Published in final edited form as:
Prog Neurobiol. 2007 December ; 83(5): 332–347.

Adenosine A_{2A} receptors in ventral striatum, hypothalamus and nociceptive circuitry. Implications for drug addiction, sleep and pain

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Abstract

Adenosine A_{2A} receptors localized in the dorsal striatum are considered as a new target for the development of antiparkinsonian drugs. Co-administration of A_{2A} receptor antagonists has shown a significant improvement of the effects of L-DOPA. The present review emphasizes the possible application of A_{2A} receptor antagonists in pathological conditions other than parkinsonism, including drug addiction, sleep disorders and pain. In addition to the dorsal striatum, the ventral striatum (nucleus accumbens) contains a high density of A_{2A} receptors, which presynaptically and postsynaptically regulate glutamatergic transmission in the cortical glutamatergic projections to the nucleus accumbens. It is currently believed that molecular adaptations of the cortico-accumbens glutamatergic synapses are involved in compulsive drug seeking and relapse. Here we review recent experimental evidence suggesting that A_{2A} antagonists could become new therapeutic agents for drug addiction. Morphological and functional studies have identified lower levels of A_{2A} receptors in brain areas other than the striatum, such as the ventrolateral preoptic area of the hypothalamus, where adenosine plays an important role in sleep regulation. Although initially believed to be mostly dependent on A_1 receptors, here we review recent studies that demonstrate that the somnogenic effects of adenosine are largely mediated by hypothalamic A_{2A} receptors. A_{2A} receptor antagonists could therefore be considered as a possible treatment for narcolepsy and other sleep-related disorders. Finally, nociception is another adenosine-regulated neural function previously thought to mostly involve A_1 receptors. Although there is some conflicting literature on the effects of agonists and antagonists, which may partly be due to the lack of selectivity of available drugs, the studies in A_{2A} receptor knockout mice suggest that A_{2A} receptor antagonists might have some therapeutic potential in pain states, in particular where high intensity stimuli are prevalent.

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Keywords

Adenosine A_{2A} receptor; striatum; hypothalamus; peripheral nervous system; drug addiction; sleep; pain

1. Introduction

There is emerging evidence that A_{2A} receptor antagonists might be useful clinically in treating Parkinson's disease. A_{2A} receptor antagonists show promising results as an adjuvant to L-DOPA therapy (see 2.3.). The dorsal striatum, which contains a high density of A_{2A} receptors (Rosin et al., 1998), appears to be the site of action for the antiparkinsonian effects of A_{2A} antagonists. The dorsal striatum receives its dopaminergic input from the substantia nigra (pars compacta), the predominant area of neurodegeneration in Parkinson's disease (Hirsch et al., 1988; Rinne, 1993). The ventral striatum, which receives its dopaminergic input from the ventral tegmental area (VTA; see 2.1.), also contains the same density of A_{2A} receptors (see Lillrank et al., 1999). The ventral striatum (nucleus accumbens) is implicated in drug addition. Here we review recent experimental evidence suggesting that A_{2A} receptor antagonists could become new therapeutic agents for drug addiction.

It is commonly stated that A_{2A} receptors are localized primarily in the striatum while A_1 receptors are distributed much more widely (see Ferré et al., 1992, 1997). Although the striatum contains the highest density of A_{2A} receptors in the brain (Rosin et al., 1998), morphological and functional studies have identified lower levels of A_{2A} receptors in other brain areas. A_{2A} receptors appear to be involved in some adenosine-regulated brain functions previously thought to be mediated solely by A_1 receptors. Adenosine is an endogenous sleep-promoting substance and it is currently believed that A_1 receptors in the cholinergic basal forebrain mediate sleep-inducing mechanisms (recently reviewed in Basheer et al., 2004). Here we review evidence demonstrating a key role of hypothalamic A_{2A} receptors in sleep regulation.

Nociception is another adenosine-regulated neural function previously thought to mostly involve A_1 receptors (recently reviewed in Liu and Salter, 2005). Here, we review recent evidence demonstrating that A_{2A} receptors in peripheral nerve endings also regulate nociception. Taken together, this review emphasizes the possible application of A_{2A} receptor ligands in pathological conditions other than Parkinson's disease.

2. Adenosine A_{2A} receptors in ventral striatum. Implications for drug addiction

2.1. The ventral striatum in drug addiction

The striatum is functionally subdivided into dorsal and ventral striatum. The dorsal striatum receives glutamatergic input from sensoriomotor and association cortical areas and dopaminergic input from the substantia nigra pars compacta (Parent and Hazrati, 1995; Gerfen, 2004). The ventral striatum, mostly represented by the nucleus accumbens (with its two compartments "shell" and "core"), receives glutamatergic input from limbic and paralimbic cortices and the amygdala and hipoccampus, as well as dopaminergic input from the VTA (Parent and Hazrati, 1995; Gerfen, 2004). Glutamatergic and dopaminergic inputs converge on the dendritic spines of the GABAergic striatal efferent neurons, also called medium-sized spiny neurons, which constitute more than 90% of the striatal neuronal population (Gerfen, 2004). Glutamatergic and dopaminergic inputs usually establish synaptic contact with the head and the neck of the dendritic spines, respectively (Gerfen, 2004), enabling dopaminergic neurotransmission to modulate glutamatergic neurotransmission (Fig. 1). Adenosine functions

as a modulator of glutamatergic and dopaminergic neurotransmission on GABAergic striatal efferent neurons, in part by acting on heteromers of adenosine receptors with metabotropic glutamate and dopamine receptors (see below).

The ventral striatum is a component of the brain circuitry involved in goal-directed behavior, in the conversion of motivation into action, i.e., in the selection of appropriate behavioral responses elicited by specific motivational stimuli (Mogenson et al., 1980). A current working model of the circuitry involved in goal-directed behaviour proposes that the glutamatergic input to the nucleus accumbens carries information about motivationally relevant stimuli to be selected for an appropriate behavioral response, which is implemented by parallel processing of cortico-striatal circuits involving both ventral and dorsal striatum. Dopaminergic input to the nucleus accumbens provides a mechanism to select the most appropriate stimuli according to predictive reward value. Furthermore, dopaminergic input modulates changes in excitatory synapses of the nucleus accumbens, thereby enhancing the probability that motivational stimuli elicit a goal-directed behaviour in the future (Horvitz, 2002; Schultz, 2002; Wolf, 2002; Kelley, 2004; Wise, 2004).

Dopamine release in the ventral striatum is a common characteristic of acute responses to addictive substances (opiates, ethanol, nicotine, amphetamine, cocaine, Δ^9-tetrahydrocannabinol) (Pontieri et al., 1995; Di Chiara et al., 1999). It is generally assumed that addictive drugs take control of dopaminergic signals in the nucleus accumbens (and other dopamine-innervated limbic areas), and convert the normal elicitation and learning of goal-directed behaviors into “drug-seeking” and “drug-taking” behaviors (Wolf, 2002; Kelley, 2004). By contrast, advanced stages of addiction, characterized by an uncontrollable urge to obtain drugs and by relapse, seem to depend mostly on adaptations in cortical glutamatergic projections to the nucleus accumbens (Kalivas and Volkow, 2005).

Relapse can be modeled in laboratory animals as reinstatement of drug-seeking behavior after the behavior has been extinguished by drug deprivation. Reinstatement can be produced by administering one dose of the originally self-administered drug (“priming”), by drug-paired environmental cues, or by stress (for recent review, see Bossert et al., 2005). With this paradigm the animals reinstate operant responding (usually lever pressing) for drug in the absence of actual drug delivery. Reinstatement of drug-seeking behavior to different addictive drugs requires the release of glutamate and stimulation of AMPA glutamate receptors in cortico-accumbens synapses, particularly in the nucleus accumbens core (reviewed in Kalivas and Volkow, 2005). It has been hypothesized that pathophysiologic changes in cortico-accumbens glutamatergic synapses promote the compulsive character of drug seeking in addicts by decreasing the value of natural rewards, diminishing cognitive control (choice), and enhancing glutamatergic drive in response to drug-associated stimuli (Kalivas and Volkow, 2005).

