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Review

Adenosine A_{2A} receptors and their role in drug addiction

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Abstract

The specific events between initial presumably manageable drug intake and the development of a drug-addicted state are not yet known. Drugs of abuse have varying mechanisms of action that create a complex pattern of behaviour related to drug consumption, drug-seeking, withdrawal and relapse. The neuromodulator adenosine has been shown to play a role in reward-related behaviour, both as an independent mediator and via interactions of adenosine receptors with other receptors. Adenosine levels are elevated upon exposure to drugs of abuse and adenosine A_{2A} receptors are enriched in brain nuclei known for their involvement in the processing of drug-related reinforcement processing. A_{2A} receptors are found in receptor clusters with dopamine and glutamate receptors. A_{2A} receptors are thus ideally situated to influence the signalling of neurotransmitters relevant in the neuronal responses and plasticity that underlie the development of drug taking and drug-seeking behaviour. In this review, we present evidence for the role of adenosine and A_{2A} receptors in drug addiction, thereby providing support for current efforts aimed at developing drug therapies to combat substance abuse that target adenosine signalling via A_{2A} receptors.

Introduction

Adenosine and drug reinforcement

The role of adenosine in the mediation of withdrawal and the consequences of abstinence following drug taking has been known for over 30 years. Adenosine is ubiquitous, being found throughout the central nervous system (CNS), and is responsible for mediating a myriad of often subtle but influential effects. Early research discounted the role of adenosine, other than as a metabolite of adenosine triphosphate (ATP) and cyclic adenosine monophosphate (cAMP); however, the importance of adenosine as a modulator of neurotransmission and complex behaviour is now beyond doubt. In this review, we focus upon the role of adenosine, the A_{2A} receptor and A_{2A} receptor interactions in the positive aspects of drug-seeking and consumptive behaviour modelled in mice and rats, and we will be restricting our discussion to ethanol, opiates and psychostimulants.

Drugs of abuse and neuronal reward mechanisms

Worldwide, the consequences of drug addiction are substantial. Substance abuse (alcohol, tobacco and illicit drugs) was estimated to account for 12.4% of deaths in 2000 (WHO 2008). Drug abuse has a significant impact on society, with reduced economic, health and social outcomes, but the concept of drug addiction as a treatable brain disease is progressing (Volkow & Li 2005). The World Health Organization estimates that for every dollar spent on drug treatment across the world, 7 dollars are saved. While some currently available therapies have experienced moderate success, there are issues, such as the development of tolerance, limited efficacy in some individuals, inconvenient formulation and dosing regimes, abuse liability and adverse side effects, that make these therapies less than ideal. The drawbacks of existing therapies impact upon completion rates or restrict the use of these interventions to specific subpopulations of drug-addicted individuals. Continuing research is therefore required to identify new therapeutic targets that have the potential to overcome these drawbacks.

Drugs of abuse appropriate the neuronal mechanisms that evolved to reinforce conventional reinforcers such as food and water intake and sexual and maternal behaviour (Nestler & Landsman 2001). Accepted theories differ with respect to the processes mediated via the mesolimbic dopaminergic system, although most investigators are in agreement regarding the

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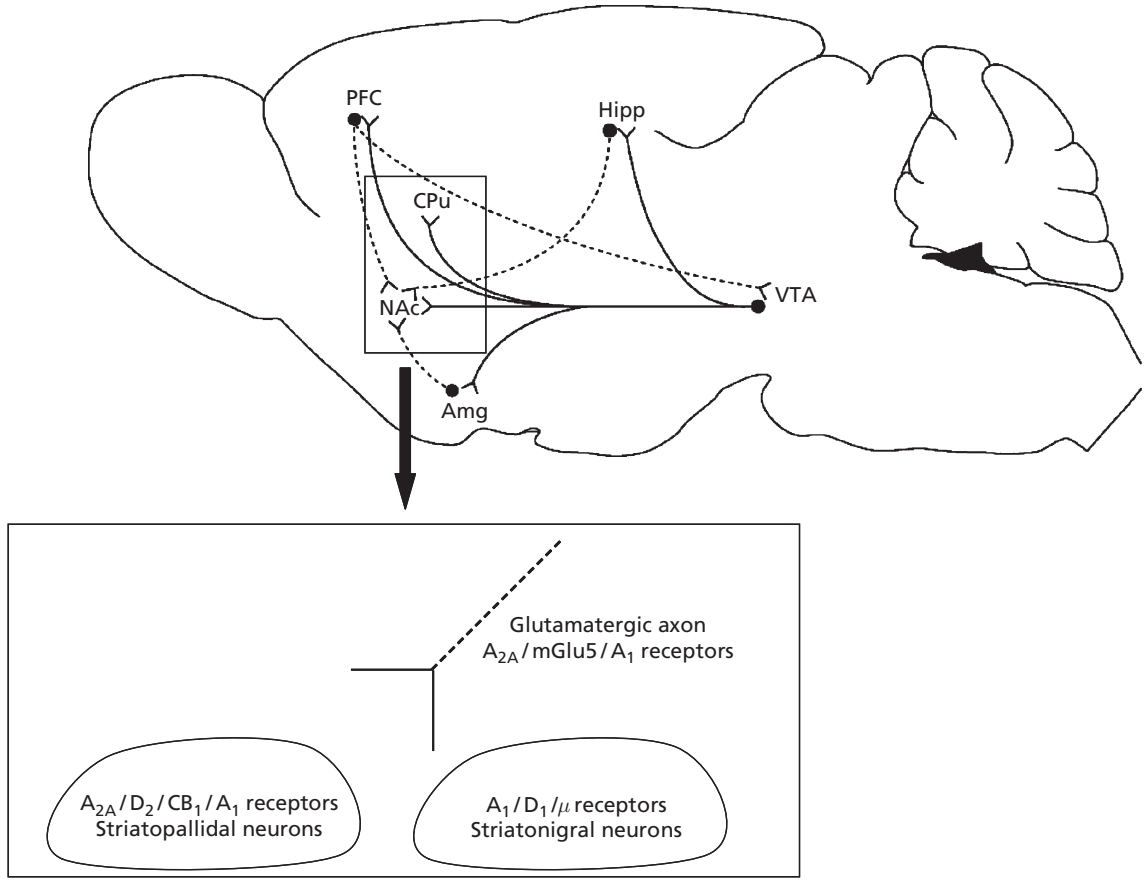

Figure 1 The dopaminergic mesolimbic pathway projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Excitation of mesolimbic neurons and release of dopamine in the NAc is a common feature underlying the reinforcement of many drugs of abuse, including ethanol, opiates and psychostimulants. Dopaminergic mechanisms are said to dominate the initial stages of drug intake, as mesolimbic dopaminergic projection neurons are able to influence pertinent situational and environmental information encoded by cortico-striatal glutamatergic neurons, and enhance the relationship between goal-directed behaviour and motivationally significant stimuli (Wolf 2002; Wise 2004). The later stages of drug addiction, characterised by 'compulsive' drug-seeking and relapse behaviours, appear related to adaptations in excitatory cortico-accumbal connections, whereby predictors of drug availability are accorded disproportionate motivational importance (Kalivas & Volkow 2005). Figure adapted from Franklin & Paxinos (1997); solid lines, dopaminergic neurons; dashed lines, glutamatergic neurons. The inset illustrates the localisation of receptors relevant in the processing of reward-related information in the striatal complex. AMG, amygdala; CPu, candate putamen; Hipp, hippocampus; PFC, prefontal cortex.

pivotal role of the mesolimbic pathway and the nucleus accumbens in the behavioural plasticity underlying reinforcement (Figure 1). (Some good reviews of this area include Koob & Bloom 1988; Koob 1992; Robinson & Berridge 1993; Di Chiara 1995; Self & Nestler 1995; Robbins & Everitt 1996; Wise 1996b; Cowen & Lawrence 1999; Schultz 1999)). Although important, dopaminergic mechanisms do not explain all facets of reinforcement and relapse (drug seeking) behaviour after abstinence. The neuronal basis of this very complicated area of behaviour involves direct dopamine signalling, dopamine-mediated interactions with other neuromodulators and dopamine-independent mechanisms. One modulator implicated to play a role is adenosine.

Mechanisms by which the level of adenosine is increased in the CNS

Within the CNS, endogenous adenosine is present extracellularly under resting conditions. Its concentration increases quite dramatically in response to many factors, both pathological and biological (Dunwiddie 1985). Biologically active adenosine may be derived via multiple methods (Figure 2). ATP or cAMP may be released from neurons or glial cells and subsequently metabolised to adenosine. Alternatively, intracellular ATP/cAMP may be metabolised to adenosine or adenosine may be produced via *S*-adenosyl-homocysteine and then undergo release via facilitated diffusion, by way of bi-directional equilibrative transporters (Dunwiddie 1985; Ledent et al 1997; Ribeiro 1999; Hack & Christie 2003). Important variables influencing adenosine-mediated transmission include the rate of formation and source of adenosine, the rate of diffusion between the intra- and extracellular environment and the rate of degradation (via phosphorylation or deamination) (Dunwiddie 1985; Hack & Christie 2003). All of these factors may play a role in the determination of adenosine-mediated effects in response to drugs of abuse. Under resting conditions the level of extracellular adenosine is estimated to be in the low

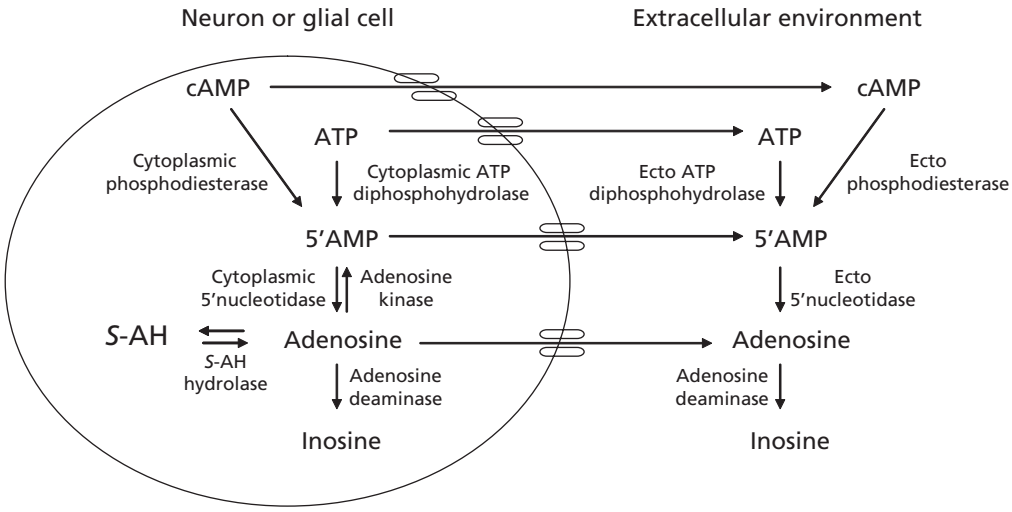

Figure 2 Conversion of adenosine triphosphate (ATP) or cyclic adenosine monophosphate (cAMP) to 5′ adenosine monophosphate (5′AMP) and subsequent metabolism to yield adenosine may occur within neurons or glial cells. Intracellular adenosine may also be produced via the metabolism of *S*-adenosyl-homocysteine (*S*-AH) (although evidence for this process is stronger in the peripheral nervous system). Adenosine produced in the cytoplasm is released via bi-directional equilibrative transporters. Alternatively, ATP or cAMP may be released from a neuron or glial cell and subsequently metabolised to adenosine. Adenosine is converted to inosine by adenosine deaminase, *S*-AH by the reversible *S*-AH hydrolase or 5′AMP by the action of adenosine kinase. (See Dunwiddie 1985; Ribeiro 1999; Hack & Christie 2003)

micromolar range (Dunwiddie 1985). This low level of adenosine is sufficient for receptor binding and the observation of functional effects, as addition of specific receptor antagonists and enzyme inhibitors will produce effects in the absence of exogenous adenosine (Dunwiddie 1985; Dunwiddie & Masino 2001). Importantly, drugs of abuse are also able to increase adenosine levels in the brain; the mechanism and extent to which ethanol, opiates and psychostimulants enhance adenosine availability will be examined in the relevant sections to follow.

Neuronal effects of adenosine

Adenosine binds to G-protein-coupled receptors, A_1, A_{2A}, A_{2B} and A_3, of which A_1 and A_{2A} are most highly expressed in the brain. Adenosine has been demonstrated to fine-tune neurotransmission in numerous regions of the CNS via a variety of avenues, pre-, post- and extra-synaptically (Sebastião & Ribeiro 2000). The formation of receptor mosaics is now apparent as an important mechanism by which neurotransmission is integrated (reviewed in Fuxe et al 2008), and adenosine receptors are commonly found within receptor clusters. While the signalling mediated via other receptors in the cluster may be given prominence (for example dopamine D_2 receptor signalling), the role of adenosine in modulating the efficacy of neurotransmission mediated via these main input signals is exceedingly important (Fuxe et al 2007).

The prevalent neuromodulatory influence of adenosine is inhibitory (Table 1). Adenosine activation of $G_{i/o}$-coupled A_1 receptors exerts a depressant effect on neuronal firing, reducing neurotransmitter release at pre-synaptic nerve terminals, while also increasing potassium conductance and reducing calcium flux in the pre- and post-synaptic cell (Snyder 1985; Fredholm & Dunwiddie 1988; Latini et al 1996). In this way, adenosine is known to inhibit the release of many neurotransmitters, including dopamine, glutamate, gamma aminobutyric acid (GABA), serotonin, noradrenaline and acetylcholine (ACh), although inhibition of excitatory neurotransmitters (e.g. glutamate) is most pronounced (for review, see Fredholm & Dunwiddie 1988; Cunha 2001; Dunwiddie & Masino 2001). In addition, excitatory actions of adenosine on neurotransmitter release have been demonstrated (e.g. glutamate and ACh in the striatum, and ACh in the hippocampus), most probably mediated by ($G_{s/olf}$-coupled) A_{2A} receptor activation (Kirkpatrick & Richardson 1993; Cunha et al 1995; Popoli et al 1995). A_1 and A_{2A} receptors exhibit different affinities for adenosine (estimated at ~70 and 150 nM, respectively (Dunwiddie & Masino 2001)) and may be activated under different conditions. Receptor discrimination may be achieved through the pattern of neuronal firing (i.e. with high neuronal discharge there may be higher levels of ATP in the synapse), the alternative sources of adenosine (intra- and extracellular formation), the relative position of adenosine release and receptor sites (synaptically or extra-synaptically) or the localisation of relevant synthetic or metabolic enzymes (James & Richardson 1993a; Cunha et al 1996; Sebastião & Ribeiro 1996, 2000; Ribeiro 1999; Cunha 2001).

Adenosine and the striatum

The localisation of the A_{2A} receptor within the brain is circumscribed – predominantly expressed within the striatum (the caudate putamen and nucleus accumbens) and olfactory tubercle (Figure 1). A_1 receptors have a widespread distribution throughout the nervous system, though with a substantial degree of co-localisation with A_{2A} receptors. The A_{2A} receptor is localised within distinct neuronal populations, and is in the main expressed on the soma of

Table 1 A summary of the signalling, localisation and effects mediated by adenosine A_1 and A_{2A} receptors in the central nervous system, and relevant agonists and antagonists used to elucidate the role of A_1 and A_{2A} receptors in behaviour associated with ethanol, opiate and psychostimulant reward

Receptor subtype	A_1	A_{2A}
Estimated affinity for adenosine	70 nM	150 nM
Signalling	$G_{i/o}$	$G_{s/olf}$
CNS distribution and localisation	Widespread; pre- and post-synaptic	Caudate putamen, nucleus accumbens, olfactory tubercle; evidence for a pre- and post-synaptic localisation
Major effects	Inhibition of adenylate cyclase Inhibition of neuronal firing, neurotransmitter release (Enhanced K^+ conductance, inhibition of Ca^{2+} channels)	Activation of adenylate cyclase Enhanced neuronal firing, increased neurotransmitter release (Activation of Ca^{2+} channels)
Agonists	CHA CPA R-PIA	APEC CGS 21680 CPCA
Antagonists	8CPT DPCPX PACPX	DMPX KW 6002 MSX-3 SCH 58261 ZM 241385
Non-selective receptor agonists	DPX NECA S-PIA (L-PIA)	
Non-selective receptor antagonists	Caffeine[a] 7-CET[a] CGS 15943 8-PT Theophylline[a]	
Nucleoside transporter inhibitors	Dilazep Dipyridamole NBTI	
Adenosine kinase inhibitors	5′-Amino-5′-deoxyadenosine 5-Iodotubericidin	

[a]Note, these drugs are also cyclic nucleotide phosphodiesterase inhibitors (for review, see Haas & Selbach 2000; Dunwiddie & Masino 2001). APEC, 2-[(2-aminoethylamino)carbonylethylphenylethylamino]-5′-*N*-ethylcarboxamidoadenosine; 7-CET, 7-(2-chloroethyl)theophylline; CGS 15943, 9-chloro-2-(2-furyl)[1,2,4]triazolol[1,5-*c*]quinazolin-5-amine; CGS 21680, 2-[4-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido]adenosine; CHA, N^6-cyclohexyladenosine; CPA, N^6-cyclopentyladenosine; CPCA, 5′-(*N*-cyclopropyl)-carboxamidoadenosine; 8CPT, 8-cyclopentyltheophylline; DMPX, 3,7-dimethyl-1-propargylxanthine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; DPX, diethylphenylxanthine; KW 6002, 1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dhydro-1*H*-purine-2,6-dione; MSX-3, 3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-7-methyl-1-propargylxanthine phosphate disodium salt; NBTI, nitrobenzylthioinosine; NECA, 5′-*N*-ethylcarboxamido-adenosine; PACPX, 1,3-dipropyl-8-(2-amino-4-chlorophenyl)-xanthine; 8-PT, 8-phenyltheophylline; R-PIA, R(-)-N^6-(2-phenylisopropyl)adenosine; SCH 58261, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-c]-1,2,4-triazolo-[1,5,-c]pyrimidine; S-PIA (L-PIA), (S(+)-N^6-(2-phenylisopropyl)adenosine; ZM 241385, 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo-[2,3-a]-[1,3,5]triazin-5-ylamino]ethyl)phenol.

