Review

Caffeine analogs: biomedical impact

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Abstract. Caffeine, widely consumed in beverages, and many xanthine analogs have had a major impact on biomedical research. Caffeine and various analogs, the latter designed to enhance potency and selectivity toward specific biological targets, have played key roles in defining the nature and role of adenosine receptors, phosphodiesterases, and calcium release channels in physiological processes. Such xanthines and other caffeine-inspired heterocycles now provide important research tools and potential therapeutic agents for intervention in Alzheimer's disease, asthma, cancer, diabetes, and Parkinson's disease. Such compounds also have activity as analgesics, antiinflammatories, antitussives, behavioral stimulants, diuretics/natriuretics, and lipolytics. Adverse effects can include anxiety, hypertension, certain drug interactions, and withdrawal symptoms.

Keywords. Adenosine receptor, caffeine, calcium, GABA receptor, phosphodiesterase, xanthine.

The stimulant properties of infusions prepared from coffee beans or tea leaves undoubtedly play a significant role in the worldwide popularity of such beverages and of cola drinks to which caffeine is added as a flavor enhancer [1]. Caffeine, the major behavioral stimulant present in coffee, was isolated in 1820 and the correct structure of this methylxanthine was finally established in the last decade of that century. However, the targets underlying the behavioral stimulant properties of methylxanthines, such as caffeine, were not clearly recognized until 1981, when correlations of the stimulant properties of caffeine and various analogs were correlated with the blockade of adenosine receptors [2]. The behavioral depression elicited by high dosages of caffeine and by some xanthine analogs was proposed to be due to inhibition of cyclic nucleotide phosphodiesterases [2, 3]. Ligands for adenosine receptors were clearly targets for drug development [4] as were inhibitors for phosphodiesterase [5]. The biological effects of caffeine are now known to span a wide range of molecular targets [6], the most important of which are the following: i) adenosine receptors, where xanthines act as antagonists; ii) phosphodiesterases, where xanthines act as inhibitors; iii) calcium release ryanodine-sensitive channels in the sarcoplasmic and endoplasmic reticulum, where xanthines act to sensitize the channels to the activation by calcium. iv) $GABA_A$ receptors, where xanthines act as antagonists at the benzodiazepine-positive modulatory site. There are many further biological targets at which caffeine and analogs can act, but those require millimolar concentrations of caffeine [For coverage of such targets see refs 6, 7].

Caffeine itself is a rather unique compound with very high solubility in both water and nonpolar organic solvents. It partitions readily across cell membranes, rapidly yielding high levels throughout the body,
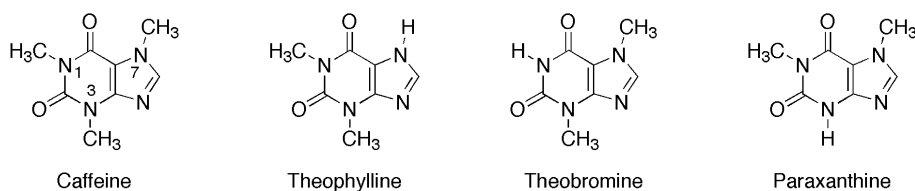
Figure 1. The natural methyl-xanthines.

including the brain [8]. Elimination *in vivo* is virtually entirely dependent on metabolism to more polar entities. Metabolism in humans leads to paraxanthine, a xanthine sharing many of the biological activities of caffeine [2]. The presence of paraxanthine in coffee beans was reported in 1980 [9]. Theophylline, another metabolite of caffeine and a significant xanthine in tea leaf infusions, also shares the biological activities of caffeine [2]. Theobromine, the third well-known natural xanthine, is present in chocolate derived from cacao beans. It is a weak adenosine antagonist and only a weak central stimulant [2]. Caffeine also is present in cacao beans, but in much lower amounts. The structures of the three major natural methylxanthines and of paraxanthine are shown in Figure 1. The various activities of caffeine have led to its extensive use as a research tool and as a starting point for the design and synthesis of a wide variety of xanthine and related heterocyclic analogs as antagonists at adenosine receptors and as inhibitors of phosphodiesterases.

Adenosine receptors

In 1969/1970, the stimulatory effects of adenosine on the generation of cyclic AMP in brain slices and the blockade of that effect by caffeine were reported [10, 11]. That the depressant effects of adenosine in heart could be blocked by caffeine had been reported a few years earlier[12]. Then in 1978, Burnstock [13] formulated the existence of two classes of purinergic receptors, namely the P_1- (adenosine) and the P_2- (ATP) receptors. Methylxanthines blocked the P_1-receptors, while having no effect on the P_2-receptors. Functional studies in the late 1970s/early 1980s provided evidence that the P_1-receptors could be divided into A_1-adenosine receptors that were inhibitory to adenylate cyclase and A_2-adenosine receptors that were stimulatory to adenylate cyclase [14, 15] and then that the A_2-adenosine receptors could be divided into A_{2A}-receptors with high affinities for agonists and A_{2B}-receptors with low affinity for agonists [16, 17]. Another low-affinity adenosine receptor, the A_3-receptor, was introduced in 1992 [18]. The A_3-adenosine receptor, like the A_1-receptor, was not only inhibitory to adenylyl cyclase, but could also stimulate phospholipase C, thereby triggering through

generation of IP_3 a calcium signal [19]. The existence of several adenosine receptor subtypes, all sensitive to blockade by xanthines, generated extensive development of agonists and selective and potent xanthine-inspired antagonists. The therapeutic potential for both adenosine receptor agonists and antagonists and the diversity of such synthetic agents was highlighted for A_1- and A_2-receptors in 1992 [20], for A_3-receptors in 2000 [21], for all adenosine receptors in 1996 [22] and for adenosine antagonists in 2001 [23]. There have been extensive reviews on adenosine receptor agonists, antagonists, and positive modulators and on possible therapeutic targets. These include, from 2006, reviews focusing on adenosine receptors as therapeutic targets [24], adenosine receptor antagonists as potential therapeutics [25], antagonists for A_1- and A_{2A}-receptors [26], antagonists for A_{2B}-receptors and potential therapeutic applications [27], ligands for A_{2B}-receptors [28, 29], adenosine receptor ligands as antiinflammatories [30], and purines as effectors of adenosine receptors and other biological targets [31]. Thus, the present section on adenosine receptors attempts only to highlight certain xanthines as selective and/or potent antagonists of adenosine receptors. The affinities of the xanthines highlighted in Figures 2–5 for A_1-, A_{2A}-, A_{2B}- and A_3-adenosine receptors are presented in Table 1.