2.2. Adenosine A_{2A} receptors in the ventral striatum and the acute behavioral effects of addictive drugs

Both in the dorsal and ventral striatum, two classes of GABAergic efferent neurons, enkephalinergic and dynorphynergic, can be distinguished. GABAergic enkephalinergic neurons contain dopamine and adenosine receptors predominantly of the D_2 and A_{2A} subtype, respectively. On the other hand, GABAergic dynorphinergic neurons express A_1 and D_1 receptors predominantly (Robertson and Jian, 1995; Ferré, 1997; Svenningsson et al., 1997a; Lu et al., 1998). In the ventral striatum GABAergic enkephalinergic and dynorphinergic cells project to the ventral pallidum, which is considered to be an output structure of the basal ganglia (reviewed in Ferré, 1997). The nucleus accumbens also projects to the ventral mesencephalon, with the shell innervating the VTA and the core innervating the substantia nigra. These accumbens-mesencephalic projections are mostly represented by GABAergic dynorphinergic neurons (Robertson and Jian, 1995; Ferré, 1997; Svenningsson et al., 1997a; Lu et al., 1998).

In the brain, adenosine A_{2A} receptors are mostly localized in the striatum (both dorsal and ventral), where they are found in two main locations: in the dendritic spines of GABAergic enkephalinergic neurons and in the glutamatergic terminals (Rosin et al., 2003). In the dendritic spines, A_{2A} receptors seem to be mostly localized in the perisynaptic ring adjacent to the postsynaptic density, where they form heteromers with D_2, glutamate $mGlu_5$ and cannabinoid CB_1 receptors (Agnati et al., 2003; Ferré et al., 2002, 2005; Ciruela et al., 2006; Carriba et al., 2007) (Fig. 1). In the glutamatergic terminals they are found intrasynaptically, forming heteromers with adenosine A_1 receptors (Ciruela et al., 2006) (Fig. 1) and possibly with presynaptic D_2, $mGlu_5$ and CB_1 receptors (Tanganelli et al., 2004; Rodrigues et al., 2005; Carriba et al., 2007). The different A_{2A} receptor-containing heteromers provide distinct molecular entities with unique functional and pharmacological properties (as reviewed in Ferré et al., 2007). The cross-talk between the A_1 and A_{2A} receptors in the A_1-A_{2A} receptor heteromer modulates glutamate release. Thus, stimulation of the A_{2A} receptor (at high intrasynaptic concentrations of adenosine) counteracts the inhibitory effect of A_1 receptor stimulation (which inhibits glutamate release) and promotes glutamate release (Ciruela et al., 2006; Ferré et al., 2007). The receptor cross-talk in A_{2A}-D_2, A_{2A}-$mGlu_5$ and A_{2A}-CB_1 receptor heteromers modulates postsynaptic changes at the striatal glutamatergic synapses of the GABAergic enkephalinergic neuron (Ferré et al., 2007).

A_{2A}-D_2 receptor interactions have been intensively studied. A_{2A} is a $G_{s\text{-}olf}$-coupled receptor and D_2 is a $G_{i\text{-}o}$-coupled receptor. Depending on the conditions of study, the A_{2A}-D_2 receptors cross-talk implies antagonistic or synergistic interactions (Ferré et al., 1997, 2005, 2007; Agnati et al., 2003, Yao et al., 2002, 2003). The antagonistic A_{2A}-D_2 receptor interactions depend on the ability of A_{2A} receptors to modulate the binding characteristics of D_2 receptors in the A_{2A}-D_2 receptor heteromer (decrease in the affinity of D_2 receptor for agonists upon A_{2A} receptor activation) and on the ability of activated D_2 receptors to counteract A_{2A} receptor-mediated type V adenylyl cyclase (ACV) activation (Ferré et al., 1997, 2005, 2007; Agnati et al., 2003). Due to the existence of strong synergistic interactions between A_{2A} and $mGlu_5$ receptors, co-activation of $mGlu_5$ receptor upon strong glutamatergic input allows A_{2A} receptor to counteract D_2 receptor antagonism (Ferré et al., 2002; 2005, 2007). The synergistic A_{2A}-D_2 receptor interactions depend on the presence of an activator of G protein signaling (AGS3), which facilitates a synergistic interaction between G_s- and G_i-coupled receptors on the activation of types II/IV adenylyl cyclase (ACII/IV; see below). Antagonistic A_{2A}-D_2 receptor interactions are however predominant in most conditions, since ACV is the most expressed type of adenylyl cyclase in the striatum (Chern, 2000). However, synergistic interactions can become important during conditions of upregulation of AGS3, such as during withdrawal from repeated treatment with cocaine (see below).

In rodents, systemic administration of A_{2A} receptor antagonists counteracts most of the biochemical as well as the motor depressant and cataleptic effects produced by pharmacological or genetic inactivation of D_2 receptors, which seems to be related to the predominant A_{2A} receptor-mediated signaling, not opposed by the antagonistic interaction with the D_2 receptor in the A_{2A}-D_2 receptor heteromer. This has been shown in several experimental models including rodents pretreated with D_2 receptor antagonists, reserpine, 6-OH-dopamine or MPTP or after genetic inactivation of D_2 receptors (Kanda et al., 1994; Pollack and Fink, 1995; Shiozaki et al., 1999; Ward and Dorsa, 1999; Chen et al., 2001, Ferré et al., 2001; Hauber et al., 2001; Wardas et al., 2001) or MPTP-treated monkeys (Kanda et al., 1998; Grondin et al., 1999). Reserpinized mice, rats with unilateral 6-OH-dopamine lesions and MPTP-treated monkeys are well-established validated models of Parkinson's disease. The results obtained in animal models of Parkinson's disease strongly support the hypothesis that A_{2A} receptor antagonists could be useful for the symptomatic treatment of this disease (Ferré et al., 1992). Indeed, clinical trials show that A_{2A} antagonists potentiate L-DOPA therapy in Parkinson's disease (Bara-Jimenez et al., 2003; Hauser et al., 2003).

However, Parkinson's disease is characterized by degeneration of dopaminergic neurons in the substantia nigra (pars compacta), reducing dopaminergic innervation of the dorsal striatum. Nevertheless, we have also demonstrated A_{2A}-D_2 receptor interactions in the ventral striatum that are similar to interactions in the dorsal striatum (reviewed in Ferré, 1997). At the behavioral level, by acting on the ventral striatum, A_{2A} receptor agonists counteract and A_{2A} antagonists potentiate the motor, discriminative and rewarding effects of psychostimulants (Heffner et al., 1989; Popoli et al., 1994; Rimondini et al., 1997; Shimazoe et al., 2000; Knapp et al., 2001; Poleszak and Malec, 2002; Justinova et al., 2003; Filip et al., 2006). The non-selective A_1 and A_{2A} antagonist caffeine also potentiates these responses to psychostimulants (Misra et al., 1986; Logan et al., 1989; Gauvin et al., 1990; Horger et al., 1991; Comer and Carroll, 1996; Gasior et al., 2000; Munzar et al., 2002). By contrast, different from the effects obtained with pharmacological blockade, A_{2A} receptor knockout mice show a reduction in psychostimulant-induced motor responses (Chen et al., 2000, 2003; Soria et al., 2005; for discussion, see Filip et al., 2006). In summary, A_{2A} receptor pharmacological blockade mostly potentiates the acute behavioral effects of psychostimulant addictive drugs, most probably involving the antagonistic interactions between A_{2A} and D_2 receptors in the ventral GABAergic enkephalinergic neurons. On the other hand, pharmacological blockade of A_{2A} receptors reduced ethanol self-administration (Arolfo et al., 2004) and genetic and pharmacological experiments also indicate that A_{2A} receptors are involved in the acute behavioral effects of cannabinoids and CB_1 receptor agonists. Thus, Soria et al. (2004) have reported a decreased place-preference to Δ^9-tetrahydrocannabinol (THC) in mice with genetic blockade of A_{2A} receptors. Furthermore, genetic and also pharmacological blockade of A_{2A} receptors significantly reduces cataleptogenic effects induced by systemic administration of the CB_1 receptor agonist CP55,940 (Andersson et al., 2005). Finally, results obtained with A_{2A} receptor knockout mice also suggest a requirement for A_{2A} receptors in morphine and THC withdrawal syndromes (Berrendero et al., 2003; Bailey et al., 2003; Soria et al., 2004).