GABAergic (enkephalin-containing, D_2-receptor-expressing) striato-pallidal projection neurons, at asymmetrical excitatory synapses at the dendrites (see Schiffmann et al 1991; Fink et al 1992; Pollack et al 1993; Schiffmann & Vanderhaeghen 1993; Augood & Emson 1994; Svenningsson et al 1997, 1999), although the degree to which the expression of the A_{2A} receptor is restricted to striatopallidal neurons is debated (James & Richardson 1993b; Dixon et al 1996; Rosin et al 1998).

Adenosine is produced upon activation of striatal circuits (see Schiffmann et al 2007). As neuronal firing is increased the consumption of ATP is also amplified to maintain homoeostatic ion gradients. Adenosine is generated intracellularly following the dephosphorylation of ATP, and thus extracellular level of adenosine is also elevated due to the activity of the bi-directional equilibrative transporters, as discussed earlier (Figure 2). Depending on the location of degradative enzymes, adenosine formed from the extracellular hydrolysis of ATP may be available for A_1 and A_{2A} receptor binding, and thus also influence dopamine transmission pre-synaptically (via inhibitory A_1 receptors) or post-synaptically (A_1 and A_{2A} receptors). Interestingly, administration of the P_2 receptor antagonist pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS) into the nucleus accumbens reduces the extracellular dopamine concentration. This indicates a modulatory role of endogenous ATP (perhaps co-released with dopamine) in stimulating the release of dopamine (Kittner et al 1999; Krugel et al 2003). ATP is also present in synaptic vesicles and co-released with neurotransmitters such as glutamate, GABA and ACh (Cunha & Ribeiro 2000;

Dunwiddie & Masino 2001). As discussed above, due to the spatial arrangement of relevant enzymes and receptor populations, adenosine formed via the activity of ecto-ATP-diphosphohydrolase and ecto-5′-nucleotidase when ATP release is high is said to favour A_{2A} receptor binding. Adenosine formed via the degradation of ATP released upon excitation of dopamine (or glutamate) neurons in the nucleus accumbens may therefore provide the main driver for A_{2A}-receptor-mediated effects upon drug reinforcement processing. Secondly, the availability of adenosine for receptor binding is increased upon receptor activation and enhanced adenylate cyclase activity. This subsequent increase in cAMP results in the movement of cAMP into the extracellular environment via probenecid-sensitive transporters before metabolism into adenosine (see Dunwiddie & Masino 2001; Hack & Christie 2003).

A_{2A} receptor co-localisation and subsequent interactions with other receptor subtypes

Due to their synaptic localisation, A_{2A} receptors are well placed to play an influential role in altering dopaminergic signalling and have been said to influence the latter via several mechanisms: direct receptor–receptor interactions, interactions at the second messenger level, trans-synaptically via striatal collaterals or interneurons, or at a post-synaptic or network level (Pollack & Fink 1996; Ferré et al 1997). Many studies have demonstrated the existence of specific interactions between co-localised ($G_{s/olf}$-coupled) A_{2A} receptors and ($G_{i/o}$-coupled) dopamine D_2 receptors in the striatal complex. The A_{2A}–D_2 receptor interaction is an example of the complexity of receptor interactions involving the A_{2A} receptor. Antagonistic and synergistic interactions have been established and interactions occurring directly between receptor complexes or at the second messenger level have been confirmed. A_{2A}–D_2 receptor interactions have been assigned a fundamental role in the behavioural effects of adenosine neuromodulation and have been reviewed elsewhere (Ferré et al 1994, 2004; Fredholm & Svenningsson 2003; Fuxe et al 2003). In addition, interactions involving the A_{2A} receptor have been described for numerous other cell-surface receptors, including adenosine A_1, dopamine D_1, cannabinoid CB_1 and subtype 5 metabotropic glutamate (mGlu5) receptors (recently reviewed in Ferré et al 2007; Schiffmann et al 2007). Adenosine, therefore, via activation of the A_{2A} receptor, is well placed to influence the reinforcement processes underlying ethanol, opiate and psychostimulant intake. The evidence supporting this statement is discussed in the subsequent sections of this review.

Ethanol

Mechanism of action

Ethanol (ethyl alcohol; CH_3CH_2OH) is an uncomplicated molecule, able to produce widespread effects in the CNS without any identifiable receptor. At low yet physiologically relevant doses, ethanol apparently acts via ethanol-receptive elements to facilitate $GABA_A$ and inhibit *N*-methyl-D-aspartic acid (NMDA) receptor function via an allosteric mechanism (Koob & Nestler 1997; Nestler 2001). Importantly, administration of ethanol increases the firing rate of ventral tegmental area (VTA) dopaminergic neurons and elevates dopamine in the nucleus accumbens (Gessa et al 1985; Di Chiara & Imperato 1986; Imperato & Di Chiara 1986; Weiss et al 1993; Appel et al 2003). Many studies have demonstrated a role for the mesolimbic pathway and dopaminergic mechanisms in the primary reinforcing effects of ethanol (for review: Nevo & Hamon 1995; Koob et al 1998; Nestler 2005). As we will describe in subsequent sections, adenosine is also involved in the acute and chronic effects of ethanol (see Table 2 for a summary of the relevant literature). Furthermore, it is probable that adenosine is able to modulate ethanol addictive processes either independently or via interactions with other signalling systems. The evidence for this role of A_{2A} receptors will be expanded upon in later sections of this review.

The link between ethanol and adenosine signalling

Work completed over the last 25 years has amassed data linking the cellular and receptor effects of ethanol with adenosine. A review by Mailliard & Diamond (2004) overviews research demonstrating that the effect of ethanol upon cAMP accumulation and eventual desensitisation of $G_{\alpha s}$-proteins is a result of increased extracellular adenosine and subsequent activation of A_{2A} receptors (Gordon et al 1986; Nagy et al 1989, 1990; Diamond et al 1991; Krauss et al 1993) (Figure 3). Acute ethanol exposure has been shown to increase adenosine levels in-vitro, via actions on the equilibrative nucleoside transporter 1 (ENT1) to inhibit adenosine influx. With chronic ethanol this effect is lost (Clark & Dar 1989a, b; Nagy et al 1990; Krauss et al 1993). The observation of concordant expression of ENT1 and strain differences in ethanol consumption in mice is consistent with a hypothesis linking adenosine and ethanol (Short et al 2006a).

Alternative ethanol interactions with adenosine have also been described. For example, the metabolism of ethanol yields acetate, and when acetate reacts with coenzyme A and ATP to form acetyl coenzyme A, adenosine monophosphate (AMP) is formed, leading to the generation of adenosine (a process that has been demonstrated in the CNS) (Carmichael et al 1991; Arolfo et al 2004; Mailliard & Diamond 2004).

Lastly, as described in earlier sections, striatal adenosine levels are likely to be elevated due to the increase in the excitability of afferents and neurons of the nucleus accumbens seen in response to ethanol. Ethanol increases the firing rate of dopaminergic neurons and increases the release of dopamine in the nucleus accumbens. Evidence exists for the co-localisation of dopamine and ATP, thus increased extracellular availability of adenosine may arise from metabolism of ATP. In turn, dopaminergic transmission alters the excitability of GABAergic target neurons, and network effects result in enhanced glutamatergic innervation to the nucleus accumbens. At each of these points in the sequence of ethanol-mediated alterations in mesolimbic signalling, there is obviously neuronal excitation and often activation of adenylate cyclase. As described in Figure 2, liberation of ATP and cAMP is therefore likely, indicating that there may be a concomitant increase in the availability of adenosine and hence activation of A_1 and A_{2A} receptors.

Table 2 The role of adenosine in ethanol-induced effects upon behaviour and function, with a focus on pharmacological data and rodent models implicating the A_{2A} receptor

Behavioural or functional effect of ethanol	Pharmacological evidence for the involvement of adenosine signalling	References
Ethanol-enhanced glucose utilisation in mice	Increased by A_1 receptor agonist CHA Decreased by adenosine deaminase and theophylline (non-selective A_1/A_{2A} receptor antagonist)	Anwer & Dar 1995
Motor incoordination in mice and rats, as measured by performance on the rotarod apparatus[a]	Potentiated by CHA and R-PIA (A_1 receptor agonists), NECA (non-selective A_1/A_{2A} receptor agonist), CPCA and CGS 21680 (A_{2A} receptor agonists), dipyridamole and dilazep (adenosine uptake inhibitors) Reduced by theophylline and 7-CET (non-selective A_1/A_{2A} receptor antagonists), reduced in ENT1 knockout mice	Dar et al 1983; Clark & Dar 1988; Meng & Dar 1995; Dar 1996, 1997; Choi et al 2004
The duration of the ethanol induced loss of the righting reflex	Potentiated by dipyridamole (adenosine uptake inhibitor) Reduced by theophylline, SCH 58261 and ZM 241385 (the latter two more selective A_{2A} receptor antagonists) and upon deletion of the A_{2A} receptor and ENT1 (knockout mice models)	Dar et al 1983; Clark & Dar 1988; Naassila et al 2002; El Yacoubi et al 2003; Choi et al 2004
Ethanol induced hypothermia	Reduced by ZM 241385 and reduced in A_{2A} receptor knockout mice	Naassila et al 2002
Ethanol-induced reductions in spontaneous motor activity in rats, as measured in automated activity chambers	Potentiated by R-PIA and dilazep Reduced by theophylline	Clark & Dar 1988
Ethanol-enhanced locomotor activity in mice, as measured in automated open field apparatus	Reduced following chronic (7 days) administration of caffeine	Daly et al 1994
Ethanol preference and consumption in mice, as assessed by free-choice, two bottle paradigm	Increased in mice with a genetic deletion of the ENT1 (an effect reversed by administration of CPA) Reduced or unaltered in A_{2A} receptor knockout mice[b]	Naassila et al 2002; Choi et al 2004; Short et al 2006b
Ethanol consumption in mice, as assessed using a no-choice paradigm	Increased by ZM 241385[c]	El Yacoubi et al 2001
Ethanol consumption in rats, as assessed in an operant paradigm	Increased by DMPX (A_{2A} receptor antagonist) at 1 mg kg^{-1}, unaltered at 3 mg kg^{-1}, reduced at 10 mg kg^{-1} (all intraperitoneal injections) Reduced by SCH 58261	Arolfo et al 2004; Thorsell et al 2007; Adams et al 2008
Ethanol-induced conditioned place preference	No publications to date	
Ethanol-induced locomotor sensitisation	No publications to date	
Reinstatement of ethanol-seeking following abstinence or extinction of responding in an operant paradigm	No publications to date	
Ethanol withdrawal induced hyperexcitability and seizures in mice, as induced by handling	Reduced by R-PIA and CGS 21680 Reduced by ZM 241385[d] and genetic deletion of the A_{2A} receptor	Kaplan et al 1999; El Yacoubi et al 2001

[a]Differences in drug administration across studies, intra-peritoneal, -striatal, and -cerebellar. [b]Procedural differences (for example, the concentration of the ethanol solution offered) may explain the discrepancy between these studies. [c,d]Note subchronic administration of ZM 241385. 7-CET, 7-(2-chloroethyl)theophylline; CGS 21680, 2-[4-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido]adenosine; CHA, N^6-cyclohexyladenosine; CPCA, 5′-(*N*-cyclopropyl)-carboxamidoadenosine; DMPX, 3,7-dimethyl-1-propargylxanthine; ENT1, equilibrative nucleoside transporter 1; NECA, 5′-*N*-ethylcarboxamido-adenosine; R-PIA, R(-)-N^6-(2-phenylisopropyl)adenosine; SCH 58261, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-c]-1,2,4-triazolo-[1,5,-c]pyrimidine; ZM 241385, 4-(2-[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol.

In-vivo behavioural and functional evidence for the involvement of adenosine signalling in ethanol-mediated effects

Indirect evidence for the role of adenosine in the functional effects of ethanol is provided from experiments examining ethanol-enhanced glucose utilisation in whole mouse brain, cerebellum and brain stem (Anwer & Dar 1995). Glucose utilisation is attenuated by adenosine receptor antagonists, and potentiated by adenosine agonists, an observation consistent with data demonstrating a functional role for adenosine receptors in ethanol-induced motor disturbances. Thus, Dar and colleagues have also determined behaviourally that adenosine receptor antagonists attenuate, while adenosine (A_1) receptor agonists and adenosine uptake inhibitors enhance, ethanol-induced motor impairment in rodents via receptor populations in the cerebellum and striatum (Table 1) (Dar et al 1983; Clark & Dar 1988; Meng & Dar 1995; Dar 1996, 1997). In the study by Meng & Dar (1995), both A_1 and A_{2A} receptor agonists injected into the striatum of rats potentiated ethanol-induced motor incoordination, although the pharmacological profile suggested this effect of adenosine was primarily modulated via the A_1 receptor subtype.

While earlier work suggested an A_1-receptor-mediated role for adenosine in the ethanol-induced loss of righting reflex, more recent work has demonstrated that A_{2A} receptors are also involved in the hypnotic effects of ethanol

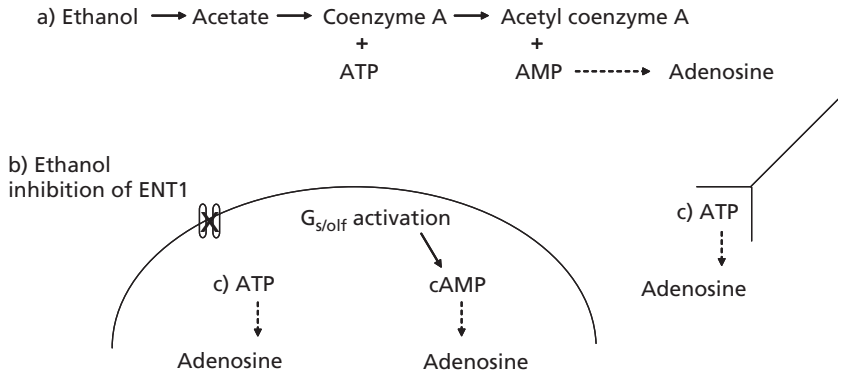

Figure 3 Potential ways in which adenosine levels may be increased following ethanol administration. (a) The metabolism of ethanol via alcohol and acetylaldehyde dehydrogenases results in acetate, a metabolite that subsequently elevates adenosine monophosphate (AMP) and may be converted to adenosine as described in Figure 2. (b) Inhibition of equilibrative nucleoside transporter type 1 (ENT1) by ethanol prevents influx of adenosine and thus increases the availability of adenosine for receptor binding. (c) In response to ethanol, enhanced activity of dopaminergic or glutamatergic inputs or intrinsic GABAergic neurons may result in increased adenosine triphosphate (ATP) and cyclic AMP (cAMP) intracellularly and extracellularly, and thus increased adenosine as outlined in Figure 2.

(El Yacoubi et al 2003). The non-selective equilibrative nucleoside transporter (ENT) inhibitor dipyridamole increases the duration of the ethanol-induced loss of righting reflex (Dar et al 1983; El Yacoubi et al 2003). Conversely, the A_{2A} receptor antagonists 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-c]-1,2,4-triazolo-[1,5-c]pyrimidine (SCH 58261) and 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo [2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol (ZM 241385) have been demonstrated to reduce the duration of the ethanol-induced loss of righting reflex (Naassila et al 2002; El Yacoubi et al 2003). This pharmacological data was further supported by the reduction in the loss of righting reflex produced by acute ethanol administration in A_{2A} receptor knockout mice (El Yacoubi et al 2003). Furthermore, A_{2A} receptor knockout mice were found to exhibit a reduced sensitivity to ethanol-induced hypothermia, a phenotype paralleled in wild-type mice upon administration of ZM 241385 (Naassila et al 2002).

