frontiers in Neuroscience

MINI REVIEW
published: 16 July 2021
doi: 10.3389/fnins.2021.702581

Adenosine A_{2A} Receptors as Biomarkers of Brain Diseases

Ana Moreira-de-Sá[1†], Vanessa S. Lourenço[1†], Paula M. Canas[1] and Rodrigo A. Cunha[1,2]*

[1] CNC—Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, [2] Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Extracellular adenosine is produced with increased metabolic activity or stress, acting as a paracrine signal of cellular effort. Adenosine receptors are most abundant in the brain, where adenosine acts through inhibitory A_1 receptors to decrease activity/noise and through facilitatory A_{2A} receptors ($A_{2A}R$) to promote plastic changes in physiological conditions. By bolstering glutamate excitotoxicity and neuroinflammation, $A_{2A}R$ also contribute to synaptic and neuronal damage, as heralded by the neuroprotection afforded by the genetic or pharmacological blockade of $A_{2A}R$ in animal models of ischemia, traumatic brain injury, convulsions/epilepsy, repeated stress or Alzheimer's or Parkinson's diseases. $A_{2A}R$ overfunction is not only necessary for the expression of brain damage but is actually sufficient to trigger brain dysfunction in the absence of brain insults or other disease triggers. Furthermore, $A_{2A}R$ overfunction seems to be an early event in the demise of brain diseases, which involves an increased formation of ATP-derived adenosine and an up-regulation of $A_{2A}R$. This prompts the novel hypothesis that the evaluation of $A_{2A}R$ density in afflicted brain circuits may become an important biomarker of susceptibility and evolution of brain diseases once faithful PET ligands are optimized. Additional relevant biomarkers would be measuring the extracellular ATP and/or adenosine levels with selective dyes, to identify stressed regions in the brain. $A_{2A}R$ display several polymorphisms in humans and preliminary studies have associated different $A_{2A}R$ polymorphisms with altered morphofunctional brain endpoints associated with neuropsychiatric diseases. This further prompts the interest in exploiting $A_{2A}R$ polymorphic analysis as an ancillary biomarker of susceptibility/evolution of brain diseases.

Keywords: adenosine A_{2A} receptors, central nervous system, antagonism, caffeine, biomarkers, polymorphisms

OPEN ACCESS

Edited by:
Rui Daniel Prediger, Federal University of Santa Catarina, Brazil

Reviewed by:
Thomas Heinbockel, Howard University, United States
Ernest Jennings, James Cook University, Australia

***Correspondence:**
Rodrigo A. Cunha
rcunha@fmed.uc.pt;
cunharod@gmail.com

† These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neuropharmacology, a section of the journal Frontiers in Neuroscience

Received: *29 April 2021*
Accepted: *22 June 2021*
Published: *16 July 2021*

Citation:
Moreira-de-Sá A, Lourenço VS, Canas PM and Cunha RA (2021) Adenosine A_{2A} Receptors as Biomarkers of Brain Diseases. Front. Neurosci. 15:702581. doi: 10.3389/fnins.2021.702581

INTRODUCTION

The increased use of intracellular ATP, either because of increased workload or need to cope with stressful conditions, is a main source of increased extracellular levels of adenosine, which generally acts as a paracrine allostatic regulator by locally decreasing metabolism through inhibitory A_1 receptors (A_1R) and increasing metabolic supply through $A_{2A}R$ (Agostinho et al., 2020). Adenosine receptors are most abundant in the brain, where adenosine fulfills a role as neuromodulator apart from its general paracrine allostatic role: post-synaptic as well as astrocytic integrative activity are major contributors of an adenosine tone acting through inhibitory A_1 receptors to decrease activity/noise in excitatory synapses; ATP release, characteristic of increased firing rate conditions associated with synaptic plasticity, is the major source of a second pool of synaptic extracellular adenosine selectively activating facilitatory A_{2A} receptors ($A_{2A}R$) to promote synaptic plastic

changes in physiological conditions (Cunha, 2016). However, ATP is also a general danger signal in the brain (Rodrigues et al., 2015), acting through a variety of ATP/ADP-activated P_2 receptors to re-shape the function of astrocytes and microglia to cope with potential threats (Agostinho et al., 2020). Such threats also require adaptive plastic changes in neuronal circuits, which may explain the increased extracellular formation of ATP-derived adenosine by ecto-nucleotidases, with a burst of its rate-limiting step—ecto-5′-nucleotidase or CD73 (Cunha, 2001)—under noxious brain conditions to sustain an overfunction of $A_{2A}R$ that contributes to synaptotoxicity and neurotoxicity in different brain diseases (Cunha, 2016).

ADENOSINE A_{2A} RECEPTORS IN BRAIN DISEASES

Upon acute brain injury, probably best exemplified by an ischemic brain stroke, concurrent pharmacological and genetic evidence show that $A_{2A}R$ blockade affords a robust neuroprotection (reviewed in Chen and Pedata, 2008). In parallel, ischemia is accompanied by ATP release (Melani et al., 2005) and up-regulation of CD73 (Braun et al., 1997), thus increasing the formation of extracellular ATP-derived adenosine (Koos et al., 1997; Chu et al., 2014). Likewise, seizure-like activity characteristic of epileptic conditions triggers a neurodegeneration that is critically controlled by pharmacological or genetic $A_{2A}R$ blockade (Canas et al., 2018). Seizure activity also increases ATP release (Wieraszko and Seyfried, 1989) and up-regulates CD73 (e.g., Schoen et al., 1999; Rebola et al., 2003), increasing the contribution of extracellular ATP-derived adenosine formation to overactivate $A_{2A}R$ (reviewed in Tescarollo et al., 2020). $A_{2A}R$ blockade also attenuates brain damage following traumatic brain injury (TBI) (e.g., Li et al., 2009); TBI also bolsters the release of ATP (Faroqi et al., 2021) and CD73 levels (Zheng et al., 2020), although the contribution of extracellular ATP-derived adenosine has not yet been tested in TBI.

Overall, this evidence is compatible with an increase of extracellular adenosine, namely extracellular ATP-derived adenosine, leading to an overactivation of $A_{2A}R$ that contributes for brain dysfunction upon acute brain injury. A similar scenario seems to occur in chronic brain conditions. Thus, the pharmacological or genetic blockade of $A_{2A}R$ affords a consistent neuroprotection in animal models of Alzheimer's disease (AD) (e.g., Canas et al., 2009; Laurent et al., 2016; Viana da Silva et al., 2016), Parkinson's disease (PD) (reviewed in Schwarzschild et al., 2006)—where $A_{2A}R$ antagonists were approved by the US-FDA as novel anti-Parkinsonian drugs (Chen and Cunha, 2020), repeated stress/depression (Batalha et al., 2013; Kaster et al., 2015; Padilla et al., 2018), Machado-Joseph disease (Gonçalves et al., 2013), amyotrophic lateral sclerosis (ALS) (Ng et al., 2015; Rei et al., 2020; Seven et al., 2020), Angelman syndrome (Moreira-de-Sá et al., 2020, 2021), or glaucoma-like disorders (Madeira et al., 2015). Most of these chronic neuropsychiatric conditions are also associated with increased release of ATP, as occurs in animal models of AD (Gonçalves et al., 2019), PD (Carmo et al., 2019; Meng et al., 2019) or as concluded by the anti-depressant effects of P2 receptor antagonists (Ribeiro et al., 2019; but see Cao et al., 2013). Moreover, there is an increased contribution of extracellular ATP-derived adenosine for $A_{2A}R$ overactivation in chronic brain diseases, as best heralded by the observation that CD73 knockout mice phenocopy $A_{2A}R$ knockout mice (Augusto et al., 2013; Carmo et al., 2019; Gonçalves et al., 2019).

