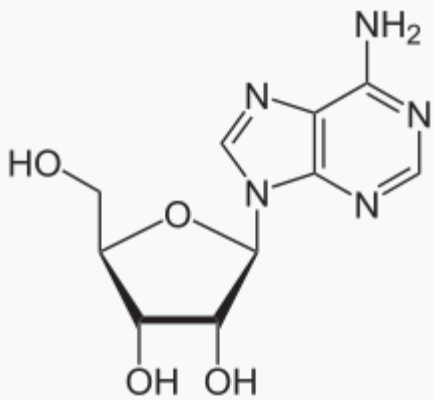
Adenosine

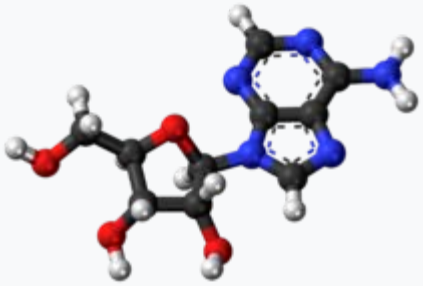
From Wikipedia, the free encyclopedia

Adenosine is both a chemical found in many living systems and a medication. As a medication it is used to treat certain forms of supraventricular tachycardia that do not improve with vagal maneuvers.[1] Common side effects include chest pain, feeling faint, shortness of breath along with tingling of the senses.[1] Serious side effects include a worsening dysrhythmia and low blood pressure.[1] It appears to be safe in pregnancy.[1]

It is a purine nucleoside composed of a molecule of adenine attached to a ribose sugar molecule (ribofuranose) moiety via a β-N_9-glycosidic bond.[2][3][4] Derivatives of adenosine are widely found in nature and play an important role in biochemical processes, such as energy transfer—as adenosine triphosphate (ATP) and adenosine diphosphate (ADP)—as well as in signal transduction as cyclic adenosine monophosphate (cAMP). Adenosine itself is a neuromodulator, believed to play a role in promoting sleep and suppressing arousal. Adenosine also plays a role in regulation of blood flow to various organs through vasodilation.[5][6][7]

Adenosine





Clinical data	
Trade names	Adenocard; Adenocor; Adenic; Adenoco; Adeno-Jec; Adenoscan; Adenosin; Adrekar; Krenosin
Synonyms	SR-96225 (developmental code name)
AHFS / Drugs.com	Monograph
Pregnancy category	C (adenosine may be safe to the fetus in pregnant women)
Routes of administration	Intravenous
ATC code	C01EB10 (WHO)
Legal status	
Legal status	In general: ℞ (Prescription only)
Pharmacokinetic data	

Contents

[hide]

1 Medical uses
- 1.1 Supraventricular tachycardia
- 1.2 Nuclear stress test
- 1.3 Dosage

2 Drug interactions
3 Contraindications
4 Side effects
5 Pharmacological effects
- 5.1 Adenosine receptors
- 5.2 Ghrelin/growth hormone secretagogue receptor
- 5.3 Mechanism of action

6 Metabolism
7 Research
- 7.1 Viruses
- 7.2 Anti-inflammatory properties
- 7.3 Central nervous system
- 7.4 Hair
- 7.5 Sleep

8 See also
9 References

Medical uses [edit]

Supraventricular tachycardia [edit]

In individuals with supraventricular tachycardia (SVT), adenosine is used to help identify and convert the rhythm.

Certain SVTs can be successfully terminated with adenosine.[8] This includes any re-entrant arrhythmias that require the AV node for the re-entry, e.g., AV reentrant tachycardia (AVRT), AV nodal reentrant tachycardia (AVNRT). In addition, atrial tachycardia can sometimes be terminated with adenosine.

Fast rhythms of the heart that are confined to the atria (e.g., atrial fibrillation, atrial flutter) or ventricles (e.g., monomorphic ventricular tachycardia) and do not involve the AV node as part of the re-entrant circuit are not typically converted by adenosine. However, the ventricular response rate is temporarily slowed with adenosine in such cases.

