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Review

Modulation of brain-derived neurotrophic factor (BDNF) actions in the nervous system by adenosine A_{2A} receptors and the role of lipid rafts ☆

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ABSTRACT

In this paper we review some novel aspects related to the way adenosine A_{2A} receptors ($A_{2A}R$) modulate the action of BDNF or its high-affinity receptors, the TrkB receptors, on synaptic transmission and plasticity, as well as upon cholinergic currents and GABA transporters. Evidence has been accumulating that adenosine $A_{2A}Rs$ are required for most of the synaptic actions of BDNF. In some cases, where $A_{2A}Rs$ are constitutively activated (e.g. by endogenous extracellular adenosine), the need for $A_{2A}R$ activation for the maintenance of the synaptic influences of BDNF can be envisaged from the loss of BDNF effects upon blockade of adenosine $A_{2A}Rs$ or upon removal of extracellular adenosine with adenosine deaminase. In some other cases, it is necessary to enhance extracellular adenosine levels (e.g. depolarization) or to further activate $A_{2A}Rs$ (e.g. with selective agonists) to trigger a BDNF neuromodulatory role at the synapses. Age- and cell-dependent differences may determine the above two possibilities, but in all cases it is quite clear that there is close interplay between adenosine $A_{2A}Rs$ and BDNF TrkB receptors at synapses. The role of lipid rafts in this cross-talk will be discussed. This article is part of a Special Issue entitled: "Adenosine Receptors".

Contents

1. Introduction

Our interest on BDNF started when we came across with the publication by Boulanger and Poo [see 1] where it was shown that the

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excitatory action of BDNF on synaptic transmission at the developing neuromuscular junction is facilitated by depolarization [1]. It is well known that depolarizing conditions are able to induce adenosine release [2]. Since the distribution of adenosine A_{2A} receptors (A_{2A}Rs) and TrkB receptors (BDNF receptors) have a considerable overlap [3,4], and considering that A_{2A}R activation can induce TrkB phosphorylation in the absence of neurotrophins, a process known as transactivation of TrkB receptors [5], the atmosphere was highly propitious to further detail the consequences and the mechanisms related to the cross-talk between A_{2A}R and BDNF in neuronal cells. However, as we will discuss below and recently suggested [6], it may happen that A_{2A}R-mediated TrkB receptor transactivation and A_{2A}R-mediated facilitation of BDNF actions at synapses constitute two different, nevertheless related, processes through which adenosine affects TrkB signalling. In this paper we will mostly focus on the triggering of synaptic actions of BDNF by A_{2A}Rs and mechanisms involved in it, but before we enter into this topic we will highlight work that preceded and prompted this line of research.

1.1. Neurotrophins

The first neurotrophin to be identified was the nerve growth factor (NGF) in the 1950s by Rita Levi-Montalcini, Stanley Cohen and Viktor Hamburger [7,8]. The neurotrophin family is composed by four members: nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). They have been classically seen as key regulators of neuronal differentiation, maturation and survival [9], but neurotrophins also have an essential role as modulators of synaptic transmission and plasticity [10–12]. It is now well known that BDNF has presynaptic regulatory actions on synaptic transmission, inducing an increase in the number of docked vesicles at the active zones [13], as well as postsynaptic regulatory actions, which include modulation of ionotropic glutamatergic [14] and cholinergic [15] receptors.

From the four neurotrophins cloned to date, the actions of BDNF are the best characterized in the brain. BDNF is a 252 amino acid protein present in many mammalian species with almost identical sequences; BDNF synthesis is highly regulated and occurs primarily in neurons. BDNF is not produced as a mature protein, but as preproBDNF in the endoplasmic reticulum. When the signal peptide is cleaved, proBDNF is formed; a great number of reports have now established that proBDNF can be secreted by the cell and that it has important biological activity [16]. Mature BDNF (mBDNF) can be produced by cleavage of proBDNF intra or extracellularly, but the precise sources and localization of mBDNF production are far from being understood [17,18].

1.1.1. Neurotrophin receptors

Neurotrophins exert their biological actions through activation of one of the two families of receptors [see, e.g.,10]: (1) the high affinity tropomyosin-related kinase receptors (Trk), which belong to the tyrosine kinase family of receptors. There are three types of Trk receptors: TrkA receptors, that specifically recognize NGF; TrkB receptors, that bind both BDNF and NT-4 and TrkC receptors, specific for NT-3; and (2) $p75^{NTR}$ receptors, which are single-transmembrane proteins of the superfamily of tumor necrosis factor (TNF) receptors. The $p75^{NTR}$ recognizes all neurotrophins with low affinity, approximately 100-fold less than the Trk receptors. However, proneurotrophins bind with high affinity to this class of receptors [19].

BDNF binds with high affinity to TrkB receptors and induces receptor dimerization and autophosphorylation. Following BDNF binding to the TrkB receptor, multiple signalling cascades are activated and this requires docking of several proteins to the intracellular domain of full-length TrkB receptors (TrkB-FL) [10]. Essentially, BDNF-induced phosphorylation of TrkB receptors activates the PLCγ, Akt and MAPK pathways, but novel partners for TrkB receptors have been reported and may contribute significantly to the TrkB-mediated effects of BDNF [see e.g. 10]. The activation of the PLCγ pathway has been more closely related to fast actions of BDNF, while the Akt and MAPK pathways are usually associated with neuronal survival pathways [20].

