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Adenosine hypothesis of schizophrenia –opportunities for pharmacotherapy

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Abstract

Pharmacotherapy of schizophrenia based on the dopamine hypothesis remains unsatisfactory for the negative and cognitive symptoms of the disease. Enhancing *N*-methyl-D-aspartate receptors (NMDAR) function is expected to alleviate such persistent symptoms, but successful development of novel clinically effective compounds remains challenging. Adenosine is a homeostatic bioenergetic network modulator that is able to affect complex networks synergistically at different levels (receptor dependent pathways, biochemistry, bioenergetics, and epigenetics). By affecting brain dopamine and glutamate activities it represents a promising candidate for restoring the functional imbalance in these neurotransmitter systems believed to underlie the genesis of schizophrenia symptoms, as well as restoring homeostasis of bioenergetics. Suggestion of an adenosine hypothesis of schizophrenia further posits that adenosinergic dysfunction might contribute to the emergence of multiple neurotransmitter dysfunctions characteristic of schizophrenia via diverse mechanisms. Given the importance of adenosine in early brain development and regulation of brain immune response, it also bears direct relevance to the aetiology of schizophrenia. Here, we provide an overview of the rationale and evidence in support of the therapeutic potential of multiple adenosinergic targets, including the high-affinity adenosine receptors (A₁R and A_{2A}R), and the regulatory enzyme adenosine kinase (ADK). Key preliminary clinical data and preclinical findings are reviewed.

Keywords

animal model; antipsychotics; dopamine; glutamate; NMDA; psychosis

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Highlights:

- Adenosine is a homeostatic bioenergetic network modulator.
- Adenosine affects brain dopamine and glutamate activities.
- Adenosine dysfunction can cause select endophenotypes of schizophrenia.
- Key preliminary clinical data and preclinical findings are reviewed.
- We propose adenosine-related therapeutics to treat schizophrenia.

1. Introduction

Schizophrenia is a debilitating mental disorder with a global prevalence of 1% and a presumed neurodevelopmental origin. The disease is incurable and its management remains symptom-oriented with the aim to expedite and sustain rehabilitation and social re-integration. The clinical features of schizophrenia are commonly divided into (i) positive symptoms characterized by functional excesses such as delusions, hallucinations, and disorganized thinking, (ii) affective symptoms such as depression or mania (iii) negative symptoms characterized by loss of normal functions such as anhedonia, blunted affect, and social withdrawal, and (iv) cognitive symptoms reflecting deterioration of memory, selective attention and executive functions (Ross et al., 2006; van Os and Kapur, 2009). Despite the continual search for genetic and environmental risk factors associated with the disease (Inta et al., 2010b; Labrie and Roder, 2010; Willi et al., 2010) the aetiology and underlying disease mechanisms remain puzzling. The current consensus essentially focuses on dysfunctions of the dopaminergic and glutamatergic neurotransmitter systems as being closely linked to the genesis of schizophrenia symptoms (Inta et al., 2010b; Labrie and Roder, 2010; Seeman, 2006; Tanaka, 2006), although interests in GABAergic dysfunction have also attracted increasing attention (Gonzalez-Burgos et al., 2010; Lewis et al., 1999; Lewis et al., 2005). Hence, existing pharmacotherapy is largely shaped by the “dopamine hyperfunction” and “glutamate hypofunction” hypotheses of schizophrenia. Positive symptoms are generally responsive to current medication that effectively blocks the dopamine D₂ receptor (D₂R). These drugs however have limited efficacy against negative and cognitive symptoms, and they are also associated with several undesirable side effects that hamper compliance. It has been hypothesised that effective treatment of negative and cognitive symptoms requires boosting of glutamatergic function, especially via *N*-methyl-D-aspartate receptors (NMDARs) that are incidentally critical for some forms of neural plasticity (Citri and Malenka, 2008; Malenka and Nicoll, 1993). However, pharmacotherapy based on direct NMDAR agonism is not feasible due to possible excitotoxicity. One approach is to target allosteric and other neuromodulators of glutamatergic transmission to achieve activity-dependent enhancement of glutamate/NMDAR function. In line with this notion, genetic disruption or pharmacological inhibition of glycine reuptake by targeting glycine transporter 1 (GlyT1) was shown to have profound pro-cognitive and antipsychotic effects (Black et al., 2009; Yang and Svensson, 2008; Yee et al., 2006). A new GlyT1 inhibitor from Roche (RG1678) was recently shown to exhibit beneficial effects in a phase II clinical trial in patients with schizophrenia (Pinard et al., 2010). A functionally meaningful enhancement is particularly relevant to the diffused and widespread cortical-subcortical glutamatergic network as opposed to the more anatomically defined mesocorticolimbic dopaminergic system.

Since the negative and cognitive symptoms represent the major hurdles for successful long-term rehabilitation, considerable human and social costs would be saved when this medical need is met. Drug targets that can offer effective normalization of both dopaminergic and glutamatergic transmissions would be innovative and highly desirable. One such promising candidate target is the neuromodulator adenosine, which modulates dopaminergic and glutamatergic signalling and is therefore positioned to integrate the dopamine and glutamate hypotheses (Boison, 2008; Lara, 2002; Lara et al., 2006; Lara and Souza 2000). This has been further developed into the adenosine hypothesis of schizophrenia suggesting that an imbalance in the ambient tone of adenosine may critically determine the susceptibility to schizophrenia. The present review attempts to (i) delineate the basic neurobiological concepts behind the adenosine hypothesis, (ii) summarize the preclinical and clinical findings supporting an adenosine deficit in schizophrenia, and (iii) evaluate the adenosine

hypothesis's compatibility with the existing neurochemical hypotheses of schizophrenia that are based primarily on dopamine and glutamate.

2. Adenosine: an important upstream neuromodulator of brain function

The purine ribonucleoside adenosine directly affects a variety of synaptic processes and signalling pathways and plays an important role in the regulation of several neurotransmitters in the central nervous system (CNS) (Boison, 2008; Boison et al., 2010; Fredholm et al., 2005; Sebastiao and Ribeiro, 2009; Stone et al., 2009). Unlike a classical neurotransmitter, adenosine is neither stored in synaptic vesicles nor released by exocytosis; and it does not act exclusively on synapses (Boison et al., 2010; Fredholm et al., 2005). Its release and up-take is mediated by bi-directional nucleoside transporters whereby the direction of transport solely depends on the concentration gradient between the cytoplasm and the extracellular space (Boison et al., 2010; Gu et al., 1995). Adenosine is therefore considered as a *neuromodulator* affecting neural activity through multiple mechanisms—presynaptically by controlling neurotransmitter release, postsynaptically by hyper- or depolarizing neurons, and non-synaptically mainly via regulatory effects on glial cells (Boison et al., 2010).

2.1 Adenosine and its receptors

Central effects of adenosine are mediated via activation of the two high-affinity adenosine receptors A_1R and $A_{2A}R$ and the two low affinity and low abundance receptors A_{2B} and A_3 (Boison, 2007; Fredholm et al., 2005; Jacobson and Gao, 2006) which are coupled to inhibitory (A_1R , A_3R) or stimulatory ($A_{2A}R$, $A_{2B}R$) metabotropic G-proteins (Fredholm et al., 2001, Fredholm et al., 2005; Linden, 2001). A_1R is the most abundant adenosine receptor and is densely expressed throughout the CNS with high abundance in the neocortex, cerebellum, hippocampus and the dorsal horn of the spinal cord. $A_{2A}Rs$ are highly enriched in striatal neurons but lower levels also occur in neurons outside of the striatum and in glial cells (Hettinger et al., 2001; Ribeiro et al., 2003; Svenningsson et al., 1999).

The main inhibitory neuromodulatory effects of adenosine involve the activation of A_1Rs , which inhibits the release of neurotransmitters such as dopamine and glutamate and decreases neural excitability by post-synaptic hyperpolarization (Dunwiddie and Masino, 2001; Fredholm et al., 2005). Activation of the facilitatory $A_{2A}Rs$ counters the action of A_1Rs and thus promotes neurotransmitter release (Ciruela et al., 2006a; Fredholm et al., 2005; (Stone et al., 2009). Additional complexity is added to the interaction between the two adenosine receptors by the formation of A_1 - A_{2A} receptor heterodimers (Ciruela et al., 2006a; Ciruela et al., 2006b), A_{2A} - D_2 receptor heterodimers (Ferre, 1997; Fredholm and Svenningsson, 2003; Fuxe et al., 2003), and $A_{2A}R$ -dependent trans-activation of the TrkB receptor (Diogenes et al., 2007; Diogenes et al., 2004). Thus, by activating receptors with opposing functions on neuronal excitability, adenosine is uniquely positioned to fine-tune and integrate excitatory and inhibitory processes in the CNS. While interactions of A_1Rs and $A_{2A}Rs$ with glutamatergic and dopaminergic neurotransmission are well understood, little is known if and how $A_{2B}Rs$ and A_3Rs (both expressed in brain) might contribute to regulating select endophenotypes of schizophrenia.

