Pharmacology Biochemistry & Behavior, Vol. 29, pp. 433–441. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Adenosine Antagonists as Potential Therapeutic Agents

MICHAEL WILLIAMS[1] AND MICHAEL F. JARVIS

Research Department, Pharmaceutical Division
CIBA-GEIGY Corporation, Summit, NJ 07901

WILLIAMS, M. AND M. F. JARVIS. *Adenosine antagonists as potential therapeutic agents.* PHARMACOL BIOCHEM BEHAV **29**(2) 433–441, 1988.—The methylxanthine caffeine has been identified in more than 60 plant species and has been in human use for its various therapeutic actions for many hundreds of years and perhaps, with the exception of aspirin and related compounds, is the most widely consumed drug today. Pharmacologically, the xanthines are prototypic inhibitors of the enzyme, cyclic nucleotide phosphodiesterase, are calcium mobilizers and have been reported to inhibit the enzymes, monoamine oxidase and cyclooxygenase as well as affect uptake of the putative neuromodulator, adenosine. However, many of the therapeutic effects ascribed to caffeine are due to its selective ability to antagonize the actions of adenosine. Many xanthines, especially those substituted in the 8-position with a phenyl derivative, are potent and selective adenosine antagonists.The xanthine adenosine antagonists have mild psychostimulant, analgesic adjuvant, diuretic, cardiotonic and antiasthmatic activity. Adenosine antagonists also have nootropic activity. A major limiting factor to the development of this class of compound has been in the lack of selectivity for either of the major classes of adenosine receptor. Several non-xanthines including the pyrazolopyrimidine, DJB-KK, the pyrazoloquinoline, CGS 8216 and the pyrazolopyridine, etazolate have been shown to have adenosine antagonist activity. The triazoloquinazoline, CGS 15943 A has been identified as the first, potent (IC_{50}=3 nM) nonxanthine, A_2-selective adenosine antagonist while the phenylquinazoline, HTQZ, has 25-fold selectivity for the A_2 receptor. The availability of such novel entities may permit the development of a new class of therapeutic agents able to affect neuromodulator, as opposed to neurotransmitter, function.

Adenosine CGS 15943 A Xanthines Caffeine Analgesia Psychostimulants Nootropics
Dopamine Self mutilation

THE xanthine caffeine (Fig. 1) was first isolated from coffee in Germany in 1820 [3] and has since been identified in more than 60 plant species [4]. The use of beverages containing caffeine has been documented for over 40 centuries, making the xanthine one of the most effectively studied compounds in human use. Caffeine is also found in chocolate, although its major ingredient use is in coffee and in a variety of soft drinks. Worldwide, the average daily consumption of caffeine has been estimated at 50 mg per person per day [45], while in the U.S. this figure is four times as high [48].

The trend toward decaffeinated beverages because of the psycho-, cardio- and respiratory stimulant properties of the xanthine [86, 91, 100, 112], together with its observed teratogenic actions [27], is indicative of the ready bioavailability and potency of this class of compounds and may reflect the less than enthusiastic reception for such compounds as therapeutic entities. Administration of xanthines can elicit biphasic actions on locomotor activity [101], changes in core temperature [14,93], seizure activity [88], bronchodilation [39], diuresis, diarrhea [86], tachycardia [5], insomnia [85], anxiety [15], respiration [108] and cardiac arrhythmias [28].

Mechanistically, caffeine and related xanthines are prototypic inhibitors of the enzyme, cyclic nucleotide phosphodiesterase and calcium mobilizers [86]. In addition, xanthines have also been reported to affect the activity of the enzymes, monoamine oxidase [36] and cyclooxygenase [109], as well as modulate the uptake of the putative neuromodulator, adenosine [56]. It is generally accepted however, that the majority of actions ascribable to therapeutic doses of the xanthine are due to its action as an adenosine receptor antagonist [25, 30, 99, 110, 113].

In the 15 years that have elapsed since it was first suggested that caffeine, and the related xanthine, theophylline were adenosine antagonists [91], considerable progress has occurred in defining the physiological role of the purine and in reappraising the mechanisms by which xanthines produce their observed therapeutic actions. Theophylline (Fig. 1) and its ethylene diamine salt, aminophylline, have been used as antiasthmatic and cardiotonic respectively [21], yet their mechanism of action remains controversial.

The development of 8-phenyl-substituted xanthines as selective adenosine antagonists [11, 23, 34, 60, 98], was a major step forward in validating the adenosine hypothesis. However, these compounds, most notably PACPX (1,3-dipropyl-8-(2-amino-4-chloro)phenylxanthine; Fig. 1; [11]), have suffered from solubility problems that have precluded their potential use as therapeutic tools. Continuing efforts have however resulted in the development of compounds

[1]Requests for reprints should be addressed to Dr. Michael Williams, RES 106, CIBA-GEIGY, 556 Morris Avenue, Summit, NJ 07901.

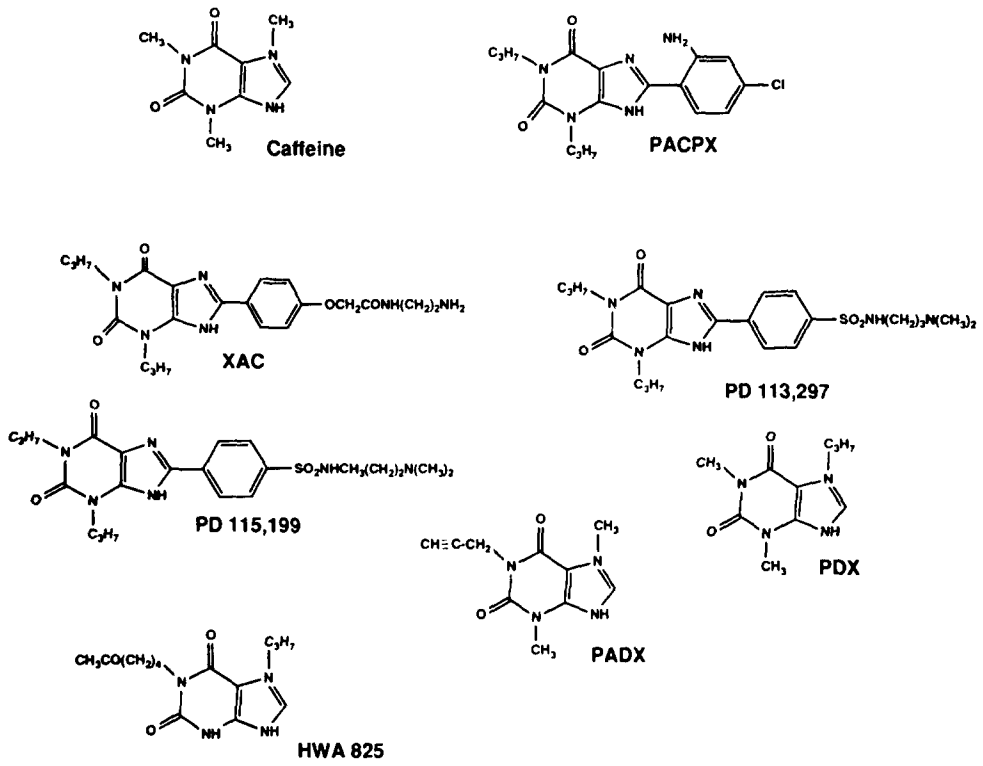

FIG. 1. Structures of xanthine adenosine antagonists.

such as the amine congener XAC (Fig. 1); [60] and PD 113,297 and related compounds (Fig. 1) [8a–10] that are relatively water soluble.