Data concerning a role for A_{2A} receptors in changes in locomotor activity following ethanol administration are unclear at this time, as the experimental paradigms and drugs employed do not allow a conclusion to be drawn. In one study in rats, ethanol decreased spontaneous motor activity, an effect potentiated by the A_1 receptor agonist N^6(R-phenylisopropyl)adenosine (R-PIA) and the nucleoside transporter inhibitor dilazep, and reduced by the non-selective A_1/A_{2A} receptor antagonist theophylline (Clark & Dar 1988). In a second study, ethanol administration increased locomotor activity, although this alteration in behaviour was also reversed upon administration of the non-selective A_1/A_{2A} receptor antagonist caffeine for 7 days (Daly et al 1994). As can be seen by the small number of studies completed, it is difficult at this stage to confirm or deny a role for the A_{2A} receptor in ethanol-induced alterations in locomotor activity. This uncertainty extends to locomotor sensitisation, an experimental paradigm in which elevations in locomotor activity are observed after chronic administration of drugs of abuse, such as ethanol. To date there have been no studies undertaken examining the role of adenosine in ethanol-induced locomotor sensitisation.

The involvement of the A_{2A} receptor in voluntary and forced ethanol consumption in mice is also unclear. In a study where mice were forced to consume ethanol, intake was increased by the subchronic administration of the A_{2A} receptor antagonist ZM 241385 (El Yacoubi et al 2001). Furthermore, at specific concentrations of ethanol (6 and 20% v/v in male mice; 6 and 10% in female mice), A_{2A} receptor knockout mice were found to exhibit a phenotype of increased ethanol preference and consumption (Naassila et al 2002). In a study of A_{2A} receptor knockout mice completed in our laboratory, however, there was no significant phenotype concerning the free-choice consumption of a 5% (v/v) ethanol solution. The absence of an observable effect of A_{2A} receptor deletion upon free-choice consumption of ethanol was consistent across the different background strains examined (CD-1, C57Bl/6J and mixed CD-1/C57Bl/6J) (Short et al 2006c and unpublished data), although as always the influence of A_{2A} receptors upon ethanol consumption may be dependent upon the experimental design.

Operant paradigms whereby rats are trained to self administer ethanol have revealed a role for A_{2A} receptors in the mediation of ethanol consumption, although the consequences of A_{2A} receptor blockade are not consistent with the data obtained in mouse drinking studies. Administration of 10 mg kg^{-1} 3,7-dimethyl-1-propargylxanthine (DMPX) reduced ethanol responding in rats (although in one study responding was enhanced upon administration of a lower dose of DMPX) (Arolfo et al 2004; Thorsell et al 2007). The reduction in active lever presses for ethanol upon administration of an A_{2A} receptor antagonist was also replicated using SCH 58261 (Adams et al 2008). These studies indicate that A_{2A} receptor activation is required in the process by which rats actively press a lever in order to receive an infusion of ethanol. Unfortunately, the three studies described above represent the only area in which work has been done to assess the role of the A_{2A} receptor in

the more complicated behaviours involved in ethanol consumption and ethanol-seeking. At this point, it should also be acknowledged that there are inherent issues when comparing data from receptor knockout mice and antagonist studies, with germline genetic ablation of a receptor representing a model more aligned with chronic receptor antagonism. The resultant phenotype, therefore, may reflect compensatory processes during development, which potentially mask or understate the contribution of the deleted receptor.

Evidence exists for a functional role of the A_{2A} receptor in the consequences of chronic ethanol administration, although the data are ambiguous. Administration of the A_{2A} receptor agonist 2-[4-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido]adenosine (CGS 21680) reduces the severity of the withdrawal signs observed after the discontinuation of a chronic ethanol diet (20–30 g kg^{-1} daily, over 14 days) (Kaplan et al 1999). This possibly indicates that during chronic exposure to ethanol changes in adenosine signalling mediated via the A_{2A} receptor are occurring. Conversely, reduced ethanol-induced seizures were observed in A_{2A} receptor knockout mice and wild-type mice following administration of the A_{2A} receptor antagonist ZM 241385 (El Yacoubi et al 2001), indicating that the role played by A_{2A} receptors in the ethanol withdrawal syndrome is far from clear.

Proposed mechanisms by which A_{2A} receptors modulate ethanol reinforcement: interactions with other receptor systems

The data linking ethanol administration and elevation in extracellular adenosine through the mechanisms outlined in the earlier section has provided evidence for the role of A_{2A} receptors in the acute effects of ethanol. The mechanism by which A_{2A} receptor activation may influence ethanol-induced behaviour is unclear, although several A_{2A}-receptor-mediated effects and interactions with other receptor systems have been proposed. The role of the A_{2A} receptor may simply be to facilitate the release of neurotransmitters such as glutamate and ACh. Deletion or pharmacological blockade of the A_{2A} receptor would thus be expected to decrease the availability of glutamate in the nucleus accumbens. This scenario would be expected to inhibit processing of cortical-driven information related to the association of environmental contexts and drug-induced effects mediated via the mesolimbic pathway. In addition, there is evidence that A_{2A} receptor activation decreases the functionality of the A_1 receptor (Dixon et al 1997; O'Kane & Stone 1998; Lopes et al 1999, 2002). This allows the potential for A_{2A}-receptor-mediated drug effects to occur because of the surmounting of a basal inhibitory A_1-receptor-driven effect. Under this scenario, pharmacological blockade or ablation of the A_{2A} receptor would be expected to allow an inhibitory A_1-receptor-mediated effect upon processing to occur, with the likely outcome of reduced glutamate availability (and other neurotransmitters).

The first intersection of adenosine and ethanol involves the described adenosine–dopamine interaction as proposed by Ferré and colleagues nearly 20 years ago. As discussed in the Introduction, the increase in dopamine release and signalling produced following administration of drugs of abuse, such as ethanol, has been accepted as an important step in the reinforcement processes leading to the development of an addicted state. Administration of dopamine D_1 and D_2 receptor antagonists has been shown to reduce ethanol seeking in rodents (e.g. Hodge et al 1997), an effect supported by data in dopamine receptor knockout mice. D_2 receptor knockout mice exhibit decreased responding for ethanol in an operant paradigm, and a reduced ethanol-induced place preference (Cunningham et al 2000; Risinger et al 2000), further confirming the role of this receptor in motivational and reward responses related to ethanol intake.

By far the bulk of behavioural and functional evidence concerning A_{2A} and D_2 receptor interactions has supported an antagonistic interaction, whereby binding at the A_{2A} receptor resulted in decreased dopaminergic transmission mediated via the D_2 receptor (Ferré et al 1997). Negation of the A_{2A} receptor-mediated antagonism of D_2 receptors (by receptor deletion or pharmacological antagonists) would therefore be expected to enable or enhance D_2 receptor responses, resulting in an increased rewarding efficacy and, perhaps, increased ethanol consumption. Indeed, as discussed in the previous section, in the study by Naassila et al (2002) A_{2A} receptor knockout mice were found to exhibit increased ethanol preference and consumption. The authors proposed several hypotheses for the alterations in ethanol-related behaviour observed in A_{2A} receptor knockout mice. Based on the previously reported hypodopaminergic tone in these mice, possible explanations included a loss of A_{2A} receptor-mediated regulation of dopamine release, or the loss of A_{2A} and dopamine receptor interactions (Naassila et al 2002). Indirect evidence for a relevant interaction between these two receptor systems is also provided neurochemically, with an elevation in striatal A_{2A} receptor expression observed in D_2 and D_3 (also a member of the D_2-like receptor family) receptor knockout mice (Short et al 2006c).

At present, while the antagonistic relationship between A_{2A} and D_2 receptors as described by Ferré and others has been supported in several experimental contexts, the link between ethanol intake and adenosine–dopamine interactions seems more supportive of a positive interaction between A_{2A} and D_2 receptors. Inoue et al (2007) have previously demonstrated a synergy between A_{2A} and D_2 receptors concerning ethanol-induced activation of accumbal neurons. As discussed previously, the spatial association of A_{2A} and D_2 receptors can facilitate not only a direct heteromer interaction but also interactions that may occur at the intracellular signalling level (Yao et al 2002; Arolfo et al 2004; Inoue et al 2007). In neurons containing activator of G protein signalling 3 (ASG3), D_2 receptor agonists are able to produce stimulatory effects, but only when A_{2A} receptors are coincidentally activated (Yao et al 2002, 2003). A_{2A} receptor antagonists have been shown to reduce ethanol responding in rats (Arolfo et al 2004; Thorsell et al 2007; Adams et al 2008), and the explanation for this reduction in ethanol consumption is more likely to result from the positive, rather than antagonistic, relationship between A_{2A} and D_2 receptors.

As with D_2 receptor knockout mice, genetic deletion of the D_1 receptor also reduces ethanol preference and consumption (El-Ghundi et al 1998; Short et al 2006b). In our laboratory, while ethanol consumption was not altered in A_2 receptor-deficient mice (as described earlier in this review), in the combined D_1A_{2A} receptor knockout ethanol consumption was reduced to a further extent than that observed in D_1 receptor knockout mice (Short et al 2006b). Although not co-localised on striatal output neurons, these findings indicate a perhaps 'network' interaction between D_1 and A_{2A} receptors relevant to ethanol reinforcement, with this hypothesis supported by the upregulation of striatal A_{2A} receptors in D_1 receptor-deficient mice (Short et al 2006b). Another explanation is that deletion of the A_{2A} receptor has removed an A_{2A}–D_2 receptor synergism that supported an overall synergistic relationship between D_1 and D_2 receptors to promote ethanol seeking.

In addition, synergistic A_{2A} and mGlu5 receptor interactions have been demonstrated (e.g. Popoli et al 2001; Diaz-Cabiale et al 2002; Ferré et al 2002; Fuxe et al 2003; Coccurello et al 2004; Domenici et al 2004; Kachroo et al 2005; Tebano et al 2005). Furthermore, the formation of heteromers between A_{2A} and mGlu5 receptors (and resultant synergistic interactions) can further alter dopamine-mediated signalling, creating an extra layer of complexity. As discussed by Adams et al (2008), endogenous adenosine activation of the A_{2A} receptor may potentiate the action of glutamate, allowing activation of the receptor complex at a lower concentration. This hypothesis was supported in an operant responding paradigm, where administration of subthreshold doses of the A_{2A} receptor antagonist SCH 58261 with the mGlu5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine (MTEP) significantly reduced ethanol self administration, increased the latency to the first lever press, and reduced reinstatement of ethanol-seeking behaviour.

Ethanol and adenosine: summary

As described above and summarised in Table 2, there is much evidence supporting a role for adenosine and A_{2A}-receptor-mediated effects in the acute and chronic effects of ethanol. Data from several research groups have suggested the mechanism of A_{2A} receptor involvement could be via an interaction with dopaminergic, especially D_2 receptor, processing. Interactions with other receptors such as D_1, A_1 and mGlu5 have also been postulated; however, the delineation of A_{2A} receptor effects mediated via receptor interactions and those occurring via independent mechanisms remains to be ascertained. Furthermore, a review of the literature reveals that studies examining the role of the A_{2A} receptor in more complicated behavioural paradigms designed to examine ethanol reinforcement, re-administration and prolonged use are long overdue.

Opiates

Mechanism of action

The rewarding effects of opiate drugs such as heroin and morphine are primarily due to actions on μ-opioid receptors (Contet et al 2004). μ-Opioid receptors are linked to G_i proteins and upon activation cause inhibition of the cAMP/protein kinase A (PKA)/cAMP response element binding protein (CREB) pathway, increased K^+ conductance and inhibition of Ca^{2+} conductance (Williams et al 2001). μ-Opioid receptor activation ultimately leads to an increase in the firing rate of midbrain dopaminergic neurons. This effect is mediated via inhibition of GABAergic interneurons within the ventral tegmental area (VTA) and results in enhanced release of dopamine in the nucleus accumbens (Johnson & North 1992). In addition to being located on GABAergic interneurons both in the VTA and nucleus accumbens, μ-opioid receptors are co-localised with D_1 receptors on striatonigral medium spiny neurons (Mansour et al 1995; Georges et al 1999). Also located on striatonigral neurons are adenosine A_1 receptors. In contrast, as mentioned previously, A_{2A} receptors are predominantly located on striatopallidal medium spiny neurons where they are co-localised with D_2 receptors.

The link between opiates and adenosine signalling

There exists an extraordinary amount of literature, spanning some 30 years, describing the link between opiates and adenosine signalling (refer to Table 3 for summary). Opioids and adenosine are alike in that they both inhibit neurotransmitter release (see Introduction and Ginsborg & Hirst 1972; Henderson & Hughes 1976; Ribeiro et al 1979). Morphine- and adenosine-mediated inhibition of ACh release is blocked by the non-selective adenosine antagonist theophylline (Sawynok & Jhamandas 1976), suggesting that these two neurotransmitter systems interact in some way. Opiates have been found to elevate adenosine levels in the CNS and spinal cord (Fredholm & Vernet 1978; Stone 1981; Sweeney et al 1993; Cahill et al 1996), leading to the proposition that adenosine could be involved directly in mediating the effects of opiates. This contention is supported by numerous behavioural data demonstrating cross-regulation by the two transmitter systems. Sweeney et al (1993) reported that the opiate-induced elevation in adenosine is mediated by a dipyridamole- and nitrobenzylthioinosine (NBTI)-sensitive transporter in the spinal cord, and neurochemical studies (discussed in the following section; see Figure 4) suggest this would also be the case in the brain. The observation that opiate-induced adenosine release is dependent on transport via the bi-directional nucleoside transporter suggests that adenosine efflux from the cell is occurring, perhaps as a result of increased ATP due to increased neuronal activity. Thus, while opiates are able to increase the release of dopamine, adenosine levels may be enhanced concomitantly (Figure 4).

With repeated administration, opiates cause a decrease in adenosine reuptake in striatal cell extracts, presumably via inhibition of adenosine transport. This decrease in reuptake is associated with increased levels of extracellular adenosine (Halimi et al 2000). In agreement is the finding that subchronic doses of morphine decrease striatal A_{2A} receptor number and function in rats (De Montis et al 1992), presumably as a consequence of increased levels of extracellular adenosine. Brundege & Williams (2002) reported increased sensitivity to exogenously applied adenosine at excitatory synapses in the nucleus accumbens

Table 3 The role of adenosine in opiate-induced effects upon behaviour and function, with a focus on pharmacological data and rodent models implicating the A_{2A} receptor

Behavioural or functional effect of opiate	Pharmacological evidence for the involvement of adenosine signalling	References
Opiate-induced elevations in extracellular adenosine	Morphine causes release of endogenous adenosine from spinal cord via NTBI-sensitive transporters Supraspinally administered morphine enhances adenosine release in the cortex in-vitro and in-vivo Chronic μ-opioid receptor activation inhibits adenosine reuptake in striatal cell extracts Chronic morphine causes upregulation of NBTI-sensitive adenosine transporter binding sites Increased sensitivity to exogenous adenosine at excitatory synapses in the NAc following chronic morphine	Fredholm & Vernet 1978; Phillis et al 1980a, b; Stone 1981; Sweeney et al 1987, 1993; Kaplan & Leite-Morris 1997; Halimi et al 2000; Brundege & Williams 2002
Opiate-induced catalepsy	Modulated by adenosine ligands: potentiated by adenosine agonists NECA, S-PIA, high dose CHA and the non-selective antagonist 8PT Decreased by non-selective antagonist theophylline, low dose CHA	Zarrindast et al 1997
Opiate-induced hypotension	Decreased by non-selective adenosine antagonist 8PT and A_1 antagonist DPCPX, but not A_2 antagonist DMPX	White et al 1995a, b
Opiate-induced respiratory depression	Reduced by non-selective antagonist caffeine	Bellville et al 1962
Opiate-induced anti-nociception	Adenosine and adenosine analogues potentiate, while methylxanthines inhibit morphine-induced anti-nociception Decreased in A_1 receptor knockout mice Cross tolerance and cross withdrawal between DAMGO (opiate agonist) and CPA (A_1 receptor agonist)	Ahlijanian & Takemori 1985; Contreras et al 1990; Malec & Michalska 1990; Aley et al 1995; Wu et al 2005
Forced swim test	Potentiation of the anti-depressant effect of sub-threshold adenosine by morphine	Kaster et al 2007
Acute locomotor response to morphine	No change in A_{2A} receptor knockout compared to wild-type	Brown et al 2008
Tolerance to locomotor effects	Absent in A_{2A} receptor knockout compared to wild-type	Brown et al 2008
Opiate self-administration (operant)	Reduced by DMPX, increased by CGS 21680 Decreased in A_{2A} receptor knockout mice compared to wild-type	Sahraei et al 1999; Brown et al 2008
Opiate seeking (operant)	Reinstatement blocked by DMPX (intra-NAc and systemically) Cue-induced opiate seeking maintained in A_{2A} receptor knockout after 3 week withdrawal period	Yao et al 2006; Brown et al 2008
Opiate-induced conditioned place preference	Absent in A_{2A} receptor knockout compared to wild-type	Brown et al 2008
Sensitisation to opiates	PACPX, an A_1 receptor selective antagonist and caffeine inhibit the development of morphine sensitisation in mice Morphine sensitisation maintained in A_{2A} receptor knockout mice	Weisberg & Kaplan 1999; Brown et al 2008
Withdrawal	Decreased by 5′-amino-5′-deoxyadenosine and 5-iodotubericidin (adenosine kinase inhibitors) and R-PIA, CGS 21680, CPA, CHA Increased by antagonists DPCPX, DMPX, IBMX, 8PT, aminophylline Enhanced in A_{2A} receptor knockout mice	Kaplan & Sears 1996; Salem & Hope 1997; Zarrindast et al 1997; Kaplan & Coyle 1998; Berrendero et al 2003; Bailey et al 2004
Quasi-morphine withdrawal syndrome	Methylxanthines produce syndrome identical to naloxone-induced morphine withdrawal syndrome in opiate-dependent rats Absent in A_{2A} receptor knockout mice	Butt et al 1979; Bilbao et al 2006
Morphine state-dependent memory of passive avoidance	Decreased by theophylline and 8-PT; increased by CHA or R-PIA and NECA Low doses of CHA, R-PIA, or NECA show additive effects with low dose morphine in restoring memory	Khavandgar et al 2002

CGS 21680, 2-[4-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido]adenosine; CHA, N^6-cyclohexyladenosine; CPA, N^6-cyclopentyladenosine; DAMGO, [D-Ala^2, *N*-MePhe^4, Gly-ol^5]enkephalin; DMPX, 3,7-dimethyl-1-propargylxanthine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; IBMX, 3-isobutyl-1-methylxanthine; NAc, nucleus accumbens; NBTI, nitrobenzylthioinosine; NECA, 5′-*N*-ethylcarboxamido-adenosine; PACPX, 1,3-dipropyl-8-(2-amino-4-chlorophenyl)-xanthine; 8-PT, 8-phenyltheophylline; R-PIA, R(-)-N^6-(2-phenylisopropyl)adenosine; S-PIA (L-PIA), (S(+)-N^6-(2-phenylisopropyl)adenosine.