Because of the effects of adenosine on AV node-dependent SVTs, adenosine is considered a class V antiarrhythmic agent. When adenosine is used to cardiovert an abnormal rhythm, it is normal for the heart to enter ventricular asystole for a few seconds. This can be disconcerting to a normally conscious patient, and is associated with angina-like sensations in the chest.[9]

Nuclear stress test [edit]

Adenosine is used as an adjunct to thallium (TI 201) or technetium (Tc99m) myocardial perfusion scintigraphy (nuclear stress test) in patients unable to undergo adequate stress testing with exercise.[10]

Dosage [edit]

When given for the evaluation or treatment of a supraventricular tachycardia (SVT), the initial dose is 6 mg to 12 mg, depending on standing orders or provider preference,[11] given as a rapid parenteral infusion. Due to adenosine's extremely short half-life, the IV line is started as proximal (near) to the heart as possible, such as the antecubital fossa. The IV push is often followed with an immediate flush of 10-20 ccs of saline. If this has no effect (i.e., no evidence of transient AV block), a dose of 12 mg can be given 1–2 minutes after the first dose. Some clinicians may prefer to administer a higher dose (typically 18 mg), rather than repeat a dose that apparently had no effect.[*dubious* – *discuss*] When given to dilate the arteries, such as in a "stress test", the dosage is typically 0.14 mg/kg/min, administered for 4 or 6 minutes, depending on the protocol.

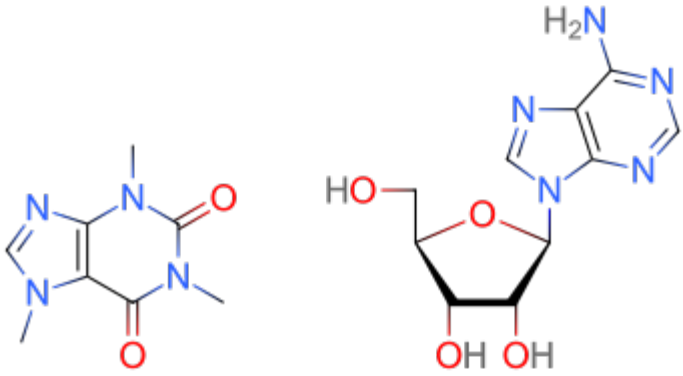
The recommended dose may be increased in patients on theophylline, since methylxanthines prevent binding of adenosine at receptor sites. The dose is often decreased in patients on dipyridamole (Persantine) and diazepam (Valium) because adenosine potentiates the effects of these drugs. The recommended dose is also reduced by half in patients presenting congestive heart failure, myocardial infarction, shock, hypoxia, and/or hepatic or renal insufficiency, and in elderly patients.

Bioavailability	Rapidly cleared from circulation via cellular uptake
Protein binding	No
Metabolism	Rapidly converted to inosine and adenosine monophosphate
Elimination half-life	cleared plasma <30 seconds – half-life <10 seconds
Excretion	can leave cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid
Identifiers	
IUPAC name	[show]
CAS Number	58-61-7 ✓
PubChem CID	60961
IUPHAR/BPS	2844
DrugBank	DB00640 ✓
ChemSpider	54923 ✓
UNII	K72T3FS567
KEGG	C00212 ✓
ChEBI	CHEBI:16335 ✓
ChEMBL	ChEMBL477 ✗
ECHA InfoCard	100.000.354
Chemical and physical data	
Formula	$C_{10}H_{13}N_5O_4$
Molar mass	267.241 g/mol
3D model (JSmol)	Interactive image
SMILES	[show]
InChI	[show]
✗✓ (what is this?) (verify)	

Drug interactions [edit]

Dipyridamole potentiates the action of adenosine, requiring the use of lower doses.

Methylxanthines (e.g., caffeine, found in coffee, or theophylline in tea, or theobromine, as found in chocolate) competitively antagonize adenosine's effects; an increased dose of adenosine may be required. By nature of caffeine's purine structure,[12] it binds to some of the same receptors as adenosine.[12] The pharmacological effects of adenosine may be blunted in individuals taking large quantities of methylxanthines.[13][*citation needed*]



Caffeine's principal mode of action is as an antagonist of adenosine receptors in the brain.

Contraindications [edit]

Common contraindications for adenosine include

- Asthma, traditionally considered an absolute contraindication. This is being contended and it is now considered a relative contraindication (however, selective adenosine antagonists are being investigated for use in treatment of asthma)[14]
- Decompensated heart failure
- Long QT syndrome
- Poison/drug-induced tachycardia
- Second- or third-degree heart block (without a pacemaker)
- Severe hypotension
- Sick sinus syndrome (without a pacemaker)

When administered via a central lumen catheter, adenosine has been shown to initiate atrial fibrillation because of its effect on atrial tissue. In individuals with accessory pathways, the onset of atrial fibrillation can lead to a life-threatening ventricular fibrillation. However, adenosine may be administered if equipment for cardioversion is immediately available as a backup.

