Caffeine, the circadian clock, and sleep

Why is caffeine intake at bedtime a sleep disrupter?

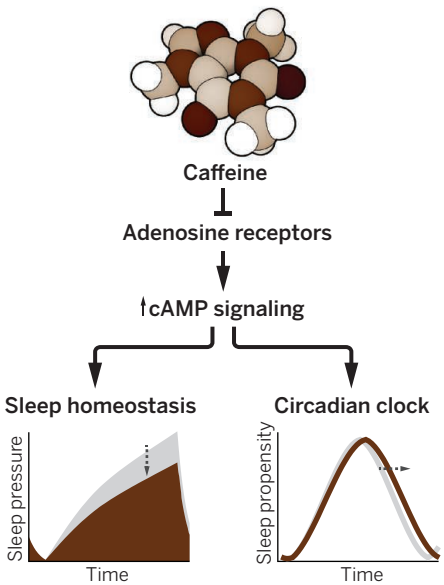
By **Hans Peter Landolt**

Caffeine wakes people up but also disrupts the quality of sleep. A new study by Burke *et al.* (*1*) reveals that consuming caffeine in the evening—the equivalent of a double espresso—delays the human endogenous circadian clock by antagonizing receptors for the endogenous sleep factor adenosine in the brain (see the figure). Mistimed caffeine consumption may contribute to the growing incidence of sleep problems in society.

Many people worldwide consume caffeine daily. Normal dietary consumption is sufficient to antagonize up to 50% of the inhibitory A_1 and the facilitatory A_{2A} adenosine receptors in the brain (*2*, *3*). This increases alertness and allays drowsiness and fatigue, but may also induce restlessness and prolong the time to fall asleep, enhance nighttime wakefulness, and reduce the depth of sleep (*4*).

Adequate sleep is required for good health and quality of life. The sleep-wake cycle is regulated by the fine-tuned interplay between homeostatic and circadian processes (*5*). Homeostatic sleep need accumulates during wakefulness and dissipates during sleep, whereas the circadian clock determines when sleep occurs. Slow-wave (or delta) neuronal activity (~0.75 to 4.5 Hz) recorded with an electroencephalogram (EEG) during deep sleep provides the most reliable biomarker of sleep need (*5*). Because caffeine attenuates sleep delta activity and blocks adenosine receptors, a role for adenosine and its receptors in sleep homeostasis has long been suggested (*4*). Burke *et al.* investigated whether caffeine also affects the human circadian clock. This is important because sleep and circadian systems are intimately linked at genetic, molecular, and behavioral levels.

Burke *et al.* used a highly sensitive protocol under strictly controlled conditions over a period of 49 days, and quantified the effects of 200 mg of caffeine on the timing of melatonin production in people when taken 3 hours before habitual bedtime in the evening. Melatonin is a hormone that in humans, entrains the circadian rhythm of many physiological processes, such as the timing of sleep, and is a reliable phase marker of the endogenous circadian pacemaker (*6*). Indeed, caffeine strongly and consistently delayed the melatonin rhythm by about 40 min, nearly half of the delay caused by bright light exposure at bedtime, a strong time cue for the circadian clock (*7*). But how does caffeine delay the circadian rhythm?



Double espresso effect. By blocking cerebral adenosine A_1 and A_{2A} receptors, caffeine increases intracellular cAMP signaling, attenuates the buildup of homeostatic sleep propensity during waking, and delays the circadian clock in vitro and in vivo.

The complex signaling cascade that regulates clock functions is expressed in nearly every cell of the body (*8*). In vitro, caffeine not only blocks adenosine receptors but also inhibits phosphodiesterase activity and activates ryanodine receptors. These actions increase cyclic adenosine monophosphate (cAMP)–dependent signaling and intracellular calcium release (*2*), both of which contribute to circadian timekeeping and resetting of the clock (*9*, *10*). Burke *et al.* measured circadian transcriptional rhythms in genetically engineered human cells expressing more than 10,000 proteins, including adenosine receptors, multiple phosphodiesterases, and ryanodine receptors. They confirmed that caffeine lengthens the circadian period and increases cAMP concentration. Although some open questions remain, their convergent pharmacological, genetic, and immunochemical data suggest an adenosine A_1 receptor–mediated, cAMP-dependent mechanism.

Caffeine-induced interference with the circadian clock may contribute to the high incidence of sleep problems in society and have a negative impact on brain functions that rely on undisturbed slow-wave sleep (*11*). Indeed, circadian rhythmicity modulates important functional characteristics of slow-wave sleep in humans (*12*). Yet, properly timed caffeine could alleviate jet lag and help patients with circadian sleep-wake disorders. Research on causal relationships among caffeine, circadian timekeeping, sleep, and health is warranted.

Apart from the circadian clock, cAMP signaling also plays an important role in sleep homeostasis and in the effects of caffeine on the consequences of sleep loss in animals (*13*, *14*). In humans, the physiological study of wakefulness and sleep is laborious, and the molecular mechanisms underlying sleep-wake regulation are difficult to elucidate. Given that cultured cells can display a sleep-like state (that is, neuronal firing activity reminiscent of sleep) (*15*), fundamental questions related to electrophysiological, genetic, and molecular features, as well as the pharmacology of sleep, can now be studied in human cells in vitro. Combined with physiological approaches, this opens up exciting new perspectives to examine the molecular bases of human sleep and to develop evidence-based therapeutic interventions for disturbed sleep in health and disease. ■

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