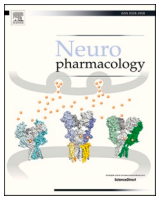
Neuropharmacology 236 (2023) 109600

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Adjusting the brakes to adjust neuronal activity: Adenosinergic modulation of GABAergic transmission

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A B S T R A C T

About 50 years elapsed from the publication of the first full paper on the neuromodulatory action of adenosine at a 'simple' synapse model, the neuromuscular junction (Ginsborg and Hirst, 1972). In that study adenosine was used as a tool to increase cyclic AMP and for the great surprise, it decreased rather than increased neurotransmitter release, and for a further surprise, its action was prevented by theophylline, at the time only known as inhibitor of phosphodiesterases. These intriguing observations opened the curiosity for immediate studies relating the action of adenine nucleotides, known to be released together with neurotransmitters, to that of adenosine (Ribeiro and Walker, 1973, 1975). Our understanding on the ways adenosine uses to modulate synapses, circuits, and brain activity, vastly expanded since then. However, except for A_{2A} receptors, whose actions upon GABAergic neurons of the striatum are well known, most of the attention given to the neuromodulatory action of adenosine has been focusing upon excitatory synapses. Evidence is growing that GABAergic transmission is also a target for adenosinergic neuromodulation through A_1 and A_{2A} receptors. Some o these actions have specific time windows during brain development, and others are selective for specific GABAergic neurons. Both tonic and phasic GABAergic transmission can be affected, and either neurons or astrocytes can be targeted. In some cases, those effects result from a concerted action with other neuromodulators. Implications of these actions in the control of neuronal function/dysfunction will be the focus of this review.

1. Introduction

Adenosine is widely known as a homeostatic molecule. Most of its homeostatic actions are mediated through membrane located G-protein coupled receptors. Four adenosine receptor (R) subtypes are known, A_1R, $A_{2A}R$, $A_{2B}R$ and A_3R (Sebastiao and Ribeiro, 2009). The A_1R and $A_{2A}R$ have high affinity for adenosine, being activated by physiological concentrations (low micromolar) of extracellular adenosine, while the $A_{2B}R$ has lower affinity for adenosine (Fredholm, 2007) being usually regarded as a receptor that in the nervous system mainly operates under pathological conditions (Coppi et al., 2020). The affinity of the A_3R is species dependent, being lower in rodents than in man, the species differences being likely related to the low homology among A_3R in different species (Gao et al., 2022). In the nervous system, the most known action of adenosine is feedback inhibition of neuronal excitability, doing so through A_1 receptors (A_1R) mostly siting in glutamatergic nerve terminals, as well as in the nerve terminals of other excitatory neurotransmitters. For the other subtype of high affinity adenosine receptors, the A_{2A} receptor ($A_{2A}R$), the most studied action is the ability to reinforce the inhibitory pathway from the basal ganglia to the cortex. This action of $A_{2A}R$ results from three main mechanisms all centred in the striatopallidal GABAergic neurons of the indirect pathway, which express $A_{2A}R$ and dopamine D_2 receptors (D_2R): 1) facilitation of the glutamatergic inputs from the cortex (through pre-synaptic receptors in glutamatergic nerve terminals, which interact with A_1R in glutamatergic nerve terminals), 2) inhibition of the inhibitory action of dopaminergic D_2Rs, and 3) direct facilitation of GABA release (through pre-synaptic receptors in the GABAergic nerve terminals) (Schwarzschild et al., 2006; Ferré et al., 2023; Borroto-Escuela et al., 2021).

In pathologic situations, adenosine-mediated homeostasis is often disrupted due to changes in adenosine receptor expression. In early stages, those changes may represent a last effort to re-establish control of neuronal activity through compensatory processes: however, they ultimately turn into an exacerbation of the pathologic state. This seems to be the case of neurodegenerative diseases, where an initial

Abbreviations: GABA, γ-aminobutyric acid; IPSCs, inhibitory postsynaptic currents; mIPSCs, miniature postsynaptic currents; EPSCs, excitatory postsynaptic currents; KCC2, potassium chloride cotransporter 2; GAT, GABA transporter; CCK, cholecystokinin; SST, somatostatin; NTS, *nucleus tractus solitarius*; TMN, tuberomammillary; VLPO, ventrolateral preoptic nucleus; CB1, cannabinoid receptor type 1; PKC, protein kinase type C; PKA, protein kinase type A; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; AC, adenylate cyclase.