Some biochemical effects of CB_1 receptor agonists had been reported to depend on A_{2A} receptor function, although it was suggested that these effects might be due to indirect interactions involving D_2 receptors (Yao et al., 2003, Andersson et al., 2005). We have recently demonstrated that A_{2A} and CB_1 receptors co-immunoprecipitate from extracts of rat striatum, where they co-localize in dendritic processes and possibly nerve terminals (Carriba et al., 2007). It was also shown that both receptors form direct physical interactions, i.e., A_{2A}-CB_1 receptor heteromers in co-transfected cells (Carriba et al., 2007). At a functional level, CB_1 receptor function was found to be dependent on A_{2A} receptor activation both *in vitro* and *in vivo*. Thus, activation of A_{2A} receptors was necessary for CB_1 receptor signaling in a human neuroblastoma cell line and blockade of A_{2A} receptors significantly decreased the motor depressant effects of the central administration of a synthetic cannabinoid receptor agonist into the rat dorsal striatum (Carriba et al., 2007). This suggests that the rewarding effects of cannabinoids might also depend on striatal A_{2A}-CB_1 receptor heteromers, since CB_1 receptors localized in the nucleus accumbens seem to be involved in those effects (Gardner, 2005). In fact, we have obtained preliminary evidence indicating that A_{2A} receptor antagonists can counteract self-administration of THC or the endocannabinoid anandamide in squirrel monkeys (Ferré and Goldberg, unpublished). In summary, A_{2A} receptor antagonists can either potentiate or attenuate the acute behavioral effects of addictive drugs, most likely depending on the receptor-receptor interactions and A_{2A} receptor heteromers involved.

2.3. Adenosine A_{2A} receptors in the ventral striatum and drug-seeking behavior

But, what about drug-seeking behavior? Although not yet demonstrated for psychostimulants, we have shown that A_{2A} receptor antagonists, either administered systemically or locally into the nucleus accumbens, completely eliminate heroin-induced reinstatement in rats addicted to self-administered heroin (Yao et al., 2006). As mentioned above, cortico-accumbens

glutamatergic neurotransmission seems to play a key role in drug seeking behaviour (Kalivas and Volkow, 2005) and the A_{2A} receptors that are included in receptor heteromers localized pre- and postsynaptically at striatal glutamatergic synapses play an important facilitatory role of glutamatergic neurotransmission (Ferré et al., 2005, 2007). In fact, we have recently shown with *in vivo* experiments that an A_{2A} receptor antagonist or the non-selective adenosine receptor antagonist caffeine, but not a selective A_1 receptor antagonist, completely prevents striatal protein phosphorylation (ERK1/2 and AMPA receptor phosphorylation) induced by a strong cortical input (cortical electrical stimulation) (Quiroz et al., 2006). These experiments involved the dorsal striatum, but ongoing experiments will soon determine if A_{2A} receptor antagonists can also impair cortico-accumbens glutamatergic neurotransmission and the involvement of pre- and presynaptic A_{2A} receptors. Another mechanism by which A_{2A} receptor blockade could prevent drug-seeking behavior is by impairing CB_1 receptor function in the A_{2A}-CB_1 receptor heteromer (see above). The rational is that several experimental data suggest that CB1 receptor antagonists are particularly effective in reducing cue-induced reinstatement of drug seeking (reviewed in De Vries and Schoffelmeer, 2005).

In addition to blocking cortico-accumbens glutamatergic neurotransmission and interfering with striatal CB_1 receptor signaling, A_{2A} receptor antagonists could be beneficial in advanced stages of addiction because of the possible involvement of A_{2A} receptors in the pre- and postsynaptic adaptations of the cortico-accumbens glutamatergic synapses associated with withdrawal from chronic exposure to addictive drugs (Fig. 1). A consistent biochemical finding associated with exposure to different addictive drugs is a reduced signaling through $G_{i/o}$ protein-coupled receptors (Nestler et al., 1990;Terwilliger et al., 1991;Striplin and Kalivas, 1993;Self et al., 1994;Zhang et al., 2000;Hummel and Unterwald, 2003;Rahman et al., 2003;Bowers et al., 2004). Recent studies suggest that these drug-induced biochemical responses involve specific accessory proteins that regulate $G_{i/o}$ protein-coupled receptors, such as RGS9-2 and AGS3 (Rahman et al., 2003;Bowers et al., 2004). Regulators of G protein signaling (RGS) constitute a large family of proteins that potently modulate G proteins by stimulating the GTPase activity of the Gα subunits, which can thus dampen G protein-mediated signaling (De Vries et al., 2000;Ross and Wilkie, 2000). RGS9-2 is an RGS family member highly enriched in the GABAergic enkephalinergic and GABAergic dynorphinergic neurons with very low expression in the rest of the brain or peripheral tissues (Thomas et al., 1998;Rahman et al., 2003). RGS9-2 is up-regulated in the dorsal and ventral striatum during chronic cocaine administration, which decreases D_2 receptor-mediated signaling in the GABAergic enkephalinergic neurons (Rahman et al., 2003) (Fig. 1).

The activator of G protein signaling (AGS) family consists of three functionally distinct groups (Blumer et al., 2005). AGS3 is particularly enriched in neurons and belongs to Group II, which has the ability to bind preferentially to $G_i\alpha$ and stabilize the GDP-bound conformation of $G_i\alpha$, thereby dampening the signaling of the receptor through $G_i\alpha$-GTP, while simultaneously increasing the activity of Gβγ-regulated effectors (Blumer et al., 2005). In primary cultures of nucleus accumbens neurons, D_2, μ-opioid and cannabinoid CB_1 receptors associate with $G_i\alpha3$ (Yao et al., 2005, 2006) and AGS3 binds preferentially to $G_i\alpha3$, preventing reassociation with released βγ subunits. Upon activation of $G_i\alpha3$-coupled receptors, unbound βγ subunits released in the presence of AGS3 are free to transiently stimulate ACII/IV which can lead to increased cAMP production and therefore to a paradoxical activation of PKA and the cAMP-dependent gene expression (Yao et al. 2002, 2003, 2005, 2006). This βγ-mediated activation of adenylyl cyclase depends on co-stimulation of a G_s-coupled receptor, such as A_{2A}. Thus, activation of D_2, μ-opioid or cannabinoid CB_1 receptors synergistically stimulates adenylyl cyclase II and IV via released Gβγ subunits. Furthermore, synergy between these receptors requires tonic activation of A_{2A} receptors (Yao et al., 2003, 2006).

It has recently been shown that withdrawal from repeated treatment with cocaine (self- or non-self-administered) up-regulates AGS3 in the prefrontal cortex and in the core region of the nucleus accumbens (Bowers et al., 2004). In rats, knocking down AGS3 expression in the prefrontal cortex or the nucleus accumbens core (with antisense oligonucleotides) counteracts reinstatement of cocaine- or heroin-seeking behaviour, respectively (Bowers et al., 2004; Yao et al., 2005). Therefore, upregulation of AGS3, with the consequent dampening of $G_i\alpha 3$ signaling while simultaneously promoting βγ-dependent signaling of G_s-coupled receptors, such as D_1 in the prefrontal cortex or in the nucleus accumbens (as suggested by Bowers et al., 2004), or A_{2A} in the nucleus accumbens (as suggested in the present review), can be an important mechanism responsible for the pathophysiologic changes in cortico-accumbens glutamatergic function associated with different addictive drugs (Fig. 1). Upregulation of AGS3 associated with the withdrawal of addictive drugs most probably leads to a predominant signaling of A_{2A} receptors over D_2 receptors in the A_{2A}-D_2 receptor heteromer and to a paradoxic βγ-mediated synergistic A_{2A}-D_2 receptor interaction in the ventral GABAergic enkephalinergic neuron. At the presynaptic level upregulation of AGS3 probably leads to a predominant signaling of A_{2A} receptors over A_1 receptors in the A_1-A_{2A} receptor heteromer (or over other G_i-coupled receptors, such as group II and III metabotropic glutamate receptors, as suggested by Kalivas and Volkow, 2005) in the cortico-accumbens glutamatergic terminals.