A_1-receptors
A range of xanthines selective and potent as antagonists for A_1-adenosine receptors have been developed [24–26]. Many of the A_1-selective xanthines are characterized by large substituents, such as a phenyl or cycloalkyl moiety, in the 8-position and by propyl groups in the 1- and 3-position (see DPCPX, KW-3902, and CVT 124 in Fig. 2). A carboxyl moiety in BG 9928 (see Fig. 2) improved water solubility and oral efficacy [32]. Introduction of an ionized sulfonic acid moiety on the 8-phenyl ring resulted in an A_1-selective antagonist, with only peripheral effects (see DPSPX in Fig. 2). The presence of polar moieties in the 1-, 3- or 7-alkyl substituents greatly reduced or abolished antagonist activity at adenosine receptors [33]. However, certain xanthines, such as propentofylline and pentoxifylline, with polar moieties in the 1-substituent (see Fig. 6), inhibit adenosine uptake [34, 35], thereby potentiating the effects of endogenous

Table 1. Affinities of xanthine antagonists for adenosine receptors.

Agent	Ki (nanomolar) A_1	A_{2A}	A_{2B}	A_3
A_1 selective				
DPCPX	3.4	130	50	4000
KW-3902	0.19*	170*	–	–
CVT-124	36	2800	760	20000
BG 9928	7.0	6400	430	>10000
DPSPX	140*	790*	250	180
XAC	6.8	18	16	26
Triazole I	1.4	420*	–	–
Triazole II	2.6	–	–	–
Triazole III	22	4400	580	>10000
A_{2A} selective				
DMPX	45000	16000	–	–
CSC	2800*	54*	–	–
KW-6002	580*	13*	–	–
KF 17837	62	1*		
A_{2B} selective				
Enprofylline	160000	32000	7000	65000
IPDX	24000	36000	630	53000
PBS 1115	>10000	24000*	53	>10000
MRS 1754	400	500	2.0	570
CVT-5440	>10000	>5000	50	8400
MRE 2030F20	>1000	>1000	12	>1000
8-PyrazolylX	100	1500	22	1200
A_3 selective				
Xanthine I	>10000	240	–	4.2
PSB-11	1600	1300	–	2.3
OT-7999	>10000	>10000	>10000	0.95
Pyrrolopurine	>1000	>1000	>1000	0.8
MRE 3008F20	1100	140	2100	0.85

Ki values from the literature [23–29, 48, 56–58] are for inhibition of binding of ligands to A_1-, A_{2A}-, A_{2B}-, and A_3-adenosine receptors of human or, when marked with an asterisk, of rat origin. For structures see Figures 2–8.

adenosine rather than blocking the activation of adenosine receptors. A functionalized congener approach to the moiety at the 8-position has resulted in a variety of xanthine antagonists [36] (see XAC in Fig. 2). A logical extension of structural alterations to the caffeine template was replacement of the xanthine ring system with other electron-rich heterocycles [see refs 25, 26]. Several have potent and/or selective antagonist activity at A_1-adenosine receptors. For example, three of the so-called extended xanthines (see triazolopurine I, II, and III in Fig. 2) have high potency and selectivity as A_1-antagonists [see refs 23, 25, 37].

A_{2A}-Receptors

The selectivity of caffeine analogs for A_{2A}-adenosine receptors was somewhat increased by the replacement of one or two methyl groups of caffeine with a propyl or propargyl substituent [38]. Indeed, 3,7-dimethyl-1-propargylxanthine [39] (see DMPX in Fig. 3) has been used as a selective A_2-antagonist, despite only modest selectivity. The presence of a 8-cycloalkyl substituent in caffeine modestly increased selectivity for A_2-receptors [40]. Ultimately, 8-styrylxanthine analogs

proved to be useful, highly selective A_{2A}-receptor antagonists [41–43] (see CSC, KW-6002 and KF17837 in Fig. 3). A variety of other 8-styrylxanthines selective for A_{2A}-receptors have been developed [44, 45]. The first nonxanthine to be developed as an A_{2A}-selective antagonist was a trizoloquinazoline, CGS 15943 [46]. Subsequently, a wide range of such heterocycles have been developed with selectivity as antagonists of A_{2A}-receptors [see refs 25, 26 and references therein].

A_{2B}-Receptors

There is currently great interest in antagonists selective for A_{2B}-adenosine receptors [27–29]. Enprofylline with a 1-propyl substituent (see Fig. 4) represents a lead xanthine with selectivity toward the A_{2B}-receptor [47]. Remarkably, an 8-substituted 3-isobutylxanthine (see IPDX in Fig. 4) proved very selective for A_{2B}-receptors [48]. A series of 1-propylxanthines with 8-phenyl moieties [43] yielded the highly A_{2B}-selective antagonist 1-propyl-8-p-sulfophenylxanthine PBS 1115 [49] (see Fig. 4), which would be active only peripherally. A series of 1,3-dipropylxanthines with functionalized 8-phenyl moieties yielded
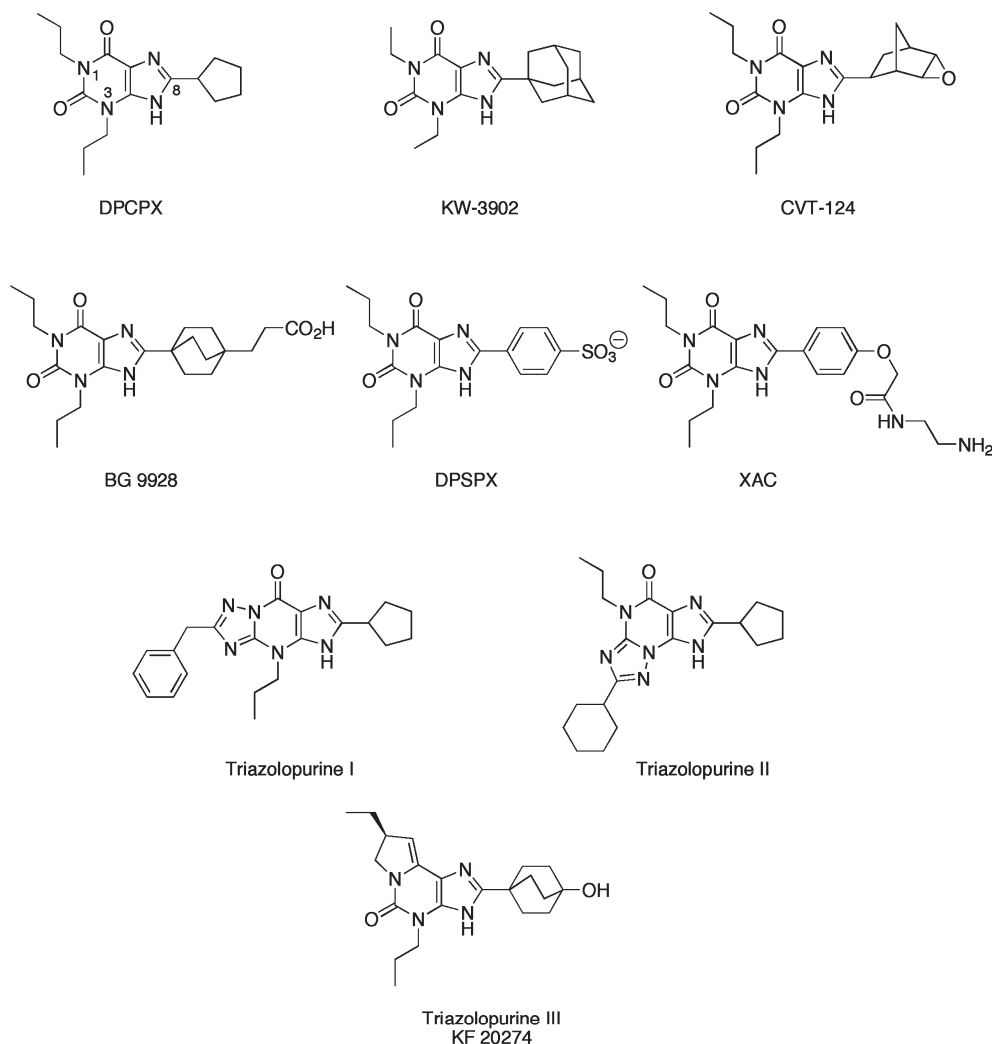
Figure 2. A$_1$-adenosine receptor antagonists. XAC is very A$_1$ selective in rat, but not in human [see ref. 25].

