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Adenosine as a neuromodulator in neurological diseases

Detlev Boison

Legacy Research, R.S. Dow Neurobiology Laboratories, 1225 NE 2nd Ave, Portland, OR 97232, USA

Abstract

Adenosine is a modulator of brain function uniquely positioned to integrate excitatory and inhibitory neurotransmission. The past few years brought a wealth of new data fostering our understanding how the adenosine system is involved in the pathogenesis of neurological diseases. Thus, dysregulation of the adenosine system is implicated in epileptogenesis and cell therapies have been developed to locally augment adenosine in an approach to prevent seizures. While activation of inhibitory adenosine A₁ receptors is beneficial in epilepsy, chronic pain and cerebral ischemia, inhibition of facilitatory A_{2A} receptors has profound neuroprotective effects, which are currently exploited in clinical trials in Parkinson's disease. A new era of adenosine-based therapies has begun, with the prospect to cover a wide range of neurological diseases.

Introduction

The purine ribonucleoside adenosine controls many brain functions in physiological and pathophysiological conditions via activation of high-affinity A₁ or A_{2A}, low-affinity A_{2B}, or low-abundance A₃ adenosine receptors (ARs) [1,2]. Coupling of the receptors to either inhibitory (A₁, A₃) or stimulatory (A_{2A}, A_{2B}) G-proteins and differential spatial distribution within the brain [1] allow a high degree of complexity in the effects of adenosine and permit the modulation of other neurotransmitter or modulator systems [3]. Due to these multifaceted properties of adenosine, an adenosine-based pharmacopoeia has been established for a variety of conditions [2]. This review covers literature from the past two years, focusing on selected newer trends on the role of adenosine in neurological disease and translation of recent research findings into adenosine-based therapies.

Adenosine: an upstream-regulator of neurotransmission

Inhibitory neuromodulation by adenosine is largely mediated by activation of A₁Rs that are coupled to inhibitory G_i or G_o containing G-proteins [1,2]. The consequences of A₁R activation are stimulation of adenylyl cyclase, activation of inwardly rectifying K⁺ channels, inhibition of Ca²⁺ channels and activation of phospholipase C. As a net result, the release of various neurotransmitters, in particular glutamate, dopamine, serotonin and acetylcholine, is inhibited. Accordingly, preclinical studies have demonstrated that activation of A₁Rs has profound antiepileptic [4] and neuroprotective [5] functions.

The highest expression of A_{2A}Rs is found in striatal neurons, which are involved in the control of motor function and habit formation [6]. Inhibitors of the A_{2A}R have profound

Corresponding author: Detlev Boison (dboison@downeurobiology.org).

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neuroprotective functions [5] and prevent apoptosis [7]. Recent findings indicate that synaptic activation of A_{2A}Rs can subsequently downregulate A₁Rs or its responses [8]. An additional layer of complexity in adenosine receptor function is created by heteromerization with each other (e.g. A₁/A_{2A} heteromers) or with other neurotransmitter receptors (e.g. A_{2A}/D₂ heteromers) [9]. Thus, adenosine, by its capability to activate receptors with opposing functions (A₁ versus A₂), is uniquely positioned as an upstream regulator for the fine-tuning and integration of excitatory and inhibitory functions within the CNS.

Astrocytic regulation of synaptic adenosine

Recent findings indicate that synaptic levels of adenosine are largely regulated by astrocytes [10–14]. The elegant experiments from Phil Haydon's group have documented that – under physiological conditions – the major source of synaptic adenosine is derived from astrocytic vesicular release of ATP, followed by extracellular degradation to adenosine via a cascade of ectonucleotidases [15•]. Using transgenic mice with a defective astrocytic vesicular release system for ATP, the authors demonstrated a reduction of the tonic suppression of neuronal networks [15•]. Intracellularly, adenosine is rapidly metabolized by phosphorylation to AMP via adenosine kinase (ADK), the key enzyme of adenosine metabolism [16], which, in adult brain, is predominantly expressed in astrocytes [13]. Thus, ADK is ideally located to control the astrocyte-based adenosine cycle (Fig. 1) by driving the influx of adenosine into the cell via bi-directional nucleoside transporters [16].

