2011-12-29

Adenosine A2A Receptors in Psychopharmacology: Modulators of Behavior, Mood and Cognition

Shen, Hai-Ying, Jiang-Fan Chen. "Adenosine A2A Receptors in Psychopharmacology: Modulators of Behavior, Mood and Cognition" Current Neuropharmacology 7(3): 195-206. (2009)
https://hdl.handle.net/2144/2676

Boston University
Adenosine $A_{2A}$ Receptors in Psychopharmacology: Modulators of Behavior, Mood and Cognition

Hai-Ying Shen$^{1,*}$ and Jiang-Fan Chen$^{2}$

$^1$Robert Stone Dow Neurobiology Laboratories, Legacy Research, Portland, OR 97232, USA; $^2$Department of Neurology, Boston University School of Medicine, Boston, MA 02118, USA

Abstract: The adenosine $A_{2A}$ receptor ($A_{2A}R$) is in the center of a neuromodulatory network affecting a wide range of neuropsychiatric functions by interacting with and integrating several neurotransmitter systems, especially dopaminergic and glutamatergic neurotransmission. These interactions and integrations occur at multiple levels, including (1) direct receptor-receptor cross-talk at the cell membrane, (2) intracellular second messenger systems, (3) trans-synaptic actions via striatal collaterals or interneurons in the striatum, (4) and interactions at the network level of the basal ganglia. Consequently, $A_{2A}Rs$ constitute a novel target to modulate various psychiatric conditions. In the present review we will first summarize the molecular interaction of adenosine receptors with other neurotransmitter systems and then discuss the potential applications of $A_{2A}R$ agonists and antagonists in physiological and pathophysiological conditions, such as psychostimulant action, drug addiction, anxiety, depression, schizophrenia and learning and memory.

Key Words: Adenosine, $A_{2A}$ receptor, caffeine, psychostimulant, amphetamine, cocaine, schizophrenia, anxiety, depression, dopamine, glutamate.

INTRODUCTION

Behavior, mood and cognition were previously considered to be mainly controlled by dopaminergic and glutamatergic neurotransmission. The ability of the adenosinergic system to modify these behaviors and cognitive function has attracted a great deal of attention as increasing evidences support the tight relationship between adenosine-based modulation and the dopaminergic and glutamatergic systems. Adenosine is ubiquitously distributed throughout the central nervous system (CNS). While early research pointed to the role of adenosine as a metabolite of adenosine triphosphate (ATP) and cyclic adenosine monophosphate (cAMP), the importance of this molecule is now widely recognized as a modulator of neurotransmission and complex behaviors. Indeed, adenosine fulfills two important roles: (1) as a homoeostatic transcellular messenger in all cells; (2) and particularly as a neuromodulator controlling neurotransmitter release and neuronal excitability [31, 63].

Endogenous extracellular adenosine, acting mainly through adenosine $A_1$ and $A_{2A}$ receptors ($A_1Rs$ and $A_{2A}Rs$) in the CNS, controls and integrates a wide range of brain functions, most notably regulation of sleep, locomotion, anxiety, cognition and memory [47, 63, 64]. Consequently, dysfunction of adenosinergic signaling is implicated in pathologies ranging from epilepsy to neurodegenerative disorders to psychiatric conditions [175]. Owing to adenosine’s unique role of integrating glutamatergic and dopaminergic neurotransmission systems, adenosine-based therapies are rapidly evolving in preclinical and clinical studies for the treatment of different neurological disorders [62] and the adenosinergic system is increasingly recognized as a potential target for the development of new therapies for psychiatric disorders [32, 34].

The distribution, molecular structure and function of $A_{2A}Rs$ in the brain, has extensively been reviewed elsewhere [22, 32, 63, 65]. Briefly, the $A_{2A}R$ belongs to the G-protein coupled adenosine receptor family and is highly expressed in the striatum [61, 182]. $A_{2A}Rs$ are also expressed at lower levels in other brain areas, including hippocampus, cerebral cortex, nucleus tractus solitarius, motor nerve terminals and glial cells. Activation of $A_{2A}Rs$ enhances the release of several neurotransmitters, such as acetylcholine, glutamate and dopamine, but inhibits gamma aminobutyric acid (GABA) release [24, 36, 47, 109]. $A_{2A}R$ activation also modulates neuronal excitability and synaptic plasticity, and affects various behaviors including locomotor activity, sleep-wake cycle, anxiety, depression and learning and memory. At the cellular level, $A_{2A}Rs$ are localized predominantly in the soma of GABAergic (enkephalin-containing, dopamine $D_2$ receptor-expressing) striato-pallidal projection neurons and to a lesser extent in asymmetrical excitatory synapses at the dendrites of cortico-striatal terminals [7, 61, 163, 182, 203]. At the molecular level, the $A_{2A}R$ has been shown to interact with other neurotransmitters and neuromodulator receptors (possibly through molecular dimerization), including dopamine $D_2$ receptor ($D_2R$), adenosine $A_1$ receptor ($A_1R$), cannabinoid CB1 receptor (CB1R), metabotropic glutamate receptor subtype 5 (mGluR5) and facilitatory nicotinic acetylcholine (Ach) receptor. These interactions expand the range of possibilities used by adenosine to interfere with neuronal function and communication [47, 57, 59, 181].

In the present overview, we mainly recapitulate some molecular features of brain $A_{2A}Rs$ and the ability of the $A_{2A}R$ to integrate several neurotransmission and signaling pathways that might be relevant to the potential therapeutic
interest of psychopharmacology, particularly in psychostimulation, drug addiction, anxiety, depression, psychiatric disorder, e.g. schizophrenia, and in learning and memory [185].

**MOLECULAR BASIS FOR A2A$_R$ MODULATION OF OTHER NEUROTRANSMITTER SYSTEMS IN THE BRAIN**

A$_2$A$_R$s are highly expressed in the striatum, a pivotal locus with high levels of neurotransmission and neurotransmitter receptors, thus providing an anatomical basis for the interaction between the A$_2$A$_R$ and other, such as dopaminergic and glutamatergic, neurotransmitter systems. These interactions occur at multiple levels, including (1) direct receptor-receptor cross-talk at the cell membrane, (2) intracellular second messenger systems, (3) trans-synaptic actions via striatal collaterals or interneurons in the striatum, (4) and interactions at the network level of the basal ganglia. Compared to other relatively “circumlocutory” interactions, the intramembrane receptor-receptor interactions are more direct in spacial connection. Agnati and Fuxe first reported experimental observations for the existence of membrane receptor-receptor interaction [1, 70, 221]. Since then, the concept has been further developed to receptor-receptor heteromers and the so called “receptor mosaic” with the discovery of aggregates of multiple receptors [67, 71]. The interactions involving the A$_2$A$_R$s have been described for several G-protein coupled receptors, including D$_1$Rs, A$_1$Rs, CB1R and mGluR5 [54, 181]. The largely antagonistic and occasionally synergistic interactions between the A$_2$A$_R$ and other receptors occurring directly between receptor complexes have been documented.

**1. Interaction Between Adenosine A$_2$A$_R$s and A$_1$Rs**

The prevalent neuromodulatory influence of adenosine is inhibitory on neuronal activity in the brain [63]. Adenosine is known to modulate the release of many neurotransmitters, including dopamine, glutamate, GABA, serotonin, noradrenaline and ACh, though the inhibition of excitatory neurotransmitters (e.g. glutamate) is most pronounced [31, 47, 66]. Adenosine modulation of neurotransmitter release is mediated through the activation of the A$_1$R and A$_2$A$_R$. Adenosine activation of G$_i$-coupled A$_1$Rs reduces neurotransmitter release at pre-synaptic nerve terminals and depresses neuronal firing at postsynaptic sites [66, 121, 194]. In contrast, adenosine activation of the G$_{olf}$-coupled A$_2$A$_R$ has been demonstrated to exert an excitatory modulation on the neurotransmitter release of glutamate and ACh in the striatum, and ACh in the hippocampus [33, 110]. The A$_2$A$_R$ also controls GABA release in the striatum [108] as well as in the hippocampus [185]. Additionally, the activation A$_2$A$_R$ decreases the functionality of the A$_1$R in some experimental settings [46, 130, 131, 155].

A$_1$Rs and A$_2$A$_R$s may be activated under different conditions; adenosine may preferentially act at A$_1$Rs under basal condition, probably due to its relatively high expression level and wide-spread distribution in the brain [31, 63]. However, the different affinities of adenosine for A$_1$Rs and A$_2$A$_R$s is still an open issue [35, 47]. It has been suggested that A$_1$Rs largely maintain tonic homeostatic adenosine functions whereas A$_2$A$_R$s mostly exert its fine-tuning modulation under some pathophysiological situations [170, 186]. Such receptor discrimination may be achieved through the pattern of neuronal firing (i.e. with high neuronal discharge, there may be higher levels of ATP and adenosine in the synapse), the different sources of adenosine (i.e. intra- and extracellular formation), the localization of relevant synthetic or metabolic enzymes, or the relative position of adenosine release and receptor sites (synaptically versus extra-synaptically) [35, 94, 174, 184]. Furthermore, the partially overlapping distributions of these two adenosine receptors may also permit local formation of heteromers to exert their opposite modulating effects directly via a so called “concentration-dependent switch” mechanism [54].