MRS 1754, (see Fig. 4), a highly A$_{2B}$-selective antagonist [50]. Further development provided CVT-5440 [51], another A$_{2B}$-selective antagonist (see Fig. 4). Further xanthines in which a substituted 8-pyrazolo ring replaced the substituted 8-phenyl ring of MRS 1754 provided A$_{2B}$-selective antagonists MRE 2030F20 and an 8-pyrazolylxanthine [52, 53] (see Fig. 4). Caffeine-inspired nonxanthine heterocyclic antagonists for A$_{2B}$-adenosine receptors have also been developed (see refs. 25, 27, 29, 30). These include a variety of 9-deaza-xanthines and 9-deaza-adenines.

A$_3$-Receptor

The A$_3$-adenosine receptors of rats show relatively low affinities for caffeine, theophylline and other xanthines, while those of humans show somewhat higher affinities [21, 54]. An unusual 3-benzylxanthine (see xanthine I, Fig. 5) has high affinity and selectivity for A$_3$-receptors [55]. In addition, so-called extended

xanthines, such as PSB-11 [56], the triazolopurine OT-7999 [57] and a pyrrolopurine [58] (see Fig. 5) have high affinity and selectivity for A$_3$-receptors. A pyrazolo-triazolo-pyrimidine, MRE 3008F20 (see Fig. 5) has been introduced as a radioligand for A$_3$-adenosine receptors [59]. Other polyheterocyclic analogs have been introduced as A$_3$-receptor antagonists as have flavonoids, dihydropyridines, pyridines, thiazoles, and adenosine analogs [see refs 24, 25].

Cyclic nucleotide phosphodiesterases

The discovery and isolation of a cyclic nucleotide phosphodiesterase was hastened by the finding that caffeine appeared to enhance the formation of cyclic AMP by the newly discovered enzyme adenylyl cyclase [60]. The three naturally occurring methyl-xanthines, namely caffeine, theophylline, and theo-
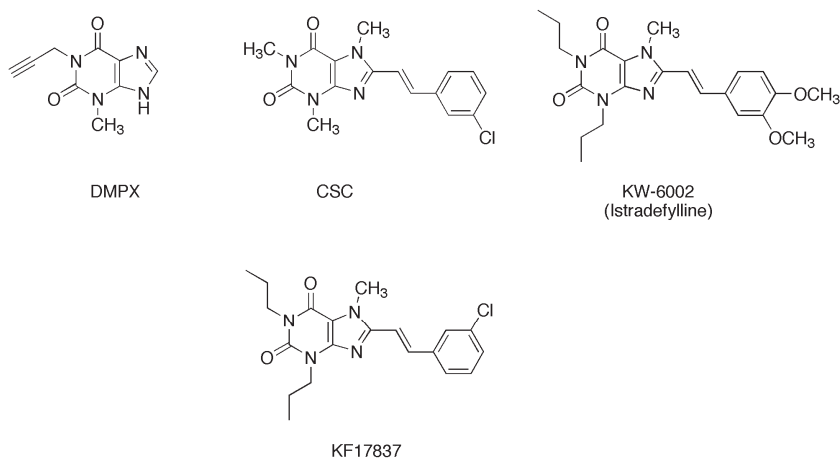
Figure 3. A_{2A}-adenosine receptor antagonists.

DMPX

CSC

KW-6002
(Istradefylline)

KF17837

bromine, were relatively weak competitive inhibitors [61], and xanthines with substituents other than methyl were prepared in efforts to enhance potency [5]. Attempts were made to correlate potencies of xanthines as phosphodiesterase inhibitors and pharmacological effects, such as lipolytic effects in adipocytes [62], relaxant effects on tracheal smooth muscle [63], contraction of striated muscle [64], and anxiogenic effects [65]. It was clear that other effects of xanthines on adenosine receptors, calcium release, and perhaps prostaglandin synthesis confounded any interpretations. Indeed, the lipolytic effects of xanthines were shown to be due to blockade of the A_1-adenosine receptors that were inhibitory to adenylyl cyclase [66].