Alternative splicing of TrkB receptors leads to the formation of truncated receptors, TrkB-T1, TrkB-T2 and TrkB-T-Shc [21,22], being TrkB-T1 the best-studied isoform. TrkB-T1 receptors lack most of the intracellular domain and, therefore, intrinsic catalytic activity [10,23]. Although the biological functions and signalling cascades activated by TrkB-T1 remain elusive, there are reports showing that TrkB-T1 increases intracellular calcium and may play a role in dendritic complexity of certain neurons [24]; additionally, TrkB-T1 may be seen as a negative modulator of TrkB-FL signaling, through sequestration of BDNF molecules [25,26].

1.1.2. BDNF functions

In the nervous system, neurotrophins regulate the development, maintenance and function of multiple neuronal networks [reviewed in 9]. Mice lacking neurotrophins die usually 2–4 weeks after birth [27–29], and heterozygous mice display functional deficits in the nervous system. For example, $NGF^{+/-}$ mice display memory deficits and loss of basal forebrain cholinergic neurons and peripheral neurons [30,31]. $BDNF^{-/-}$ mice display severe alterations in coordination and balance and degeneration in several sensory ganglia; $BDNF^{+/-}$ mice are obese, develop hyperphagia and aggressiveness [32,33]. Additionally, $BDNF^{+/-}$ mice have increased striatal dopamine levels that are correlated with altered behavioral responses involving the nigrostriatal dopaminergic system [34].

BDNF and TrkB mRNA are widely distributed in the central nervous system (CNS) [35–37]. In addition to its well-known effects on the regulation of neuronal survival, differentiation and growth, BDNF is also able to modulate neurotransmitter release in different brain areas. Presynaptic effects of BDNF on synaptic activity have been first demonstrated at the neuromuscular junction [38]. Other studies established the role of BDNF in increasing the release of acetylcholine and glutamate, both in the hippocampus and cerebral cortex [13,39–42]. Effects on the GABAergic transmission have also been reported, involving both presynaptic [43] and postsynaptic [44] actions, as well as stimulatory effects of BDNF on dopamine release in mesencephalic neurons [45].

The fast actions of BDNF at synapses can occur in a time scale of less than 1 h, leading to facilitation of synaptic transmission [46,47]. These relatively fast synaptic actions of BDNF may require de novo protein synthesis, as it has been shown to occur in relation to the BDNF-induced increases in AMPA [48] and NMDA [49] receptor levels in the membrane of cultured neurons. In addition, some of the synaptic BDNF actions result from a local, very fast action at synapses; this neurotrophin is able to facilitate glutamate release from synaptosomes [42,50,51], which are isolated nerve endings and therefore lack the somatic machinery for modulation at the gene transcription level.

The physiological role of endogenous BDNF in synaptic plasticity has been clearly demonstrated in the BDNF-deficient mice, where long-term potentiation (LTP) was severely impaired [52,53]. While mBDNF facilitates LTP through activation of TrkB receptors [54], proBDNF facilitates long-term depression (LTD) through activation of $p75^{NTR}$ receptors [55]. The control of proBDNF cleavage into BDNF is regulated by activity. Low-frequency firing induces LTD and favours proBDNF actions, while high-frequency firing induces LTP and favours mBDNF actions in the hippocampus [56].

Furthermore, intense synaptic activity increases the levels of TrkB mRNA and its translocation to dendrites [57,58], as well as TrkB receptor insertion in the plasma membrane [59,60]. These activity-dependent actions of BDNF may play an important role in the regulation and specificity observed in BDNF actions upon active synapses and may involve translocation of TrkB receptors to specific membrane microdomains, as we will discuss in Section 2.5 below.

1.1.3. Pathophysiological implications of BDNF actions

The interest on neurotrophins in a context of neurodegenerative diseases started soon after the discovery of NGF and the identification that this neurotrophin promotes the survival and function of basal forebrain cholinergic neurons [61], which project to the hippocampus and are specifically affected in patients with Alzheimer's disease (AD). The identification of other members of the neurotrophin family, like BDNF, and the knowledge of its physiological functions, inspired many studies [for a review see e.g. 62] correlating the pathogenesis of human neurodegenerative disorders with alterations in BDNF actions. These could be a result of genetic polymorphisms in the BDNF gene or receptors, alterations in the levels of mRNA for BDNF, modifications in levels of BDNF protein and changes in BDNF receptor densities.

A polymorphism in BDNF gene leading to a different BDNF protein (BDNF Val66Met) appears to alter susceptibility to neuropsychiatric disorders, such as AD [63], Parkinson's disease (PD) [64], depression [65], and bipolar disorders [66,67]. In 1991, Phillips and colleagues [68] reported a selective reduction of BDNF mRNA expression in the hippocampus of individuals with AD, which was later corroborated by others [69,70]. Moreover, a decrease in BDNF protein levels in the hippocampus has been associated with depression [71,72]. Decreased BDNF protein levels were also found in nigrostriatal dopamine-rich regions of PD brains [73]. A decrease in the expression of the BDNF protein in the hippocampus of people with dementia exhibiting Lewy bodies [74] in patients with diabetic brain neuropathies [75] and in the striatum of individuals with Huntington's disease (HD) [see 76] was also reported. BDNF levels are also severely affected in HD patients [76].

Concerning modifications in TrkB receptors, a mutation in the kinase domain of TrkB, leading to impaired intracellular signalling, was associated with obesity and developmental delay [77]. On the other hand, the expression of different TrkB splice variants may be related to cognitive capacity, as overexpression of the kinase-containing form enhances memory and learning in transgenic mice [78]; conversely, overexpression of the TrkB-T1 isoform in adult neurons impairs long-term memory [79]. Interestingly, increased content of the TrkB-T1 isoform and decreased TrkB expression has been observed in AD patients [80]. Finally, polymorphisms of the gene encoding $p75^{NTR}$ may lead to an increased susceptibility to depressive disorders [81].

