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Modulation of neuroimmunity by adenosine and its receptors: Metabolism to mental illness

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Abstract

Adenosine is a pleiotropic bioactive with potent neuromodulatory properties. Due to its ability to easily cross the blood-brain barrier, it can act as a signaling molecule between the periphery and the brain. It functions through four (A1, A2A, A2B, and A3) cell surface G protein-coupled adenosine receptors (AR) that are expressed in some combination on nearly all cells types within the CNS. By regulating the activity of adenylyl cyclase and changing the intracellular concentration of cAMP, adenosine can alter neuronal function and neurotransmission. A variety of illnesses related to metabolic dysregulation, such as type 1 diabetes and Alzheimer's disease, are associated with an elevated serum concentration of adenosine and a pathogenesis rooted in inflammation. This review describes the accepted physiologic function of adenosine in neurological disease and explores its new potential as a peripheral to central danger signal that can activate the neuroimmune system and contribute to symptoms of sickness and psychopathologies.

Keywords

adenosine; adenosine receptors; Alzheimer's disease; anxiety; diabetes; depression; hypoxia; interleukin 1; neuroimmunity; Parkinson's disease; sickness

Introduction

Adenosine is an endogenous purine nucleoside that works through four described G protein-coupled receptors [1]. The A1 and A3 ARs inhibit and the A2A and A2B ARs activate adenylyl cyclase causing decreases and increases in the intracellular concentration of cAMP, respectively. Under physiological conditions, adenosine, which is a metabolic intermediate

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of ATP metabolism, serves as a neuromodulator [1]. Adenosine exhibits various tonic effects throughout the body, but this review focuses on diseases in which energy imbalance and neurological dysfunction are intertwined, leading to perturbations in sleep [2], arousal [3] and memory [4]. Normally, the extracellular concentration of adenosine fluctuates diurnally within a narrow range, reaching a peak concentration of 30 nM near the end of wakefulness [5]. During sleep, the concentration of adenosine falls to approximately 24 nM [5, 6]. However, metabolic stress and inflammation can increase local brain concentrations of adenosine by nearly 1000-fold [7] via phosphohydrolysis of extracellular ATP, ADP, and AMP released from injured cells [8, 9, 10, 11].

Adenosine generation (Figure 1)

Purine nucleotides and nucleosides are metabolized in all tissues and cell types [12, 13]. Due to the size and charge of ATP, it cannot diffuse through cell membranes [14]; thus, its liberation from cells is tightly regulated by vesicular release [15] and active transport [16]. In contrast, the uncontrolled release of ATP from cells is often the result of cytolysis [17]. The intracellular concentration of ATP is approximately 1 mM, while its extracellular concentration is between 100–1000-fold lower [18]. In contrast, the concentration difference of adenosine across cell membranes is considerably smaller, nearly 1:1 [5, 6]. This is due to ubiquitous adenosine transporters [19] and the *de novo* generation of adenosine both in and out of the cell [20].

AMP is a principal source of adenosine [18] both inside and outside the cell [20]. The hydrolysis of ATP and ADP to AMP is primarily catalyzed by ATP-diphosphohydrolase (apyrase) with an extracellular *K_m* between 10–20 μ M [21, 22]. In addition, specific ATP- and ADPases and ecto-nucleotide pyrophosphatases can also generate AMP [18, 21, 22]. The formation of ATP and AMP from ADP is also possible via ATP:AMP phosphotransferase [21]; thus, a variety of different metabolic pathways contribute to adenosine precursor production.

Adenosine is generated from AMP by a single family of 5'-nucleotidases, of which ecto-5'-nucleotidase is the most well described [20, 23]. Ecto-5'-nucleotidase is responsible for the degradation of AMP in the interstitial space; thus, it generates most extracellular adenosine [20, 21]. Although ecto-5'-nucleotidase catalyzes the rate-limiting step in adenosine generation, the purines metabolized outside of the cell have a half-life of less than one second [23]. Intracellularly, 5'-nucleotidase converts AMP to adenosine with a mM *K_m* for AMP [23]. In contrast, ecto-5'-nucleotidase has a μ M *K_m* for AMP [21, 22]. Uncommonly, intracellular adenosine is generated from the hydrolysis of S-adenosylhomocysteine [24], but, unlike AMP-derived adenosine, its formation rarely occurs in the CNS [25] and decoupled from cellular energy balance [24, 25].