3-Isobutyl-1-methylxanthine (IBMX, see Fig. 6) became established as a potent phosphodiesterase inhibitor that, however, was even more potent as an adenosine receptor antagonist [3]. The phosphodiesterase isozymes (PDEs) were found to be expressed to
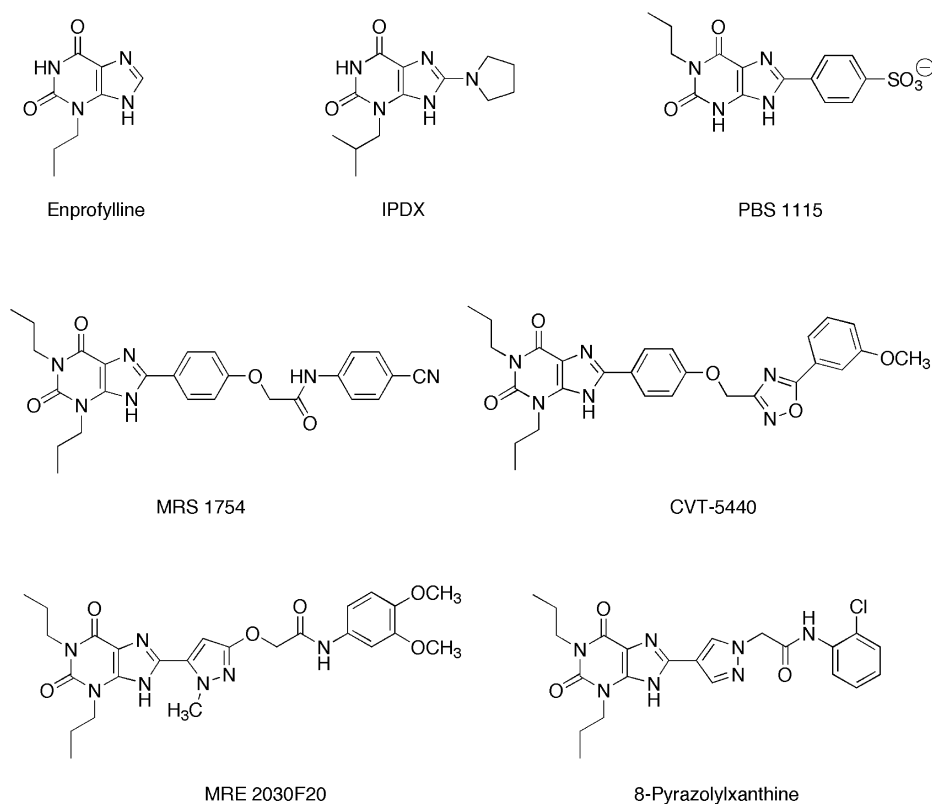

Enprofylline

IPDX

PBS 1115

MRS 1754

CVT-5440

MRE 2030F20

8-Pyrazolylxanthine

Figure 4. A_{2B}-adenosine receptor antagonists.

Xanthine I

PSB-11   Triazolopurine OT-7999
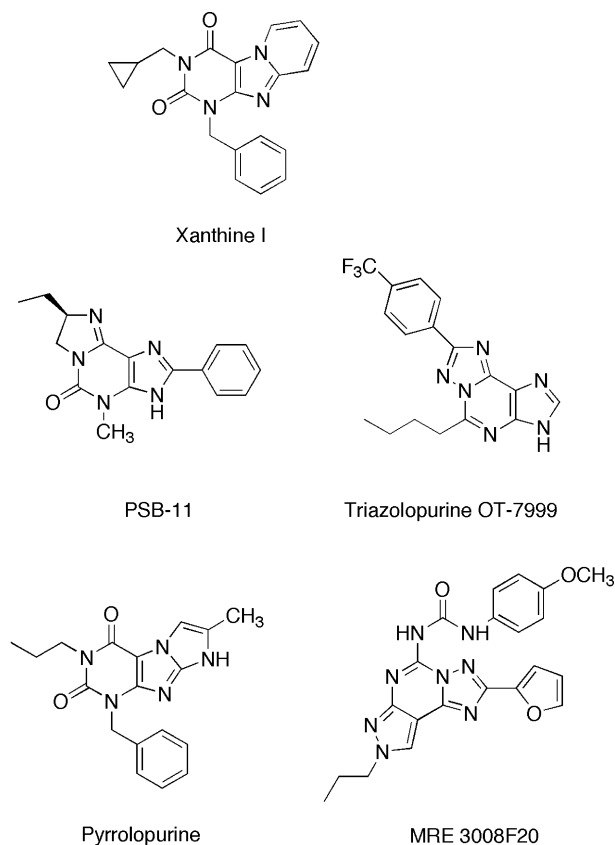
Pyrrolopurine   MRE 3008F20

Figure 5. A$_3$-adenosine receptor antagonists.

varying degrees in different tissues and the goal became the discovery of isozyme-selective agents [67]. 3-Isobutyl-1-methylxanthine (IBMX) proved relatively unselective toward five of the isozymes [68]. However, a recent report indicated that IBMX has no effect on PDE8 [69]. Extensive pioneering studies on alkylxanthines by Wells and colleagues [70, 71] led to xanthines with some selectivity, namely 3-isobutyl-1-isoamylxanthine (IIX, see Fig. 6) toward PDE4 and 8-methoxymethylIBMX (8-MeOCH$_2$-IBMX, see Fig. 6) toward PDE1 [63]. IIX was relatively weak as an antagonist at adenosine receptors [72, 73]. Alkylxanthines that were potent inhibitors of PDE4 all appeared to be behavioral depressants [3, 72].

There are now at least 12 PDEs [74, 75]. The therapeutic potential of selective phosphodiesterase inhibitors has been reviewed frequently over the past three decades. Two such reviews appeared in 2005 [76, 77]. Because multiple isozymes often occur in the same cell type and because there are few if any specific inhibitors, therapeutic targeting remains difficult. The following are broad generalizations for inhibitor targets: antiinflammatory, asthma treatment, and immunosuppressant (PDE3, 4); angina, hypertension, and cardiac failure (PDE2, 3); antithrombotic

(PDE4); vasodilation, hypertension, and erectile dysfunction (PDE5); and vascular relaxant (PDE1) [see refs 31, 74–77].

Unlike the adenosine receptor field where most antagonists owe their origin to caffeine/theophylline as lead compounds, most of the current phosphodiesterase inhibitors are not derived from xanthines [see refs 76, 77]. As mentioned above, IIX and 8-MeOCH$_2$-IBMX are somewhat selective for PDE4 and PDE1, respectively. Denbutylline, doxofylline, and arofylline are somewhat selective for PDE4, and KMUP-1 [78] for PDE3, 4, while pentoxifylline and propentofylline are characterized as weak PDE4 inhibitors (for structures see Fig. 6). A variety of other xanthines (R-lisofylline, isobufylline, torbaphylline, bamiphylline and furafylline) have been introduced, some with antiinflammatory activity. The extended xanthine SCH51866 (PDE1) [79], the extended 8-MeO-xanthine (PDE5) [80] and an 8-m-sulfamidophenyl-xanthine (PDE5) [81] have been developed (see Fig. 6 for structures). Finally, zaprinast, analogous to a 2-phenylhypoxanthine (see Fig. 6) and selective for PDE1 and PDE5, represented a lead structure for development of sildenafil for erectile dysfunction [82]. A number of ring-extended xanthines with nanomolar potency at PDE5 have now been developed [see refs 80, 81]. Many of the xanthines that inhibit phosphodiesterases are also antagonists at adenosine receptors and block adenosine uptake [see refs 7, 34, 35].