Side effects [edit]

Many individuals experience facial flushing, a temporary rash on the chest, lightheadedness, diaphoresis, or nausea after administration of adenosine due to its vasodilatory effects. Metallic taste is a hallmark side-effect of adenosine administration. These symptoms are transitory, usually lasting less than one minute. It is classically associated with a sense of "impending doom", more prosaically described as apprehension. This lasts a few seconds after administration of a bolus dose, during transient asystole induced by intravenous administration. In some cases, adenosine can make patients' limbs feel numb for about 2–5 minutes after administration intravenously depending on the dosage (usually above 12 mg).

Pharmacological effects [edit]

Adenosine is an endogenous purine nucleoside that modulates many physiological processes. Cellular signaling by adenosine occurs through four known adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3).[15]

Extracellular adenosine concentrations from normal cells are approximately 300 nM; however, in response to cellular damage (e.g. in inflammatory or ischemic tissue), these concentrations are quickly elevated (600–1,200 nM). Thus, in regard to stress or injury, the function of adenosine is primarily that of cytoprotection preventing tissue damage during instances of hypoxia, ischemia, and seizure activity. Activation of A_{2A} receptors produces a constellation of responses that in general can be classified as anti-

inflammatory.[16]

Adenosine receptors [edit]

Main article: Adenosine receptor

All adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3) are G-protein-coupled receptors. The four receptor subtypes are further classified based on their ability to either stimulate or inhibit adenylate cyclase activity. The A_1 receptors couple to $G_{i/o}$ and decreases cAMP levels, while the A_2 adenosine receptors couple to G_s, which stimulates adenylate cyclase activity. In addition, A_1 receptors couple to G_o, which has been reported to mediate adenosine inhibition of Ca^{2+} conductance, whereas A_{2B} and A_3 receptors also couple to G_q and stimulate phospholipase activity. Researchers at Cornell University have recently shown adenosine receptors to be key in opening the blood-brain barrier (BBB). Mice dosed with adenosine have shown increased transport across the BBB of amyloid plaque antibodies and prodrugs associated with Parkinson's disease, Alzheimer's, multiple sclerosis, and cancers of the central nervous system.[17]

Ghrelin/growth hormone secretagogue receptor [edit]

Adenosine is an endogenous agonist of the ghrelin/growth hormone secretagogue receptor.[18] However, while it is able to increase appetite, unlike other agonists of this receptor, adenosine is unable to induce the secretion of growth hormone and increase its plasma levels.[18]

Mechanism of action [edit]

When it is administered intravenously, adenosine causes transient heart block in the atrioventricular (AV) node. This is mediated via the A_1 receptor, inhibiting adenylyl cyclase, reducing cAMP and so causing cell hyperpolarization by increasing K^+ efflux via inward rectifier K^+ channels, subsequently inhibiting Ca^{2+} current.[19] It also causes endothelial-dependent relaxation of smooth muscle as is found inside the artery walls. This causes dilation of the "normal" segments of arteries, i.e. where the endothelium is not separated from the tunica media by atherosclerotic plaque. This feature allows physicians to use adenosine to test for blockages in the coronary arteries, by exaggerating the difference between the normal and abnormal segments.

The administration of adenosine also reduces blood flow to coronary arteries past the occlusion. Other coronary arteries dilate when adenosine is administered while the segment past the occlusion is already maximally dilated, which is a process called coronary steal. This leads to less blood reaching the ischemic tissue, which in turn produces the characteristic chest pain.

Metabolism [edit]

Adenosine used as a second messenger can be the result of *de novo* purine biosynthesis via adenosine monophosphate (AMP), though it is possible other pathways exist.[20]

When adenosine enters the circulation, it is broken down by adenosine deaminase, which is present in red cells and the vessel wall.

Dipyridamole, an inhibitor of adenosine nucleoside transporter, allows adenosine to accumulate in the blood stream. This causes an increase in coronary vasodilatation.

Adenosine deaminase deficiency is a known cause of immunodeficiency.