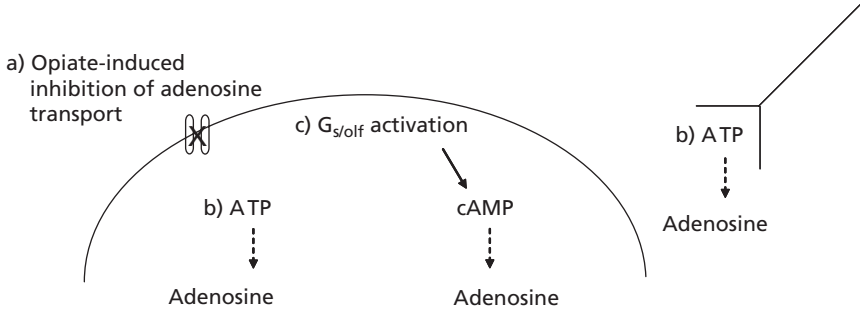

Figure 4 Potential ways in which adenosine levels may be increased following opiate administration. (a) Inhibition of the dipyridamole- and nitrobenzylthioinosine (NBTI)-sensitive transporter by opiates prevents influx of adenosine and thus increases the availability of adenosine for receptor binding. (b) In response to opiates, enhanced activity of dopaminergic or glutamatergic inputs or intrinsic GABAergic neurons may result in increased adenosine triphosphate (ATP) intracellularly and extracellularly, and thus increased adenosine as outlined in Figure 2. (c) Activation of a receptor positively coupled to cyclic adenosine monophosphate (cAMP) as a second messenger (e.g. dopamine D_1 receptors) will cause increases in cAMP and ultimately increased levels of intracellular adenosine.

following chronic morphine, an effect that was prevented by blocking adenosine transport. The authors explain that nucleoside transporters do not usually operate at saturation point (Dunwiddie & Diao 1994), and thus in naïve tissue any exogenously applied adenosine is preferentially transported into the cell and metabolised, with little reaching the receptors. With chronic opiate administration on the other hand, exogenous adenosine has a greater effect on nucleus accumbens slices (the dose–response curve is shifted to the left). In apparent conflict is the observation that chronic morphine administration upregulates NBTI-sensitive nucleoside transporter binding sites in mice (Kaplan & Leite-Morris 1997), though in this study the nucleus accumbens was not examined and only NBTI binding was assessed, thus any changes in dipyridamole-sensitive NBTI-insensitive transporter binding sites could not be measured.

Chronic administration of opiates causes long-lasting cellular, molecular and neuronal adaptations which lead to tolerance and ultimately addiction. Specifically, chronic administration of opiates causes upregulation of the AC/cAMP/PKA/CREB pathway (Nestler 1996). Adenosine is synthesised from the breakdown of cAMP, both inside and outside the cell (Hack & Christie 2003), hence implicit in adenylate cyclase/cAMP upregulation is a concomitant increase in adenosine. Upon withdrawal from opiates cAMP superactivation occurs as the influence of the agonist has been removed (Nestler 1996). This cAMP is metabolised to adenosine and is transported out of the cell, acting on adenosine receptors. This hypothesis is supported by the observation of increased levels of adenosine metabolites in striatal and accumbal dialysate during opiate withdrawal in rats (Salem & Hope 1999).

In-vivo behavioural and functional evidence for the involvement of adenosine signalling in opiate effects

Further evidence exists to support the involvement of adenosine in mediating the acute effects of opiates. Adenosine antagonists decrease the manifestation of many of the acute effects of opiate drugs, such as catalepsy (Zarrindast et al 1997), hypotension (White et al 1995a, b), respiratory depression (Bellville et al 1962) and anti-nociception (Ahlijanian & Takemori 1985). Experiments with agonists have shown the inverse to be the case. Firstly, the catalepsy-inducing effects of morphine are potentiated by the adenosine agonists 5′-*N*-ethylcarboxamido-adenosine (NECA), S(+)-N^6-(2-phenylisopropyl)adenosine (S-PIA) and high-dose N^6-cyclohexyladenosine (CHA) (Zarrindast et al 1997). One study examining the impact of adenosine ligands on morphine state-dependent memory of passive avoidance found that adenosine agonists had a promnesiac effect similar to morphine in the task, which was reversed by non-selective antagonists (Khavandgar et al 2002). This indicates that adenosine receptor activation following opiate administration may be important for the state-dependent cognitive effects of morphine. Adenosine and its analogues have also been found to potentiate opiate-induced anti-nociception when injected systemically (Ahlijanian & Takemori 1985; Contreras et al 1990; Malec & Michalska 1990). In the case of nociception, the A_1 receptor appears to play a role, with opiate-induced anti-nociception found to be reduced in A_1 knockout mice (Wu et al 2005) and cross-tolerance and withdrawal occurring between the A_1 agonist N^6-cyclopentyladenosine (CPA) and μ-opiate agonist [D-Ala^2, *N*-MePhe^4, Gly-ol^5]enkephalin (DAMGO). Further studies exploring the role of the A_{2A} receptor would be of benefit.

An additive memory-restoring effect of adenosine agonists and morphine was observed in the passive avoidance task, as described above, and this effect was blocked by theophylline and naloxone (Khavandgar et al 2002). Another interesting example of adenosine–opioid synergy is a recent study in which morphine potentiated the antidepressant effect of a subthreshold dose of adenosine in the forced swim test (Kaster et al 2007). These authors also observed that the antidepressant effect of adenosine was blocked by naloxone, providing evidence that the endogenous opioid system potentially plays a role in mediating the central effects of adenosine.

Despite the above data demonstrating the involvement of adenosine in many of the effects of opiates, it does not appear to have a role in mediating the acute locomotor response to opiates. Both 1,3-dipropyl-8-(2-amino-4-chlorophenyl)-xanthine (PACPX; an A_1 receptor antagonist) and caffeine

have no effect on the acute locomotor response to morphine in C57/BL6 mice (Weisberg & Kaplan 1999), and there is no difference between A_{2A} knockout and wild-type mice with respect to their acute locomotor response to morphine (Brown et al 2008). There does appear to be a role for the A_{2A} receptor in the development of tolerance to the locomotor-activating properties of morphine, however, as this does not occur in mice lacking the A_{2A} receptor (Brown et al 2008). Interestingly, one study has found an increase in sensitivity to the locomotor-activating properties of caffeine in morphine-treated mice (Ahlijanian & Takemori 1986).

The studies described in the previous section suggest that adenosine plays a predominantly facilitative role in the mediation of the effects of opiates. Not surprisingly, this has been found to be the case regarding the mediation of the rewarding effects of opiates also. When administered during acquisition, the A_{2A} receptor antagonist DMPX reduces morphine self-administration in rats while CGS 21680, a selective A_{2A} receptor agonist, increases morphine self-administration (Sahraei et al 1999). In agreement with a role for A_{2A} receptors in the mediation of opioid reward processes is the observation of decreased morphine self-administration and conditioned place preference in mice lacking the A_{2A} receptor. A_{2A} knockout mice also display a reduced break-point on a progressive ratio schedule, indicating a reduced motivation to self-administer morphine (Brown et al 2008).

Repeated exposure to opiates causes an increase in motor stimulation induced by a subsequent dose, an effect known as sensitisation (Babbini & Davis 1972; Lett 1989). This behavioural sensitisation is believed to reflect some of the motivational aspects of drug addiction, such as incentive motivation and drug-seeking (Robinson & Berridge 1993). Previous work has demonstrated a definitive role for glutamate, but not necessarily dopamine, in behavioural sensitisation to opiates (Vanderschuren & Kalivas 2000). One study has shown that both caffeine and an A_1 receptor antagonist inhibit the development of morphine sensitisation in mice (Weisberg & Kaplan 1999), and thus it is possible that sensitisation to morphine is facilitated by adenosine acting at A_1 receptors. In mice lacking the A_{2A} receptor, however, sensitisation is maintained (Brown et al 2008). Compensation in the case of A_{2A} receptor knockout mice cannot be ruled out and, as yet, there are no studies using A_{2A}-specific ligands, thus the role of the A_{2A} receptor in morphine sensitisation and this facet of drug-induced plasticity remains unclear.

As with sensitisation, reinstatement of drug-seeking is mediated by activation of corticostriatal afferent inputs into the basal ganglia (Kalivas & McFarland 2003). In humans, drug-associated stimuli play an important role in drug relapse after prolonged abstinence and the cue-induced reinstatement paradigm models this formation of contextual or cued associations with drugs of abuse. Like sensitisation, drug-seeking behaviour is a result of neuroadaptations that occur over time with repeated drug administration. Drug-seeking behaviour is associated with increased glutamate release in the nucleus accumbens and requires NMDA receptor stimulation at cortico-accumbal synapses (Kalivas & Volkow 2005). A recent study reported that the A_{2A} receptor antagonist DMPX reduced reinstatement of heroin seeking in rats when infused directly into the nucleus accumbens or injected systemically (Yao et al 2006). In a different model of drug-seeking behaviour, A_{2A} knockout mice exhibited robust cue-induced drug-seeking after a period of withdrawal (Brown et al 2008). This raises the possibility of a differential role for the A_{2A} receptor in the neuroadaptations that occur in these two different drug-seeking paradigms.

A role for adenosine has been demonstrated in opiate withdrawal. Adenosine agonists reduce, and antagonists increase, symptoms associated with opiate withdrawal (Kaplan & Sears 1996; Salem & Hope 1997). Increased levels of adenosine metabolites have been reported during opiate withdrawal in rats (Salem & Hope 1999). Adenosine kinase inhibitors significantly reduce morphine withdrawal symptoms in mice, an effect which can be blocked by the adenosine antagonist caffeine (Kaplan & Coyle 1998), suggesting that the amelioration of withdrawal symptoms is due to activation of A_1 or A_{2A} receptors by adenosine. In agreement with these findings, two studies have found an enhancement in the expression of some morphine-withdrawal signs in morphine-dependent A_{2A} knockout mice (Berrendero et al 2003; Bailey et al 2004). This implicates the A_{2A}, as opposed to A_1, receptor in opiate withdrawal. Interestingly, it was discovered in 1979 that blockade of adenosine receptors in opiate-dependent rodents produced symptoms similar to those observed during opiate withdrawal (Butt et al 1979), a behavioural phenomenon termed 'quasi morphine withdrawal syndrome', since demonstrated to be mediated via the A_{2A} receptor (Bilbao et al 2006).

Proposed mechanisms by which A_{2A} receptors modulate opiate reinforcement: interactions with other receptor systems

The dopamine D_2 receptor appears to play a pivotal role in the mediation of opioid reward. Thus, D_2 knockout mice fail to self-administer opiates (Elmer et al 2002) and fail to develop a conditioned place preference to morphine (Maldonado et al 1997). As discussed previously, there is an abundance of literature supporting interactions between A_{2A} and D_2 receptors, and therefore a role for the A_{2A} receptor in opiate reward can be reasonably posited. As described in the previous section, administration of DMPX reduces, while CGS 21680 increases, morphine self-administration in rats (Sahraei et al 1999). In agreement with a role for A_{2A} receptors in the mediation of opiate reward processes is the observation of decreased morphine self-administration and conditioned place preference in mice lacking the A_{2A} receptor (Brown et al 2008). These studies are consistent with a D_2–A_{2A} synergistic rather than antagonistic interaction, as a reduction in the rewarding properties of morphine is observed when A_{2A} receptor function is impaired. Further support for a positive interaction is garnered by the observation that A_{2A} receptor antagonists abolish synergy on PKA signalling between opioid and D_2 receptors (Yao et al 2003). The dopamine- and cAMP-regulated phosphoprotein, M(r) 32 kDa (DARPP-32) is a downstream effector molecule of D_2 receptors, and it has been shown that the A_{2A} antagonist SCH 58261 counteracts the increase in threonine 34 (Thr34)-DARPP-32 phosphorylation observed following treatment with selective D_2 receptor

antagonists (Svenningsson et al 2000). This is particularly relevant in the context of morphine reward as DARPP-32 phosphorylation at Thr34 is increased following morphine administration (Lindskog et al 1999).

Though much evidence points towards a key role for dopamine in mediating the reinforcing effects of opiate drugs, dopamine-independent mechanisms of reward have been proposed (Bechara et al 1998). One possible candidate is the CB_1 receptor, which is co-expressed with μ-opioid receptors in the nucleus accumbens (Pickel et al 2004). A_{2A} receptors have been shown to form heteromers with CB_1 receptors and, using in-vitro neuroblastoma models, CB_1 signalling has been shown to be dependent on A_{2A} receptor activation (Carriba et al 2007). Recently, Yao et al (2006) demonstrated that A_{2A} receptor blockade prevents synergy between μ-opioid and CB_1 receptor signalling, which implicates an A_{2A} receptor-dependent CB_1-mediated mechanism of opiate reward. This interaction between opioid, CB_1 and A_{2A} receptors in relation to opiate reward is supported at a behavioural level by the observation of increased morphine withdrawal in A_{2A} knockout mice but no change in A_{2A}–CB_1 double knockout mice (Berrendero et al 2003). Further studies with these mice would be beneficial. Significant interactions between A_{2A} and CB_1 receptors point also to a role for the A_{2A} receptor in mediating the rewarding effects of Δ^9-tetrahydrocannabinol (THC). Indeed, a reduction in conditioned place preference to THC was found as a result of A_{2A} receptor deletion as well as the attenuation of somatic manifestations of CB_1 antagonist-precipitated withdrawal (Soria et al 2004).

Both behavioural sensitisation and drug-seeking behaviour are associated with increased glutamatergic transmission (Vanderschuren & Kalivas 2000; Kalivas & Volkow 2005), and release of glutamate from cortico-accumbal neurons drives the long-term neuroadaptive changes that cause this behaviour. Presynaptic A_{2A} receptors are located on cortical glutamatergic afferents projecting to the nucleus accumbens and form heteromers with mGlu5 receptors (Ferré et al 2002) and A_1 receptors (Ciruela et al 2006) (Figure 1). A_{2A} receptors modulate glutamatergic input to the nucleus accumbens via interactions with these other receptors. As discussed previously, pharmacological studies have shown that adenosine antagonists block both opiate sensitisation (via A_1 or A_1/A_{2A} receptors) and reinstatement of opiate-seeking (via A_{2A} receptors). This implicates adenosine in the pathophysiological changes in this glutamatergic pathway that result in compulsive drug-seeking behaviour and sensitisation. Presynaptic A_{2A} receptors interact synergistically with mGlu5 receptors, presumably in the form of heteromers (Ferré et al 2002), and regulate striatal glutamatergic input. A_{2A} receptors also form heteromers with A_1 receptors, thus allowing for fine-tuning modulation of glutamatergic transmission in the striatum (Ciruela et al 2006). Decreased opiate-seeking upon administration of a selective A_{2A} receptor antagonist is possibly a consequence of blockade of these facilitatory presynaptic A_{2A} receptors. Blockade of presynaptic A_{2A} receptors would presumably prevent A_{2A}–mGlu5 synergy and result in an A_1-mediated inhibition of the increased glutamate release that occurs in cortico-accumbens circuitry upon reinstatement of drug seeking (Kalivas & Volkow 2005). Studies with knockout mice have not been consistent with pharmacological data however, as A_{2A} knockout mice exhibit robust opiate-seeking behaviour after a period of withdrawal and also maintain sensitisation to opiates (Brown et al 2008). The possibility exists that reorganisation of A_{2A}–D_2 and/or A_{2A}–mGlu5 heteromer 'mosaics' may occur as a form of developmental compensation in knockout mice, leading to the differential modulation of dopaminergic and glutamatergic transmission. Indeed, basal dopamine levels are decreased and glutamate levels are increased in A_{2A} knockout mice (Dassesse et al 2001), while antagonist studies yield conflicting results with respect to the modulation of dopamine and glutamate levels (Marcoli et al 2003; Domenici et al 2004; Golembiowska & Dziubina 2004; Rodrigues et al 2005).