Calcium release

Caffeine continues to be widely used as a research tool to elicit release of intracellular calcium through activation in consort with calcium of the ryanodine-sensitive calcium release channels of the endoplasmic and sarcoplasmic reticulum [see ref 7]. Decades ago caffeine had been found to cause muscle contractures through release of intracellular calcium [83, 84]. Caffeine at the millimolar concentrations required to cause activation of ryanodine-sensitive calcium channels has many other effects on calcium homeostasis [see ref. 7] and hence cannot be used as a selective research tool for activation of ryanodine-sensitive channels. Reports on inhibition of IP$_3$-elicited calcium release by caffeine have appeared [85–87], and enhancement of capacitative calcium entry by caffeine has been reported [88, 89].

There have been only a few studies on structure-activity relationships for the efficacy/potency of xanthines in affecting intracellular or intravesicular calcium [90–92]. In human pheochromocytoma cells, two xanthines, 1-propyl- and 1-propargyl-theobro-
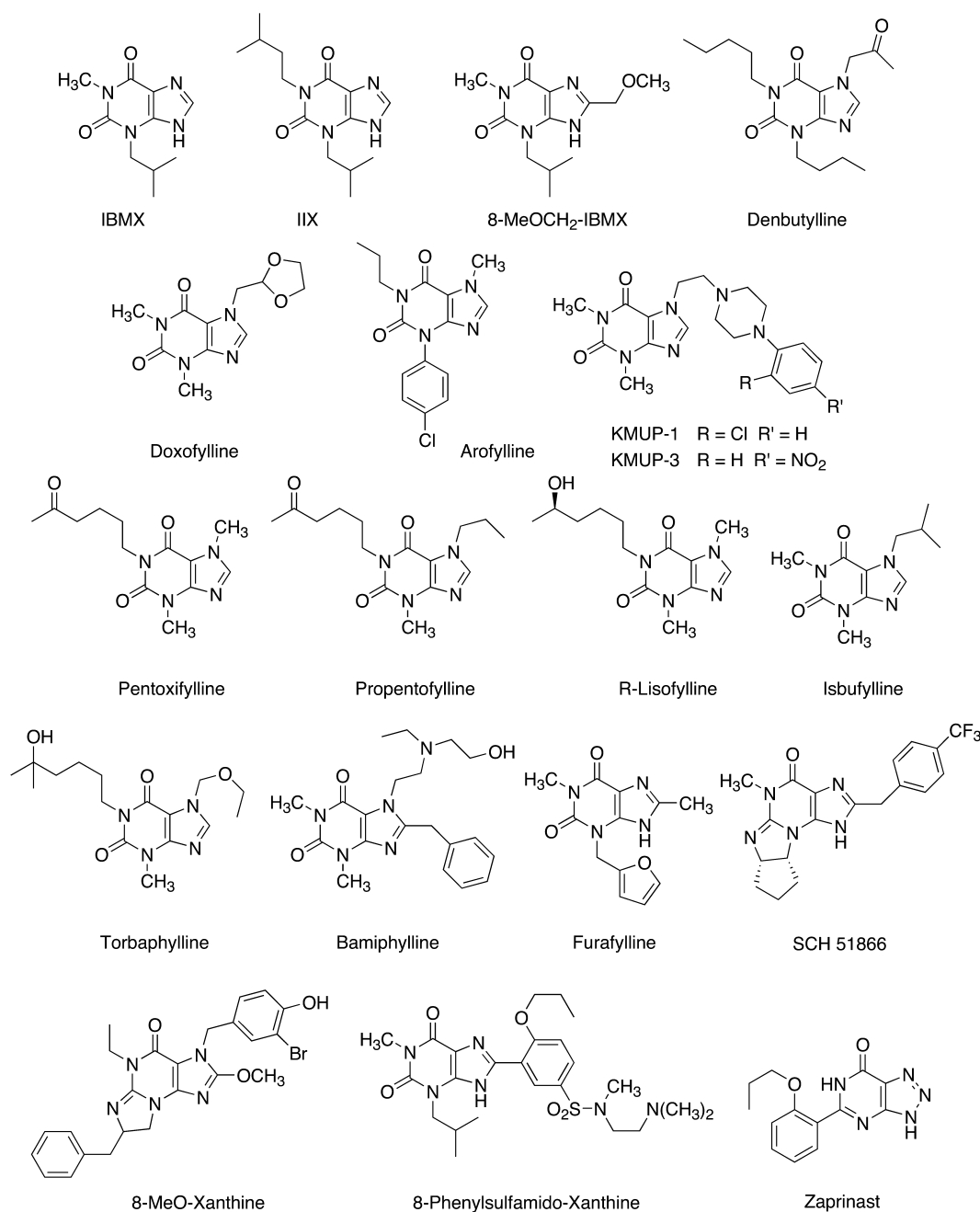
Figure 6. Phosphodiesterase inhibitors.

mine (see Fig. 7), were about fourfold more potent than caffeine [90]. In sea urchin eggs, a 7-oxoheptyl-xanthine (see Fig. 7) was about fourfold more potent than caffeine [91]. Caffeine enhances the binding of [³H]ryanodine to calcium-release channels [93]. In an extensive series of 30 xanthines, the most efficacious in enhancing [³H]ryanodine binding to vesicles of rabbit muscle sarcoplasmic reticulum [94] was 1-hexyltheo-bromine (see Fig. 7). Several other xanthines, includ-ing 1-propargyltheobromine were somewhat more efficacious at 1.5 mM than caffeine. In a similar study