$A_{2A}R$ overactivation is not only necessary, but actually sufficient to trigger brain dysfunction, as concluded from the observation that the pharmacological overactivation of $A_{2A}R$ (Pagnussat et al., 2015), the optogenetic activation of $A_{2A}R$ transducing system (Li et al., 2015) or the over-expression of $A_{2A}R$ in the hippocampus (Coelho et al., 2014; Carvalho et al., 2019; Temido-Ferreira et al., 2020) are sufficient to trigger or aggravate brain dysfunction. Notably, $A_{2A}R$ overfunction seems to be an early event in different brain disorders (reviewed in Cunha, 2016), although $A_{2A}R$ antagonists seem to maintain their neuroprotective profile after the establishment of symptoms (e.g., Kaster et al., 2015; Faivre et al., 2018; Orr et al., 2018; Silva et al., 2018).

The tight association between increased release of ATP and its extracellular catabolism to overactivate $A_{2A}R$ as part of the expression of neuronal dysfunction at the onset and throughout the evolution of several brain diseases prompts exploiting this danger signaling pathway as new biomarkers to identify dysfunctional brain circuits in brain diseases. Although the tools are yet to developed, it may be promising to devise soluble sensors to detect altered levels of extracellular ATP to allow an *in vivo* estimate of brain circuits undergoing a particular purinergic pressure and, consequently, are at risk of undergoing dysfunction. An alternative could be the development of PET ligands (not yet available) to assess the density of CD73, which is paramount to link ATP upsurge with the selective overactivation of $A_{2A}R$; CD73 seems to be consistently up-regulated upon brain stressful conditions and may be a selective biomarker of glia and synapses undergoing adaptive processes (Schoen and Kreutzberg, 1997).

UP-REGULATION OF ADENOSINE A_{2A} RECEPTORS IN BRAIN DISEASES

The $A_{2A}R$ overactivation associated with brain dysfunction and disease is not only sustained by an increased bioavailability of the trigger of $A_{2A}R$—ATP-derived extracellular adenosine—but also involves an up-regulation of $A_{2A}R$ in the afflicted brain areas (reviewed in Cunha, 2016). Indeed, an increased density of cortical $A_{2A}R$ has been reported in animal models of epilepsy (Rebola et al., 2005; Cognato et al., 2010; Canas et al., 2018; Crespo et al., 2018), Rasmussen's encephalopathy (He et al., 2020), TBI (Zhao et al., 2017), AD (Espinosa et al., 2013; Viana da Silva et al., 2016; Silva et al., 2018), Lyme neuroborreliosis (Smith et al., 2014), ALS (Seven et al., 2020), or chronic stress/depression (Kaster et al., 2015; Machado et al., 2017), as well as in the diseased human brain (Albasanz et al., 2008; Temido-Ferreira et al., 2020). Likewise, $A_{2A}R$ levels are also increased in the cerebellum of Machado-Joseph's ataxic mice (Gonçalves et al., 2013) and in the

amygdala or fear-conditioned mice (Simões et al., 2016). $A_{2A}R$ up-regulation is in fact an upsurge since it occurs shortly (within hours) after abnormal neuronal function (i.e., convulsions; Canas et al., 2018), but it gradually increases with aggravation of brain dysfunction (Temido-Ferreira et al., 2020). $A_{2A}R$ up-regulation mostly occurs in synapses, in accordance with the involvement of synaptic alterations at the onset of most brain diseases (e.g., Rebola et al., 2005; Kaster et al., 2015; Viana da Silva et al., 2016; Canas et al., 2018), but is also observed in glia cells in the progression of chronic brain diseases (Matos et al., 2012; Orr et al., 2015; Barros-Barbosa et al., 2016; Patodia et al., 2020). It is still unclear if this $A_{2A}R$ up-regulation only involves an increased readout of $A_{2A}R$ mRNAs (Canas et al., 2018) or also involves an overexpression of $A_{2A}R$ mRNA, which has been reported in the dysfunctional or diseased brain (e.g., Costenla et al., 2011; Espinosa et al., 2013; Hu et al., 2016; Dias et al., 2021). In fact, the triggers and mechanisms of this $A_{2A}R$ up-regulation in the diseased brain are essentially unknown. The $A_{2A}R$ gene in both

TABLE 1 | Summary of the reported associations between known polymorphic variants of the human adenosine A_{2A} receptor gene (*ADORA2A*) and different response susceptibility to either pathological threats **(A)** or distinct physiological responses to external stimulus **(B)**.

(A) SNP	Type/Position	Risk allele/Genotype	Associated CNS Disorder	References
rs5751876	Exon 2	TT	Huntington's disease (significant variability in age of onset)	Taherzadeh-Fard et al., 2010
		T	Susceptibility locus for Panic Disorder and Agoraphobia	Deckert et al., 1998; Hamilton et al., 2004; Domschke et al., 2012
		T	Prevalent in Gilles de la Tourette syndrome (GTS) patients	Janik et al., 2015
rs2298383	5′ UTR	TT	Huntington's disease (significant variability in age of onset)	Taherzadeh-Fard et al., 2010
		CT	Higher predisposition for Childhood Epilepsy (CE)	Fan et al., 2020
		CC	Greater risk for CE patients to develop comorbid neurologic disorders	Fan et al., 2020
		CC/CT	Increased risk of Depression, Attention Deficits and Sleep-disturbances	Oliveira et al., 2019
		CC	Possible risk factor for Schizophrenia	Miao et al., 2019
rs2236624	Intron 4	CC	Associated with Autism Spectrum Disorders symptom severity	Freitag et al., 2010
rs71651683	5′ UTR	T	Inverse association with the likelihood to develop Parkinson's disease (∼49%)	Popat et al., 2011
rs5996696	Promoter variant region	C	Inverse association with the likelihood to develop Parkinson's disease (∼30%)	Popat et al., 2011
rs2298383, rs5751876, rs35320474, and rs4822492	5′ UTR, Exon 2, Exon 4, and 3′ UTR	C, T, deletion and C, respectively, (Haplotype A)	Predisposition of children to develop Acute Encephalopathy with biphasic seizures and late reduced diffusion (AESD)	Shinohara et al., 2013
(B) SNP	**Type/Position**	**Risk allele/Genotype**	**Physiological Response to Stimuli**	**References**
rs5751876	Exon 2	TT	Significant enhancement of caffeine-induced anxiety	Alsene et al., 2003; Childs et al., 2008
		TT	Associated with an overall lower caffeine intake and a prospective lesser vulnerability to caffeine dependence	Cornelis et al., 2007
		TT	Highest startle magnitudes upon caffeine administration in response to unpleasant pictures (maladaptive emotional processing)	Domschke et al., 2012
		TT	Associated with an ergogenic beneficial effect upon caffeine consumption	Loy et al., 2015
		TT	Higher anxiogenic response susceptibility to caffeine ingestion in usual non-consumers or low consumers (<40 mg per day), but no significant correlation with habitual caffeine intake	Rogers et al., 2010
		C	Sleep disturbances (and insomnia) triggered by caffeine intake, higher β-activity in non-REM sleep	Rétey et al., 2007
		T	Lower total sleep time in habitual low caffeine consumers	Erblang et al., 2019
		T	Increased sleep latency associated with caffeine consumption, lower percentage of N3 sleep stage	Nunes et al., 2017
rs2298383	5′ UTR	CC	Significant enhancement of caffeine-induced anxiety	Childs et al., 2008
		C	Lower total sleep time in habitual low caffeine consumers	Erblang et al., 2019
rs4822492	3′ UTR	CC	Significant enhancement of caffeine-induced anxiety	Childs et al., 2008
		CC	Lower total sleep time in habitual low caffeine consumers	Erblang et al., 2019
rs3761422	5′ UTR	TT	Greater increase in anxiety upon caffeine ingestion in habitual non-consumers or low consumers (<40 mg per day)	Rogers et al., 2010
		T	Lower total sleep time in habitual low caffeine consumers	Erblang et al., 2019