Opiates and adenosine: summary

The data presented and reviewed above support a facilitative role for adenosine in opiate reward and reinforcement as well as opiate-seeking behaviour. Although this role appears to be predominantly mediated via the A_{2A} receptor, further studies are required with more A_{2A}-specific ligands and conditional knockout mouse models for confirmation. In addition, it is yet to be determined whether adenosine influences opiate reward via direct interactions with the opioidergic system or indirectly via interactions with other neurotransmitter systems such as dopamine, cannabinoids or glutamate.

Psychostimulants

Mechanism of action

Cocaine causes an increase in extracellular dopamine by blocking reuptake by the dopamine transporter (DAT) (Wise 1996a; Andrews & Lucki 2001) and an increase in the level of glutamate, an effect which appear dependent on D_1 receptor activation (Kalivas & Duffy 1995). Amphetamines also increase extracellular dopamine, binding as a false substrate to DAT and hence promoting reverse transport of dopamine (Seiden et al 1993). This net increase in extracellular dopamine is thought to underpin the rewarding properties of psychostimulant drugs. Indeed, the role of dopamine in mediating the actions of psychostimulants is firmly established and has been thoroughly reviewed elsewhere.

The link between psychostimulant signalling and adenosine

There does not appear to be the same direct interaction with adenosine in the case of psychostimulant signalling as there is with opiates, as any potential involvement is inherently associated with influences on dopamine or glutamate transmission. As described above, psychostimulants exert their rewarding effects via direct elevation of extracellular dopamine in the nucleus accumbens. Dopamine acts on dopamine D_1 receptors, which are positively coupled to adenylate cyclase; hence, D_1 receptor activation causes an increase in cAMP (Hack & Christie 2003). As discussed previously, adenosine is synthesised from the breakdown of cAMP both inside and outside the cell (Hack & Christie 2003). Thus, activation of D_1 receptors as a consequence of psychostimulant administration presumably causes a

subsequent rise in adenosine. Indeed, a small number of studies exist supporting this possible link between psychostimulant signalling and adenosine (refer to Table 4 for more detail). Increased adenosine tone in the VTA has been found with repeated cocaine treatment in both guinea-pig (Bonci & Williams 1996) and rat (Fiorillo & Williams 2000) when slices were compared with those from saline-treated animals. The former study showed that with repeated D_1 stimulation, levels of cAMP are increased. This cAMP is metabolised to adenosine and causes presynaptic inhibition of transmitter release via A_1 receptors. Administration of the D_1 antagonist 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) blocked the effects of 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (RO 201724), an inhibitor of cAMP-dependent phosphodiesterase, on the GABA-mediated inhibitory post synaptic potential (IPSP), suggesting that activation of D_1 receptors maintained a level of cAMP in order to provide this source of adenosine (Bonci & Williams 1996).

A different study by Manzoni et al (1998) examined the involvement of adenosine in glutamate transmission in the nucleus accumbens following repeated cocaine administration. The same increase in extracellular adenosine was not observed in this brain region, demonstrating the regional specificity of these psychostimulant-induced adaptations. Interestingly, the potency of adenosine to presynaptically inhibit glutamate release was found to be reduced upon withdrawal from cocaine (Manzoni et al 1998). This reduction in potency was shown to be a result of increased adenosine reuptake as blockade of adenosine transport by NBTI and dipyridamole returned the response to that seen in naïve animals. As with the two studies discussed previously, the source of the adenosine seemed to be cAMP, as inhibition of cAMP-dependent phosphodiesterase considerably reduced the extracellular accumulation of adenosine caused by the uptake blockers (Manzoni et al 1998). These data suggest that cocaine withdrawal causes an upregulation in adenosine transport via an undetermined mechanism. This is consistent with the observation that transporter binding sites are upregulated following morphine treatment in mice (Kaplan & Leite-Morris 1997), though is in conflict with the majority of the other literature concerning opiates (opiates decrease adenosine transport, thereby increasing extracellular adenosine, see section on opiates, above). An increase in functional A_{2A} receptors following chronic cocaine and disappearance by day 7 of withdrawal suggest that plasticity is occurring in terms of these effects on adenosine transport and signalling (Marcellino et al 2007). Indeed, previous authors have suggested the adenosine transporter may be a common target for drug of abuse-induced plasticity (Manzoni et al 1998). The valency of these interactions in the nucleus accumbens is, however, in contrast with those put forward in the previous section (see references therein) for opiates. Opiate administration appears to increase the level of extracellular adenosine via blockade of adenosine transport (hence causing downregulation of A_{2A} receptor number and function). Upon withdrawal from opiates an increase in adenosine is observed, presumably due to the superactivation of cAMP following upregulation of the AC/cAMP/PKA pathway with repeated opiate use. In the case of psychostimulants, increased adenosine tone is observed in the VTA but not nucleus accumbens with repeated administration. Increased adenosine transport is observed upon psychostimulant withdrawal, which reduces the ability of adenosine to presynaptically inhibit glutamate release. Increased functional A_{2A} receptors are observed, presumably as a result of increased adenosine transport, though this upregulation has disappeared by day 7 of withdrawal.

In addition, Harvey & Lacey (1997) demonstrated that D_1 agonists enhance synaptic activation of NMDA receptors, resulting in elevated extracellular adenosine and subsequent presynaptic inhibition of glutamate release. This suggests that there is a possible role for adenosine in the dopaminergic modulation of glutamatergic input to the nucleus accumbens possibly via complex network interactions with D_1 receptors. This provides another possible mechanism by which adenosine can modulate dopamine-mediated striatal input and hence possibly play a role in psychostimulant signalling.

Collectively, these data suggest that adenosine, through influences on dopamine or glutamate transmission (or both), may be involved in psychostimulant signalling, or at least in the neuronal adaptations that occur with repeated psychostimulant administration and subsequent withdrawal. In addition, established interactions with dopamine receptors provide ample opportunity for adenosine acting at A_{2A} receptors to modulate psychostimulant signalling. These potential interactions will be discussed below.

In-vivo behavioural and functional evidence for the involvement of adenosine signalling in psychostimulant effects

The majority of pharmacological data reporting the effects of A_{2A} receptor blockade support a role for the A_{2A} receptor in mediating the actions of psychostimulants (summarised in Table 4). These data appear to be consistent with A_{2A} receptor activation opposing, and blockade facilitating, the effects of dopamine. Thus, CGS 21680 counteracts stereotypies induced by the dopamine agonist apomorphine and yawning induced by the D_2 selective agonist quinpirole in rats (Rimondini et al 1998). The acute locomotor effects of cocaine and amphetamine are attenuated by A_{2A} receptor agonists (CGS 21680 and 2-[(2-aminoethylamino)carbonylethylphenylethylamino]-5′-*N*-ethylcarboxamidoadenosine (APEC)) and enhanced by A_{2A} receptor antagonists (DMPX and 3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-7-methyl-1-propargylxanthine phosphate disodium salt (MSX-3)) in both rats (Turgeon et al 1996; Rimondini et al 1997; Filip et al 2006) and mice (Poleszak & Malec 2002a).

Indeed, the bulk of the data concerning the role of the A_{2A} receptor in the mediation of psychostimulant reward is in agreement with these findings (summarised in Table 4). Activation of A_{2A} receptors inhibits brain stimulation reward and cocaine withdrawal (Baldo et al 1999) as well as the initiation of cocaine self-administration (Knapp et al 2001), while A_{2A} antagonists enhance cocaine-evoked discriminative stimulus effects (Justinova et al 2003) and reinstate

Table 4 The role of adenosine in psychostimulant-induced effects upon behaviour and function, with a focus on pharmacological data and rodent models implicating the A_{2A} receptor

Behavioural or functional effect of psychostimulant	Pharmacological evidence for the involvement of adenosine signalling	References
Psychostimulant-induced elevations in extracellular adenosine	Repeated cocaine treatment increases adenosine tone in the ventral tegmental area D_1 receptor agonists enhance synaptic activation of NMDA receptors, resulting in elevated adenosine release Repeated cocaine self-administration results in an upregulation of A_{2A} receptors in the nucleus accumbens Cocaine withdrawal produces a decreased presynaptic sensitivity to adenosine	Bonci & Williams 1996; Harvey & Lacey 1997; Manzoni et al 1998; Fiorillo & Williams 2000; Marcellino et al 2007
Acute locomotor response to pyschostimulants	Attenuated by A_{2A} receptor agonists CGS 21680 and enhanced by A_{2A} receptor antagonists MSX-3, DMPX Attenuated in one line of mice lacking the A_{2A} receptor; unchanged in a different A_{2A} receptor knockout Enhanced in striatal-specific A_{2A} receptor knockout; attenuated in forebrain-specific A_{2A} receptor knockout	Rimondini et al 1997; Chen et al 2000; Poleszak & Malec 2002; Filip et al 2006; Soria et al 2006; Shen et al 2008
Psychostimulant-induced stereotypies	Counteracted by CGS 21680 (A_{2A} selective agonist) but not CPA (A_1 selective agonist)	Rimondini et al 1998
Psychostimulant-induced yawning	Counteracted by both CGS 21680 and CPA	Rimondini et al 1998
Psychostimulant-induced psychosis	Phenylcyclidine-induced disruptions in sensorimotor gating reduced by CGS 21680	Wardas et al 2003
Tolerance to locomotor effects	No publications to date	
Psychostimulant self-administration (operant)	Adenosine A_{2A} receptor agonist CGS 21680 inhibits initiation of cocaine self-administration Non-selective antagonist CGS 15943 reinstates cocaine self-administration Decreased upon deletion of A_{2A} receptor	Knapp et al 2001; Weerts & Griffiths 2003; Soria et al 2006
Psychostimulant-seeking (operant)	No publications to date	
Psychostimulant-induced conditioned place preference	Attenuated by A_{2A} receptor antagonist DMPX, A_1 antagonist 8CPT and non-selective antagonist caffeine No alteration in cocaine-induced place preference in A_{2A} receptor knockout mice	Poleszak & Malec 2002b; Soria et al 2006
Sensitisation to psychostimulants	Attenuated in conditional forebrain-specific A_{2A} receptor knockout mice A_{2A} receptor antagonists KW 6002 and SCH 58261 prevent the induction (but not expression) of behavioural sensitisation to amphetamine in one strain of mice; prevents both in another strain CGS 21680 prevents methamphetamine sensitisation Enhanced by A_{2A} receptor antagonist MSX-3, attenuated by A_{2A} receptor agonist CGS 21680 Maintained in a germline strain of mice with a global A_{2A} receptor deletion	Shimazoe et al 2000; Bastia et al 2005; Filip et al 2006; Soria et al 2006
Cocaine withdrawal	Inhibited by A_{2A} receptor agonist CGS 21680	Baldo et al 1999
Brain stimulation reward	Inhibited by A_{2A} receptor agonist CGS 21680	Baldo et al 1999
Cocaine-evoked discriminative stimulus effects	Enhanced by adenosine A_{2A} antagonist MSX-3	Justinova et al 2003

CGS 15943, 9-chloro-2-(2-furyl)[1,2,4]triazolol[1,5-*c*]quinazolin-5-amine; CGS 21680, 2-[4-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido]adenosine; CPA, N^6-cyclopentyladenosine; 8CPT, 8-cyclopentyltheophylline; DMPX, 3,7-dimethyl-1-propargylxanthine; KW 6002, 1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dhydro-1*H*-purine-2,6-dione; MSX-3, 3-(3-hydroxypropyl)-8-(*m*-methoxystryryl)-7-methyl-1-propargylxanthine phosphate disodium salt; NMDA, *N*-methyl-D-aspartic acid; SCH 58261, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-c]-1,2,4-triazolo-[1,5,-c]pyrimidine.

cocaine self-administration (Weerts & Griffiths 2003). Regarding sensitisation, Shimazoe et al (2000) observed that the A_{2A} agonist CGS 21680 prevents methamphetamine sensitisation in rats, and a recent study has shown enhancement of cocaine sensitisation by an A_{2A} receptor antagonist and attenuation by an A_{2A} receptor agonist (Filip et al 2006).

Studies with various A_{2A} knockout mice are in apparent conflict with the above data, yet genetic inactivation represents a model of chronic antagonism, and therefore the results are not necessarily directly comparable with those from acute antagonism of a receptor. In addition, differential effects of striatal versus non-striatal A_{2A} receptors could

potentially explain these discrepancies and will be discussed in a later section. In one study, decreased self-administration of cocaine was observed as a result of global A_{2A} receptor deletion, as well as a reduction in breakpoint or motivation to obtain a cocaine reward (Soria et al 2006). The acute locomotor response to cocaine was unchanged in these mice (Soria et al 2006), yet in a different line of A_{2A} knockout mice the acute locomotor response to both amphetamine and cocaine was attenuated (Chen et al 2000). Development of a conditional forebrain-specific A_{2A} receptor knockout mouse led to the observation of attenuated amphetamine sensitisation in this model (Bastia et al 2005). The same study used A_{2A}-receptor-specific antagonists 1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dhydro-1*H*-purine-2,6-dione (KW 6002) and SCH 58261 to demonstrate that A_{2A} receptor antagonism prevents the induction but not expression of behavioural sensitisation to amphetamine in one strain of mice and prevents both in another strain. On the other hand, mice lacking the A_{2A} receptor are still capable of cocaine sensitisation (Soria et al 2006).

The team responsible for the forebrain-specific A_{2A} knockout mouse have now developed a new striatal-specific A_{2A} knockout mouse and comparisons between this mouse and the forebrain-specific A_{2A} knockout mouse have yielded some fascinating results (Shen et al 2008). Strikingly, cocaine-induced locomotor activity was enhanced in the striatal A_{2A} knockout mice but attenuated in forebrain-specific A_{2A} receptor knockout mice. Furthermore, administration of the selective A_{2A} antagonist KW 6002 to striatal A_{2A} knockout mice attenuated the locomotor-activating effects of cocaine whereas in the case of wild-type mice these effects were enhanced (Shen et al 2008). Striatal deletion of A_{2A} receptors is therefore consistent with pharmacological data (A_{2A} receptor activation opposing, and blockade facilitating, the actions of dopamine) and forebrain deletion of A_{2A} receptors is consistent with data from the global deletion of A_{2A} receptors. Moreover, when forebrain A_{2A} receptors are pharmacologically blocked in striatal-specific A_{2A} knockout mice, the locomotor response observed mirrors that of forebrain-specific A_{2A} receptor knockout mice (Shen et al 2008).

These data suggest that there are two actions of A_{2A} receptors on striatal transmission and hence psychostimulant-induced effects. One action is negatively modulating (striatal), and one is positively modulating (non-striatal). Blockade of the former with specific deletion will cause an enhancement of the psychostimulant-mediated response and blockade of the latter will cause attenuation of the psychostimulant-mediated response. The latter positively modulating effect appears to dominate, as in the case of the global knockout where the observed phenotype is that of the forebrain-specific knockout. This also potentially explains the continual discrepancy between various studies relating to A_{2A} receptors and the behavioural effects of psychostimulants. As with all studies, the degree to which the striatal and non-striatal A_{2A} receptors influence any particular behaviour could vary depending on a number of factors, including animal strain, drug specificity, selectivity, dosage and paradigm.

Proposed mechanisms by which A_{2A} receptors modulate psychostimulant reinforcement: interactions with other receptor systems

The above data clearly indicate that the interactions between adenosine receptors and other receptor systems relating to the mediation of reward are not merely restricted to a simple antagonism between A_{2A} and D_2 receptors on striatopallidal neurons. That said, the bulk of data describing the involvement of adenosine in the actions of psychostimulants does support a negative A_{2A}–D_2 receptor interaction. Given the presence of A_{2A}–D_2 heteromers and the known antagonistic interactions between these receptors there is a definite possibility that the direct effects of adenosine on the mediation of psychostimulant reward are via A_{2A} receptors, which negatively modulate the actions of dopamine at D_2 receptors. This is in contrast to the A_{2A}-receptor-mediated facilitative role of adenosine in the context of ethanol and opiate reward. Concerning the elevations in extracellular adenosine arising upon psychostimulant administration, increased adenosine could be a result of increased neuronal activity (hence increased ATP) or increased activation of receptors positively coupled to adenylate cyclase (e.g. activation of D_1 receptors), or both, with receptor activation resulting in increased cAMP. Adenosine derived via these mechanisms may activate A_{2A} receptors on striatopallidal neurons, but is also able to positively modulate glutamatergic input to the nucleus accumbens through the activation of A_{2A} receptors located on cortical glutamatergic afferents projecting to the nucleus accumbens (as discussed previously). In the context of the data described earlier, it becomes clear that for some psychostimulant-induced behaviours, adenosine acting at presynaptic facilitatory A_{2A} receptors plays a larger role than adenosine effects mediated via A_{2A} receptors expressed on striatopallidal dendrites or soma in the striatum. With reference to the locomotor-activating effects of psychostimulants this appears to be the case, as it is the forebrain-specific deletion of A_{2A} receptors which attenuates these effects (Shen et al 2008), indicating that it is the glutamatergic inputs to the nucleus accumbens which are primarily responsible for the mediation of this behaviour.

