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REVIEW

Triggering neurotrophic factor actions through adenosine A2A receptor activation: implications for neuroprotection

Ana M Sebastião and Joaquim A Ribeiro

Institute of Pharmacology and Neurosciences, Faculty of Medicine and Unit of Neurosciences, Institute of Molecular Medicine, University of Lisbon, Lisbon, Portugal

G protein coupled receptors and tropomyosin-related kinase (Trk) receptors have distinct structure and transducing mechanisms; therefore, cross-talk among them was unexpected. Evidence has, however, accumulated showing that tonic adenosine A2A receptor activity is a required step to allow synaptic actions of neurotrophic factors, namely upon synaptic transmission at both pre- and post-synaptic level as well as upon synaptic plasticity. An enhancement of A2A receptor tonus upon ageing may partially compensate the loss of TrkB receptors, rescuing to certain degree the facilitatory action of brain derived neurotrophic factor in aged animals, which might prove particularly relevant in the prevention of neurodegeneration upon ageing. A2A receptors also trigger synaptic actions of other neurotrophic factors, such as glial derived neurotrophic factor at dopaminergic striatal nerve endings. The growing evidence that tonic adenosine A2A receptor activity is a crucial step to allow actions of neurotrophic factors in neurones will be reviewed and discussed in the light of therapeutic strategies for neurodegenerative diseases.
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Keywords: adenosine; A2A receptors; neurotrophic factors; brain derived neurotrophic factor; neurodegenerative diseases; Parkinson's disease; Hungtington's disease; Alzheimer's disease

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BDNF, brain derived neurotrophic factor; ENTs, equilibrative nucleoside transporters; GAT, GABA transporters; GDNF, glial derived neurotrophic factor; GPCRs, G protein coupled receptors; LTP, long term potentiation; nAChRs, nicotinic acetylcholine receptors; NT-3, neurotrophin-3; NT-4/5, neurotrophin 4/5; NGF, nerve growth factor; Trk, tropomyosin-related kinase

Introduction

G protein coupled receptors (GPCRs) are structurally very different from the receptors for neurotrophic factors. GPCRs are a single peptide chain that crosses the lipid bilayer seven-fold, being therefore also known as seven transmembrane domain receptors. They may operate as monomeric, as well as homo- or hetero- dimers, but a monomeric protein *per se*, once activated, has the ability to interact with a G protein and to trigger a transducing pathway, which most frequently involves changes in adenylate cyclase activity or phosphoinositide metabolism.

Tropomyosin-related kinase (Trk) receptors are a distinct class of membrane receptors, each receptor being a dimer of two identical peptide chains, which share the extracellular binding site for the neurotrophin. These receptors have an intracellular catalytic domain that possesses enzymatic capability and initiates a cascade of phosphorylation steps that involve at least three distinct pathways, the PLCγ pathway involved in fast signalling, the MEK/MAP Kinase mostly involved in differentiation, the PI3K/Akt survival pathway, among others (Kaplan and Miller, 2000; Lee *et al.*, 2002).

Correspondence: Ana M Sebastião, Institute of Pharmacology and Neurosciences, Faculty of Medicine and Unit of Neurosciences, Institute of Molecular Medicine, University of Lisbon, 1649-028 Lisbon, Portugal. E-mail: anaseb@fm.ul.pt
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Due to structural dissimilarities, interactions between these so distinct classes of membrane receptors were therefore less expected to occur than between two GPCRs. However, three different lines of evidence triggered the interest of evaluating a possible cross-talk between adenosine receptors, which are GPCRs, and receptors for neurotrophic factors, namely:

1. The ability of cyclic adenosine 3′,5′-monophosphate (cyclic AMP) to gate the facilitatory action of brain derived neurotrophic factor (BDNF) on transmission in developing synapses (Boulanger and Poo, 1999a), together with the well-known positive coupling of adenosine A2 receptors to the adenylate cyclase/cyclic AMP transducing system in the brain (van Calker *et al.*, 1979).
2. The ability of depolarization to trigger a facilitatoty action of BDNF on transmission in developing synapses (Boulanger and Poo, 1999b), together with the well-known depolarization-induced adenosine release (Latini and Pedata, 2001).
3. The ability of adenosine A2A receptors to transactivate TrkB BDNF receptors (Lee and Chao, 2001).