1.2. Adenosine

Adenosine is a ubiquitous molecule that acts in a paracrine way, i.e., in the cells adjacent to the adenosine-releasing cell, due to its extremely short half-life [82]. Adenosine can be formed both intra and extracellularly, and cross the plasma membrane through equilibrative (ENT) or concentrative transporters. Intracellular formation of adenosine occurs mainly through two pathways: from the sequential dephosphorylation of ATP or from the hydrolysis of S-adenosylhomocysteine [83]. Intracellular adenosine metabolism occurs mostly through phosphorylation into AMP or through deamination to inosine. Inactivation of extracellular adenosine predominantly occurs through reuptake; however, metabolism of extracellular adenosine through deamination to inosine or phosphorylation to 5'-adenosine monophosphate (5'-AMP) [84] can also occur. Extracellular formation of adenosine is due to hydrolysis of released adenine nucleotides, namely ATP, through a cascade of ecto-nucleotidases [85]. In resting conditions, the extracellular adenosine concentration in the brain are around 25-250 nM [86], but those levels can increase dramatically under energy misbalance [87]. For this reason, adenosine is described as a retaliatory metabolite and plays an important role during seizure, hypoxic and ischemic events, where it acts as a protective signal in the nervous system [87–89]. Importantly, adenosine not only directly modulates synaptic transmission and plasticity but also modulates the actions of other neurotransmitters or modulators, such as neurotrophins, dopamine and cannabinoids [reviewed in 90].

1.2.1. Adenosine receptors

Four adenosine receptors have been cloned to date: adenosine A_1, A_{2A}, A_{2B} and A_3 receptors, all belonging to the superfamily of G-protein coupled receptors (GPCRs). Adenosine A_1 and A_3 receptors are mainly coupled to G_i proteins, while the A_{2A} and A_{2B} receptors act mainly through activation of G_s proteins [91], though coupling to G_q can also occur. A_1 and A_{2A} receptors are considered to be the high affinity receptors for adenosine, and in basal conditions are probably tonically activated [86]. However, this should be considered carefully since most cells express multiple adenosine receptors in very different levels, limiting the study of native receptors behaviour in response to the endogenous ligand adenosine.

In the brain, adenosine receptors are widely distributed, with marked differences in receptor expression depending on the brain area, age and cell sublocalization [92]. A_1 receptors (A_1R) are the predominant subtype in the forebrain, cerebellum and dorsal horn of spinal cord, while $A_{2A}R$ are highly expressed in the striatopallidal GABAergic neurons and the olfactory bulb. Adenosine A_{2B} and A_3 receptors are also expressed in the brain, but their expression is considerably more restricted and their role in the nervous system is much less understood [see, e.g., 90,92]. Both A_1 and A_{2A} receptors can be localized in the same nerve terminal, and can be activated by endogenous adenosine simultaneously [93,94].

Regarding synaptic transmission, A_1Rs are typically inhibitory; tonically, adenosine exerts an inhibitory effect upon hippocampal transmission [95,96]. When A_1Rs are blocked, an excitatory effect is observed, via both the lack of A_1R activation and increase in $A_{2A}R$ activation. This suggests that although the net effect of endogenous adenosine is inhibitory, it is possible to observe the activation of both receptors under physiological concentrations of adenosine. Moreover, preferential activation of A_1R or $A_{2A}R$ may be regulated according to the source of adenosine. High-frequency stimulation of neurons induces the release of ATP, and it has been demonstrated that ATP-derived adenosine predominantly activates excitatory $A_{2A}R$ [97–99]. In contrast, low-frequency stimulation leads to preferential activation of the inhibitory A_1 receptors, as a consequence of the release of adenosine as such [97]. Interestingly in motor nerve endings of infant rats (peri-weaning) activation of $A_{2A}Rs$ predominates over A_1Rs even when an increase of extracellular adenosine is originated by ENT reversal [94].

Modulation of adenosine receptors has long thought to be a useful strategy in the treatment of multiple pathological states in the nervous system, such as sleep disorders, epilepsy, stroke, pain and multiple neurodegenerative diseases [100]. In many cases, activation of A_1R or inactivation of $A_{2A}R$ has a protective role in the nervous system [88,92]. Recent epidemiological data, together with experiments in mice, have correlated caffeine consumption, a non-specific adenosine receptor antagonist, with decreased risk of developing AD [101,102]. Importantly, $A_{2A}R$ antagonists have been tested in clinical trials for the treatment of PD. $A_{2A}R$ are highly abundant in the basal ganglia and form complexes with dopamine D_2 receptors, displaying reciprocal antagonist properties. Accordingly, antagonism of adenosine $A_{2A}R$ is protective in PD models and potentiates the effects of L-DOPA, which is commonly used in the treatment of this disease [103,104].

1.2.1.1. Adenosine A_{2A} receptors. The discovery in 1992 [105] that $A_{2A}Rs$, in spite of their low density distribution, facilitate synaptic transmission in the hippocampus, raised the intriguing issue of identifying their major role in this brain area (like in Pirandello's play—*Sei Personaggi in Cerca d'Autore*). Out of doubt, in what concerns modulation of hippocampal synaptic transmission, the clearest influence of adenosine is inhibitory [106], operating through A_1R [107].