The role of dopamine in the mediation of the rewarding effects of psychostimulants has been firmly established. The dominant effect of striatal A_{2A} receptors is observed in behaviour relating to direct reward and reinforcement, such as self-administration, brain stimulus reward and conditioned place preference (all decreased as a result of A_{2A} receptor activation, due to the antagonistic A_{2A}–D_2 receptor interaction). One study examining the impact of global A_{2A} deletion found the opposite to be the case (Soria et al 2006) but as discussed earlier, the possibility exists that developmental compensation in germline knockout mice has resulted in altered modulation of dopaminergic and glutamatergic transmission in these mice.

The role of glutamate in the drug-induced plasticity relating to psychostimulants is firmly established. In the case of cocaine, expression of mutant NMDA receptors in dopamine D_1-receptor-containing cells prevents cocaine sensitisation and decreases cocaine preference (Heusner & Palmiter 2005). Amphetamine also causes an elevation in

glutamate levels in areas involved in behavioural sensitisation, such as the striatum and VTA (for review see Vanderschuren & Kalivas 2000). The pivotal role of glutamate in psychostimulant sensitisation indicates a possible role for the mGlu–A_{2A} heteromer in governing the glutamate transmission required for this drug-induced plasticity to occur. Indeed, activation of A_{2A} receptors enhances the release of dopamine and glutamate, which contributes to the development of sensitisation (Quarta et al 2004). Antagonism or specific deletion of the A_{2A} receptor would inhibit positive interactions between mGlu5 and A_{2A} receptors on glutamatergic transmission to the nucleus accumbens and the development or expression of sensitisation would be attenuated. This was found to be the case when the A_{2A} receptor was conditionally deleted in the forebrain (Bastia et al 2005), supporting the hypothesis that the presynaptic A_{2A} receptors on these glutamatergic afferents play the dominant role in drug-induced plasticity.

Psychostimulants and adenosine: summary

The above data indicate that adenosine plays a differential role in the mediation of psychostimulant effects depending on the involvement of either striatal A_{2A} receptors located on the medium spiny neurons themselves or A_{2A} receptors located on the cortical glutamatergic afferents that synapse on these striatal neurons. Through negative interactions with dopamine D_2 receptors, adenosine acting at A_{2A} receptors attenuates the rewarding effects of psychostimulant drugs. Conversely, adenosine acting at A_{2A} receptors positively modulates glutamatergic input to the nucleus accumbens through synergistic interactions with mGlu5 receptors, and hence maintains a facilitative role in behaviour such as locomotor sensitisation.

Adenosine A_{2A} receptors and their role in drug addiction

In this review, we have described the role for A_{2A}-receptor-driven interactions with other neurotransmitter systems in the development and expression of drug-seeking behaviour. In rodent models, antagonism or deletion of the A_{2A} receptor reduces ethanol, opiate and psychostimulant self-administration. Based on the literature to date, it is proposed that the specificity of A_{2A} receptor interactions within certain nuclei, neuronal populations and receptor clusters may allow for a degree of therapeutic tailoring. A major challenge in the future is to directly target particular subpopulations or heterodimers. Before progressing further along this path, however, it is essential that studies to fully characterise the role of the A_{2A} receptor in all facets of drug-taking and drug-seeking behaviours are completed. A comprehensive body of work assessing the role of the A_{2A} receptor in behaviour related to, and consequences of, continual drug intake (across all drug classes) would allow the preclinical evaluation of newly developed drug therapies to be better directed against the appropriate aspects of drug addiction for which the role of A_{2A} receptors is most influential.

References

Adams, C. L., Cowen, M. S., Short, J. L., Lawrence, A. J. (2008) Combined antagonism of glutamate mGlu5 and adenosine A_{2A} receptors interact to regulate alcohol-seeking in rats. *Int. J. Neuropsychopharm.* **11**: 229–241

Ahlijanian, M. K., Takemori, A. E. (1985) Effects of (-)-N^6-(R-phenylisopropyl)-adenosine (PIA) and caffeine on nociception and morphine-induced analgesia, tolerance and dependence in mice. *Eur. J. Pharmacol.* **112**: 171–179

Ahlijanian, M. K., Takemori, A. E. (1986) Cross-tolerance studies between caffeine and (-)-N^6-(phenylisopropyl)-adenosine (PIA) in mice. *Life Sci.* **38**: 577–588

Aley, K. O., Green, P. G., Levine, J. D. (1995) Opioid and adenosine peripheral antinociception are subject to tolerance and withdrawal. *J. Neurosci.* **15**: 8031–8038

Andrews, C. M., Lucki, I. (2001) Effects of cocaine on extracellular dopamine and serotonin levels in the nucleus accumbens. *Psychopharmacology (Berl.)* **155**: 221–229

Anwer, J., Dar, M. S. (1995) Possible central adenosinergic modulation of ethanol-induced alterations in [^{14}C]glucose utilization in mice. *Alcohol. Clin. Exp. Res.* **19**: 777–783

Appel, S. B., Liu, Z., McElvain, M. A., Brodie, M. S. (2003) Ethanol excitation of dopaminergic ventral tegmental area neurons is blocked by quinidine. *J. Pharmacol. Exp. Ther.* **306**: 437–446

Arolfo, M. P., Yao, L., Gordon, A. S., Diamond, I., Janak, P. H. (2004) Ethanol operant self-administration in rats is regulated by adenosine A_2 receptors. *Alcohol. Clin. Exp. Res.* **28**: 1308–1316

Augood, S. J., Emson, P. C. (1994) Adenosine A_{2a} receptor mRNA is expressed by enkephalin cells but not by somatostatin cells in rat striatum: a co-expression study. *Mol. Brain Res.* **22**: 204–210

Babbini, M., Davis, W. M. (1972) Time-dose relationships for locomotor activity effects of morphine after acute or repeated treatment. *Br. J. Pharmacol.* **46**: 213–224

Bailey, A., Davis, L., Lesscher, H. M., Kelly, M. D., Ledent, C., Hourani, S. M., Kitchen, I. (2004) Enhanced morphine withdrawal and μ-opioid receptor G-protein coupling in A_{2A} adenosine receptor knockout mice. *J. Neurochem.* **88**: 827–834

Baldo, B. A., Koob, G. F., Markou, A. (1999) Role of adenosine A_2 receptors in brain stimulation reward under baseline conditions and during cocaine withdrawal in rats. *J. Neurosci.* **19**: 11017–11026

Bastia, E., Xu, Y. H., Scibelli, A. C., Day, Y. J., Linden, J., Chen, J. F., Schwarzschild, M. A. (2005) A crucial role for forebrain adenosine A_{2A} receptors in amphetamine sensitization. *Neuropsychopharmacology* **30**: 891–900

Bechara, A., Nader, K., Van Der Kooy, D. (1998) A two-separate-motivational-systems hypothesis of opioid addiction. *Pharmacol. Biochem. Behav.* **59**: 1–17

Bellville, J. W., Escarraga, L. A., Wallenstein, S. L., Wang, K. C., Howland, W. S., Houde, R. W. (1962) Antagonism by caffeine of the respiratory effects of codeine and morphine. *J. Pharmacol. Exp. Ther.* **136**: 38–42

Berrendero, F., Castane, A., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O. (2003) Increase of morphine withdrawal in mice lacking A_{2a} receptors and no changes in CB_1/A_{2a} double knockout mice. *Eur. J. Neurosci.* **17**: 315–324

Bilbao, A., Cippitelli, A., Martin, A. B., Granado, N., Ortiz, O., Bezard, E., Chen, J. F., Navarro, M., Rodriguez De Fonseca, F., Moratalla, R. (2006) Absence of quasi-morphine withdrawal syndrome in adenosine A_{2A} receptor knockout mice. *Psychopharmacology (Berl.)* **185**: 160–168

Bonci, A., Williams, J. T. (1996) A common mechanism mediates long-term changes in synaptic transmission after chronic cocaine and morphine. *Neuron* **16**: 631–639

Brown, R. M., Short, J. L., Cowen, M. S., Lawrence, A. J. (2008) A differential role for the adenosine A_{2A} receptor in opiate reinforcement versus opiate-seeking behaviour. *Neuropsychopharmacology* In press

Brundege, J. M., Williams, J. T. (2002) Increase in adenosine sensitivity in the nucleus accumbens following chronic morphine treatment. *J. Neurophysiol.* **87**: 1369–1375

Butt, N. M., Collier, H. O., Cuthbert, N. J., Francis, D. L., Saeed, S. A. (1979) Mechanism of quasi-morphine withdrawal behaviour induced by methylxanthines. *Eur. J. Pharmacol.* **53**: 375–378

Cahill, C. M., White, T. D., Sawynok, J. (1996) Synergy between mu/delta-opioid receptors mediates adenosine release from spinal cord synaptosomes. *Eur. J. Pharmacol.* **298**: 45–49

Carmichael, F. J., Israel, Y., Crawford, M., Minhas, K., Saldivia, V., Sandrin, S., Campisi, P., Orrego, H. (1991) Central nervous system effects of acetate: contribution to the central effects of ethanol. *J. Pharmacol. Exp. Ther.* **259**: 403–408

Carriba, P., Ortiz, O., Patkar, K., Justinova, Z., Stroik, J., Themann, A., Muller, C., Woods, A. S., Hope, B. T., Ciruela, F., Casado, V., Canela, E. I., Lluis, C., Goldberg, S. R., Moratalla, R., Franco, R., Ferre, S. (2007) Striatal adenosine A_{2A} and cannabinoid CB_1 receptors form functional heteromeric complexes that mediate the motor effects of cannabinoids. *Neuropsychopharmacology* **32**: 2249–2259

Chen, J. F., Beilstein, M., Xu, Y. H., Turner, T. J., Moratalla, R., Standaert, D. G., Aloyo, V. J., Fink, J. S., Schwarzschild, M. A. (2000) Selective attenuation of psychostimulant-induced behavioral responses in mice lacking A_{2A} adenosine receptors. *Neuroscience* **97**: 195–204

Choi, D. S., Cascini, M. G., Mailliard, W., Young, H., Paredes, P., McMahon, T., Diamond, I., Bonci, A., Messing, R. O. (2004) The type 1 equilibrative nucleoside transporter regulates ethanol intoxication and preference. *Nat. Neurosci.* **7**: 855–861

Ciruela, F., Casado, V., Rodrigues, R. J., Lujan, R., Burgueno, J., Canals, M., Borycz, J., Rebola, N., Goldberg, S. R., Mallol, J., Cortes, A., Canela, E. I., Lopez-Gimenez, J. F., Milligan, G., Lluis, C., Cunha, R. A., Ferré, S., Franco, R. (2006) Presynaptic control of striatal glutamatergic neurotransmission by adenosine A_1-A_{2A} receptor heteromers. *J. Neurosci.* **26**: 2080–2087

Clark, M., Dar, M. S. (1988) Mediation of acute ethanol-induced motor disturbances by cerebellar adenosine in rats. *Pharmacol. Biochem. Behav.* **30**: 155–161

Clark, M., Dar, M. S. (1989a) Effect of acute ethanol on release of endogenous adenosine from rat cerebellar synaptosomes. *J. Neurochem.* **52**: 1859–1865

Clark, M., Dar, M. S. (1989b) Effect of acute ethanol on uptake of [^{3}H]adenosine by rat cerebellar synaptosomes. *Alcohol. Clin. Exp. Res.* **13**: 371–377

Coccurello, R., Breysse, N., Amalric, M. (2004) Simultaneous blockade of adenosine A_{2A} and metabotropic glutamate mGlu5 receptors increase their efficacy in reversing Parkinsonian deficits in rats. *Neuropsychopharmacology* **29**: 1451–1461

Contet, C., Kieffer, B. L., Befort, K. (2004) Mu opioid receptor: a gateway to drug addiction. *Curr. Opin. Neurobiol.* **14**: 370–378

Contreras, E., Germany, A., Villar, M. (1990) Effects of some adenosine analogs on morphine-induced analgesia and tolerance. *Gen Pharmacol* **21**: 763–767

Cowen, M. S., Lawrence, A. J. (1999) The role of opioid-dopamine interactions in the induction and maintenance of ethanol consumption. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **23**: 1171–1212

Cunha, R. A. (2001) Adenosine as a neuromodulator and as a homeostatic regulator in the nervous system: different roles, different sources and different receptors. *Neurochem. Int.* **38**: 107–125

Cunha, R. A., Ribeiro, J. A. (2000) ATP as a presynaptic modulator. *Life Sci.* **68**: 119–137

Cunha, R. A., Johansson, B., Fredholm, B. B., Ribeiro, J. A., Sebastião, A. M. (1995) Adenosine A_{2A} receptors stimulate acetylcholine release from nerve terminals of the rat hippocampus. *Neurosci. Lett.* **196**: 41–44

Cunha, R. A., Correia-De-Sa, P., Sebastião, A. M., Ribeiro, J. A. (1996) Preferential activation of excitatory adenosine receptors at rat hippocampal and neuromuscular synapses by adenosine formed from released adenine nucleotides. *Br. J. Pharmacol.* **119**: 253–260

Cunningham, C. L., Howard, M. A., Gill, S. J., Rubinstein, M., Low, M. J., Grandy, D. K. (2000) Ethanol-conditioned place preference is reduced in dopamine D_2 receptor-deficient mice. *Pharmacol. Biochem. Behav.* **67**: 693–699

Daly, J. W., Shi, D., Wong, V., Nikodijevic, O. (1994) Chronic effects of ethanol on central adenosine function of mice. *Brain Res.* **650**: 153–156

Dar, M. S. (1996) Mouse cerebellar $GABA_B$ participation in the expression of acute ethanol-induced ataxia and in its modulation by the cerebellar adenosinergic A_1 system. *Brain Res. Bull.* **41**: 53–59

Dar, M. S. (1997) Mouse cerebellar adenosinergic modulation of ethanol-induced motor incoordination: possible involvement of cAMP. *Brain Res.* **749**: 263–274

Dar, M. S., Mustafa, S. J., Wooles, W. R. (1983) Possible role of adenosine in the CNS effects of ethanol. *Life Sci.* **33**: 1363–1374

Dassesse, D., Massie, A., Ferrari, R., Ledent, C., Parmentier, M., Arckens, L., Zoli, M., Schiffmann, S. N. (2001) Functional striatal hypodopaminergic activity in mice lacking adenosine A_{2A} receptors. *J. Neurochem.* **78**: 183–198

De Montis, M. G., Devoto, P., Meloni, D., Saba, P. L., Tagliamonte, A. (1992) Decreased adenosine A_{2A} receptor function in morphine dependent rats. *Pharmacol. Res.* **25**: 232–233

Di Chiara, G. (1995) The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug Alcohol Depend.* **38**: 95–137

Di Chiara, G., Imperato, A. (1986) Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with transcerebral dialysis in freely moving rats. *Ann. NY Acad. Sci.* **473**: 367–381

Diamond, I., Nagy, L., Mochly-Rosen, D., Gordon, A. (1991) The role of adenosine and adenosine transport in ethanol-induced cellular tolerance and dependence. Possible biologic and genetic markers of alcoholism. *Ann. NY Acad. Sci.* **625**: 473–487

Diaz-Cabiale, Z., Vivo, M., Del Arco, A., O'Connor, W. T., Harte, M. K., Muller, C. E., Martinez, E., Popoli, P., Fuxe, K., Ferre, S. (2002) Metabotropic glutamate mGlu5 receptor-mediated modulation of the ventral striopallidal GABA pathway in rats. Interactions with adenosine A_{2A} and dopamine D_2 receptors. *Neurosci. Lett.* **324**: 154–158

Dixon, A. K., Gubitz, A. K., Sirinathsinghji, D. J., Richardson, P. J., Freeman, T. C. (1996) Tissue distribution of adenosine receptor mRNAs in the rat. *Br. J. Pharmacol.* **118**: 1461–1468

Dixon, A. K., Widdowson, L., Richardson, P. J. (1997) Desensitisation of the adenosine A_1 receptor by the A_{2A} receptor in the rat striatum. *J. Neurochem.* **69**: 315–321

Domenici, M. R., Pepponi, R., Martire, A., Tebano, M. T., Potenza, R. L., Popoli, P. (2004) Permissive role of adenosine A_{2A} receptors on metabotropic glutamate receptor 5 (mGluR5)-mediated effects in the striatum. *J. Neurochem.* **90**: 1276–1279

Dunwiddie, T. V. (1985) The physiological role of adenosine in the central nervous system. *Int. Rev. Neurobiol.* **27**: 63–139

Dunwiddie, T. V., Diao, L. (1994) Extracellular adenosine concentrations in hippocampal brain slices and the tonic inhibitory modulation of evoked excitatory responses. *J. Pharmacol. Exp. Ther.* **268**: 537–545