In this paper the so far accumulated evidence that tonic adenosine A2A receptor activity is a crucial step to allow actions of neurotrophic factors in neurones will be reviewed and discussed in the light of therapeutic strategies for neurodegenerative diseases.

Neurotrophic factors and their receptors

It is now widely accepted that the influence of neurotrophins on the nervous system spans from neuronal development (Lewin and Barde, 1996) and survival (Murer *et al.*, 2001), to activity-dependent forms of synaptic plasticity (McAllister *et al.*, 1999; Nagappan and Lu, 2005). The neurotrophin family, in mammals, includes nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5). Each neurotrophin shows binding specificity for a Trk receptor, such as TrkA for NGF, TrkB for BDNF and TrkC for NT-3. Neurotrophins also bind to another receptor, the p75. This receptor binds to nearly equal affinity to BDNF, NGF, NT-3 and NT-4. In contrast to Trk receptors, which have a well-known survival and trophic role according to the cascades of phosphorylation steps that are activated, the p75 has no intrinsic kinase property and has activities ranging from trophism to apoptosis (see Blöchl and Blöchl, 2007).

Receptors for other neurotrophic factors, such as the GFRα1/Ret for glial derived neurotrophic factor (GDNF) operate in a way similar to that of Trk receptors, with binding of GDNF to a GFRα1/RET complex to initiate the phosphorylation cascades (Bespalov and Saarma, 2007).

Lack of neurotrophic factors has been involved in several neurodegenerative diseases, namely GDNF in Parkinson's disease (see Bespalov and Saarma, 2007), NGF and/or BDNF in amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) (see e.g. Schulte-Herbrüggen *et al.*, 2007).

Adenosine as an ubiquitous neuromodulator

There are two ways for extracellular adenosine accumulation (Figure 1), one derived from released adenosine 5′-triphosphate (ATP), followed by metabolism into adenosine through a cascade of ectonucleotidases; the other through the equilibrative nucleoside transporters (ENTs). Transport inhibition, therefore, usually leads to an enhancement of extracellular adenosine levels, in particular during high neuronal activity as under this condition substantial amounts of ATP are released together with neurotransmitters.

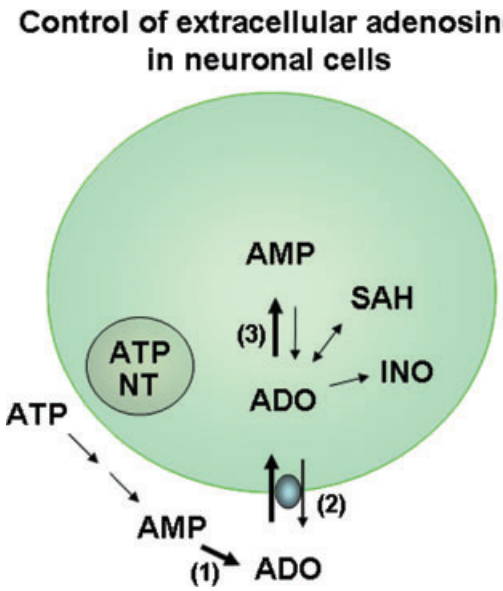

Figure 1 Main mechanisms involved in the control of extracellular levels of adenosine in neuronal cells. Adenosine (ADO) can be formed extracellularly from the breakdown of released ATP through a cascade of ectoenzymes, the last step being hydrolysis of AMP by ecto-5′-nucleotidase. Adenosine is also released as such through equilibrative transporters; as the intracellular adenosine concentrations are kept low, mainly due to the activity of adenosine kinase (3), and as considerable amounts of adenosine are formed from released ATP, the main direction of adenosine transport is inwards. However, under some conditions (e.g. low oxygen, low glucose, depolarization), the intracellular adenosine levels rise and outward transport of adenosine occurs. Interconversion of adenosine into S-adenosyl-homocysteine (SAH) or deamination into inosine (INO) also contributes to the low intracellular adenosine levels. AMP, adenosine 5′-monophosphate; ATP, adenosine 5′-triphosphate.