2.2 Control of extracellular adenosine levels by adenosine kinase

The extra-cellular levels of adenosine are largely controlled by an astrocyte-based adenosine cycle (Boison, 2008; Boison et al., 2010; Halassa et al., 2007a; Halassa et al., 2007b; Haydon and Carmignoto, 2006; Martin et al., 2007) (Figure 1). The major source for synaptic adenosine is the release of its precursor 5'-adenosinetriphosphate (ATP) from astrocytes, which can occur via vesicular release (Pascual et al., 2005) or via secretion through

hemichannels (Kang et al., 2008; Kawamura et al., 2010). ATP release is followed by rapid extracellular degradation to adenosine via ectonucleotidases (Pascual et al., 2005; Zimmermann, 2000). In addition, adenosine can be directly released through nucleoside transporters from astrocytes due to augmentation of intracellular adenosine (Geiger and Fyda, 1991). In contrast to conventional neurotransmitters, the reuptake of adenosine does not depend on energy-driven transporter-mediated systems. Instead, astrocyte membranes contain two types of equilibrative nucleoside transporters, which allow for rapid exchange between extra- and intracellular levels of adenosine (Baldwin et al., 2004). Reuptake of adenosine into the astrocytes is driven by its efficient and rapid removal by adenosine kinase (ADK), a ribokinase, which phosphorylates adenosine into 5'-adenosine monophosphate (AMP) (Boison, 2006; Etherington et al., 2009; Park and Gupta, 2008; Pignataro et al., 2007; Studer et al., 2006). Several lines of evidence now indicate that astrocytic ADK is the main regulator of extra-cellular adenosine by driving adenosine influx into astrocytes via bi-directional nucleoside transporters (Boison et al., 2010).

3. Adenosine as a mediator for homeostatic bioenergetic network regulation

Due to its tight biochemical link to bioenergetics (adenosine as molecular component of ATP) and due to its involvement in the control of nucleic acid function (adenosine as molecular component of RNA), adenosine is a prime homeostatic regulator and 'retaliatory metabolite' (Newby et al., 1985). As a bioenergetic regulator, adenosine can directly affect the equilibrium of enzymatic pathways including transmethylation reactions (e.g. of DNA methylation) (Boison et al., 2002). Due to its ability to affect basic biochemistry (i.e. adenosine receptor independent effects) as well as specific pathways linked to adenosine receptors, adenosine is strategically positioned to affect several molecular pathways synergistically and thereby to provide homeostatic control of whole networks. Apart from directly affecting neural activity, adenosine can thus interact with many different neurotransmitter systems at multiple levels. Activities of adenosine have extensively been reviewed elsewhere (e.g., Cunha, 2008; Ferre et al., 2007; Fredholm et al., 2005; Sebastiao and Ribeiro, 2009). Here, we briefly summarize the interplay between adenosine receptors and dopamine receptors as well as the ionotropic glutamate receptor NMDAR because of their relevance to schizophrenia (Figure 2).

3.1 Interactions with dopamine D1 and D2 receptors

An increasing number of behavioural and neurochemical studies provide strong evidence for an antagonistic interaction between adenosine and dopamine receptors especially within the basal ganglia. A_2A Rs are highly expressed in GABAergic striatopallidal neurons where they co-localize with dopamine D_2 Rs. A_1 Rs, on the other hand, are found in close proximity to dopamine D1 receptors (D_1 Rs) in striatonigral GABAergic neurons (Ferre et al., 1997; Ferre et al., 2005; Fink et al., 1992; Schiffmann et al., 1991; Schiffmann and Vanderhaeghen, 1993; Svenningsson et al., 1999). A_1 Rs and D_1 Rs as well as A_2A Rs and D_2 Rs can structurally interact by forming receptor heteromers which are critically involved in the basal ganglia control of basal motor functions, motivation and reward. These reciprocal antagonistic adenosine-dopamine interactions are thought to underlie the motor stimulant effect of the non-selective adenosine receptor antagonist caffeine (Chen et al., 2001; Kuzmin et al., 2000). However, recent data suggest that activation of A_2A Rs in extrastriatal cells may oppose the postsynaptic effects of A_2A R function in striatopallidal neurons by affecting glutamatergic inputs to the striatum (Shen and Chen, 2009; Yu et al., 2009a; Yu et al., 2009b) resulting in an excitatory tone on striatal neurons via D_2 R-independent mechanisms (see also Schiffmann et al., 2007).

3.2 Interactions with NMDARs

In the hippocampus, adenosine exerts a tonic inhibitory effect on NMDAR function via stimulation of A₁Rs, thus attenuating NMDAR-mediated currents and inhibiting NMDAR-dependent neuroplastic events including long-term potentiation (LTP) and depression (LTD) (de Mendonça and Ribeiro, 1997; de Mendonça and Ribeiro, 2000; Rebola et al., 2008). Accordingly, A₁R antagonism has been shown to augment NMDAR activation (Thummler and Dunwiddie, 2000). A₁R-mediated inhibition of the NMDAR together with the A₁R-mediated inhibition of glutamate release is also the basis of the neuroprotective effect of adenosine during hypoxia or against excitotoxicity due to prolonged NMDAR stimulation (Boeck et al., 2005; Dunwiddie and Masino, 2001). Conversely, the activation of NMDARs can inhibit the actions of A₁R agonists on presynaptic terminals, thus providing an additional layer of feedback control (Bartrup and Stone, 1990; Bartrup et al., 1991; Nikbakht and Stone, 2001). In the striatum, activation of A_{2A}Rs inhibits NMDAR-evoked currents in medium spiny neurons (Wirkner et al., 2000; Wirkner et al., 2004). By contrast, activation of hippocampal A_{2A}Rs located postsynaptically between mossy fibres and CA3 pyramidal cells are required for the induction of NMDA-dependent LTP (Rebola et al., 2008), whereas A_{2A}R activation in hippocampal CA1 induces a form of NMDAR-independent LTP (Kessey and Mogul, 1997). Thus, adenosine exerts a critical role in the fine-tuning of hippocampal synaptic plasticity which is widely believed to underlie certain forms of learning and memory (Rebola et al., 2008; Stone et al., 2009; Yu et al., 2009a). Furthermore, striatal activity may be synergistically regulated by NMDAR/A_{2A}R interactions because activation of either the NMDAR or the A_{2A}R stimulates adenylyl cyclase, which in turn elevates cAMP and therefore activity of downstream second messenger system (Nash and Brotchie, 2000).

4. The adenosine hypothesis of schizophrenia

Current pharmacotherapy for schizophrenia is based on the “dopamine” and “glutamate” hypotheses, which emphasize the contribution of dopaminergic hyperfunction and NMDAR hypofunction, respectively, in the pathophysiology of the disease (Gordon, 2010; Heinz and Schlagenhauf, 2010; Inta et al., 2010a; Inta et al., 2010b; Javitt, 2008). However, as outlined in the Introduction, dopaminergic treatment is frequently associated with debilitating side effects, and generally targets the positive symptoms of the disease while leaving the negative and cognitive symptoms unaffected. In contrast, non-dopaminergic approaches, such as GlyT1 inhibition (Black et al., 2009; Javitt, 2008; Yee et al., 2007), have recently shown to be effective in the amelioration of negative and cognitive symptoms of schizophrenia and more research of non-dopaminergic alternatives is needed. Based on the neurochemical rationale outlined above, adenosine in its role as homeostatic bioenergetic network regulator is suited to modulate both dopaminergic and glutamatergic neurotransmission. A purinergic hypothesis of schizophrenia was first proposed by Lara and colleagues. They suggested that a dysfunction in purinergic system would result in reduced adenosinergic activity as a possible common explanation for the imbalance between dopaminergic and glutamatergic neurotransmission and the dysregulation of neuro-immunological interaction that are characteristic hallmarks of schizophrenia (Lara et al., 2006; Lara and Souza, 2000). The hypothesis was largely based on preliminary data suggesting a beneficial therapeutic activity of the purine derivative allopurinol in patients with schizophrenia and a moderate efficacy against aggressive behaviour (Lara et al., 2000; Lara et al., 2001; Lara et al., 2003). Next, we will review the support for the adenosine hypothesis of schizophrenia by highlighting adenosine's interactions with dopaminergic and glutamatergic neurotransmission, as well as its possible roles in the neurodevelopmental aspects of disease aetiology.

4.1 Adenosine and the dopamine hypothesis

The dopamine hypothesis of schizophrenia is largely based on complementary effects of dopamine 2receptor (D₂R) antagonists and agonists to suppress and to promote psychotic symptoms, respectively (Figure 3). Thus, the efficacy of many antipsychotics correlates with their ability to block dopamine D₂Rs (Seeman, 2006; Seeman et al., 2006), while dopamine releasing drugs such as amphetamine can exacerbate psychotic symptoms in schizophrenia, and its prolonged abuse can produce psychotic symptoms in healthy subjects (Laruelle and Abi-Dargham, 1999). In addition, elevated basal occupation of D₂Rs by dopamine (Abi-Dargham et al., 2000), increased dopamine turnover (Lindstrom et al., 1999), and enhanced amphetamine-induced dopaminerelease (Laruelle and Abi-Dargham, 1999) have been shown in schizophreniapatients by functional PET imaging. The latter two findings in particular are compatible with a deficiency in adenosine. An adenosine deficit can (i) enhance dopamine activity by reducing the inhibitory effect of adenosine A₁Rs on dopamine release (Golembiowska and Zylewska, 1998), and within the striatum it can (ii) potentiate amphetamine-induced locomotion (Popoli et al., 1994) and dopamine release in the nucleus accumbens as suggested by the effects of A₁R antagonists (Solinas et al., 2002). Interactions between A_{2A}Rs and D₂Rs (Ferre et al., 1991a; Ferre et al., 1991b) allow further opportunity for mutual modulation between the adenosine and dopamine systems (Ferre et al., 2001). Thus, increased basal D₂R occupancy in schizophreniapatients (Abi-Dargham et al., 2000) could reduce the A_{2A}R's effect on D₂Rs, and thereby increase D₂R's affinity for dopamine (Ferre et al., 1991a; Ferre et al., 1991b; Ferre et al., 1991c). These mechanisms could provide the rationale for a typical neuroleptic-like profile of adenosine receptor agonists.

