ORIGINAL PAPER

Adenosine A$_{2A}$ receptors modulate BDNF both in normal conditions and in experimental models of Huntington's disease

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Abstract Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, enhances synaptic transmission and regulates neuronal proliferation and survival. Functional interactions between adenosine A$_{2A}$ receptors (A$_{2A}$Rs) and BDNF have been recently reported. In this article, we report some recent findings from our group showing that A$_{2A}$Rs regulate both BDNF functions and levels in the brain. Whereas BDNF (10 ng/ml) increased the slope of excitatory postsynaptic field potentials (fEPSPs) in hippocampal slices from wild-type (WT) mice, it was completely ineffective in slices taken from A$_{2A}$R knock-out (KO) mice. Furthermore, enzyme immunoassay studies showed a significant reduction in hippocampal BDNF levels in A$_{2A}$R KO vs. WT mice. Having found an even marked reduction in the striatum of A$_{2A}$R KO mice, and as both BDNF and A$_{2A}$Rs have been implicated in the pathogenesis of Huntington's disease (HD), an inherited striatal neurodegenerative disease, we then evaluated whether the pharmacological blockade of A$_{2A}$Rs could influence striatal levels of BDNF in an experimental model of HD-like striatal degeneration (quinolinic acid-lesioned rats) and in a transgenic mice model of HD (R6/2 mice). In both QA-lesioned rats and early symptomatic R6/2 mice (8 weeks), the systemic administration of the A$_{2A}$R antagonist SCH58261 significantly reduced striatal BDNF levels. These results indicate that the presence and the tonic activation of A$_{2A}$Rs are necessary to allow BDNF-induced potentiation of synaptic transmission and to sustain a normal BDNF tone. The possible functional consequences of reducing striatal BDNF levels in HD models need further investigation.

Keywords Adenosine A$_{2A}$ receptors · BDNF levels · Hippocampus · Huntington's disease · Striatum · Synaptic transmission

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Introduction

Brain-derived neurotrophic factor (BDNF) is an endogenous glycoprotein belonging to neurotrophins, a family of signalling molecules that play a key role in regulating neuronal proliferation, differentiation and survival [1–3]. Among the neurotrophins, BDNF has the widest distribution in the central nervous system [4, 5]. In the adult hippocampus, BDNF is critically involved in the regulation of synaptic plasticity [6] and facilitates long-term potentiation (LTP) [7–10; see 11 for review]. Most biological effects of BDNF are mediated by the tyrosine kinase receptor TrkB. Both BDNF and its receptors are highly expressed in the hippocampus, and the activation state of the complex BDNF/TrkB appears critical for modulating synaptic efficacy [12] and the response to excitotoxic injury [13, 14].

In hippocampal neurones, adenosine has been reported to transactivate TrkB receptors, an effect involving the A$_{2A}$

receptor subtype (A_{2A}Rs) [15]. Furthermore, Diogenes et al. [16] reported that A_{2A}Rs facilitate the excitatory action of BDNF on hippocampal synaptic transmission.

Besides its involvement in hippocampal functions, BDNF is also very important for the survival of striatal neurons and the activity of corticostriatal synapses [17]. Impairment in BDNF function is though to play a major role in Huntington's disease (HD), an inherited neurodegenerative disease caused by a mutation in the protein huntingtin and characterised by marked striatal degeneration (see [18] for review). Specifically, it has been shown that the activity of BDNF depends on the presence of normal huntingtin [19–21]. In vitro and in vivo data showed that wild-type huntingtin, but not the mutant protein, stimulates cortical BDNF production by acting at the level of *Bdnf* gene transcription [20, 21]. At the corticostriatal synapse, BDNF controls glutamate release and its exogenous administration allows striatal neurons to survive excitotoxin-induced neurodegeneration [22].