Dunwiddie, T. V., Masino, S. A. (2001) The role and regulation of adenosine in the central nervous system. *Annu. Rev. Neurosci.* **24**: 31–55

El Yacoubi, M., Ledent, C., Parmentier, M., Daoust, M., Costentin, J., Vaugeois, J. (2001) Absence of the adenosine A_{2A} receptor or its chronic blockade decrease ethanol withdrawal-induced seizures in mice. *Neuropharmacology* **40**: 424–432

El Yacoubi, M., Ledent, C., Parmentier, M., Costentin, J., Vaugeois, J. M. (2003) Caffeine reduces hypnotic effects of alcohol through adenosine A_{2A} receptor blockade. *Neuropharmacology* **45**: 977–985

El-Ghundi, M., George, S. R., Drago, J., Fletcher, P. J., Fan, T., Nguyen, T., Liu, C., Sibley, D. R., Westphal, H., O'Dowd, B. F. (1998) Disruption of dopamine D_1 receptor gene expression attenuates alcohol-seeking behavior. *Eur. J. Pharmacol.* **353**: 149–158

Elmer, G. I., Pieper, J. O., Rubinstein, M., Low, M. J., Grandy, D. K., Wise, R. A. (2002) Failure of intravenous morphine to serve as an effective instrumental reinforcer in dopamine D_2 receptor knock-out mice. *J. Neurosci.* **22**: RC224

Ferré, S., O'Connor, W. T., Snaprud, P., Ungerstedt, U., Fuxe, K. (1994) Antagonistic interaction between adenosine A_{2A} receptors and dopamine D_2 receptors in the ventral striopallidal system. Implications for the treatment of schizophrenia. *Neuroscience* **63**: 765–773

Ferré, S., Fredholm, B. B., Morelli, M., Popoli, P., Fuxe, K. (1997) Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. *Trends Neurosci.* **20**: 482–487

Ferré, S., Karcz-Kubicha, M., Hope, B. T., Popoli, P., Burgueno, J., Gutierrez, M. A., Casado, V., Fuxe, K., Goldberg, S. R., Lluis, C., Franco, R., Ciruela, F. (2002) Synergistic interaction between adenosine A_{2A} and glutamate mGlu5 receptors: implications for striatal neuronal function. *Proc. Natl Acad. Sci. USA* **99**: 11940–11945

Ferré, S., Ciruela, F., Canals, M., Marcellino, D., Burgueno, J., Casado, V., Hillion, J., Torvinen, M., Fanelli, F., Benedetti Pd, P., Goldberg, S. R., Bouvier, M., Fuxe, K., Agnati, L. F., Lluis, C., Franco, R., Woods, A. (2004) Adenosine A_{2A}-dopamine D_2 receptor-receptor heteromers. Targets for neuro-psychiatric disorders. *Parkinsonism Relat. Disord.* **10**: 265–271

Ferré, S., Diamond, I., Goldberg, S. R., Yao, L., Hourani, S. M., Huang, Z. L., Urade, Y., Kitchen, I. (2007) Adenosine A_{2A} receptors in ventral striatum, hypothalamus and nociceptive circuitry implications for drug addiction, sleep and pain. *Prog. Neurobiol.* **83**: 332–347

Filip, M., Frankowska, M., Zaniewska, M., Przegalinski, E., Muller, C. E., Agnati, L., Franco, R., Roberts, D. C., Fuxe, K. (2006) Involvement of adenosine A_{2A} and dopamine receptors in the locomotor and sensitizing effects of cocaine. *Brain Res.* **1077**: 67–80

Fink, J. S., Weaver, D. R., Rivkees, S. A., Peterfreund, R. A., Pollack, A. E., Adler, E. M., Reppert, S. M. (1992) Molecular cloning of the rat A_2 adenosine receptor: selective co-expression with D_2 dopamine receptors in rat striatum. *Mol. Brain Res.* **14**: 186–195

Fiorillo, C. D., Williams, J. T. (2000) Selective inhibition by adenosine of mGluR IPSPs in dopamine neurons after cocaine treatment. *J. Neurophysiol.* **83**: 1307–1314

Franklin, K. B. J., Paxinos, G. (1997) *The mouse brain in stereotaxic coordinates*. Academic Press, Inc., San Diego

Fredholm, B. B., Dunwiddie, T. V. (1988) How does adenosine inhibit transmitter release? *Trends Pharmacol. Sci.* **9**: 130–134

Fredholm, B. B., Svenningsson, P. (2003) Adenosine-dopamine interactions: development of a concept and some comments on therapeutic possibilities. *Neurology* **61**: S5–S9

Fredholm, B. B., Vernet, L. (1978) Morphine increases depolarization induced purine release from rat cortical slices. *Acta Physiol. Scand.* **104**: 502–504

Fuxe, K., Agnati, L. F., Jacobsen, K., Hillion, J., Canals, M., Torvinen, M., Tinner-Staines, B., Staines, W., Rosin, D., Terasmaa, A., Popoli, P., Leo, G., Vergoni, V., Lluis, C., Ciruela, F., Franco, R., Ferre, S. (2003) Receptor heteromerization in adenosine A_{2A} receptor signaling: relevance for striatal function and Parkinson's disease. *Neurology* **61**: S19–S23

Fuxe, K., Ferre, S., Genedani, S., Franco, R., Agnati, L. F. (2007) Adenosine receptor-dopamine receptor interactions in the basal ganglia and their relevance for brain function. *Physiol. Behav.* **92**: 210–217

Fuxe, K., Marcellino, D., Rivera, A., Diaz-Cabiale, Z., Filip, M., Gago, B., Roberts, D. C., Langel, U., Genedani, S., Ferraro, L., De La Calle, A., Narvaez, J., Tanganelli, S., Woods, A., Agnati, L. F. (2008) Receptor-receptor interactions within receptor mosaics. Impact on neuropsychopharmacology. *Brain. Res. Rev.* In press

Georges, F., Stinus, L., Bloch, B., Le Moine, C. (1999) Chronic morphine exposure and spontaneous withdrawal are associated with modifications of dopamine receptor and neuropeptide gene expression in the rat striatum. *Eur. J. Neurosci.* **11**: 481–490

Gessa, G. L., Muntoni, F., Collu, M., Vargiu, L., Mereu, G. (1985) Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. *Brain Res.* **348**: 201–203

Ginsborg, B. L., Hirst, G. D. (1972) The effect of adenosine on the release of the transmitter from the phrenic nerve of the rat. *J. Physiol.* **224**: 629–645

Golembiowska, K., Dziubina, A. (2004) Striatal adenosine A_{2A} receptor blockade increases extracellular dopamine release following l-DOPA administration in intact and dopamine-denervated rats. *Neuropharmacology* **47**: 414–426

Gordon, A. S., Collier, K., Diamond, I. (1986) Ethanol regulation of adenosine receptor-stimulated cAMP levels in a clonal neural cell line: an *in vitro* model of cellular tolerance to ethanol. *Proc. Natl Acad. Sci. USA* **83**: 2105–2108

Haas, H. L., Selbach, O. (2000) Functions of neuronal adenosine receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **362**: 375–381

Hack, S. P., Christie, M. J. (2003) Adaptations in adenosine signaling in drug dependence: therapeutic implications. *Crit. Rev. Neurobiol.* **15**: 235–274

Halimi, G., Devaux, C., Clot-Faybesse, O., Sampol, J., Legof, L., Rochat, H., Guieu, R. (2000) Modulation of adenosine concentration by opioid receptor agonists in rat striatum. *Eur. J. Pharmacol.* **398**: 217–224

Harvey, J., Lacey, M. G. (1997) A postsynaptic interaction between dopamine D_1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. *J. Neurosci.* **17**: 5271–5280

Henderson, G., Hughes, J. (1976) The effects of morphine on the release of noradrenaline from the mouse vas deferens. *Br. J. Pharmacol.* **57**: 551–557

Heusner, C. L., Palmiter, R. D. (2005) Expression of mutant NMDA receptors in dopamine D_1 receptor-containing cells prevents cocaine sensitization and decreases cocaine preference. *J. Neurosci.* **25**: 6651–6657

Hodge, C. W., Samson, H. H., Chappelle, A. M. (1997) Alcohol self-administration: further examination of the role of dopamine receptors in the nucleus accumbens. *Alcohol. Clin. Exp. Res.* **21**: 1083–1091

Imperato, A., Di Chiara, G. (1986) Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. *J. Pharmacol. Exp. Ther.* **239**: 219–228

Inoue, Y., Yao, L., Hopf, F. W., Fan, P., Jiang, Z., Bonci, A., Diamond, I. (2007) Nicotine and ethanol activate protein kinase A synergistically via G_i $\beta\gamma$ subunits in nucleus accumbens/ventral tegmental cocultures: the role of dopamine D_1/D_2 and adenosine A_{2A} receptors. *J. Pharmacol. Exp. Ther.* **322**: 23–29

James, S., Richardson, P. J. (1993a) The subcellular distribution of [^{3}H]-CGS 21680 binding sites in the rat striatum: copurification with cholinergic nerve terminals. *Neurochem. Int.* **23**: 115–122

James, S., Richardson, P. J. (1993b) Production of adenosine from extracellular ATP at the striatal cholinergic synapse. *J. Neurochem.* **60**: 219–227

Johnson, S. W., North, R. A. (1992) Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J. Neurosci.* **12**: 483–488

Justinova, Z., Ferre, S., Segal, P. N., Antoniou, K., Solinas, M., Pappas, L. A., Highkin, J. L., Hockemeyer, J., Munzar, P., Goldberg, S. R. (2003) Involvement of adenosine A_1 and A_{2A} receptors in the adenosinergic modulation of the discriminative-stimulus effects of cocaine and methamphetamine in rats. *J. Pharmacol. Exp. Ther.* **307**: 977–986

Kachroo, A., Orlando, L. R., Grandy, D. K., Chen, J. F., Young, A. B., Schwarzschild, M. A. (2005) Interactions between metabotropic glutamate 5 and adenosine A_{2A} receptors in normal and parkinsonian mice. *J. Neurosci.* **25**: 10414–10419

Kalivas, P. W., Duffy, P. (1995) D_1 receptors modulate glutamate transmission in the ventral tegmental area. *J. Neurosci.* **15**: 5379–5388

Kalivas, P. W., McFarland, K. (2003) Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology (Berl.)* **168**: 44–56

Kalivas, P. W., Volkow, N. D. (2005) The neural basis of addiction: a pathology of motivation and choice. *Am. J. Psychiatry* **162**: 1403–1413

Kaplan, G. B., Coyle, T. S. (1998) Adenosine kinase inhibitors attenuate opiate withdrawal via adenosine receptor activation. *Eur. J. Pharmacol.* **362**: 1–8

Kaplan, G. B., Leite-Morris, K. A. (1997) Up-regulation of adenosine transporter-binding sites in striatum and hypothalamus of opiate tolerant mice. *Brain Res.* **763**: 215–220

Kaplan, G. B., Sears, M. T. (1996) Adenosine receptor agonists attenuate and adenosine receptor antagonists exacerbate opiate withdrawal signs. *Psychopharmacology (Berl.)* **123**: 64–70

Kaplan, G. B., Bharmal, N. H., Leite-Morris, K. A., Adams, W. R. (1999) Role of adenosine A_1 and A_{2A} receptors in the alcohol withdrawal syndrome. *Alcohol* **19**: 157–162

Kaster, M. P., Budni, J., Santos, A. R., Rodrigues, A. L. (2007) Pharmacological evidence for the involvement of the opioid system in the antidepressant-like effect of adenosine in the mouse forced swimming test. *Eur. J. Pharmacol.* **576**: 91–98

Khavandgar, S., Homayoun, H., Torkaman-Boutorabi, A., Zarrindast, M. R. (2002) The effects of adenosine receptor agonists and antagonists on morphine state-dependent memory of passive avoidance. *Neurobiol. Learn. Mem.* **78**: 390–405

Kirkpatrick, K. A., Richardson, P. J. (1993) Adenosine receptor-mediated modulation of acetylcholine release from rat striatal synaptosomes. *Br. J. Pharmacol.* **110**: 949–954

Kittner, H., Krugel, U., Poelchen, W., Sieler, D., Reinhardt, R., Von Kugelgen, I., Illes, P. (1999) P_2 receptor-mediated activation of noradrenergic and dopaminergic neurons in the rat brain. *Prog. Brain Res.* **120**: 223–235

Knapp, C. M., Foye, M. M., Cottam, N., Ciraulo, D. A., Kornetsky, C. (2001) Adenosine agonists CGS 21680 and NECA inhibit the initiation of cocaine self-administration. *Pharmacol. Biochem. Behav.* **68**: 797–803

Koob, G. F. (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol. Sci.* **13**: 177–184

Koob, G. F., Bloom, F. E. (1988) Cellular and molecular mechanisms of drug dependence. *Science* **242**: 715–723

Koob, G. F., Nestler, E. J. (1997) The neurobiology of drug addiction. *J. Neuropsychiatry Clin. Neurosci.* **9**: 482–497

Koob, G. F., Roberts, A. J., Schulteis, G., Parsons, L. H., Heyser, C. J., Hyytia, P., Merlo-Pich, E., Weiss, F. (1998) Neurocircuitry targets in ethanol reward and dependence. *Alcohol. Clin. Exp. Res.* **22**: 3–9

Krauss, S. W., Ghirnikar, R. B., Diamond, I., Gordon, A. S. (1993) Inhibition of adenosine uptake by ethanol is specific for one class of nucleoside transporters. *Mol. Pharm.* **44**: 1021–1026

Krugel, U., Kittner, H., Franke, H., Illes, P. (2003) Purinergic modulation of neuronal activity in the mesolimbic dopaminergic system *in vivo*. *Synapse* **47**: 134–142

Latini, S., Pazzagli, M., Pepeu, G., Pedata, F. (1996) A_2 adenosine receptors: their presence and neuromodulatory role in the central nervous system. *Gen. Pharmacol.* **27**: 925–933

Ledent, C., Vaugeois, J. M., Schiffmann, S. N., Pedrazzini, T., El Yacoubi, M., Vanderhaeghen, J. J., Costentin, J., Heath, J. K., Vassart, G., Parmentier, M. (1997) Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine A_{2a} receptor. *Nature* **388**: 674–678

Lett, B. T. (1989) Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. *Psychopharmacology (Berl.)* **98**: 357–362

Lindskog, M., Svenningsson, P., Fredholm, B., Greengard, P., Fisone, G. (1999) Mu- and delta-opioid receptor agonists inhibit DARPP-32 phosphorylation in distinct populations of striatal projection neurons. *Eur. J. Neurosci.* **11**: 2182–2186

Lopes, L. V., Cunha, R. A., Ribeiro, J. A. (1999) Cross talk between A_1 and A_{2A} adenosine receptors in the hippocampus and cortex of young adult and old rats. *J. Neurophysiol.* **82**: 3196–3203

Lopes, L. V., Cunha, R. A., Kull, B., Fredholm, B. B., Ribeiro, J. A. (2002) Adenosine A_{2A} receptor facilitation of hippocampal synaptic transmission is dependent on tonic A_1 receptor inhibition. *Neuroscience* **112**: 319–329

Mailliard, W. S., Diamond, I. (2004) Recent advances in the neurobiology of alcoholism: the role of adenosine. *Pharmacol. Ther.* **101**: 39–46

Maldonado, R., Saiardi, A., Valverde, O., Samad, T. A., Roques, B. P., Borrelli, E. (1997) Absence of opiate rewarding effects in mice lacking dopamine D_2 receptors. *Nature* **388**: 586–589

Malec, D., Michalska, E. (1990) The effect of adenosine receptor agonists on analgesic effects of morphine. *Pol. J. Pharmacol. Pharm.* **42**: 1–11

Mansour, A., Fox, C. A., Akil, H., Watson, S. J. (1995) Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. *Trends Neurosci.* **18**: 22–29

Manzoni, O., Pujalte, D., Williams, J., Bockaert, J. (1998) Decreased presynaptic sensitivity to adenosine after cocaine withdrawal. *J. Neurosci.* **18**: 7996–8002

Marcellino, D., Roberts, D. C., Navarro, G., Filip, M., Agnati, L., Lluis, C., Franco, R., Fuxe, K. (2007) Increase in A_{2A} receptors in the nucleus accumbens after extended cocaine self-administration and its disappearance after cocaine withdrawal. *Brain Res.* **1143**: 208–220

Marcoli, M., Raiteri, L., Bonfanti, A., Monopoli, A., Ongini, E., Raiteri, M., Maura, G. (2003) Sensitivity to selective adenosine A_1 and A_{2A} receptor antagonists of the release of glutamate induced by ischemia in rat cerebrocortical slices. *Neuropharmacology* **45**: 201–210

Meng, Z. H., Dar, M. S. (1995) Possible role of striatal adenosine in the modulation of acute ethanol-induced motor incoordination in rats. *Alcohol. Clin. Exp. Res.* **19**: 892–901

Naassila, M., Ledent, C., Daoust, M. (2002) Low ethanol sensitivity and increased ethanol consumption in mice lacking adenosine A_{2A} receptors. *J. Neurosci.* **22**: 10487–10493

