mechanisms and anesthetic action. *Proc Natl Acad Sci U S A* 2009;**106**(41):17546–17551. doi:10.1073/pnas.0907228106
2. Yoshida K, Shi S, Ukai-Tadenuma M, Fujishima H, Ohno RI, Ueda HR. Leak potassium channels regulate sleep duration. *Proc Natl Acad Sci U S A* 2018;**115**(40):E9459–E9468. doi:10.1073/pnas.1806486115
3. Douglas CL, Vyazovskiy V, Southard T, *et al*. Sleep in Kcna2 knockout mice. *BMC Biol* 2007;**5**:42. doi:10.1186/1741-7007-5-42
4. Steinberg EA, Wafford KA, Brickley SG, Franks NP, Wisden W. The role of K(2)p channels in anaesthesia and sleep. *Pflugers Arch* 2015;**467**(5):907–916. doi:10.1007/s00424-014-1654-4
5. Tobler I, Borbely AA. Sleep EEG in the rat as a function of prior waking. *Electroencephalogr Clin Neurophysiol* 1986;**64**(1):74–76. doi:10.1016/0013-4694(86)90044-1
6. Dijk DJ, Brunner DP, Beersma DG, Borbely AA. Electroencephalogram power density and slow wave sleep as a function of prior waking and circadian phase. *Sleep*. 199010.1093/sleep/13.5.430
7. Franken P, Chollet D, Tafti M. The homeostatic regulation of sleep need is under genetic control. *J Neurosci* 2001;**21**(8):2610–2621. doi:10.1523/JNEUROSCI.21-08-02610.2001
8. Bjorness TE, Kelly CL, Gao T, Poffenberger V, Greene RW. Control and function of the homeostatic sleep response by adenosine A1 receptors. *J Neurosci* 2009;**29**(5):1267–1276. doi:10.1523/JNEUROSCI.2942-08.2009
9. Bjorness TE, Dale N, Mettlach G, *et al*. An adenosine-mediated glial-neuronal circuit for homeostatic sleep. *J Neurosci* 2016;**36**(13):3709–3721. doi:10.1523/JNEUROSCI.3906-15.2016
10. Zhou R, Zhang C, Gan R, *et al*. Transcriptional regulation of daily sleep amount by TCF4-HDAC4-CREB complex in mice. *Sleep*. 2025;**48**(5):1–12. doi:10.1093/sleep/zsae313
11. Marie H, Morishita W, Yu X, Calakos N, Malenka RC. Generation of silent synapses by acute in vivo expression of CaMKIV and CREB. *Neuron*. 2005;**45**(5):741–752. doi:10.1016/j.neuron.2005.01.039
12. Dong Y, Green T, Saal D, *et al*. CREB modulates excitability of nucleus accumbens neurons. *Nat Neurosci* 2006;**9**(4):475–477. doi:10.1038/nn1661
13. Graves LA, Hellman K, Veasey S, Blendy JA, Pack AI, Abel T. Genetic evidence for a role of CREB in sustained cortical arousal. *J Neurophysiol* 2003;**90**(2):1152–1159. doi:10.1152/jn.00882.2002
14. Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. *Nature*. 2005;**437**(7058):556–559. doi:10.1038/nature04071
15. Zhou R, Wang G, Li Q, *et al*. A signalling pathway for transcriptional regulation of sleep amount in mice. *Nature*. 2022;**612**(7940):519–527. doi:10.1038/s41586-022-05510-6
16. Kim SJ, Hotta-Hirashima N, Asano F, *et al*. Kinase signalling in excitatory neurons regulates sleep quantity and depth. *Nature*. 2022;**612**(7940):512–518. doi:10.1038/s41586-022-05450-1
17. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci* 2001;**24**(12):726–731. doi:10.1016/s0166-2236(00)02002-6
18. Cirelli C, Gutierrez CM, Tononi G. Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron*. 2004;**41**(1):35–43. doi:10.1016/s0896-6273(03)00814-6
19. Liu ZW, Faraguna U, Cirelli C, Tononi G, Gao XB. Direct evidence for wake-related increases and sleep-related decreases in synaptic strength in rodent cortex. *J Neurosci* 2010;**30**(25):8671–8675. doi:10.1523/JNEUROSCI.1409-10.2010
20. Bjorness TE, Kulkarni A, Rybalchenko V, *et al*. An essential role for MEF2C in the cortical response to loss of sleep in mice. *Elife*. 2020;**9**:e58331. doi:10.7554/eLife.58331
21. Vogt KE, Kulkarni A, Pandi R, Dehnad M, Konopka G, Greene RW. Sleep need driven oscillation of glutamate synaptic phenotype. *Elife*. 2025;**13**:98280.