4.2 Adenosine and the glutamate hypothesis

According to the glutamate hypothesis of schizophrenia, reduced NMDAR function may contribute to cognitive and negative symptoms of schizophrenia (Coyle and Tsai, 2004; Farber, 2003). Blockade of NMDARs is known to impair the induction of LTP and learning in animals (Davis et al., 1992; Morris, 1989; Morris et al., 1986). Moreover, NMDAR blockade can give rise to behavioural dysfunction such as impulsivity (Tonkiss et al., 1988) and psychotic-like behaviour. For instance, phencyclidine (PCP) and ketamine (two non-competitive NMDAR antagonists classified as dissociative anaesthetics) are well known psychomimetics (Farber, 2003). In contrast, co-agonists of the NMDAR, such as D-serine and glycine, improve cognition and negative symptoms in schizophrenia (Coyle and Tsai, 2004; Javitt, 2008). Similarly, disruption of glycine transporter 1 has also been found to possess promnesic and antipsychotic potentials by increasing synaptic glycine levels (Mohler et al., 2008; Singer et al., 2007a; Singer et al., 2007b; Yee et al., 2006).

Adenosine is an endogenous modulator of glutamatergic activity, providing bidirectional and region-specific control over neuronal excitation. In the hippocampus, via A₁Rs, adenosine can inhibit glutamate release and the post-synaptic action of excitatory glutamatergic transmission (Dunwiddie and Masino, 2001). A₁R antagonists might therefore be expected to potentiate glutamatergic activity including NMDAR-dependent activation, leading to cognitive improvement. This is consistent with the pro-cognitive effects of the non-specific adenosine receptor antagonist, caffeine, reported in humans (Lara, 2010; Takahashi et al., 2008). On the other hand, adenosine also acts synergistically with NMDARs in the A_{2A}R-enriched striatum (Wardas et al., 2003). This interaction may partly explain the efficacy A_{2A}R agonists against the psychostimulant effects of NMDAR antagonists which are believed to be at least partly mediated via the striatum (Kafka and Corbett, 1996; Popoli et al., 1998). Hence, there exist A₁R- and A_{2A}R-dependent mechanisms whereby adenosine homeostasis can regulate multiple and disparate neuronal networks, which might support antipsychotic action. For example A₁R agonists are also effective against some behavioural as well as neurophysiological (EEG and prepulse

inhibition) effects induced by NMDAR antagonists (Kafka and Corbett, 1996; Popoli et al., 1998). Indeed, the complexity of adenosine-glutamate interaction is far from fully understood as will be discussed further in Section 5.

4.3 Adenosine and the neurodevelopmental hypothesis

MRI findings from patients with schizophrenia suggest a neurodevelopmental hypothesis of pathogenesis (Kubicki et al., 2007; Shenton et al., 2001; Shenton et al., 2010). Among other structural alterations MRI studies demonstrated preferential involvement of medial temporal lobe structures and neocortical temporal lobe regions (Shenton et al., 2001). In addition, changes in white matter suggest a disturbance in connectivity between different brain regions (Kubicki et al., 2007; Shenton et al., 2010). Evidence from imaging studies suggests that a subset of brain abnormalities may change during pathogenesis. Thus, some brain abnormalities might be neurodevelopmental in origin but unfold later in development, suggesting the requirement for “two hits” to trigger symptoms of schizophrenia (Shenton et al., 2001). Findings from human imaging studies are supported by neurodevelopmental rodent models of schizophrenia. Thus, a single injection of the inflammatory viral mimetic polyriboinosinic-polyribocytidilic acid (Poly-I:C) administered to pregnant mouse dams during a critical period of pregnancy can precipitate the emergence of select endophenotypes of schizophrenia in offspring when they reach early adulthood (Meyer et al., 2008; Meyer et al., 2007b). Furthermore, the characteristic clustering of distinct endophenotypes critically depends on the developmental time-window during which the immune challenge is triggered (Meyer et al., 2006; Meyer et al., 2007b). These studies suggest that an imbalance between pro- and anti-inflammatory cytokines may critically determine the final impact on neurodevelopment following early life infection or innate imbalances of immune functions (Meyer et al., 2007a).

The following arguments support the novel hypothesis that dysfunction of adenosine-based homeostatic networks might critically affect neurodevelopmental processes. First, the adenosine degrading enzyme adenosine deaminase (ADA) is expressed at high levels in placenta (Nagy et al., 1990) implying that the embryo needs to be protected from systemic adenosine fluctuations in the pregnant dams. Indeed, pharmacological inhibition of ADA disrupts foetal development (Knudsen et al., 1992) and transgenic expression of ADA can prevent perinatal lethality of ADA knockout mice (Blackburn et al., 1995). These findings demonstrate that increased levels of adenosine interfere with neonatal development. Second, ADK expression in the developing brain is subjected to a coordinated switch from neuronal expression during perinatal brain development to astrocytic expression during progressive brain maturation (Studer et al., 2006). Therefore tight control of adenosine levels likely plays an important role for brain development and neural plasticity (Studer et al., 2006). Third, adenosine is an important modulator of the brain immune system; any dysfunction in adenosine's homeostatic control of immune functions can offset the balance of pro- and anti-inflammatory cytokines that are critical for normal brain development (Hasko et al., 2005) as exemplified by the early immune challenge model of schizophrenia (Meyer et al., 2007a; Meyer et al., 2007b). Fourth, any kind of systemic or local stressor, such as infection (Hasko et al., 2005), or injury (Clark et al., 1997; Pignataro et al., 2008) is associated with a surge of adenosine beyond normal physiological levels (Clark et al., 1997). Together, these arguments suggest that dysfunction of normal adenosine homeostasis during critical periods of pregnancy, as might be triggered by prenatal infection (or a viral mimetic), might set off a cascade of neurodevelopmental events implicated in schizophrenia. Future studies and experimental validation of this hypothesis are urgently needed to unravel the neurodevelopmental role of adenosine homeostasis during pre- and perinatal brain development given that this also bears relevance for other diseases with a presumed neurodevelopmental origin, such as autism.

5. Evidence for the adenosine hypothesis

5.1 Clinical data in support of the adenosine hypothesis

Several lines of evidence support dysfunction of the adenosine system in patients with schizophrenia. Thus, increased density of A_{2A}Rs was found in the striatum of patients in a post mortem study (Kurumaji and Toru, 1998). Upregulation of striatal A_{2A}Rs could be a compensatory response triggered by reduced adenosinergic activity, which in turn could produce a hyperdopaminergic state (Lara et al., 2006; Lara and Souza, 2000). Interestingly, the olfactory G-protein G_{olf} that is coupled to A_{2A}Rs (Kull et al., 2000) is a candidate gene for schizophrenia (Schwab et al., 1998a; Schwab et al., 1998b), although linkage studies suggest, that the A_{2A}R gene as such is not a candidate gene for schizophrenia (Hong et al., 2005; Deckert et al., 1996; Deckert et al., 1997). In contrast, studies from a Japanese patient pool of schizophrenics suggest an involvement of A₁R polymorphisms in the pathophysiology of schizophrenia (Gotoh et al., 2009). Most recently, a variant of adenosine deaminase with lower enzymatic activity was shown to occur with a lower frequency in patients with schizophrenia, suggesting reduced levels of ambient adenosine in those patients (Dutra, et al., 2010). (Dutra et al., 2010)

Although adenosine-based drugs have not yet been tested in schizophrenia, the xanthine oxidase inhibitor allopurinol was studied as add-on therapy for schizophrenia (Akhondzadeh et al., 2005; Brunstein et al., 2004; Lara et al., 2001). By inhibiting a major degradation pathway of purines, allopurinol is believed to exert some of its beneficial effects by raising the endogenous pool of purines, including adenosine. Adjunctive allopurinol was moderately effective on positive and general symptoms (20% improvement of symptoms) in a double-blind, placebo-controlled, crossover clinical trial of add-on allopurinol (300 mg b.i.d.) for poorly responsive schizophrenia or schizoaffective disorder (Brunstein et al., 2005); however, this study was only based on 22 patients that completed the study and larger patient pools are needed to substantiate those initial findings. Of note, a case report from a single schizophrenia patient with gout who was prescribed allopurinol describes a relapse of symptoms (Gomberg, 2007). In support of the allopurinol findings from Brunstein and colleagues, the adenosine transport inhibitor dipyrnidole (by raising adenosine) was beneficial in patients with schizophrenia (Akhondzadeh et al., 2000).

Thus, while some of the available clinical data seem to support the adenosine hypothesis of schizophrenia, some of the findings are controversial and larger patient populations are needed to derive valid conclusions. In contrast, and as will be outlined in more detail below, a significant set of preclinical data suggests a link between adenosine dysfunction and the etiopathology of schizophrenia.

5.2 Preclinical data in support of the adenosine hypothesis

Studies performed in rodent models provide additional support to the adenosine hypothesis of schizophrenia. Those studies fall into three categories: (i) Behavioural effects of adenosinergic drugs in schizophrenia-related paradigms using normal non-perturbed animals. (ii) Effects of adenosinergic drugs on psychostimulant-induced behavioural responses. (iii) Behavioural assessment of genetically engineered mice with specific alternations to the adenosinergic system.