**2. Interaction Between Adenosine A$_2$A$_R$s and Dopamine D$_1$Rs**

Striatal A$_1$Rs and A$_2$A$_R$s are major neuromodulator receptors that exert profound effects on D$_1$Rs- and D$_2$R-mediated dopamine signalling and function in the striatum. Evidence suggests the existence of antagonistic A$_1$R-D$_1$R heteromeric receptor complexes in the basal ganglia and prefrontal cortex, particularly in the direct striatonigral GABA pathways. The antagonistic A$_1$R-D$_1$R interactions at the neurochemical and behavioral levels can be explained in part by the existence of such A$_1$R-D$_1$R heteromeric receptor complexes and by antagonistic interactions at the level of the second messengers. On the other hand, A$_2$A$_R$-D$_2$R heteromers have been demonstrated as the first example of epitope-epitope electrostatic interactions underlying receptor heteromerization [55]. A large number of studies with different techniques, i.e. coimmunoprecipitation, fluorescence resonance energy transfer (FRET), bioluminescence resonance energy transfer (BRET), biochemical binding and signaling, microdialysis and behavioral pharmacology have indicated the existence of A$_2$A$_R$-D$_1$R heterodimers in the striatonigral GABA neurons, where activation of A$_2$A$_R$s reduces binding, coupling and signaling of D$_1$Rs [18, 23, 52, 91, 207]. However, since supporting evidence from in vivo coimmunoprecipitation studies could be subjected to other interpretations, the evidence of A$_2$A$_R$-D$_1$R dimmers in intact brain tissues is still not clear yet. Further studies are needed to conclusively demonstrate the functional significance of receptor heterodimer in vivo.

The antagonistic A$_2$A$_R$-D$_1$R interactions in brain have also been demonstrated at the second messenger levels [146, 183, 199], through which the A$_2$A$_R$ strongly modulates the excitability in the striato-pallidal GABA neurons probably via its ability to counteract D$_1$R signaling to multiple effectors. For example, the activation of the A$_2$A$_R$ can counter the D$_1$R-induced inhibition of the Ca$^{2+}$ influx over the L-type voltage-dependent Ca$^{2+}$ channels (CAV3.1 channels) via the activation of phospholipase C and protein phosphatase-2B [54, 90]. The counteraction of this cascade by A$_2$A$_R$s may involveG$_o$ and/or G$_{olf}$ protein with release of the $\beta y$ subunits, and leads to increased phosphorylation of CAV3.1 channels and favoring an upstate of the striatal neuronal firing [200]. Furthermore, the D$_1$R-induced reduction of firing rates in the dopamine-denervated striatum is enhanced by A$_2$A$_R$ antagonists and attenuated by A$_2$A$_R$ agonists [199]. There also ex-
ists a reciprocal interaction between A\textsubscript{2A}R-D\textsubscript{1}R receptors, through which the activation of D\textsubscript{2}Rs can inhibit the A\textsubscript{2A}R-induced increase in cAMP accumulation via G\textsubscript{i/o} at the level of adenylate cyclases [54, 69, 114].

3. Interaction Between Adenosine A\textsubscript{2A}Rs and Dopamine D\textsubscript{1}Rs

Pharmacological studies have revealed functional interaction between A\textsubscript{2A}R and D\textsubscript{1}R [144, 145, 162, 163]. At the systemic level, pharmacological blockade of A\textsubscript{2A}R potentiates D\textsubscript{1}R agonist-induced rotational behavior [145] and c-fos expression in dopamine-depleted striatum [162]. The modulation of phosphorylation on neuronal dopamine and cAMP-regulated phosphoprotein 32 (DARRP-32) by the interaction of A\textsubscript{2A}R and D\textsubscript{1}R has been investigated in brain slices and intact animals [85, 205]. DARRP-32 is expressed in the medium spiny neurons of both the direct and indirect pathways. Stimulation of D\textsubscript{1}Rs and A\textsubscript{2A}Rs or blockade of D\textsubscript{2}Rs increases DARRP-32 phosphorylation in distinct cell populations of the striatum [204]. Blockade of A\textsubscript{2A}Rs or stimulation of D\textsubscript{2}Rs not only abolishes D\textsubscript{2}R antagonist- or A\textsubscript{2A}R agonist-induced DARRP-32 phosphorylation, but also antagonizes the D\textsubscript{1}R agonist-induced DARRP-32 phosphorylation in the striatum [201]. Furthermore, tetrodotoxin (TTX) blocks this A\textsubscript{2A}R-D\textsubscript{1}R interaction, suggesting a trans-synaptic (network) cross-talk between A\textsubscript{2A}Rs and D\textsubscript{1}Rs [127]. Importantly, DARRP-32 can integrate two distinct pathways, adenosine and dopamine signaling, thus providing a possible molecular explanation for the long-known behavioral interaction between A\textsubscript{2A}Rs and D\textsubscript{1}Rs [63]. Lindskog et al. (2002) suggested that DARRP-32 is required for A\textsubscript{2A}R inhibition-induced persistent motor stimulation since caffeine-induced motor activity is greatly reduced in DARPP-32 knockout mice [128]. At the molecular level, caffeine treatment reduces phosphorylation of DARPP-32 at the Thr34 site by blocking A\textsubscript{2A}Rs [201]. Conversely, caffeine increases phosphorylation of DARPP-32 at the Thr75 site via an inhibitory feedback loop of protein kinase A (PKA), which leads to further reduction of PKA activity through feedback inhibition [14, 128, 152]. Thus, DARPP-32 appears to be an important molecular target for integration of adenosine and dopamine signaling through phosphorylation at Thr34 and Thr75 sites.

Recently, a genetic study of drug addiction showed that D\textsubscript{1}R-A\textsubscript{2A}R double knockout mice shared phenotypic similarities of some behavioral components with A\textsubscript{2A}R knockout mice or the mice with sole deficiency of D\textsubscript{1}Rs in terms of preference for ethanol and saccharin; whereas other components of behavioral phenotypes in the D\textsubscript{1}R-A\textsubscript{2A}R double knockouts were likely attributable to the loss of both receptors [191]. These data suggest an interaction of D\textsubscript{1}Rs and A\textsubscript{2A}Rs in the reinforcement processes underlying the intake of rewarding substances. In addition, there is limited evidence for the interaction of A\textsubscript{2A}R and D\textsubscript{1}R [210].

4. Interaction Between A\textsubscript{2A}Rs and Glutamatergic Neurotransmission

Glutamate is the main excitatory neurotransmitter in the CNS. Glutamate activates either ionotropic receptors (including NMDAR, AMPAR and kainate-type receptor) that are mostly localized in the postsynaptic density [12] or G protein-coupled metabotropic glutamate receptors (mGluRs) that are mostly localized extrasynaptically [209]. A\textsubscript{2A}Rs interact with glutamatergic system at several levels in the brain. First, ultrastructural findings suggest that extra-striatal A\textsubscript{2A}Rs are mostly synaptically-located [171], particularly in glutamatergic synapses [173]. These presynaptic A\textsubscript{2A}Rs have been demonstrated to control the release of glutamate in the striatum, cerebral cortex and hippocampus [24, 130, 134, 164] and NMDAR activity in the striatum [172]. Second, it has been reported that A\textsubscript{2A}Rs may indirectly control the level of extracellular glutamate by modulating the activity of glutamate transporter in astrocytes [72, 154].

Third, the receptor heterodimer mechanism is also suggested to underlie the interaction of A\textsubscript{2A}R and the glutamatergic system, particularly with mGluR. The immunoreactivities of A\textsubscript{2A}R and mGluR5 were found to be colocalized in primary cultures of striatal neurons [68] as well as in striatal glutamate nerve terminals [177]. Furthermore, communique precipitation studies suggest that the existence of possible heteromeric receptor complexes containing A\textsubscript{2A}R and mGluR5, where synergism may occur between A\textsubscript{2A}R and mGluR5 [57]. This heteromeric receptor complex is believed to underlie the finding that agonists of A\textsubscript{2A}R and group I mGluR could synergistically reduce the affinity of D\textsubscript{1}R agonist binding sites in striatal membranes [58].

Fourth, concurrent stimulation of A\textsubscript{2A}R and mGluR5 results in synergistic interactions at the level of c-fos expression and phosphorylation of extracellular signal-regulated kinases (ERK) and DARPP-32 in the striatum [57, 153]. Combined A\textsubscript{2A}R and mGluR5 activation have also led to synergistic cellular effects on GABA release in the ventral striato-pallidal GABA neurons [44]. Recently, Coccrello et al. (2004) first demonstrated a synergism between A\textsubscript{2A}R and mGluR5 in the control of locomotion [25], which provides a direct functional link between A\textsubscript{2A}R and the glutamatergic system and also strengthens the A\textsubscript{2A}R as potential target to modulate psychostimulant effects. In addition, a study from Schwarzschild’s group (2005) demonstrated that co-administration of the selective mGluR5 antagonist MPEP and selective A\textsubscript{2A}R antagonist KW-6002 exerts synergistic locomotor stimulation in both normal and Parkinsonian mice [98]. The dependence of MPEP-induced motor activity on the A\textsubscript{2A}R and mGlu5R further demonstrates the functional interaction between A\textsubscript{2A}R and mGluR5 at the behavioral level.

