THE IDEA THAT THE REGULATION OF SLEEP IS UNDER CONTROL OF ONE PHYSIOLOGICAL MECHANISM, ONE NEUROCHEMICAL PATHWAY, OR ONE BRAIN REGION has seduced many of us.1,2 Part of the appeal of the hypothesis—that elevated extracellular adenosine produced by basal forebrain (BF) cholinergic neurons during wake functions to promote sleep by inhibiting those same cholinergic neurons—is its simplicity.3,4 Such hypotheses have great value in generating definitive experimental analyses. The fact that Blanco-Centurion and colleagues4 have provided evidence that BF cholinergic neurons are not necessary for homeostatic sleep regulation means that we have to alter our thinking about adenosinergic sleep-regulatory mechanisms, but we should not forget the concepts that made the hypothesis appealing in the first place. There is merit in the ideas that sleep is somehow coupled with cerebral metabolic energy reserves, that adenosine production is an established signal of reduced energy supply, and that adenosine has well known receptor-mediated effects that could yield suppression of waking neuronal activity and promote sleep. It is well established that the adenosine antagonist, caffeine, is a potent stimulant.

The adenosine model proposed by McCarley, Basheer, Porkka-Heiskanen, and colleagues has 3 key elements.2,3 First, adenosine production by BF cholinergic neurons is hypothesized to increase progressively during waking and, therefore, to provide a sleep-promoting stimulus that is proportional to prior time awake, a key aspect of homeostatic sleep regulation. Second, that among all BF waking-active cell types, cholinergic neurons are hypothesized to be uniquely responsive to elevated extracellular adenosine. Third, by virtue of their widespread projections to the neocortex and limbic telencephalon, adenosine-mediated inhibition of BF cholinergic neurons could promote cortical and hippocampal deactivation and the synchronous EEG activity characteristic of sleep. A series of published studies offered support for each of these key elements.2,3,5

Blanco-Centurion and colleagues4 present a rigorous test of the hypothesis that adenosine-mediated inhibition of BF cholinergic neurons is a critical aspect of sleep homeostasis. They demonstrate that homeostatic regulation after sleep deprivation, as measured by sleep amounts, delta power, or sleep attempts, is unchanged following selective neurotoxic lesions of BF cholinergic neurons. They also show that local BF administration of A1 receptor agonist continues to promote sleep in the absence of cholinergic neurons. The study shows that BF cholinergic neurons are not necessary for homeostatic sleep regulation or for expression of the sleep-promoting effects of exogenous adenosine, but it does not rule out an important sleep regulatory role for adenosine. Several substances, including prostaglandin-D2, interleukin-1β, and antihistamines promote sleep when applied either systemically or locally in brain. However, in each of these cases, the corresponding substrate knock-out has no effect, or only very subtle effects, on overall sleep parameters.6,7 How do we rationalize these discrepancies? One model is that of Krueger and colleagues, who emphasize that sleep may be regulated by several interacting molecular systems.8 Perhaps sleep is best viewed as comprising several compensatory/regulated processes that can be expressed concurrently. Neither baseline sleep parameters nor results of sleep deprivation-compensation experiments provide good tests of the role of any particular sleep factor. Adenosine signaling in the BF may rise and decline during deprivation and rebound, even if these signals do not affect the overall parameters of sleep rebound. If adenosine signaling through cholinergic neurons is one of many concurrent processes, removal of the process may not be reflected in the gross parameters of sleep homeostasis.

Blanco-Centurion and colleagues4 have shown that application of an adenosine A1 receptor agonist in the BF increased NREM sleep in animals in which cholinergic neurons were absent. As pointed out by Lee et al. (2005) cholinergic neurons constitute only about 5% of BF neurons; cholinergic neurons exhibit bursting discharge during wake and REM.9 We previously showed that adenosinergic agonists applied locally in the BF inhibited discharge of most adjacent wake-related neurons, many of which did not exhibit bursting.10 Thus, noncholinergic BF neurons may mediate hypnogenic responses to adenosine agonists. In addition, even in the presence of blockade of A1 responses, wake-active neurons continued to exhibit reduced discharge in NREM sleep. Thus, changes in A1 adenosinergic inhibitory tone do not completely explain reductions in BF wake-active neuronal discharge during NREM sleep, supporting a concept of multiple factors in control of sleep. Furthermore, application of A1 receptor agonist into the hypocretin (orexin) neuronal field in the perifornical lateral hypothalamic area also induces sleep.11 These findings suggest that hypnogenic responses to adenosine agonists may not be specific to the BF, but can be observed in brain regions containing high density of wake-promoting neurons.

Blanco-Centurion and colleagues4 review several findings supporting a role for A2A rather than A1 receptor mediated hypnogenic effects, and evidence that A2A effects may be mediated by sites outside of the BF. In the lateral preoptic area (LPOA), which lacks cholinergic neurons, microdialytic application of A2A agonists increases NREM sleep.14 In the same site, A1 agonists increase wake rather than sleep. Since nonspecific blockade of adenosine receptors by caffeine increases wakefulness, in LPOA the predominating response would be mediated by A2A receptors. This idea is also supported by a recent study showing that responses to caffeine are lost in A2A receptor knock-out—but not A1 receptor knock-out—mice.15 Thus, as noted by Blanco-Centurion et al., the adenosine hypothesis is not dead.4 Rather, the next logical step may be to delineate additional brain regions and cell types where adenosine is acting to modulate sleep through A1

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and/or A2A receptors.

REFERENCES

Basal Forebrain and Saporin Cholinergic Lesions: The Devil Dwells in Delivery Details.

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THE CHOLINERGIC BASAL FOREBRAIN (CBF) AND ADENOSINE AS A HOMEOSTATIC SLEEP FACTOR ARE CURRENT “HOT TOPICS”, AS DEMONSTRATED BY the very active work going on in several research groups. This comment places the just-published article by Blanco-Centurion et al.1 in the context of the work of other research groups, much of which has been presented at APSS and other meetings and now is in preparation for publication. We here comment on the similarities of findings and attempt to suggest reasons for the differences.

First, a bit of background: The CBF complex includes the medial septum (MS) rostrally to the nucleus basalis magnocellularis caudally and provides widespread afferent cholinergic, GABAergic, and glutamatergic innervation to the cortical mantle, hippocampus, and amygdalae. A recent commentary in Sleep2 outlined the connection with adenosine effects in inhibiting wakefulness promoting CBF neurons, and the role of the CBF and adenosine in mediating recovery sleep.

Recent advances in selective destruction of CBF cholinergic neurons include using the immunotoxin 192 IgG-Saporin. This consists of a ribosome inactivating enzyme conjugated with monoclonal antibody targeted to the low affinity p75 nerve growth factor receptor expressed only on cholinergic neurons.

A chronological list of 192 IgG-saporin experiments and sleep effects on sleep,13,14,15,16 These altered systems may alter the response to sleep

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