5.2.1 Behavioural pharmacological evidence—Behavioural evidence for the potential antipsychotic effects of adenosinergic drugs are reviewed below. Most studies are focused on agonists and antagonists, and no study has yet examined the antipsychotic potential of pharmacological treatment targeting ADK. A large body of studies are

summarized in Tables 1-3 in which findings suggestive of antipsychotic action or promnesic efficacy are highlighted in red to facilitate their identification.

5.2.1.1 Psychostimulant-induced hyperlocomotion: The motor stimulant effects of dopamine receptor agonists and NMDAR antagonists are widely used to assess psychotic-like behaviour linked to dopaminergic hyperfunction and NMDAR hypofunction, respectively (Arguello and Gogos, 2006). As summarized in Table 1, both A₁R and A_{2A}R agonists effectively antagonize the motor stimulant effects induced by either class of psychostimulant drug. The effect is highly consistent against dopamine agonist-induced hyperlocomotion – there was, essentially, only one exceptional study reporting a null effect of an agonist (Ferre et al., 1994). These findings are also consistent with the opposite effect exerted by A₁R and A_{2A}R antagonists, which exacerbated the motor-stimulant effect of dopamine agonists.

A₁R and A_{2A}R agonists are similarly effective in countering the hyperlocomotor effects of the non-competitive NMDAR antagonists (PCP, MK-801, and ketamine). However, unlike the clear impression obtained based on experiments with dopaminergic stimulants, adenosine antagonists do not consistently induce an opposite effect. Thus, the reported effects of adenosine antagonists on NMDAR antagonist-induced hyperlocomotion are mixed — both attenuation and exacerbation have been reported (see Table 1). A closer inspection of the data reveals that a potentiation is only seen for mixed A₁R/A_{2R} and A_{2A}R-selective antagonists, whereas A₁R-specific antagonists are without any effect. Indeed, it has been suggested that blockade of A_{2A}R but not A₁R is responsible for the exacerbation of the motor-stimulant effects of NMDAR antagonist (Malec and Poleszak, 2006). Given that the motor-stimulant effects of NMDAR antagonists are partly mediated via an increase of dopaminergic activity within the striatum (Breier et al., 1998; Smith et al., 1998; Steinpreis, 1996; Steinpreis et al., 1993), where A_{2A}R antagonistically interact with D₂Rs, the attenuating and potentiating effects of A_{2A}R agonists and antagonists, respectively, may be attributed to modifications of striatal dopamine activity (see also Malec and Poleszak, 2006). Apart from the receptor-receptor interactions described above and adding to the complexity of adenosine receptor mediated effects, activation of presynaptic A₁Rs directly provides presynaptic inhibition of the release of both glutamate and dopamine, a mechanism that contributes to the complexity of striatal function and which has extensively been reviewed elsewhere (Calabresi et al., 2000a; Calabresi et al., 2000b; Lovinger, 2010). Taken together, evidence for antipsychotic potential of A₁R and A_{2A}R agonists are overwhelming, and seemingly effective against both dopaminergic hyperfunction and NMDAR hypofunction. The efficacy of caffeine and theophylline (both are mixed A₁R/A_{2A}R antagonists at non-toxic doses that do not affect phosphodiesterases) to reverse MK-801-induced hyperlocomotion demonstrated in two separate studies certainly warrant further investigations, as this might further represent a novel mechanism of anti-psychoticism.

5.2.1.2 Prepulse inhibition: An important translational paradigm for assessing attentional dysfunction in schizophrenia is prepulse inhibition (PPI) of the acoustic startle reflex. PPI refers to the phenomenon that the startle reflex to a brief startle-eliciting *pulse* stimulus can be substantially weakened when it is shortly preceded by a weak non-startling *prepulse* stimulus (Graham, 1975; Hoffman and Searle, 1968). PPI deficiency is linked to perceptual dysfunction in schizophrenia and reflects a gating deficit leading to higher susceptibility to intruding stimuli that could be responsible for sensory flooding in schizophrenia (for reviews see Geyer et al., 2001; Swerdlow et al., 2008). It has been further suggested that PPI might predict schizophrenia cognitive deficits (Geyer, 2006); and PPI magnitude has been shown to correlate with effortful sustained attention in animals (Bitanirwe et al., 2010). Antipsychotic drugs are reported to potentiate PPI in normal subjects but this might depend on baseline PPI levels (Swerdlow et al., 2006; Vollenweider et al., 2006). Existing studies of

adenosinergic drugs so far have yielded no indication of such a PPI-enhancing effect in normal animals (see Table 2).

On the other hand, antipsychotic drugs more consistently reverse PPI deficits induced by psychostimulant drugs, acting either through dopaminergic or glutamatergic/NMDAR mechanisms (Geyer et al., 2001; Swerdlow et al., 2008). Similar to the overall impression obtained in the review of psychostimulant-induced hyperactivity (Table 1), both A₁R and A_{2A}R agonists are again consistently effective in attenuating PPI deficits induced by direct/indirect dopamine agonists as well as NMDAR blockers. In combination with a low dose of the direct dopamine agonist apomorphine that is insufficient alone to affect PPI, the adenosine receptor antagonist theophylline (20 mg/kg) significantly disrupted PPI in rats, whereas theophylline alone had no effect. PPI-disruption resulting from the synergistic action of apomorphine/theophylline was dose-dependently antagonized by the co-administration of the selective A₁R agonist, CPA (0.15-1.5 mg/kg, i.p.), but not by the A_{2A}R agonist CGS21680 (0.1-2.0 mg/kg, i.p.) (Koch and Hauber, 1998). Together, these data suggest that antagonistic interactions between dopaminergic and adenosinergic signalling, involving A₁Rs, are implicated in the regulation of PPI.

Blockade of the conditioned avoidance response in rats is indicative for the alleviation of schizophrenia. Thus, adenosine receptor agonists (A₁R-selective, A_{2A}R selective, and non-selective) were shown to block the conditioned avoidance response (pressing a lever) in response to a light and tone-coupled footshock (Martin et al., 1993). These findings suggest an involvement of A₁Rs and A_{2A}Rs in the control of the conditioned avoidance response.

5.2.1.3 Learning and memory: A survey of published psychopharmacological studies with adenosinergic drugs in normal wild type animals (Table 3A) reveals that the promnesic effects were only associated with adenosine receptor antagonists, except one study reporting that the A₁R agonist, CPA, improved performance on spatial learning in the water maze (Von Lubitz et al., 1993). On the other hand, there are also reports of learning impairments following adenosine receptor antagonist treatment. By comparison, however, agonists more consistently resulted in memory deficits regardless of A₁/A_{2A} receptor selectivity. Amongst the various rodent behavioural models of memory function summarized in Table 3A, there is little evidence that improvement in spatial working memory can be obtained by adenosinergic manipulations. This is particularly relevant for schizophrenia-related cognitive deficits. In contrast, several studies have indicated a beneficial effect on spatial reference memory learning by the non-specific antagonists, caffeine or theophylline, suggestive of enhanced hippocampus-dependent learning processes.

Many of the common rodent memory models or paradigms were originally developed to capture deficits rather than memory enhancing effects, so it is imperative also to examine the efficacy of adenosinergic drugs in memory impairment models. This is particularly important in terms of identifying any therapeutic potential. Existing studies however have not employed memory impairment models that could be considered as closely related to schizophrenia-related cognitive deficits, except arguably memory deficiency induced by NMDAR antagonists. Hence, we have included a diverse spectrum of pathological models in this review (Table 3B).

Although there is a bias towards studies of adenosine receptor antagonists with relatively few examining agonists, this survey gives a strong impression that A₁R or A_{2A}R antagonism can ameliorate loss of memory functions. This is in agreement with the overview of non-pathological models summarized in Table 3A. Only one study reported that caffeine exacerbated the social memory impairment associated with aging (Prediger et al., 2005b).

Admittedly, the mechanisms underlying the memory loss in some of these models are far from understood and are likely to involve multiple pathological causes (e.g., aging). However, the promising outcomes in multiple models based on amnesic effects of NMDAR antagonists are supportive of the use of adenosinergic blockers to counter cognitive impairments resulting directly from glutamatergic hypofunction.

5.2.1.4 Neurodevelopmental Perspective: Pharmacological evidence suggests that dysregulated A₁R signalling might be implicated in neurodevelopmental disturbances thought to be critical to the aetiology of schizophrenia. Treatment of neonatal rats with pregnenolone (a main precursor of the neurosteroidogenesis) from postnatal day 3 to 7, which corresponds to the time window of neuronal expression of ADK (Studer et al., 2006), resulted in later life in a decrease in the K_D values for the A₁R antagonist, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), increased dopamine turnover, and stimulated locomotor activity in the open field (Muneoka et al., 2002). Neonatal pregnenolone-treatment is also known to decrease adenosine A_{2A} receptor density in the brain (Shirayama et al., 2001). Despite being correlative in nature, these results are suggestive of a link between deficient adenosine signalling caused by transient exposure to a neurosteroid during a critical time window of early postnatal brain development with subsequent dopaminergic hyperfunction and increases in spontaneous locomotor activity in later life.