PSYCHIATRIC BEHAVIORAL EFFECTS AND THERAPEUTIC POTENTIAL OF A\textsubscript{2A}R MANIPULATION IN THE BRAIN

1. Psychostimulant Effects

A\textsubscript{2A}Rs in medium spiny neurons have been established to be the determinant for the control of motor function, since A\textsubscript{2A}R ligands produce most significant motor effects [63, 64, 181, 183] that were abolished in mice deficient in A\textsubscript{2A}Rs [126]. In fact, A\textsubscript{2A}R modulation of normal or hyperdopaminergic conditions is relevant to psychopharmacology [117, 118], whereas the A\textsubscript{2A}R control of the hypodopaminergic condition is directly relevant to Parkinson’s disease (PD) therapy [38, 180]. In dopamine depleted animals, the main
mechanism by which A2aR antagonists increase motor activity is proposed to be via modulation of GABA release. Thus, the systemic administration of A2aR antagonists increases motor activity in animals pretreated with D2R antagonists, reserpine, 6-OH-dopamine or after genetic inactivation of D2R [21, 88, 102, 161, 190, 214] or MPTP-treated monkeys [86, 103].

On the other hand, the antagonistic interaction of A2aR-D2R is considered to be the basis for the potential therapy of neuropsychiatric disorders. A2aR agonists inhibit, and A2aR antagonists potentiate the motor, discriminative, and rewarding effects of psychostimulants [60, 89, 97, 111, 160, 165, 176, 189]. The non-selective A1R and A2aR antagonist, caffeine, also potentiates these effects of psychostimulants [26, 73, 74, 143, 147]. Intriguingly, genetic inactivation of global A2aR or A2aR in forebrain neurons has been shown to attenuate acute psychostimulant effects as well as psychostimulant behavioral sensitization [10, 20, 21]. To provide an explanation for the well-known discrepancies - pharmacological blockade and genetic deletion of A2aR potentiates and attenuates, respectively, psychostimulant effects [10, 20, 21, 60], we recently showed that the selective inactivation of striatal A2aRs enhances the psychostimulant effect while inactivation of forebrain (including striatal, cortical and hippocampal) A2aRs attenuates psychostimulant effects. This study suggests that striatal A2aR and extra-striatal A2aR offer opposite modulation, possibly through different effects of pre- and post-synaptic A2aRs in the striatum [188].

Furthermore, a recent communoprecipitation study demonstrates that A2aRs are able to form receptor complexes with CB1R in the rat striatum, where they are colocalized in dendritic processes and possibly nerve terminals [19]. Thus, the function of CB1R is apparently dependent on A2aR activation and modulation of A2aRs may affect the rewarding behavior of cannabinoid [6, 219]. In fact, the finding of A2aR-mediated glutamate release and A2aR-CB1R interaction in the striatum opens up an interesting possibility of A2aR-based psychopharmacological therapy.

2. Drug Addiction

Drugs of abuse have varying mechanisms of actions that create complex behavioral patterns related to drug consumption, drug-seeking, withdrawal and relapse. The extracellular levels of adenosine are elevated upon exposure to drugs of abuse [9] and may modify addiction-related behavior [16]. By acting at the A2aR in the ventral striatum, modulation of A2aR activity may influence the reinforcement processes underlying opiate, ethanol and psychostimulant intake [17].

For example, the facilitative role for the A2aR has been suggested in opiate reward, reinforcement as well as opiate-seeking behavior. The A2aR agonist CGS 21680 increases, while the A2aR antagonist DMPX reduces, morphine self-administration in rats [178]. Recently, using A2aR knockout mice, Soria et al. (2006) showed that A2aR knockout mice display a lower rate of cocaine self-administration, a reduction in the maximal effort to obtain a cocaine infusion, and a vertical shift of the cocaine dose-response curve [196]. This indicates that A2aRs seem to be required to develop the addictive effects of this drug. Furthermore, decreased morphine self-administration, breakpoint and conditioned place preference were also observed in A2aR knockout mice [17]. These data support a decrease in motivation of morphine consumption, perhaps reflecting diminished rewarding effects of morphine, in A2aR knockout mice. The mechanism underlying attenuated reward behavior of A2aR knockout mice is not clear, but these findings are consistent with previous studies showing a synergistic rather than an antagonistic D2R-A2aR interaction [16]. Furthermore, a dysregulation of glutamatergic signaling caused by inactivation of presynaptic A2aR could be partially responsible for this phenotype. This is in line with the notion that molecular adaptations of the corticocaudate glutamatergic synapses are involved in compulsive drug seeking and relapse.

However, A2aR inactivation may play a differential role in the modulation of psychostimulant effects, depending on the involvement of either striatal A2aRs located on the medium spiny neurons themselves, or A2aRs located on the cortical glutamatergic afferents that synapse on these striatal neurons [188]. On one hand, the activation of A2aRs can positively modulate glutamatergic input to the nucleus accumbens through synergistic interactions with mGlur5, and thus maintain a facilitative role in behavior such as psycho-motor sensitization and addictive behavior as described above. Alternatively, through antagonistic interaction with D2Rs, activation of A2aRs can attenuate the rewarding effects of psychostimulant drugs. Indeed, in the study of reinstatement of cocaine-seeking behavior [215], the A2aR antagonist CGS15943 was found to reinstate cocaine-seeking and functions as an intravenous reinforcer, while the A2aRs agonist CGS21680 was found to produce a rightward shift in the CGS15943 reinstatement dose-effect curve. Thus, it remains to be determined whether A2aR influences reward via striatal A2aRs or extra-striatal A2aRs. It is also possible that A2aRs may either directly interact with the reward (i.e. dopamine or opioid) system or indirectly via interaction with other neurotransmitter systems such as glutamate or cannabinoids in the brain.

3. Anxiety

Clinical investigations, pharmacological studies and models of genetically modified rodents have implicated adenosine receptors in the etiology and modulation of various types of anxiety. Caffeine and alcohol have been involved in anxiety-related behavior, due to their antagonism at adenosine receptors and ability to increase adenosine levels, respectively. The adenosine effects on anxiety have been partly attributed to the anxiogenic effects of A1R antagonism. However, there are several lines of evidence indicating the involvement of the A2aR in anxiety. First, spontaneous anxiety-like behavior is enhanced in A2aR knockout mice compared to their WT littermates [13, 15, 122], indicating that adaptive mechanisms in A2aR knockouts may result in increased propensity for anxiety. Second, human genetic association studies indicate the association between A2aR gene polymorphisms and caffeine-induced anxiety [4, 5, 211]. Third, pharmacological studies with caffeine suggest the involvement of adenosine receptor in anxiety-related behavior. It is reported that adenosine has anxiolytic effects, which could be reversed by pretreatment with caffeine and...
the depression levels in the hippocampus [218]. Given the increasingly re
caffeine, probably
m
target.
in A
D
behavioral despair’ in these two screening tests [48]. The same
motionally, A
stress [30]. A
in the hippocampus of rats subjected to sub
early
inescapabl
sine and its analogues caused depressant
of adenosine receptors, the NO
has an antidepressant effect, which involves the r
clear yet. A series of studies showed that administr
the pharmacological effect of adenosine on depression is not
[41]. Thus, the classical antidepressants also r
the activity of ecto-nucleotidases in cortical nerve terminals
[112, 113]. However, the
pharmacological effect of adenosine on depression is not clear yet. A series of studies showed that administration of
adenosine, either peripherally or intra-cerebroventricularly, has an antidepressant effect, which involves the recruitment of
adenosine receptors, the NO-cGMP system, or the opioid
system [104-106]. However, other studies found that aden
sine and its analogues caused depressant-like behavioral ef
fects by increasing immobilization time in rats submitted to
inescapable shocks and forced swim tests [93, 141, 142,
17].

At the receptor level, the blockade of A
Rs relieves the early stress-induced loss of synaptophysin, a synaptic marker, in the hippocampus of rats subjected to sub
chronic restraint stress [30]. A
R antagonists prolong escape-directed beha
or in the tail suspension and forced swim tests [49]. Addi
tionally, A
R knockout mice displayed an attenuated ‘be
havioral despair’ in these two screening tests [48]. The same
research group furthermore demonstrated that haloperidol (a
D
R antagonist) prevented the antidepressant effects result
ng from A
Rs blockade [48, 49]. This evidence suggests a
potential role of A
R modulation as novel anti-depressant target.

However, mechanisms by which the A
R exerts its modula
tion of depression are not clear yet, but adenosine modula
tion of the serotoninergic system may in part be re
sponsible [78]. For example, adenosine receptors have been
shown to control the release of serotonin [156]. Furthermore,
caffeine, probably via blockade of A
R, relieves restraint
induced stress, which correlates with reduction of serotonin
levels in the hippocampus [218]. Given the increasingly rec
ognized role of neurogenesis and neuronal trophic factors in
the depression-related behavior [136, 137], it is interesting to
note the novel interaction between A
Rs and Trk-B recep
tors [95], and neurotrophins, such as brain-derived neurotrophic
factor (BDNF) [45, 123], which may provide another potential mechanism for the involvement of A
Rs in anxiety
modulation. Thus, beyond interaction with D
Rs, the interaction
of the A
R with other neurotransmitter systems, such as glutamatergic, serotoninergic, and corticotrophin system as
well as trophic factors should be examined.

5. Schizophrenia

Schizophrenia is a complex neuropsychiatric disorder charac
terized by cognitive deficits, and positive and negative
symptoms [99, 150]. Almost all antipsychotics currently
used in clinical practice are dopamine D
Rs antagonists, though they produce many side effects. The development
of novel pharmacological targets for antipsychotics is still very
limited, primarily due to the heterogeneity, lack of solid ana
tomical or neurochemical basis of the disorder, and lack of
an adequate animal model that faithfully mimics the features
of behavioral changes found in this psychiatric disorder [28,
51, 100, 101]. To date, many biochemical and neurochemical
markers as well as a rather broad brain area have been impli
cated in the pathogenesis of diverse psychiatric disorders
[11, 133, 149, 195, 197]. On the other hand, the current
evaluation of the efficacy of novel antipsychotics still largely
relies on the alleviation of behavioral changes that charac
terize schizophrenia.