Research [edit]

Viruses [edit]

See also: Nucleoside analogue

The adenosine analog NITD008 has been reported to directly inhibit the recombinant RNA-dependent RNA polymerase of the dengue virus by terminating its RNA chain synthesis. This suppresses peak viremia and rise in cytokines and prevented lethality in infected animals, raising the possibility of a new treatment for this flavivirus.[21] The 7-deaza-adenosine analog has been shown to inhibit the replication of the hepatitis C virus.[22] BCX4430 is protective against Ebola and Marburg viruses.[23] Such adenosine analogs are potentially clinically useful since they can be taken orally.

Anti-inflammatory properties [edit]

Adenosine is believed to be an anti-inflammatory agent at the A_{2A} receptor.[24][25] Topical treatment of adenosine to foot wounds in diabetes mellitus has been shown in lab animals to drastically increase tissue repair and reconstruction. Topical administration of adenosine for use in wound-healing deficiencies and diabetes mellitus in humans is currently under clinical investigation.

Methotrexate's anti-inflammatory effect may be due to its stimulation of adenosine release.[26]

Central nervous system [edit]

In general, adenosine has an inhibitory effect in the central nervous system (CNS). Caffeine's stimulatory effects are credited primarily (although not entirely) to its capacity to block adenosine receptors, thereby reducing the inhibitory tonus of adenosine in the CNS. This reduction in adenosine activity leads to increased activity of the neurotransmitters dopamine and glutamate.[27] Experimental evidence suggests that adenosine and adenosine agonists can activate Trk receptor phosphorylation through a mechanism that requires the adenosine A_{2A} receptor.[28]

Hair [edit]

Adenosine has been shown to promote thickening of hair on people with thinning hair.[29][30] A 2013 study compared topical adenosine with minoxidil in male androgenetic alopecia, finding it was not superior to minoxidil and further trials were needed.[31]

Sleep [edit]

The principal component of marijuana, delta-9-tetrahydrocannabinol (THC) and the endocannabinoid anandamide (AEA) induce sleep in rats by increasing adenosine levels in the basal forebrain. They also significantly increase slow-wave sleep during the third hour, mediated by CB1 receptor activation. These findings identify a potential therapeutic use of cannabinoids to induce sleep in conditions where sleep may be severely attenuated.[32]

See also [edit]

- Adenosine receptor
- Adenosine reuptake inhibitor
- List of growth hormone secretagogues

References [edit]