rodents and humans has a complex promoter region and can give raise to multiple transcripts (Peterfreund et al., 1996; Lee et al., 2003a; Yu et al., 2004; Kreth et al., 2008; Huin et al., 2019). Although multiple controllers of the $A_{2A}R$ gene have been proposed, such as methylation patterns of the promoter (Falconi et al., 2019; Micioni Di Bonaventura et al., 2019), transcription factors ZBP-89 and Yin Yang-1 (Buira et al., 2010), microRNAs (e.g., Heyn et al., 2012; Villar-Menéndez et al., 2014; Zhao et al., 2015; Tian et al., 2016), NFk-B (Morello et al., 2006), cAMP-response element-binding protein (Chiang et al., 2005), hypoxia inducible factor-2α (Ahmad et al., 2009; Brown et al., 2011), AP1 transcription factor (Kobayashi and Millhorn, 1999; Lee et al., 2014), or nuclear factor 1 (Lee et al., 2003b), the regulation of the relative expression of these transcripts is largely unknown (Yu et al., 2004; Huin et al., 2019) and little is also known about the relative stability of the different mRNA transcripts. This is certainly an area of research that might open new avenues to design neuroprotective strategies linked to $A_{2A}R$.

The association of $A_{2A}R$ up-regulation with brain diseases offers another promising opportunity to develop informative biomarkers of the susceptibility and/or evolution of different brain diseases once PET ligands are optimized to detect extra-striatal $A_{2A}R$. In fact, $A_{2A}R$ throughout the brain are most abundant in the striatum (reviewed in Svenningsson et al., 1999) and the available PET ligands have been optimized to detect striatal $A_{2A}R$ (e.g., Mishina et al., 2011; Ishibashi et al., 2018); however, this population of $A_{2A}R$ has a different pharmacology (Orrú et al., 2011; Cunha, 2016), a different adaptive profile (Cunha et al., 1995) and a different role in most brain conditions (Shen et al., 2008, 2013; Yu et al., 2008; Wei et al., 2014). Thus, it is likely that the currently available PET ligands might not be useful to assess modifications of extra-striatal $A_{2A}R$. New cortical $A_{2A}R$-directed PET ligands need to be designed based on the particular properties and interacting partners of cortical $A_{2A}R$ (reviewed in Franco et al., 2020) to allow an *in vivo* detection of $A_{2A}R$ upsurge as potential general biomarkers of brain dysfunction (Sun et al., 2020).

$A_{2A}R$ are not only located in the brain, but are also present in several peripheral tissues, namely in different blood cells such as leukocytes and platelets (reviewed in Gessi et al., 2000). Based on the association of brain diseases with $A_{2A}R$ up-regulation in afflicted brain regions, several studies explored if $A_{2A}R$ in blood cells could be biomarkers of brain diseases, such as AD (Arosio et al., 2010, 2016; Merighi et al., 2021), PD (Falconi et al., 2019), or ALS (Vincenzi et al., 2013). However, only the understanding of the mechanisms underlying $A_{2A}R$ up-regulation in brain diseases will allow providing a rationale (or lack of thereof) to consider alterations of the density of peripheral $A_{2A}R$ as valid readouts of altered $A_{2A}R$ density that occurs selectively in afflicted brain circuits in the diseased brain.

POLYMORPHISMS OF ADENOSINE A_{2A} RECEPTORS AND BRAIN DISEASES

The gene encoding human $A_{2A}R$ (ADORA2A gene) harbors several single nucleotide polymorphisms (SPNs), which have been associated to an altered susceptibility to several neuropsychiatric and neurodegenerative disorders (Huin et al., 2019). In fact, as listed in **Tables 1A,B**, naturally occurring variabilities in the ADORA2A gene collectively influence predisposition risk and even age of onset for several CNS disorders as well as individual susceptibility to the anxiogenic and sleep-related consequences of caffeine. Although, it is still unknown if the different $A_{2A}R$ polymorphisms are associated with a different expression, subcellular location, trafficking, heteromerization or pharmacological properties of $A_{2A}R$, the relation between $A_{2A}R$ polymorphisms and the susceptibility and age of onset of brain dysfunction prompts the interest in exploiting $A_{2A}R$ polymorphic analysis as an ancillary biomarker of susceptibility/evolution of brain diseases.

DISCUSSION

$A_{2A}R$ overfunction is necessary and actually sufficient for the expression of neuronal dysfunction upon brain diseases. In particular, $A_{2A}R$ overfunction associated with aberrant synaptic plasticity and synaptotoxicity seems to be associated with the onset of symptoms of brain diseases. However, some of these symptoms are comorbidities of other brain diseases, associated with their aggravation, which often involves a spreading of neuroinflammation, also known to be controlled by $A_{2A}R$. Thus, it is also likely that $A_{2A}R$ overfunction might be also associated with the evolution of brain diseases. These neuropathological roles of $A_{2A}R$ prompts considering the exploitation of this system as candidate biomarkers of the susceptibility and evolution of brain diseases. The development of PET ligand with adequate signal-to-noise ratio and selectivity to detect the relevant extra-striatal $A_{2A}R$ may allow a minimally invasive assessment of $A_{2A}R$ in different brain regions. This may be complemented by the definition of $A_{2A}R$ polymorphisms as an ancillary biomarker for the susceptibility and evolution of brain diseases, which still requires a firm establishment of structural-functional relationships between $A_{2A}R$ polymorphisms and brain dysfunction. Finally, the future development of PET-based sensors of extracellular ATP and/or adenosine may well be of additional interest as a biomarker of the status of brain diseases to be used in complement of other available methods.

AUTHOR CONTRIBUTIONS

All authors contribute to the organization and writing of the review.

FUNDING

This study was supported by La Caixa Foundation (LCF/PR/HP17/52190001), Centro 2020 (CENTRO-01-0145-FEDER-000008:BrainHealth 2020 and CENTRO-01-0246-FEDER-000010), and FCT (POCI-01-0145-FEDER-03127 and UIDB/04539/2020).