Thus, A_{2A} receptor antagonists, although they can potentiate the acute effects of psychostimulants, could be useful in the treatment of drug addiction and relapse during drug withdrawal. This hypothesis might seem at odds with the results of several reports that indicate that caffeine can reinstate or prevent the extinction of cocaine-seeking behaviour (Worley et al., 1994; Schenk et al., 1996; Self et al., 1996; Kuzmin et al., 1999; Green and Schenk, 2002; Weerts and Griffiths, 2003). However, these effects of caffeine appear to be due to A_1 rather than A_{2A} receptor blockade (Kuzmin et al., 1999; Green and Schenk, 2002, Solinas et al, 2002, 2005; Karcz-Kubicha et al., 2003; Quarta et al., 2004 Quarta et al., 2005; Antoniou et al., 2005). Thus, caffeine and selective A_1 receptor antagonists have many behavioral, subjective and biochemical similarities to other psychostimulants, including their ability to induce dopamine release in the nucleus accumbens (Solinas et al, 2002, 2005; Karcz-Kubicha et al., 2003; Quarta et al., 2004a, 2004b; Antoniou et al., 2005). Nevertheless, we should distinguish between acute and chronic caffeine treatment. We recently demonstrated that A_1 receptor antagonism plays a key role in the acute motor-activating, discriminative stimulus and dopamine-releasing effects of systemically administered caffeine in rats (Solinas et al, 2002, 2005; Karcz-Kubicha et al., 2003; Quarta et al., 2004a, 2004b; Antoniou et al., 2005). However, the A_1 receptor antagonistic effects disappear with chronic treatment with caffeine, while A_{2A} receptor antagonistic effects remain (Karcz-Kubicha et al., 2003; Quarta et al., 2004a). Thus, although acute caffeine use can enhance the effects of addictive drugs, chronic caffeine use could be beneficial to avoid relapse. Although more preclinical work needs to be done, particularly using different reinstatement paradigms to study different addictive drugs, the current literature suggests that A_{2A} receptor antagonists could be clinically useful to treat relapse whereas A_1 antagonists may be contraindicated.

3. Adenosine A_{2A} receptors in hypothalamus. Implications for sleep regulation

3.1. Adenosine and its role in sleep

The concept of humoral, rather than neural, regulation of sleep dates as far back as almost 100 years ago when Kuniomi Ishimori and Henri Piéron demonstrated the presence of some endogenous sleep-promoting substance(s) that accumulated in the cerebrospinal fluid (CSF) of sleep-deprived dogs (Kubota, 1989). More than 30 so-called endogenous sleep substances in the brain, CSF, urine, and other organs and tissues of animals have been reported since then

by numerous investigators. For example, delta-sleep-inducing peptide, muramyl peptides, uridine, oxidized glutathione, vitamin B_{12}, prostaglandin (PG) D_2 and adenosine have been identified as endogenous somnogenic substances (Inoué, 1989; Hayaishi, 1991; Basheer et al., 2004). Among these compounds, PGD_2 and adenosine are the most plausible candidates for endogenous sleep-promoting substances.

PGD_2 is the most potent endogenous sleep substance and adenosine has been proposed to be involved in the somnogenic effect of PGD_2 (Hayaishi et al., 2004; Hayaishi and Urade, 2007). PGD_2 is produced as a major PG in the brain of various mammals including humans by lipocalin-type PGD synthase (L-PGDS; Qu et al, 2006), which is dominantly present in the arachnoid membrane surrounding the brain, the choroid plexus in the ventricles, and oligodendrocytes in the brain parenchyma (Beuckmann et al., 2000). From its sites of synthesis, it is secreted into the CSF and bound to DP receptors (Qu et al, 2006), which are also present in the arachnoid membrane yet limited to that of the rostral basal forebrain (Mizoguchi et al., 2001). The binding of PGD_2 to DP receptors on the meninges is followed by an increase in the extracellular concentration of adenosine (Mizoguchi et al., 2001), which transfers the somnogenic signal from the meningeal membrane into the brain parenchyma including the sleep and wake centers in the hypothalamus (Scammell et al., 1998; 2001).

Adenosine has been considered to be an endogenous sleep substance based on experimental evidence obtained from a variety of pharmacological and behavioral studies. For example, adenosine and its stable analogues are known to induce sleep when administered to rats, cats, and other experimental animals (Basheer et al., 2004). The concentration of extracellular adenosine increases in the cortex and basal forebrain during sleep deprivation of cats and decreases during the recovery period after sleep deprivation (Pokka-Heiskanen et al., 2000). Because energy restoration is one of the functions of sleep, adenosine is proposed to be produced as a terminal product of energy metabolism and to act as a homeostatic regulator of energy in the brain during sleep. Caffeine inhibits sleep by acting as an adenosine antagonist (Fredholm et al., 1999), as described later in detail.

3.2. Adenosine A_1 and A_{2A} receptors in sleep regulation

Increased evidences indicate that A_{2A} receptors play a crucial role in the sleep promoting effect of both PGD_2 and adenosine (Huang et al., 2007). PGD_2-induced sleep is inhibited by pretreatment of rats with the A_{2A} receptor antagonist, KF17837 (Satoh et al., 1996). A_{2A} receptor agonists, such as CGS 21680 and APEC, induce non-rapid eye movement (NREM) sleep when infused into the PGD_2-sensitive zone of the basal forebrain of rats during the night (Satoh et al., 1998). On the other hand, A_1 receptor agonists, such as CPA, are ineffective. However, previous results suggested that A_1 receptors are involved in sleep regulation by inhibiting ascending cholinergic neurons of the basal forebrain (Porkka-Heiskanen et al., 2000).

When CGS 21680 or CPA are infused into the lateral ventricle of wild-type mice, CGS 21680 induces both NREM and REM sleep in a dose- and time-dependent manner, while CPA does not affect their sleep-wake patterns (Urade et al., 2003). A high concentration of CPA slightly increases NREM sleep of wild-type mice. However, CPA-induced sleep was not observed in A_{2A} receptor knockout mice, suggesting that the effect of high concentration of CPA is due to its loss of selectivity for A_1 receptors. Thus, although the subtype of adenosine receptor responsible for sleep regulation is still a matter of debate (Basheer et al., 2004), these results strongly suggest a predominant role of A_{2A} receptors in sleep regulation.

3.3. Activation of hypothalamic sleep center in adenosine A_{2A} agonist-induced sleep

There are two important nuclei related to sleep-wake regulation in the hypothalamus, one is ventrolateral preoptic (VLPO) area, a sleep center, and the other is the histaminergic tuberomammillary nucleus (TMN), a wake center. To determine which neuronal groups respond to adenosine, especially to A_{2A} receptor agonists, Fos-immunoreactivity was examined (Satoh et al., 1999; Scammell et al., 2001). When the A_{2A} receptor agonist CGS 21680 was infused for 2 h into the subarachnoid space of the ventral surface of the rat basal forebrain, a marked increase in the number of Fos-positive cells was observed in the VLPO of the anterior hypothalamusr, concomitant with the induction of NREM sleep. In contrast, the number of Fos-positive neurons decreased markedly in the histaminergic TMN of the posterior hypothalamus. Using Fos-immunoreactivity, Sherin et al. (1996) showed a discrete cluster of neurons in the VLPO play a critical role in the generation of sleep. The VLPO is known to send specific inhibitory GABAergic and galaninergic efferents to the TMN, which nucleus contains the ascending histaminergic arousal system. These VLPO neurons may directly induce NREM sleep or send inhibitory signals to the TMN to down-regulate the wake neurons. Thus, the sleep-wake cycle is proposed to be regulated by a flip-flop mechanism involving the interaction between these two centers (Hayaishi and Huang, 2004; Saper et al., 2005).

CGS 21680 was recently demonstrated to inhibit histamine release in both the frontal cortex and medial preoptic area in a dose-dependent manner, and to increase GABA release specifically in the TMN but not in the frontal cortex (Hong et al., 2005). Furthermore, CGS 21680-induced inhibition of histamine release was antagonized by perfusion of the TMN with a $GABA_A$ antagonist, picrotoxin, suggesting that the A_{2A} receptor agonist induces sleep by increasing GABA release in the TMN and, therefore, inhibiting the histaminergic arousal system. These results provide further evidence to support the original idea of a flip-flop mechanism by which sleep is promoted by up-regulating the activity of the sleep neurons in the VLPO and, at the same time, down-regulating the activity of the wake neurons in the TMN (Saper et al., 2001, Hayaishi et al., 2004).