1. ^ [a](#) [b](#) [c](#) [d](#) "Adenosine". The American Society of Health-System Pharmacists. Retrieved Jan 12, 2015.
2. ^ I.K. Morton; Judith M. Hall (6 December 2012). *Concise Dictionary of Pharmacological Agents: Properties and Synonyms*. Springer Science & Business Media. pp. 106–. ISBN 978-94-011-4439-1.
3. ^ J. Buckingham (1987). *Dictionary of Organic Compounds*. CRC Press. pp. 75–. ISBN 978-0-412-54090-5.
4. ^ *Index Nominum 2000: International Drug Directory*. Taylor & Francis. January 2000. pp. 18–. ISBN 978-3-88763-075-1.
5. ^ Sato, A (April 2005). "Mechanism of vasodilation to adenosine in coronary arterioles from patients with heart disease". *American Journal of Physiology. Heart and Circulatory Physiology*. **288** (4): H1633–40. doi:10.1152/ajpheart.00575.2004. PMID 15772334.
6. ^ Costa, F; Biaggioni, I (May 1998). "Role of nitric oxide in adenosine-induced vasodilation in humans". *Hypertension*. **31** (5): 1061–4. doi:10.1161/01.HYP.31.5.1061. PMID 9576114.
7. ^ Morgan, JM; McCormack, DG; Griffiths, MJ; Morgan, CJ; Barnes, PJ; Evans, TW (September 1991). "Adenosine as a vasodilator in primary pulmonary hypertension". *Circulation*. **84** (3): 1145–9. doi:10.1161/01.CIR.84.3.1145. PMID 1884445.
8. ^ Mitchell J, Lazarenko G (November 2008). "Wide QRS complex tachycardia. Diagnosis: Supraventricular tachycardia with aberrant conduction; intravenous (IV) adenosine". *CJEM*. **10** (6): 572–3, 581. PMID 19000353.
9. ^ Pijls, Nico H. J.; Bernard De Bruyne (2000). *Coronary Pressure*. Springer. ISBN 0-7923-6170-9.
10. ^ O'Keefe, JH; Bateman, TM; Silverstri, R; et al. (1992). "Safety and diagnostic accuracy of adenosine thallium-201 scintigraphy in patients unable to exercise and those with left bundle branch block". *Am. Heart J.* **124** (3): 614–21. doi:10.1016/0002-8703(92)90268-z. PMID 1514488.
11. ^ http://www.regionsems.com/wp-content/uploads/2016/04/2014-Guidelines.pdf
12. ^ [a](#) [b](#) "Caffeine". Chemistry Explained.
13. ^ "Vitamin B4". R&S Pharmchem. April 2011. Archived from the original on 2011-07-15.
14. ^ Brown RA, Spina D, Page CP (March 2008). "Adenosine receptors and asthma". *Br. J. Pharmacol*. 153 Suppl 1 (S1): S446–56. doi:10.1038/bjp.2008.22. PMC 2268070. PMID 18311158.
15. ^ Haskó G, Linden J, Cronstein B, Pacher P (September 2008). "Adenosine receptors: therapeutic aspects for inflammatory and immune diseases". *Nat Rev Drug Discov*. **7** (9): 759–70. doi:10.1038/nrd2638. PMC 2568887. PMID 18758473.
16. ^ Haskó, G (January 2004). "Adenosine: an endogenous regulator of innate immunity". *Trends in Immunology*. **25** (1): 33–39. doi:10.1016/j.it.2003.11.003. PMID 14698282.
17. ^ Carman, A. J.; Mills, J. H.; Krenz, A; Kim, D. G.; Bynoe, M. S. (2011). "Adenosine receptor signaling modulates permeability of the blood-brain barrier". *J. Neurosci*. **31** (37): 13272–80. doi:10.1523/JNEUROSCI.3337-11.2011. PMC 3328085. PMID 21917810.
18. ^ [a](#) [b](#) Claude Kordon; I. Robinson; Jacques Hanoune; R. Dantzer (6 December 2012). *Brain Somatic Cross-Talk and the Central Control of Metabolism*. Springer Science & Business Media. pp. 42–. ISBN 978-3-642-18999-9.
19. ^ Katzung, Bertram (2012). *Basic & Clinical Pharmacology* (12th ed.). McGraw Hill. p. 245. ISBN 978-0-07-176402-5.
20. ^ Miller-Patrick K, Vincent DL, Early RJ, et al. (1993). "Effects of the purine biosynthesis pathway inhibitors azaserine, hadacidin, and mycophenolic acid on the developing ovine corpus luteum". *Chin J Physiol*. **36** (4): 245–52. PMID 8020339.
21. ^ Yin, Z; Chen, YL; Schul, W; Wang, QY; Gu, F; Duraiswamy, J; Reddy Kondreddi, R; Niyomrattanakit, P; Lakshminarayana, SB; Goh, A; Xu, HY; Liu, W; Liu, B; Lim, JY; Ng, CY; Qing, M; Lim, CC; Yip, A; Wang, G; Chan, WL; Tan, HP; Lin, K; Zhang, B; Zou, G; Bernard, KA; Garrett, C; Beltz, K; Dong, M; Weaver, M; He, H; Pichota, A; Dartois, V; Keller, TH; Shi, PY (2009). "An adenosine nucleoside inhibitor of dengue virus". *Proc Natl Acad Sci U S A*. **106** (48): 20435–20439. Bibcode:2009PNAS..10620435Y. doi:10.1073/pnas.0907010106. PMC 2787148. PMID 19918064.
22. ^ Olsen, DB; Eldrup, AB; Bartholomew, L; Bhat, B; Bosserman, MR; Ceccacci, A; Colwell, LF; Fay, JF; Flores, OA; Getty, K. L.; Grobler, J. A.; Lafemina, R. L.; Markel, E. J.; Migliaccio, G.; Prhavc, M.; Stahlhut, M. W.; Tomassini, J. E.; MacCoss, M.; Hazuda, D. J.; Carroll, S. S. (2004). "A 7-Deaza-Adenosine Analog Is a Potent and Selective Inhibitor of Hepatitis C Virus Replication with Excellent Pharmacokinetic Properties". *Antimicrobial Agents and Chemotherapy*. **48** (10): 3944–53. doi:10.1128/AAC.48.10.3944-3953.2004. PMC 521892. PMID 15388457.
23. ^ Warren, T. K.; Wells, J.; Panchal, R. G.; Stuthman, K. S.; Garza, N. L.; Van Tongeren, S. A.; Dong, L.; Retterer, C. J.; Eaton, B. P.; Pegoraro, G.; Honnold, S.; Bantia, S.; Kotian, P.; Chen, X.; Taubenheim, B. R.; Welch, L. S.; Minning, D. M.; Babu, Y. S.; Sheridan, W. P.; Bavari, S. (2014). "Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430". *Nature*. **508** (7496): 402–5. Bibcode:2014Natur.508..402W. doi:10.1038/nature13027. PMID 24590073.
24. ^ Nakav S, Chaimovitz C, Sufaro Y (2008). Bozza P, ed. "Anti-Inflammatory Preconditioning by Agonists of Adenosine A1 Receptor". *PLoS ONE*. **3** (5): e2107. Bibcode:2008PLoSO...3.2107N. doi:10.1371/journal.pone.0002107. PMC 2329854. PMID 18461129.