One of the most well-established effects of adenosine at the CNS is its capacity to increase intracellular cyclic AMP (cAMP) levels in several brain areas [see 108]; it was from the very beginning recognized that cAMP enhancing actions of adenosine operate through A_2 receptors

[109]. These receptors can act synergistically with other receptors involved in the increase of cAMP in brain slices (e.g. histamine, norepinephrine, serotonin), causing more than additive effects on cAMP accumulation. An interesting aspect reviewed more than 35 years ago by Daly [108] is that the accumulation in cAMP induced by adenosine and by electrical stimulation is similar in magnitude. Moreover, Sattin and Rall [110] demonstrated that methylxanthines block adenosine-mediated actions, by blocking cell membrane adenosine receptors [111]. These xanthine-sensitive effects of adenosine, detected more than 20 years ago, reveal the importance of the nucleoside to regulate putative facilitatory functions in the CNS.

Although the inhibitory effects of adenosine on synaptic transmission and their non-correlation with increases in cAMP levels were described early [112,113], the investigations of the excitatory effects of adenosine were delayed due to the unique distribution of the $A_{2A}R$. The striatum was identified as the "headquarters" of the $A_{2A}R$ and it took several years to establish that the $A_{2A}R$ outside the striatum could play relevant actions in neuronal cells. As we will highlight in the remaining sections of this review, a relevant action is the ability to trigger BDNF actions at synapses.

2. Synaptic effects of BDNF and their dependence on adenosine A_{2A} receptor activation

2.1. Cross-talk between adenosine A_{2A} and TrkB receptors

The actions of GPCRs and receptor tyrosine kinases (RTKs) can be tightly related, and to date different cross-talk mechanisms have been proposed [114]. The effects of GPCR agonists on RTKs typically involve: (1) facilitation/sensitization of RTKs for their cognate ligands [47,115–118]; (2) increase of the synthesis of the endogenous RTK ligand [119,120]; or (3) activation of RTKs in the absence of ligand, a phenomenon called transactivation [for examples, see 121,122].

It has been shown that activation of $A_{2A}R$ or pituitary adenylyl cyclase-activating polypeptide receptor 1 (PAC1), among the different GPCR agonists tested, were able to directly activate TrkA and TrkB receptors in the absence of NGF or BDNF (transactivation), respectively [5,121]. Further studies demonstrated that transactivation of Trk receptors by $A_{2A}R$ is maximal after 3 h of agonist treatment and involves mostly immature, intracellular Trk receptors located in Golgi-associated membranes [5,123]. Furthermore, direct activation of Trk receptors by adenosine requires cAMP, increases in intracellular calcium, protein synthesis and activation of Fyn, a member of the Src-family kinases. In fact, Fyn is able to directly phosphorylate TrkB receptors in response to adenosine, and is colocalized with intracellular TrkB receptors [124]. Neurotrophin receptors can be also directly activated by dopamine D_1 receptors [125], glucocorticoids [126] and zinc [127]. Importantly, transactivation of TrkB receptors by adenosine, dopamine, glucocorticoids or zinc does not involve increased expression of BDNF or NGF [5,125–127].

Besides inducing RTK transactivation, $A_{2A}R$ activation also increase the biological effects of a RTK ligand, i.e., activation of $A_{2A}Rs$ is able to trigger various TrkB-mediated BDNF actions in the nervous system. These two influences of $A_{2A}Rs$ over RTKs might occur on different time spans and through different mechanisms. Below, we will mostly discuss evidence for $A_{2A}R$-induced triggering of TrkB receptors.

2.2. Basal synaptic transmission

The cross-talk between adenosine A_{2A} and TrkB receptors has been carefully investigated in the hippocampus. It became clear that $A_{2A}R$ activation facilitates BDNF effects at synapses, and that this occurs after a short period (30–45 min) of superfusion of $A_{2A}R$ receptor agonists to hippocampal slices [47]. Incubation of neurons with the $A_{2A}R$ agonist for the same short period does not induce TrkB transactivation, i.e., TrkB phosphorylation in the absence of BDNF [5]. Interestingly, in infant (peri-weaning) rats a BDNF-induced facilitation of basal, low-frequency-evoked excitatory synaptic transmission can only be observed if $A_{2A}R$ are exogenously activated by an agonist, or if adenosine release is enhanced by either a depolarization pulse or by inhibiting adenosine kinase [47]. In contrast, in adult rats [128] or mice [129] the levels of extracellular adenosine and of tonic $A_{2A}R$ activation are enough to trigger a BDNF response. Thus, in adult animals, exogenous application of BDNF *per se* is enough to facilitate synaptic transmission, but this effect is fully lost when $A_{2A}R$ are blocked, demonstrating the requirement of co-activation of $A_{2A}R$ by endogenous adenosine. As pointed out [128], differences in age or in basal levels of extracellular adenosine may therefore explain several discrepancies in literature regarding effects of BDNF on synaptic transmission in the hippocampus. How BDNF is delivered to cells, namely in a sudden or gradual way, also influences BDNF signalling, synaptic BDNF actions, and the profile of BDNF-induced morphological changes in cultured neurons, suggesting that the kinetics of TrkB activation is critical for cell signalling and functions [130].

The mechanisms underlying the facilitatory effect of $A_{2A}R$ on TrkB function involve the cAMP/protein kinase A (PKA) pathway and can be mimicked by a previous depolarization pulse, suggesting that activity-induced release of adenosine can physiologically have a permissive role in the synaptic effects of BDNF [47]. Altogether, the available information allows to conclude that the excitatory effect induced by BDNF on synaptic transmission in the hippocampus is dependent on TrkB and on $A_{2A}R$ activation, through a mechanism that requires cAMP formation and protein kinase A (PKA) activity. This effect on excitatory transmission at hippocampal slices may be related to glutamatergic presynaptic actions of BDNF, since this neurotrophin facilitates glutamate release from isolated nerve endings [42,50], an action also dependent on $A_{2A}R$ activation by endogenous adenosine [6].

