AD-A187 897 ROLE OF ADENOSINE ANALOGS AND GROWTH HORMONE IN WAKING AND SLEEP(U) ILLINOIS UNIV AT THE MEDICAL CENTER CHICAGO COLL OF MEDICINE. M RADULOVACKI 16 OCT 87 1/1

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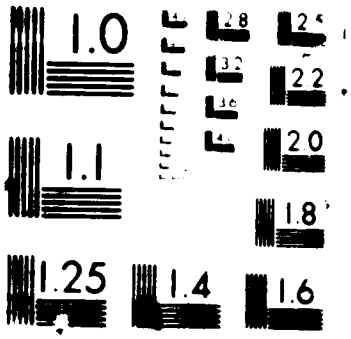
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The role of adenosine in sleep has been further investigated using electroencephalography to document the dose-response effects of newly developed specific adenosine A_1 and A_2 receptor stimulants and 8-cyclopropyltheophylline (CPRT), a substituted xanthine. The results with adenosine agonists suggest that both A_1 and A_2 receptors play a role in the hypnotic action of adenosine. The data with CPRT point out that stimulant effect of xanthines is obtained by the blockade of A_1 receptors. Densensitization of adenosine A_2 receptors was found following the chronic treatment of adenosine agonists L-PIA, NECA and deoxycoformycim. Chronic administration of caffeine "up-regulates" A_1 receptors in cerebral cortex in a manner similar to that following deprivation of REM sleep. This suggests the existence of an "endocaffeine" whose normal role is to block adenosine receptors during prolonged sleep deprivation- a mechanism that could be responsible for the increased number of adenosine receptors.

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2. Research Objectives

A. Our first objective in determining the mechanism of hypnotic action of adenosines was to test the dose-response effects on sleep of newly developed adenosine A_1 and A_2 receptor stimulants, i.e. N^6-1-methylcyclopentyladenosine (RAO 119-A), N^6-cyclopentyladenosine (CPA) and 2-(phenyl-amino) adenosine (CV-1808), respectively.

B. Our second najor objective in determining the mechanism of hypnotic effects on sleep of 8-cyclopropyltheophylline (CPRT), a substituted xanthine which preferentially antagonises adenosine 1 receptors. Our objective was to find out whether blockade of A_1 receptors would increase waking, since xanthines block both A_1 and A_2 receptors.

C. The third important objective in our research was to investigate the effect of chronic administration of adenosine agonists (1-PIA, NECA, dexoycoformycin) and non-specific antagonists (caffeine) on central A_1 and A_2 receptors in rats. It was of interest to establish whether and in which brain structures adenosine receptors can be "down-regulated" or "up-regulated".

3. Status of Research

A. When newly developed specific adenosine A_1 receptor stimulants became available, we examined the dose response effects on sleep of N^6-1-methylcyclopentyladenosine (Rao 119-A), a specific A_1 receptor agonist (1). The various doses of the drug administered intraperitoneally to rats affected sleep stages differently and the data are in agreement with previously reported effects on sleep of adenosine receptor stimulants. Of the newly developed adenosine A_1 and A_2 receptor stimulants we tested the dose-response effects on sleep in N^6-cyclopentyladenosine (CPA), the most potent and selective adenosine A_1 receptor agonist, and 2-(phenylamino) adenosine (CV-1808) the most selective adenosine A_2 receptor agonist. Both drugs were administered intraperitoneally to rats and the results suggest that both adenosine A_1 and A_2 receptors play a role in the hypnotic action of adenosine (2).

B. In order to accomplish our second major objective we tested the dose-response effects on sleep of 8-cyclopropyltheophylline (CPRT) (3). Although a substituted xanthine, CPRT has been reported to have sedative and hypnotic effects in high doses. However, in reported experiments only gross behavioral measures

of sedation were employed. We found that CPRT produces biphasic and dose-dependent effects on sleep and wakefulness in rats. Thus, 20 and 40 mg/kg doses decreased sleep (an indirect evidence of a selective A_1 receptor blockade) and 80 mg/kg dose (toxic) increased sleep.

In these experiments we have shown that selective blockade of A_1 receptors is able to produce a state of sustained wakefulness. The findings suggest that adenosinergic system, particularly A_1 receptors, play important role in sleep and wakefulness.