REFERENCES

Agostinho, P., Madeira, D., Dias, L., Simões, A. P., Cunha, R. A., and Canas, P. M. (2020). Purinergic signaling orchestrating neuron-glia communication. *Pharmacol. Res.* 162:105253. doi: 10.1016/j.phrs.2020.105253

Ahmad, A., Ahmad, S., Glover, L., Miller, S. M., Shannon, J. M., Guo, X., et al. (2009). Adenosine A_{2A} receptor is a unique angiogenic target of HIF-2alpha in pulmonary endothelial cells. *Proc. Natl. Acad. Sci. USA* 106, 10684–10689. doi: 10.1073/pnas.0901326106

Albasanz, J. L., Perez, S., Barrachina, M., Ferrer, I., and Martín, M. (2008). Up-regulation of adenosine receptors in the frontal cortex in Alzheimer's disease. *Brain Pathol.* 18, 211–219. doi: 10.1111/j.1750-3639.2007.00112.x

Alsene, K., Deckert, J., Sand, P., and de Wit, H. (2003). Association between A_{2A} receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 28, 1694–1702. doi: 10.1038/sj.npp.1300232

Arosio, B., Casati, M., Gussago, C., Ferri, E., Abbate, C., Scortichini, V., et al. (2016). Adenosine type A_{2A} receptor in peripheral cell from patients with Alzheimer's disease, vascular dementia, and idiopathic normal pressure hydrocephalus: a new/old potential target. *J. Alzheimers. Dis.* 54, 417–425. doi: 10.3233/JAD-160324

Arosio, B., Viazzoli, C., Mastronardi, L., Bilotta, C., Vergani, C., and Bergamaschini, L. (2010). Adenosine A_{2A} receptor expression in peripheral blood mononuclear cells of patients with mild cognitive impairment. *J. Alzheimers. Dis.* 20, 991–996. doi: 10.3233/JAD-2010-090814

Augusto, E., Matos, M., Sevigny, J., El-Tayeb, A., Bynoe, M. S., Müller, C. E., et al. (2013). Ecto-5′-nucleotidase (CD73)-mediated formation of adenosine is critical for the striatal adenosine A_{2A} receptor functions. *J. Neurosci.* 33, 11390–11399. doi: 10.1523/JNEUROSCI.5817-12.2013

Barros-Barbosa, A. R., Ferreirinha, F., Oliveira, A., Mendes, M., Lobo, M. G., Santos, A., et al. (2016). Adenosine A_{2A} receptor and ecto-5′-nucleotidase/CD73 are upregulated in hippocampal astrocytes of human patients with mesial temporal lobe epilepsy (MTLE). *Purinergic Signal.* 12, 719–734. doi: 10.1007/s11302-016-9535-2

Batalha, V. L., Pego, J. M., Fontinha, B. M., Costenla, A. R., Valadas, J. S., Baqi, Y., et al. (2013). Adenosine A_{2A} receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. *Mol. Psychiatry* 18, 320–331. doi: 10.1038/mp.2012.8

Braun, N., Lenz, C., Gillardon, F., Zimmermann, M., and Zimmermann, H. (1997). Focal cerebral ischemia enhances glial expression of ecto-5′-nucleotidase. *Brain Res.* 766, 213–226. doi: 10.1016/s0006-8993(97)00559-3

Brown, S. T., Reyes, E. P., and Nurse, C. A. (2011). Chronic hypoxia upregulates adenosine 2A receptor expression in chromaffin cells via hypoxia inducible factor-2alpha: role in modulating secretion. *Biochem. Biophys. Res. Commun.* 412, 466–472. doi: 10.1016/j.bbrc.2011.07.122

Buira, S. P., Dentesano, G., Albasanz, J. L., Moreno, J., Martín, M., Ferrer, I., et al. (2010). DNA methylation and Yin Yang-1 repress adenosine A_{2A} receptor levels in human brain. *J. Neurochem.* 115, 283–295. doi: 10.1111/j.1471-4159.2010.06928.x

Canas, P. M., Porciúncula, L. O., Cunha, G. M., Silva, C. G., Machado, N. J., Oliveira, J. M., et al. (2009). Adenosine A_{2A} receptor blockade prevents synaptotoxicity and memory dysfunction caused by beta-amyloid peptides via p38 mitogen-activated protein kinase pathway. *J. Neurosci.* 29, 14741–14751. doi: 10.1523/jneurosci.3728-09.2009

Canas, P. M., Porciúncula, L. O., Simões, A. P., Augusto, E., Silva, H. B., Machado, N. J., et al. (2018). Neuronal adenosine A_{2A} receptors are critical mediators of neurodegeneration triggered by convulsions. *eNeuro* 5:ENEURO.0385-18.2018. doi: 10.1523/ENEURO.0385-18.2018

Cao, X., Li, L. P., Wang, Q., Wu, Q., Hu, H. H., Zhang, M., et al. (2013). Astrocyte-derived ATP modulates depressive-like behaviors. *Nat. Med.* 19, 773–777. doi: 10.1038/nm.3162

Carmo, M., Gonçalves, F. Q., Canas, P. M., Oses, J. P., Fernandes, F. D., Duarte, F. V., et al. (2019). Enhanced ATP release and CD73-mediated adenosine formation sustain adenosine A_{2A} receptor over-activation in a rat model of Parkinson's disease. *Br. J. Pharmacol.* 176, 3666–3680. doi: 10.1111/bph.14771

Carvalho, K., Faivre, E., Pietrowski, M. J., Marques, X., Gomez-Murcia, V., Deleau, A., et al. (2019). Exacerbation of C1q dysregulation, synaptic loss and memory deficits in tau pathology linked to neuronal adenosine A_{2A} receptor. *Brain* 142, 3636–3654. doi: 10.1093/brain/awz288

Chen, J. F., and Pedata, F. (2008). Modulation of ischemic brain injury and neuroinflammation by adenosine A_{2A} receptors. *Curr. Pharm. Des.* 14, 1490–1499. doi: 10.2174/138161208784480126

Chen, J., and Cunha, R. A. (2020). The belated US FDA approval of the adenosine A_{2A} receptor antagonist istradefylline for treatment of Parkinson's disease. *Purinergic Signal.* 16, 167–174. doi: 10.1007/s11302-020-09694-2

Chiang, M. C., Lee, Y. C., Huang, C. L., and Chern, Y. (2005). cAMP-response element-binding protein contributes to suppression of the A_{2A} adenosine receptor promoter by mutant Huntingtin with expanded polyglutamine residues. *J. Biol. Chem.* 280, 14331–14340. doi: 10.1074/jbc.M413279200

Childs, E., Hohoff, C., Deckert, J., Xu, K., Badner, J., and de Wit, H. (2008). Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 33, 2791–2800. doi: 10.1038/npp.2008.17

Chu, S., Xiong, W., and Parkinson, F. E. (2014). Effect of ecto-5′-nucleotidase (eN) in astrocytes on adenosine and inosine formation. *Purinergic Signal.* 10, 603–609. doi: 10.1007/s11302-014-9421-8

Coelho, J. E., Alves, P., Canas, P. M., Valadas, J. S., Shmidt, T., Batalha, V. L., et al. (2014). Overexpression of adenosine A_{2A} receptors in rats: effects on depression, locomotion, and anxiety. *Front. Psychiatry* 5:67. doi: 10.3389/fpsyt.2014.00067

Cognato, G. P., Agostinho, P. M., Hockemeyer, J., Müller, C. E., Souza, D. O., and Cunha, R. A. (2010). Caffeine and an adenosine A_{2A} receptor antagonist prevent memory impairment and synaptotoxicity in adult rats triggered by a convulsive episode in early life. *J. Neurochem.* 112, 453–462. doi: 10.1111/j.1471-4159.2009.06465.x

Cornelis, M. C., El-Sohemy, A., and Campos, H. (2007). Genetic polymorphism of the adenosine A_{2A} receptor is associated with habitual caffeine consumption. *Am. J. Clin. Nutr.* 86, 240–244. doi: 10.1093/ajcn/86.1.240

Costenla, A. R., Diógenes, M. J., Canas, P. M., Rodrigues, R. J., Nogueira, C., Maroco, J., et al. (2011). Enhanced role of adenosine A_{2A} receptors in the modulation of LTP in the rat hippocampus upon ageing. *Eur. J. Neurosci.* 34, 12–21. doi: 10.1111/j.1460-9568.2011.07719.x

Crespo, M., León-Navarro, D. A., and Martín, M. (2018). Early-life hyperthermic seizures upregulate adenosine A_{2A} receptors in the cortex and promote depressive-like behavior in adult rats. *Epilepsy Behav.* 86, 173–178. doi: 10.1016/j.yebeh.2018.06.048