Throughout the brain, ecto-5'-nucleotidase is chiefly expressed on astrocytes, oligodendrocytes and microglia [26, 27]. Only neurons in the hippocampus express ecto-5'-nucleotidase, at least in rodents [20, 21, 26]. Because hippocampal neurons predominantly express G_i-linked A1 ARs as opposed to G_s-linked A2A ARs, hippocampally generated adenosine may serve as a counter-regulatory signal for excitability [28, 29, 30].

Adenosine transporters

Two types of molecules are known to be responsible for the transport of adenosine in and out of the cell: facilitated diffusion carriers and active gradient transporters [31]. Bi-directional facilitated diffusion carriers broadly recognize purines and pyrimidines but have the greatest affinity for adenosine [32]. This class of adenosine carriers exhibit cell-type specific variability that manifests as an inconsistent sensitivity to adenosine reuptake inhibitors, such as dipyridamole [31]. Adenosine can also pass through cell membranes via sodium co-transporters during sodium influx [31, 33]. In neurons, adenosine co-transport has been shown to be important in maintaining membrane charge [31]. Interestingly, sodium-dependent nucleoside transporters are highly expressed in the choroid plexus where they significantly contribute to the conveyance of adenosine into the central nervous system [34].

Adenosine degradation

In the interstitial space, adenosine is irreversibly deaminated to inosine by adenosine deaminase (ADA). The importance of adenosine deamination is seen in the inherited disorder ADA-severe combined immunodeficiency (ADA-SCID). In humans, polymorphisms that reduce ADA expression cause ADA-SCID [35], which is characterized by pan-lymphocytopenia [36, 37, 38]. Buildup of extracellular adenosine due to the loss of ADA-mediated deamination leads to AR-dependent impaired T cell activation [39, 40] and A2A AR-mediated thymocyte apoptosis [41, 42]. In addition, 2'-deoxyadenosine, DNA nucleoside A, accumulates in the absence of ADA, triggering apoptosis [43].

Adenosine signaling (Figure 1)

Adenosine signals are generated by four recognized trans-membrane G protein-coupled ARs (A1, A2A, A2B, and A3) that compose a subclass of the P1 purine receptor family [44]. All ARs recognize extracellular adenosine and are antagonized by caffeine [45]. Adenosine exerts its effects by regulating the concentration of intracellular cAMP. Nanomolar concentrations of adenosine drive A1 AR signaling, which results in reduced intracellular cAMP via G_i inhibition of adenylyl cyclase; this especially occurs in the brain [46, 47]. This is similar in A3 AR signaling; however, A3 ARs are expressed in limited levels in the brain [46]. In injurious states when extracellular adenosine rises above the nM range, A2A ARs are engaged resulting in increased adenylyl cyclase activity and intracellular cAMP [47]. A2B ARs act similarly to A2A ARs but have a much lower affinity for adenosine [48, 49]. As we and others have shown, the activation of A2A AR initiates a cAMP/protein kinase A (PKA) dependent signaling cascade [50] that results in the opening of ATP-sensitive potassium (K_{ATP}) channels [50, 51]. The efflux of potassium hyperpolarizes myocytes causing vasodilation [50] and decreased electrical activity in neurons [52]. Clinically, the administration of sulfonylurea and the K_{ATP} channel blocker glyburide can inhibit the aforementioned hyperpolarizations [50, 51, 52]. In addition, A2A ARs on microglia drive increases in cyclooxygenase-2 expression and prostaglandin E2 release by a pathway unlinked to K_{ATP} channels [53].

Finally, at supraphysiological levels of adenosine, the $G\beta\gamma$ subunit of the A1 AR can activate a phospholipase C (PLC) dependent/cAMP independent pathway leading to increased intracellular calcium [54, 55]. This PLC-mediated response results in vasoconstriction [54,55]. A3 ARs, which are expressed mainly in the striatum, can also trigger this vasoconstriction response [56].