Disinhibition of VLPO sleep-active neurons through presynaptic reduction of GABA release by adenosine was suggested by the intracellular recording of VLPO neurons *in vitro* (Morairty et al., 2004). More recent experiments using intracellular recording of VLPO neurons in rat brain slices demonstrated the existence of two distinct types of VLPO neurons, type-1 and type-2, in terms of their responses to serotonin and adenosine (Gallopin et al., 2005). VLPO neurons are inhibited uniformly by two arousal neurotransmitters, noradrenaline and acetylcholine, and mostly by the A_1 receptor agonist CPA. Serotonin inhibits type-1 neurons but excites type-2 neurons. The A_{2A} receptor agonist CGS 21680 excites postsynaptically type-2, but not type-1, neurons. These results suggest that type-2 neurons are involved in the initiation of sleep and that type-1 neurons contribute to sleep consolidation, since they are activated only when released from inhibition by arousal systems.

3.4. Sleep-wake regulation in adenosine A_1 and A_{2A} receptor knockout mice

The sleep-wake patterns of A_1 receptor knockout mice of the inbred C57BL/6 strain generated by Dr. Fredholm and collaborators (Johansson et al., 2001) and of A_{2A} receptor knockout mice generated by Dr. Chen and collaborators (Chen et al., 2001) were compared with those of wild-type mice. Both knockout mice showed clear circadian variations of sleep-stage distribution during basal conditions, similar to WT mice (Fig. 2). However, A_{2A} receptor knockout mice showed REM sleep rebound after sleep deprivation but not NREM sleep rebound at all, similar to L-PGDS knockout mice and DP receptor knockout mice, indicating that the L-PGDS-DP receptor-A_{2A} receptor system plays a crucial role in the homeostatic regulation of NREM sleep (Hayaishi et al., 2004). On the other hand, A_1 receptor knockout mice showed almost the same

amounts of NREM and REM sleep rebound after sleep deprivation as those of wild-type mice, suggesting that A_1 receptors are not essential for the homeostatic regulation of NREM sleep.

Caffeine binds to A_1 and A_{2A} receptors and acts as a non-selective antagonist and induces insomnia and wakefulness (Fredholm et al., 1999). We have recently obtained evidence for a predominant role of A_{2A} receptor in caffeine-induced wakefulness using A_1 and A_{2A} receptor knockout mice. Thus, caffeine increased wakefulness in both wild-type and A_1 receptor knockout mice, but not in A_{2A} receptor knockout mice (Huang et al., 2005). When caffeine is administered by the intraperitoneal route to wild-type mice (Fig. 2a and 2c) and A_1 receptor knockout mice (Fig. 2d) at a dose of 15 mg/kg, it suppresses both NREM and REM sleep almost completely for 2 hr after the administration. NREM and REM sleep returned to the normal levels by 4 hr after the caffeine injection. In contrast, caffeine given to A_{2A} receptor knockout mice does not change the profiles of NREM and REM sleep (Fig. 2b). Thus, insomnia should be considered as a possible side effect when considering the application of A_{2A} receptor antagonists in Parkinson's disease, drug addiction or pain, which could probably be counteracted by avoiding evening administration. Also, A_{2A} receptor antagonists could be considered as a possible treatment for narcolepsy and other sleep-related disorders.

4. Adenosine A_{2A} receptors in nociceptive circuitry. Implications for pain

4.1. Adenosine and its role in pain

In considering the role of the A_{2A} receptor in pain it should first be stressed that the evidence comes predominantly from experimental animal studies, and thus strictly speaking we are talking about the role of the A_{2A} receptor in nociception (i.e. a response to a noxious stimulus). The description of pain requires verbalization and is thus exclusively a human phenomenon. Nevertheless, there has been clinical use of adenosine in pain and thus some aspects of adenosine receptor modulation can truly be described as pain modulation. Throughout this review there will be some synonymous use of the terms pain and nociception and also of analgesia and antinociception, recognizing that animal models of nociception have led to the development and clinical use of analgesics for pain conditions.

The endogenous mediator adenosine has complex effects in pain, and can be either pronociceptive or antinociceptive depending on the site of administration and the receptor subtype activated (see Sawynok, 1998; Sawynok and Liu, 2003). In addition, as adenosine has similar nanomolar affinities for both A_1 and A_{2A} receptors (see Fredholm et al., 2001b) their relative contribution to the endogenous role of adenosine in pain processing may be finely balanced. Also, inevitably ascribing a role to each receptor in the action of adenosine is dependent on the use of highly subtype-selective receptor ligands or receptor knockout mouse models.

Most attention has been focused on the effects on pain pathways of adenosine acting via the A_1 receptor. There is ample evidence that activation of spinal A_1 receptors results in antinociceptive effects in a wide range of animal models, including both acute nociceptive tests and models of neuropathic and inflammatory pain (see Dickenson et al., 2000; Sawynok, 1998). There is debate as to whether A_1 receptors on peripheral sensory nerves are pro- or antinociceptive, as inhibition of PGE_2-induced nociception (Aley et al., 1995; Aley and Levine, 1997) and stimulation of sensory afferents (Dowd et al., 1998; Kirkup et al., 1998) has been reported after A_1 receptor activation. Overall, however, the antinociceptive effects of central A_1 receptors dominate and this is confirmed in A_1 receptor gene knockout mice, which have an enhanced response to nociceptive stimuli (Johansson et al., 2001).

In humans, systemic infusion or intrathecal injection of adenosine has been demonstrated to have long-lasting clinical benefit in patients with neuropathic pain (Belfrage et al., 1995,

1999) and also after major surgery (Segerdahl, 1997; Segerdahl et al., 1995; Segerdahl and Sollevi, 1998). It is believed that this is largely A_1 receptor mediated. Accordingly most of the interest in adenosine and pain has related to its A_1 effects and the importance of the A_{2A} receptor and the endogenous role of adenosine at this site has been relatively neglected.

4.2. Pain circuitry and localization of adenosine A_{2A} receptors

The production of pain and its amelioration involves sites in the periphery, the spinal cord and via ascending and descending pathways to and from the brain. Clearly the localization of any receptor potentially involved in pain circuitry has a bearing on where any pain modulation resulting from receptor agonism or antagonism might occur. Both ascending and descending pain pathways have been well characterized (see Millan, 1999; 2002) and several mid and hindbrain regions, such as the thalamus, hypothalamus, parabrachial nucleus, pons, superior colliculus, raphe, periaqueductal grey and locus coreleus, are well established as key relay structures in pain circuitry. In addition, integration of pain signals involves the somatosensory cortex and other frontal cortical regions. It might be easy to be dismissive of a central role for A_{2A} receptors in pain processing as autoradiographic mapping of the receptor with highly selective ligands in both rat (Johansson et al., 1997; Svenningsson et al., 1999) and mouse (Bailey et al., 2002; Bailey et al., 2004; Kelly et al., 2004) as well as in humans (Svenningsson et al., 1997b; Ishiwata et al., 2005) shows predominantly a localization to the dorsal and ventral striatum, structures with no major recognized role in pain circuitry. However, there is some evidence that both the dorsal and ventral striatum are directly accessed by nociceptive neurones (Newman et al., 1996) and that the ventral striatum, like many parts of the limbic system, modulates pain processing (see Millan, 1999). Using immunohistochemical techniques, most of the receptor expression is also seen in the basal ganglia (Rosin et al., 1998). However, it should be stressed that A_{2A} receptors are found at relatively low levels in somatosensory cortex (Johansson et al., 1997; Kelly et al., 2004) and their presence in the cortex has been confirmed by western blotting (Lopes et al., 2004), and thus a potential role of A_{2A} receptors in the central integration of pain cannot be completely ignored.