Motor nerve terminals also express TrkB and A_{2A}Receptors. BDNF facilitates transmission at developing neuromuscular junctions [1], an action regulated by cAMP [131]. Similarly to the rat hippocampus, depolarizing conditions and $A_{2A}R$ activation are required to trigger an excitatory action of BDNF on neuromuscular transmission [132]. This cross-talk between TrkB and A_{2A} receptors also requires relatively short (about 45 min) times of bath superfusion with the $A_{2A}R$ agonist [132], being therefore faster than TrkB transactivation by $A_{2A}R$. Activation of $A_{2A}Rs$ per se enhances neuromuscular transmission [93], and this allowed to understand the hierarchy between TrkB receptors and $A_{2A}Rs$ to control transmitter release at motor nerve endings. Since the excitatory action of $A_{2A}R$ agonists on end-plate potentials (EPPs) is not influenced by the inhibitor of tyrosine kinases, K252a, one can conclude that the effect of the $A_{2A}R$ agonist on neuromuscular transmission does not require TrkB receptor activation [132]. Conversely, the facilitatory effect of BDNF upon EPP amplitude is blocked not only by $A_{2A}R$ antagonists but also by PKA inhibitors, indicating that the $A_{2A}R$/cAMP/PKA cascade is a necessary triggering signal for TrkB activation. The conclusion that $A_{2A}Rs$ are upstream of TrkB receptor activation is reinforced from evidence that phospholipase C (PLC) inhibition did not prevent the excitatory action of the $A_{2A}R$ agonist on neuromuscular transmission, but abolished the action of BDNF [132]. Since BDNF actions are facilitated by depolarization [1] and by cAMP [131], the sequence of events leading to facilitation of BDNF effects by depolarization might be: a depolarization-induced raise in adenosine levels, leading to activation of $A_{2A}R$ and consequent activation of the cAMP/PKA pathway (see Fig. 1), which in turn facilitates TrkB-induced activation of its signalling cascade, including the PLC pathway (see Fig. 1).

2.3. Long-term potentiation (LTP)

The influence of neurotrophins in the nervous system also spans to activity-dependent forms of synaptic plasticity [133], LTP, the neurophysiological basis for learning and memory [134]. Most of these actions have been seen in the hippocampus, where BDNF and TrkB