Mounting evidence also indicates an involvement of striatal A_{2A} receptors in HD (see [23] and [24] for reviews). First, A_{2A}Rs are mainly localised on the neurons that degenerate early in HD [25]. Second, A_{2A}Rs and underlying signalling systems undergo profound changes in cellular and animal models of HD (see [24] for review). Thus, not only A_{2A}Rs seem to regulate BDNF functions in the brain, but both BDNF and A_{2A}Rs seem to be implicated in HD.

In this article we report and critically discuss some recent findings on the following issues obtained by our group: (1) the regulatory role exerted by hippocampal A_{2A}Rs on BDNF functions and levels as revealed by studies performed in A_{2A}R KO mice, and (2) the effects of A_{2A}R blockade on striatal BDNF levels in experimental models of HD or HD-like striatal degeneration.

In hippocampal slices from wild-type mice, the facilitatory effects exerted by BDNF on synaptic transmission require the endogenous activation of A_{2A}R

In hippocampal slices from wild-type (WT) mice (400-μm thick, see [26] for a detailed methodological description), BDNF (10 ng/ml over 30 min) induced a long-lasting increase in the slope of field excitatory postsynaptic potential (fEPSP) recorded in the CA1 area (Fig. 1). This effect was abolished not only by the inhibitor of Trk phosphorylation K-252a, but also by the selective adenosine A_{2A} antagonists ZM241385 and SCH58261 (Tebano et al., manuscript in preparation). The effects of A_{2A}Rs seem to involve the cyclic adenosine monophosphate/protein kinase A (cAMP-PKA) pathway, the main transduction mechanism operated by A_{2A}Rs, as the selective PKA inhibitor KT 5720 abolished the excitatory action of BDNF (Tebano et al., manuscript in preparation).
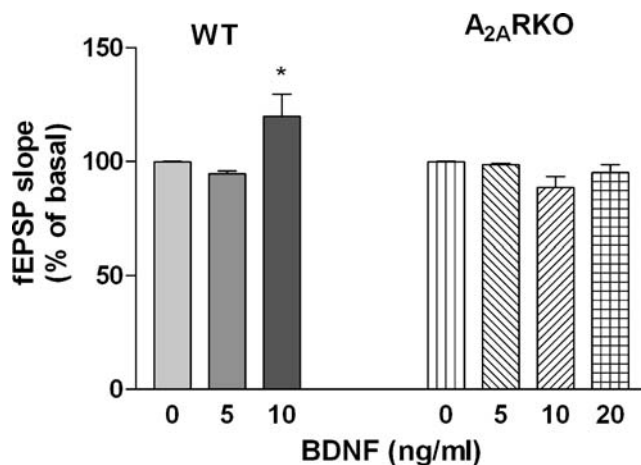

Fig. 1 Brain-derived neurotrophic factor (BDNF) facilitates synaptic transmission in hippocampal slices from wild-type (WT) but not A_{2A} receptor (R) knock-out (KO) mice. In hippocampal slices from WT mice, BDNF (10 ng/ml) induces an increase of the excitatory postsynaptic field potentials (fEPSP) slope, whereas a lower concentration (5 ng/ml) is ineffective. BDNF (5, 10 and 20 ng/ml) was totally ineffective in hippocampal slices from A_{2A}R KO mice. *$P < 0.05$ vs. baseline (paired *t* test)

The finding that BDNF enhances synaptic transmission in mice hippocampal slices confirms and strengthens previous data on the acute synaptic effects of BDNF at adult central synapses [17, 27]. Although the mechanisms responsible for such synaptic effects are not completely understood, they do not seem to be related to the neuroprotective ability of BDNF. That the above functions of BDNF recognise different molecular mechanisms is indicated by the fact that ligand-induced TrB translocation into lipid rafts is required for short-term synaptic modulation, but not neuronal survival, by BDNF [28]. Whatever the mechanisms, the blocking effect of ZM241385 and SCH58261 suggests that A_{2A}Rs have to be tonically activated by endogenous adenosine to manifest BDNF effects. To further explore the apparently "permissive" role of adenosine A_{2A}Rs on the synaptic effects of BDNF, A_{2A}R KO mice were used.