with 35 xanthines, only 7-propyltheophylline (see Fig. 7) was slightly more efficacious at 10 mM than caffeine [95]. It would appear unlikely that a xanthine much more potent and selective than caffeine for the ryanodine-sensitive calcium-release channel will be developed.
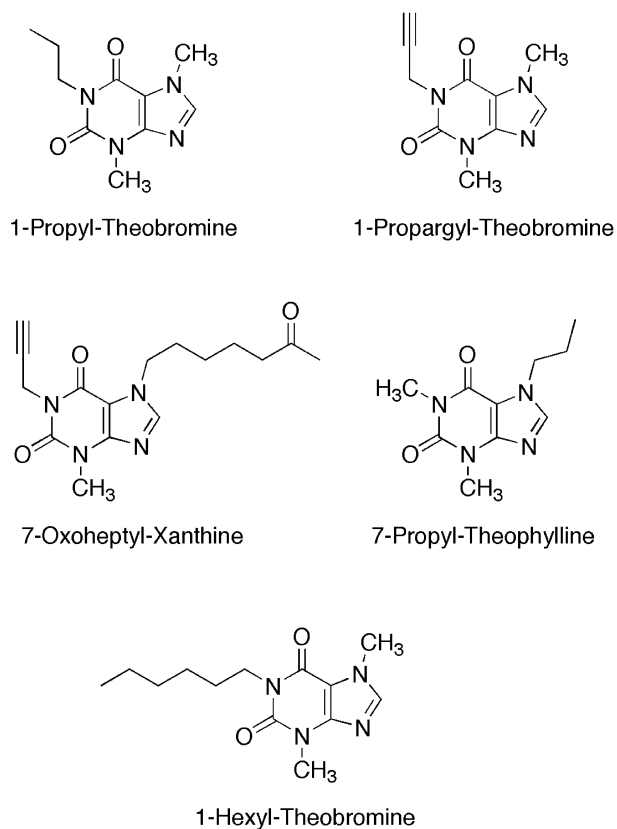
1-Propyl-Theobromine   1-Propargyl-Theobromine

7-Oxoheptyl-Xanthine   7-Propyl-Theophylline

1-Hexyl-Theobromine

Figure 7. Calcium-releasing agents.

GABA$_A$ receptors

Caffeine is one of many compounds that interact with GABA$_A$ receptors. Such compounds include the alkaloid antagonist bicuculline, the picrotoxinin channel blockers, the barbiturates and steroids that increase channel open time, and the benzodiazepine allosteric positive modulators [96, 97]. There have been limited studies on xanthine interactions with GABA$_A$ receptors since the initial report in 1979 on the inhibition of [^{3}H]diazepam binding by caffeine [98]. Conversely, at that time, diazepam was found to antagonize caffeine-induced convulsions [99]. Further studies indicated that caffeine and theophylline act as antagonists or perhaps reverse agonists at benzodiazepine sites, while also interacting with the picrotoxinin and GABA sites [see ref. 95]. A series of 23 xanthines has been studied for effects on the binding of ligands to the benzodiazepine and picrotoxinin sites of GABA$_A$ receptors in mouse cerebral cortical membranes [95]. Caffeine had an IC$_{50}$ versus [^{3}H]diazepam of 500 μM, while two xanthines, namely 1-propargyl-theobromine and 1,3-dipropargyl-7-methylxanthine (see Fig. 8) were nearly fivefold more potent. However, both of these xanthines have relatively potent activity at adenosine receptors [38,

100] and activity similar to that of caffeine at phosphodiesterases [3] and at the ryanodine-sensitive calcium release channels [95]. Many of the xanthines at 1 mM stimulated binding [^{35}S]TBPS binding to the picrotoxinin site of the GABA$_A$ receptor, as did caffeine, while others had no effect or inhibited binding [95]. It would appear that prospects for developing a xanthine with potent and selective effects on GABA$_A$ receptors are poor.

A comparison of xanthines as blockers of GABA- and glycine-mediated chloride currents in rat hippocampal neurous indicated the caffeine was several-fold more potent against the glycine response (IC$_{50}$ 450 μM) than against the GABA response [101]. Theophylline had a similar potency to caffeine, while pentoxifylline (see Fig. 6) was twofold more potent than caffeine against the glycine response. Pentoxifylline was later shown to have potency similar to that of caffeine for inhibition of [^{3}H]diazepam binding to GABA$_A$ receptors [95].

Other targets

There are many reports on other potential sites of action for caffeine [see refs 6, 7]. These include several ion channels, neurotransmitter release, and various enzymes, but millimolar concentrations of caffeine are usually required. The effect for ion channels and enzymes is usually inhibitory. However, stimulation of the Na/K-ATPase by caffeine and theophylline occurs at millimolar concentrations [102] and an apparent activation of capacitative calcium entry [88, 89, 103] and calcium-activated potassium channels [104] by caffeine have been reported. Caffeine appeared to sensitize a Mg-ATPase to the stimulatory effects of calcium in cardiac myofibrils [105].

Therapeutic prospects

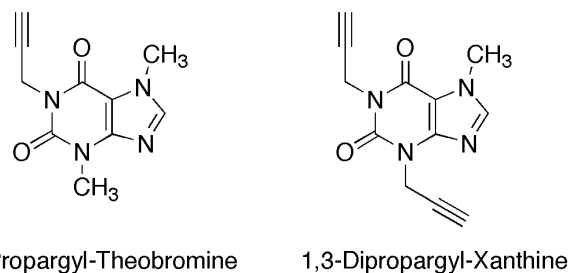There are several major therapeutic targets toward which xanthines and heterocyclic xanthine analogs are

1-Propargyl-Theobromine   1,3-Dipropargyl-Xanthine

Figure 8. GABA$_A$ receptor modulators.

being directed. Some of the molecular targets for such xanthines are as follows:

1) Alzheimer's disease: A_{2A}- and A_{2B}- adenosine receptor antagonists;

2) Asthma – antiinflammatories: A_1-, A_{2A}-, and A_{2B}-adenosine receptor antagonists and phosphodiesterase inhibitors;

3) behavioral targets – antidepressant, anxiolytic, cognitive enhancement, neuroprotection: adenosine receptor antagonists and phosphodiesterase inhibitors;

4) cancer: G2 checkpoint inhibitors;

5) diabetes: A_{2B}-adenosine receptor antagonists; phosphoenolpyruvate carboxykinase inhibitors; dipeptidyl peptidase IV inhibitors;

6) pain: A_{2A}- and A_{2B}-adenosine receptor antagonists, phosphodiesterase inhibitors;

7) Parkinsonism: A_{2A}-adenosine receptor antagonists, phosphodiesterase inhibitors;

8) renal effects – diuretics: A_1- and A_{2A}- adenosine receptor antagonists;

9) respiratory targets – antitussives, apnea, chronic obstructive pulmonary disease, cystic fibrosis: adenosine receptor antagonists.

The following provides an overview of some of the current literature in these areas.