Recent progress in adenosine neurobiology supports the
notion of adenosine-based therapy and the A
R as a novel
therapeutic target for the treatment of psychiatric disorders.
The first line of evidence came from pharmacological and
genetic studies showing that A
R activity affects schizo
phrenia-like behaviors in patients. Caffeine exacerbates posi
tive symptoms [39, 132, 138, 140, 151] of schizophrenia,
whereas adenosine transport inhibitors (such as dipyrida
mole) and xanthine oxidase inhibitors (such as allopurinol)
may be beneficial for schizophrenia [2, 3]. Intriguingly, a
clinical report suggests that poorly responsive schizophrenic
patients improved considerably with add-on of allopurinol
[116]. Early studies found that a single-nucleotide polymor
phism (SNP) of the A
R gene was a candidate for a schizo
phrenia susceptibility gene on chromosome 22q12-13 [42,
92], but this has not been replicated by others. Furthermore,
theophylline was shown to mimic deficiency of sensorimotor
gating [77], as evaluated by a disturbed prepulse inhibition
or P50 evoked potential found in schizophrenic individuals
[167]. These observations of clinical genetics warrant further
investigation.

Second, the adenosine-hypofunction hypothesis of schizo
phrenia is further supported by studies from Yee et al. (2007)
[220] using a transgenic mouse model with overexpression
of adenosine kinase, causing decreased adenosine levels in
forebrain. They demonstrated that subtle changes in aden
sine levels in forebrain could lead to the emergence of be
havioral endophenotypes implicated in schizophrenia and
abnormal response to psychostimulants, i.e. amphetamine
and MK-801 [220]. It is also reported that startle habituation
(a measure of sensorimotor function) was reduced by A
R
antagonists [148] and genetic deletion of A
Rs in mice
[213]. The third line of evidence in supporting a role of
A$_{2A}$Rs in the pathophysiology of schizophrenia came from observations that treatment with antipsychotic drugs alter the adenosinergic system in animals and in humans [4, 135, 148, 159, 213]. It was also observed that clozapine, an atypical antipsychotic, induced c-fos expression that could be blocked by A$_{2A}$R antagonists in rodents [159]. In addition, this clozapine-induced antipsychotic effect also affects the ectonucleotidase pathway, thus consequently modulates adenosine levels and resulting activation of A$_{2A}$Rs [119]. In clinical studies, Martini et al. (2006) demonstrated an upregulation of A$_{2A}$R in platelets from patients under treatment with haloperidol, a typical antipsychotic [135]. This study also revealed the co-expression of A$_{2A}$Rs and D$_2$Rs assembled into heteromeric complexes in human platelets. Conversely, chronic treatment with non-dopamine based atypical antipsychotic was not able to induce any significant alterations in A$_{2A}$R equilibrium binding parameters and receptor responsiveness. In line with this finding, an upregulation of striatal A$_{2A}$Rs has been demonstrated to occur in schizophrenia patients with antipsychotic treatment [4]. Noticeably, the increased A$_{2A}$R density correlated with the dose of antipsychotics in chlorpromazine equivalents, which suggests a role of A$_{2A}$Rs in the molecular effects of antipsychotic drugs.

The fourth line of evidence came from molecular studies suggesting a modulatory role of A$_{2A}$Rs as a fine-tuner in rebalancing an impaired glutamatergic-dopaminergic communication. Regarding dopaminergic function, the antagonistic interaction of A$_{2A}$R-D$_2$R in the striatum suggested antipsychotic behavior in schizophrenia by A$_{2A}$R agonist to function as a dopamine receptor antagonist. The activation of A$_{2A}$Rs can reduce D$_2$R affinity and function, which may potentially underlie the antipsychotic-like profile of adenosine agonists [56], the hyperdopaminergic effect of caffeine [53, 56] and the exacerbation of psychotic symptoms by caffeine in schizophrenic patients [132]. More data discussed in other reviews suggested the relationship between hyperdopaminergic transmission and unbalanced adenosinergic modulation in the striatum [82, 120, 187, 202]. These observations support the possibility that the manipulation of A$_{2A}$Rs (by activation of A$_{2A}$R) may help restore an adequate dopaminergic signaling. Regarding glutamatergic function, A$_{1}$R and A$_{2A}$R agonists have both been shown to prevent behavioral and EEG effects induced by NMDAR antagonists [166, 193]. In an NMDAR hypofunction model of schizophrenia [157], the function of NMDARs could be modified by both A$_{1}$R and A$_{2A}$R activities [40, 76, 172, 208, 216]. Furthermore, both A$_{1}$Rs and A$_{2A}$Rs control the evoked release of glutamate in striatum [24, 177]. Conversely, the activation of the NMDAR increases the adenosine tone [139], while inhibition of the NMDAR reduced adenosine release [43]. Importantly, the psychostimulant effects of NMDAR antagonists are largely abolished by genetic inactivation or pharmacological blockade of A$_{2A}$Rs [176, 188]. These studies suggest that modulation of A$_{2A}$Rs may re-balance the hypofunction of NMDARs in models of schizophrenia. As reviewed in the above sections, the existence of heteromeric A$_{2A}$R-D$_2$R and A$_{2A}$R-mGluR5 receptor complexes may also strengthen the potential modulation of A$_{2A}$R on schizophrenia therapy [206].

However, the effect of adenosine modulation on psychiatric disorders is likely more complex, with involvement of different neurotransmitter systems in various brain regions. For example, we recently demonstrated that striatal deletion of A$_{2A}$Rs enhances the actions of psychostimulants, whereas deletion of A$_{2A}$Rs in forebrain (including striatum, cortex and hippocampus) attenuates the effect of psychostimulants. These data suggest that striatal A$_{2A}$Rs and extra-striatal A$_{2A}$Rs exert different effects on psychomotor activity. Thus, adenosine-based psychopharmacological therapy may rely on the status or degree of dysfunction in other neurotransmitters, or spatial targeting of adenosine agonists/antagonists, or drug specificity, selectivity, dosage and paradigm.

6. Learning and Memory

Several recent pharmacological and genetic studies suggest a potential modulatory role of brain A$_{2A}$R activity on learning, memory, and other cognitive process [34, 181]. For example, local administration of A$_{2A}$R agonists into the posterior cingulate cortex impaired memory retrieval in rats [158]. Conversely, the A$_{2A}$R antagonist SCH58261 and caffeine have been shown to improve social recognition memory [169] and improve memory performance in rodents through different tasks [206]. Genetic inactivation of the A$_{2A}$Rs enhanced spatial recognition memory and novelty exploration in Y-maze testing in mice [212]. Recently, two studies demonstrated that both pharmacological blockade and genetic inactivation of A$_{2A}$Rs attenuated β-amyloid-induced memory loss [29, 37]. The above results suggest that the A$_{2A}$R activity can modify the spatial memory process in rodents.

On the other hand, working memory primarily depends on the integrity of prefrontal cortical function [80] and is critical to human reasoning and judgment, which is at the core of pathophysiology for many neuropsychiatric disorders such as Alzheimer’s disease [8, 107, 126] and schizophrenia [81]. The control of working memory by A$_{2A}$Rs [169] is supported by several elegant behavioral studies showing an impact of caffeine [168]. Recently, transgenic overexpression of A$_{2A}$Rs in cortex has been shown to impair spatial working memory in radial maze, repeated trials of Morris water maze and objective recognition tests [79]. In agreement with this finding, we recently observed (unpublished data) that genetic inactivation of A$_{2A}$Rs significantly improved working memory; furthermore, the improved working memory was selective for this specific short-term memory whereas the performance of spatial reference memory and the memory retention after prolonged training was largely indistinguishable between A$_{2A}$R knockout mice and their WT littermates. These results suggest a selective modulatory role of A$_{2A}$R activity in working memory.

CONCLUDING REMARKS

In this review, we have described the role of adenosine A$_{2A}$ receptor-driven interactions with other neurotransmitter systems, at multiple levels of psychopharmacology, from the molecular basis of receptor-receptor cross-talk, to pharmacological and genetic manipulations of A$_{2A}$R activity, and the alteration of neuropsychiatric phenotypes in psychostimulant addiction, anxiety and depression, schizophrenia-
nia and learning and memory. Based on the literature to date, the A$_2$AR is involved in multiple receptor-receptor interactions, multiple neurotransmissions and multiple neuropsychiatric disorders. In particular, it tightly interacts with two main neurotransmitter systems, the dopaminergic and glutamatergic signaling pathways, with implications for a wide range of psychiatric behaviors and several psychiatric disorders. Hence, A$_2$ARs are ideally positioned as a fine-tuner, providing integrated effects between glutamatergic and dopaminergic signaling, and may represent a novel neuropsychopharmacology target.

Despite its attractive therapeutic potential, several concerns need to be introduced, when evaluating the putative role(s) of A$_2$ARs in psychopharmacology. First, since adenosine system works via neuromodulation, the modulatory ability of the adenosine system (including the A$_2$AR) may depend on and may intrinsically be linked with the activity of other "potent" neurotransmission systems, i.e. dopaminergic, glutamatergic and serotonergic systems. Second, a primary role of the adenosine neuromodulatory system seems to be maintenance of homeostasis or promotion of the adaptation of multiple neurotransmitter systems in the brain. Thus, adenosine, and A$_2$Rs in particular, seem to curtail extremes (i.e. over-stimulation or under-stimulation) of these neurotransmitter systems in the brain. A$_2$AR-based modulation may largely be exerted, once disequilibrium of neurotransmitter systems occurs. Third, extracellular adenosine may act at A$_2$ARs and A$_1$Rs with globally opposite functions, or may act at the A$_2$AR in different brain regions with its differential action to exert modulating effects. The balanced outcome of adenosine actions may be in part controlled by neuroadaptation or maladaptation of neurotransmission, by which it exerts its effect and may in part depend on the preferential sites of pharmacological reagent activity.