BDNF is no longer able to facilitate synaptic transmission in hippocampal slices from A_{2A} KO mice

A_{2A}R KO mice ($A_{2A}R^{-/-}$) were generated, as previously described [29]. In hippocampal slices from A_{2A}R KO mice, BDNF was no longer able to increase the fEPSP slope (Tebano et al., manuscript in preparation). As shown in Fig. 1, none of the tested concentrations of BDNF (5, 10 and 20 ng/ml) potentiated the synaptic response in slices from A_{2A}R KO mice. Since the effectiveness of BDNF may depend on the proper expression of its receptors, we compared the levels of TrkB protein in WT and A_{2A} KO mice by Western blotting. By using primary anti-TrkB antibody (Bioscience), we found that the levels of full-length TrkB

isoforms were very similar in hippocampal extracts from WT and $A_{2A}R$ KO mice (Tebano et al., manuscript in preparation). Thus, the loss of BDNF activity observed in $A_{2A}R$ KO mice is not associated with a reduced density of TrkB receptors.

BDNF protein levels are significantly reduced in the brain of $A_{2A}R$ KO vs. WT mice

The BDNF protein levels were then measured on hippocampal extracts from $A_{2A}R$ KO and WT mice using the BDNF immunoassay system [enzyme-linked immunosorbent assay (ELISA) kit; Promega]. Interestingly, hippocampal BDNF levels were significantly lower in the $A_{2A}R$ KO mice compared with the WT littermates. As shown in Fig. 2,
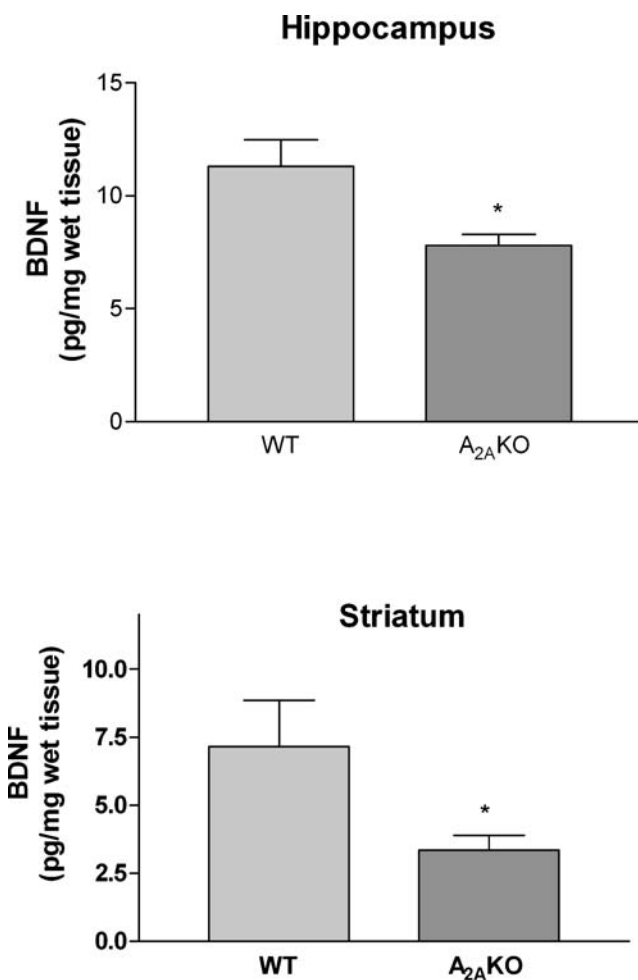

Fig. 2 Brain-derived neurotrophic factor (BDNF) levels are significantly reduced in the hippocampus and striatum of A_{2A} receptor (R) knock-out (KO) mice. BDNF concentration was significantly reduced in extracts of hippocampal and striatal tissues prepared from $A_{2A}R$ mice compared with wild-type WT mice. The amount of BDNF (total) is expressed as pg/mg of wet tissue [means ± standard error of the mean (SEM) from five mice/group]. *$P<0.05$ vs. WT

such an effect was not confined to the hippocampus, as a significant loss of BDNF levels was observed also in the striatum of A_{2A} KO vs. WT mice.