Adenosine and neurological disease

Given the complex nature and ubiquitous distribution of the adenosine system, any imbalance is expected to lead to neurological disease. The following sections describe recent findings on the role of the adenosine system in neurological diseases (Table 1).

Epilepsy

Adenosine is an endogenous anticonvulsant [17]. The past few years have brought new insights in our understanding that dysfunction of astrocyte-mediated gliotransmission [12], and in particular dysfunction of the adenosine system [16,18] can cause seizures [17], or augment the spread of kainic acid- or traumatic brain injury- induced seizures and associated neuronal cell loss [18,19]. The adenosine system is critically involved in regulating proliferation and hypertrophy of astrocytes leading to astrogliosis [20], a hallmark of epilepsy. Consequently, changes in the homeostasis of the astrocyte-based adenosine cycle are to be expected in epileptic brain. Thus, upregulation of the astrocyte-based enzyme ADK has been identified as a consequence of astrogliosis, leading to a reduced tone of the endogenous anticonvulsant adenosine [16]. During epileptogenesis, upregulation of ADK coincides with the emergence of spontaneous chronic seizures [16]. Likewise, high neuronal expression of ADK in the immature mouse brain [13] may explain increased susceptibility to hypoglycemia-induced seizures in the immature brain [21]. The hypothesis that upregulated ADK might be a culprit of epileptogenesis is further supported by transgenic mice overexpressing ADK in brain; these animals display reduced seizure thresholds and spontaneous seizures [22•]. These findings suggest, that local restoration of the inhibitory adenosine tone should prevent seizures. Indeed, intraventricular implants of cells engineered to release adenosine, prevent seizures in a rat model of epilepsy [4]. More recently, it was demonstrated that intrahippocampal implants of ADK deficient stem cell derived neural precursors suppress kindling epileptogenesis [23•]. These findings suggest, that focal augmentation of the adenosine system has the potential not only to suppress seizures, but also to prevent epileptogenesis. Thus, adenosine-augmenting cell and gene therapies might lead to improved treatment options for patients suffering from intractable epilepsy [24].

Cerebral ischemia

A rapid increase in adenosine as an acute response to cerebral ischemia [25,26••] likely represents an endogenous neuroprotective mechanism, which might be involved in the initial phase of ischemic preconditioning leading to a cerebroprotective state known as ischaemic tolerance [27]. This is a complex phenomenon, in which reprogramming of the genome [28] and astrocytes appear to play key roles [29]. Recently, the astrocytic enzyme ADK was shown to be downregulated within a time frame of 3 hours following middle cerebral artery occlusion (MCAO) in the mouse [30]. As expected, downregulation of ADK led to a marked increase in ambient adenosine, which might be a mechanistic cue for the acute endogenous protective response of the brain to injury [30]. Indeed, ADK expression levels appear to play a key role in regulating neuronal vulnerability. Transgenic mice overexpressing ADK are characterized by increased susceptibility to MCAO-induced cell death [31]. Conversely, transplantation of ADK-deficient neural or glial progenitor cells into the striatum of mice one week prior to MCAO, led to a striking reduction of the injured brain volume [32]. These findings indicate that susceptibility to ischemia-induced cell death is tightly balanced by the tone of ambient adenosine.