25. ^ Trevethick MA, Mantell SJ, Stuart EF, Barnard A, Wright KN, Yeadon M (October 2008). "Treating lung inflammation with agonists of the adenosine A2A receptor: promises, problems and potential solutions". *Br. J. Pharmacol*. **155** (4): 463–74. doi:10.1038/bjp.2008.329. PMC 2579671 . PMID 18846036.
26. ^ Cronstein B (2010). "How does methotrexate suppress inflammation?". *Clin Exp Rheumatol*. **28** (5 Suppl 61): S21–3. PMID 21044428.
27. ^ Solinas, M; Ferré, S; You, Z. B; Karcz-Kubicha, M; Popoli, P; Goldberg, S. R (2002). "Caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens". *The Journal of Neuroscience*. **22** (15): 6321–4. PMID 12151508.
28. ^ Lee, FS; Chao, MV; Lee (March 2001). "Activation of Trk neurotrophin receptors in the absence of neurotrophins". *PNAS*. **98** (6): 3555–3560. Bibcode:2001PNAS...98.3555L. doi:10.1073/pnas.061020198. PMC 30691 . PMID 11248116.
29. ^ Oura, H; Iino, M; Nakazawa, Y; Tajima, M; Ideta, R; Nakaya, Y; Arase, S; Kishimoto, J (December 2008). "Adenosine increases anagen hair growth and thick hairs in Japanese women with female pattern hair loss: a pilot, double-blind, randomized, placebo-controlled trial". *The Journal of dermatology*. **35** (12): 763–7. doi:10.1111/j.1346-8138.2008.00564.x. PMID 19239555.
30. ^ Hwang, KA; Hwang, YL; Lee, MH; Kim, NR; Roh, SS; Lee, Y; Kim, CD; Lee, JH; Choi, KC (February 2012). "Adenosine stimulates growth of dermal papilla and lengthens the anagen phase by increasing the cysteine level via fibroblast growth factors 2 and 7 in an organ culture of mouse vibrissae hair follicles". *International Journal of Molecular Medicine*. **29** (2): 195–201. doi:10.3892/ijmm.2011.817. PMID 22020741.
31. ^ Faghihi, G; Iraji, F; Rajaee Harandi, M; Nilforoushzadeh, M. A.; Askari, G (2013). "Comparison of the efficacy of topical minoxidil 5% and adenosine 0.75% solutions on male androgenetic alopecia and measuring patient satisfaction rate". *Acta Dermatovenerol Croat*. **21** (3): 155–9. PMID 24183218.
32. ^ Murillo-Rodriguez, Eric; Blanco-Centurion, Carlos; Sanchez, Cristina; Daniele, Piomelli; Shiromani, Priyattam J. (2003). "Anandamide Enhances Extracellular Levels of Adenosine and Induces Sleep: An In Vivo Microdialysis Study". *Sleep*. **26** (8): 943–947. doi:10.1093/sleep/26.8.943. ISSN 0161-8105.

v · t · e ·	**Neurotransmitters**	[show]
v · t · e ·	**Nucleic acid constituents**	[show]
v · t · e ·	**Antiarrhythmic agents (C01B)**	[show]
v · t · e ·	**Purine receptor modulators**	[show]
v · t · e ·	**GH / IGF-1 axis signaling modulators**	[show]

Authority control NDL: 00575511 ·

Categories: Adenosine receptor agonists | Antiarrhythmic agents | Chemical substances for emergency medicine | Drugs acting on the cardiovascular system | Ghrelin receptor agonists | Nucleosides | Purines | Vasodilators