Alzheimer's disease

The consumption of caffeine-containing beverages appeared to possibly confer some protective effects from Alzheimer's disease [106]. In recent studies with model Alzheimer mice, chronic caffeine protected against cognitive impairment and resulted in reduced brain levels of β-amyloid protein [107]. In cortical neurons from model Alzheimer mice, the caffeine-elicited release of intracellular calcium was significantly greater than that in neurons from control mice [108]. A variety of therapeutic interventions are being explored for treatment of Alzheimer's disease; however, most of them involve cholinergic functions [109]. Nevertheless, A_{2B}-adenosine receptor antagonists have been proposed as possible therapeutics for Alzheimer's disease [110]. Both caffeine and the selective nonxanthine A_{2A}-adenosine receptor antagonist ZM 241385 protected rat cerebellar neurons from the toxic effects of β-amyloid protein [111]. ZM 241385 is a triazolotriazine [112] related in structure to the widely used A_{2A}-receptor antagonist triazoloquinazoline CGS15943 [46]. The phosphodiesterase inhibitor propentofylline (see Figure 6) has cognitive-enhancing effects and thus might be beneficial for Alzheimer's disease [see however ref. 113].

Asthma – Antiinflammatories

The xanthines theophylline and enprofylline have been used therapeutically for asthma, and other agents that target A_{2B}-adenosine receptors are being sought for the treatment of asthma [see refs 114, 115]. Asthma is a chronic inflammatory condition and caffeine and other xanthines, such as theophylline, pentoxifylline, and lisofylline (see Fig. 6), do have immunosuppressant effects and thus may have utility for autoimmune diseases [see ref. 116]. A recent review covers subtype selective adenosine receptor agonists and antagonists as antiinflammatory agents [30]. Other xanthines have been proposed to have potential for treatment of asthma, emphysema, and chronic bronchitis. These include CVT-5440 [117] and KMUP-3 [118] (see Figs 4, 6). Xanthines functionalized with alkylpiperazines in the 7-position of theophylline or the 3-position of theobromine were studied in 1985 as antihistaminics for the treatment of bronchospasm [119]. Activation of a nuclear enzyme poly(ADP-ribose)polymerase-1 appears to be associated with inflammatory diseases, and paraxanthine (see Fig. 1) was a relatively potent inhibitor, while caffeine was weak [120].

Behavior targets – antidepressant – anxiolytic – cognitive enhancement – neuroprotection

The behavioral stimulant properties of caffeine undoubtedly underlie the consumption of coffee and other caffeine-containing beverages by many individuals worldwide. Caffeine is perceived as increasing alertness and wakefulness, combating fatigue, and generally providing a sense of well-being. True addiction does not seem to occur although there are withdrawal symptoms [121]. At high doses and in certain individuals, unpleasant effects, including anxiety, occur. The molecular targets underlying the behavioral effects of caffeine have been extensively investigated, primarily in rodents. While blockade of adenosine receptors is clearly paramount in the behavioral effects of caffeine, the relative role of the subtypes remains under investigation [see ref. 122]. The dopaminergic reward system is closely involved [123]. The extensive on-going research on behavioral effects of caffeine and other xanthines and the implications for treatment of depression, anxiety, cognitive impairment, ischemic effects of stroke, and even drug dependency and schizophrenia is beyond the scope of the present overview [see ref. 124]. It should be noted that the acute and chronic effects of caffeine can be quite different [125]. Most of the central effects of caffeine at levels attained from beverages are due to blockade of adenosine receptors [121].
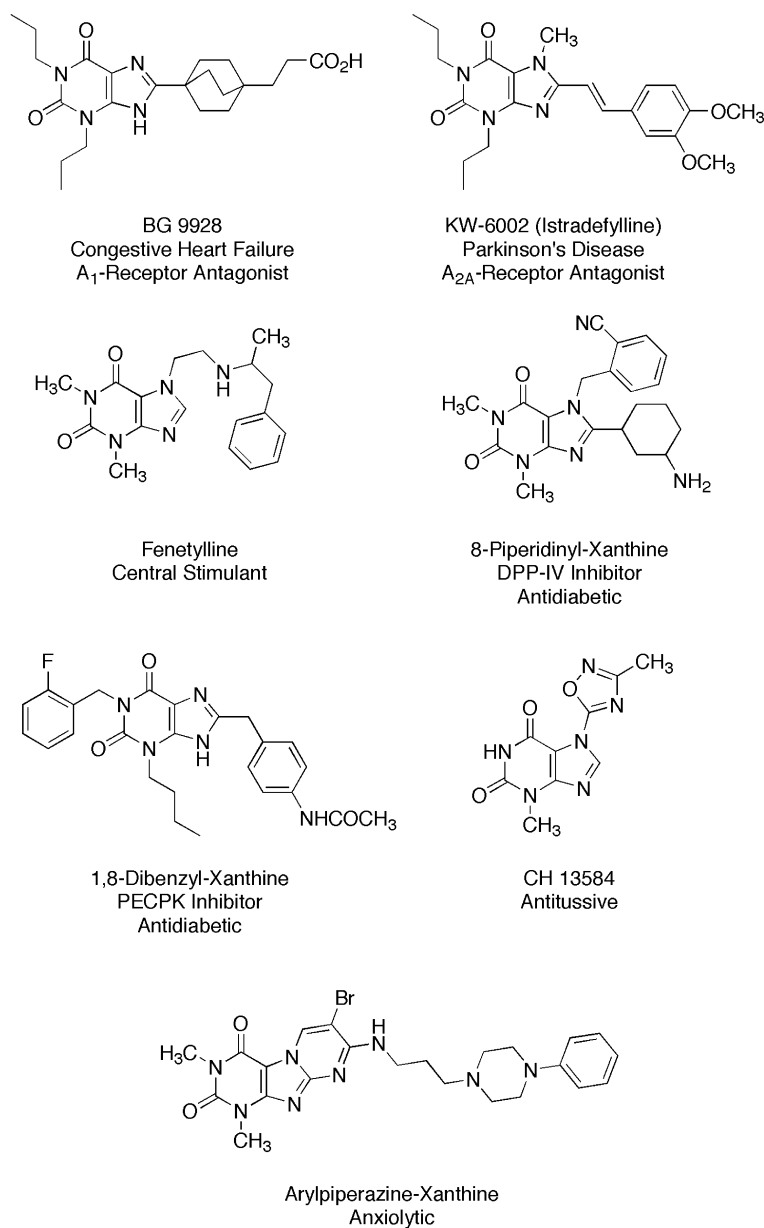
Figure 9. Potential therapeutic xanthines.

Recent behavioral studies include that of the selective A_{2A}-receptor antagonist KW-6002 (see Fig. 3) [126]. Pentoxifylline and propentofylline (see Fig. 6) ameliorate brain ischemic effects in mice paradigms [127, 128]. The anxiolytic effects of an extended-ring xanthine, containing an arylpiperazine moiety (see Fig. 9) appears due to agonist activity at serotonin receptors [129]. A xanthine, fenetylline, containing an amphetamine moiety (see Fig. 9) has been used therapeutically in place of amphetamines [130] and now has become a drug of abuse. A recent report focused on the possibility that A_{2A}-receptor antagonists might be used in problems of addiction [131].

