Adenosine serves a “good night sleep” via the A_{2A} receptor

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Adenosine is a neuromodulator in the central nervous system with sedative, anticonvulsant, hypnogenic, ataxic, and antinociceptive properties. This endogenous purine nucleoside is well-recognized in the sleep research community, since the wakefulness-enhancing effect of the widely used psychostimulant caffeine was discovered to result from antagonizing adenosine A₁ and A_{2A} receptors [1] supporting earlier pharmacological studies showing somnogenic effects of adenosine [2]. Given the underlying mechanism of how adenosine promotes sleep, it was postulated that adenosine is produced during wakefulness [3], and evidence suggested that extracellular adenosine accumulates in the basal forebrain and cortex during spontaneous wakefulness or in response to sleep deprivation [4].

The neuromodulatory effects of adenosine are mediated by specific cell-surface receptors, namely, the G protein coupled A₁, A_{2A}, A_{2B}, and A₃ subtypes. Which receptor subtype(s) play a dominant role in sleep regulation remains controversial. Initially, a significant contribution of A₁ receptors to adenosine-enhanced sleep was proposed [5], while the role of A_{2A} receptors was considered excitatory. Conventional A₁ receptor knockout mice normally accumulate sleep pressure in response to sleep deprivation though; conditional A₁ receptor knockout mice fail to respond, indicating brain-site specific function of A₁ receptors and its involvement in sleep homeostasis. On the other hand, A_{2A} receptors are required for caffeine-induced arousal and ethanol-mediating drowsiness. Moreover, activating A_{2A} receptors by specific agonists increased non-REM sleep, whereas A₁ receptor agonists failed to affect sleep in A_{2A} knockout mice [6]. Evidently, the A₁ and A_{2A} systems have distinct roles in controlling vigilance states [7].

A recent article published in *Sleep and Biological Rhythms* by Tsai et al. [8] adds further evidence for the

importance of adenosine A_{2A} receptors in spontaneous sleep–wake regulation. The authors performed a comprehensive analysis on sleep architecture in A_{2A} receptor knockout mice and described modest but significant changes in sleep architecture. Compared with wild-type littermates, A_{2A} receptor knockout mice display fragmented non-REM and REM sleep, and slightly reduced EEG delta power during non-REM sleep in the light period, although the total sleep amounts were nearly comparable between 2 genotypes. These effects were detected during light-phase sleep, suggesting that adenosine A_{2A} receptors are responsible for stabilizing the sleep cycle and, therefore, contribute to a better homeostatic control of sleep. The further importance of A_{2A} receptors emerges in the study by Tsai et al. that indicated impaired sleep quality linked to their congenital deficiency, implicating A_{2A} receptors in maintaining healthy sleep patterns. How the A₁ and A_{2A} systems work together along with other receptor systems will be a future research aim.

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