Early studies suggested that A_2 as well as A_1 receptors were present in the dorsal spinal cord of the rat (Choca et al., 1987). However, the A_{2A} receptor gene does not appear to be expressed in the spinal cord (Kaelin-Lang et al., 1998) and autoradiographic techniques with selective A_{2A} receptor ligands, at concentrations well above K_D values, confirm the absence of spinal cord receptor binding (Bailey et al., 2002). Despite this evidence, recent immunohistochemistry studies coupled with functional electrophysiology have shown responses to the A_{2A} selective agonist CGS 21680 in spinal cord (Brooke et al., 2004) and it has been proposed that these receptors are located on presynaptic inhibitory terminals of descending fibers from higher centers (Brooke et al., 2004). Thus, as for the central nervous system, the possibility of spinal effects of A_{2A} receptor activation cannot be completely excluded.

The A_{2A} receptor gene is expressed in the dorsal root ganglion (Kaelin-Lang et al., 1998) and this had led to the suggestion that there is retrograde transport of the receptor to the peripheral terminals in sensory nerve fibres. Added to this the effects of pharmacological modulation (see 4.3) at sensory nerve sites, the primary site of A_{2A} receptor modulation of pain is most likely to be at peripheral nerve terminals (Sawynok, 1998).

4.3. Pharmacological studies with adenosine A_{2A} receptor agonists and antagonists (Table 1)

Much of the pharmacological evidence for A_2 receptor involvement in nociception comes from studies using pharmacological tools with limited selectivity over the A_1 receptor. Because the A_1 receptor has potent effects on nociception at peripheral, spinal and supraspinal sites, it is highly likely that many of these studies are confounded by lack of selectivity for the A_{2A}

receptor of the compounds used. Nonetheless, studies with A_{2A} receptor agonists have shown antinociceptive effects in some, but not all, nociceptive tests. For example, CGS 21680 is antinociceptive in the writhing test, a visceral pain model (Bastia et al., 2002), an effect reversed by the A_{2A} receptor antagonist, SCH 58261. Antinociception in the writhing test is also observed with the A_{2A} receptor agonist DPMA (Pechlivanova and Georgiev, 2002). CGS 21680 has also been shown to induce antinociception in thermal tests after intrathecal administration (Suh et al., 1997) and also in inflammatory (Poon and Sawynok, 1998) and neuropathic models (Lee and Yaksh, 1996). Some of these studies represent high dose pharmacology and raise the issue of possible activation of the A_1 receptor, and several did not benefit from reversal by selective A_{2A} receptor antagonists that are available now.

Local administration of formalin into the hindpaw activates both C- and Aδ fibers, results in peripheral release of adenosine (Liu et al., 2001) and produces licking, biting and flinching behaviours indicative of pain. In the formalin test CGS 21680 has been shown to be both antinociceptive (Borghi et al., 2002) and pronociceptive in rats (Doak and Sawynok, 1995) as is the A_2 receptor agonist APEC in mice (Karlsten et al., 1992). A_2 receptor agonists are also pronociceptive in a mechanical paw pressure test in the rat (Taiwo and Levine, 1990), though these early studies used very poorly selective drugs. Added to this, the recent development of highly selective A_{2B} antagonists shows that these compounds have antinociceptive activity in the hot-plate test (Abo-Salem et al., 2004) and thus the A_{2A}-A_{2B} selectivity of the pharmacological tools used in nociceptive studies also needs to be considered alongside their A_1 activity. The literature on A_{2A} receptor agonists is therefore contradictory although microdialysis studies of the release of adenosine in the hind paw in response to formalin has led to the proposal that adenosine may act at pronociceptive A_{2A} receptors. (Liu et al., 2000)

Studies with A_{2A} receptor antagonists have been rather more consistent showing predominantly antinociception, which would accord with a pronociceptive effect of A_{2A} receptor agonism and also with the hypoalgesia observed in A_{2A} receptor gene knockout mice (see 4.4). SCH 58261 is antinociceptive in both the writing test (Bastia et al., 2002) and in the tail flick and hot plate test, two acute thermal pain tests (Godfrey et al., 2006). A less selective A_{2A} receptor antagonist, DMPX, is not antinociceptive in the writhing test in mice (Pechlivanova and Georgiev, 2002), but does reverse formalin-induced flinching responses in the rat (Doak and Sawynok, 1995), again indicative of pronociceptive A_{2A} receptors on peripheral nerves.

4.4. Adenosine A_{2A} receptor gene knockouts and nociception (Table 1)

Deletion of the A_{2A} receptor gene was first achieved in 1997 and the original behavioural phenotyping of the A_{2A} receptor knockout mice showed a hypoalgesia in thermal tests of pain (Ledent et al., 1997). These observations have been extended, and although hypoalgesia is observed in the tail immersion test and hot-plate test at 55°C (Bailey et al., 2002; Godfrey et al., 2006) and in the tail immersion test at 53°C (Godfrey et al., 2006) in A_{2A} receptor knockout mice, at the lower temperature of 52°C nociceptive responses are not altered (Bailey et al., 2002). In addition, there are no significant differences in nociceptive latencies in the knockout mice in the tail pressure test (Bailey et al., 2002). Thus, alteration in pain sensitivity from deletion of the A_{2A} receptor gene is stimulus dependent, both in terms of intensity and modality, but under some circumstances loss of the A_{2A} receptor leads to reduced pain, suggesting a role for the receptor in activating pain processing. Other observations support this concept of a tonic role for the receptor in pain transmission from peripheral sensory nerves to the spinal cord. For example, A_{2A} receptor knockout mice have greatly reduced NMDA receptor binding in all laminae and regions of the spinal cord, perhaps because of altered glutamate signaling in C-fibres (Hussey et al., 2007). In addition, A_{2A} receptor knockout mice have reduced biting and flinching responses to intraplantar formalin injections in the first phase (0–15min) of the

formalin test and reduced flinching only in the second phase (15–60min) of the test (Hussey et al., 2007). As the first phase of the formalin test is recognized to be due to direct stimulation of peripheral sensory nerves whilst the second phase results from an inflammatory component and involves more complex pain circuitry (Dickenson and Sullivan, 1987), this data further implicates A_{2A} receptors on peripheral sensory nerves in pain modulation. The effect on the second phase also suggests that A_{2A} receptors on inflammatory cells might be of importance in pain modulation and a well defined regulatory role and a potential therapeutic target has been suggested (Lappas et al., 2005). In addition, a potential for A_{2A} receptor antagonists in inflammatory pain is further supported by blockade of both phases of the formalin response by SCH 58261 (Hussey et al, 2007).

4.5. Adenosine A_{2A} receptors and interactions with opioid nociception

Important interactions between adenosine systems and opioid (μ, δ and κ) receptors in the central nervous system and spinal cord have long been recognized. In relation to pain, in the spinal cord there is evidence that a component of the action of morphine is due to the release of adenosine (Sweeney et al., 1987; Sweeney et al., 1989) and there is also evidence of analgesic synergy between adenosine and opioid agonists active at the δ and κ but not the μ opioid receptors (De Lander and Keil II, 1994). Others have shown that the relatively selective A_{2A} receptor antagonist DMPX administered intrathecally antagonises morphine analgesia after intracerebroventricular administration, suggesting a spinal A_{2A} receptor involvement in the supraspinal action of morphine (Suh et al., 1997). The adenosine receptor subtype involved in the adenosine released by morphine has not been defined though at the spinal level much of the pharmacology points to a key role for A_1 receptors (Montegazza et al., 1984; Reeve and Dickenson, 1995; Zarrindast and Nikfar, 1994). Several studies have also reported morphine-induced or enhanced release of adenosine in the brain (Fredholm and Vernet, 1978; Phillis and Jiang, 1980; Stone, 1981) but much of the behavioural interactions have been focused to addiction rather than pain. Although central administration of theophylline does not alter morphine antinociception (De Lander et al., 1992), the adenosine analogue and A_1 receptor agonist L-PIA can potentiate tolerance to the analgesic effect of morphine (Ahlijanian and Takemori, 1985). There are also a number of studies that show plasticity in both A_1 and A_{2A} receptors in the brain after chronic administration of opioids (Kaplan and Leite-Morris, 1997; Kaplan et al., 1994), and A_{2A} receptor knockout mice show altered expression of the opioid peptide precursors proenkephalin, prodynorphin (Ledent et al., 1997) and pro-opiomelanocortin (Jegou et al., 2003) though not opioid receptors (Bailey et al., 2002). Although A_1 receptor knockout mice are hyperalgesic, antinociceptive responses to morphine after systemic injection are unaffected in the A_1 receptor knockout mice which would point to a lack of involvement of the A_1 receptor in morphine's effect on pain (Johansson et al., 2001). However, if injected intrathecally, the morphine response is reduced in the A_1 receptor knockout mice implying a spinal interaction (Wu et al., 2005). In addition, it should be noted that changes in μ opioid receptor expression in the spinal cord in response to formalin injections in the paw can be counteracted by treatment with either A_1 or A_{2A} receptor agonists and thus both receptors may play a role in spinal responses to opioids (Borghi et al., 2002).