Cunha, R. A. (2001). Regulation of the ecto-nucleotidase pathway in rat hippocampal nerve terminals. *Neurochem. Res.* 26, 979–991. doi: 10.1023/a:1012392719601

Cunha, R. A. (2016). How does adenosine control neuronal dysfunction and neurodegeneration? *J. Neurochem.* 139, 1019–1055. doi: 10.1111/jnc.13724

Cunha, R. A., Constantino, M. C., Sebastião, A. M., and Ribeiro, J. A. (1995). Modification of A_1 and A_{2A} adenosine receptor binding in aged striatum, hippocampus and cortex of the rat. *Neuroreport* 6, 1583–1588. doi: 10.1097/00001756-199507310-00029

Deckert, J., Nöthen, M. M., Franke, P., Delmo, C., Fritze, J., Knapp, M., et al. (1998). Systematic mutation screening and association study of the A_1 and A_{2A} adenosine receptor genes in panic disorder suggest a contribution of the A_{2A} gene to the development of disease. *Mol. Psychiatry* 3, 81–85. doi: 10.1038/sj.mp.4000345

Dias, L., Lopes, C. R., Gonçalves, F. Q., Nunes, A., Pochmann, D., Machado, N. J., et al. (2021). Crosstalk between ATP-P2X7 and adenosine A_{2A} receptors controlling neuroinflammation in rats subject to repeated restraint stress. *Front. Cell. Neurosci.* 15:639322. doi: 10.3389/fncel.2021.639322

Domschke, K., Gajewska, A., Winter, B., Herrmann, M. J., Warrings, B., Muhlberger, A., et al. (2012). ADORA2A Gene variation, caffeine, and emotional processing: a multi-level interaction on startle reflex. *Neuropsychopharmacology* 37, 759–769. doi: 10.1038/npp.2011.253

Erblang, M., Drogou, C., Gomez-Merino, D., Metlaine, A., Boland, A., Deleuze, J. F., et al. (2019). The impact of genetic variations in *ADORA2A* in the association between caffeine consumption and sleep. *Genes* 10:1012. doi: 10.3390/genes10121021

Espinosa, J., Rocha, A., Nunes, F., Costa, M. S., Schein, V., Kazlauckas, V., et al. (2013). Caffeine consumption prevents memory impairment, neuronal damage, and adenosine A_{2A} receptors upregulation in the hippocampus of a rat model of sporadic dementia. *J. Alzheimers. Dis.* 34, 509–518. doi: 10.3233/JAD-111982

Faivre, E., Coelho, J. E., Zornbach, K., Malik, E., Baqi, Y., Schneider, M., et al. (2018). Beneficial effect of a selective adenosine A_{2A} receptor antagonist in the APPswe/PS1dE9 mouse model of Alzheimer's disease. *Front. Mol. Neurosci.* 11:235. doi: 10.3389/fnmol.2018.00235

Falconi, A., Bonito-Oliva, A., Di Bartolomeo, M., Massimini, M., Fattapposta, F., Locuratolo, N., et al. (2019). On the role of adenosine A_{2A} receptor gene transcriptional regulation in Parkinson's disease. *Front. Neurosci.* 13:683. doi: 10.3389/fnins.2019.00683

Fan, X., Chen, Y., Li, W., Xia, H., Liu, B., Guo, H., et al. (2020). Genetic polymorphism of ADORA2A is associated with the risk of epilepsy and predisposition to neurologic comorbidity in Chinese southern children. *Front. Neurosci.* 14:590605. doi: 10.3389/fnins.2020.590605

Faroqi, A. H., Lim, M. J., Kee, E. C., Lee, J. H., Burgess, J. D., Chen, R., et al. (2021). *In vivo* detection of extracellular adenosine triphosphate in a mouse model of traumatic brain injury. *J. Neurotrauma* 38, 655–664. doi: 10.1089/neu.2020.7226

Franco, R., Rivas-Santisteban, R., Reyes-Resina, I., and Navarro, G. (2020). The old and new visions of biased agonism through the prism of adenosine receptor signaling and receptor/receptor and receptor/protein interactions. *Front. Pharmacol.* 11:628601. doi: 10.3389/fphar.2020.628601

Freitag, C. M., Agelopoulos, K., Huy, E., Rothermundt, M., Krakowitzky, P., Meyer, J., et al. (2010). Adenosine A_{2A} receptor gene ADORA2A variants may increase autistic symptoms and anxiety in autism spectrum disorder. *Eur. Child Adolesc. Psychiatry* 19, 67–74. doi: 10.1007/s00787-009-0043-6

Gessi, S., Varani, K., Merighi, S., Ongini, E., and Borea, P. A. (2000). A_{2A} adenosine receptors in human peripheral blood cells. *Br. J. Pharmacol.* 129, 2–11. doi: 10.1038/sj.bjp.0703045

Gonçalves, F. Q., Lopes, J. P., Silva, H. B., Lemos, C., Silva, A. C., Gonçalves, N., et al. (2019). Synaptic and memory dysfunction in a beta-amyloid model of early Alzheimer's disease depends on increased formation of ATP-derived extracellular adenosine. *Neurobiol. Dis.* 132:104570. doi: 10.1016/j.nbd.2019.104570

Gonçalves, N., Simões, A. T., Cunha, R. A., and de Almeida, L. P. (2013). Caffeine and adenosine A_{2A} receptor inactivation decrease striatal neuropathology in a lentiviral-based model of Machado-Joseph disease. *Ann. Neurol.* 73, 655–666. doi: 10.1002/ana.23866

Hamilton, S. P., Slager, S. L., De Leon, A. B., Heiman, G. A., Klein, D. F., Hodge, S. E., et al. (2004). Evidence for genetic linkage between a polymorphism in the adenosine A_{2A} receptor and panic disorder. *Neuropsychopharmacology* 29, 558–565. doi: 10.1038/sj.npp.1300311

He, X., Chen, F., Zhang, Y., Gao, Q., Guan, Y., Wang, J., et al. (2020). Upregulation of adenosine A_{2A} receptor and downregulation of GLT1 is associated with neuronal cell death in Rasmussen's encephalitis. *Brain Pathol.* 30, 246–260. doi: 10.1111/bpa.12770

Heyn, J., Ledderose, C., Hinske, L. C., Limbeck, E., Mohnle, P., Lindner, H. A., et al. (2012). Adenosine A_{2A} receptor upregulation in human PMNs is controlled by miRNA-214, miRNA-15, and miRNA-16. *Shock* 37, 156–163. doi: 10.1097/SHK.0b013e31823f16bc

Hu, Q., Ren, X., Liu, Y., Li, Z., Zhang, L., Chen, X., et al. (2016). Aberrant adenosine A_{2A} receptor signaling contributes to neurodegeneration and cognitive impairments in a mouse model of synucleinopathy. *Exp. Neurol.* 283, 213–223. doi: 10.1016/j.expneurol.2016.05.040

Huin, V., Dhaenens, C.-M., Homa, M., Carvalho, K., Buée, L., and Sablonnière, B. (2019). Neurogenetics of the human adenosine receptor genes: genetic structures and involvement in brain diseases. *J. Caffeine Adenosine Res.* 9, 73–88. doi: 10.1089/caff.2019.0011

Ishibashi, K., Miura, Y., Wagatsuma, K., Toyohara, J., Ishiwata, K., and Ishii, K. (2018). Occupancy of adenosine A_{2A} receptors by istradefylline in patients with Parkinson's disease using ^{11}C-preladenant PET. *Neuropharmacology* 143, 106–112. doi: 10.1016/j.neuropharm.2018.09.036