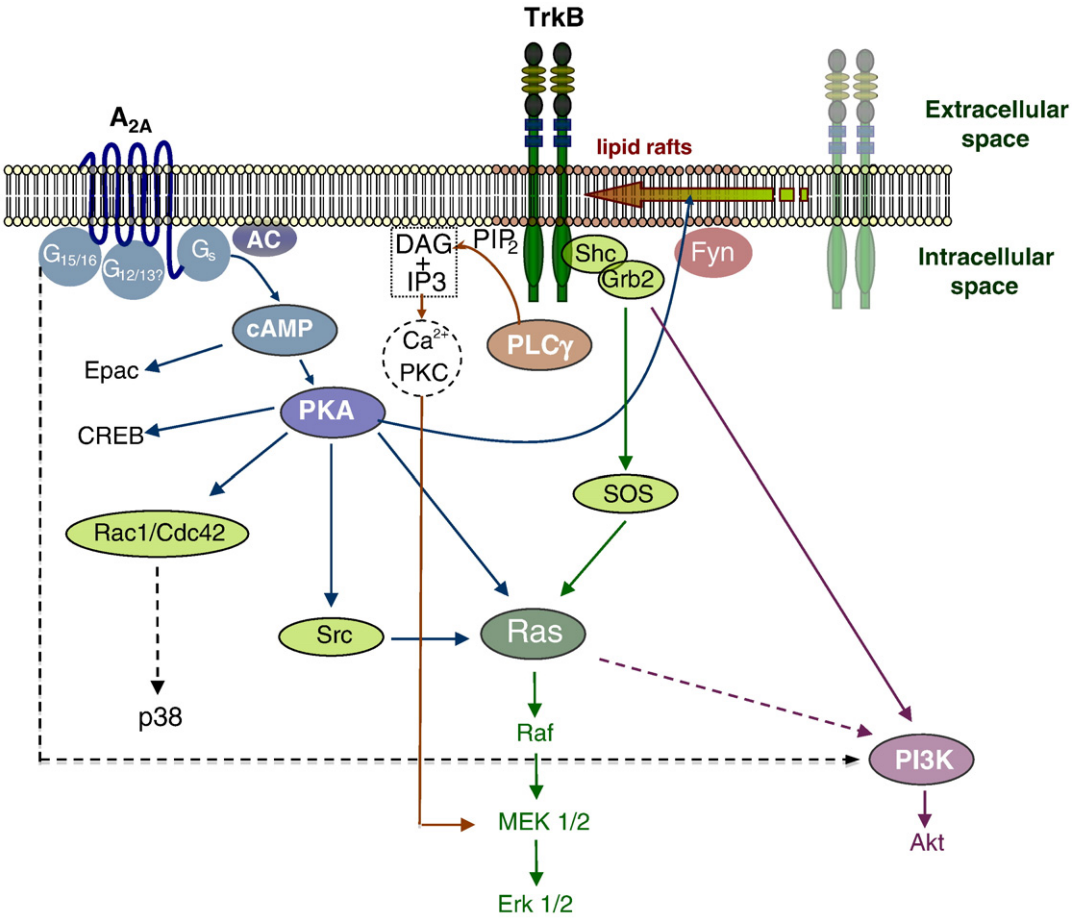

Fig. 1. Signalling cascades activated by adenosine A_{2A} and TrkB receptors. Adenosine A_{2A}R are mainly implicated in the activation of G_s proteins and the cAMP/PKA signalling pathway. TrkB receptors predominantly signal through the activation of PLCγ, Akt and MAPK pathways. As schematized in the figure, the presence of common signalling intermediates downstream A_{2A} and TrkB receptors might account for the facilitatory action of adenosine A_{2A}R activation upon TrkB-mediated effects. Activation of A_{2A}R also induces translocation of TrkB receptors to lipid rafts. TrkB localization in these membrane microdomains is important for BDNF actions and may be involved in the modulation of TrkB-mediated signalling cascades by A_{2A}R. Abbreviations: AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; Cdc42, cell division control protein 42 homolog; CREB, cAMP response element binding protein; DAG, diacylglycerol; Epac, exchange protein activated by cAMP; Erk 1/2-extracellular signal-regulated protein kinases; Grb2, growth factor receptor-bound protein 2; IP_3, inositol 1,4,5-trisphosphate; MAPK, mitogen-activated protein kinase; MEK 1/2, mitogen-activated protein kinase 1/2; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PLC, Phospholipase C; PKA, Protein kinase A; Rac1, Ras-related C3 botulinum toxin substrate 1; Ras, small GTP-binding protein Ras; SOS, son of sevenless.

protein immunoreactivity is particularly high [135,136]. It was shown that hippocampal LTP is strongly impaired in both BDNF [52,53] and TrkB [137,138] knockout mice, a deficit that could be rescued by adenoviral-mediated (re)expression of BDNF [139], or even by administration of exogenous BDNF [53]. Extracellular adenosine also plays an important role in the modulation of synaptic plasticity, and can both decrease (A_1R-mediated) and increase (A_{2A}R-mediated) synaptic plasticity events [140].

As previously mentioned, BDNF expression and release [141,142], as well as release of adenosine [2] and of its precursor ATP [99], are much more pronounced upon depolarization and during physiologically relevant patterns of neuronal activity, namely those that induce hippocampal LTP. Therefore, high neuronal activity seems to create ideal physiological conditions for the interplay between A_{2A} and TrkB receptors to take place. We were able to clearly show that BDNF facilitatory effects upon LTP are completely dependent on A_{2A}R activation by endogenous adenosine and that this process requires active PKA [117]. This clearly identifies adenosine as an endogenous "gate" that unravels BDNF actions upon LTP, and adds a new physiologic partner to the TrkB signalling process that influences synaptic plasticity phenomena. Remarkably, cAMP was also proposed to function as a gating signal that enables BDNF modulation of synaptic plasticity [see 11]. Indeed, the cAMP/PKA pathway is not a downstream effector in the BDNF/TrkB signaling cascade [143], but neuronal activity increases the local intracellular concentration of cAMP [144], which may facilitate BDNF actions either by facilitating the trafficking of TrkB receptors into active sites at synapses and/or by facilitating BDNF-induced TrkB phosphorylation [145]. Since A_{2A}R activation enhances the adenylate cyclase/cAMP/PKA signalling pathway [see 146], the increase in cAMP levels may be a key pivot to relate the influence of adenosine, A_{2A}Rs, high neuronal frequency rate, and BDNF upon synaptic plasticity. Interestingly, endogenous activation of adenosine A_{2A}Rs plays a pivotal effect on the associative learning process and its relevant hippocampal circuits, including activity-dependent long-lasting changes at the CA3-CA1 synapse [147]. It remains to be established if this loss of synaptic plasticity and concomitant associative learning induced by A_{2A}R blockade in vivo results from impairment of BDNF signalling. It may well be so because TrkB receptors modulate specific phases of conditional learning and synaptic plasticity recorded concomitantly [148].

2.4. Postsynaptic modulation of cholinergic transmission in the hippocampus

Neuronal nicotinic acetylcholine receptors (nAChRs) are widely expressed in the brain. The homopentameric α7 subtype of nAChR, in

particular, has determinant actions in the hippocampus by supplying calcium signals that depolarize cells and influence several calcium-dependent events, including transmitter release and plasticity [149–152]. Recent evidence has established that BDNF leads to an increase in α7nAChR number and clustering over a time course of several hours to days [153–155]. In contrast, BDNF induces a fast (maximal effect within less than 60 min) decrease of α7nAChR-mediated responses in hippocampal interneurons of the CA1 stratum radiatum [15]. Such inhibitory effect of BDNF involves the actin cytoskeleton and occurs through TrkB-mediated activation of the phospholipase C (PLC)/protein kinase C (PKC) pathway, requiring Ca^{2+} ions as a cofactor [15]. Additionally, constitutively released adenosine, acting on A_{2A}R, is required to gate the action of BDNF [15]. Although corroborating several evidences on the tight relationship between tyrosine kinase TrkB and adenosine A_{2A}R, this set of results contrasts with BDNF-induced modulation of synaptic inputs to pyramidal cells, which in rats of similar age (peri-weaning) requires exogenous activation of A_{2A}R [47]. In both cases, however, the action of BDNF is lost if A_{2A}R are blocked. It is thus possible that adenosine levels are greater in the vicinity of interneurons or, alternatively, that interneurons might exhibit an increased sensitivity for the basal levels of adenosine. In fact, both possibilities are consistent with several reports showing that extracellular adenosine levels affect interneurons in a more powerful manner than pyramidal cells [156,157].

It remains to be investigated which signalling cascades are involved in the long-term effect of BDNF upon the expression of α7nAChRs [155] and whether this effect is correlated with functional long lasting enhancement of nicotinic responses [154]. The fast inhibition of α7nAChR-mediated responses by BDNF can be mimicked by direct activation of PKC with phorbol esters [15]. Interestingly, there are no predicted consensus sequences for PKC phosphorylation in the intracellular domains of α7 subunits [158,159]. Thus, as it has been pointed out [15], it is possible that the acute inhibitory effect of BDNF on α7nAChR function involve the regulation of phosphorylation of intermediate proteins that regulate trafficking, clustering, and/or lateral diffusion of the receptors.