An enhancement of extracellular adenosine levels can also be achieved by inhibition of intracellular enzymes that are responsible for keeping intracellular adenosine concentrations low, such as adenosine kinase that phosphorylates adenosine into AMP. Inhibition of this enzyme selectively amplifies extracellular adenosine concentrations at cell and tissue sites where adenosine release occurs. The therapeutic antiepileptic potential of adenosine kinase inhibition or of its underexpression in implanted cells has been highlighted recently (Li *et al.*, 2007).

Other mechanisms that lead to pronounced changes in the extracellular levels of adenosine are depolarization, and in this case most of the adenosine seems to be released through ENTs (Latini and Pedata, 2001). Similarly, hypoxia, ischaemia or glucose deprivation are highly efficient adenosine releasing stimuli (Fowler, 1993; Frenguelli *et al.*, 2007), and this occurs even before signs of anoxic depolarization. Extracellular accumulation of adenosine during low-energy and oxygen availability is highly important to protect cells. Indeed, adenosine,

by activating membrane located inhibitory A1 receptor, is a well-known neuroprotective agent under ischaemic situations (de Mendonça *et al.*, 2000). At synapses, this neuroprotection is directly related to the ability of adenosine A1 receptors to inhibit synaptic transmission during the insult (Sebastião *et al.*, 2001) and this is most probably due to a concerted inhibitory action upon glutamate release at the presynaptic level and upon N-methyl-D-aspartate (NMDA) receptor activation at the post-synaptic level. Adenosine A1 receptor-related mechanisms are involved in the preconditioning-induced neuroprotection (Nakamura *et al.*, 2002; Pugliese *et al.*, 2003).

High-frequency neuronal firing, which leads to an enhancement of ATP release (most of it probably together with neurotransmitters) and subsequent extracellular adenosine formation, is another way to enhance extracellular adenosine levels. As recently pointed out (Bekar *et al.*, 2008), the increase in extracellular adenosine caused by high-frequency neuronal firing may be one of the major causes of the beneficial influence of deep brain stimulation in some pathological conditions.

Four different adenosine receptors have been identified and cloned up to now, namely, the A1, A2A, A2B and A3 receptors. All are GPCRs that lead not only to changes in second messenger levels but also to modulation of ion channels, such as calcium and potassium channels. Through these processes, adenosine modulates neuronal activity, pre-synaptically by inhibiting or facilitating transmitter release, post-synaptically by affecting the action of other neurotransmitters and non-synaptically by hyperpolarizing or depolarizing neurones (see e.g. Ribeiro *et al.*, 2003). The A1 and A2A receptors are high-affinity receptors, whereas the A2B is a low-affinity one. The A1 is mostly an inhibitory receptor, whereas the A2A receptors are mostly excitatory, being positively coupled to adenylate cyclase. For detailed pharmacological characteristics of the different adenosine receptors, see for example Fredholm *et al.* (2001).

The past few years have brought new insights in our understanding of the role of tripartite synapses, with its pre- post- and glial component, in neurological diseases (Halassa *et al.*, 2007). Adenosine and ATP are among the most relevant players in neuron–glia communication (Fields and Burnstock, 2006). ATP has a dual role as it acts upon its own receptors, mostly of the P2Y subtype, which are abundant in astrocytes and are relevant for calcium signalling; ATP is a substrate of ectonucleotidases, leading to adenosine formation, which then operates its own receptors. Actions of adenosine upon glial cell functions include modulation of glycogen metabolism, neurotransmitter transporters, astrogliosis and astrocyte swelling (Daré *et al.*, 2007). Adenosine receptors at oligodendrocytes regulate white matter development and myelinization (Fields and Burnstock, 2006; Daré *et al.*, 2007).