Janik, P., Berdynski, M., Safranow, K., and Zekanowski, C. (2015). Association of ADORA1 rs2228079 and ADORA2A rs5751876 polymorphisms with Gilles de la Tourette syndrome in the Polish population. *PLoS One* 10:e0136754. doi: 10.1371/journal.pone.0136754

Kaster, M. P., Machado, N. J., Silva, H. B., Nunes, A., Ardais, A. P., Santana, M., et al. (2015). Caffeine acts through neuronal adenosine A_{2A} receptors to prevent mood and memory dysfunction triggered by chronic stress. *Proc. Natl. Acad. Sci. USA* 112, 7833–7838. doi: 10.1073/pnas.1423088112

Kobayashi, S., and Millhorn, D. E. (1999). Stimulation of expression for the adenosine A_{2A} receptor gene by hypoxia in PC12 cells. A potential role in cell protection. *J. Biol. Chem.* 274, 20358–20365. doi: 10.1074/jbc.274.29.20358

Koos, B. J., Kruger, L., and Murray, T. F. (1997). Source of extracellular brain adenosine during hypoxia in fetal sheep. *Brain Res.* 778, 439–442. doi: 10.1016/s0006-8993(97)01207-9

Kreth, S., Ledderose, C., Kaufmann, I., Groeger, G., and Thiel, M. (2008). Differential expression of 5′-UTR splice variants of the adenosine A_{2A} receptor gene in human granulocytes: identification, characterization, and functional impact on activation. *FASEB J.* 22, 3276–3286. doi: 10.1096/fj.07-101097

Laurent, C., Burnouf, S., Ferry, B., Batalha, V. L., Coelho, J. E., Baqi, Y., et al. (2016). A_{2A} adenosine receptor deletion is protective in a mouse model of Tauopathy. *Mol. Psychiatry* 21, 97–107. doi: 10.1038/mp.2015.115

Lee, C. F., Lai, H. L., Lee, Y. C., Chien, C. L., and Chern, Y. (2014). The A_{2A} adenosine receptor is a dual coding gene: a novel mechanism of gene usage and signal transduction. *J. Biol. Chem.* 289, 1257–1270. doi: 10.1074/jbc.M113.509059

Lee, Y. C., Chien, C. L., Sun, C. N., Huang, C. L., Huang, N. K., Chiang, M. C., et al. (2003a). Characterization of the rat A_{2A} adenosine receptor gene: a 4.8-kb promoter-proximal DNA fragment confers selective expression in the central nervous system. *Eur. J. Neurosci.* 18, 1786–1796. doi: 10.1046/j.1460-9568.2003.02907.x

Lee, Y. C., Lai, H. L., Sun, C. N., Chien, C. L., and Chern, Y. (2003b). Identification of nuclear factor 1 (NF1) as a transcriptional modulator of rat A_{2A} adenosine receptor. *Brain Res. Mol. Brain Res.* 111, 61–73. doi: 10.1016/s0169-328x(02)00670-8

Li, P., Rial, D., Canas, P. M., Yoo, J. H., Li, W., Zhou, X., et al. (2015). Optogenetic activation of intracellular adenosine A_{2A} receptor signaling in the hippocampus is sufficient to trigger CREB phosphorylation and impair memory. *Mol. Psychiatry* 20, 1339–1349. doi: 10.1038/mp.2015.43

Li, W., Dai, S., An, J., Xiong, R., Li, P., Chen, X., et al. (2009). Genetic inactivation of adenosine A_{2A} receptors attenuates acute traumatic brain injury in the mouse cortical impact model. *Exp. Neurol.* 215, 69–76. doi: 10.1016/j.expneurol.2008.09.012

Loy, B. D., O'Connor, P. J., Lindheimer, J. B., and Covert, S. F. (2015). Caffeine is ergogenic for adenosine A_{2A} receptor gene (ADORA2A) T allele homozygotes: a pilot study. *J. Caffeine Res.* 5, 73–81. doi: 10.1089/jcr.2014.0035

Machado, N. J., Simões, A. P., Silva, H. B., Ardais, A. P., Kaster, M. P., Garção, P., et al. (2017). Caffeine reverts memory but not mood impairment in a depression-prone mouse strain with up-regulated adenosine A_{2A} receptor in hippocampal glutamate synapses. *Mol. Neurobiol.* 54, 1552–1563. doi: 10.1007/s12035-016-9774-9

Madeira, M. H., Elvas, F., Boia, R., Gonçalves, F. Q., Cunha, R. A., Ambrósio, A. F., et al. (2015). Adenosine A_{2A}R blockade prevents neuroinflammation-induced death of retinal ganglion cells caused by elevated pressure. *J. Neuroinflammation* 12:115. doi: 10.1186/s12974-015-0333-5

Matos, M., Augusto, E., Machado, N. J., dos Santos-Rodrigues, A., Cunha, R. A., and Agostinho, P. (2012). Astrocytic adenosine A_{2A} receptors control the amyloid-beta peptide-induced decrease of glutamate uptake. *J. Alzheimers. Dis.* 31, 555–567. doi: 10.3233/JAD-2012-120469

Melani, A., Turchi, D., Vannucchi, M. G., Cipriani, S., Gianfriddo, M., and Pedata, F. (2005). ATP extracellular concentrations are increased in the rat striatum during in vivo ischemia. *Neurochem. Int.* 47, 442–448. doi: 10.1016/j.neuint.2005.05.014

Meng, F., Guo, Z., Hu, Y., Mai, W., Zhang, Z., Zhang, B., et al. (2019). CD73-derived adenosine controls inflammation and neurodegeneration by modulating dopamine signalling. *Brain* 142, 700–718. doi: 10.1093/brain/awy351

Merighi, S., Battistello, E., Casetta, I., Gragnaniello, D., Poloni, T. E., Medici, V., et al. (2021). Upregulation of cortical A_{2A} adenosine receptors is reflected in platelets of patients with Alzheimer's disease. *J. Alzheimers. Dis.* 80, 1105–1117. doi: 10.3233/jad-201437

Miao, J., Liu, L., Yan, C., Zhu, X., Fan, M., Yu, P., et al. (2019). Association between ADORA2A gene polymorphisms and schizophrenia in the North Chinese Han population. *Neuropsychiatr. Dis. Treat.* 15, 2451–2458. doi: 10.2147/NDT.S205014

Micioni Di Bonaventura, M. V., Pucci, M., Giusepponi, M. E., Romano, A., Lambertucci, C., Volpini, R., et al. (2019). Regulation of adenosine A_{2A} receptor

gene expression in a model of binge eating in the amygdaloid complex of female rats. *J. Psychopharmacol.* 33, 1550–1561. doi: 10.1177/0269881119845798

Mishina, M., Ishiwata, K., Naganawa, M., Kimura, Y., Kitamura, S., Suzuki, M., et al. (2011). Adenosine A_{2A} receptors measured with [^{11}C]TMSX PET in the striata of Parkinson's disease patients. *PLoS One* 6:e17338. doi: 10.1371/journal.pone.0017338

Moreira-de-Sá, A., Gonçalves, F. Q., Lopes, J. P., Silva, H. B., Tomé, A. R., Cunha, R. A., et al. (2020). Adenosine A_{2A} receptors format long-term depression and memory strategies in a mouse model of Angelman syndrome. *Neurobiol. Dis.* 146:105137. doi: 10.1016/j.nbd.2020.105137