Nagy, L. E., Diamond, I., Collier, K., Lopez, L., Ullman, B., Gordon, A. S. (1989) Adenosine is required for ethanol-induced heterologous desensitization. *Mol. Pharm.* **36**: 744–748

Nagy, L. E., Diamond, I., Casso, D. J., Franklin, C., Gordon, A. S. (1990) Ethanol increases extracellular adenosine by inhibiting adenosine uptake via the nucleoside transporter. *J. Biol. Chem.* **265**: 1946–1951

Nestler, E. J. (1996) Under siege: The brain on opiates. *Neuron* **16**: 897–900

Nestler, E. J. (2001) Molecular basis of long-term plasticity underlying addiction. *Nature Rev. Neurosci.* **2**: 119–128

Nestler, E. J. (2005) Is there a common molecular pathway for addiction? *Nat. Neurosci.* **8**: 1445–1449

Nestler, E. J., Landsman, D. (2001) Learning about addiction from the genome. *Nature* **409**: 834–835

Nevo, I., Hamon, M. (1995) Neurotransmitter and neuromodulatory mechanisms involved in alcohol abuse and alcoholism. *Neurochem. Int.* **26**: 305–342

O'Kane, E. M., Stone, T. W. (1998) Interaction between adenosine A_1 and A_2 receptor-mediated responses in the rat hippocampus *in vitro*. *Eur. J. Pharmacol.* **362**: 17–25

Phillis, J. W., Jiang, Z. G., Chelack, B. J., Wu, P. H. (1980a) The effect of morphine on purine and acetylcholine release from rat cerebral cortex: evidence for a purinergic component in morphine's action. *Pharmacol. Biochem. Behav.* **13**: 421–427

Phillis, J. W., Jiang, Z. G., Chelack, B. J., Wu, P. H. (1980b) Morphine enhances adenosine release from the *in vivo* rat cerebral cortex. *Eur. J. Pharmacol.* **65**: 97–100

Pickel, V. M., Chan, J., Kash, T. L., Rodriguez, J. J., Mackie, K. (2004) Compartment-specific localization of cannabinoid 1 (CB_1) and mu-opioid receptors in rat nucleus accumbens. *Neuroscience* **127**: 101–112

Poleszak, E., Malec, D. (2002a) Adenosine receptor ligands and cocaine in conditioned place preference (CPP) test in rats. *Pol. J. Pharmacol.* **54**: 119–126

Poleszak, E., Malec, D. (2002b) Cocaine-induced hyperactivity is more influenced by adenosine receptor agonists than amphetamine-induced hyperactivity. *Pol. J. Pharmacol.* **54**: 359–366

Pollack, A. E., Fink, J. S. (1996) Synergistic interaction between an adenosine antagonist and a D_1 dopamine agonist on rotational behavior and striatal c-Fos induction in 6-hydroxydopamine-lesioned rats. *Brain Res.* **743**: 124–130

Pollack, A. E., Harrison, M. B., Wooten, G. F., Fink, J. S. (1993) Differential localization of A_{2a} adenosine receptor mRNA with D_1 and D_2 dopamine receptor mRNA in striatal output pathways following a selective lesion of striatonigral neurons. *Brain Res.* **631**: 161–166

Popoli, P., Betto, P., Reggio, R., Ricciarello, G. (1995) Adenosine A_{2A} receptor stimulation enhances striatal extracellular glutamate levels in rats. *Eur. J. Pharmacol.* **287**: 215–217

Popoli, P., Pezzola, A., Torvinen, M., Reggio, R., Pintor, A., Scarchilli, L., Fuxe, K., Ferre, S. (2001) The selective $mGlu_5$ receptor agonist CHPG inhibits quinpirole-induced turning in 6-hydroxydopamine-lesioned rats and modulates the binding characteristics of dopamine D_2 receptors in the rat striatum: interactions with adenosine A_{2a} receptors. *Neuropsychopharmacology* **25**: 505–513

Quarta, D., Ferre, S., Solinas, M., You, Z. B., Hockemeyer, J., Popoli, P., Goldberg, S. R. (2004) Opposite modulatory roles for adenosine A_1 and A_{2A} receptors on glutamate and dopamine release in the shell of the nucleus accumbens. Effects of chronic caffeine exposure. *J. Neurochem.* **88**: 1151–1158

Ribeiro, J. A. (1999) Adenosine A_{2A} receptor interactions with receptors for other neurotransmitters and neuromodulators. *Eur. J. Pharmacol.* **375**: 101–113

Ribeiro, J. A., Dominguez, M. L., Goncalves, M. J. (1979) Purine effects at the neuromuscular junction and their modification by theophylline, imidazole and verapamil. *Arch. Int. Pharmacodyn. Ther.* **238**: 206–219

Rimondini, R., Ferré, S., Ögren, S. O., Fuxe, K. (1997) Adenosine A_{2A} agonists: a potential new type of atypical antipsychotic. *Neuropsychopharmacology* **17**: 82–91

Rimondini, R., Ferré, S., Giménez-Llort, L., Ögren, S. O., Fuxe, K. (1998) Differential effects of selective adenosine A_1 and A_{2A} receptor agonists on dopamine receptor agonist-induced behavioural responses in rats. *Eur. J. Pharmacol.* **347**: 153–158

Risinger, F. O., Freeman, P. A., Rubinstein, M., Low, M. J., Grandy, D. K. (2000) Lack of operant ethanol self-administration in dopamine D_2 receptor knockout mice. *Psychopharmacology* **152**: 343–350

Robbins, T. W., Everitt, B. J. (1996) Neurobehavioural mechanisms of reward and motivation. *Curr. Opin. Neurobiol.* **6**: 228–236

Robinson, T. E., Berridge, K. C. (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* **18**: 247–291

Rodrigues, R. J., Alfaro, T. M., Rebola, N., Oliveira, C. R., Cunha, R. A. (2005) Co-localization and functional interaction between adenosine A_{2A} and metabotropic group 5 receptors in glutamatergic nerve terminals of the rat striatum. *J. Neurochem.* **92**: 433–441

Rosin, D. L., Robeva, A., Woodard, R. L., Guyenet, P. G., Linden, J. (1998) Immunohistochemical localization of adenosine A_{2A} receptors in the rat central nervous system. *J. Comp. Neurol.* **401**: 163–186

Sahraei, H., Motamedi, F., Khoshbaten, A., Zarrindast, M. R. (1999) Adenosine A_2 receptors inhibit morphine self-administration in rats. *Eur. J. Pharmacol.* **383**: 107–113

Salem, A., Hope, W. (1997) Effect of adenosine receptor agonists and antagonists on the expression of opiate withdrawal in rats. *Pharmacol. Biochem. Behav.* **57**: 671–679

Salem, A., Hope, W. (1999) Role of endogenous adenosine in the expression of opiate withdrawal in rats. *Eur. J. Pharmacol.* **369**: 39–42

Sawynok, J., Jhamandas, K. H. (1976) Inhibition of acetylcholine release from cholinergic nerves by adenosine, adenine nucleotides and morphine: antagonism by theophylline. *J. Pharmacol. Exp. Ther.* **197**: 379–390

Schiffmann, S. N., Vanderhaeghen, J. J. (1993) Adenosine A_2 receptors regulate the gene expression of striatopallidal and striatonigral neurons. *J. Neurosci.* **13**: 1080–1087

Schiffmann, S. N., Jacobs, O., Vanderhaeghen, J. J. (1991) Striatal restricted adenosine A_2 receptor (RDC8) is expressed by enkephalin but not by substance P neurons: an *in situ* hybridization histochemistry study. *J. Neurochem.* **57**: 1062–1067

Schiffmann, S. N., Fisone, G., Moresco, R., Cunha, R. A., Ferré, S. (2007) Adenosine A_{2A} receptors and basal ganglia physiology. *Prog. Neurobiol.* **83**: 277–292

Schultz, W. (1999) The reward signal of midbrain dopamine neurons. *News Physiol. Sci.* **14**: 249–255

Sebastião, A. M., Ribeiro, J. A. (1996) Adenosine A_2 receptor-mediated excitatory actions on the nervous system. *Prog. Neurobiol.* **48**: 167–189

Sebastião, A. M., Ribeiro, J. A. (2000) Fine-tuning neuromodulation by adenosine. *Trends Pharmacol. Sci.* **21**: 341–346

Seiden, L. S., Sabol, K. E., Ricaurte, G. A. (1993) Amphetamine: effects on catecholamine systems and behavior. *Annu. Rev. Pharmacol. Toxicol.* **33**: 639–677

Self, D. W., Nestler, E. J. (1995) Molecular mechanisms of drug reinforcement and addiction. *Annu. Rev. Neurosci.* **18**: 463–495

Shen, H. Y., Coelho, J. E., Ohtsuka, N., Canas, P. M., Day, Y. J., Huang, Q. Y., Rebola, N., Yu, L., Boison, D., Cunha, R. A., Linden, J.,

Tsien, J. Z., Chen, J. F. (2008) A critical role of the adenosine A_{2A} receptor in extrastriatal neurons in modulating psychomotor activity as revealed by opposite phenotypes of striatum and forebrain A_{2A} receptor knock-outs. *J. Neurosci.* **28**: 2970–2975

Shimazoe, T., Yoshimatsu, A., Kawashimo, A., Watanabe, S. (2000) Roles of adenosine A_1 and A_{2A} receptors in the expression and development of methamphetamine-induced sensitization. *Eur. J. Pharmacol.* **388**: 249–254

Short, J. L., Drago, J., Lawrence, A. J. (2006a) Comparison of ethanol preference and neurochemical measures of mesolimbic dopamine and adenosine systems across different strains of mice. *Alcohol. Clin. Exp. Res.* **30**: 606–620

Short, J. L., Ledent, C., Drago, J., Lawrence, A. J. (2006b) Receptor crosstalk: characterization of mice deficient in dopamine D_1 and adenosine A_{2A} receptors. *Neuropsychopharmacology* **31**: 525–534

Short, J. L., Ledent, C., Borrelli, E., Drago, J., Lawrence, A. J. (2006c) Genetic interdependence of adenosine and dopamine receptors: Evidence from receptor knockout mice. *Neuroscience* **139**: 661–670

Snyder, S. H. (1985) Adenosine as a neuromodulator. *Annu. Rev. Neurosci.* **8**: 103–124

Soria, G., Castane, A., Berrendero, F., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O. (2004) Adenosine A_{2A} receptors are involved in physical dependence and place conditioning induced by THC. *Eur. J. Neurosci.* **20**: 2203–2213

Soria, G., Castane, A., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O. (2006) The lack of A_{2A} adenosine receptors diminishes the reinforcing efficacy of cocaine. *Neuropsychopharmacology* **31**: 978–987

Stone, T. W. (1981) The effects of morphine and methionine-enkephalin on the release of purines from cerebral cortex slices of rats and mice. *Br. J. Pharmacol.* **74**: 171–176

Svenningsson, P., Le Moine, C., Kull, B., Sunahara, R., Bloch, B., Fredholm, B. B. (1997) Cellular expression of adenosine A_{2A} receptor messenger RNA in the rat central nervous system with special reference to dopamine innervated areas. *Neuroscience* **80**: 1171–1185

Svenningsson, P., Le Moine, C., Fisone, G., Fredholm, B. B. (1999) Distribution, biochemistry and function of striatal adenosine A_{2A} receptors. *Prog. Neurobiol.* **59**: 355–396

Svenningsson, P., Lindskog, M., Ledent, C., Parmentier, M., Greengard, P., Fredholm, B. B., Fisone, G. (2000) Regulation of the phosphorylation of the dopamine- and cAMP-regulated phosphoprotein of 32 kDa *in vivo* by dopamine D_1, dopamine D_2, and adenosine A_{2A} receptors. *Proc. Natl Acad. Sci. USA* **97**: 1856–1860

Sweeney, M. I., White, T. D., Jhamandas, K. H., Sawynok, J. (1987) Morphine releases endogenous adenosine from the spinal cord *in vivo*. *Eur. J. Pharmacol.* **141**: 169–170

Sweeney, M. I., White, T. D., Sawynok, J. (1993) Morphine-evoked release of adenosine from the spinal cord occurs via a nucleoside carrier with differential sensitivity to dipyridamole and nitrobenzylthioinosine. *Brain Res.* **614**: 301–307

Tebano, M. T., Martire, A., Rebola, N., Pepponi, R., Domenici, M. R., Gro, M. C., Schwarzschild, M. A., Chen, J. F., Cunha, R. A., Popoli, P. (2005) Adenosine A_{2A} receptors and metabotropic glutamate 5 receptors are co-localized and functionally interact in the hippocampus: a possible key mechanism in the modulation of N-methyl-D-aspartate effects. *J. Neurochem.* **95**: 1188–1200

Thorsell, A., Johnson, J., Heilig, M. (2007) Effect of the adenosine A_{2a} receptor antagonist 3,7-dimethyl-propargylxanthine on anxiety-like and depression-like behavior and alcohol consumption in Wistar rats. *Alcohol. Clin. Exp. Res.* **31**: 1302–1307

Turgeon, S. M., Pollack, A. E., Schusheim, L., Fink, J. S. (1996) Effects of selective adenosine A_1 and A_{2a} agonists on amphetamine-induced locomotion and c-Fos in striatum and nucleus accumbens. *Brain Res.* **707**: 75–80

Vanderschuren, L. J., Kalivas, P. W. (2000) Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl.)* **151**: 99–120

Volkow, N. D., Li, T. K. (2005) Drugs and alcohol: treating and preventing abuse, addiction and their medical consequences. *Pharmacol. Ther.* **108**: 3–17

Wardas, J., Konieczny, J., Pietraszek, M. (2003) Influence of CGS 21680, a selective adenosine A_{2A} agonist, on the phencyclidine-induced sensorimotor gating deficit and motor behaviour in rats. *Psychopharmacology (Berl.)* **168**: 299–306

Weerts, E. M., Griffiths, R. R. (2003) The adenosine receptor antagonist CGS15943 reinstates cocaine-seeking behavior and maintains self-administration in baboons. *Psychopharmacology (Berl.)* **168**: 155–163

Weisberg, S. P., Kaplan, G. B. (1999) Adenosine receptor antagonists inhibit the development of morphine sensitization in the C57BL/6 mouse. *Neurosci. Lett.* **264**: 89–92

Weiss, F., Lorang, M. T., Bloom, F. E., Koob, G. F. (1993) Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. *J. Pharmacol. Exp. Ther.* **267**: 250–258

White, P. J., Hope, W., Rose'meyer, R. B. (1995a) The role of adenosine in the hypotensive actions of morphine. *Eur. J. Pharmacol.* **286**: 315–319

White, P. J., Rose'meyer, R. B., Hope, W. (1995b) Changes in adenosine receptors mediating hypotension in morphine-dependent rats. *Eur. J. Pharmacol.* **294**: 215–220

WHO (2008) *Management of substance abuse: facts and figures*. World Health Organization, Geneva

Williams, J. T., Christie, M. J., Manzoni, O. (2001) Cellular and synaptic adaptations mediating opioid dependence. *Physiol. Rev.* **81**: 299–343

Wise, R. A. (1996a) Neurobiology of addiction. *Curr. Opin. Neurobiol.* **6**: 243–251

Wise, R. A. (1996b) Addictive drugs and brain stimulation reward. *Annu. Rev. Neurosci.* **19**: 319–340

Wise, R. A. (2004) Dopamine, learning and motivation. *Nat. Rev. Neurosci.* **5**: 483–494

Wolf, M. E. (2002) Addiction: making the connection between behavioral changes and neuronal plasticity in specific pathways. *Mol. Interv.* **2**: 146–157

Wu, W. P., Hao, J. X., Halldner, L., Lovdahl, C., Delander, G. E., Wiesenfeld-Hallin, Z., Fredholm, B. B., Xu, X. J. (2005) Increased nociceptive response in mice lacking the adenosine A_1 receptor. *Pain* **113**: 395–404

Yao, L., Arolfo, M. P., Dohrman, D. P., Jiang, Z., Fan, P., Fuchs, S., Janak, P. H., Gordon, A. S., Diamond, I. (2002) $\beta\gamma$ Dimers mediate synergy of dopamine D_2 and adenosine A_2 receptor-stimulated PKA signaling and regulate ethanol consumption. *Cell* **109**: 733–743

Yao, L., Fan, P., Jiang, Z., Mailliard, W. S., Gordon, A. S., Diamond, I. (2003) Addicting drugs utilize a synergistic molecular mechanism in common requiring adenosine and G_i-$\beta\gamma$ dimers. *Proc. Natl Acad. Sci. USA* **100**: 14379–14384

Yao, L., McFarland, K., Fan, P., Jiang, Z., Ueda, T., Diamond, I. (2006) Adenosine A_{2a} blockade prevents synergy between mu-opiate and cannabinoid CB_1 receptors and eliminates heroin-seeking behavior in addicted rats. *Proc. Natl Acad. Sci. USA* **103**: 7877–7882

Zarrindast, M. R., Iraie, F., Heidari, M. R., Mohagheghi-Badi, M. (1997) Effect of adenosine receptor agonists and antagonists on morphine-induced catalepsy in mice. *Eur. J. Pharmacol.* **338**: 11–16