Adenosine as a modulator of other neuromodulators

Besides its direct pre- and post- synaptic actions on neurones, adenosine is rich in nuances of priming, triggering and braking the action of several neurotransmitters and neuromodulators. Adenosine was, therefore, proposed as a fine tuner, considering that in this way, adenosine is a partner of a very sophisticated interplay between its own receptors and with receptors for other neurotransmitters and/or neuromodulators. Several possibilities exist for this interplay, either at the transducing system level (Sebastião and Ribeiro, 2000) or as a consequence of receptor–receptor heteromerization (Ferré *et al.*, 2007), greatly expanding the number of receptor combination possibilities to modulate cell signalling.

It is not difficult to envisage the different possibilities adenosine receptors may use to interact with other GPCRs. Dimerization of GPCRs, either homo- or heteromerization, is nowadays easily accepted since the strong evidence that GABAB receptors are dimers of two seven transmembrane domain GABAB receptor molecules (White *et al.*, 1998). First hints of A2A/D2 heterodimers in the striatum were several years a head (Ferré *et al.*, 1991) and their functional relevance is now firmly established (see Ferré *et al.*, 2007). Futhermore, GPCRs most frequently share α subunits, not to speak of the $\beta\gamma$ subunits, which are common to all G proteins and may change activation equilibrium of other GPCRs. Last, but not least, there are many possibilities of cross-talk with related transduction pathways that may have several kinases and other key molecules in common. Adenosine receptors can also interact with ionotropic receptors with putative implications for neuroprotection, plasticity and learning, as it is the case of AMPA and NMDA glutamate receptors, as well as nicotinic acetylcholine receptors (nAChRs). Some of these interactions involve cyclic AMP – mediated ionotropic receptor phosphorylation followed by enhanced desensitization; others involve more complex transduction pathways. For a detailed review on interactions between adenosine receptors and other GPCRs as well as between adenosine receptors and ionotropic receptors, see Sebastião and Ribeiro (2009).

Interaction between adenosine receptors and receptors for neurotrophic factors

As mentioned above, it is known for several years that presynaptic depolarization (Boulanger and Poo, 1999b), which increases extracellular adenosine levels, as well as enhancement of intracellular cAMP (Boulanger and Poo, 1999a), the most frequent adenosine A2 receptor transducing pathway, triggers synaptic actions of BDNF. On the other hand, adenosine A2A receptors are able to transactivate TrkB receptors in the absence of the neurotrophin (Lee and Chao, 2001). This transactivation requires long-term incubation with GPCR agonists and receptor internalization (Rajagopal *et al.*, 2004) and it is not yet clear whether it operates the same mechanism as the more recently identified ability of adenosine A2A receptors to trigger and promote synaptic and survival actions of neurotrophic factors.

Evidence has been accumulated clearly showing that adenosine A2A receptor activation is a crucial requisite for the functioning of neurotrophic receptors at synapses. This has been shown for the facilitatory actions of BDNF on synaptic transmission (Diógenes *et al.* 2004; Tebano *et al.*, 2008) and

on long term potentiation (LTP) (Fontinha *et al.*, 2008) at the CA1 area of the hippocampus as well as for the action of GDNF at striatal dopaminergic nerve ending (Gomes *et al.*, 2006) and cortico-striatal pathway (Gomes *et al.*, 2009). Interestingly, A2A receptors, adenosine A2A receptors and TrkB BDNF receptors can coexist in the same nerve ending as the facilitatory action of adenosine A2A receptors upon TrkB-mediated BDNF action is also visible at the neuromuscular junction (Pousinha *et al.*, 2006), a single nerve ending synapse model.