Moreira-de-Sá, A., Gonçalves, F. Q., Lopes, J. P., Silva, H. B., Tomé, A. R., Cunha, R. A., et al. (2021). Motor deficits coupled to cerebellar and striatal alterations in Ube3a$^{m-/p+}$ mice modelling Angelman syndrome are attenuated by adenosine A_{2A} receptor blockade. *Mol. Neurobiol.* 58, 2543–2557. doi: 10.1007/s12035-020-02275-9

Morello, S., Ito, K., Yamamura, S., Lee, K. Y., Jazrawi, E., Desouza, P., et al. (2006). IL-1 beta and TNF-alpha regulation of the adenosine receptor A_{2A} expression: differential requirement for NF-kappa B binding to the proximal promoter. *J. Immunol.* 177, 7173–7183. doi: 10.4049/jimmunol.177.10.7173

Ng, S. K., Higashimori, H., Tolman, M., and Yang, Y. (2015). Suppression of adenosine 2A receptor (A_{2A}R)-mediated adenosine signaling improves disease phenotypes in a mouse model of amyotrophic lateral sclerosis. *Exp. Neurol.* 267, 115–122. doi: 10.1016/j.expneurol.2015.03.004

Nunes, R. A., Mazzotti, D. R., Hirotsu, C., Andersen, M. L., Tufik, S., and Bittencourt, L. (2017). The association between caffeine consumption and objective sleep variables is dependent on ADORA2A c.1083T>C genotypes. *Sleep Med.* 30, 210–215. doi: 10.1016/j.sleep.2016.06.038

Oliveira, S., Ardais, A. P., Bastos, C. R., Gazal, M., Jansen, K., de Mattos Souza, L., et al. (2019). Impact of genetic variations in ADORA2A gene on depression and symptoms: a cross-sectional population-based study. *Purinergic Signal.* 15, 37–44. doi: 10.1007/s11302-018-9635-2

Orr, A. G., Hsiao, E. C., Wang, M. M., Ho, K., Kim, D. H., Wang, X., et al. (2015). Astrocytic adenosine receptor A_{2A} and G_s-coupled signaling regulate memory. *Nat. Neurosci.* 18, 423–434. doi: 10.1038/nn.3930

Orr, A. G., Lo, I., Schumacher, H., Ho, K., Gill, M., Guo, W., et al. (2018). Istradefylline reduces memory deficits in aging mice with amyloid pathology. *Neurobiol. Dis.* 110, 29–36. doi: 10.1016/j.nbd.2017.10.014

Orrú, M., Quiroz, C., Guitart, X., and Ferré, S. (2011). Pharmacological evidence for different populations of postsynaptic adenosine A_{2A} receptors in the rat striatum. *Neuropharmacology* 61, 967–974. doi: 10.1016/j.neuropharm.2011.06.025

Padilla, K. M., Quintanar-Setephano, A., López-Vallejo, F., Berumen, L. C., Miledi, R., and Garcia-Alcocer, G. (2018). Behavioral changes induced through adenosine A_{2A} receptor ligands in a rat depression model induced by olfactory bulbectomy. *Brain Behav.* 8:e00952. doi: 10.1002/brb3.952

Pagnussat, N., Almeida, A. S., Marques, D. M., Nunes, F., Chenet, G. C., Botton, P. H., et al. (2015). Adenosine A_{2A} receptors are necessary and sufficient to trigger memory impairment in adult mice. *Br. J. Pharmacol.* 172, 3831–3845. doi: 10.1111/bph.13180

Patodia, S., Paradiso, B., Garcia, M., Ellis, M., Diehl, B., Thom, M., et al. (2020). Adenosine kinase and adenosine receptors A_1R and A_{2A}R in temporal lobe epilepsy and hippocampal sclerosis and association with risk factors for SUDEP. *Epilepsia* 61, 787–797. doi: 10.1111/epi.16487

Peterfreund, R. A., MacCollin, M., Gusella, J., and Fink, J. S. (1996). Characterization and expression of the human A_{2A} adenosine receptor gene. *J. Neurochem.* 66, 362–368. doi: 10.1046/j.1471-4159.1996.66010362.x

Popat, R. A., Van Den Eeden, S. K., Tanner, C. M., Kamel, F., Umbach, D. M., Marder, K., et al. (2011). Coffee, *ADORA2A*, and *CYP1A2*: the caffeine connection in Parkinson's disease. *Eur. J. Neurol.* 18, 756–765. doi: 10.1111/j.1468-1331.2011.03353.x

Rebola, N., Coelho, J. E., Costenla, A. R., Lopes, L. V., Parada, A., Oliveira, C. R., et al. (2003). Decrease of adenosine A_1 receptor density and of adenosine neuromodulation in the hippocampus of kindled rats. *Eur. J. Neurosci.* 18, 820–828. doi: 10.1046/j.1460-9568.2003.02815.x

Rebola, N., Porciúncula, L. O., Lopes, L. V., Oliveira, C. R., Soares-da-Silva, P., and Cunha, R. A. (2005). Long-term effect of convulsive behavior on the density of adenosine A_1 and A_{2A} receptors in the rat cerebral cortex. *Epilepsia* 46(Suppl. 5), 159–165. doi: 10.1111/j.1528-1167.2005.01026.x

Rei, N., Rombo, D. M., Ferreira, M. F., Baqi, Y., Müller, C. E., Ribeiro, J. A., et al. (2020). Hippocampal synaptic dysfunction in the SOD1(G93A) mouse model of Amyotrophic Lateral Sclerosis: Reversal by adenosine A_{2A}R blockade. *Neuropharmacology* 171:108106. doi: 10.1016/j.neuropharm.2020.108106

Rétey, J. V., Adam, M., Khatami, R., Luhmann, U. F., Jung, H. H., Berger, W., et al. (2007). A genetic variation in the adenosine A_{2A} receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin. Pharmacol. Ther.* 81, 692–698. doi: 10.1038/sj.clpt.6100102

Ribeiro, D. E., Roncalho, A. L., Glaser, T., Ulrich, H., Wegener, G., and Joca, S. (2019). P2X7 receptor signaling in stress and depression. *Int. J. Mol. Sci.* 20:2778. doi: 10.3390/ijms20112778

Rodrigues, R. J., Tomé, A. R., and Cunha, R. A. (2015). ATP as a multi-target danger signal in the brain. *Front. Neurosci.* 9:148. doi: 10.3389/fnins.2015.00148

Rogers, P. J., Hohoff, C., Heatherley, S. V., Mullings, E. L., Maxfield, P. J., Evershed, R. P., et al. (2010). Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. *Neuropsychopharmacology* 35, 1973–1983. doi: 10.1038/npp.2010.71

Schoen, S. W., and Kreutzberg, G. W. (1997). 5′-nucleotidase enzyme cytochemistry as a tool for revealing activated glial cells and malleable synapses in CNS development and regeneration. *Brain Res. Brain Res. Protoc.* 1, 33–43. doi: 10.1016/s1385-299x(96)00006-2

Schoen, S. W., Ebert, U., and Löscher, W. (1999). 5′-Nucleotidase activity of mossy fibers in the dentate gyrus of normal and epileptic rats. *Neuroscience* 93, 519–526. doi: 10.1016/s0306-4522(99)00135-9

Schwarzschild, M. A., Agnati, L., Fuxe, K., Chen, J. F., and Morelli, M. (2006). Targeting adenosine A_{2A} receptors in Parkinson's disease. *Trends Neurosci.* 29, 647–654. doi: 10.1016/j.tins.2006.09.004