5.2.1.5 Summary: Existing pharmacological data reveal the following picture. Adenosine receptor agonists convincingly exert antipsychotic-like efficacy in dopamine-hyperfunction and NMDAR-hypofunction models of schizophrenia. This, however, appears in sharp contrast to their predominantly negative impact on learning and memory functions. On the other hand, adenosine antagonists, which yield mainly psychotic-like behavioural outcomes in animal models of schizophrenia, consistently show pro-cognitive properties, ameliorating cognitive deficits in a variety of impairment models and enhancing mnemonic performance under non-pathological conditions. Although relatively few studies have investigated adenosine agonists in memory deficiency models, adenosine agonists might be particularly effective against schizophrenia symptoms linked to dopaminergic hyperfunction and/or NMDAR hypofunction, while adenosine antagonists might be useful as adjuvant treatment to ameliorate cognitive deficits in schizophrenia that are resistant to conventional antipsychotics.

5.2.2 Mice with engineered mutations in adenosine signalling—Several genetic models have been generated to assess adenosine-dependent changes in homeostatic bioenergetic network regulation and implications for the expression of selected endophenotypes of schizophrenia. Within the last decade, animals with genetic manipulations targeted at A_{2A}R, A₁R or *Adk* have been subjected to behavioural characterisation (Table 4), providing support and insights in the regulation of dopaminergic and glutamatergic elements in the genesis of schizophrenia-like behavioural traits by altered adenosine signalling.

5.2.2.1 Reducing adenosinergic tone: *Adk*^{tm1^{-/-}}-Tg(UbiAdk) mice: Genetically engineered *Adk*^{tm1^{-/-}}-Tg(*UbiAdk*) mice have been generated by breeding a loxP-flanked *Adk* transgene under the control of a human ubiquitin promoter into ADK knockout mice (Boison et al., 2002). These animals (henceforth referred to as *Adk*-tg mice) have an elevated global expression of ADK in the brain 47% above normal (Fedele et al., 2005; Pignataro et al., 2007; Yee et al., 2007). As a result of increased adenosine clearance, *Adk*-tg mice are characterized by global brain adenosine deficiency (Li et al., 2007; Li et al., 2008). This is expected to down-regulate both A_{2A}R and A₁R-dependent adenosine signalling, providing a unique model to evaluate the behavioural impact of a global adenosine deficiency.

Adk-tg mice showed transient hyperlocomotion when exposed to a novel place which rapidly declined to control levels or below, demonstrating intact locomotor habituation (Fedele et al., 2005; Yee et al., 2007). Evidence for disturbed dopaminergic and glutamatergic homeostasis readily emerged when these animals were challenged with amphetamine (a dopamine releasing agent with similar action to cocaine) and MK-801 (a non-competitive NMDAR antagonist). Both drugs have psychostimulant properties and stimulate spontaneous locomotor activity at sufficiently high doses. The motor stimulating effect of amphetamine was abolished, while that of MK-801 was potentiated in Adk-tg mice (Yee et al., 2007). The effect of global adenosine deficiency therefore depends on the psychostimulant used and cannot be attributed to additive account based on non-specific overall changes in locomotor activity. The MK-801 induced phenotype is suggestive of NMDAR hypofunction, which is opposite to that seen following manipulation designed to augment activity-dependent NMDAR signalling (e.g., Yee et al., 2006; Singer et al., 2009). Adk-tg mice may therefore serve as a model to study NMDAR deficiency within the context of adenosine-NMDAR interactions and schizophrenia-related symptoms attributed to NMDAR hypofunction. The latter is encouraged by the severe learning deficits demonstrated in these animals that span across reference memory, working memory and associative learning.

The amphetamine-induced locomotor activity phenotype (attenuation) was opposite to that induced by MK801 (potentiation) in Adk-tg mice. This seemingly paradoxical outcome is not at all surprising, given that the psychostimulant effects of the two drugs are based on distinct pharmacological actions. It suggests that reduction of brain adenosinergic tone can potentiate as well as suppress psychotic-like responses depending on the neurotransmitter system being challenged. This is particularly relevant to the context of schizophrenia, because it shows that brain-wide manipulation of the adenosine system not only affects the separate functioning of glutamate and the dopamine neurotransmission, but also their complex interactions. Evidence that such interactions may be antagonistic comes from the suggestion that systemic NMDAR blockade attenuated the response to cocaine (Uzbay et al., 2000), which is consistent with the pattern revealed in the Adk-tg mice, although a precise causal relationship cannot be easily established here. Nonetheless, the amphetamine-induced phenotype in the Adk-tg mice is also suggestive of some forms of dopaminergic hypofunction. Indeed deficient frontal dopaminergic activity is critical to the network of associational cortices supporting effective and efficient working memory function (e.g., Simpson et al., 2010; Williams and Castner, 2006). The role of the striatum which is rich in dopamine and receives predominantly glutamatergic inputs from limbic cortices may be more closely related to the pathogenesis of the cognitive symptoms of schizophrenia than previously envisaged (Simpson et al., 2010). Hence, the resulting severe cognitive deficits seen in Adk-tg mice are likely the result of a combination of NMDAR and dopaminergic dysfunction implicated in schizophrenia pathophysiology.

5.2.2.2 Genetic manipulations targeting A_{2A}R: The severe phenotypes seen in Adk-tg mice readily suggest that reduction of brain adenosinergic tone is critical for normal behavioural functioning. Selective adenosine receptor subtype deletion and/or over-expression would be instructive in further dissecting the relative contributions of the two key receptor subtypes: A_{2A}R and A₁R (see Table 4).

The examination of the A_{2A}R-dependent pathway of adenosine within the conceptual framework of schizophrenia has utilized both constitutive and conditional A_{2A}R knockout mice (Chen et al., 1999; Shen et al., 2008; Yu et al., 2009a) as well as rats with brain A_{2A}R over-expression (Giménez-Llort et al., 2002). Constitutive A_{2A}R knockout mice were characterized by attenuated locomotor responses to amphetamine and cocaine, which resembled that seen in Adk-tg mice (Yee et al., 2007). Unlike indirect dopamine receptor

agonists such as amphetamine and cocaine which potentiate activity dependent dopamine release, response to either direct D₁R (locomotor stimulation and grooming) or D₂R agonist (motor-depression and stereotypy) did not distinguish between wild-type and A_{2A}R knockout mice (Chen et al., 2000). This is an important distinction suggesting that adenosine interacts with the effects of psychostimulant drugs on activity-dependent dopaminergic transmission, rather than tonically up- or down-regulating dopaminergic function. Differentiating between these two modes of modulation is central to the understanding of dopamine neurophysiology (Goto et al., 2007).

The behavioural significance of distinguishing between A_{2A}R and A₁R is highlighted by the clear demarcation of their contribution to caffeine-induced wakefulness. The arousal effects of caffeine were completely abolished in A_{2A}R^{-/-} mice, but remained intact in A₁R^{-/-} mice (Huang et al., 2005), suggesting that A_{2A}R-dependent mechanism is more closely related to the arousal and alertness of which dopaminergic control is also relevant (Robbins and Arnsten, 2009).

The regionally distinct functions of A_{2A}Rs in modulating psychomotor activity can be further dissected with conditional knockout mice generated by Chen and colleagues (Table 4). Comparison between CaMKII α -Cre(+)A_{2A}R^{flox+/+} mice with forebrain (including striatum) A_{2A}R deletion and Dlx5/6-Cre(+)A_{2A}R^{flox+/+} mice with selective striatal A_{2A}R deletion has provided important insights into the synergism and antagonism exist between these two populations of A_{2A}Rs: i.e., striatal vs extra-striatal forebrain A_{2A}Rs. First, both mutant lines were less responsive to the motor stimulating effect of the A_{2A}R antagonist KW6002 (Shen et al., 2008; Yu et al., 2008), suggesting that the motor striatal A_{2A}R deletion alone is sufficient to significantly attenuate KW6002-induced hyperactivity and that extra-striatal A_{2A}Rs are either not critical to this effect or contributing to the same direction. It is likely that the attenuated response to the A_{2A}R agonist CSG21680 in CaMKII α -Cre(+)A_{2A}R^{flox+/+} mice is reproducible also in Dlx5/6-Cre(+)A_{2A}R^{flox+/+} mice. Second, CaMKII α -Cre(+)A_{2A}R^{flox+/+} and Dlx5/6-Cre(+)A_{2A}R^{flox+/+} mice began to diverge with respect to their response to the psychostimulant drugs, cocaine and PCP (Table 4). While striatal A_{2A}R deletion enhanced the motor stimulant response to both drugs, an opposite effect was observed, namely an attenuated response to both drugs, when the deletion was extended to the entire forebrain (Shen et al., 2008). This comparison suggests that striatal and extra-striatal (forebrain) A_{2A}R provide antagonistic control over responses to psychostimulant drugs. Thus, the blockade of extra-striatal A_{2A}R might confer antipsychotic action induced either by dopamine hyperfunction or NMDAR hypofunction, effects that are distinct from the systemic pharmacological activation of A_{2A}Rs, which generally block dopamine-induced hyperfunction (see above). Recalling that global adenosine reduction in Adk-mice abolished response to amphetamine but potentiated that to MK-801, these disparate effects match onto hypoactivity of extra-striatal A_{2A}R and striatal A_{2A}R, respectively. Thus, the seemingly opposite phenotypic profile against the two classes of psychostimulant drugs observed in Adk-tg mice might be understood in terms of the antagonistic contributions of striatal versus extra-striatal A_{2A}Rs hypoactivity.