Studies on peripheral mechanisms of pain have pointed to important interactions of adenosine and opioid systems at sensory nerves. Intradermal co-injections of μ opioid and A_1 receptor agonists with the inflammatory mediator PGE_2 show a bi-directional cross-tolerance to peripheral antinociception, suggesting a common cellular role for the μ opioid and A_1 receptors on primary afferent nociceptors (Aley et al., 1995). Further cross-tolerance and cross-withdrawal studies have led to the proposal that a μ opioid, α_2 adrenergic, A_1 receptor complex mediates antinociception in the periphery (Aley and Levine, 1997). A role for the A_{2A} receptor on peripheral nerve terminals altering opioid mediated responses has also been suggested (Bailey et al., 2002). Whilst antinociceptive responses to the μ opioid receptor agonist morphine

are unaffected in A_{2A} receptor knockout mice, δ opioid receptor-mediated antinocieption is decreased and κ opioid antinociception is increased. These behavioural effects can be correlated with parallel changes in spinal opioid receptor expression and suggest that lack of the A_{2A} receptor at peripheral terminals alters pain processing to the spinal cord resulting in altered opioid modulation (Bailey et al., 2002).

In conclusion, the evidence points to opioid-adenosine interactions at all levels of pain processing. At peripheral sites, A_1 receptors synergise with MOP receptors, and this is also the predominant response in the spinal cord. Spinal interactions of the A_{2A} receptor are also evident for the δ and κ opioid receptors, but not the μ opioid receptor. In the brain, although opioid-adenosine interactions have been reported for other behaviors their potential co-operative role in supraspinal nociception is less clear.

4.6. Therapeutic potential of adenosine A_{2A} receptor modulation and pain

Overall the evidence suggests that A_1 receptors exert inhibitory effects on nociception at peripheral and spinal sites whilst the A_{2A} receptor has an opposing role. Our current understanding suggests that the A_{2A} receptor plays a role in pain processing and that, although spinal and supraspinal sites cannot be completely ignored, peripheral A_{2A} receptors on sensory nerves are probably the most important in this regard. Although there is some conflicting literature on the effects of agonists and antagonists, which may be partly due to the lack of selectivity of available drugs, the studies in A_{2A} receptor knockout mice and the analgesic effects of SCH 58261 in inflammatory models, suggest that blockade of the A_{2A} receptor might have some therapeutic potential in pain states. As there appear to be some differences in the involvement of the A_{2A} receptor dependent on the intensity and modality of the stimulus, more detailed studies are needed to determine whether A_{2A} receptor antagonists might have clinical utility in certain types of pain conditions, in particular where high intensity stimuli are prevalent.

Acknowledgements

This work has been supported by the National Institute on Drug Abuse Intramural Research Funds, by EC (LSHM-CT-2004-005166) and Glaxo Smith Kline.

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Abbreviations

AGS

activator of G protein signaling

AMPA
α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionate

APEC
2-[(2-aminoethylamino)carbonylethyl phenylethylamino]-5’-N-ethylcarboxamido adenosine

CGS 21680
2-[p-(2-carboxyethyl)phenethylamino]-5’-N-ethylcarboxamido- adenosine

CSF
cerebrospinal fluid

DMPX
3,7-dimethyl-1-propargylxanthine

CPA
N(6)-cyclopentyladenosine

GABA
γ-aminobutyric acid

DPMA
N6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine. KF17837, (E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine

L-PIA
[L(−)N(6)-(2-phenylisopropyl)adenosine]

L-PGDS
lipocalin-type prostaglandin D synthase

MPTP
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NMDA
N-methyl-D-aspartate

NREM
non-rapid eye movement

PG
prostaglandin

PKA
protein kinase A

REM
rapid eye movement

RGS
regulator of G protein signaling

SCH 58261
[5-amino-7-(2-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-epsilon]-1,2,4-triazolo [1,5-c]-pyrimidine

TMN
tuberomammillary nucleus

VLPO

ventrolateral preoptic

VTA

ventral tegmental area

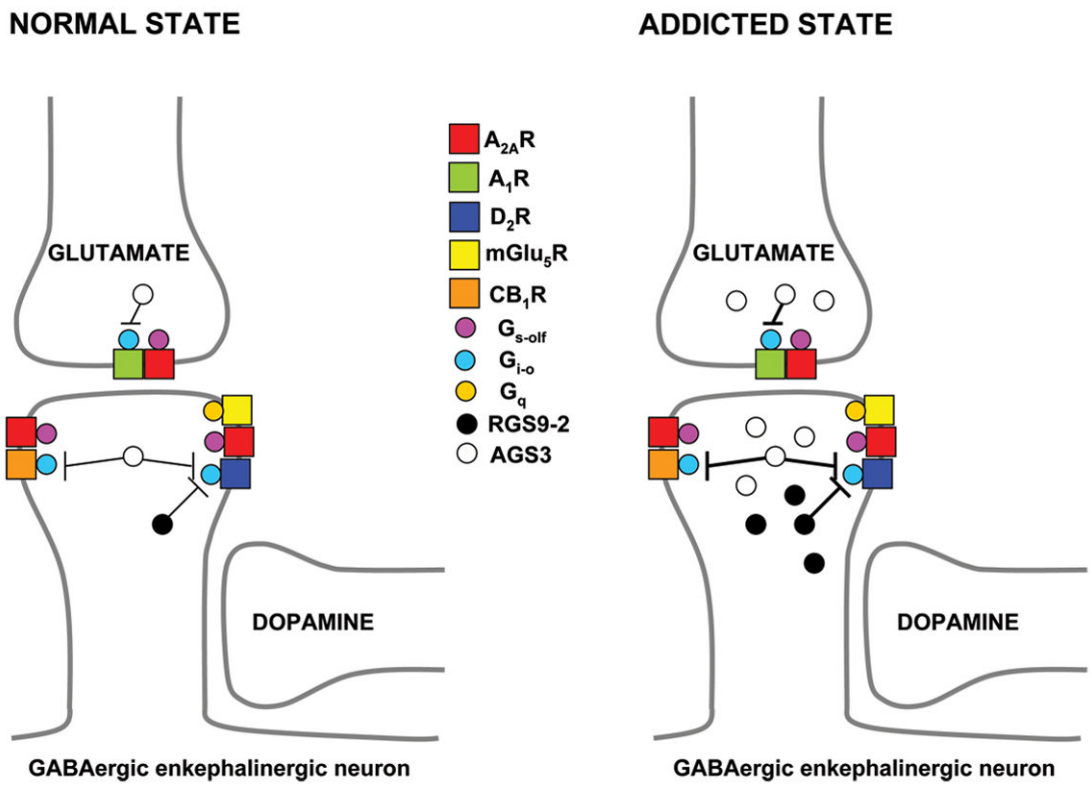

Figure 1. Scheme of a dendritic spine of the GABAergic enkephalinergic neuron and the A_{2A} receptor-dependent mechanisms involved in drug addiction

Glutamatergic and dopaminergic inputs usually establish synaptic contact with the head and the neck of the dendritic spines. In the dendritic spines, A_{2A} receptors ($A_{2A}R$) are localized in the perisynaptic ring adjacent to the postsynaptic density, where they form heteromers with D_2. glutamate $mGlu_5$ and cannabinoid CB_1 receptors (D_2R, $mGlu_5R$ and CB_1R, respectively). In the glutamatergic terminals A_{2A} receptors are found intrasynaptically, forming heteromers with adenosine A_1 receptors (A_1R). Involvement of A_{2A} receptors in drug-seeking behavior seems to be related to its modulation of CB_1 receptor signaling and its key role in both pre- and postsynaptic glutamatergic neurotransmission, including neuroadaptations such as upregulation of specific accessory proteins (RGS9-2 and AGS3) that dampen Gi/o protein-dependent signaling and promote A_{2A} receptor signaling (see text).