This result indicates that the presence of $A_{2A}Rs$ is required to maintain normal BDNF levels in the brain. Although the mechanism by which $A_{2A}Rs$ regulate BDNF is yet undetermined, it is worth mentioning that the cAMP-PKA pathway (the main transduction system operated by $A_{2A}Rs$) has been implicated not only in "gating" BDNF functions [30], but also in modulating BDNF gene transcription [31] and release [32]. Furthermore, Kolarow et al. [33] showed that the PKA inhibitor Rp-cAMP significantly inhibited and delayed BDNF secretion in hippocampal neurons. Interestingly, the endogenous state of activation of $A_{2A}Rs$ seems to be adequate to sustain a normal BDNF tone in WT mice, as no increase in the hippocampal levels of BDNF were observed in WT mice treated with a single (0.5 mg/kg i.p sacrifice 24 h later) or with repeated (0.5 mg/kg per day over 5 days) doses of the A_{2A} agonist CGS 21680.

On their whole, the experiments performed in A_{2A} KO mice indicate that $A_{2A}Rs$ are essential for the tone and synaptic activity of BDNF. It should be noted, however, that the stimulation or the blockade of $A_{2A}Rs$ can induce effects very different from those achieved after stimulation or blockade of the BDNF/TRkB system. For instance, whereas BDNF is thought to play an important role in memory processes [34, 35], adenosine $A_{2A}Rs$ seem to negatively influence them. Indeed, an improvement in spatial memory has been reported in $A_{2A}R$ KO mice [36], whereas working memory was impaired in rats overexpressing $A_{2A}Rs$ [37]. Another consideration that apparently weakens the importance of the $A_{2A}R$/BDNF interaction is that $A_{2A}Rs$ and TrkB Rs undergo opposite age-related changes in the hippocampus [38]. According to the authors' interpretation, however, the relationship between age-related changes in the density of TrkB and $A_{2A}R$ receptors does play a role in the modulation of BDNF effects, thus even reinforcing the hypothesis of a close functional interplay between $A_{2A}Rs$ and BDNF.

$A_{2A}Rs$ regulate striatal BDNF levels in experimental models of HD or HD-like striatal degeneration

Two different models of HD were used: the quinolinic-acid (QA)-lesioned rats (pathogenetic model of HD-like striatal degeneration, [39]) and transgenic R6/2 mice (genetic HD model, [40]). For the method of QA-induced striatal lesions, see [41]. Briefly, QA (180 nmol/1 μl) was unilaterally injected in the striatum of anaesthetised rats, whereas vehicle [1 μl phosphate-buffered saline (PBS)] was injected in the other side. SCH58261 was administered at the doses of 0.01 and 1 mg/kg i.p. 20 min before QA lesion. The

Fig. 3 The A$_{2A}$ receptor (R)-antagonist SCH58261 reduces striatal brain-derived neurotrophic factor (BDNF) levels in control and quinolinic-acid (QA)-lesioned rats. QA (180 nmol/1 µl) was unilaterally injected in the striatum of anaesthetised rats, whereas vehicle [1 µl phosphate-buffered saline (PBS)] was injected in the other side. SCH58261 was administered at the doses o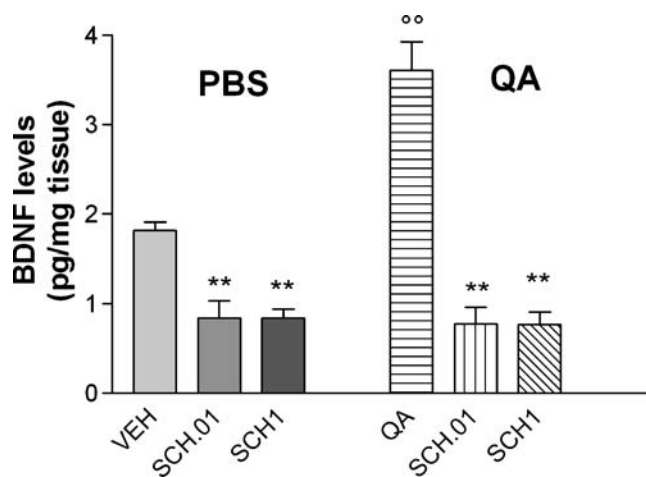f 0.01 and 1 mg/kg i.p., 20 min before QA lesion. The levels of free mature BDNF were measured 24 h after surgery. BDNF levels were significantly increased in the QA-lesioned vs. the control side. In animals pretreated with both doses of SCH58261, the rise in striatal BDNF was completely prevented. N5/group. °$P<0.05$ vs. PBS. *$P<0.05$ vs. corresponding vehicle