ACKNOWLEDGEMENT

This work has been supported by the National Institute of Health (MH083973 and DA19362).

REFERENCES

[1] Agnati, L.F., Fuxe, K., Zini, I., Lenzi, P., Hokfelt, T. (1980) Aspects on receptor regulation and isoreceptor identification. Med. Biol., 58, 182-187.

[2] Akhondzadeh, S., Safarcherati, A., Amini, H. (2005) Beneficial antipsychotic effects of allopurinol as add-on therapy for schizophrenia: a double blind, randomized and placebo controlled trial. Prog. Neuropsychopharmacol. Biol. Psychiatry, 29, 253-259.

[3] Akhondzadeh, S., Shasavand, E., Jamilian, H., Shabestari, O., Kamalipour, A. (2000) Dipyridamole in the treatment of schizophrenia: adenosine-dopamine receptor interactions. J. Clin. Pharm. Ther., 25, 131-137.

[4] Alsene, K., Deckert, J., Sand, P., de Wit, H. (2003) Association between A2A receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology, 28, 1694-1702.

[5] Alsene, K.M., Wachtel, S., Jurgen, D., Wit, H.d. (2002) Polymorphisms in the adenosine A2A receptor gene are related to caffeine-induced anxiety. Annual meeting for Society for Neuroscience. Orlando, Florida.

[6] Andersson, M., Usiello, A., Borgkvist, A., Pozzi, L., Dominguez, C., Fienberg, A.A., Svenningsson, P., Fredholm, B.B., Borrelli, E., Greengard, P., Fisone, G. (2005) Cannabinoid action depends on phosphorylation of dopamine- and cAMP-regulated phosphoprotein of 32 kDa at the protein kinase A site in striatal projection neurons. J. Neurosci., 25, 8432-8438.

[7] Augood, S.J., Emson, P.C. (1994) Adenosine A2A receptor mRNA is expressed by enkephalin cells but not by somatostatin cells in rat striatum: a co-expression study. Brain. Res. Mol. Brain Res., 22, 204-210.

[8] Baddeley, A.D., Bressi, S., Dellu Sala, S., Logie, R., Spinnler, H. (1991) The decline of working memory in Alzheimer's disease. A longitudinal study. Brain, 114 (Pt 6), 2531-2542.

[9] Baldo, B.A., Koob, G.F., Markou, A. (1999) Role of adenosine A2 receptors in brain stimulation reward under baseline conditions and during cocaine withdrawal in rats. J. Neurosci., 19, 11017-11026.

[10] 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. Neuropharmacology, 30, 891-900.

[11] Belmaker, R.H., Agam, G., Berdyskay, Y. (2008) Role of GSK3beta in behavioral abnormalities induced by serotonin deficiency. Proc. Natl. Acad. Sci. USA, 105, E23.

[12] Bernard, V., Bolam, J.P. (1998) Subcellular and subsynaptic distribution of the NR1 subunit of the NMDA receptor in the neostriatum and globus pallidus of the rat: co-localization at synapses with the GluR2/3 subunit of the AMPA receptor. Eur. J. Neurosci., 10, 3721-3736.

[13] Berrendero, F., Castane, A., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O. (2003) Increase of morphine withdrawal in mice lacking A2A receptors and no changes in CB1/CB2 double knockout mice. Eur. J. Neurosci., 17, 315-324.

[14] Bibb, J.A., Snyder, G.L., Nishi, A., Yan, Z., Meijer, L., Fienberg, A.A., Tsai, L.H., Kwon, Y.T., Girault, J.A., Czersnik, A.J., Huganir, R.L., Hemmings, H.C., Jr., Nairn, A.C., Greengard, P. (1999) Phosphorylation of DARPP-32 by Cdk5 modulates dopamine signaling in neurons. Nature, 402, 669-671.

[15] Bilbao, A., Cippitelli, A., Marini, A.B., Granado, N., Ortis, O., Bezard, E., Chen, J.F., Navarro, M., Rodríguez de Fonseca, F., Morattalla, R. (2006) Absence of quasi-morphine withdrawal syndrome in adenosine A2A receptor knockout mice. Psychopharmacology (Berl.), 185, 160-168.

[16] Brown, R.M., Short, J.L. (2008) Adenosine A2A receptors and their role in drug addiction. J. Pharm. Pharmacol., 60, 1409-1430.

[17] Brown, R.M., Short, J.L., Cowen, M.S., Ledent, C., Lawrence, A.J. (2009) A differential role for the adenosine A2A receptor in opiate reinforcement vs opiate-seeking behavior. Neuropsychopharmacology, 34, 844-856.

[18] Canals, M., Marcellino, D., Fanelli, F., Ciruela, F., de Benedetti, P., Goldberg, S.R., Neve, K., Fuxe, K., Agnati, L.F., Woods, A.S., Ferre, S., Lluis, C., Boulvier, M., Franco, R. (2003) Adenosine A2A-dopamine D2 receptor-receptor heteromerization: qualitative and quantitative assessment by fluorescence and bioluminescence energy transfer. J. Biol. Chem., 278, 46741-46749.

[19] Carriba, P., Ortiz, O., Patkar, K., Justinoa, Z., Strom, J., Themann, A., Muller, C., Woods, A.S., Hope, B.T., Ciruela, F., Casado, V., Canals, E., Lluis, C., Goldberg, S.R., Moc, C., Franco, R., Ferre, S. (2007) Striatal adenosine A2A and cannabinoid CB1 receptors form functional heteromeric complexes that mediate the motor effects of cannabinoids. Neuropsychopharmacology, 32, 2249-2259.

[20] Chen, J.-F., Morattalla, R., Yu, L-Q, Ana B. Mart, A.B., Xu, K., Bastia, E., Hackett, E., Israel Alberti, I., Schwarzschild, M.A. (2003) Inactivation of adenosine A2A receptors selectively attenuates amphetamine-induced behavioral sensitization. Neuropsychopharmacology, 28, 1086-1095.

[21] Chen, J.F., Morattalla, R., Impagnatiello, F., Grandy, D.K., Cuellar, B., Rubinstein, M., Beilstein, M.A., Hackett, E., Fink, J.S., Low, M., Ogini, E., Schwarzschild, M.A. (2001) The role of the D2 dopamine receptor (D(2)R) in A(2A) adenosine receptor (A(2A)R)-mediated behavioral and cellular responses as revealed by A(2A) and D(2) receptor knockout mice. Proc. Natl. Acad. Sci. USA, 98, 1970-1975.

[22] Chen, J.F., Sonnalis, P.K., Pedata, F., Melani, A., Domenici, M.R., Popoli, P., Geiger, J., Lopes, L.V., de Mendonca, A. (2007) Adenosine A2A receptors and brain injury: broad spectrum of neuroprotection, multifaceted actions and "fine tuning" modulation. Prog. Neurobiol., 83, 310-331.

[23] Ciruela, F., Burguete, J., Casado, V., Canals, M., Marcellino, D., Goldberg, S.R., Bader, M., Fuxe, K., Agnati, L.F., Lluis, C., Franco, R., Ferre, S., Woods, A.S. (2004) Combining mass spec-
adenosine and class II metabotropic glutamate receptors in the regulation of purine and glutamate release from rat hippocampal slices. J. Neurochem., 67, 302-309.

Diaz-Cabiale, Z., Vivo, M., Del Arco, A., O'Connor, W.T., Harte, M.K., Muller, C.E., Martinez, E., Polop, P., Fuxe, K., Ferre, S. (2002) Metabotropic glutamate mGlu5 receptor-mediated modulation of the ventral striatal GABA pathway in rats. Interactions with adenosine A2A and dopamine D2 receptors. Neuroni Sci., 324, 154-158.

Diogenes, M.J., Fernandes, C.C., Sebastiao, A.M., Ribeiro, J.A. (2004) Activation of adenosine A2A receptor facilitates brain-derived neurotrophic factor modulation of synaptic transmission in hippocampal slices. J. Neurosci., 24, 2905-2913.

Dyson, A.K., Widdowson, L., Richardson, P.J. (1997) Desensitisation of the adenosine A1 receptor by the A2A receptor in the rat striatum. J. Neurochem., 69, 315-321.

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., Vaugeois, J.M. (2007) Genetic rodent models of depression. Curr. Opin. Pharmacol., 7, 3-7.

El Yacoubi, M., Ledent, C., Parmentier, M., Bertorelli, R., Ongini, E., Costentin, J., Vaugeois, J.M. (2001) Adenosine A2A receptor antagonists are potential antidepressants: evidence based on pharmacology and A2A receptor knockout mice. Br. J. Pharmacol., 134, 68-77.

El Yacoubi, M., Ledent, C., Parmentier, M., Costentin, J., Vaugeois, J.M. (2000) The anxiogenic-like effect of caffeine in two experimental procedures measuring anxiety in the mouse is not shared by selective A2A adenosine receptor antagonists. Psychopharmacology (Berl.), 148, 153-163.