Adenosine in disease

As adenosine is the backbone of both ATP and cAMP, it is tied to the metabolic state of a cell. An increase in extracellular adenosine occurs when energy expenditure increases [57]. Adenosine can also regulate various metabolic pathways, including glucose metabolism [58, 59] and inflammation [60]. In mouse models of diabetes, hyperglycemia is attenuated by A1 and A3 agonism [58]. Similarly, overexpression of A1 ARs appears to protect mice from diet-induced insulin resistance [59]. Activation of A1 ARs inhibits lipolysis in an adenylyl cyclase-dependent manner [61] and potentiates insulin-induced activation of phosphoinositide 3-kinase [61]. Conversely, A2A AR stimulation promotes glycogenolysis [62]. Overall, the adenosine-dependent inhibition of adenylyl cyclase promotes insulin action [58]. Thus, elevations in serum adenosine seen with obesity [63] may be compensatory but are likely negated by overnutrition-associated increases in serum ADA activity [64]. Interestingly, diabetes enhances adenosine-dependent inhibition of hippocampal neuronal action [65], which suggests a link between diabetes and cognitive impairment.

Adenosine in neurodegeneration (Table 1)

Activation of A1 ARs during times of high energy need decreases neuronal function by inhibiting the release of glutamate, dopamine, serotonin, and acetylcholine neurotransmitters [29, 56, 66, 67]. Extracellular adenosine is elevated during neuronal firing as it is co-released with some neurotransmitters [68]. The ability of adenosine to down-regulate brain activity during intense energy demands is thought to be an auto-protective mechanism [68], while diurnal fluctuations in adenosine appear relevant to sleep and wakefulness [5, 6, 56]. Injurious processes are also associated with increased extracellular adenosine in the brain [68], but in these conditions the adenosine concentration is thought to be greater [67, 68, 69] resulting in A2A AR engagement [69]. This rationale is derived from A2A AR inhibitor studies where antagonism was shown to be neuroprotective [67].

A1 and A2A ARs can complex with neurotransmitter receptors to further influence neurotransmission [67]. In general, these heterodimerizations are antagonistic and best studied in the dopaminergic system and for the possible treatment of Parkinson's disease [70], but they can also be metabotropic as indicated by studies that modified the glutamate receptor to modulate cognition [71], memory [4], sleep [2] and arousal [3]. Studies using the pan AR antagonist caffeine have demonstrated that its stimulatory effects are nullified when dopamine receptor (DR) signaling is simultaneously inhibited. Conversely, AR agonism inhibits DR agonism [70], suggesting a role for AR antagonism in neurodegenerative diseases, such as Parkinson's disease, where dopamine signaling imbalances are pathogenic [70, 72, 73]. Interestingly, A2A AR antagonism, with either caffeine [72] or subtype specific

antagonists [73], has shown promise in the treatment of Parkinson's disease [74, 75], especially in Japan [76]. Finally, ARs in addition to DRs interact with glutamate receptors by inhibiting excitatory neurotransmitters during conditions in which excitatory neurotoxicity can manifest [66]. In summary, A1 AR agonism or A2A AR antagonism can both yield neuroprotection [77]. Table 1 provides an expanded list of known interactions between adenosine signaling and cognitive and mental disorders, including Alzheimer's disease, depression, and anxiety.