The ability of BDNF to facilitate synaptic transmission is dependent on the age of the animals (Diógenes *et al.*, 2007) and this may be related to the degree of activation of adenosine A2A receptors by endogenous adenosine at different ages. Thus, in infant animals, that is, immediately after weaning, to trigger a BDNF facilitatory action, it is necessary to increase the extracellular levels of adenosine, either by inhibiting adenosine kinase or by a brief depolarization (Diógenes *et al.* 2004; Pousinha *et al.*, 2006) or by inducing high-frequency neuronal firing, such as LTP-inducing paradigms (Fontinha *et al.*, 2008); in all cases, the actions of BDNF are lost by blocking adenosine A2A receptors with selective antagonists. The actions of BDNF are also blocked by inhibition of Trk phosphorylation, but the Trk phosphorylation inhibitor does not prevent A2A receptor-mediated facilitation of synaptic transmission (Pousinha *et al.*, 2006), indicating that the A2A receptor operates upstream of TrkB activation. In adult animals, BDNF *per se*, through TrkB receptor activation, can facilitate synaptic transmission but this effect is also fully lost with blockade of adenosine A2A receptors (Diógenes *et al.*, 2007) or in A2A receptor knockout mice (Tebano *et al.*, 2008). Nicotinic α-7 cholinergic currents in GABAergic hippocampal neurons are inhibited by BDNF, and this also requires co-activation of adenosine A2A receptors (Fernandes *et al.*, 2008). Inhibition of GABA transporters (GAT) of the predominant neural subtype, GAT1, by BDNF does not fully depend upon co-activation of A2A receptors, as it is not abolished by A2A receptor blockade; however, A2A receptor activation can facilitate this BDNF action (Vaz *et al.*, 2008).

A2A receptors, due to their ability to enhance excitotoxicity phenomena, including glutamate release and action, are mostly regarded as promoters of neuronal death. However, in some cases, such as cultured retinal neurones, A2A receptors have been shown to protect neurones against glutamate-induced excitotoxicity (Ferreira and Paes-de-Carvalho, 2001). Whether this is due to the ability of A2A receptors to facilitate actions of neurotrophic factors, as it has been shown to occur in relation to A2A receptor-mediated neuroprotection of motor neurones (Wiese *et al.*, 2007), requires further investigation. It is worthwhile to note that while Wiese *et al.* (2007) reported a TrkB-mediated enhancement of survival of injured facial motor neurons *in vivo*, TrkB receptor activation by BDNF may render spinal cord cultured motor neurons more vulnerable to insult (Mojsilovic-Petrovic *et al.*, 2006). However, another recent study reported an A2A receptor-mediated increase in TrkB signalling through Akt, leading to strengthened synaptic pathways to phrenic motoneurons, as well as to increased breathing in unanesthetized rats, and improved breathing in rats with cervical spinal injuries (Golder *et al.*, 2008). Interestingly enough, A2A receptor antagonism prevented both the favourable (Wiese *et al.*, 2007) and the deleterious (Mojsilovic-Petrovic *et al.*, 2006) TrkB-mediated actions.

Activation of adenosine A2A receptors enhances NGF-induced neurite outgrowth in PC12 cells and rescues NGF-induced neurite outgrowth impaired by blockade of the mitogen-activated protein kinase cascade, an action that requires protein kinase A (PKA) activation (Cheng *et al.*, 2002). Furthermore, activation of adenosine A2A receptors, through Trk-dependent and phosphatidylinositol 3-kinase/Akt-mechanisms, promotes PC12 cell survival after NGF withdrawal (Lee and Chao, 2001). A similar A2A receptor-mediated neuroprotection mechanism has been shown to occur in hippocampal neurones after BDNF withdrawal (Lee and Chao, 2001). Contrasting with A2A receptors which usually promote the actions of neurotrophic factors, adenosine A1 receptors inhibit neurite outgrowth of cultured dorsal root ganglion neurons, both in the absence and in the presence of NGF (Thevananther *et al.*, 2001). It is worthwhile to note that while synaptic actions of adenosine, such as modulation of neurotransmitter release, are visible within minutes after adenosine receptor activation, the trophic neuroprotective adenosine actions might involve prolonged or even tonic activation of adenosine receptors.

Besides interactions at the neurotrophin receptor level, adenosine receptor activation may also induce release of neurotrophic factors. Thus, the expression and/or release of NGF are enhanced by activation of A2A receptors in microglia (Heese *et al.* 1997) and by activation of A1 receptors in astrocytes (Ciccarelli *et al.*, 1999). Adenosine A2B receptors in astrocytes are also able to enhance GDNF expression (Yamagata *et al.*, 2007). In the whole hippocampus, A2A receptors are required for normal BDNF levels (Tebano *et al.*, 2008). Interestingly, in a mice model of Hungtington's disease, A2A receptors are also required to keep striatal BDNF levels close to those obtained in wild-type mice (Potenza *et al.*, 2007).