2.5. BDNF and GABA

GABA activity at synapses is ended by rapid reuptake through specific neuronal and astrocytic GABA transporters, which are regulated by several signalling cascades that include kinases and phosphatases [160]. The number of functional GABA transporters (GAT-1) in cultured neurons is increased by BDNF [161]. Interestingly, BDNF inhibits GABA transport at isolated nerve endings, an action observed either when transport is inward [162] or reversed in the outward direction [42]. One should keep in mind that both actions of BDNF might contribute to a facilitation of GABAergic tonus since an inhibition of GABA transport at the nerve endings may lead to an increase in the amounts of synaptic GABA, whereas an increase in GABA transport in other neuronal membrane compartments may rescue GABA to replenish the releasable pool. The molecular mechanisms that underlie the different ways BDNF uses to differentially modulate GAT-1 at nerve endings or entire neurons is not entirely understood yet, but the evidence so far available points towards the involvement of different signalling cascades, with PLCγ involvement into the inhibition at nerve endings [51], but not in cultured neurons [161,163].

Interestingly, the effect of BDNF on synaptosomal GABA uptake was not appreciably affected by A_{2A}R blockade or removal of endogenous adenosine with adenosine deaminase, suggesting that A_{2A}R co-activation is not an essential step for this action of BDNF. This contrasts with the facilitatory action of BDNF on excitatory synaptic transmission [47,132], where A_{2A}R blockade fully prevents the action of BDNF. However, in spite of not being essential, exogenously added A_{2A}R agonists are able to enhance BDNF-induced inhibition of GAT-1 transport at nerve endings, an effect prevented by A_{2A}R antagonists [163].

BDNF has been shown to rapidly modulate GABAergic transmission in the hippocampus through pre- and postsynaptic mechanisms, but it is still not known how these actions are affected by adenosine A_{2A} receptors. Presynaptically, a decrease in GABAergic input to glutamatergic neurones has been reported [43]. Postsynaptically, BDNF decreases GABAergic transmission to pyramidal neurones [44], inducing a rapid downregulation of $GABA_A$ receptor surface expression [164]. Interestingly, in immature neurons BDNF enhances, rather than inhibits, GABA release, and this is part of a positive feedback loop between GABA and BDNF expression [165]. Since GAT-1 mediated transport in nerve terminals appears to contribute to the maturation of point-to-point GABAergic synapses [see 166], a fine control of GABAergic transmission that simultaneously involves BDNF and GAT-1 may be particularly relevant in the shaping GABAergic synapses under maturation, and it would be highly interesting to know whether adenosine A_{2A} receptors play any role in this process.

2.6. Trophic effects of BDNF and adenosine A_{2A}R

BDNF is involved in neuronal maturation [see e.g. 167], an effect regulated by cAMP [145]; therefore, one could anticipate that this action of BDNF could be influenced by activation of A_{2A}R. However, A_{2A}R agonists do not seem to influence the actions of BDNF on neurite outgrowth in cortical neurons [168]. Nevertheless A_{2A}Rs can rescue neurite outgrowth impairment caused by interference with the NGF signalling cascade in PC12 cells [169] as well as to promote PC12 cell survival upon NGF withdrawal [5].

2.7. Lipid raft localization of TrkB receptors as a mechanism to trigger BDNF effects on synaptic transmission

Lipid rafts are membrane microdomains enriched in cholesterol, glicosphingolipids and specific proteins. Convincing proteomic data have been reinforcing the role of lipid rafts as coordinators of signal transduction; for example, receptors inside lipid rafts may activate distinct signalling cascades from receptors localized outside rafts [170].

There is now evidence that lipid rafts are essential for BDNF signalling, and both TrkB and $p75^{NTR}$ receptors can be located in these membrane domains [171–173]. Translocation of TrkB receptors to lipid rafts is regulated by BDNF, and this movement of receptors is required for its effects on glutamate release, synaptic fatigue [173] and for activation of the PLC pathway [174]. It is also of interest to note that BDNF itself enhances cholesterol biosynthesis, which results in higher levels of presynaptic proteins in lipid rafts and proper synapse development [175].

The localization of adenosine A_{2A}R in lipid rafts is still mostly unknown. In a recent study, using A_{2A}-overexpressing PC12 cells, it was suggested that A_{2A}R-induced adenylate cyclase activation is dependent on the cholesterol levels of the membrane, while A_{2A}-induced MAPK activation was not affected by lipid raft disruption [176]. Additionally, it was suggested that A_{2A}R localize in lipid raft domains of motor neurons, where A_{2A}R physically interact with Fyn and TrkB receptors [177].

2.7.1. Role of lipid rafts in A_{2A}-TrkB receptor signalling

Recent evidence has shown that activation of A_{2A}R increases the levels of TrkB receptors in lipid rafts and potentiates BDNF-induced TrkB phosphorylation in these membrane microdomains [6]. Although both A_{2A}R and TrkB receptor activation promote translocation of TrkB receptors to lipid rafts, the mechanisms used by A_{2A}R agonists are different from those used by BDNF, and involve cAMP and Src-family kinase activation (see Fig. 1). Fyn, a member of the Src-family kinases, is a good candidate for mediating A_{2A}-induced TrkB translocation to lipid rafts, since it can be activated by A_{2A} agonists and is required for TrkB localization in lipid rafts [124,174].