Non-xanthines such as the pyrazolopyridine, etozolate (Fig. 2) [115] and the pyrazolopyrimidine, DJB-KK (Fig. 2) [26] have also been reported to have some degree of adenosine antagonist activity. The serendipitous identification of such activity in the pyrazoloquinoline benzodiazepine inverse agonist, CGS 8216 (Fig. 2) [22,115] led to the subsequent identification of a series of non-xanthine adenosine antagonists, the triazoloquinazolines [37], typified by CGS 15943 A (Fig. 2) [43,116].

RECEPTOR SELECTIVE ADENOSINE ANTAGONISTS

In addition to selectivity for the adenosine receptor, as opposed to their other potential sites of action, xanthines selective for the two types of adenosine receptor are attractive in defining therapeutic targets for adenosine antagonists. Despite the fact that the physiological actions of adenosine were demonstrated over 50 years ago [29], it is only in the past decade that tangible evidence has accumulated for the existence of distinct adenosine receptors located on the cell surface and, subsequently, receptor subtypes. Two major receptor subclasses exist, termed A_1 and A_2 [25,53]. These differ in their pharmacological selectivity for adenosine agonists. At the A_1 receptor, purine nucleosides substituted in the N^6 position, i.e., N^6cyclohexyladenosine (CHA), N^6cyclopentyladenosine (CPA) and N^6phenylisopropyladenosine (PIA) are the most active with nucleosides substituted in the 5′ (N-ethylcarboxamidoadenosine; NECA) and 2 positions (2-aminophenyladenosine; CV 1808), being less active. The converse is true at the A_2 receptor although it should be noted that while there are A_1 selective agonists such as CPA that are over 700-fold selective [9], at the A_2 receptor the compounds available are either equiactive at both receptor subtypes (NECA) or are approximately 5-times more selective for the A_2 than the A_1 receptors (CV 1808). The lack of availability of really selective agonists has hampered basic research efforts in the area and has to some extent led to an untenable *a priori* situation in that effects elicited by NECA have been ascribed to A_2 receptor activation when, in fact, it is only those responses that are elicited by NECA and not by A_1 selective compounds such as CPA, that can be legitimately called A_2 in nature. Receptor delineation is additionally complicated by reports [62, 66, 79, 87] that receptors sensitive to adenosine agonists may exist in additional subtypes that can be classified as neither A_1 nor A_2 although it is possible that these are, in fact, subtypes of the two major subclasses [9,24].

The development of receptor selective adenosine antagonists has proved difficult. While the majority of xanthine antagonists are A_1 selective (Table 1) with only PD 115, 199 [10], 1-propargyl 3,7-dimethylxanthine (PADX; Fig. 1) and 7-propyl 1,3 dimethylxanthine (PDX) (Fig. 1) [103] showing an increase in activity at the A_2 receptor, PADX and PDX are 3- to 7-fold selective for the A_2- receptor. These xanthines are, however, relatively weak antagonists with activities in the micromolar range [103] (Table 1). On the other hand, while PD 115,199 is active in the nanomolar range at the A_2 receptor [10], like NECA, it is non-selective rather than A_2 selective. The triazoloquinazoline, CGS 15943 A [116] is an A_2 selective antagonist with an approximate 8-fold separation in activity between the two receptor subtypes while HTQZ (3(3-hydroxyphenyl)5H-thiazolo [2,3b]-quinazoline (Fig. 2) is 25-fold A_2 selective [8].

TABLE 1

RECEPTOR SELECTIVITY OF SELECTED ADENOSINE ANTAGONISTS

Compound	IC_{50} (nM) A_1	A_2	A_2/A_1
Theophylline	14900	37530	39
PACPX	54	589	109
PD 113,297	8.2	104	12.7
PD 115,199	14	16	1.1
PADX*	94000	4000	0.04
PDX*	109000	9300	0.09
Etazolate	6100	13800	2.3
DJB-KK	168	736	4.4
CGS 15943 A	21	3.3	0.16
HTQZ	3070	124	0.04
XAC	15	83	5.5

*Data derived from fat cell and platelet adenylate cyclase data [103]. All remaining data based on brain binding, [10, 11, 102, 112, 116].

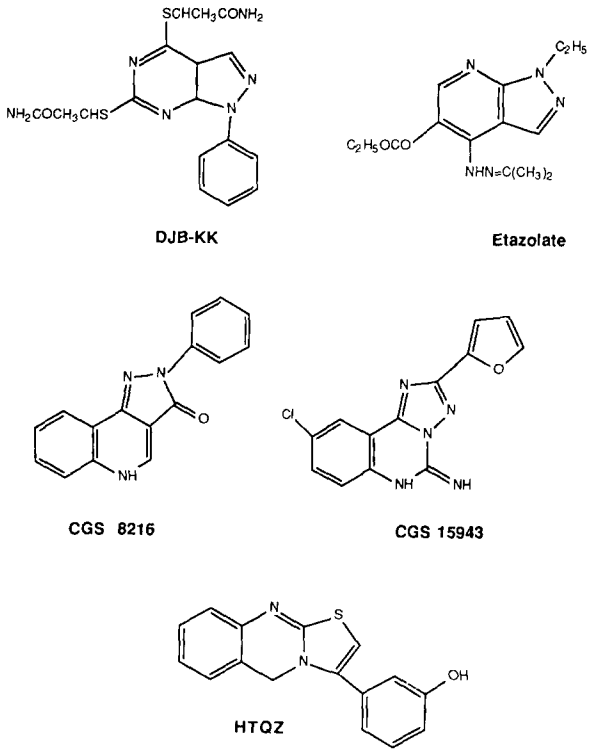

FIG. 2. Structures of atypical adenosine antagonists.

INTERSPECIES VARIATIONS IN XANTHINE RELATED EFFECTS

The effects of caffeine in humans vary widely between individuals, from those to whom a single cup of coffee can cause mild tremors to others who can imbibe 10–15 cups a day with no apparent ill effects. While such responses may be attributable to differences in the metabolism of the xanthine [49], adenosine systems including A_1 [34, 74, 94, 96] and A_2 [102] receptors, uptake sites for the purine [106] and 5'-nucleotidase [65] the enzyme responsible for formation of adenosine from 5'-AMP, appear to have marked interspecies differences [110]. In regard to receptor pharmacology, such differences are especially pronounced for xanthine interactions with PACPX having a Ki value of 0.18 nM at A_1 receptors in calf brain and a Ki of 71 nM in guinea pig brain [102]. These findings present problems for the identification of selective xanthine adenosine antagonists even when comparing interactions at A_1 and A_2 receptors in the same species. In man for instance, PACPX, based on its receptor binding profile is slightly A_2 selective (A_2/A_1 Ki ratio=0.6). However, in calf brain, this ratio is 233 [102].