Interactions among purinergic, growth factors and cytokine signalling are relevant to regulate neuronal and glial maturation as well as development. In neuronal-dependent glial maturation, both ATP and adenosine purinoceptors are involved (Fields and Burnstock, 2006). The extracellular adenosine levels attained during high-frequency neuronal firing are sufficient to stimulate adenosine receptors in oligodendrocyte ancestor cells inhibiting their proliferation and stimulating their differentiation into myelinating oligodendrocytes (Stevens *et al.*, 2002) but unfortunatelly, the nature of the adenosine receptor involved was not identified in this work. In premyelinating Schwann cells, A2A receptors activate phosphorylation of extracellular signal-regulated kinases (ERKs), namely ERK1/2, and inhibit Schwann cell proliferation without arresting differentiation (Stevens *et al.*, 2004).

Physiological and pathophysiological implications

Brain derived neurotrophic factor has an important role upon synaptic plasticity even in the adult hippocampus (McAllister *et al.*, 1999). BDNF expression and release (Hartmann *et al.*, 2001); (Balkowiec and Katz, 2002), as well as release of adenosine (Pazzagli *et al.*, 1993), or of its precursor ATP

(Wieraszko *et al.*, 1989), is more pronounced upon depolarization and during physiologically relevant patterns of neuronal activity, namely those that induce hippocampal LTP. Accordingly, released ATP (Cunha *et al.*, 1996) and high-frequency neuronal stimulation (Correia-de-Sá *et al.*, 1996) favours A_{2A} receptor activation. Therefore, high neuronal activity seems to create ideal physiological conditions for the interplay between adenosine A_{2A} and TrkB receptors to occur. The finding that the facilitatory action of BDNF upon LTP in the CA1 area of the hippocampus is fully lost upon blockade of adenosine A2A receptors as well as upon depletion of extracellular adenosine (Fontinha *et al.*, 2008) highlights the A2A receptor as a new physiologic partner, to the TrkB signalling processes that influences synaptic plasticity phenomena.

Another way A2A receptors have to influence BDNF-related plasticity is through the interplay with the homopentameric α-7 subtype of nAChR, which is particularly relevant for transmitter release and plasticity (Gray *et al.*, 1996; Ji *et al.*, 2001) due to its high-calcium permeability. Adenosine, through A2A receptors, and BDNF, through TrkB receptors, exert double control over α-7-nicotinic currents at GABAergic interneurons in the hippocampus, as it can be concluded from the finding that blockade of A2A receptors abolishes the BDNF-induced current inhibition (Fernandes *et al.*, 2008). As postsynaptic α-7 nAChR-mediated inputs to GABAergic interneurons regulate inhibition within the hippocampus, A2A receptors by allowing the inhibition of cholinergic currents by BDNF might temporarily relieve GABAergic inhibition, therefore facilitating plasticity phenomena.

A decrease in levels and/or action of neurotrophic factors have been implicated in the pathophysiological mechanisms of many diseases of the nervous system, such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, diabetic neuropathies, ALS and even depression, therefore making the use of the naturally occurring neurotrophic factors promising for treatment of these disorders (Castrén *et al.*, 2007; Schulte-Herbrüggen *et al.*, 2007) (Figure 2). However, until now the pharmacological administration of neurotrophic factors *in vivo* has not been easy as these molecules are unable to cross the blood brain barrier, making invasive application strategies like intracerebroventricular infusion necessary. As pointed out by Thoenen and Sendtner (2002), repeated failures of clinical trials using neurotrophic factors claim for improved methods for regulated local supply of these substances to specific populations of neurons together with a more detailed knowledge of the signal transduction pathways activated by neurotrophins via their receptors. The evidence that adenosine A2A receptors trigger or facilitate actions of neurotrophins upon synaptic strength and neuronal survival opens a new therapeutic strategy (Figure 2), as there are adenosine A2A receptor agonists that cross the blood brain barrier, which can be explored as tools to potentiate neurotrophic actions in the brain. The expression (Cunha *et al.*, 1995) and functioning (Rebola *et al.*, 2003) of A2A receptors in the forebrain increases with age, whereas the number of TrkB receptors is markedly lower in the hippocampus of aged rats (Silhol *et al.*, 2005). The increase in the adenosine A2A receptor tonus partially compensates the loss of TrkB receptors upon ageing, rescuing to certain degree the facilitatory action of BDNF in aged animals (Diógenes *et al.*,