El Yacoubi, M., Vaugeois, J.M. (2007) Animal models of mood disorders: current developments. Curr. Opin. Psychiatry, 20, 1-7.

Filip, M., Frankowska, M., Zaniewska, M., Przegalinski, E. (2003) Stimulation of high-affinity binding sites for [3H]CGP 12177 and [3H]NECA by adenosine A2A receptors upon sub-chronic restraint stress. Neuroscience, 141, 1775-1781.

Fredholm, B.B. (1996) Evidence for high-affinity binding sites for adenosine in aged striatum, hippocampus and cortex of the rat. Exp. Neurol., 210, 776-781.

Fredholm, B.B., Fuxe, K., Agnati, L.F., Lluis, C., Ciruela, F., Woods, A.S., Fuxe, K., Franco, R. (1996) Signalling and co-operative mechanisms underlying the regulation of striatal neuronal function. Trends Pharmacol. Sci., 17, 1167.

Fredholm, B.B., Fuxe, K., Agnati, L.F., Lluis, C., Woods, A.S., Fuxe, K., Franco, R. (1996) Evidence for high-affinity binding sites for adenosine A2A receptors and depression. Nature, 382, 80-87.

Fredholm, B.B., Fuxe, K., Agnati, L.F., Lluis, C., Woods, A.S., Fuxe, K., Franco, R. (1996) Evidence for high-affinity binding sites for adenosine A2A receptors and depression. Nature, 382, 80-87.

Fredholm, B.B., Fuxe, K., Agnati, L.F., Lluis, C., Woods, A.S., Fuxe, K., Franco, R. (1996) Evidence for high-affinity binding sites for adenosine A2A receptors and depression. Neurology, 49, 1383-1389.

Fredholm, B.B., Fuxe, K., Agnati, L.F., Lluis, C., Woods, A.S., Fuxe, K., Franco, R. (1996) Evidence for high-affinity binding sites for adenosine A2A receptors and depression. Neurology, 49, 1383-1389.
Adenosine A<sub>2A</sub> Receptors in Psychopharmacology

Current Neuropharmacology, 2009, Vol. 7, No. 3 203

Fredholm, B.B. (2003) Adenosine targets as drug development. Drug News Perspect., 16, 283-289.

Fredholm, B.B., Chen, J.F., Cunha, R.A., Svenningsson, P., Vaeggoes, J.M. (2005) Adenosine and brain function. Int. Rev. Neurobiol., 63, 191-270.

Fredholm, B.B., Chen, J.F., Masino, S.A., Vaeggoes, J.M. (2005) Actions of adenosine at its receptors in the CNS: insights from knockouts and drugs. Annu. Rev. Pharmacol. Toxicol., 45, 385-412.

Fredholm, B.B., Cunha, R.A., Svenningsson, P. (2003) Pharmacology of Adenosine A2A Receptors and Therapeutic Applications. Chem. Top. Med. Chem., 3, 413-426.

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

Furlan, E., Koelh, P. (1998) Influence of protein structure databases on the predictive power of statistical potentials. Proteins Struct. Funct. Genetics, 31, 139-149.

Fuxe, K., Agnati, L.F., Jacobsen, K., Hillion, J., Canals, M., Torvinen, M., Tinner-Staines, B., Staines, W., Rosin, D., Terasmaa, A., Poloppi, P., Leo, G., Vergoni, V., Lluís, C., Ciruela, F., Franco, R., Ferre, S. (2003) Receptor heteromerization in adenosine A2A receptor signaling: relevance for striatal function and Parkinson's disease. Neurology, 61, S19-23.

Fuxe, K., Ferre, S., Canals, M., Torvinen, M., Terasmaa, A., Marcelino, D., Goldberg, S.R., Staines, W., Jacobsen, K.K., Lluís, C., Woods, A.S., Agnati, L.F., Franco, R. (2005) Adenosine A2A and dopamine D2 heteromer receptor complexes and their function. J. Mol. Neurosci., 26, 209-220.

Fuxe, K., Kohler, C., Agnati, L.F., Andersson, K., Ogren, S.O., Eneroth, P., Perez de la Mora, M., Karobath, M., Krogsgaard-Larsen, P. (1981) GABA and benzodiazepine receptors. Studies on their localization in the hippocampus and their interaction with central dopamine neurons in the rat brain. Adv. Biochem. Psychopharmacol., 26, 61-76.

Fuxe, K., Marcellin, D., Guidolin, D., Woods, A.S., Agnati, L.F. (2008) Heterodimers and receptor mosaics of different types of G-protein-coupled receptors. Physiology (Bethesda), 23, 322-332.

Gao, W.J., Krimer, L.S., Goldman-Rakic, P.S. (2001) Presynaptic regulation of recurrent excitation by D1 receptors in prefrontal circuits. Proc. Natl. Acad. Sci. USA, 98, 295-300.

Gasior, M., Jaszyna, M., Peters, J., Goldberg, S.R. (2000) Changes in the ambulatory activity and discriminative stimulus effects of psychostimulant drugs in rats chronically exposed to caffeine: effect of caffeine dose. J. Pharmacol. Exp. Ther., 295, 1101-1111.

Gavin, D.V., Criado, J.R., Moore, K.R., Holloway, F.A. (1999) Comparison of the behavioral effects of adenosine agonists and dopamine antagonists in mice. Psychopharmacology, 98, 31-37.

Hernandez-Lopez, S., Tkatch, T., Perez-Garcì, E., Galaraga, E., Burgas, J., Hamm, H., Surmeier, D.J. (2000) D2 dopamine receptors in striatal medium spiny neurons reduce L-type Ca2+ currents and excitability via a novel PLC[beta]1-IP3-calcineurin-signaling cascade. J. Neurosci., 20, 8987-8995.

Hillion, J., Canals, M., Torvinen, M., Casado, V., Scott, R., Terasmaa, A., Hansson, A., Watson, S., Olah, M.E., Mallol, J., Canela, E.I., Zoli, M., Agnati, L.F., Ibanez, C.F., Lluís, C., Franco, R., Ferre, S., Fuxe, K. (2002) Coaggregation, cointernalization, and their localization in the hippocampus and their interaction with central dopamine neurons in the rat brain. Adv. Biochem. Psychopharmacol., 26, 61-76.

Gierer, Z., Wirkner, K., Illés, P. (2002) Adenosine A2A receptors inhibit the N-methyl-D-aspartate component of excitatory synaptic currents in rat striatal neurons. Eur. J. Pharmacol., 451, 161-164.

Ghisoili, E.S., Prokopuik, A.S., Becker, J., Ehlers, J.A., Belmonte-de-Abreu, F., Souza, D.O., Lara, D.R. (2002) The adenosine antagonist theophylline impairs p50 auditory sensory gating in normal subjects. Neuropsychopharmacology, 27, 629-637.

Gillman, P.K. (2007) Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br. J. Pharmacol., 151, 737-748.

Gomez-Llort, L., Fernandez-Teniel, A., Escorialua, R.M., Fredholm, B.B., Tobena, A., Pekny, M., Johansson, B. (2002) Mice lacking the adenosine A1 receptor are anxious and aggressive, but are normal learners with reduced muscle strength and survival rate. Eur. J. Neurosci., 16, 547-550.

Goldman-Rakic, P.S. (1999) The physiological approach: functional architecture of working memory and Disorders in cognition in schizophrenia. Rev. Perinol. Neurobiol., 46, 659-661.

Goldman-Rakic, P.S., Castner, S.A., Svenness, T.H., Siever, L.J., Williams, G.V. (2004) Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. Psychopharmacology (Berl.), 174, 3-16.
Kanda, T., Shiozaki, S., Shimada, J., Suzuki, F., Nakamura, J. (1994) FK17837: a novel selective adenosine A2A receptor antagonist with antialcetile activity. *Eur. J. Pharmacol.*, 256, 263-268.

Kanda, T., Tashiro, T., Kuwana, Y., Jenner, P. (1998) Adenosine A2A receptors modify motor function in MPTP-treated common marmosets. *Neuroreport*, 9, 2857-2860.

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.

Kaster, M.P., Rosa, A.O., Rosso, M.M., Goulart, E.C., Santos, A.R., Rodrigues, A.L. (2004) Adenosine administration produces an antidepressant-like effect in mice: evidence for the involvement of A1 and A2A receptors. *Neurosci. Lett.*, 355, 21-24.

Kaster, M.P., Rosa, A.O., Santos, A.R., Rodrigues, A.L. (2005) Involvement of nitric oxide-cGMP pathway in the antidepressant-like effects of adenosine in the forced swimming test. *Int. J. Neuropsychopharmacol.*, 8, 601-606.

Kensinger, E.A., Shearer, D.K., Locascio, J.J., Growdon, J.H., Corkin, S. (2003) Working memory in mild Alzheimer's disease and early Parkinson's disease. *Neuropsychology*, 17, 230-239.

Kirk, I.P., Richardson, P.J. (1994) Adenosine A2A receptor-mediated modulation of striatal [3H]GABA and [3H]acetylcholine release. *J. Neurochem.*, 62, 960-966.

Kirk, I.P., Richardson, P.J. (1995) Inhibition of striatal GABA release by the adenosine A2A receptor is not mediated by increases in cyclic AMP. *J. Neurochem.*, 64, 2801-2809.

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

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.

Kulkarni, S.K., Mehta, A.K. (1985) Purine nucleoside-mediated immobility in mice: reversal by antidepressants. *Psychopharmacology (Berl)*, 85, 460-463.