Synaptic actions of BDNF, such as facilitation of glutamate release and synaptic plasticity [6], require both lipid raft integrity and $A_{2A}R$ activation, probably due to an activity-dependent recruitment of TrkB receptors to lipid rafts. Interestingly, high-frequency stimulation of hippocampal slices resulted in a higher density of TrkB receptors in lipid rafts, an effect totally abolished when endogenous extracellular adenosine is removed [6]. To our knowledge, this is the unique demonstration of an activity-dependent recruitment of TrkB receptors to lipid rafts, and notably, this recruitment is fully dependent upon the presence of extracellular adenosine. As previously discussed, the levels of extracellular adenosine increase and $A_{2A}R$ activation are favoured after high-frequency neuronal firing [for a review, see 178]. Therefore, adenosine $A_{2A}R$-induced translocation of TrkB receptors to lipid rafts may be a link through which adenosine A_{2A} and TrkB receptors act as coincident detectors of high frequency neuronal firing and amplify excitatory synaptic transmission [6].

3. Potential therapeutic interest of the cross-talk between $A_{2A}R$ and TrkB receptors in neurodegenerative diseases

Enhancement of neurotrophic-like effects might be desirable to delay the progression of some neurodegenerative diseases, where lack neurotrophic factors may be a direct or indirect cause of exacerbated neuronal death [for a review, see 179]. Indeed, the knowledge of the regulatory actions of neurotrophic factors in neuronal functions and in response to neuronal injury, together with the evidence that changes in BDNF signalling are associated with a wide variety of pathologies (see Section 1.1.3), triggered in the past decade a number of clinical trials involving the use of BDNF for neurodegenerative disorders such as amyotrophic lateral sclerosis and diabetic neuropathy. However, BDNF had minimal beneficial effects and produced side effects such as pain and gastrointestinal symptoms [180]. Furthermore, major problems related to BDNF-based therapies are the half-life of this peptide in the bloodstream as well as its the inability to cross the blood brain barrier; these problems have limited the possibility of using BDNF as a non-invasive and effective treatment for neurological disorders [181]. Therefore, the lack of controlled levels of BDNF at the site of action and the presence of endogenous compensative processes that may regulate BDNF levels in the brain, may have contributed to some negative results in clinical trials. An approach that could circumvent some of the above-mentioned difficulties would be modulation of neurotrophin receptor signalling with the use of small molecules, which may be considerably cheaper, less invasive and more feasible in terms of molecule design [181,182]. Therefore, adenosine $A_{2A}R$ agonists may prove useful in a near future as promoters of neurotrophic-like effects in the nervous system. Of high relevance in this context is the report that in a HD mouse model that involves genetic mutation of Huntingtin, therefore most probably, a reduction of striatal BDNF levels, daily administration of an $A_{2A}R$ agonist delays progressive deterioration of motor performance and huntingtin aggregation [183]. In the same mouse model, i.p. administration of the A_{2A} receptor agonist for 3 weeks induces changes in the subunit composition of NMDA receptors compatible with a decreased susceptibility to excitotoxicity [184]; interestingly this action was specific for the striatum and for the HD mice [184], highly suggestive of an A_{2A} receptor mediated neuroprotection selective for BDNF deficient HD pathology.

4. Concluding remarks

A summary of the main data obtained on A_{2A}-BDNF interactions is presented in Fig. 2, where we can see that $A_{2A}R$ activation is required for the BDNF effects on synaptic transmission and LTP in the hippocampus, and on transmission at the neuromuscular junction. $A_{2A}R$ activation is dispensable in the case of BDNF effects on GABA uptake and also on actions of BDNF upon neuronal branching. These differences may reside upon the mechanisms required for each specific BDNF action. It is possible that acutely triggering of neurotrophic factor actions through adenosine receptors results from a requirement of fast translocation of Trk receptors to lipid rafts, which may wake up the remaining "silent" neurotrophin receptors at synapses.

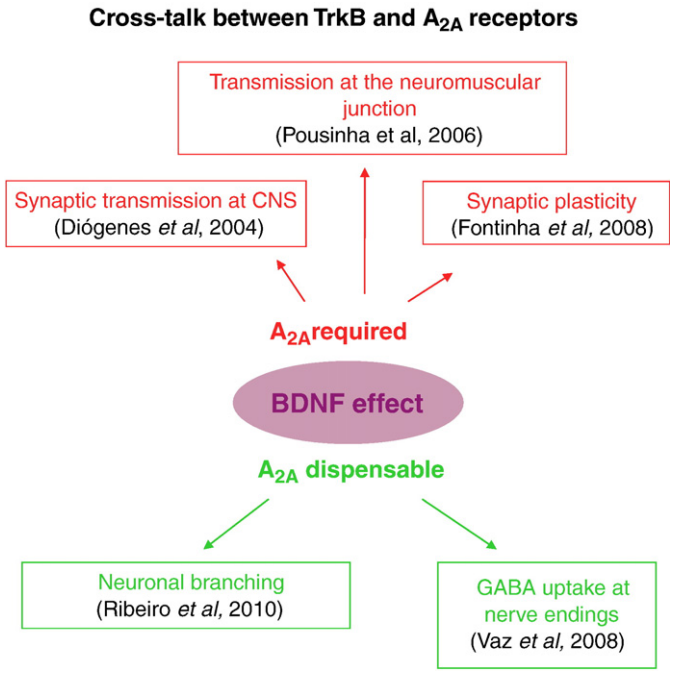

Fig. 2. Schematic representation of cross-talk between TrkB and $A_{2A}R$, where it highlighted the dependence of $A_{2A}R$ activation for BDNF actions on the nervous system.

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