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Adenosine receptor ligands: differences with acute versus chronic treatment

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Abstract

Adenosine receptors have been the target of intense research with respect to potential use of selective ligands in a variety of therapeutic areas. Caffeine and theophylline are adenosine receptor antagonists, and over the past three decades a wide range of selective agonists and antagonists for adenosine receptor subtypes have been developed. A complication to the therapeutic use of adenosine receptor ligands is the observation that the effects of acute administration of a particular ligand can be diametrically opposite to the chronic effects of the same ligand. This 'effect inversion' is discussed here by **Ken Jacobson and colleagues**, and has been observed for effects on cognitive processes, seizures and ischaemic damage.

Caffeine, the most widely consumed of all psychoactive drugs, is an adenosine receptor antagonist¹⁻³. It is regularly ingested by more than half of the adult population in Western countries, mainly because of the mild stimulant effects of this methylxanthine. Acute and chronic effects of caffeine have been extensively studied, and the phenomena of tolerance and withdrawal are well-documented in animals and humans. The only known biochemical targets for caffeine, at which it has significant activity at concentrations achieved during normal human use, are A₁ and A₂ adenosine receptors. Xanthines were envisaged to have therapeutic potential as central stimulants and cognitive enhancers, as cardiac stimulants, as anti-asthmatics, as anti-Parkinson's disease agents, anti-obesity agents, as analgesic adjuvants, and as diuretics. Many of the xanthines are selective for adenosine receptor subtypes, and many are more potent than caffeine. Conversely, a variety of adenosine analogues (Fig. 1) have been developed with envisaged therapeutic potential as analgesics, antipsychotics, anticonvulsants, or for treatment of stroke. However, over the past few years it has become apparent that the effect of acute or chronic treatment with caffeine, or other adenosine receptor ligands, can be qualitatively different. Thus, long-term treatment with adenosine receptor antagonists can have effects that resemble the acute effects of adenosine receptor agonists, and vice versa. Such diametrically opposed actions of chronic versus acute treatments have important implications in the development of adenosine receptor ligands as therapeutic agents.

Changes after chronic administration of caffeine

The effects of chronic administration of caffeine on the amount of and function of central A₁ and A_{2A} adenosine receptors have been examined in many laboratories using a variety of dose regimens and different periods of time after the last administration²⁻⁸. The A₁ receptors

were found to be up-regulated in most studies, without any changes in adenosine A₁ receptor mRNA (Ref. 4). This is consonant with the antagonism of an endogenous agonist that downregulates A₁ receptors via a post-transcriptional mechanism. In contrast, in most, but not all, studies, A_{2A} receptor binding and mRNA expression were unaltered.

Recently, a broad survey of biochemical alterations, following chronic caffeine ingestion by mice, was carried out;^{7,8} the effects on receptor levels were deduced from radioligand binding (Fig. 2). In addition to A₁ adenosine receptors, 5-HT receptors, acetylcholine receptors, GABA receptors and δ -opioid receptors were up-regulated. Only β -adrenoceptors were downregulated. However, it should be noted that an apparent up-regulation of nicotinic acetylcholine receptors probably represents conversion to a desensitized, high-affinity state, and thus, actually represents a downregulation, as has been reported after chronic nicotine treatment⁹. Adenosine A_{2A} receptors, α -adrenoceptors, dopamine receptors, and excitatory amino acid receptors were unaltered. Among other biochemical alterations, the apparent increase in levels of L-type Ca²⁺ channels after chronic caffeine administration is noteworthy.

There is now good evidence that treatment with adenosine receptor antagonists can alter immediate early gene expression and the expression of secondary gene products, such as neuropeptides. High doses of caffeine (>50mg kg⁻¹) are known to induce *c-fos*, *junB*, *c-jun*, nerve growth factor-induced clone A (NGFI-A), and NGFI-B mRNA (Refs 10-12). The first three can form the AP-1 transcription factor, which also increases after caffeine administration¹¹, and the latter two are transcriptional factors in their own right. Lower doses of caffeine can cause a decrease in the expression of certain gene products, particularly in the striatopallidal neurones in the cortex¹². Thus, there are marked phenotypic changes in selected neurones following acute and long-term caffeine administration. It is reasonable to assume that these changes are also manifested in adaptations of their functional characteristics. Indeed, the various biochemical changes after chronic caffeine administration are paralleled by altered behavioural responses to caffeine and to other agents.