Kulkarni, S.K., Singh, K., Bishnoi, M. (2007) Involvement of adenosinergic receptors in anxiety related behaviours. *Indian J. Exp. Biol.*, 45, 439-443.

Kull, B., Ferre, S., Arslan, G., Svenningson, P., Fuxe, K., Owman, C., Fredholm, B.B. (1999) Reciprocal interactions between adenosine A2A and dopamine D2 receptors in Chinese hamster ovary cells co-transfected with the two receptors. *Biochem. Pharmacol.*, 58, 1035-1045.

Lader, M., Bruce, M. (1986) States of anxiety and their induction by drugs. *Br. J. Clin. Pharmacol.*, 22, 251-261.

Lara, D.R., Brunstein, M.G., Ghisolfi, E.S., Lobato, M.I., Belmonte-de-Abrue, P., Souza, D.O. (2001) Alliporinil augmentation for poorly responsive schizoaffective. *Int. Clin. Psychopharmacol.*, 16, 235-237.

Lara, D.R., Dall'Igna, O.P., Ghisolfi, E.S., Brunstein, M.G. (2006) Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 30, 617-629.

Lee, F.S., Chao, M.V. (2001) Activation of TrkB neurotrophin receptors in the absence of neurotrophins. *Proc. Natl. Acad. Sci. USA*, 98, 3555-3560.

Lieberman, H.R., Tharian, W.J., Shukitt-Hale, B., Speckman, K.L., Tulley, R. (2002) Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. *Sea-Air-Land. Psychopharmacology (Berl)*, 164, 250-261.

Lee, M.R., Wurtman, R.J., Emde, G.G., Covilla, I.L. (1987) The effects of caffeine and aspirin on mood and performance. *J. Clin. Psychopharmacol.*, 7, 315-320.

Limen, H.K., Juh, R., Pae, C.U., Lee, B.T., Yoo, S.S., Ryu, H.S., Kwak, K.R., Lee, C., Lee, C.U. (2008) Altered verbal working memory process in patients with Alzheimer's disease: an fMRI investigation. *Neuropsychopharmacology*, 32, 181-187.

Lindskog, M., Svenningson, P., Fredholm, B.B., Greengard, P., Fisone, G. (1999) Activation of dopamine D2 receptors decreases DARPP-32 phosphorylation in striatognal and striatopallidal projection neurons via different mechanisms. *Neuroscience*, 88, 1005-1008.

Lindskog, M., Svenningson, P., Pozzi, L., Kim, Y., Fienberg, A.A., Bibb, J.A., Fredholm, B.B., Nairn, A.C., Greengard, P., Fisone, G. (2002) Involvement of DARPP-32 phosphorylation in the stimulant action of caffeine. *Nature*, 418, 774-778.

Loke, W.H. (1988) Effects of caffeine on mood and memory. *Physiol. Behav.*, 44, 367-372.

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.

Lopes, L.V., Cunha, R.A., Ribeiro, J.A. (1999) Cross talk between A1 and A2A adenosine receptors in the hippocampus and cortex of young adult and old rats. *J. Neurophysiol.*, 82, 3196-3203.

Lucas, P.B., Pickar, D., Kelsoe, J., Rapaport, M., Pato, C., Homer, D. (1990) Effects of the acute administration of caffeine in patients with schizophrenia. *Biol. Psychiatry*, 28, 35-40.

Maletic, V., Robinson, M., Oakes, T., Iyengar, S., Ball, S.G., Russell, J. (2007) Neuropsychology of depression: an integrated view of key findings. *Int. J. Clin. Pract.*, 61, 2030-2040.

Marchi, M., Raiteri, L., Risso, F., Vallarino, A., Bonfanti, A., Monopolii, A., Onegi, E., Raiteri, M. (2002) Effects of adenosine A1 and A2A receptor activation on the evoked release of glutamate from rat cerebrocortical synaptosomes. *Br. J. Pharmacol.*, 136, 434-440.

Martini, C., Tuscano, D., Trincavelli, M.L., Ceraui, E., Bianchi, M., Ciapparelli, A., Alessio, L., Novelli, L., Catena, M., Lucacchini, A., Cassano, G.B., Dell'Osso, L. (2006) Upregulation of A2A adenosine receptors in platelets from patients affected by bipolar disorders under treatment with typical antipsychotics. *J. Psychiatric. Res.*, 40, 81-88.

Matsushima, K., Hogan, M.J., Hakim, A.M. (1996) Cortical spreading depression protects against subsequent focal cerebral ischemia in rats. *J. Cereb. Blood Flow Metab.*, 16, 221-226.

Matsushima, K., Schmidt-Kastner, R., Hogan, M.J., Hakim, A.M. (1998) Cortical spreading depression activates trophic factor expression in neurons and astrocytes and protects against subsequent focal brain ischemia. *Brain Res.*, 807, 47-60.

Mayo, K.M., Falkowski, W., Jones, C.A. (1996) Caffeine: use and effects in long-stay psychiatric patients. *Br. J. Psychiatry*, 162, 543-545.

Melani, A., Corsi, C., Gimenez-Llort, L., Martinez, E., Ogren, S.O., Petada, F., Ferre, S. (1999) Effect of N-methyl-D-aspartate on motor activity and in vivo adenosine striatal outflow in the rat. *J. Pharmacol. Exp. Ther.*, 289, 15-19.

Mikkelsen, E.J. (1978) Caffeine and schizophrenia. *J. Clin. Psychiatry*, 39, 732-736.

Minor, T.R., Huang, Q., Foley, E.A. (2003) Cytokine-purine interactions in behavioral depression in rats. *Integr. Physiol. Behav. Sci.*, 38, 189-202.

Minor, T.R., Winslow, J.L., Chang, W.C. (1994) Stress and adenosine: II. Adenosine analogs mimic the effect of inescapable shock escape performance in rats. *Behav. Neurosci.*, 108, 265-276.

Misra, A.L., Vadlamani, N.L., Pontani, R.B. (1986) Effect of caffeine on cocaine locomotor stimulant activity in rats. *Pharmacol. Biochem. Behav.*, 24, 761-764.
Adenosine A2A Receptors in Psychopharmacology

Popoli, P., Reggio, R., Pezzola, A. (1997) Adenosine A1 and A2 receptor agonists significantly prevent the electroencephalographic effects induced by MK-801 in rats. *Eur. J. Pharmacol.*, 333, 143-146.

Potter, D., Summerfelt, A., Gold, J., Buchanan, R.W. (2006) Review of clinical correlates of P5 sensory gating abnormalities in patients with schizophrenia. *Schizophr. Bull.*, 32, 602-700.

Prediger, R.D., Da Cunha, C., Takahashi, R.N. (2005) Antagonistic interaction between adenosine A2 and dopamine D2 receptors modulates the social recognition memory in reserpine-treated rats. *Behav. Pharmacol.*, 16, 209-218.

Prediger, R.D., Fernandes, D., Takahashi, R.N. (2005) Blockade of adenosine A2A receptors reverses short-term social memory impairments in spontaneously hypertensive rats. *Behav. Brain Res.*, 159, 197-205.

Queiroz, G., Talia, C., Goncalves, J. (2003) Adenosine A2A receptor-mediated facilitation of noradrenaline release involves protein kinase C activation and attenuation of presynaptic inhibitory receptor-mediated effects in the rat vas deferens. *J. Neurochem.*, 85, 740-748.

Rebola, N., Canas, P.M., Oliveira, C.R., Cunha, R.A. (2005) Different synaptic and subcortical localization of adenosine A2A receptors in the hippocampus and striatum of the rat. *Neuroscience*, 132, 893-903.

Rebola, N., Lujan, R., Cunha, R.A., Mullen, C. (2008) Adenosine A2A receptors are essential for long-term potentiation of NMDA-EPSCs at hippocampal mossy fiber synapses. *Neuron*, 57, 121-134.

Rebola, N., Rodrigues, R.J., Lopes, L.V., Richardson, P.J., Oliveira, C.R., Cunha, R.A. (2005) Adenosine A1 and A2A receptors are co-expressed in pyramidal neurons and co-localized in glutamatergic nerve terminals of the rat hippocampus. *Neuroscience*, 133, 79-83.

Ribeiro, J.A. (1999) Adenosine A2A receptor interactions with receptors for neurotransmitters and neuromodulators. *Eur. J. Pharmacol.*, 375, 101-113.

Ribeiro, J.A., Sebastiao, A.M., de Mendonca, A. (2002) Adenosine receptors in the nervous system: pathophysiological implications. *Prog. Neurobiol.*, 68, 377-392.

Rimondini, R., Ferre, S., Ogren, S.O., Fuxe, K. (1997) Adenosine A2A agonists: a potential new type of atypical antipsychotic. *Neuropsychopharmacology*, 17, 82-91.

Rodrigues, R.J., Alfaro, T.M., Rebola, N., Oliveira, C.R., Cunha, R.A. (2005) Co-localization and functional interaction between adenosine A2A and metabotropic group 5 receptors in glutamatergic nerve terminals of the rat striatum. *Eur. J. Pharmacol.*, 506, 464-470.

Sahraei, H., Motamedi, F., Khoshbaten, A., Zarrindast, M.R. (1999) Adenosine A2 receptors inhibit morphine self-administration in rats. *Eur. J. Pharmacol.*, 383, 107-113.

Scaccianoce, S., Navarra, D., Di Sciuolo, A., Angelucci, L., Endrozi, E. (1989) Adenosine and pituitary-adrenocortical axis activity in the rat. *Neuroendocrinology*, 48, S24-S27.