Such studies have been expanded at the behavioral level to examine interstrain differences in the CNS responses of mice to methylxanthines [95], such differences being related to complex genetic determinants. Extrapolation from mice to humans may given some clues as to why caffeine responses vary from individual. However, in considering the reported species, as opposed to strain, differences in xanthine interactions with adenosine receptors which are far more dramatic than those seen for antagonists [35,102], it is worthwhile considering, from a theoretical viewpoint what such differences may mean. The receptor charcteristics (Kd, Bmax) for both A_1 and A_2 receptors do not appreciably differ between the two species, hence it is unlikely that calves are more sensitive to PACPX than guinea pigs because of the presence of supersensitive receptors. This conclusion is reinforced by the finding that the adenosine agonist, CHA, is only 10-fold less active at A_1 receptors in guinea pig as compared to calf [35] and 3-fold more active at A_2 receptors in guinea pig [102]. If can be speculated that guinea pig has more of some endogenous inhibitory substance than calf that would dramatically interfere with the interactions of xanthines with adenosine receptors but would have less of an effect on purine interactions. This delineation between the effects of adenosine antagonists and agonists have been considered in relation to the chronic effects of caffeine on acetylcholine release [18]. Alternatively it is possible that the portion of the adenosine receptor responsible for xanthine binding is different between species. The xanthine congener, [^{3}H]XAC, has higher affinity in calf than in guinea pig [60]. Whatever the reasons for such differences, their teleological significance is not readily apparent.

Again, using PACPX as an example, the rank order of activity for the xanthine at A_1 receptors in six species is: calf > rabbit > rat=mouse > man > guinea pig [35] while at the A_2 receptor, this order is: rabbit > man > calf > guinea pig > mouse > rat [102]. Thus the species order is not consistent between the receptor subtypes and, in addition, there is no clear hierarchy in the xanthine responses that could be of phylogenetic significance. An additional complicating factor is that while there is a substantial amount of data indicating that caffeine is a competitive antagonist at adenosine receptors [25], there is some controversy as to whether PACPX is competitive or non-competitive [11, 13, 110]. Additional studies in this area, with the availability of CGS 15943 A and HTQZ, may clarify as to whether these species differences are observed with all adenosine antagonists or are unique for the xanthines.

THERAPEUTIC POTENTIAL—PRECLINICAL PREDICTIONS

The development of adenosine antagonists as therapeutic agents has been predicated on the physiological actions of the natural ligand for the adenosine receptor, namely the purine itself. There is a wealth of evidence to indicate that adenosine antagonists are effective modulators of tissue

function because of the general availability of endogenous adenosine in the vicinity of cell surface receptors. The concept of a general purinergic inhibitory tone [54] has been demonstrated in the ability of xanthines to potentiate locomotor activity [40,101] and increase neurotransmitter release [82] and cell firing [31]. The lack of availability of potent and selective compounds that are as bioavailable as caffeine and theophylline has resulted in much of the therapeutic potential of adenosine antagonists per se being more conjecture than fact. This is hardly surprising when considering the tremendous advances that have been made in regard to the drug discover process in the last decade [114]. There are in fact many theories, based on basic and applied research at the preclinical level, that have yet to be tested in the final human paradigm for validation. Many of the peptide neuromodulators that represent current targets for the development of novel therapeutic agents are in a similar situation to adenosine and it is equally apparent that many of the predictions based on the study of known compounds by what might be a *posteri* approach are not subject to validation because of the lack of selective compounds.

In the area of adenosine modulation there are several attractive targets that reflect the importance of the purine in cellular physiology, yet the very ubiquity of the compound together with marked species differences described above has led to a degree of skepticism that has been further reinforced by the use of theophylline and aminophylline as antiasthmatics and cardiotonics. In either instance the therapeutic usefulness of the compounds has been complicated by side effects associated with the putative blockade of adenosine receptor related events in tissue systems other than those targeted for in the therapeutic indication. However, since the chemical entities used were not dramatically different from that isolated in the early 19th century [3], it is difficult to objectively view this as a natural limitation of the system as opposed to the relative mediocrity of the tools available. With hindsight, one would be hard pressed to argue for the enormous benefits of H_2-receptor antagonists such as cimetidine, if only pyrilamine were available and had been shown to be ineffective in the treatment of gastric ulceration.

CNS INDICATIONS

Nootropic/Cognitive Enhancer

The psychostimulant actions of caffeine are attributed to the xanthine blocking the purinergic inhibitory tone that reduces neurotransmitter release and in doing so increase 'alertness.' The effects of the xanthine have been studied using the 2-deoxyglucose method [78] leading to the conclusion that caffeine increases functional activity. These effects are dose dependent and show some degree of regional specifity that has been attributed to blockade of A_2 receptors [78] an interesting conclusion in light of the fact that the xanthine is non-selective in its effects on receptor blockade.

The psychostimulant actions of caffeine provide a plausible link for the use of an adenosine antagonist as a nootropic or cognitive enhancer. One xanthine, HWA 825 (Fig. 1) [56], has been tested in humans for this indication and positive results have been reported. It may be noted, however, that HWA 825 has an unusual profile of activity in vivo and has been described as an agonist at adenosine receptors [52]. Although the differences may be semantic, compounds that cause a general increase in alertness (cognitive or vigilance enhancers) and nootropics, compounds used to arrest or reverse the general effects of the aging process on CNS function via as yet unknown mechanisms, are generally considered to reflect closely associated, yet different classes of compound. Caffeine at doses higher than those at which it acts as a psychostimulant is an anxiogenic [15,86] and it is of interest that CGS 8216, the pyrazoloquinazoline benzodiazepine inverse agonist with weak adenosine antagonist activity (Table 1) [22,115], has activity as a vigilance enhancer [6]. It is of further interest that compounds of the benzodiazepine inverse agonist class have demonstrated nootropic activity [105]. A major problem in further exploring the validity of the concept that xanthines may be nootropic agents is their lack of tissue selectivity. In dealing with the geriatric population, the side effects associated with human use of xanthines, i.e., cardiac stimulant and diuretic, assume proportions that preclude any consideration of a viable therapeutic index.

Cerebral Blood Flow Modulator

In assessing the effects of compounds on CNS function, it is usual to focus attention on the target organ, more specifically, the effects of a given compound on synaptic transmission. However, the brain, like other tissues is dependent on oxygen for function and there has been a continuing controversy as to whether the effects of peripherally administered adenosine on CNS function are due to direct actions on brain function or are indirect via a decrease in blood pressure [61, 83, 101].

Xanthines are effective modulators of cerebral blood flow [32, 51, 78] presumably acting via blockade of adenosine receptors present in cerebral arteries. Cerebral blood flow appears to be under direct metabolic control, increases in glucose and oxygen demand being reflected by increases in blood flow [69]. However, caffine has been reported to increase cerebral glucose utilization while concomitantly decreasing cerebral blood flow [51]. In contrast, the putative nootropic HWA 825 [56] can increase cerebral blood flow while decreasing glucose utilization [51]. Despite the fact that adenosine can be formed from the endothial cells of the microvasculature [72] and has been proposed as the chemical link between brain metabolism and cerebral blood flow [119,120], it has been reported [81] that caffeine cannot affect autoregulatory flow responses during hypotensive episodes in rats. The situation in regard to the effects of xanthines and, by extrapolation, purines, in the regulation of cerebral blood flow is therefore complex. The possibility that compounds affecting the purinergic innervation to cerebral microvessels might be of use in migraine [12] remains to be evaluated.