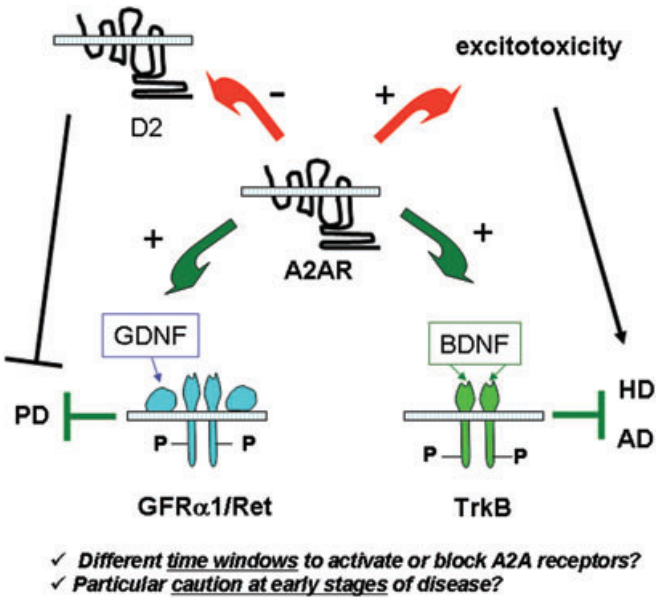

Figure 2 Interplay between adenosine A2A receptors and receptors for neurotrophic factors and its putative influence. Beneficial influences that may contribute to slow down disease progression are represented by the green arrows; those that operate as aggravating factors are represented by red arrows. A2A receptors facilitate actions of GDNF in the striatum as well as the actions of BDNF in the hippocampus. These neurotrophic factors and their receptors (GFRα/Ret for GDNF; and TrkB for BDNF) may slow down progression of Parkinson's disease (PD) or Alzheimer's disease (AD) and this is probably most relevant in early stages of the disease, where neurotrophic influences start to diminish. However, A2A receptors negatively interact with dopamine D2 receptors in medium spiny striatal neurones; under late stages of the disease, blockade of A2A receptors may be advantageous, to relieve this negative interaction that constitutes an aggravating factor in PD. A2A receptors, though facilitation of glutamate release, may also enhance excitotoxicity phenomena, and this might be particularly relevant when neuronal death involves enhanced glutamate signalling. Therefore, both the timing and the nature of neuronal injury may determine whether blockade or activation of adenosine A2A receptors is desirable to protect neurones. BDNF, brain derived neurotrophic factor; GDNF, glial derived neurotrophic factor; Trk, tropomyosin-related kinase.

2007). This might prove particularly important in the prevention of neurodegeneration, as neurodegenerative diseases are most frequent upon ageing; furthermore, it reinforces the therapeutic potential of adenosine-related therapies to influence the actions of neurotrophic factors in old subjects. Interestingly, daily administration of the A2A receptor agonist, CGS 21680 delays progressive deterioration of motor performance, huntingtin aggregation and increase in striatal choline levels in a transgenic mouse model (R6/2) of Huntington's disease (Chou *et al.*, 2005). This animal model involves genetic mutation of Huntingtin, therefore most probably, a reduction of striatal BDNF levels. Indeed, there is strong evidence that a major contributing pathway to striatal degeneration in Huntington's disease is an impairment of anterograde transport BDNF from the cortex to the striatum, due to loss of function of mutated huntingtin (Zuccato *et al.*, 2001; Baquet *et al.*, 2004; Gauthier *et al.*, 2004; Strand *et al.*, 2007). How the low BDNF signalling can be compensated by A2A receptor activation deserves detailed investigation.