Cognitive assessments to date have largely been restricted to analysis of constitutive A_{2A}R knockout mice. Duan et al. (2009) employed the 4-baited/4-unbaited radial arm maze procedure (Jarrard, 1986) to study concurrently both reference and working memory functions, and failed to identify any difference between A_{2A}R^{-/-} mice and wild type controls in either performance indices. A similar study by Zhou et al. (2009), on the other hand, reported tentative evidence for a promnesic effect in the eight arm radial maze, based on only a subset of working memory error, i.e. re-entries of the animals into once-baited arms. These authors mistakenly counted re-entries into never-baited arms as reference memory errors and therefore it remains uncertain whether the same effect might be seen in terms of re-entry

errors into never-baited arms. This distinction bears important psychological significance especially with respect to the first re-entry error into a given arm. The first re-entry (working memory) error into once-baited arms does not follow any experience of non-reward in that arm, whereas all other re-entry errors could be influenced by recent experience of non-reward. The latter is relevant to the finding that striatal neurons specific A_{2A}R knockout mice exhibited enhanced sensitivity to devaluation (Yu et al., 2009a). Over-training on an operant task was sufficient to render control mice insensitive to devaluation of the reinforcer that was used to sustain acquisition of the operant act, i.e., they continued to respond despite not obtaining the expected reward. In contrast, striatal A_{2A}R knockout mice responded by reducing their response rate (Yu et al., 2009a). This finding indicates that striatal A_{2A}Rs can regulate the formation and maintenance of habit in relation to changing reinforcement contingency, thus bearing relevance also to addictive behaviour, depression-related traits (see Shen and Chen, 2009), and compulsive-like behaviour in decision making (Mott et al., 2009).

Cognitive function following brain A_{2A}R over-expression has also been studied in rats with indication of some subtle forms of mnemonic impairments (Gimenez-Llort et al., 2007). The reported object recognition memory deficit was weak in magnitude. The working memory deficiency in the water maze was purely transient and was confounded by previous reference memory training that yielded no difference between mutant and controls. A 6-arm radial tunnel maze procedure was used to assess avoidance of blind alleys during spontaneous spatial exploration, but the increase in entries in the blind alleys seen in the mutant rats was again transient and not easily interpreted as a form of memory deficit as such, because T-maze delayed alternation performance was unaffected. This data set therefore must be interpreted with caution, although other genetic mouse models are lending some support for procognitive effects specific to working memory and modulation of habit strength – both speaking in favour of the beneficial potential of A_{2A}Rs blockade against inflexible executive functions characteristic of schizophrenia negative and cognitive symptoms.

5.2.2.3 Genetic manipulations targeting A₁R: As summarized in Table 2, relatively few studies have been conducted to date regarding genetic deletion of A₁R, and these are restricted to homozygous and heterozygous A₁R constitutive knockout mice (Gimenez-Llort et al., 2002; Johansson et al., 2001). Notably, no evidence for any cognitive effect has been reported, based primarily on a single study by Gimenez-Llort et al., (2002) using the Morris water maze procedures for spatial reference and working memory, even though A₁R constitutive knockout reduced life expectancy in a manner that clearly depended on the dosage of gene knockout (Gimenez-Llort et al., 2002). In a similar gene-dosage dependent manner, A₁R deletion also appeared to be anxiogenic and to reduce peak spontaneous activity close to the onset of the dark phase of the diurnal cycle (Gimenez-Llort et al., 2002; Johansson et al., 2001). A reduction in pain threshold has also been reported in these mice (Johansson et al., 2001). Some seemingly bidirectional effects between homozygous and heterozygous A₁R knockout mice on aggression and explorative behaviour were reported (Gimenez-Llort et al., 2002).

Existing data are insufficient to provide a clear impression on the effects of genetic deletion of A₁R. As mentioned above, A₁Rs do not contribute to the arousing effect of caffeine (Huang et al., 2005), and it seems that they are also not essential for normal learning in the water maze. The latter impression adds further intrigue to the severe learning deficits seen in Adk-tg mice. The global reduction in adenosine signalling in Adk-tg mice is expected to combine the effects of A₁R and A_{2A}R hypofunction. The possibility that the phenotypic profile of Adk-tg mice cannot be readily understood as the summative effects of A₁R and A_{2A}R hypofunction therefore cannot be excluded. Further comparison with double A₁R/A_{2A}R knockout mice (Xiao et al., 2010) would be highly instructive in this respect.

Similarly, there is also an urgent need to examine the psychostimulant response in A₁R knockout mice.

5.2.2.4 Summary: We may conclude from the overview of studies from knockout and transgenic animals that: (i) Deficiency in adenosine simultaneously affects dopaminergic and glutamatergic neurotransmissions resulting in severe cognitive impairment. (ii) Multiple pathways related to adenosine receptor signalling are involved. (iii) Those pathways are subject to functional segregation as exemplified by the divergent/opposing involvements between A₁R and A_{2A}R systems, and also the regional distinction between striatal and extra-striatal (forebrain) A_{2A}Rs. These conclusions imply that any imbalance in the ambient tone of adenosine, and its key metabolic regulator ADK, will affect homeostatic control of network regulation, and thus may trigger the wide spectrum of endophenotypes commonly associated with schizophrenia. More focused behavioural assays are necessary to consolidate these hypotheses and to allow the necessary specifications needed for successful translation into clinically relevant compounds.

6. Conclusions and Outlook

Conventional pharmacotherapeutic strategies to ameliorate select symptoms but not the whole spectrum of endophenotypes of schizophrenia are based on the dogma to achieve specificity of symptom control by enhancing the selectivity of drugs acting on specific downstream targets (e.g., D₂R). As highlighted in this review, adenosine can be considered as a homeostatic bioenergetic network regulator affecting multiple pathways simultaneously by activating different types of adenosine receptors in a spatial-temporally refined manner (Figure 4). As outlined above, the influence on schizophrenia-related endophenotypes by adenosine receptors depends highly on the brain region and receptor subtype. For example, A_{2A}R agonists might be of value due to their antipsychotic potential, but the systemic use of A_{2A}R agonists might be associated with impairment in cognitive performance and with peripheral side effects. Therefore, individual adenosine receptors most likely do not represent suitable drug targets for schizophrenia treatment.

In addition to its action on adenosine receptors, adenosine can exert effects independent of its receptors: Biochemically, adenosine links energy homeostasis with nucleic acid metabolism (Newby et al., 1985) and is an important feedback regulator of transmethylation reactions (Boison et al., 2002; Studer et al., 2006), including DNA methylation, and thus poised to regulate homeostatic networks through bioenergetic and epigenetic mechanisms. These adenosine receptor-independent activities of adenosine add to the complexity of adenosine receptor-dependent effects discussed in this review. Thus it is conceivable to predict that any pathological disturbance in adenosine signaling will affect bioenergetic network homeostasis, which could at least partly explain the broad symptomatology seen in schizophrenia. Therefore, controlling and rebalancing the upstream regulator adenosine might uniquely be suited to modulate brain function on the network level. This goal might be achievable by targeting enzymes (e.g. adenosine kinase) or nucleoside transporters that control the tone of ambient adenosine. Modulating the tone of ambient adenosine might uniquely be suited to synergistically affect complex networks via different mechanisms. However, the focal targeting of those approaches to select brain areas might become a necessity to avoid brain-wide effects, given the widespread peripheral and central side effects of the systemic use of drugs that affect adenosine signaling. Focal adenosine augmentation has already been explored within the context of epilepsy (Wilz et al., 2008), and the technical advances in cell and gene therapies developed to augment adenosine (Boison, 2007) might provide future avenues for antipsychotic therapy development with the introduction of the novel concept of homeostatic bioenergetic network regulation to the neurobiology of schizophrenia.

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Figure 1. Adenosine metabolic pathways and major enzymes involved: ecto-nucleotidase (ecto-NT), 5'-nucleotidase (5'-NT), adenosine kinase (ADK), S-adenosylhomocysteine hydrolase (SAH hydrolase), S-adenosylmethionine (SAM), equilibrative nucleoside transporter (ent).

Figure 2.

Molecular basis and pathways of adenosine-based manipulation of glutamatergic and dopaminergic neurotransmission: dopamine receptors (DRs), long-term potentiation (LTP) and depression (LTD), *N*-methyl-D-aspartic acid receptors (NMDARs), schizophrenia (SZ).

Figure 3.

Adk-tg mutant mice are an established animal model with reduced adenosine function in brain, which leads to dysfunction of hippocampal glutamatergic and striatal dopaminergic neurotransmission and results in severe deficiency of learning and memory as well as in altered sensitivity to psychomimetic drugs.

Figure 4.

Adenosine hypothesis of schizophrenia. Adenosine integrates glutamatergic and dopaminergic function on multiple-levels. Imbalance in adenosine function can result in hypoglutamatergic and hyperdopaminergic activity in schizophrenia.