levels of BDNF were measured 24 h after surgery. As shown in Fig. 3, BDNF levels were significantly increased in the QA-lesioned vs. the control side. In animals pretreated with both doses of SCH58261 the rise in striatal BDNF was completely prevented. Worthy of note, SCH58261 markedly reduced BDNF levels in the control (vehicle-injected) side also (Fig. 3). As the early rise in BDNF levels most probably reflects a compensatory mechanism following QA injection, one can consider that SCH58261 may worsen QA effects by preventing BDNF increase. Previous studies have, however, demonstrated that this is not the case. We found, indeed, that whereas SCH58261 exerted very clear neuroprotective effects towards QA at 0.01 mg/kg i.p., it was no longer neuroprotective when administered at 1 mg/kg [39]. The finding that SCH58261 reduces BDNF levels irrespective of the dose (neuroprotective or non-neuroprotective) indicates that early changes in the striatal BDNF levels do not seem to correlate with the clinical and neuropathological outcome in the QA model.

R6/2 HD mice may represent a more suitable model to evaluate whether A$_{2A}$R antagonists have a worsening influence through the reduction of striatal BDNF levels. Indeed, the administration of BDNF has been reported to have beneficial effects in transgenic models of HD [42, 43]. Considering that in the transgenic mice the neurodegenerative process progressively takes place over several weeks, to ascertain whether A$_{2A}$R blockade could influence striatal BDNF levels, we decided to treat R6/2 mice chronically

with SCH58261. The drug was administered at the dose of 0.01 mg/kg per day i.p. over 1 or 3 weeks starting from the fifth week of age. Another group of R6/2 mice was treated with vehicle over 3 weeks. BDNF levels were then assayed at the beginning of the symptomatic phase (8 weeks of age). Three groups of age-matched WT littermates were used as controls and treated in the same way described as above. As shown in Fig. 4, BDNF protein levels were not reduced, and showed instead a nonsignificant tendency to increase, in the striatum of early symptomatic R6/2 vs. WT mice. This finding was unexpected, as a significant decrease in BDNF mRNA has been recently reported in the striatum of R6/2 mice of the same age [43]. Although we have not explored the mechanisms responsible for such a discrepancy, a dissociation between the levels of BDNF protein and mRNA has already been observed in the brains of transgenic R6/1 HD mice [44]. Another reason for which one would expect a reduction in BDNF levels in the striatum of R6/2 mice is that a marked reduction in the expression of A$_{2A}$Rs (which, as mentioned above, are very important to maintain normal BDNF levels) was reported in these mice [45]. More recently, however, the A$_{2A}$R-stimulated adenylyl cyclase, the A$_{2A}$R density, and their affinity for the agonist CGS21680 were found unchanged in the striatum of clearly symptomatic R6/2 mice [46].