Respiratory Stimulants

Methylxanthines are widely used in the treatment of apnea (sudden infant death syndrome: SIDS) of preterm infants [2], an action that appears to be due to their ability to antagonize the effects of the adenosine released during hypoxemia [63]. Adenosine is an effective respiratory depressant [33, 73, 108] producing its actions via A_2 receptors associated with carotid chemoreceptors [70,71]. Cessation of blood flow to the brain as a result of cardiac arrest can lead to ischemic episodes that result in stroke and the attendant loss of CNS function. The reactive hyperemia that results in cardiac tissues from hypoxia and which is thought to contribute significantly to the tissue damage resulting from the reduction in oxygen supply [44] can be attenuated by

theophylline, suggesting that adenosine mediates this phenomenon and also that xanthines may have potential in limiting the tissue damage associated with ischemia.

Analgesia

Xanthines have been reported to reduce morphine analgesia [58], produce algesia [104] and have antinociceptive activity [122]. Adenosine has also been reported to have similar conflicting activities [1, 46, 104]. IBMX (3-isobutyl-1-methylxanthine), a xanthine that is a weak adenosine antagonist and a prototypic phosphodiesterase inhibitor, can elict a 'quasi-morphine withdrawal syndrome' (QMWS) [17] that appears to be associated with increases in norepinephrine turnover [42]. Caffeine is used clinically as an analgesic adjuvant [64] an action that may be attributed to the ability of xanthines to inhibit cyclooxygenase activity [109].

Xanthines, Locomotor Activity and Central Dopaminergic Systems

The increase in locomotor activity associated with caffeine and theophylline administration [40,61], is manifest as contralateral rotational behaviour in rats unilaterally lesioned in the nigrostriatal dopamine pathway, an effect similar to that observed following administration of selective dopamine agonists [41]. The xanthines can also potentiate the effects of dopamine agonists as well as the ipsilateral turning produced by amphetamine. These effects appear to be due to the adenosine antagonist actions of the xanthines [40] and can be antagonized by the dopamine antagonist, haloperidol [41,90], suggesting that the monoamine is mediating the effects of the xanthines. Since caffeine has no direct interactions with dopamine receptors either in vitro or in vivo [108] it is likely that the locomotor stimulatory actions of caffeine and theophylline are due to removal of the purinergic inhibitory tone [54] and a consequent increase in the intersynaptic availability of dopamine. Striatal dopamine metabolism can be reduced by administration of stable adenosine agonists [77], and while xanthines can affect the availability of a number of putative neurotransmitters [82,114], in vivo, caffeine can selectively modulate dopaminergic function [47]. In this regard, caffeine has been suggested as a therapeutic adjuvant with dopamine agonists in the treatment of Parkinsonism [41]. A selective disruption of dopaminergic nerve terminals occurs in brains from patients with Lesch-Nyhan syndrome [68], a self-mutilatory disease characterized by a deficit in purine metabolism. Such neurological disease states may result from an excessive stimulation of adenosine receptors by the accumulated purines [57], although it may be noted that a large dose of caffeine can elicit self-destructive behaviour similar to that observed in Lesch-Nyhan syndrome [7]. Purinergic mechanisms have also been implicated in the apomorphine-induced self mutilation behavioral syndrome [50]. There is thus a considerable amount of experimental data linking dopamine with central adenosine systems, a relationship reinforced by the preferential localization of high affinity A_2 receptors in striatum [9, 24, 84, 118, 121] and by the observation that caffeine effects on brain glucose utilization are most pronounced in dopamine-rich regions [78]. Furthermore, adenosine agonists have been reported to have antipsychotic-like actions in certain animal models [55] presumably related to their ability to decrease dopamine synthesis [77]. The effects of xanthines on central neurotransmitter metabolism and release appear to be tolerated following chronic treatment [123], an effect attributed to the increases in A_1 receptor density observed following chronic treatment [38,76]. However, using an in vitro slice release paradigm, it has been reported [18] that chronic caffeine treatment can attenuate the enhancing effects of the xanthine on acetylcholine release without affecting the inhibitory actions of CHA. This observation may indicate that adaptive changes to chronic caffeine treatment may involve mechanisms more complex than the interaction of the xanthine with adenosine receptors although it may be noted that changes in A_2 receptors following chronic studies have not been documented.

Miscellaneous

Based on anecdotal evidence [27], caffeine, in the form of coffee, has been suggested to facilitate nicotine consumption and increase the hedonia associated with chocolate consumption, an effect that may be related to a purinergic component in taste intensity [92]. Xanthines may also modify the effects of purines on food intake [67].

ANTIASTHMATICS

Theophylline, along with β-adrenoceptor agonists, is one of the major therapeutic agents used as bronchodilator in the treatment of asthma [21] and is generally considered to produce its actions via inhibition of phosphodiesterase activity which parallel the effects of β-agonists and forskolin in increasing tissue cyclic AMP levels. Adenosine can potentiate histamine release from mast cells following an allergic challenge [16]. Broncoconstriction can be produced in asthmatics but not normal subjects by the purine, an effect that can be antagonized by theophylline. While there still appears to be a cyclic AMP component related to the bronchodilatory actions of antiasthmatics it seems highly probable that the adenosine antagonist activity of theophylline contributes significantly to its therapeutic actions in pulmonary tissue. Enprofylline (3-propylxanthine) is an especially effective antiasthmatic agent [80] with a minimal incidence of side effects related to interactions with other tissues. This has been ascribed to the pharmacodynamic properties of this xanthine derivative.

CARDIOTONIC ACTIONS

Aminophylline, as already mentioned, has had limited use as a cardiotonic agent via its ability to block the negative chronotropic and dromotropic actions of adenosine [5]. The concentrations of the xanthine to block adenosine activity are sufficiently high, however, to also elicit ventricular arrhythmias due to increases in cardiac cyclic AMP levels. More selective adenosine antagonists, may therefore be useful as cardiotonics.

RENAL MODULATORS

Adenosine is an effective modulator of renin release from the macula densa cells of the kidney, acting as a signal transducer in response to increase renal sodium loads [59,75]. Both A_1 and A_2 receptors are able to mediate renin release in a biphasic manner, the former inhibiting and the latter stimulating, release of this important blood pressure regulating peptide [97]. The purine can also cause renal vasoconstriction. Caffeine may thus affect renin release by

blocking an inhibitory action of adenosine at A_1 receptors. The diuretic actions of caffeine appear to be due to an inhibition of solute reabsorption [86].