Adenosine as a danger signal

Inflammation, especially acute inflammation, is associated with increased extracellular [7] and serum adenosine [78]. It has been well established that the periphery communicates inflammatory status to the brain [79] and that sickness behaviors are a phenotypic manifestation of these peripheral to central signals [79]. One of the key bioactives relevant to inflammation-associated behavioral perturbations is the inflammatory cytokine IL-1 β [80, 81, 82]. Importantly, IL-1 β negatively impacts memory [81, 82], mood [79] and anxiety [79], which implicates it in the psychopathology of mood and anxiety disorders. Increasingly, mood and anxiety disorders are co-morbid with inflammatory conditions, such as overnutrition and the diabetes disease spectrum [83]. Canonically, IL-1 β is constitutively transcribed in a pro-form that requires enzymatic maturation by the cysteine-aspartic acid protease family member caspase-1 as part of the multiprotein inflammasome [84, 85]. Reactive oxygen species [86], products of lysosomal rupture [86], uric acid [87], ATP [88] and low intracellular potassium [89] are known activators of the inflammasome, but recently, adenosine was shown to be a potent caspase-1 activator in the brain [51] through a mechanism that appears dependent on A2A AR-mediated potassium efflux. Recent work has shown that doubling serum adenosine concentration in mice not only increases caspase-1 activity in the brain but also causes augmented expression of IL-1 β protein [51]. This increase in circulating adenosine perturbs amygdala-sensitive memory and induces anxiety-like behaviors in an A2A AR-, caspase-1- and IL-1 receptor 1-dependent manner [51, 82]. Furthermore, the anxiogenic effect of adenosine was nullified in mice that were co-administered the K_{ATP} channel blocker glyburide [51]. Overall, these studies suggest that systemic adenosine can induce inflammatory bioactives in the brain that have the potential to cause or contribute to neuroinflammation.

Adenosine and mental illness

Insight into the relationship of adenosine with psychiatric conditions can be gleaned from the near ubiquitous consumption of the pan-AR antagonist caffeine. Caffeine is the most used stimulant in the world, with more than 150 million adults in the United States ingesting it daily [90]. Caffeine administration in low to moderate doses (30–300 mg) demonstrates beneficial effects when reaction time, learning, cognition, and mood are examined [45]. It most notably increases alertness and mental energy [91]. Although caffeine has been actively explored as a causative agent of certain psychiatric disorders, no direct relationship between caffeine and mental illness has been defined. A few studies, however, link acute caffeine intake to anxiety and panic attacks in healthy adults [92,93] with a possibly stronger effect in individuals with pre-existing anxiety disorders [94]. In contrast, a more recent study

in healthy adult twins showed no significant correlation between caffeine ingestion, generalized anxiety disorder, depression, or panic disorder when genetic and environmental factors were controlled for [95]. Interestingly, some works have shown a beneficial relationship between increasing caffeine intake and decreasing depressive-like symptoms [96, 97]. It is important to note that the phenotypic effects of caffeine are principally due to its AR antagonism in the CNS. Therefore, the self-perceived salutary actions of caffeine are associated with the inhibition of adenosine signaling. In fact, the adverse actions of adenosine on brain function may best be exemplified by caffeine withdrawal, which has not been recognized until fairly recently. Caffeine withdrawal is associated with a variety of symptoms, including headache, fatigue, depression, and irritability [99], that may be partially due to both the up-regulation of ARs and circulating adenosine during a chronic course of caffeine intake [100–102]. In addition, a causative relationship between increased serum adenosine and anxiety was recently shown in mice, which suggests a direct relationship between mental illness and metabolism. [51]. Although caffeine fails to meet the full requirements for a drug of dependence, the Diagnostic and Statistical Manual of Mental Disorder (DSM)-5 recommends further research into caffeine dependency [98].

Conclusion

The metabolism and signal transduction pathways associated with adenosine and its principal receptor subtypes, A1 and A2A, are well documented. In the brain, A1 ARs and A2A ARs appear to have opposing actions based on their regulation of adenylyl cyclase [1]. The CNS distribution of ARs on neurons is non-homogenous, indicating that different regions of the brain [51] are impacted uniquely by adenosine. Pathologic states, such as hypoxia and infection, during which the extracellular adenosine concentration can approach 50 μ M [7], have been studied extensively, and these studies have provided the current knowledge regarding the role of adenosine in brain injury. More recent work, however, suggests that smaller changes in serum adenosine can impact the brain, lending insight into the popularity of caffeine as a neuroprotectant [103, 104]. In addition, caffeine has long been thought to be anxiogenic in humans [105], but contradictory results in animal models have been widely reported [51, 106, 107]. Until recently, many of the seminal studies involving AR receptor-specific agonism/antagonism utilized cell culture and/or rodent models [51, 106, 107, 110, 111] that required correlative connections to human health [74, 110, 113]. Use of A2A AR antagonists in the clinical treatment of Parkinson's disease [76] opens the door for the critical evaluation of receptor-specific adenosine interactions and the key action of adenosine as a metabolite that regulates mental processes [115]. Furthermore, with the recently described role of serum adenosine as an IL-1 β generator in the brain, it may now need to be considered a danger signal that communicates metabolic status [51]. While these exciting newly identified functions for adenosine are intriguing, much work is needed to determine if adenosine is a critical player in the etiology of mental illness.