TABLE 1

Effects of adenosinergic drugs on psychostimulant-induced hyperlocomotion: The full (IUPAC) names of the drugs are: APEC (2-[(2-aminoethylamino)carbonylethylphenylethylamino]-5'-N-ethylcarboxamidoadenosine), caffeine (1,3,7-trimethylxanthine), CGS21680 (2-(4-(2-carboxyethyl)phenylethylamino)adenosine-5'-N-ethylcarboxamidoadenosine), CHA (N6-cyclohexyladenosine), CLA (2-chloroadenosine), CPA (N6-cyclopentyladenosine), CPT (8-cyclopentyltheophylline), CPX (8-cyclopentyl-1,3-dipropylxanthine), CV-1808 (2-(phenylamino)adenosine), DPMA (N6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)-ethyl]adenosine), DMPX (3,7-dimethyl-1-propargylxanthine), L-PIA (L-N6-phenylisopropyladenosine), NECA (5'-(N-ethylcarboxamido)-adenosine), R-PIA (R-N6-phenylisopropyladenosine), theophylline (1,3-dimethyl-7H-purine-2,6-dione). ↓ / ↑: attenuates / potentiates the drug-induced effect on locomotor activity; ↔ no effect

• Drug used to induced hyperlocomotion							
Dopamine receptor agonists	Adenosinergic action	Drug	Effect	References			
Amphetamine	A ₁ R agonist	2-CLA	↓	Heffner et al., 1989			
		CHA	↓	Heffner et al., 1989 Turgeon et al., 1996			
		CPA	↓	Heffner et al., 1989 Poleszak and Malec, 2002			
		PIA	↓	Heffner et al., 1989			
		APEC	#x2193;	Turgeon et al., 1996 Popoli et al., 1994			
	A _{2A} R agonist	CGS 21680	#x2193;	Rimondin et al., 1997 Poleszak and Malec, 2002 Sills et al., 2001			
		A ₂ R agonist	CV-1808	#x2193;	Heffner et al., 1989		
	A ₁ R/A ₂ R agonist	NECA	#x2193;	Heffner et al., 1989 Shi et al., 1994 Poleszak and Malec, 2002			
				A _{2A} R antagonist	DMPX	↑	Poleszak and Malec, 2002
				A ₁ R/A ₂ R antagonist	Caffeine	↑	
	Cocaine	A ₁ R agonist	CPA	#x2193;	Poleszak and Malec, 2002		
		A _{2A} R agonist	CGS 21680	#x2193;			
		A ₁ R/A ₂ R agonist	NECA	#x2193;	Shi et al., 1994 Poleszak and Malec, 2002		
					A ₁ R antagonist	CPT	↔
A _{2A} R antagonist		DMPX	↑				
A ₁ R/A ₂ R antagonist		Caffeine	↑				
SKF38393 (D ₁ R agonist)		A ₁ R agonist	CPA	#x2193;	Ferré et al., 1994		
	A ₁ R antagonist	8-CPT2	↑	Popoli et al., 1996			
Bromocriptine (D ₂ R agonist)	A ₁ R agonist	CPA	↔	Ferré et al., 1994			
		L-PIA	#x2193;	Ferré et al., 1991b			

• Drug used to induced hyperlocomotion				
	A ₁ R/A ₂ R agonist	NECA	#x2193;	Ferré et al., 1991b
	A ₁ R/A ₂ R antagonist	Caffeine	↑	Ferré et al., 1991a
		Theophylline	↑	
NMDAR channel blockers	Adenosinergic action	Drug	Effect	References
MK-801	A ₁ R agonist	CPA	#x2193;	Malec and Poleszak, 2006
			↔	Fraser et al., 1997
	A _{2A} R agonist	CGS 21680	#x2193;	Malec and Poleszak, 2006
		DPMA	#x2193;	Fraser et al., 1997
	A ₁ /A ₂ R agonist	NECA	#x2193;	Malec and Poleszak, 2006
	A ₁ R antagonist	CPT	↔	
	A _{2A} R antagonist	DPMX	↑	Malec and Poleszak, 2006
			↑	Kuribara et al., 1992
			#x2193;	de Oliveira et al., 2005
			#x2193;	Dall'Igna et al., 2003
PCP	A ₁ R/A _{2A} R antagonist	Theophylline	↑	Malec and Poleszak, 2006
	A ₁ R agonist	CPA	#x2193;	Gotoh et al., 2002
Ketamine	A _{2A} R agonist	CGS 21680	#x2193;	Rimondini et al., 1997
	A ₁ R antagonist	DPCPX	↔	Mandryk et al., 2005
	A _{2A} R antagonist	DMPX	↑	
	A ₁ R/A ₂ R antagonist	Caffeine	↑	

TABLE 2

Effects of adenosinergic drugs on PPI and its disruption by psychostimulants: MSX-3 (((E)-phosphoric acid mono-[3-[8-[2-(3-methoxyphenyl)]]]); the full names of the other drugs are provided in Table 1. ↓ / ↑: attenuates / potentiates basal PPI or the drug-induced PPI disruption; ↔ no effect.

• Adenosinergic drugs on Sensorimotor gating measured by prepulse inhibition (PPI)				
Adenosinergic drugs	Adenosinergic action	Effect	References	
CPA	A ₁ R agonist	↔	Sills et al., 1999	
			Schwienbacher et al., 2002	
CGS21680	A _{2A} R agonist	↔	Hauber and Koch, 1997	
			Sills et al., 2001	
Caffeine	A _{2A} R antagonist	↔	Bakshi et al., 1995	
MSX-3	A ₁ R/A ₂ R antagonist	#x2193;	Nagel et al., 2003	
Theophylline		↔	Koch and Hauber, 1998	
↓ / ↑: impairs / enhances PPI; ↔ no effect				
• Adenosinergic drugs against psychostimulant-induced ppi deficit				
PPI-disrupting agents	Adenosinergic action	Adenosinergic drugs	Effect against PPI disrption	References
Amphetamine	A _{2A} R agonist	CGS 21680	↔	Sills et al., 2001
Apomorphine	A ₁ R agonist	CPA	#x2193;	Koch and Hauber, 1998
	A _{2A} R agonist	CGS 21680	#x2193;	Hauber and Koch, 1997
			↔	Sills et al., 2001
	A ₁ R/A ₂ R antagonist	Theophylline	↑	Koch and Hauber, 1998
MK-801 / PCP	A _{2A} R agonist	CPA	#x2193;	Sills et al., 1999
	A _{2A} R agonist	CGS 21680	↓	Sills et al., 2001
				Wardas et al., 2003

TABLE 3A

Effects of adenosinergic drugs on learning and memory in normal animals: CCPA (2-chloro-N6-cyclopentyladenosine), SCH 58261 ({7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5c]-pyrimidine}), ZM 241385 (4-(2-[7-amino-2-(2-furyl{1,2,4}-triazolo{2,3a}-{1,3,5}triazin-5-yl-amino]ethyl)phenol), 8-PT (8-phenyltheophylline); the full names of the other drugs are provided in Table 1. ↓ / ↑: impairs / enhances memory performance; ↔ no effect. * indicates that the direction of caffeine's effect on retention of inhibitory avoidance learning was dependent on whether the drug was administered before (leading to retention impairment) or after (leading to retention enhancement) the learning phase of the experiment.

• Adenosinergic drugs on memory functions in non-pathological models				
<i>Associative learning</i>	<i>Adenosinergic action</i>	<i>Drug</i>	<i>Effects on memory performance</i>	<i>References</i>
• Active avoidance	A ₁ R agonist	L-PIA	↓	Haraguchi and Kuribara, 1991
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	Yonkov, 1984
• Contextual conditoning	A ₁ R agonist	CPA	↓	Corodimas and Tomita, 2001
• Eyeblink conditioning	A _{2A} R antagonist	SCH 58261	↓	Fontinha et al., 2009
• Inhibitory avoidance		CCPA	↓	Pereira et al., 2005
		CPA	↓	Normile and Barraco, 1991
		CGS 21680	↓	Pereira et al., 2005
		CPX	↔	Von Lubitz et al., 1993
	A ₁ R antagonist	DPCPX	#x2191;	Pereira et al., 2002
			↔	Pereira et al., 2005
			↔	Prediger et al., 2005d
			↔	Kopf et al., 1999
			↔	Normile and Barraco, 1991
	A _{2A} R antagonist	SCH 58261	#x2191;	Kopf et al., 1999
		ZM 241385	↔	Pereira et al., 2005
	A ₁ R/A ₂ R antagonist	Caffeine	↑ / ↓ *	Angelucci et al., 1999
			#x2191;	Kopf et al., 1999
				Cestari and Castellano, 1996
• Passive avoidance	A ₁ R agonist	CHA	↓	Tabata et al., 2001
				Homayoun et al., 2001
				Zarrindast and Shafaghi, 1994
		CPA	↓	Tabata et al., 2001
	A ₁ R/A ₂ R antagonist	R-PIA	↓	Homayoun et al., 2001
				Zarrindast and Shafaghi, 1994
				Suzuki et al., 1993
		Theophylline	↓	
• Active avoidance learning	A ₁ R agonist	8-PT	↓	Zarrindast and Shafaghi, 1994
		Caffeine	#x2191;	
		CPA	↓	
		R-PIA	↓	Martin et al., 1993

