Purinergic Signalling (2020) 16:475–476
https://doi.org/10.1007/s11302-020-09758-3

JOURNAL CLUB

Extracellular levels of the sleep homeostasis mediator, adenosine, are regulated by glutamatergic neurons during wakefulness and sleep

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Received: 1 December 2020 / Accepted: 3 December 2020 / Published online: 6 January 2021

Commentary

The basal forebrain (BF) is recognized as one of the crucial brain regions that regulate sleep and wakefulness and an increase in the extracellular concentration of adenosine in the BF during wakefulness and associated stimulation of A_1 receptors are known to increase the pressure to sleep. How different neuronal populations control adenosine release is, however, unclear. Blanco-Centurion et al. [1] investigated the role of cholinergic neurons in the BF by administering 192–IgG–saporin to lesion them, but surprisingly the results indicated that adenosine from cholinergic neurons in BF are not essential to sleep induction. Then, Xu et al. [2] showed that BF glutamatergic activity had a stronger arousal effect than cholinergic neurons. However, how to measure the concentration of adenosine in the BF dynamically, especially during REM sleep, is a big challenge.

In the present paper [3], the team first developed the adenosine sensor, $GRAB_{Ado}$, by replacing the third intracellular loop of the adenosine A_{2A} receptor with a conformation-sensitive form of enhanced GFP. Binding of this construct by adenosine induces a conformational change that increases the GFP fluorescence with a temporal resolution of tens of milliseconds, which is much faster than the microdialysis techniques used previously. The sensor did not modify cAMP levels or alter Ca^{2+} signaling, so it does not appear to affect the cell physiology. They then expressed $GRAB_{Ado}$ in the BF of mice and measured changes in fluorescence using fiber photometry through an implanted optical fiber. They found that the concentration of extracellular adenosine in the BF was higher during wakefulness and lower during NREM sleep, which is consistent with previous studies using microdialysis to measure changes in adenosine concentration. Unfortunately, the duration of REM sleep in mice is short, and traditional microdialysis methods cannot accurately measure adenosine concentration during REM sleep. However, the high temporal resolution of $GRAB_{Ado}$ revealed not only that adenosine is also present at high concentrations during REM sleep but also that it is actually higher than during waking and NREM sleep. Moreover, the authors observed rapid changes in adenosine concentration during phase transitions during sleep.

The authors then investigated how the activity of the cholinergic and glutamatergic neurons in BF contributes to these changes in adenosine levels during the sleep-wake cycle by simultaneously measuring intracellular Ca^{2+} levels in these neurons in the contralateral BF. The activity of both types of neuron was highly correlated with adenosine concentration changes, but always preceded changes in adenosine levels by tens of seconds. Next, by using optogenetic stimulation, the authors observed that the activation of glutamate neurons caused a more substantial and robust increase in extracellular adenosine compared to cholinergic neurons. Finally, the team selectively ablated the BF glutamatergic neurons and found that the rises in extracellular adenosine during wakefulness and REM sleep were significantly reduced. In addition, these mice spent more time in an awake state than untreated mice. Therefore, the activity of glutamatergic neurons is implicated in the regulation of extracellular adenosine accumulation and in the sleep-awake cycle.

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Thus, this study used a novel tool to measure the concentration of extracellular adenosine in the BF and demonstrated higher amounts of adenosine, not only during wakefulness but also during REM sleep. It also showed that these changes are highly correlated with glutamatergic neuronal activity and that both contribute to the change in sleep pressure. Thus these data greatly advance our understanding of how neuronal activity in the BF during wakefulness contributes to sleep pressure through the release of the sleep-inducing agent, adenosine.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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