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Adenosine sleep theory: how I postulated it

[Neurological Research](#), [Mar 2005](#) by [Radulovacki, Miodrag](#)

INTRODUCTION

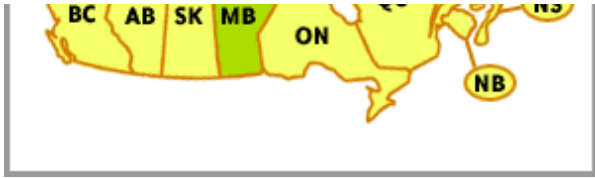
My thinking about the adenosine role in sleep started when I read the paper by Snyder et al.1 about the importance of adenosine receptors in behavioral actions of methylxanthines. There, the authors correlated the behavioral excitation produced by theophylline with the blockade of adenosine receptors. This was an important finding because, until then, it was considered that methylxanthines, i.e. caffeine and theophylline, produce behavioral excitation by blocking an enzyme, phosphodiesterase, which converts cAMP, a second messenger at the post-synaptic nerve terminal, to AMP. The authors found that micromolar concentrations of theophylline are sufficient to block adenosine receptors and produce behavioral excitation whereas millimolar concentrations of theophylline were needed to block phosphodiesterase. The old assumption was that the blockade of phosphodiesterase would leave more of cAMP to enhance the transmission of normally released excitatory neurotransmitters, glutamate, serotonin, norepinephrine and dopamine from a pre-synaptic nerve terminal, which would then result in behavioral excitation.

After reading the paper of Snyder et al.1, I reasoned that if blockade of adenosine receptors produces excitation, then perhaps stimulation of the same receptors could induce sleep. I knew the experiments with iontophoretic application of adenosine in the brain done by John Phillis and his group, which showed that adenosine had a depressant effect on the responses of neurons in several brain regions2 and that general neurophysiological effects of adenosine were shown to be inhibitory3,4. In addition, preliminary experiments in dogs by Haulica et al.5, and the administration of adenosine into the brains of rats, cats and fowl was shown to produce behavioral sleep6-8. Thus, there was enough of supporting evidence from the literature to suggest that adenosine may play a role in sleep.

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EXPERIMENTS IN SUPPORT OF ADENOSINE SLEEP THEORY

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