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Abbreviations

e-5'-NT	5'-nucleotidase
ADA	Adenosine deaminase
ADP	Adenosine diphosphate
ADK	Adenosine kinase
AR	Adenosine receptor
ATP	Adenosine triphosphate
AC	Adenylate cyclase
AD	Alzheimer's disease
KATP	ATP-sensitive potassium
cAMP	Cyclic 3',5'-adenosine monophosphate
DR	Dopamine receptor
e-5'-NT	Ecto-5'-nucleotidase
IL	Interleukin
KO	Knockout
mGluR	Metabotropic glutamate receptor
PD	Parkinson's disease
PLC	Phospholipase C
PKA	Protein kinase A
ROS	Reactive oxygen species
SCID	Severe combined immunodeficiency

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Fig. 1. Purine metabolism and adenosine signaling. 5'-nucleotidase (5'-NT), Adenosine deaminase (ADA), adenosine diphosphate (ADP), adenosine kinase (ADK), adenosine triphosphate (ATP), adenylyl cyclase (AC), cyclic 3',5'-adenosine monophosphate (cAMP), ecto-5'-nucleotidase (e-5'-NT).

Table 1

Effects of adenosine on neurological disorders

Disease	Experimental Model	Interaction with Adenosine	Reference
Metabolic Disorders			
Ischemia/Hypoxia	Various	Adenosine rapidly increases after hypoxia and ischemia	[108]
		Adenosine antagonism delays hypoxia-induced depression	[109]
Type 1 Diabetes	Non-obese diabetic rats (streptozotocin- induced hyperglycemia) hippocampal slice culture	Diabetic-like state enhances adenosine-evoked inhibition	[65]
Cognitive Disorders			
Alzheimer's Disease	Alzheimer's Disease Patients	AD patients show increased expression of A1 and A2A receptors	[110]
		A1 agonist increases production of soluble amyloid precursor protein	
	Cultured Neurons	Caffeine protects against β -amyloid-induced toxicity	[111]
		A2A but not A1 antagonism protects against β -amyloid-induced toxicity	
	ICV administration of β -amyloid (Mouse)	12-d caffeine treatment in drinking water plus acute caffeine injection prevents β -amyloid- induced cognitive impairment 4-d caffeine treatment plus A2A antagonist injection prevents β -amyloid-induced cognitive impairment	[112]
	Striatum from AD patients	Loss of A1 receptors in AD striatum parallels a loss of choline acetyltransferase activity	[113]
	APPsw transgenic mice	Daily caffeine intake improves behavior and reduces hippocampal β -amyloid	[114]
Parkinson's Disease	Various	Heteromeric antagonistic D2/A2A receptors	[29]
		A2A opposes the action of D2 on GABAergic neurons	[74]
		Heteromeric synergistic A2A/mGlu receptors Slows progression of PD	
		KW-6002 (A2A antagonist) shows potential in phase IIb and III in PD patients	[115]
Mental Disorders			
Depression	Various	Adenosine antagonism delays hypoxia-induced depression	[109]
		Adenosine antagonism exhibits antidepressant-like properties	[116]
		A2A KO displays less depressive-like behavior when compared to wild-type control	[117]
		A2A antagonism elicits antidepressant-like properties	
		D2 antagonist blocks antidepressant-like properties of A2A antagonists	
Anxiety	Transgenic mice	Anxiolytic effects of A1 agonism	[106]
		Anxiety-like behavior in A1 KO	[107]
		Anxiety-like behavior after adenosine injection, protection in A2A KO	[51]