Changes in behavioural responses after chronic administration of caffeine

Chronic ingestion of caffeine by humans can lead to tolerance, and withdrawal syndromes can occur, including apathy, drowsiness, headaches, nausea and anxiety¹³. True dependence, that is addiction, probably does not occur in humans and has been difficult to demonstrate in animals. In rats, chronic caffeine administration appears to result in almost complete tolerance to the motor stimulant effects of caffeine¹⁴, an adaptation difficult to rationalize solely on the basis of an up-regulation of adenosine receptors because this should not cause complete tolerance to a competitive antagonist, such as caffeine. One explanation of complete tolerance to the behavioural stimulant effects of caffeine may be based on the biphasic concentration-response curve for caffeine. At low doses of caffeine, there is an increase in locomotor activity, presumed to be the result of antagonism at adenosine receptors, while higher doses cause depression. An increase in adenosine receptor function, after chronic administration of caffeine, might be expected to increase the threshold for the stimulatory action of caffeine to the point where the depressant action, which occurs at a different site (possibly inhibition of phosphodiesterases), overrides the stimulatory effects of adenosine receptor antagonism. It is also possible that alteration in other receptors, in pathways modulated by adenosine receptors, accounts for the tolerance to caffeine.

The depressant locomotor effects of selective A₁ receptor analogues in mice are somewhat enhanced after chronic caffeine administration^{15,16}, consonant with an up-regulation of A₁ receptors. However, responses to selective A_{2A} receptor agonists are also enhanced, despite

the fact that A_{2A} receptors are not up-regulated. This may be the result of locomotor synergism between A₁ and A_{2A} receptors¹⁷.

Alterations in behavioural responses to cholinomimetic agents after chronic caffeine administration in mice can be explained in terms of desensitization of nicotinic acetylcholine receptors, that is, a tolerance to locomotor effects of nicotine, and in terms of up-regulation of muscarinic receptors – an increase in the threshold for locomotor stimulant effects of the muscarinic acetylcholine receptor antagonist, scopolamine^{15,16}. The lack of alteration in striatal dopamine receptors^{7,8} and the responses to drugs such as amphetamine or cocaine, which affect dopamine systems^{15,16}, after chronic caffeine administration is remarkable, as there is considerable evidence implicating dopamine systems as a major target for the pharmacological effects of caffeine and theophylline¹⁸. A possible clue to both the tolerance to caffeine and the apparent lack of alteration in dopamine-mediated responses has now been forthcoming. Thus, rats rendered tolerant to caffeine are also tolerant to agonists selective for either D₁ and D₂ receptors, but remain responsive to agonists that activate both D₁ and D₂ receptors¹⁹.

Further correlative studies on behavioural and biochemical alterations after chronic caffeine administration may lead to a more integrated view of the central sites of action of this agent. Although complete, or nearly complete, tolerance to stimulant locomotor effects of caffeine occurs in rats^{14,20}, it does not occur in NIH Swiss strain mice^{15,16} or CD-1 mice²¹. Instead, chronic caffeine ingestion results in a behavioural depression of activity in the mice, in marked contrast to the behavioural stimulation caused by acute administration of caffeine.

Chronic versus acute effects of adenosine receptor ligands

Chronic effects of xanthines, other than caffeine and theophylline, have not been extensively studied, in contrast to the plethora of data on acute effects of various xanthines. Similarly, chronic effects of adenosine analogues have not been extensively studied, while acute effects are well documented. Chronic treatment with an adenosine analogue results in an increase in the behavioural stimulant effect of caffeine²². Three clinically relevant effects of adenosine receptor ligands, namely cognition enhancement (by xanthines), neuroprotection from seizures and from ischaemia (by adenosine analogues), have now been investigated following acute and chronic administration. In most cases, a regimen-dependent ‘effect inversion’ was observed following chronic administration. For example, acute administration of adenosine analogues have neuroprotective effects, while chronic treatment exacerbates neuronal injury. Such ‘effect inversions’ may depend on drug administration method, frequency, dose, and washout time before measuring functional changes.