Cancer

There is extensive literature on the possible anticancer activity of caffeine and other xanthines [see ref. 132 and references therein]. Recently, the antimetastatic effects of caffeine in a mouse mammary tumor model were reported [133] as were further studies on the inhibition by caffeine of ultraviolet-induced skin tumors in hairless mice [134]. Caffeine is well-known to be an inhibitor of the G2 checkpoint for repair of damaged DNA [135]. In cancer cells defective for tumor suppressor protein p53, the G1 checkpoint for repair is defective. Thus, caffeine can enhance toxicity of tumor cells to DNA-damaging treatment by blocking the G2 checkpoint. Caffeine and a series of xanthines were assayed for G2 checkpoint inhibition

[136]. However, even at millimolar concentrations most were inactive or less active than caffeine, with only 1-ethyl- and 1-propyl-theobromine being somewhat more active than caffeine. A number were cytotoxic.

Diabetes

A_{2B}-adenosine receptor antagonists have been suggested to have potential for treatment of type 2 diabetes [137], based on reported effects of adenosine receptor antagonists on glucose in rodents. Several relatively potent 1,8-dibenzyl-3-butyl- xanthines (see Fig. 9) were developed as inhibitors of phosphoenolpyruvate carboxykinase, the rate-limiting step in hepatic gluconeogenesis [138]. Several studies have indicated that the antiinflammatory xanthine lisofylline (see Fig. 6) has antidiabetic effects in a nonobese diabetic mouse model [139, 140] and has protective effects on pancreatic β-cells [see ref. 141 and references therein]. Pentoxifylline also has antidiabetic effects in the mouse model [142]. Attempts to correlate caffeine consumption and risk of type 2 diabetes have been inconsistent (see ref. 143 and refs. therein). Indeed, reports that caffeine ingestion caused a reduction in insulin-stimulated glucose uptake have appeared [143, 144]. Recently, a series of xanthines (see 8-piperidinyl-xanthine Fig. 9) and related heterocycles were introduced as potent and selective inhibitors of dipeptidyl peptidase IV, a clinically relevant target for treatment of type 2 diabetes [see ref. 145 and references therein].

Pain

Caffeine has a long history as an analgesic adjuvant [146, 147]. Other adenosine receptor antagonists have antinociceptive effects with A_{2B}-receptors appearing to be the targets [148]. Some of the xanthines that are A_{2B}-antagonists and thus perhaps represent lead compounds are shown in Figure 4. There are a multitude of pathological and acute pain states and a variety of receptors, including opioid, adenosine, cannabinoid, galanin, GABA, glycine, vanilloid, and nicotinic receptors, and ion channels including sodium and calcium, that represent therapeutic targets [149 – 151].

Parkinson's disease

The potential therapeutic treatment of Parkinson's diseases by A_{2A}-adenosine receptor antagonists has been the subject of recent comprehensive reviews [152 – 154]. A number of xanthines (CSC, KW 6002, KF17837, see Figs 3 and 9) and nonxanthines (MSX-2, SCH 58261, ZM241385 [25]) are under development as antiparkinsonism agents. All are selective for A_{2A}-receptors as is an 8-triazoyladenine, ST 1535, which

represents another potential new agent [155]. However, A_{2A}-receptor antagonists represent only one of several therapeutic approaches to Parkinson's disease [see ref. 156]. Selective inhibition of monoamine oxidase B represents another approach, and the A_{2A}-receptor antagonist 3-chlorostyrylcaffeine (CSC, see Fig. 3) was recently reported to be a potent inhibitor of that enzyme [157]. Caffeine consumption in beverages has been proposed to be associated with a reduced risk of Parkinson's disease [see ref. 152 and references therein) and caffeine in rodent models has protective effects [see ref. 158].

Renal effects – diuretics

The diuretic and natriuretic effects of caffeine and theophylline are well-known and both have been used to treat edema associated with congestive heart failure [see ref. 159 and references therein]. The diuretic effect seems likely due to antagonism of A_1-adenosine receptors [see ref. 160 and references therein). Thus, the highly selective A_1-adenosine receptor antagonist CVT-124 (see Fig. 2) appears potentially useful as a diuretic in patients with congestive heart failure [161 – 163]. Blockade of A_{2A}-receptors may be of value in prevention of hepatic cirrhosis [164], and pentoxifylline through phosphodiesterase inhibition can provide renal protection [see ref. 165 and references therein].

Respiratory targets – antitussives, apnea, chronic obstructive pulmonary disease, cystic fibrosis

The antitussive effects of theobromine are well-known [see ref. 166 and references therein]. The synthetic theobromine analog CH 13584 (see Fig. 9) has been developed with antitussive activity in a guinea pig model [166, 167]. Caffeine and to a lesser extent theophylline are widely used for the apnea that frequently occurs in premature infants, with a minimum of adverse effects [168]. The respiratory stimulatory effects of the xanthine are undoubtedly due to antagonism at adenosine receptors of central respiratory centers [169]. Indeed, in the periphery, caffeine through blockade of A_2-adenosine receptors of the carotid body has inhibitory effects on respiration [see ref 170 and references therein]. Chronic obstructive pulmonary disease, an inflammatory disease characterized by airflow obstruction and an alteration in adenosine receptors represents another target for intervention with adenosine receptor agonists or antagonists [see ref. 171 and references therein]. The xanthine 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, see Fig. 2), well-established as a potent, selective A_1-adenosine receptor antagonist, was shown to stimulate chloride-efflux from cystic fibrosis cells, and thus appeared as a lead compound for therapeutic use in treatment of cystic fibrosis [172]. Further studies demonstrated that the

effect was not due to antagonism of adenosine receptors, but to activation of so-called cystic fibrosis transmembrane conductance (CFTR) channels by DPCPX and its diallyl analog, 8-cyclohexyl-1,3-diallylxanthine [173]. A wide range of xanthines have been tested for activation of the CFTR channel [174]. Several, including theophylline, enprofylline, pentoxifylline, and IBMX, activated the channel. All were tested at 500 µM. In another study, DPCPX was not found to activate whole-cell conductance in cells expressing CFTR channels [175].

Conclusion

The broad range of effects of caffeine, both as a research tool and as a lead structure for the synthesis and study of diverse xanthine and other related heterocyclics, has had far-reaching impact on biomedical research. Research continues, with a focus in several therapeutic areas in which development of further selective and potent xanthines as antagonists of adenosine receptors and as phosphodiesterase inhibitors may have further impact.

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