C. Our third major objective was accomplished when

a. Maximally tolerated doses of N^6-R-PIA (0.50 nmoles/hr/2 weeks) NECA (0.04 nmoles/hr/2 wk) or deoxycoformycin (DCF, 5 nmoles/hr/1 wk) were administered intracerebroventricularly to rats using ALZET mini-osmotic pumps. Adenosine receptor function was subsequently assayed using both ligand binding and adenylate cyclase assays. Binding to A_1 receptors was quantitated using [^{3}H]R-PIA, a selective agonist ligand at A_1 receptors. Differences in the binding of this ligand and that of [^{3}H]NECA, which binds to A_1 and A_2 receptors with similar affinities, were used to quantitate A_2 receptors. None of the treatments affected A_1 receptor function. A_2 receptor binding and A_2 receptor mediated stimulation of adenylate cyclase were blunted in striatal membranes from NECA and DCF treated rats. The results suggest that only A_2 receptors were desensitized following the treatment of adenosine agonists (4).

b. We administered to rats caffeine (75 mg/kg/day, i.p.) for 12 days and obtained a significant increase in high affinity [^{3}H]R-PIA binding in cerebral cortex (14%, $p<0.02$). [^{3}H]R-PIA minus [^{3}H]NECA binding for the estimation of A_2 receptors in striatum showed only an upward trend in B_{max}. The results show that chronic treatment with high doses of caffeine can selectively increase A_1 receptor population in cortex, while these doses have no effect on A_2 receptors. (5)

4. Written Publications

1. Radulovacki, M., Hajduk, P., Stefanovich, P. and Porter, N.: The effects of N^6-1-Methylcyclopentyladenosine on sleep in rats. Res. Comm. Psych. Behav. 12(1) 1-8, 1987.

2. Porter, N.M., Stefanovich, P., Hajduk, P. and Radulovacki, M.: The effects of N^6-cyclopentyladenosine and 2-(phenylamino) adenosine on sleep in rats. Brain Res. Bull. (submitted).

3. Virus, R.M. and Radulovacki, M.: Dose-response effects of 8-cyclopropyltheophylline on sleep and wakefulness in rats. Psychopharmacology (in press).

4. Porter, N.M., Radulovacki, M. and Green, R.D.: Desensitization of adenosine and dopamine receptors in rat brain following treatment with adenosine analogues. J. Pharmacol. Exp. Ther. (in press).

5. Dugich, M., Hawkins, M., Porter, N.M. and Radulovacki, M.: Effect of chronic caffeine administration on adenosine A_1, adenosine A_2 and benzodiazepine receptors in specific areas of the rat brain. Soc. Neurosci. Abstr. 13: (Part 2) 1346, 1987.

5. Professional Personnel

Marjorie Hawkins, M.D.
Robert M. Virus, Ph.D.
Nada Porter, Graduate Student
Millicent Dugich, Graduate Student
Phillip Hajduk, Undergraduate Student
Alex Radetich, Undergraduate Student
Peter Stefanovich, Medical Student

6. Interactions

Hawkins, M., M. Pravica, and M. Radulovacki: Effects of chronic administration of diazepam and RO-15-1788 on adenosine A_1 and A_2 receptors in the rat brain. Soc. Neurosci. Meeting, Nov. 9-14, 1986, Washington, D.C.

Glaum, S.R., G. Yanik, W. Pan, P. Hajduk and M. Radulovacki: Low doses of caffeine affect sleep composition in a manner opposite to that of adenosine analogs in rats. Soc. Neurosci. Meeting, Nov. 9-14, 1986, Washington, D.C.

Porter, N.M., F.M. Clark, R.D. Green and M. Radulovacki: Down-regulation of adenosine A_2 receptors is associated with an increase in deep slow wave sleep. Soc. Neurosci. Meeting, Nov. 9-14, Washington, D.C.

Radulovacki, M.: Adenosine compounds and sleep. International Symposium "Current Trends in Slow Wave Sleep Research', June 25-27, 1987, Beerse, Belgium. (a co-organizer)

Radulovacki, M.: Central adenosine receptors and sleep. Symposium on "Receptor Mechanisms in Sleep" 5th International Congress of Sleep Research, June 28-July 3, 1987, Copenhagen, Denmark, (invited speaker)

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