Chronic pain

Adenosine has complex effects on pain and can either be pro- or antinociceptive depending on the site of application or the receptor(s) involved [33]. Most attention has been devoted to pain pathways involving the A₁R, which dominates in mediating the antinociceptive effects of adenosine, as has been documented in animal models of neuropathic and inflammatory pain [33]. Apart from direct administration of adenosine or A₁ agonists, ADK inhibitors have been considered for the treatment of chronic pain [34]. More recently, antagonism of A_{2A}Rs has been suggested as a novel strategy for the management of chronic pain [35]. Thus, the A_{2A} selective antagonist SCH 58261 produced antinociception in two acute thermal pain tests [36]. Following intraplantar formalin injection, A_{2A}R knockout mice displayed reduced biting and flinching responses [37]. These findings suggest that the A_{2A}R has significant potential as a novel target for pain control.

Parkinson's disease

Due to its high abundance in striatopallidal neurons, the adenosine A_{2A}R has emerged as the prime non-dopaminergic target in the search for improved therapeutics for Parkinson's disease (PD) [38•]. Most importantly, A_{2A}Rs can form functional heteromeric complexes with dopamine D₂Rs and A₁Rs, and thus have the capability to integrate and fine-tune neurotransmission in the basal ganglia [9,39,40]. Due to reciprocal antagonistic interactions between A_{2A} and D₂Rs, the blockade of the adenosine A_{2A}R in striatopallidal neurons leads to a reduction of the postsynaptic effects of dopamine deficiency and thus to an amelioration of the motor deficits in PD [40]. In addition, antagonism of the A_{2A}R has direct neuroprotective effects, with the potential to slow down disease progression [38•]. Consequently, A_{2A} antagonists have been developed for clinical trials in PD. The A_{2A} antagonist KW-6002 has shown potential in phase IIb and III clinical trials in patients in an advanced stage of PD [2]. The initial clinical results are promising and illustrate a translational drug discovery approach, which is based on the discovery of A_{2A}/D₂ interactions.

Alzheimer's disease

Epidemiological studies indicate that caffeine consumption is inversely correlated with the incidence of Alzheimer's disease (AD) [1]. In line with these observations, long-term caffeine treatment in AD transgenic mice resulted in improved reference and working memory, and in reduced brain β -amyloid production [41]. Likewise, caffeine and selective A_{2A}R antagonists prevented β -amyloid induced cognitive deficits in mice [42]. The potential of adenosine-based

therapies for AD is just emerging and – in contrast to PD – has not yet been translated into clinical trials.

Huntington's disease

Similar to its role and therapeutic potential in PD and AD, the A_{2A}R has gained recent interest in the pathophysiology of Huntington's disease (HD) [43]. Since A_{2A}Rs stimulate glutamate outflow and inflammatory gliosis, it is of interest to note that A_{2A}Rs are mainly localized on those neurons, which degenerate early in HD; consequently, changes in A_{2A}R expression and signalling have been reported in models of HD, leading to the concept that the aberrant A_{2A}R phenotype may represent a novel biomarker for HD [44]. This conclusion is supported by findings in a mouse model of HD, demonstrating a transient increase in A_{2A}R density and A_{2A}R-dependent cAMP production at early presymptomatic ages, i.e. well before the onset of symptoms [45]. These findings suggest that modulation of A_{2A}Rs might be an interesting therapeutic strategy for HD.

Schizophrenia

Currently, schizophrenia is best explained by the dopamine and glutamate hypotheses of schizophrenia. However, each hypothesis alone can only incompletely explain the complex pathophysiology of schizophrenia. The newly proposed adenosine hypothesis of schizophrenia [46•] might constitute a critical link between the two hypotheses.

The dopamine hypothesis of schizophrenia is largely based on effects of dopamine receptor antagonists and agonists to suppress and to promote psychotic symptoms, respectively. Thus, the efficacy of many antipsychotics correlates with their ability to block dopamine D₂Rs [47, 48]. In addition, increased dopamine turnover, and enhanced amphetamine-induced dopamine-release have been documented in schizophrenia patients [46•]. These findings are compatible with a deficiency in adenosine, which can enhance dopamine release due to the inhibitory effect of A₁Rs on dopamine release [1], and potentiate amphetamine-induced locomotion and dopamine release as suggested by effects of A₁R antagonists [39]. Interactions between A_{2A}Rs and D₂Rs allow further opportunity for mutual modulation between the adenosine and dopamine systems. These mechanisms could provide a rationale for an antipsychotic-like profile of adenosine receptor agonists.