Acute versus chronic administration on cognition

Adenosine receptors may play a significant role in the process of cognition. Indeed, caffeine ingestion is commonly thought to improve intellectual performance in humans, although cognitive performance is often difficult to gauge both in humans and in animals¹.

The effects of selective A₁ receptor agonists and antagonists on cognition, when administered acutely, have been inconsistent. Thus, although the A₁ receptor agonists *N*⁶-cyclopentyladenosine (CPA) and *N*⁶-(1-methyl-2-phenylethyl)adenosine (*r*-PIA) have been shown to impair retention in passive avoidance tests^{23,24}, *r*-PIA has no effect on the working memory of rats²⁵. Similarly, although the selective A₁ receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (CPX) has no effect on responses in passive avoidance test²³, another selective A₁ receptor antagonist, KFM19, produces an increase in memory acquisition in the Y-maze²⁶; another A₁ receptor antagonist, MDL102503, reverses scopolamine-induced memory deficit in rats subjected to water-maze tests²⁷.

Prolonged exposure of A₁ receptors to their ligands can result in adaptive changes, hence it is not surprising that chronic exposure to either selective agonists or antagonists results in cognitive responses that differ from those observed following acute administration of these compounds. Thus, contrary to the expected pro-cognitive effects following acute administration of A₁ receptor antagonists, chronic administration of the A₁ receptor antagonist CPX in C57B] mice is entirely ineffective, or may even slightly impair memory acquisition in the water maze²⁸. However, chronic treatment with the A₁ receptor agonist CPA significantly improves both memory acquisition and retention. Chronic treatment with the selective A₁ receptor agonist R-PIA prevented loss of memory in trained rats, while chronic caffeine treatment had no effect²⁹.

Acute versus chronic administration on neuroprotection from seizure

Acute administration of adenosine analogues have anticonvulsant effects, while xanthines including caffeine are proconvulsant, and at sufficiently high doses are convulsants¹⁻³. Adenosine A₁ receptors appear to be involved. Acute administration of A₁ receptor agonists ameliorates, or even prevents, seizures elicited by chemical and electrical stimuli in a wide range of animal models^{30,31}. The anti-epileptic effects both of adenosine and its analogues appear to be related to the inhibition of seizure initiation and propagation. It should be noted that proconvulsant effects of adenosine receptor agonists and anticonvulsant effects of adenosine receptor antagonists have been noted in some paradigms³².

Involvement of A_{2A} receptors in the control of epileptic discharge is unclear at present. The selective A_{2A} receptor agonist N⁶-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine (DPMA) antagonized seizures induced by methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM)³². However, the selective A_{2A} receptor agonist CGS21680 had only a limited ability to antagonize bicuculline-induced seizures³¹. Further studies, in particular with selective A_{2A} receptor antagonists, are required to delineate the role of such receptors in the various seizure paradigms.

It is unclear as to whether acute stimulation of the A₃ receptor directly antagonizes seizure generation. A significant protective effect of acutely administered N⁶-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine (IB-MECA), a selective A₃ receptor agonist, against NMDA- and pentylenetetrazole-induced seizures has been demonstrated recently³³. Acute administration of IB-MECA was, however, entirely ineffective in ameliorating tonic convulsions produced by electroshock. Hence, there is a possibility that for chemically induced seizures, the protection afforded by IB-MECA is caused by phenomena unrelated to the direct interruption of neuronal hyperexcitability by this compound. Since agonist stimulation of A₃ receptors results in arteriolar constriction³⁴, it is possible that administration of IB-MECA constricts cerebral arterioles, resulting in subconvulsant amounts of the chemical convulsants reaching their target within the brain.