IMMUNE FUNCTION

Xanthines have been implicated as teratogens [27] and by their implied effects as adenosine antagonists may be expected to reverse the actions of adenosine on immune system function. The purine can modulate antigen expression, inhibit mitogenic stimulation and has marked immunosuppressant activity [89]. Adenosine antagonists may also modify the effects of adenosine on neutrophil function [19]. Adenosine can inhibit neutrophil superoxide formation and xanthines can overcome this effect [20]. While this effect would be beneficial in regard to the etiology of atherosclerosis, such effects would be delterious to the role of neutrophils in protecting against infection.

CONCLUSIONS

An increased chemical effort to make more potent, selective and bioavailable xanthines has shown this class of compound to be prototypic adenosine antagonists. Based on the knowledge regarding the in vivo actions of caffeine and theophylline it appears probable that such agents will be effective as antiasthmatic and cardiotonic agents. In addition, however, a considerable body of evidence would indicate that adenosine antagonists may have potential use in other therapeutic areas where the purine is known to exert physiological influence. The possibility that brain specific adenosine antagonists may represent a truely novel and effective class of cognitive enhancers awaits further chemical effort in this area with a continued focus on non-xanthine compounds.

ACKNOWLEDGEMENT

The authors would like to thank Dr. D. J. Brown for the gift of DJB-KK.

REFERENCES

1. Ahiljanian, M. K. and A. E. Takemori. Effects of (−) N^6(phenylisopropyl)adenosine (PIA) and caffeine on nociception and morphine-induced analgesia, tolerance and dependence in mice. *Eur J Pharmacol* **112:** 171–179, 1985.
2. Aranada, J. V. and T. Turmen. Methylxanthines in apnea of prematurity. *Clin Perinatol* **6:** 87, 1979.
3. Arnaud, M. J. Products of the metabolism of caffeine. In: *Caffeine*, edited by P. B. Dews. New York: Springer Verlag, 1984, pp. 59–73.
4. Barone, J. J. and H. Roberts. Human consumption of caffeine. In: *Caffeine*, edited by P. B. Dews. New York: Springer Verlag, 1984, pp. 59–73.
5. Bellardinelli, L. A. West, R. Crampton and R. M. Berne. Chrontropic and dromotropic effects of adenosine. In: *Regulatory Function of Adenosine*, edited by R. M. Berne, T. W. Rall and R. Rubio. Boston: Martinius Nijhoff, 1983, pp. 377–398.
6. Bennett, D. A. and B. Petrack. CGS 9896: A nonbenzodiazepine, non-sedating potential anxiolytic. *Drug Dev Res* **4:** 75–82, 1984.
7. Boyd, E. M., M. Dolman, L. M. Knight and E. P. Sheppard. The chronic oral toxicity of caffeine. *Can J Physiol Pharmacol* **43:** 995–1007, 1965.
8. Bruns, R. F. and L. Coughenour. New non-xanthine adenosine antagonists. *Pharmacologist* **29:** 146, 1987.

8a. Bruns, R. F., G. H. Lu and T. A. Pugsley. Towards selective adenosine antagonists. In: *Adenosine: Receptors and Modulation of Cell Function*, edited by V. Stefanovich, K. K. Rudophi and P. Schubert. Oxford, UK: IRL Press, 1985, pp. 51–58.

9. Bruns, R. F., G. H. Lu and T. A. Pugsley. Characterization of the A-2 adenosine receptor labeled by (^{3}H)NECA in rat striatal membranes. *Mol Pharmacol* **29:** 331–346, 1986.
10. Bruns, R. F., G. H. Lu and T. A. Pugsley. Adenosine receptor subtypes: binding studies. In: *Topics and Perspectives in Adenosine Research*, edited by E. Gerlach and B. F. Becker. Berlin: Springer-Verlag, 1987, pp. 59–73.
11. Bruns, R. F., J. W. Daly and S. H. Snyder. Adenosine receptor binding: structure activity analysis generates extremely potent xanthine antagonists. *Proc Natl Acad Sci USA* **80:** 2077–2080, 1983.
12. Burnstock, G. Neurochemical control of blood vessels: some future directions. *J Cardiovasc Pharmacol* **7:** 5137–5146, 1985.
13. Burnstock, G. and C. H. V. Hoyle. PACPX—a substituted xanthine antagonizes both the A-1 and A-2 subclasses of the P-1 purinoceptor: antagonism of the A-2 subclass is competitive but antagonism of the A-1 is not. *Br J Pharmacol* **85:** 291–296, 1985.
14. Carney, J. M., T. W. Seale, L. Logan and S. B. McMaster. Sensitivity of inbred mice to methxanthines is not determined by plasma xanthine concentration. *Neurosci Lett* **56:** 27–31, 1985.
15. Charney, D. S., G. R. Heninger and P. I. Jatlow. Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiatry* **42:** 233–243, 1985.
16. Church, M. K. and S. T. Holgate. Adenosine and asthma. *Trends Pharmacol Sci* **7:** 49–50, 1986.
17. Collier, H. O. J. N. Cutbert and D. L. Francis. Character and meaning of quasi-morphine withdrawal phenomena elicted by methylxanthines. *Fed Proc* **40:** 1513–1518, 1981.
18. Corradetti, R. F. Pedata, G. Pepeu and M. Vannuchi. Chronic caffeine treatment reduces caffeine but not adenosine effects on cortical acetylcholine-choline release. *Br J Pharmacol* **88:** 671–676, 1986.
19. Cronstein, B. N., S. B. Krammer, G. Weissmann and R. Hirschhorn. Adenosine, a physiologic modulator of superoxide anion generation by human neutrophils. *J Exp Med* **158:** 1160–1177, 1985.
20. Cronstein, B. N., R. I. Levin, J. Belanoff, G. Weissmann and R. Hirshhorn. A new function for adenosine: protection of vascular endothelial cells from neutrophil-mediated injury. In: *Topics and Perspectives in Adenosine Research*, edited by E. Gerlach and B. F. Becker. Berlin: Springer-Verlag, 1987, pp. 299–308.
21. Czasky, T. Z. and B. A. Barnes. *Cutting's Handbook of Pharmacology, 7th Edition*, Norwalk, CT: Appleton-Century-Crofts Publishers, 1984, pp. 282–284.