Seven, Y. B., Simon, A. K., Sajjadi, E., Zwick, A., Satriotomo, I., and Mitchell, G. S. (2020). Adenosine A_{2A} receptor inhibition protects phrenic motor neurons from cell death induced by protein synthesis inhibition. *Exp. Neurol.* 323:113067. doi: 10.1016/j.expneurol.2019.113067

Shen, H. Y., Canas, P. M., Garcia-Sanz, P., Lan, J. Q., Boison, D., Moratalla, R., et al. (2013). Adenosine A_{2A} receptors in striatal glutamatergic terminals and GABAergic neurons oppositely modulate psychostimulant action and DARPP-32 phosphorylation. *PLoS One* 8:e80902. doi: 10.1371/journal.pone.0080902

Shen, H. Y., Coelho, J. E., Ohtsuka, N., Canas, P. M., Day, Y. J., Huang, Q. Y., et al. (2008). A critical role of the adenosine A_{2A} receptor in extrastriatal neurons in modulating psychomotor activity as revealed by opposite phenotypes of striatum and forebrain A_{2A} receptor knock-outs. *J. Neurosci.* 28, 2970–2975. doi: 10.1523/JNEUROSCI.5255-07.2008

Shinohara, M., Saitoh, M., Nishizawa, D., Ikeda, K., Hirose, S., Takanashi, J., et al. (2013). ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus. *Neurology* 80, 1571–1576. doi: 10.1212/WNL.0b013e31828f18d8

Silva, A. C., Lemos, C., Gonçalves, F. Q., Pliássova, A. V., Machado, N. J., Silva, H. B., et al. (2018). Blockade of adenosine A_{2A} receptors recovers early deficits of memory and plasticity in the triple transgenic mouse model of Alzheimer's disease. *Neurobiol. Dis.* 117, 72–81. doi: 10.1016/j.nbd.2018.05.024

Simões, A. P., Machado, N. J., Gonçalves, N., Kaster, M. P., Simões, A. T., Nunes, A., et al. (2016). Adenosine A_{2A} receptors in the amygdala control synaptic plasticity and contextual fear memory. *Neuropsychopharmacology* 41, 2862–2871. doi: 10.1038/npp.2016.98

Smith, M. D., Bhatt, D. P., Geiger, J. D., and Rosenberger, T. A. (2014). Acetate supplementation modulates brain adenosine metabolizing enzymes and adenosine A_{2A} receptor levels in rats subjected to neuroinflammation. *J. Neuroinflammation* 11:99. doi: 10.1186/1742-2094-11-99

Sun, M. J., Liu, F., Zhao, Y. F., and Wu, X. A. (2020). *In vivo* positron emission tomography imaging of adenosine A_{2A} receptors. *Front. Pharmacol.* 11:599857. doi: 10.3389/fphar.2020.599857

Svenningsson, P., Le Moine, C., Fisone, G., and Fredholm, B. B. (1999). Distribution, biochemistry and function of striatal adenosine A_{2A} receptors. *Prog. Neurobiol.* 59, 355–396. doi: 10.1016/s0301-0082(99)00011-8

Taherzadeh-Fard, E., Saft, C., Wieczorek, S., Epplen, J. T., and Arning, L. (2010). Age at onset in Huntington's disease: replication study on the associations of ADORA2A, HAP1 and OGG1. *Neurogenetics* 11, 435–439. doi: 10.1007/s10048-010-0248-3

Temido-Ferreira, M., Ferreira, D. G., Batalha, V. L., Marques-Morgado, I., Coelho, J. E., Pereira, P., et al. (2020). Age-related shift in LTD is dependent on neuronal adenosine A_{2A} receptors interplay with mGluR5 and NMDA receptors. *Mol. Psychiatry* 25, 1876–1900. doi: 10.1038/s41380-018-0110-9

Tescarollo, F. C., Rombo, D. M., DeLiberto, L. K., Fedele, D. E., Alharfoush, E., Tomé, A. R., et al. (2020). Role of adenosine in epilepsy and seizures. *J. Caffeine Adenosine Res.* 10, 45–60. doi: 10.1089/caff.2019.0022

Tian, T., Zhou, Y., Feng, X., Ye, S., Wang, H., Wu, W., et al. (2016). MicroRNA-16 is putatively involved in the NF-kappaB pathway regulation in ulcerative colitis through adenosine A_{2A} receptor (A_{2A}R) mRNA targeting. *Sci. Rep.* 6:30824. doi: 10.1038/srep30824

Viana da Silva, S., Haberl, M. G., Zhang, P., Bethge, P., Lemos, C., Gonçalves, N., et al. (2016). Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A_{2A} receptors. *Nat. Commun.* 7:11915. doi: 10.1038/ncomms11915

Villar-Menéndez, I., Porta, S., Buira, S. P., Pereira-Veiga, T., Díaz-Sánchez, S., Albasanz, J. L., et al. (2014). Increased striatal adenosine A_{2A} receptor levels is an early event in Parkinson's disease-related pathology and it is potentially regulated by miR-34b. *Neurobiol. Dis.* 69, 206–214.

Vincenzi, F., Corciulo, C., Targa, M., Casetta, I., Gentile, M., Granieri, E., et al. (2013). A_{2A} adenosine receptors are up-regulated in lymphocytes from amyotrophic lateral sclerosis patients. *Amyotroph. Lateral Scler. Frontotemporal Degener.* 14, 406–413. doi: 10.3109/21678421.2013.793358

Wei, C. J., Augusto, E., Gomes, C. A., Singer, P., Wang, Y., Boison, D., et al. (2014). Regulation of fear responses by striatal and extrastriatal adenosine A_{2A} receptors in forebrain. *Biol. Psychiatry* 75, 855–863. doi: 10.1016/j.biopsych.2013.05.003

Wieraszko, A., and Seyfried, T. N. (1989). Increased amount of extracellular ATP in stimulated hippocampal slices of seizure prone mice. *Neurosci. Lett.* 106, 287–293. doi: 10.1016/0304-3940(89)90178-x

Yu, L., Frith, M. C., Suzuki, Y., Peterfreund, R. A., Gearan, T., Sugano, S., et al. (2004). Characterization of genomic organization of the adenosine A_{2A} receptor gene by molecular and bioinformatics analyses. *Brain Res.* 1000, 156–173. doi: 10.1016/j.brainres.2003.11.072

Yu, L., Shen, H. Y., Coelho, J. E., Araújo, I. M., Huang, Q. Y., Day, Y. J., et al. (2008). Adenosine A_{2A} receptor antagonists exert motor and neuroprotective effects by distinct cellular mechanisms. *Ann. Neurol.* 63, 338–346. doi: 10.1002/ana.21313

Zhao, L., Liu, Y. W., Yang, T., Gan, L., Yang, N., Dai, S. S., et al. (2015). The mutual regulation between miR-214 and A_{2A}R signaling plays an important role in inflammatory response. *Cell Signal.* 27, 2026–2034. doi: 10.1016/j.cellsig.2015.07.007

Zhao, Z. A., Li, P., Ye, S. Y., Ning, Y. L., Wang, H., Peng, Y., et al. (2017). Perivascular AQP4 dysregulation in the hippocampal CA1 area after traumatic brain injury is alleviated by adenosine A_{2A} receptor inactivation. *Sci. Rep.* 7:2254. doi: 10.1038/s41598-017-02505-6

Zheng, F., Zhou, Y. T., Feng, D. D., Li, P. F., Tang, T., Luo, J. K., et al. (2020). Metabolomics analysis of the hippocampus in a rat model of traumatic brain injury during the acute phase. *Brain Behav.* 10:e01520. doi: 10.1002/brb3.1520

Conflict of Interest: RC is a scientific consultant for the Institute for Scientific Information on Coffee.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.