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https://doi.org/10.1016/j.neuropharm.2023.109600
Received 7 February 2023; Received in revised form 20 April 2023; Accepted 16 May 2023
Available online 22 May 2023
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overexpression of facilitatory A_{2A}Rs occurs in brain areas where they have a low expression, as in the forebrain. In such a way adenosine A_{2A}Rs may be compensatory of reduced neuronal activity but at expenses of exacerbated excitotoxicity, thus neurodegeneration. Opposite changes in A_1R function, or at least of their ability to reduce A_{2A}R activity may also occur, which further contribute to homeostatic disregulation in disease conditions. This leads to a general assumption that adenosine A_{2A}Rs are mostly devoted to exacerbate neuronal death. However, as now known, adenosine A_{2A}Rs play relevant roles to promote the actions of neurotrophins. Even more recently, it become clear that adenosine A_{2A}Rs play highly important roles in the maturation of GABAergic neurons during very early stages of neuronal development, an issue that we will further discuss in this review.

Being adenosine A_1Rs inhibitory, it would be expected that their

Table 1
A1R modulation of GABAergic transmission.

Brain area	Methodological details	Type of effect	Notes	Ref
Hippocampus	slices; electrophysiology	No effect on IPSCs or mIPSCs in either I-E or I–I synapses	No effect on phasic GABAergic input to either excitatory (I-E synapses) or inhibitory (I–I synapses) neurons	Kamiya (1991); Lambert and Teyler, 1991; Yoon and Rothman (1991); Rombo et al., 2016
Hippocampus	[^{3}H]GABA release from sinaptosomes	No effect on K^+-evoked GABA release	Effect by A_{2A}R agonist	Cunha and Ribeiro (2000)
Hippocampus	slices, electrophysiology	Reduces tonic inhibition of a CB1/CCK$^+$ interneurons	disinhibition of interneurons; likely, control of neuronal gain	Rombo et al. (2016a)
Hippocampus or cortex	cultured immature neurons, electrophysiology	decreased mIPSCs frequency	effect detected up to P15 but not P30 neurons, suggesting that presynaptic inhibition of phasic GABAergic transmission at the forebrain occurs only in the developmental stage where GABA is depolarizing	Jeong et al., 2003; Kirmse et al. (2008)
Hippocampus	[^{3}H]GABA release from sinaptosomes	Modulation of the action of VIP or cannabinoids upon GABA release	Interaction between A1R and other neuromodulators	Cunha-Reis et al. (2008); Sousa et al. (2011)
Hippocampus	Slices, electrophysiology	Reciprocal interactions between A_1R and $GABA_A$Rs to affect excitatory transmission	Inhibition of A_1R actions by endogenous GABA; inhibition of $GABA_A$R actions by endogenous adenosine (A1R)	Lucchi et al. (1996); Fragata et al. (2006);
Entorhinal cortex (EC)	slices, electrophysiology	Decrease in frequency of mIPSCs	decrease of GABAergic input to the main output from the EC to the hippocampus	Li et al. (2011)
Lateral amygdala	slices; electrophysiology	Decrease in IPSCs	likely presynaptic effect	Heinbockel and Pape (1999)
Visual cortex	slices, electrophysiology	Reduces the long-lasting decrease of IPSCs in pyramidal neurons caused by intense stimulation of SST$^+$ interneurons (I-E synapses)	post-synaptic facilitation of phasic GABAergic currents (IPSCs), counteraction the inhibition caused by somatostatin; astrocytes are involved	Henriques et al. (2022)
Cortex or hippocampus	slices, electrophysiology; synaptoneurosomes; membranes	Modulation of $GABA_A$R function or density	Both facilitation and inhibition has been reported; A1Ragonists as well as caffeine actions also reported	Lopez et al. (1989); Concas et al. (1993); Shi et al. (1993); Akhondzadeh and Stone (1994)
Cortex	GABA uptake; astrocytes	Inhibition of GAT1- and GAT3-mediated GABA transport	Heteromerization between A_1R and A_{2A}Rs to exert a dual control; no effect in isolated nerve endings	Cristóvão-Ferreira et al. (2009); Cristóvão-Ferreira et al. (2013)
Cerebellum	slices, electrophysiology	Inhibition of both phasic and tonic components of GABAergic transmission	Effect mainly presynaptic and leading to increase of excitability of granule cells	Courjaret et al. (2009)
Cerebellum	isolated membranes	Interaction between A_1R and $GABA_B$ receptors	Non-additivity; competition for transducing system	Wojcik et al., 1985
Basal ganglia	in vivo microdialysis; slices; electrophysiology	inhibition of the D_1R-mediated action on GABAergic neurons	Endogenous adenosine is able to blunt D_1R-mediated actions upon GABAergic neurons	Ferré et al. (1996), Mayfield et al. (1999); Mango et al. (2014); Badimon et al. (2020)
Basal ganglia; thalamus	slices; electrophysiology	Presynaptic inhibition of GABAergic inputs to the *subthalamic nucleus*, to the *substantia nigra reticulata* and to the thalamus	GABAergic synapses at both the direct and indirect pathway are affected	Shen and Johnson, 1997; Ulrich and Huguenard (1995); Centonze et al. (2001)
Basal ganglia	slices, GABA uptake	Inhibition of GAT-1 mediated GABA transport	Endogenous adenosine is effective	Kubrusly et al. (2021)
Hypothalamus	slices, electrophysiology	decreased mIPSCs frequency	GABAergic inputs to tuberomammillary, hypocretin, ventrolateral preoptic, supraoptic nucleus and paraventricular nucleus, suprachiasmatic nucleus neurons of the hypothalamus and midbrain periaqueductal grey neurons	Oliet and Poulain. (1999); Chen and van den Pol (1997); Bagley et al. (1999); Morairty et al. (2004); Yum et al. (2008); Han et al. (2011); Xia et al., 2012
Retina	[^{14}C]GABA release	No effect on K^+-evoked GABA release	Effect upon [^{3}H]acetylcholine release	Santos et al. (2000)
Retina	[3H]GABA release	Inhibition of GAT1 mediated release	NMDA receptor triggered release, mediated by reversal of GABA transporter; caffeine is active; impact in retinal development	Ferreira et al. (2014); Borges-Martins et al. (2019)
Retina	prenatal exposure to caffeine or selective A1R antagonist during critical period of synaptogenesis	modulation of the expression of the chloride co-transporter KCC2	caffeine is protective; effect involving A_1R, likely due to upregulation; delayed developmental shift of GABAergic signalling	Pereira-Figueiredo et al. (2020)