As for the influence of A$_{2A}$R blockade, both schedules (1 and 3 weeks) of SCH treatment significantly reduced
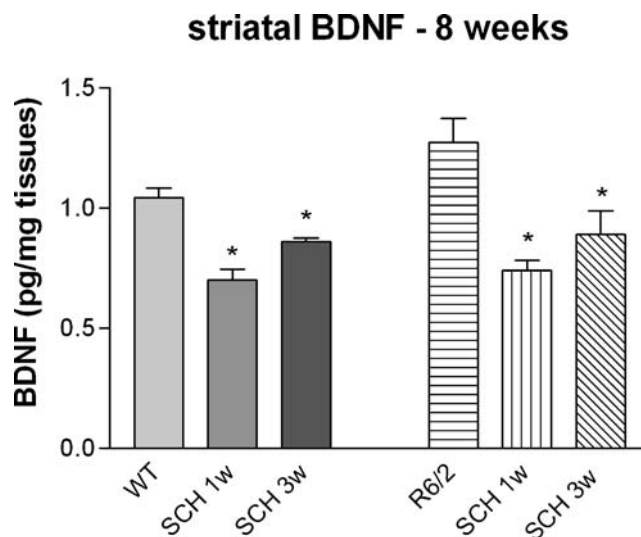
striatal BDNF - 8 weeks

Fig. 4 The A$_{2A}$ receptor (R)-antagonist SCH58261 reduces striatal brain-derived neurotrophic factor (BDNF) levels in R6/2 HD mice SCH58261 was administered at the dose of 0.01 mg/kg per day i.p. over 1 or 3 weeks starting from the fifth week of age. Free mature BDNF levels were then assayed at the beginning of the symptomatic phase (8 weeks of age). Three groups of age-matched wild-type (WT) littermates were used as controls and treated in the same way as described above. Both schedules (1 and 3 weeks) of SCH treatment significantly reduced BDNF levels in the striatum of either R6/2 and WT mice. N4–7/group. *$P<0.05$ vs. corresponding control group (two-tailed unpaired t test)

BDNF levels in the striatum of either R6/2 and WT mice (Fig. 4). Again, however, such an effect does not necessarily imply a negative influence of SCH58261 on HD mice. Indeed, in recent experiments, we found that SCH treatment (0.01 mg/kg per day i.p. between the 5th and the 6th weeks of age) exerted some beneficial effects, namely, normalisation of emotional behaviour and restoration of a normal sensitivity to NMDA in corticostriatal slices (Domenici et al., manuscript in preparation). Thus, although the pharmacological blockade of A_{2A}Rs significantly reduces striatal BDNF levels in experimental models of HD or HD-like neurodegeneration, this does not seem to have a negative impact on the course of the disease. Of course, it is still possible that reducing BDNF levels at other time points of the pathological process has a much marked influence on the disease. This issue, as well as the evaluation of BDNF protein changes at different stages of the disease, will be the object of future studies.

Conclusions

Over the last several years, BDNF has emerged not only as a potent neuromodulator but also as a substance exerting fast excitatory actions in neurons, controlling resting membrane potential, neuronal excitability and synaptic transmission and participating in the induction of long-term changes in synaptic transmission [47]. In agreement with the recent evidence that A_{2A}Rs play a major role in regulating BDNF functions [16, 48], data reported in this article indicate that the presence and tonic activation of A_{2A}Rs are necessary to allow BDNF-induced potentiation of synaptic transmission. As for the mechanisms responsible for the permissive effects of A_{2A}Rs, data indicate an involvement of the cAMP-PKA pathway, the main transduction mechanism operated by A_{2A}Rs. The finding of reduced BDNF levels in the brain of A_{2A}R KO mice indicates that A_{2A}Rs are critical not only to allow the synaptic effects of BDNF but also to maintain normal BDNF levels. Findings also point out that A_{2A}Rs tonically regulate BDNF levels in different areas of the brain, irrespective of their levels of expression. The tonic effect exerted by A_{2A}Rs in the regulation of BDNF levels is also evident in experimental models of HD (R6/2 mice) and of HD-like striatal degeneration (QA lesion in rats).

Given that BDNF delivery has beneficial effects in models of HD [42, 43], the possible functional consequences of reducing striatal BDNF levels in those models need to be clarified. In particular, further investigations on trophic factors and associated signal pathways are warranted before A_{2A}R antagonists can be considered as a suitable therapeutic approach to HD [24].

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