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Phillis J W & Wu P H. The role ot adenosine and its nucleotides in central synaptic transmission, Prog. N*eumbiol.* **16**:137-239. 1981. [Department of Physiology. University of Saskatchewan. Canada]

This review described the results of nearly a decade of progress in identifying the actions of adenosine in the central nervous system. It started with the discovery that adenosine was a potent inhibitor of neuronal activity, and its actions were antagonized by the widely used psychostimulants, caffeine and theophylline. [The SCI® indicates that this paper has been cited in more than 480 publications, making it the most-cited paper published in this journal.]

Adenosine as a CNS Neurotransmitter

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This paper was one of the first to review, in a comprehensive manner, all of the emerging information pertaining to a role for adenosine as a neurotransmitter in the central nervous system. The possibility that adenosine might function as an inhibitory neurotransmitter in the brain was proposed in 1975,[1] based on the serendipitous discovery in the preceding year of potent inhibitory effects of this substance, and related adenine nucleotides, on the activity of cerebral cortical neurons.[2] This finding occurred when, during an evaluation of the inhibitory action of adenosine 5'-triphosphate (ATP) on the firing of rat corticospinal neurons, adenosine itself was observed to have potent depressant actions. Studies with stable analogs of ATP established that prior degradation of the nucleotide to adenosine was a prerequisite for inhibitory activity. That adenosine could have this action was somewhat of a surprise at the time, as it was widely believed that only 3',5'-cyclic AMP, but not adenosine or its noncyclic nucleotides, could depress neuronal firing.[3,4] Indeed, our initial report on adenosine's action was promptly rejected by *Nature.* Equally exciting was the discovery that the stimulant methylxanthines, caffeine and theophylline, antagonized the inhibitory effects of adenosine. It was therefore possible for us to suggest in 1975 that the well-known stimulant action of these substances was due to their block of the actions of endogenous adenosine.

The role of cyclic AMP in adenosine's action has been controversial. Adenosine stimulates cyclic AMP formation in brain tissues—an action that is antagonized by the methylxanthines. A. Sattin and T.W. Rall[5] speculated that this action of the methylxanthines could account for their stimulant activity, rather than this being a result of their inhibition of phosphodiesterases and enhancement of cyclic AMP levels. It was subsequently found that adenosine, acting at a high-affinity receptor, could inhibit the accumulation of cyclic AMP.[6] This finding naturally initially started a reevaluation of the potential mechanisms by which adenosine depresses neuronal activity, but even now it is uncertain as to whether cyclic AMP is involved in the inhibitory actions of adenosine, which currently include depression of transmitter release, blocking of calcium channels, and the opening of K* and Cl" channels.

My collaborator at the University of Saskatchewan, Peter H. Wu, had been conducting studies on the transport of adenosine by brain tissues, finding that several groups of psychopharmacclogically active substances including the opiates, benzodiazepines, phenothiazines, and alcohol possess the ability to antagonize adenosine uptake. An involvement of adenosine in the central actions of these substances was subsequently confirmed by the demonstration that their inhibitory actions on central neurons were antagonized by methylxanthines.

Since the publication of this review, the increasing availability of selective agonists and antagonists for the high (A_1) and low (A_2) affinity adenosine receptors has facilitated further evaluation of the actions of adenosine, including its role as an inhibitory synaptic transmitter[7] in the central nervous system.

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2. **Phillis J W, Kostopoulos G K & Limacher J J.** Depression of corticospinal cells by various purines and pynmidines. *Can. J. Physiol. Pharmacol.* 52:1226-9. 1974. (Cited 120 limes.)
3. **Hoffer B J, Siggins G R, Oliver A P & Bloom F** E. Cyclic AMP mediation of norepinephrine inhibition in rat cerebcllar cortex. A unique class of synaptic responses. *Ann. NY Acad. Sci.* 185:531-49. 1971.
4. **McAfee D A & Greengard P.** Adenosine 3'.5'-monophosphaie: electrophysiological evidence for a role in synaptic transmission. *Science* 178:310-2. 1972. (Cited 265 times.)
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6. **Van Calker D, Muller M & Hamprecht B.** Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. J . *Neurochem.* 33:999-1005. 1979. (Cited 680 times.)
7. **De Koninck Y & Henry J L.** Peripheral inhibitor causes an adenosine-mediated posisynaptic inhibitory potential in dorsal horn neurons of the cat spinal cord. N*euroscience* 50:435-13. 1992.

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