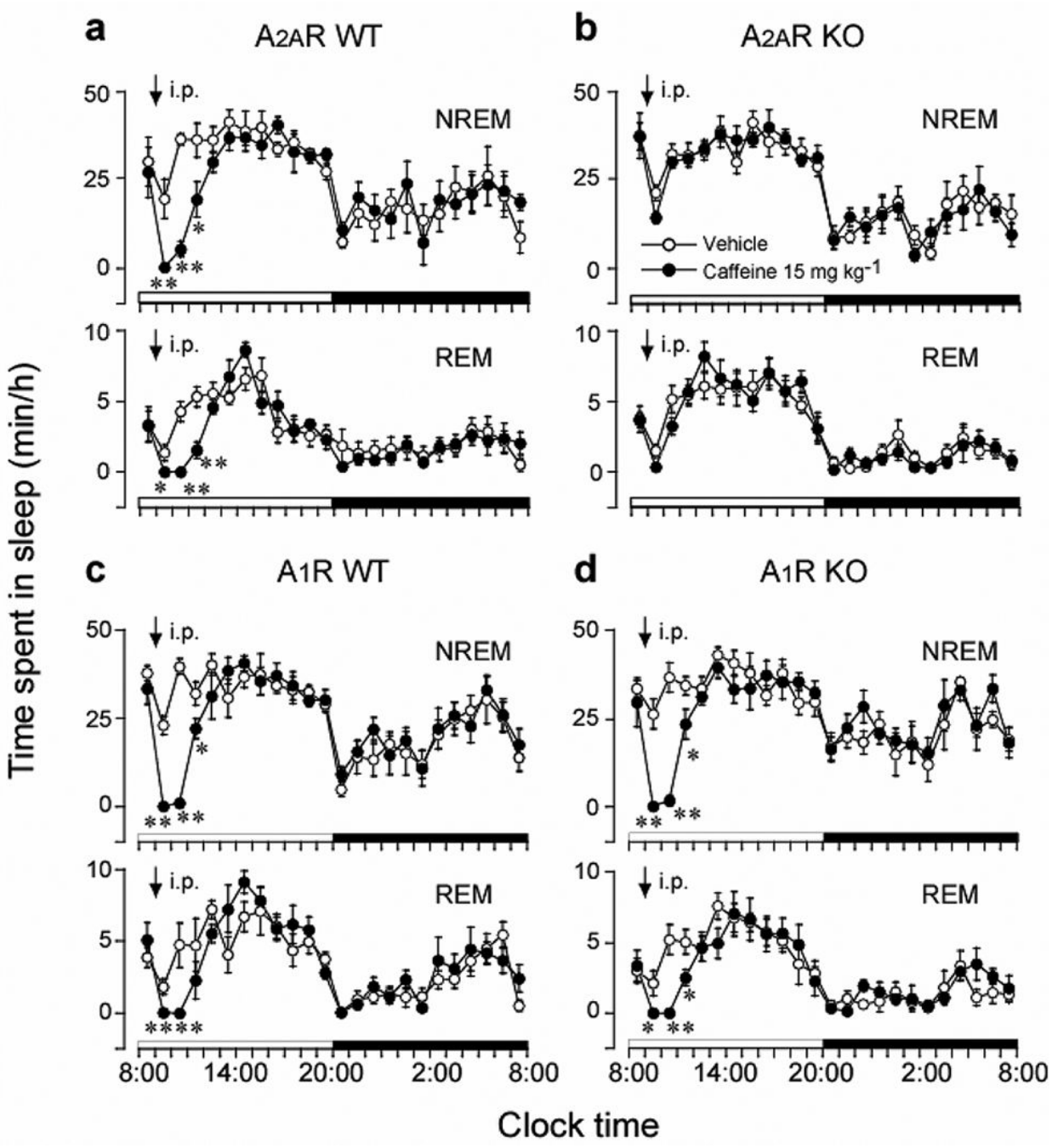

Figure 2. Time course of changes in NREM and REM sleep after caffeine (15 mg/kg) treatment in adenosine A_{2A} receptor wild-type (A_{2A}R WT, a) and knockout (A_{2A}R KO, b), and A_1 receptor wild-type (A_1R WT, c) and knockout (A_1R KO, d) mice

Each circle represents the hourly mean ± s.e.m. (n = 5-7). Open and closed circles stand for the baseline and experimental day profiles, respectively. The arrows indicate the injection time (9 a.m.). *, $P < 0.05$; **. $P < 0.01$, significantly different from the vehicle, by the paired t-test. Reprinted by permission from Macmillan Publishers Ltd: Nature Neuroscience, Huang et al., 2005).

Table 1

Pain responses to modulation of the adenosine A_{2A} receptor

A_{2A} modulation	Species, dose and route	Nociceptive test	Effect	Reference
A_{2A} agonists				
CGS 21680	Mouse, 10 μg i.th.	Tail flick	Analgesia	Suh et al., 1997
	Rat, 0.1–10 nmol i.th.	Carrageenan (2 mg/100 μl)	Analgesia	Poon and Sawynok, 1998
	Rat, 2–40 nmol i.th.	Neuropathic spinal ligation	Analgesia	Lee and Yaksh, 1996
	Mouse, 0.015–0.3 mg/kg i.p.	Formalin (5%)	Analgesia (early phase)	Borghi et al., 2002
	Mouse, 0.01–0.1 mg/kg i.p.	Writhing (0.6% acetic acid)	Analgesia (not dose related)	Bastia et al., 2002
	Mouse, 1–10 mg/kg i.p	Hot plate 52.5°C	Hyperalgesia (0.01 mg/kg only)	Bastia et al., 2002
	Rat, 1.5–50 nmol i.pl.	Formalin (0.5%)	Hyperalgesia (1.5 nmol) Analgesia (50 nmol)	Doak and Sawynok, 1995
DPMA	Mouse, 0.1–1 mg/kg i.p.	Writhing (1% acetic acid)	Analgesia (not dose-related)	Pechlivanova and Georgiev, 2002
APEC	Mouse, 0.1 μM i.pl.	Formalin	Hyperalgesia	Karlsten et al., 1992
A_{2A} antagonists				
SCH 58261	Mouse, 1–10 mg/kg i.p	Writhing (0.6% acetic acid)	Analgesia	Bastia et al., 2002
	Mouse, 1–10 mg/kg i.p	Hot plate52.5°C	No effect	Bastia et al., 2002
	Mouse 3 mg/kg i.p.	Hot plate 55°C	Analgesia	Godfrey et al, 2006
	Mouse 3 mg/kg i.p.	Tail immersion 53°C	Analgesia	Godfrey et al., 2006
DMPX	Mouse, 0.05–1 mg/kg i.p.	Writhing (1% acetic acid)	No effect	Pechlivanova and Georgiev, 2002
	Rat, 50 nmol i.pl.	Formalin (2.5%)	Analgesia	Doak and Sawynok, 1995
	Mouse, 1–40 μg i.th.	Tail flick	No effect	Suh et al, 1997
MSX-3	Mouse 30–100 mg/kg i.p.	Hot plate 52°C	No effect	Abo-Salem et al., 2004
A_{2A} gene knockout	Mouse	Hot plate 55°C	Hypoalgesia	Ledent et al., 1997
		Tail flick	Hypoalgesia	Ledent et al., 1997
		Tail immersion 55°C	Hypoalgesia	Bailey et al., 2002
		Tail immersion 53°C	Hypoalgesia	Godfrey et al., 2006
		Tail immersion 52°C	No effect	Bailey et al., 2002
		Tail pressure	No effect	Bailey et al., 2002
		Formalin (5%)	Analgesia (flinches and bites, early phase; flinches only late phase)	Hussey et al., 2007

i.p. intraperitoneal, i.pl. intraplantar, i.th. intrathecal. CGS 21680, DMPA, APEC, SCH 58261, DMPX, MSX-3