According to the glutamate hypothesis, reduced *N*-methyl-D-aspartate receptor (NMDAR) function may contribute to the cognitive and negative symptoms of schizophrenia [49]. NMDAR blockade can give rise to behavioral dysfunction and psychotic-like behavior, while co-agonists of the NMDAR, such as D-serine and glycine, improve cognition and negative symptoms in schizophrenia [49]. Similarly, disruption of the glycine transporter 1 has promnesic and antipsychotic potential [50]. Adenosine inhibits glutamate release and the post-synaptic action of excitatory neurotransmitters upon neuronal hyperpolarization via A₁Rs [1]. Thus, in animal models of schizophrenia, AR agonists were effective against behavioral as well as neurophysiological effects induced by NMDAR antagonists, thus indicating their potential antipsychotic efficacy in humans [46•].

Conclusions

The examples outlined above in a variety of neurological disorders indicate that adenosine concentrations need to be under tight control. Any increases or decreases in ambient adenosine above or below certain thresholds is expected to lead to characteristic pathologies via an imbalance of adenosine receptor mediated secondary effects. Due to interactions with glutamatergic and dopaminergic neurotransmission, adenosine can be regarded as a “master regulator” to integrate and fine-tune various neurotransmitter systems in the brain (Fig. 2).

ADK and astrocytes as the key regulators of synaptic adenosine have therefore important upstream functions. Thus, therapeutic modulation of ADK has great promise for future treatment strategies for the wide range of pathologies discussed here (Table 1). To further promote ADK-based therapies, a detailed understanding how the enzyme is regulated *in vivo* is urgently needed.

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Figure 1. The adenosine cycle

The regulation of extracellular levels of adenosine is largely dependent on the astrocyte-based adenosine cycle. A major source of synaptic adenosine is vesicular release of ATP (in orange circle) followed by its extracellular degradation to adenosine (ADO) via ectonucleotidases. Nucleoside transporters (NT) equilibrate extra- and intracellular levels of adenosine. Intracellular metabolism of adenosine depends on the activity of adenosine kinase (ADK), which, together with 5'-nucleotidase (5'-NT), forms a substrate cycle between AMP and adenosine. Thus, intracellular metabolism of adenosine via ADK drives the influx of adenosine into the cell.

Figure 2. Adenosine kinase – the key regulator to fine-tune neurotransmission

Adenosine kinase as the key sensor and regulator of ambient adenosine, plays a pivotal role in fine-tuning glutamatergic and dopaminergic neurotransmission based on adenosine's activation of adenosine receptors with opposing activities (A_1R versus $A_{2A}R$). Crosstalk between receptors and components of glutamatergic and dopaminergic neurotransmissions allows integrating and fine-tuning these transmitter systems. Thus, any imbalance in the adenosine system will have pathological downstream effects via altered glutamatergic and dopaminergic neurotransmission.

Table 1

Possible adenosine-based therapeutic strategies for neurological diseases

Condition	A ₁ R agonists	A _{2A} R antagonists	ADK inhibitors	adenosine delivery
Epilepsy	X [1]	? [1]	X [16]	cell therapy [4]
Stroke	X [1]	X [1]	? [16]	cell therapy [32]
Chronic pain	X* [2]	X [37]	X* [34]	intrathecal adenosine* [34]
Parkinson's		X* [38]		
Alzheimer's		X [42]		
Huntington's		? [45]		
Schizophrenia	? [46]	? [46]	? [46]	

“X” indicates successful experimental studies, those marked with an asterisk* have been studied in clinical trials. “?” indicates therapeutic potential based on theoretical considerations and/or preliminary data, but experimental evidence needs to be established. References, with a focus on recent review articles, are given in brackets.