22. Czernik, A. J., B. Petrack, H. J. Kalinsk, S. Psychoyos, W. D. Cash, C. Tsai, R. K. Rinehart, F. R. Granat, R. A. Lovell, D. E. Brundish and R. Wade. CGS 8216: Receptor binding characteristics of a potent benzodiazepine antagonist. *Life Sci* **30:** 363–372, 1982.
23. Daly, J. W., W. Padgett, M. T. Shamin, P. Butts-Lamb and J. Walters, 1,3-Dialkyl-8-(p-sulfophenyl)xanthines: potent water-soluble antagonists for A-1 and A-2 adenosine receptors. *J Med Chem* **28:** 487–492, 1985.
24. Daly, J. W. P. Butts-Lamb and W. Padgett. Subclasses of adenosine receptors in the central nervous system. Interactions with caffeine and related methylxanthines. *Cell Mol Neurobiol* **3:** 69–80, 1983.
25. Daly, J. W. Adenosine receptors: target sites for drugs. *J Med Chem* **25:** 197–207, 1982.
26. Davies, L. P., S. Chom, J. H. Skerritt, D. J. Brown and G. A. R. Johnston. Pyrazolo(3,4-d)pyrimidines as adenosine antagonists. *Life Sci* **34:** 2117–2128, 1984.
27. Dews, P. B. *Caffeine* New York: Springer Verlag, 1984.
28. Dobmeyer, D. J., R. A. Stine, C. V. Leier, R. Greenberg and S. F. Shcaal. The arrythmogenic effects of caffeine in human beings. *N Engl J Med* **308:** 814–816, 1983.
29. Drury, A. N. and A. Szent-Gyorgi. The physiological activity of adenosine compound with special reference to their action upon the mammalian heart. *J Physiol (Lond)* **68:** 213–237, 1929.
30. Dunwiddie, T. V. The physiological roles of adenosine in the central nervous system. *Int Rev Neurobiol* **27:** 63–139, 1985.
31. Dunwiddie, T. V., B. J. Hoffer and B. B. Fredholm. Alkylxanthines elevate hippocampal excitability. *Naunyn Schmiedebergs Arch Pharmacol* **316:** 326–330, 1983.
32. Edvinsson, L. and B. B. Fredholm. Characteristics of adenosine receptors in isolated cerebral arteries of cats. *Br J Pharmacol* **80:** 631–637, 1983.
33. Eldridge, F. L., D. E. Millhorn and J. P. Kiley. Respiratory effects of a long-acting analog of adenosine. *Brain Res* **301:** 273–280, 1984.
34. Ferkany, J. M., R. Hicks, J. Connor and L. Noronha-Blob. Potent and selective adenosine (A-1) receptor antagonists. *Pharmacologist* **27:** 292, 1985.
35. Ferkany, J. M., H. Valentine, G. Stone and M. Williams. Adenosine A-1 receptors in mammalian brain: species differences in their interactions with agonist and antagonists. *Drug Dev Res* **9:** 85–93, 1986.
36. Fernstrom, J. D. and M. H. Fernstrom. Effects of caffeine on monoamine neurotransmitters in the central and peripheral nervous system. In: *Caffeine,* edited by P. B. Dews. New York: Springer Verlag, 1984, pp. 107–118.
37. Francis, J. E., S. Psychoyos, G. Ghai, P. Wenk, R. C. Freidmann, C. Atkins, V. Warren, P. Furness. T. C. Hyan, G. A. Stone, M. Desai, W. D. Cash and M. Williams. Structure activity profile of a series of novel triazoloquinazoline adenosine antagonists. *J Med Chem,* submitted, 1988.
38. Fredholm, B. B. Adenosine receptors. *Med Biol* **70:** 289–293, 1982.
39. Fredholm, B. B. and G. C. Persson. Xanthine derivatives as adenosine antagonists. *Eur J Pharmacol* **81:** 673–676, 1982.
40. Fredholm, B. B., M. Herrana-Maschitz, B. Jonzon, K. Lindstrom and U. Ungerstedt. On the mechanism by which methylxanthines enhance apomorphine-induced rotation behaviour in the rat. *Pharmacol Biochem Behav* **19:** 535–541, 1983.
41. Fuxe, K. and U. Ungerstedt. Action of caffeine and theophylline on supersensitive dopamine receptors: considerable enhancement of receptor response to treatment with dopa and dopamine agonists. *Med Biol* **52:** 48–54, 1974.
42. Galloway, M. and R. Roth. Neuropharmacology of 3-isobutylmethyl-xanthine: effects on central noradrenergic systems in vivo. *J Pharmacol Exp Ther* **227:** 1–8, 1983.
43. Ghai, G., J. Francis, M. Williams, M. Zimmerman, F. R. Goodman, M. Hopkins and D. Cote. Pharmacological characterization of CGS 15943 A, novel non-xanthine adenosine antagonist. *J Pharmacol Exp Ther* **242:** 784–790, 1987.
44. Gidday, J. M., S. W. El, J. W. Esther, R. M. Berne. Attenuation of coronary reactive hyperemia with increasing interstitial theophylline permeation. *Fed Proc* **43:** 1084, 1984.
45. Gilbert, R. M. Caffeine: overview and anthology. In: *Nutrition and Behavior,* edited by S. A. Miller. Philadelphia: Franklin Inst. Press, 1981, pp. 145–166.
46. Gourley, D. R. H. and S. K. Beckner. Antagonism of morphine analgesia by adenine adenosine and adenine nucleotides. *Proc Soc Exp Biol Med* **144:** 774–780, 1973.
47. Govoni, S., V. Perkov, O. Montefusco, C. Missale, F. Battain, P. F. Spano and M. Trabuchi. Differential effects of caffeine on dihydroxyphenylacetic acid concentration in various rat brain dopaminergic structures. *J Pharm Pharmacol* **36:** 458–460, 1984.
48. Graham, D. M. Caffeine—its identity in dietary sources, intake and biological effects. *Nutr Rev* **36:** 97–101, 1978.
49. Grant, D. M., B. K. Tang and W. Kalow. Variability in caffeine metabolism. *Clin Pharmacol Ther* **33:** 591–602, 1983.
50. Green, R. D., H. K. Proudfit and S-H. Yeung. Modulation of striatal dopaminergic function by local injection of 5′-N-ethylcarboxamide adenosine. *Science* **218:** 58–61, 1982.
51. Grome, J. J. and V. Stefanovich. Differential effects of xanthine derivatives on local cerebral blood flow and glucose utilization in the conscious rat. In: *Adenosine: Receptors and Modulation of Cell Function,* edited by V. Stefanovich, K. Rudolphi and P. Schubert. Oxford, U.K.: IRL Press, 1985, pp. 453–457.
52. Grome, J. J. and V. Stefanovich. Differential effects of methylxanthines on local cerebral flow and glucose utilization in the conscious rat. *Naunyn Schimedebergs Arch Pharmacol* **333:** 172–179, 1986.
53. Hamprecht, B. and D. Van Calker. Nomenclature of adenosine receptors. *Trends Pharmacol Sci* **6:** 153–154, 1985.
54. Harms, H. H., G. Wardeh and A. H. Mulder. Adenosine modulates depolarization-induced release of ^{3}H-noradrenaline from slices of rat neocortex. *Eur J Pharmacol* **49:** 305–308, 1978.
55. Heffner, T. G., D. A. Downs, J. A. Bristol, R. F. Bruns, S. E. Harrigan, W. H. Moos, K. L. Sledge and J. N. Wiley. Antipschotic-like effects of adenosine receptor agonists. *Pharmacologist* **27:** 293, 1985.
56. Hindmarch, I. and Z. Subhan. A preliminary investigation of "Albert 285" HWA 285 on psychomotor performance, mood and memory. *Drug Dev Res* **5:** 379–386, 1985.
57. Hischhorn, R., P. S. Papageor, H. H. Kesarwal and L. L. Taft. Amerlioration of neurologic abnormalities after enzyme replacement in adenosine deaminase defficiency. *N Engl J Med* **303:** 377–380, 1980.
58. Ho, I.K., H. H. Loh and E. L. Way. Cyclic adenosine monophosphate antagonism of morphine analgesia. *J Pharmacol Exp Ther* **189:** 51–60, 1973.
59. Itoh, S., O. A. Carretero and R. D. Murray. Possible role of adenosine in the macula densa mechanism of renin release in rabbits. *J Clin Invest* **76:** 1412–1417, 1985.
60. Jacobson, K. A., D. Ukena, K. L. Kirk and J. W. Daly. [^{3}H]Xanthine amine congener of 1,3-dipropyl-8-phenylxanthine: An antagonist radioligand for adenosine receptors. *Proc Natl Acad Sci USA* **83:** 4089–4093, 1986.
61. Katims, J. J., Z. Annau and S. H. Snyder. Interactions in the behavioral effects of methylxanthines and adenosine derivatives. *J Pharmacol Exp Ther* **227:** 167–173, 1983.
62. Kusachi, S., R. D. Thompson, N. J. Yamada, J. W. Daly and R. A. Olsson. Dog coronary artery adenosine receptor: structure of the N^6 aryl sub-region. *J Med Chem* **29:** 989–996, 1986.
63. Lagercrantz, H., C. Yamamoto, B. B. Fredholm, N. Prabhakar and C. Euler. Adenosine analogues depress ventilation in rabbit neonates: theophylline stimulation of respiration via adenosine receptors. *Pediatr Res* **18:** 387–390, 1984.
64. Laska, E. M., A. Sunshine, F. Mueller, W. B. Elvers, C. Siegel and A. Rubin. Caffeine as an analgesic adjuvant. *JAMA* **251:** 1711–1718, 1984.