A particular mention has to be made about epilepsy, where neurotrophic factors have been considered both harmful, being causal mediators in the development of acquired epileptic syndromes, and eventually useful to treat epilepsy-associated damage (Simonato *et al.*, 2006; Scharfman and Hen, 2007). On the top of this controversy, we can add discrepant findings of both anti-convulsive (Huber *et al.*, 2002) and pro-convulsive (Zeraati *et al.*, 2006) adenosine A2A receptor-mediated actions, the pro-convulsive being much more expected due to the usually excitatory nature of these receptors. The evaluation of a putative interplay between A2A and TrkB receptors in epileptogenic conditions could help and provide hints to solve some of these discrepancies.

Results from clinical and basic studies have demonstrated that stress and depression decrease BDNF expression and neurogenesis, leading to the neurotrophic hypothesis of depression (Castrén *et al.*, 2007; Kozisek *et al.*, 2008). As A2A receptor activation may have anti-depressive action (Kaster *et al.*, 2004), one may, therefore, speculate that the ability of A2A receptors to facilitation the actions BDNF may contribute to the antidepressive actions of adenosine. It is worthwhile to note that deep brain stimulation, now widely used by neurosurgeons to treat tremor and other movement disorders, as well as in a number of psychiatric diseases, including obsessive-compulsive disorders and depression (Larson, 2008), produces its effects by inducing the release of ATP which is subsequently converted extracellularly to adenosine (Bekar *et al.*, 2008). Whether adenosine, through facilitation of BDNF actions, contributes to the antidepresssive properties of deep brain stimulation also awaits further evaluation.

Finally, the cross-talk between adenosine A2A receptors and receptors for neurotrophins also points to the need of caution about therapies with A2A receptor antagonists in neurodegenerative diseases, as it has been proposed for Parkinson's disease to ameliorate L-DOPA-induced dyskinesias (see Morelli *et al.*, 2007). Indeed, the identification of postsynaptic A2A/D2 receptor interactions in the striatum together with the findings that A2A receptor antagonists are neuroprotective in Parkinson's disease models (Chase *et al.*, 2003) and increase dopamine synthesis from L-DOPA (Golembiowska and Dziubina, 2004) led to the proposal for the use of A2A receptor antagonists in Parkinson's disease. On the other hand, neurotrophic factors, in particular GDNF, may be a potential therapeutic approach in the management of Parkinson's disease (Love *et al.*, 2005; Patel *et al.*, 2005). Enhancing GDNF actions, as it is the case of adenosine A2A receptor agonists (Gomes *et al.*, 2006) might also be of high therapeutic interest. In any case, the finding that GDNF actions on dopamine release in the striatum are prevented by A2A receptor antagonism (Gomes *et al.*, 2006) points towards the need for further studies on the consequences of long-term therapy with A2A receptor blockers in neurodegenerative diseases where neurotrophic factors may play a beneficial role. One issue that should be explored in the future is the optimal time window for combined beneficial effects for neurotrophic factors and adenosine A2A receptor agonists/antagonists. Perhaps, in the late stages of neurodegenerative diseases, A2A receptor antagonists may be advantageous to prevent and/or attenuate diskenesias; however, in the early stages, where neurones are struggling for life and an enhancement of neurotrophic factors is highly desirable, A2A receptor antagonists should be avoided and perhaps A2A agonists could be considered to potentiate neurotrophic influences.

Conclusions

The neuromodulator adenosine, through A2A receptor activation, has profound influence upon the actions of neurotrophic factors. Due to the role of neurotrophic factors upon neuronal survival, neuronal plasticity and neuronal differentiation, the adenosine-induced control of neurotrophic factors opens new windows of adenosinergic influence on neuronal cells and novel therapeutic perspectives in neuronal dysfunction.

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Conflicts of interest

None.

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