• Adenosinergic drugs on memory functions in non-pathological models				
	A ₂ R agonist	CV-1808	↓	
	A ₁ R/A ₂ R agonist	NECA	↓	
	A ₁ R/A ₂ R antagonist	Caffeine	↓	Zimmerberg et al., 1991
			#x2191;	Haraguchi and Kuribara, 1991
Spatial reference memory	Adenosinergic action	Drug	Effects on memory performance	References
• Morris water maze	A ₁ R agonist	CPA	#x2191;	Von Lubitz et al., 1993
	A ₁ R antagonist	CPX	↓	
				Angelucci et al., 2002
		Caffeine	#x2191;	Prediger et al., 2005e
• Water multiple-alley maze	A ₁ R/A ₂ R antagonist		↓	Kant, 1993
• Radial arm maze		Theophylline	#x2191;	Hauber and Bareiss, 2001
Working memory	Adenosinergic action	Drug	Effects on memory performance	References
• Delayed alternation	A _{2A} R agonist	DPMA	↔	Fraser et al., 1997
	A ₁ R antagonist	CPX	↔	
• Three-panel runway setup	A _{2A} R agonist	CPA	↓	Ohno and Watanabe, 1996
		CGS 21680	↔	
• Non-matching to sample	A ₁ R/A ₂ R antagonist	Caffeine	↔	Furusawa, 1991
• Radial arm maze		Theophylline	↔	Hauber and Bareiss, 2001
Recognition memory	Adenosinergic action	Drug	Effects on memory performance	References
• Social recognition	A _{2A} R agonist	DPMA	↓	Prediger et al., 2005a
		CCPA	↓	
	A ₁ R antagonist	DPCPX	#x2191;	
	A _{2A} R antagonist	ZM 241385	#x2191;	
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	

TABLE 3B

Effects of adenosinergic drugs in memory deficiency models: BIIP 20 ((S)-(-)-8-(3-oxocyclopentyl)-1,3-dipropyl-7H-purine-2,6-dione), FR 194921 (2-(1-methyl-4-piperidinyl)-6-(2-phenylpyrazolol[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone), KF 15372 (8-Dicyclopropylmethyl- 1,3-dipropylxanthine), KW 6002 ((E)-1,3-diethyl-8-(3, 4-dimethoxystyryl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione), ZM 241385 (4-(2-[7-amino-2-(2-furyl){1,2,4}-triazolo{2,3-a}{1,3,5}triazin-5-ylaminoethyl} phenol); the full names of the other drugs are provided in Table 1. ↓ / ↑: potentiates/ attenuates the memory impairment; ↔ no effect.

• Adenosinergic drugs on memory functions in memory impairment models						
Memory impairment models	Behavioural models	Adenosinergic action	Drug	Effects on amnesic effect	References	
NMDAR-antagonist	Inhibitory avoidance	A ₁ R/A ₂ R antagonist	Caffeine	↔	Dall'Igna et al., 2003	
				#x2191;	de Oliveira et al., 2005	
		A ₁ R agonist	CPA	↔		
	Delayed alternation	A _{2A} R agonist	DPMA		#x2191;	Fraser et al., 1997
		A ₁ R antagonist	CPX		#x2191;	
		A _{2A} R antagonist	KW 6002	↔	Cunha et al., 2008	
			SCH 58261	↔		
	A ₁ R/A ₂ R antagonist	Caffeine		#x2191;	de Oliveira et al., 2005	
				↔	Dall'Igna et al., 2003	
	Spontaneously hypertensive rats	Passive avoidance	A ₁ R antagonist	BIIP 20	#x2191;	Pitsikas and Borsini, 1997
A ₁ R antagonist			DPCPX	#x2191;		
Object recognition		A _{2A} R antagonist	7M 241385	#x2191;	Pires et al. 2009	
		A ₁ R/A ₂ R antagonist	Caffeine	#x2191;		
Social recognition		A ₁ R antagonist	DPCPX	#x2191;	Prediger et al., 2005a	
		A ₁ R antagonist	DPCPX	↔		
Aging	olfactory discrimination	A _{2A} R antagonist	ZM 241385	#x2191;	Prediger et al., 2005c	
		A ₁ R/A ₂ R antagonist	Caffeine	#x2191;		
	Social recognition	A ₁ R/A ₂ R antagonist	Caffeine	↓	Prediger et al., 2005b	
Scopolamine	Passive avoidance		KF 15377	#x2191;		
		A ₁ R antagonist	dicyclopropylmethyl	#x2191;	Suzuki et al., 1993	
			3-oxocyclopentyl	#x2191;		
	Inhibitory avoidance	A ₁ R antagonist	FR 194921	#x2191;	Maemoto et al., 2004	

• Adenosinergic drugs on memory functions in memory impairment models				
Delayed alternation	A ₁ R/A ₂ R antagonist	Theophylline	#x2191;	Jin et al., 2000
	A _{2A} R agonist	DPMA	↔	Fraser et al., 1997
	A _{2A} R antagonist	KW 6002 SCH 58261	↔	Cunha et al., 2008
	A ₁ R antagonist	CPX	↔	
Delayed alternation	A _{2A} R antagonist	KW 6002	#x2191;	Cunha et al., 2008
		SCH 58261	#x2191;	Cunha et al., 2008 Dall'Igna et al., 2007
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	Dall'Igna et al., 2007
	A _{2A} R antagonist	SCH 58261	#x2191;	Dall'Igna et al., 2007
Inhibitory avoidance	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	
	A _{2A} R antagonist	SCH 58261	#x2191;	
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	
	A _{2A} R antagonist	SCH 58261	#x2191;	Canas et al., 2009
Spatial & object recognition	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	
Reference memory	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	Arendash et al., 2006
			#x2191;	
Working memory				
Social recognition	A _{2A} R antagonist	ZM 241385	#x2191;	Prediger et al., 2005d
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	
Convulsion in early in life	A _{2A} R antagonist	ZM 241385	#x2191;	Cognato et al., 2010
	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	
Morphine	A ₁ R/A ₂ R agonist	NECA	#x2191;	Khavandgar et al., 2002
Pentyleneetetrazole	A ₁ R/A ₂ R antagonist	Theophylline	#x2191;	Honayoun et al., 2001
Alcohol	A ₁ R/A ₂ R antagonist	Caffeine	#x2191;	Spinetta et al., 2008

TABLE 4

Summary of the behavioural phenotypes in engineered mice targeting A_{2A}R, A₁R or Adk.

Adenosine kinase (Adk) over-expression			
	Locomotor activity	Hyperactive	Fedele et al. (2005)
Brain overexpression Adk ^{tm1^{-/-}} -Tg(UblAdk) mice	Locomotor activity	Transient hyperactivity, followed by facilitated habituation	
	Hyperactivity response to Amphetamine	Abolished	
	Hyperactivity response to MK-801	Enhanced	
	Motor coordination	Normal	Yee et al., (2007)
	Anxiety	Normal	
	Water maze reference memory	Severely impaired	
	Water maze working memory	Severely impaired	
Pavlovian conditioned freezing	Severely impaired		
Adenosine A _{2A} receptor deletion & over-expression			
Constitutive homozygous KO A _{2A} R ^{-/-} mice	Hyperactive response to D ₁ R agonist (SKF81297)	Normal	Chen et al. (2000)
	Hypoactive response to D ₂ R agonist (Quinpirole)	Normal	
	Hyperactive response to Amphetamine	Attenuated	
	Hyperactive response to Cocaine	Attenuated	
	Caffeine-induced wakefulness	Abolished	Huang et al. (2005)
Working memory function (radial arm maze)	Working memory function (radial arm maze)	Normal	Duan et al. (2009)
	Enhanced only with short retention (15s) demand		
	Enhanced	Zhou et al. (2009)	
Reference memory function (radial arm maze)	No effect		
Forebrain neurons homozygous KO CaMKII α -Cre(+)A _{2A} R ^{flox/+} mice	Hyperactive response to A _{2A} antagonist (KW6002)	Attenuated	Shen et al. (2008)
	Hyperactive response to Cocaine	Attenuated	
	Hyperactive response to Phencyclidine	Attenuated	
	KW6002's additive effect on cocaine-induced hyperactivity	Absent	
	Hyperactive response to Caffeine	Attenuated	
	Hypoactive response to A _{2A} agonist (CSG21680)	Attenuated	Yu et al (2008)

Hyperactive response to A _{2A} antagonist (KW6002)	Attenuated		
	Operant conditioning	Weaker habit formation / Enhanced sensitivity to reward devaluation	Yu et al. (2009a)
Striatum-specific A _{2A} R deletion Dlx5/6-Cre(+)A _{2A} R ^{fllox+/+} mice	Hyperactive response to A _{2A} antagonist (KW6002)	Attenuated	
	Hyperactive response to Cocaine	Enhanced	Shen et al. (2008)
	Hyperactive response to Phencyclidine	Enhanced	
KW6002's additive effect on cocaine-induced hyperactivity	Reversed		
	Activity	Normal	
	Spontaneous alternation	Normal	
Brain over-expression TGR(NSEhA2A) transgenic rats	Avoidance of blind alleys in hexagon maze	Impaired (transient)	Giménez-Llort et al. (2007)
	Object recognition memory	Impaired	
	Water maze reference memory	Normal	
	Working memory	Impaired? (questionable conclusion)	
Adenosine A₁ receptor deletion			
Constitutive homozygous A ₁ R ^{-/-} & heterozygous A ₁ R ^{+/-} KO mice	Nocturnal peak activity	Reduced (gene-dose dependent)	
	Motor function	Reduced (gene-dose dependent)	
	Anxiety	Anxiogenic (gene-dose dependent)	
	Explorative behaviour	Increase in A ^{+/-} , Decrease in A ^{1-/-} mice	Giménez-Llort et al. (2002)
	Aggressiveness	Reduced in A ^{1+/-} , Enhanced in A ^{1-/-} mice	
	Water maze reference memory	Normal	
	Sensitivity to pain	Increase in both A ^{1+/-} and A ^{1-/-} KO mice	Johansson et al. (2001)
Anxiety	Anxiogenic (gene-dose dependent)		
Constitutive homozygous A ₁ R ^{-/-} KO mice	Caffeine-induced wakefulness	Normal	Huang et al. (2005)