65. Lee, K. S., P. Schubert, M. Reddington and G. W. Kreutzberg. The distribution of 5'-nucleotidase and adenosine A-1 receptors for diversification and conversation in the hippocampi of several commonly employed experimental animals. *Acta Histochem (Jena) [Suppl]* **31:** 45–52, 1985.
66. Leung, E., C. I. Johnston and E. A. Woodcock. An investigation of the receptors involved in the coronary vasodilator effect of adenosine analogues. *Clin Exp Pharmacol Physiol* **12:** 515–519, 1985.
67. Levin, R. M. and J. E. Morley. Effect of intraventricular adenosine on food intake in rats. *Pharmacol Biochem Behav* **19:** 23–26, 1983.
68. Lloyd, D. G., O. Hornykiewicz, L. Davidson, K. Shannak, I. Farley, M. Goldstein, M. Shibua, W. N. Keller and I. H. Fox. Biochemical evidence of dysfunction of brain neurotransmitters in the Lesh-Nyhan syndrome. *N Engl J Med* **305:** 1106–1111, 1981.
69. McCulloch, J., P. A. T. Kelly and I. Ford. Effect of apomorphine on the relationship between cerebral glucose utilization and local cerebral blood flow. *J Cereb Blood Flow Metab* **2:** 487–499, 1982.
70. McQueen, D. S. and J. A. Riberio. Pharmacological characterization of the receptor involved in chemoexcitation induced by adenosine. *Br J Pharmacol* **88:** 615–620, 1986.
71. McQueen, D. S. and J. A. Riberio. Effect of adenosine on carotid chemoreceptor activity in the cat. *Br J Pharmacol* **74:** 129–136, 1981.
72. Mistry, G. and G. I. Drummond. Adenosine metabolism in microvessels from heart and brain. *J Mol Cell Cardiol* **18:** 13–22, 1986.
73. Mueller, R. A., E. Wilderlof and G. R. Breese. Antagonism of 2-chloroadenosine induced respiratory depression by aminophylline and naloxone. *Anesthesiology* **57:** 494–503, 1982.
74. Murphy, K. M. M. and S. H. Snyder. Heterogeneity of adenosine A-1 receptor binding in brain tissue. *Mol Pharmacol* **21:** 250–257, 1982.
75. Murray, R. D. and P. Churchill. Concentration dependency of the renal vascular and renin secretory responses to adenosine receptor agonists. *J Pharmacol Exp Ther* **232:** 189–193, 1985.
76. Murray, T. F. Up-regulation of rat cortical adenosine receptors following chronic administration of theophylline. *Eur J Pharmacol* **892:** 113–114, 1982.
77. Myers, J. and T. A. Pugsley. Decrease in rat striatal dopamine synthesis and metabolism in vivo by metabolically stable adenosine receptor agonists. *Brain Res* **375:** 193–197, 1986.
78. Nehlig, A., G. Luicignani, M. Kadekaro, L. J. Porrino and L. Sokoloff. Effects of acute administration of caffeine on local cerebral glucose utilization in the rat. *Eur J Pharmacol* **101:** 91–100, 1984.
79. Olsson, R. A. Structure of the coronary artery adenosine receptor. *Trends Pharmacol Sci* **5:** 113–116, 1984.
80. Persson, C. G. A., K. E. Anderson and G. Kjellin. Effects of enprofylline and theophylline may show the role of adenosine. *Life Sci* **38:**1057–1072, 1986.
81. Phillis, J. W. and R. E. De Long. The role of adenosine in cerebral vascular regulation during reductions in perfusion pressure. *J Pharm Pharmacol* **38:** 460–462, 1986.
82. Phillis, J. W. and P. H. Wu. The role of adenosine and its nucleotides in central synaptic transmission. *Prog Neurobiol* **16:** 187–193, 1981.
83. Phillis, J. W and P. H. Wu. The role of adenosine in central neuromodulation. In: *Regulatory Functions of Adenosine*, edited by R. M. Berne, T. W. Rall and R. Rubio. Boston: Martinius Nijhoff, 1983, pp. 429–437.
84. Premont, J., M. Perez, J. Bockaert. Adenosine-sensitive adenylate cyclase in rat striatal homogenates and its relationship to dopamine and Ca^{2+} sensitive adenylate cyclase. *Mol Pharmacol* **13:** 662–670, 1977.
85. Radulovacki, M., R. M. Virus, M. Djuricic-Nedelson and R. D. Green. Adenosine analogs and sleep in rats. *J Pharmacol Exp Ther* **228:** 268–274, 1984.
86. Rall, T. W. Central nervous system stimulants: the xanthine. In: *The Pharmacological Basis of Therapeutics, 7th Edition*, edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: Macmillan Publishing Co., 1985, pp. 589–602.
87. Riberio, J. A. and A. M. Sebastio. Adenosine and calcium: basis for proposing a third (A-3) adenosine receptor. *Prog Neurobiol* **26:** 179–209, 1986.
88. Richards, W., J. A. Chuieh and D. K. Brent. Theophylline-associated seizures in children. *Ann Allergy* **54:** 276–279, 1985.
89. Samet, M. K. Inhibition of antibody production by 2-chloroadenosine. *Life Sci* **37:** 225–233, 1985.
90. Satoh, H., T. Satoh, Y. Notsu and F. Honda. Adenosine 3'-5'-cyclic monophosphate as a possible mediator of rotational behavior induced by dopaminergic receptor stimulation in rats lesioned unilaterally in the substantia nigra. *Eur J Pharmacol* **39:** 365–377, 1976.
91. Sattin, A. and T. W. Rall. The effect of adenosine and adenine nucleotides on the cyclic adenosine 3'-5'-phosphate content of guinea pig cerebral cortex slices. *Mol Pharmacol* **6:** 13–23, 1970.
92. Schiffman, S. S., C. Diaz and T. Beeker. Caffeine intensifies taste of certain sweetners: Role of adenosine receptor. *Pharmacol Biochem Behav* **24:** 429–432, 1986.
93. Schlosberg, A. J. Temperature responses in rats after acute and chronic administration of caffeine. *Pharmacol Biochem Behav* **18:** 934–942, 1983.
94. Schwabe, U., D. Ukena and M. J. Loshe. Xanthine derivatives as antagonists at A-1 and A-1 adenosine receptors. *Naunyn Schmiedebergs Arch Pharmacol* **330:** 212–221, 1985.
95. Seale, T. W., J. M. Carney, P. Johnson and O. M. Rennert. Genetic control of caffeine-induced alterations of core temperature in in-bred mice. *Pharmacol Biochem Behav*, submitted, 1987.
96. Siebenaller, J. F. and T. F. Murray. Phylogenetic distribution of [^{3}H] cyclohexyladenosine binding sites in nervous tissue. *Biochem Biophys Res Commun* **137:** 182–189, 1986.
97. Skott, O. and C. Baumbach. Effects of adenosine on renin release from isolated rat glomeruli and kidney slices. *Pflugers Arch* **404:** 232–237, 1985.
98. Smellie, F. W., C. W. Davis, J. W. Daly and J. N. Wells. Alkylxanthines: inhibition of adenosine-elicited accumulation of cyclic AMP in brain slices and of phosphodiesterase activity. *Life Sci* **24:** 2475, 1979.
99. Snyder, S. H. Adenosine as a neuromedulator. *Annu Rev Neurosci* **8:** 103–124, 1985.
100. Snyder, S. H. and P. Sklar. Behavioral and molecular actions of caffeine: focus on adenosine. *J Psychiatry Res* **18:** 91–109, 1984.
101. Snyder, S. H., J. J. Katims, Z. Annau, R. F. Bruns and J. W. Daly. Adenosine receptors and behavioral actions of methylxanthines. *Proc Natl Acad Sci USA* **78:** 3260–3264, 1981.
102. Stone, G. A., M. F. Jarvis, M. A. Sills, B. Weeks, E. W. Snowhill and M. Williams. Species differences in high affinity adenosine A-2 receptors binding in mammalian striatal membranes. *Naunyn Schmiedebergs Arch Pharmacol*, in press, 1988.
103. Ukena, D., M. Shamin, W. Padgett and J. W. Daly. Analogs of caffeine: antagonists with selectivity for A-2 adenosine receptors. *Life Sci* **39:** 743–750, 1986.
104. Vapataalo, H., D. Onken, P. J. Neuvonen and E. Weissman. Stereospecificity in some central and circulatory effects of phenylisopropyl adenosine (PIA). *Arzneimittelforsch* **25:** 407, 1975.
105. Venault, P., G. Chapouthier, L. Prado de Carvalho, J. Siminad, M. Morre, R. H. Dodd and J. Rossier. Benzodiazepine impairs and β-carboline enhances performance in learning and memory tasks. *Nature* **321:** 864–866, 1986.
106. Verma, A. and P. J. Marangos. Nitrobenzylthioinosine binding in brain: an interspecies study. *Life Sci* **36:** 283–291, 1985.
107. Watanabe, H. and H. Uramato. Caffeine mimics dopamine receptor agonists without stimulation of dopamine receptors. *Neuropharmacology* **25:** 577–581, 1986.