The effect of A₁ receptor ligands on seizures appears to be highly regimen-dependent. Thus, while the acute administration of an A₁ receptor agonist usually results in amelioration, and acute administration of an A₁ receptor antagonist has pro-convulsive effects, chronic treatment produces diametrically opposite consequences (Table 1). Chronic administration of either a nonselective adenosine antagonist (such as caffeine or theophylline^{35,36}) or a selective A₁ receptor antagonist (such as CPX³⁷) leads to a significant protection against NMDA-induced seizures. Chronic administration of theophylline leads to a prolongation of refractory periods for amygdala-kindled seizures in rats³⁸. Long-term, low-dose caffeine treatment also protects against bicuculline- and pentylenetetrazole-induced seizures³⁷, as does long-term, high-dose theophylline treatment³⁶. The high-dose xanthine treatment is accompanied by significant changes in the amount of A₁ receptors, the low-dose treatment is

not. The protective effect of caffeine treatment against NMDA-induced seizures was observed both during and after treatment with low doses of caffeine³⁵. Chronic treatment with CPA results in a pronounced increase in seizure intensity and seizure-associated mortality³⁷, a result diametrically opposite to the protective effects observed following acute treatment. The effects of chronic administration of selective A_{2A} receptor agonists and antagonists on seizure susceptibility need to be studied.

Chronic treatment with the A₃ receptor agonist *IB*-MECA results in almost complete protection against NMDA-induced seizures and a significant reduction of mortality accompanying both pentylenetetrazole- and electroshock-induced convulsions³³. Acute administration of *IB*-MECA was ineffective versus electroshock-induced seizures, but did ameliorate chemically induced seizures. It should be noted that selective antagonists to A₃ receptors have yet to be developed.

Acute versus chronic administration on neuroprotection from ischaemia

Adenosine analogues, particularly selective A₁ receptor agonists, following acute administration have wellknown neuroprotective actions during ischaemia³⁹. Hence, adenosine-based therapies represent an approach to treating seizures, stroke and neurodegenerative diseases⁴⁰. In contrast, antagonists such as caffeine, exacerbate ischaemic damage. Acute administration of A₁ receptor agonists, such as CPA, has been shown to protect neurones against the damage induced both by focal and by global ischaemia^{39,40}. Acute treatment with an A₁ receptor agonist is effective even when administered up to 30 min post-ischaemia⁴¹. The critical role of adenosine as an endogenous neuroprotective agent is demonstrated by the very significant increase in neuronal destruction following pre-ischaemic administration of either nonselctive (caffeine or theophylline) or selective A₁ receptor (CPX) antagonists³⁹⁻⁴².

As yet, little is known about the effects of acute administration of A_{2A} receptor ligands on the extent and nature of ischaemic damage. The selective A_{2A} receptor agonist 2-[(2-aminoethylamino)-carbonyl-ethylphenyl-ethylamino]-5'-*N*-ethylcarboxamidoadenosine (APEC) improved recovery of post-ischaemic blood flow and survival of gerbils, but had no effect on loss of hippocampal neurones⁴³. Pretreatment with an A₂ receptor antagonist CGS15943 was found to reduce the extent of morphological and neurological impairment following brief cerebral ischaemia in gerbils⁴⁴. The selective A_{2A} receptor antagonist 8-(3-chlorostyryl)caffeine (CSC) protected hippocampal neurones and improved survival during the first ten days post-ischaemia⁴³; however, deaths occurred at later times, and the mortality endpoint following acute administration of CSC was not significantly different from control.

A regimen-dependent inversion of effects of exposure to adenosine receptor ligands (Table 1) has been observed with respect to consequences of cerebral ischaemia. Rudolphi and co-workers were the first to describe the protective effect of chronic caffeine treatment on post-ischaemic morphology of the gerbil brain⁴⁵. Recently, chronic administration of CPX in gerbils was found to afford a large amount of protection against brain ischaemia, while chronic administration of CPA resulted in damage and mortality significantly exceeding that of the controls⁴². A similar neuroprotective effect was observed in neonatal rats that had received low doses of caffeine in their mother's milk⁴⁶. The neuroprotective effect was not associated with any significant change in the numbers of A₁ and A_{2A} receptors.

