THE VERY IMPORTANT AND WELL-DESIGNED STUDY BY
BLANCO-CENTURION ET AL.1 HAS ESTABLISHED THAT
NEITHER THE ACTIVITY OF THE BASAL FOREBRAIN
(BF) cholinergic neurons, which release adenosine (AD), nor the
accumulation of AD in the BF during wake is necessary for sleep
drive. These findings run against the hypothesis that AD released
from the BF during waking is responsible for sleep homeostasis
1-2 and also against the notion that localized buildup of AD during
waking shuts off the activity of the cholinergic BF neurons—a
necessary step for sleep drive.

So, what do we now believe is the mechanism of AD hypnotic action? If accumulation of AD, which stimulates both A1 and A2 receptors, is not the cause for sleep drive, the question still remains as to why sleep is increased by administration of AD into the preoptic area (PO). Why is sleep increased by peripheral administration of adenosine deaminase—an inhibitor of adenosine deaminase that elevates the levels of AD in the central nervous system (CNS)? Why is sleep increased by in vivo microdialysis perfusion of AD into the brain? Why does peripheral or central administration of adenosine A1 receptor agonists induce sleep in rats?1-7 While these and other studies have suggested a role for A1 receptors in sleep drive, only a couple of studies have found that A2a receptors also play a role in adenosine’s hypnotic action.10 This is of interest since A1 receptors are widely distributed throughout the brain including the brainstem, whereas A2 receptors have high densities in only several brain regions and are absent from the hypothalamus.12

Another way to evaluate the roles of A1 and A2 receptors in sleep homeostasis is to use caffeine, which blocks both subsets of AD receptors and produces wakefulness, and to compare caffeine’s sleep suppressant action with two other xanthines that antagonize either A1 or A2 receptors. Thus, when 8-cyclopent-

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Jerome Siegel, PhD

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What follows is a series of commentaries and a response by the authors to a paper by Blanco-Centurion et al. entitled Adenosine and Sleep Homeostasis in the Basal Forebrain. The paper is available in the Journal of Neuroscience and from the authors. Adenosine is a metabolic byproduct that has been shown to induce sleep. The blockade of adenosine receptors by caffeine is the biochemical cause of the arousing effect of this drug. It has been hypothesized that a progressive increase in adenosine release during waking by cholinergic cells in the basal forebrain inhibits these cells and thereby underlies the regulation of the sleep wake cycle. Blanco-Centurion et al. challenge this important hypothesis in their paper, showing that destruction of the basal forebrain cholinergic cell group has little effect on sleep-wake regulation or sleep homeostasis. Other scientists vested in the topic provide their perspectives on this report.

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**Adenosine and Sleep Homeostasis in the Basal Forebrain: Commentary on Blanco-Centurion et al. (2006)**

Miodrag Radulovacki, MD, PhD

Department of Pharmacology, University of Illinois at Chicago, Chicago, IL

THE VERY IMPORTANT AND WELL-DESIGNED STUDY BY BLANCO-CENTURION ET AL.1 HAS ESTABLISHED THAT NEITHER THE ACTIVITY OF THE BASAL FOREBRAIN (BF) cholinergic neurons, which release adenosine (AD), nor the accumulation of AD in the BF during wake is necessary for sleep drive. These findings run against the hypothesis that AD released from the BF during waking is responsible for sleep homeostasis1-2 and also against the notion that localized buildup of AD during waking shuts off the activity of the cholinergic BF neurons—a necessary step for sleep drive.3

Disclosure Statement
Dr. Radulovacki has received research support from Organon NV and BTG International. Also, Dr. Radulovacki was named inventor of a technology for pharmacologic treatments of sleep apnea assigned to the University of Illinois. The University has licensed this technology to both Organon and to BTG International for different fields of use.

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**Forum on Critical Topics – Sleep, Adenosine, and the Basal Forebrain**

David F. Dinges, PhD

Editor-in-Chief, SLEEP; University of Pennsylvania School of Medicine, Philadelphia, PA

Beginning with this issue, SLEEP will periodically publish a forum on controversial topics important to our field. The focus will be on reactions to a provocative paper—regardless of where it was published—that broadly impacts our field. The format consists of brief invited commentaries by experts in the area. The intent is to stimulate a timely, candid, and thoughtful discussion on critical topics. Each Forum will be managed by one of the Editors of SLEEP.

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**EDITORIAL**


Jerome Siegel, PhD

Deputy Editor, SLEEP; Department of Psychiatry and Behavioral Sciences, University of California Los Angeles, Los Angeles, CA

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tyltheoppyline (CPT), a selective A1 receptor antagonist, or alloxazine (ALX), an AD receptor antagonist that displays slightly greater affinity for A2 receptors, were individually administered to rats and compared to caffeine, both produced sleep suppression qualitatively similar to that produced by caffeine, but of smaller magnitude. However, CPT, a highly selective A1 adenosine receptor antagonist in vitro, produced a degree of CNS stimulation more similar to that observed after caffeine than did ALX. When CPT and ALX were injected together, their sleep suppressant effect was of the same magnitude as that of caffeine.

We still have a way to go to understand the complex phenomenon of sleep homeostasis. The authors have produced a seminal study and I congratulate them. Their work deepens our knowledge into the mystery of the mechanisms of sleep and is an important stepping stone for future directions.

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A Global Rather than Local Role for Adenosine in Sleep Homeostasis

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THE SIGNIFICANCE OF THE PAPER BY BLANCO-CENTURION ET AL. MAY BE THAT IT STIMULATES MANY SLEEP RESEARCHERS TO ABANDON A SINGLE-MINDED focus on the basal forebrain as the site of the homeostatic regulation of sleep. The authors, however, do not seem ready to take that step.

The experiments reported set out to test 2 hypotheses originally advanced by Rainnie et al. and expounded upon in Strecker et al. 1: 1) during prolonged wakefulness, the release of adenosine from cholinergic (ACh) neurons in the basal forebrain (BF) is the signal that controls the homeostatic response in recovery sleep, and 2) that adenosine feedback signal works through inhibition of the same ACh neurons that are wake promoting. Blanco-Centurion et al. disprove these hypotheses. After treating rats with 192-IgG-saporin, they show greater than 95% loss of ACh neurons in the BF. These rats no longer show an increase in BF adenosine levels in response to sleep deprivation, but they still show normal sleep homeostatic responses to sleep deprivation. However, infusion of an agonist of the adenosine A1 receptor induces equivalent sleep responses in lesioned and nonlesioned rats. Thus, as the authors conclude, adenosine released by BF ACh neurons is not the feedback signal in sleep homeostasis, and the ACh neurons in the BF are not the primary transducers of sleep drive. One aspect of the first hypothesis — that the adenosine released in the BF during wake comes from the ACh neurons — is neither proven nor disproven by the experiments. The ACh input is depolarizing and thus enhances activity of neurons generally. Thus, with the loss of the ACh excitation, overall neural activity in the BF should be lower, and the loss of the BF adenosine response to sleep deprivation could be due to lower levels of activity of noncholinergic neurons. The authors do not put forth alternative hypotheses to replace those that their results have called into question.

There is an alternative set of hypotheses for the involvement of adenosine in the homeostatic regulation of sleep. These hypotheses ascribe to adenosine a global feedback role on the cells of the thalamus and cortex that are responsible for generating the EEG slow wave activity that is the hallmark of recovery sleep. Why is this line of reasoning ignored by the authors? I think there are three leading reasons.

First, there has been a tendency for investigators in this area of research to operate from a false assumption illustrated in Strecker...