Schiffrin, S.N., Dassesse, D., d’Alcantara, P., Ledent, C., Swillens, S., Zoli, M. (2003) A2A receptor and striatal cellular functions: regulation of gene expression, currents, and synaptic transmission. *Neurona*, 61, S24-29.

Schiffrin, S.N., Fisone, G., Moreasco, R., Cunha, R.A., Ferre, S. (2007) Adenosine A2A receptors and basal ganglia physiology. *Prog. Neurobiol.*, 83, 277-292.

Schiffrin, S.N., Jacobs, O., Vanderhaeghen, J.J. (1991) Striatal restricted adenosine A2 receptor (RD2C) is expressed by enkephalin but not by substance P neurons: an in situ hybridization histochemistry study. *J. Neurochem.*, 57, 1062-1067.

Schwarzchild, M.A., Agnati, L., Fuxe, K., Chen, J.F., Morelli, M. (2006) Targeting adenosine A2A receptors in Parkinson's disease. *Trends Neurosci.*, 29, 647-654.

Sebastiao, A.M., Ribeiro, J.A. (1996) Adenosine A2 receptor-mediated excitatory actions on the nervous system. *Prog. Neurobiol.*, 48, 167-189.

Sebastiao, A.M., Ribeiro, J.A. (1996) Adenosine A2 receptor-mediated excitatory actions on the nervous system. *Prog. Neurobiol.*, 48, 167-189.

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

Seeman, P., Schwarz, J., Chen, J.F., Szechtman, H., Perreault, M., McKnight, G.S., Roder, J.C., Quirion, R., Bolsa, P., Srivastava, L.K.,
Yanai, K., Weinschenker, D., Sumiyoshi, T. (2006) Psychosis pathways converge via D2-dopamine receptors. *Synapse*, 60, 319-346.

Schen, 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., Tien, J.Z., Chen, J.F. (2008) A critical role of the adenine A2A receptor in extrastriatal neurons in modulating psychomotor activity as revealed by opposite phenotypes of striatum and forebrain A2A receptor knock-outs. *J. Neurosci.*, 28, 2970-2975.

Shimazoe, T., Yoshimatsu, A., Kawashimo, A., Watanabe, S. (2000) Roles of adenine A(1) and A(2A) receptors in the expression and development of methamphetamine-induced sensitization. *Eur. J. Pharmacol.*, 388, 249-254.

Shiozaki, S., Ichikawa, S., Nakamura, J., Kitamura, S., Yamada, K., Kuwana, Y. (1999) Actions of adenine A2A receptor antagonist KW-6002 on drug-induced catalepsy and hypokinesia caused by reserpine or MPTP. *Psychopharmacology (Berl.)*, 147, 90-95.

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

Sicard, B.A., Perault, M.C., Enslen, M., Chauflard, F., Vandel, B., Tachon, P. (1996) The effects of 600 mg of slow release caffeine on mood and alertness. *Aviat. Space. Environ. Med.*, 67, 859-862.

Sills, T.L., Azampanah, A., Fletcher, P.J. (1999) The adenine A1 receptor agonist N6-cyclopentyladenosine blocks the disruptive effect of phencyclidine on prepulse inhibition of the acoustic startle response in the rat. *Eur. J. Pharmacol.*, 369, 325-329.

Snyder, S.H. (1985) Adenine as a neuromodulator. *Annu. Rev. Neurosci.*, 8, 103-124.

Soares, J.C., Gershon, S. (1997) Therapeutic targets in late-life psychoses: review of concepts and critical issues. *Schizopr. Res.*, 27, 227-239.

Soria, G., Castane, A., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O. (2006) The lack of A2A adenine receptors diminishes the reinforcing efficacy of cocaine. *Neuropsychopharmacology*, 31, 978-987.

Southwick, S.M., Vythilingam, M., Charney, D.S. (2005) The psychobiology of depression and resilience to stress: implications for prevention and treatment. *Annu. Rev. Clin. Psychol.*, 1, 255-291.

Stern, K.N., Chait, L.D., Johanson, C.E. (1989) Reinforcing and subjective effects of caffeine in normal human volunteers. *Psychopharmacology (Berl.)*, 98, 81-88.

Stromberg, I., Popoli, P., Muller, C.E., Ferre, S., Fuxe, K. (2000) Electrophysiological and behavioural evidence for an antagonistic modulation role of adenine A2A receptors in dopamine D2 receptor regulation in the rat dopaminergic system. *Eur. J. Neurosci.*, 12, 4033-4037.

Surmeier, D.J. (2007) Calcium, ageing, and neuronal vulnerability in Parkinson's disease. *Lancet Neurol.*, 6, 933-938.

Svensenngsson, P., Fienberg, A.A., Allen, P.B., Moine, C.L., Lindskog, M., Fison, G., Greengard, P., Fredholm, B.B. (2000) Dopaminergic D2 (D2) receptor-induced gene transcription is modulated by DARPP-32. *J. Neurochem.*, 75, 248-257.

Svensenngsson, P., Pourreau, L., Bloch, B., Fredholm, B.B., Gonon, F., Le Moine, C. (1999) Opposite tonic modulation of dopamine and adenosine on c-fos gene expression in striatopallidal neurons. *Neuroscience*, 89, 827-837.

Svensenngsson, P., Le Moine, C., Fison, G., Fredholm, B.B. (1999) Distribution, biochemistry and function of striatal adenine A2A receptors. *Prog. Neurobiol.*, 59, 355-396.

Svensenngsson, P., Lindskog, M., Rognoni, F., Fredholm, B.B., Greengard, P., Fison, G. (1998) Activation of adenine A2A and dopamine D1 receptors stimulates cyclic AMP-dependent phosphorylation of DARPP-32 in distinct populations of striatal projection neurons. *Neuroscience*, 84, 223-228.

Svensenngsson, P., Nishi, A., Fison, G., Girault, J.A., Nairn, A.C., Greengard, P. (2004) DARPP-32: an integrator of neurotransmission. *Annu. Rev. Pharmacol. Toxicol.*, 44, 269-296.

Takahashi, R.N., Pamplona, F.A., Prediger, R.D. (2008) Adenosine receptor antagonists for cognitive dysfunction: a review of animal studies. *Front. Biosci.*, 13, 2614-2632.

Tanganelli, S., Sundager Nielsen, K., Ferraro, L., Antonelli, T., Kehr, J., Franco, R., Ferre, S., Agnati, L.F., Fuxe, K., Scheel-Kruger, J. (2004) Striatal plasticity at the network level. Focus on adenosine A2 and D2 receptors in models of Parkinson's Disease. *Parkinsonism Relat. Disord.*, 10, 273-280.

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 A2A receptors and metabotropic gluta- mate 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.

Testa, C.M., Standaert, D.G., Young, A.B., Penney, J.B., Jr. (1994) Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat. *J. Neurosci.*, 14, 3005-3018.

Torvinen, M., Marcellino, D., Canals, M., Agnati, L.F., Lluís, C., Franco, R., Fuxe, K. (2005) Adenosine A2A receptor and dopamine D3 receptor interactions: evidence of functional A2A/D3 heteromeric complexes. *Mol. Pharmacol.*, 67, 400-407.

Tsai, S.J., Hong, C.J., Hou, S.J., Yen, F.C. (2006) Association study of adenine A2A receptor (1976C–T) genetic polymorphism and mood disorders and age of onset. *Psychiatr. Genet.*, 16, 185.

Wang, J.H., Ma, Y.Y., van den Buse, M. (2006) Improved spatial recognition memory in mice lacking adenine A2A receptors. *Exp. Neurol.*, 199, 438-445.

Wang, J.H., Short, J., Ledent, C., Lawrence, A.J., van den Buse, M. (2003) Reduced startle habituation and prepulse inhibition in mice lacking the adenine A2A receptor. *Behav. Brain Res.*, 143, 201-207.

Ward, R.P., Dorsa, D.M. (1999) Molecular and behavioral effects mediated by Gi-coupled adenine A2a, but not serotonin 5-HT4 or 5-HT6 receptors following antipsychotic administration. *Neuroscience*, 89, 927-938.

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

Wirkner, K., Gerevich, Z., Krause, T., Gunther, A., Koles, L., Schneider, D., Norenberg, W., Illes, P. (2004) Adenosine A2A receptor-induced inhibition of NMDA and GABA<sub>A</sub> receptor-mediated synaptic currents in a subpopulation of rat striatal neurons. *Neuropsychopharmacology*, 46, 994-1007.

Woodson, J.C., Minor, T.R., Job, R.F. (1998) Inhibition of adenine deaminase by erythrophy-9-(2-hydroxy-3-yl) adenine (EHNA) mimics the effect of inescapable shock on escape learning in rats. *Behav. Neurol.*, 112, 399-409.

Yamamoto, T., Yamashita, K., Misumi, Y., Kino, M., Obata, T., Aomine, M. (2002) Modulation of the stress response by coffee: an in vivo microdialysis study of hippocampal serotonin and dopamine levels in rat. *Neurosci. Lett.*, 332, 87-90.

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

Yee, B.K., Singer, P., Chen, J.F., Feldon, J., Boison, D. (2007) Transgenic overexpression of adenine kinase in brain leads to multiple learning impairments and altered sensitivity to psychomimetic drugs. *Eur. J. Neurosci.*, 26, 3237-3252.

Zoli, M., Agnati, L.F., Heidlund, P.B., Li, X.M., Ferre, S., Fuxe, K. (1993) Receptor–receptor interactions as an integrative mechanism in nerve cells. *Mol. Neurobiol.*, 7, 293-334.