Chronic treatment of gerbils with CSC leads to a slight, but statistically insignificant, protection against ischaemic damage; chronic administration of APEC, however, leads to a significant reduction of ischaemic damage⁴³. However, acute administration of CSC also protects against ischaemic damage, but acute administration of APEC does not. Thus, the

evidence for a regimen-dependent ‘effect inversion’ appears to be much weaker for A_{2A} receptors than for A₁ receptors. Since stimulation of A_{2A} receptors causes vasodilation, chronic administration of CSC may induce adaptive changes of vascular A_{2A} receptors, resulting in an enhanced normalization of post-ischaemic blood flow. Indeed, such improvement has been recently observed following chronic treatment with CSC and forebrain ischaemia in gerbils⁴³. A rapid restoration of normal blood perfusion may be expected to lead to a better outcome from an ischaemic insult. It should be noted that the tolerance to the hypotensive effects of selective A_{2A} receptor agonists has been reported after continuous infusion⁴⁷, but not after chronic injections⁴⁸.

The role of the A₃ receptors in ischaemia is poorly understood⁴⁹, and the involvement of mast-cell activation⁵⁰ complicates the interpretation of findings. It is known, however, that acute pre-ischaemic stimulation of A₃ receptors with IB-MECA results in a significant increase in morphological damage and enhancement of post-ischaemic mortality⁴⁷. As mentioned previously, stimulation of A₃ receptors results in arteriolar constriction. Hence, it is not surprising that the pre-ischaemic treatment with IB-MECA leads to a substantial delay in the normalization of post-ischaemic blood flow. Chronic treatment with IB-MECA results in a significant reduction of post-ischaemic cerebral damage and mortality following 10 min and 20 min occlusion of both carotid arteries in gerbils⁴⁹. This effect is the opposite of that seen following the acute administration of the compound.

Concluding remarks

The presence of the regimen-dependent ‘effect inversion’ for adenosine receptor agonists and antagonists leads to questions concerning the extent to which up- or downregulation participates in these phenomena. Many studies have demonstrated that chronic exposure to non-selective A₁ receptor antagonists, such as caffeine or theophylline, results in up-regulation of A₁ receptors. Indeed, this may be the explanation of the protective effect of chronic administration of caffeine prior to cerebral ischaemia in gerbils. However, in at least one study, the regimen of chronic administration of caffeine administration failed to produce any detectable up-regulation of A₁ receptors³⁵. In another study, chronic exposure to selective agonists or antagonists at A₁ receptors appeared not to have any effect on A₁ receptor density⁴². In spite of the lack of changes in A₁ receptors ‘effect inversion’ occurred in both studies. Thus, the role of up- or down-regulation of adenosine receptors in the processes of regimen-dependent ‘effect inversion’ remains an enigma. The presence or absence of ‘effect inversion’ may be directly dependent upon the duration of exposure, withdrawal, and nature of the non-selective and selective adenosine receptor ligands, and further studies are required. At present, for caffeine and other adenosine receptor ligands, evidence for such inversions has been obtained with respect to behavioural activity, cognition, seizure liability, and neuroprotection during ischaemia. The ‘effect inversion’ for such agents is highly relevant in the development of behavioural stimulants, cognitive enhancers, anticonvulsants, and possible therapies in the treatment of stroke.

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Fig. 2.

Effect of chronic administration of caffeine on the densities of several receptors and an ion channel in various brain regions. (■, cortex; □, cerebellum; and ■, striatum.) Caffeine was ingested in drinking water (1 g l^{-1}) for 4 days by male NIH Swiss mice. Binding assays were carried out four hours after cessation of caffeine administration via the drinking water. Values are calculated from data in Refs 15, 16, and expressed as percent of control levels.

* $p < 0.05$ significantly different from control values.

Table 1Regimen-dependent effects of adenosine, A₁ receptor ligands

Effect	<u>Period of administration</u>	
	acute	Chronic ^a
2Neuroprotective anticonvulsant	agonists	antagonista
Cognition enhancer	Antagonists	Agonists

^a In these studies at least 24 h was allowed between the time of last drug administration and the measurement of functional change.