108. Wessberg, P., J. Hedner, T. Hedner, B. Persson and J. Jonason. Adenosine mechanisms in the regulation of breathing in the rat. *Eur J Pharmacol* **106:** 59–67, 1985.
109. Whorton, A. R., J. B. Collawn, M. E. Montgomery, S. L. Young and R. S. Kent. Arachidonic acid metabolism in cultured aortic endothelial cells: effects of cAMP and 3-isobutyl 1-methylxanthine. *Biochem Pharmacol* **34:** 119–123, 1985.
110. Williams, M. Adenosine—a selective neuromodulator in the mammalian CNS. *Trends Neurosci* **7:** 164–168, 1984.
111. Williams, M. Purinergic receptors in the CNS. In: *Neuromethods, Vol 4: Receptor Binding*, edited by A. A. Boulton, G. B. Baker and P. D. Hrdina. Clifton, NJ: Humana, 1986, pp. 365–413.
112. Williams, M. Tissue and species differences in adenosine receptors and their possible relevance to drug development. In: *Adenosine: Receptors and Modulation of Cell Function*, edited by V. Stefanovich, K. Rudolph and P. Schubert. Oxford: UK: IRL Press, 1986, pp. 73–83.
113. Williams, M. Purine receptors in mammalian tissues: pharmacology and functional significance. *Annu Rev Pharmacol Toxicol* **27:** 315–345, 1987.
114. Williams, M. and J. B. Malick. Drug development: reflections and projections. In: *Drug Discover and Development*, edited by M. Williams and J. B. Malick. Clifton, NJ: Humana Press, 1987, pp. 3–29.
115. Williams, M. and E. A. Risley. Interaction of the benzodiazepine antagonists CGS 8216 and Ro 15-1788 with central adenosine A-1 receptors. *Arch Int Pharmacodyn* **260:** 50–53, 1982.
116. Williams, M., J. Francis, G. Ghai, S. Psychoyos, A. Braunwalder, G. A. Stone and W. D. Cash. Biochemical characterization of CGS 15943 A, a novel, non-xanthine adenosine agonist. *J Pharmacol Exp Ther* **241:** 415–420, 1987.
117. Williams, M., A. Braunwalder and T. E. Erickson. Evaluation of the binding of A-1 selective adenosine radioligand, cyclopentyl adenosine (CPA), to rat brain tissue. *Naunyn Schmiedebergs Arch Pharmacol* **332:** 179–183, 1986.
118. Williams, M. and M. F. Jarvis. Autoradiographic localization of adenosine receptors in methylxanthine-sensitive and insensitive mice. *Fed Proc* **46:** 5802, 1987.
119. Winn, H. R., R. Rubio and R. M. Berne. Brain adenosine concentrations during hypoxia in rats. *Am J Physiol* **241:** H235, 1981.
120. Winn, H. R., S. Morri and R. M. Berne. The role of adenosine in the auto-regulation of cerebral blood flow. *Ann Biomed Eng* **13:** 321–328, 1985.
121. Wojcik, W. J. and N. H. Neff. Differential location of adenosine A-1 and A-2 receptors in striatum. *Neurosci Lett* **41:** 55–60, 1983.
122. Yarbrough, B. V. and J. McGuffin-Clineschmidt. In vivo behavioral assessment of central nervous system purinergic receptors. *Eur J Pharmacol* **76:** 137–144, 1981.
123. Zielke, H. R. and C. L. Zielke. Lack of sustained effects on catecholamines and indoles in mouse brain after long-term subcutaneous administration of caffeine and theophylline. *Life Sci* **39:** 565–572, 1986.