Abbreviations – IPSCs: inhibitory postsynaptic currents; mIPSCs: miniature inhibitory postsynaptic currents; CB1/CCK$^+$: immunopositive for cannabinoid type 1 receptors and cholecystokinin; VIP: vasoactive intestinal peptide; SST: somatostatin; GAT: GABA transporter.

main action would be inhibition of excitatory neurons. Inhibition of the release of excitatory neurotransmitters, was indeed, the first known action of adenosine upon neuronal activity, highlighted in seminal papers showing inhibition of the release of acetylcholine at the neuromuscular junction (Ginsborg and Hirst, 1972; Ribeiro and Walker, 1975) and ileum (Gustafsson et al., 1978). Mimicry of the action of adenosine by ATP, known to be released together with acetylcholine at the neuromuscular junction, was also soon reported (Ribeiro and Walker, 1973). In what concerns the central nervous system, the first known actions of A_1Rs were also over glutamatergic excitatory neurons in the forebrain (Dunwiddie and Fredholm, 1984). Shortly after, it was shown that adenosine A_1Rs in the hippocampus do not exert direct inhibitory actions in GABAergic nerve terminals (Kamiya, 1991; Lambert and Teyler, 1991; Yoon and Rothman, 1991). This led to some overstatements that adenosine A_1Rs are absent in GABAergic neurons. Though being clear that adenosine A_1Rs in hippocampal GABAergic nerve terminals do not inhibit GABA release, as we will herein detail, they do interact with other neuromodulators to control the release of this inhibitory neurotransmitter. Furthermore, even at the hippocampus A_1Rs affect tonic inhibition of a subpopulation of GABAergic neurons, likely by interacting with extrasynaptic $GABA_A$ receptors ($GABA_A$Rs); Rombo et al. (2016a). In addition, adenosine A_1Rs inhibit GABA uptake by astrocytes, which may further contribute to an enhancement of tonic inhibition (Cristóvão-Ferreira et al., 2013). Lastly, in other areas of the central nervous system, as the spinal cord, the cerebellum and even the basal ganglia, adenosine A_1Rs do affect GABAergic transmission. In this review, we will highlight some of these actions of adenosine that have been matter of less attention. A few reviews focusing the actions of adenosine upon GABAergic transmission already appeared (Sebastião et al., 2015; Rombo et al., 2016b, 2018). Therefore, in the present paper we will update the existing information while also briefly referring to previously existing one. We will also mention the influence of A_{2A}Rs but leave out the influence of the neuromodulatory actions of A_{2A}Rs upon GABAergic transmission in the basal ganglia since this matter has been recently reviewed (Schwarzschild et al., 2006; Ferré et al., 2023 Borroto-Escuela et al., 2021). Information on A_3 adenosine receptors (A_3Rs) to control excitability is scarce (see Rombo et al., 2018) and even scarcer in what concerns modulation of GABAergic transmission by these receptors. A_3R-mediated control of GABAergic transmission may prove relevant to fight neuropathic pain (Ford et al., 2015) and we will also refer to it while briefly addressing the adenosinergic control of GABAergic function in disease conditions.

In Table 1 and 2 we put together in a very summarized way available information on the neuromodulatory action of A_1R and A_{2A}R upon GABAergic transmission, to allow comparison in different areas and methodologies. More detailed information can be found throughout the text.

2. Modulation by A_1 receptors

2.1. Forebrain

Early evidence for an action of A_1Rs upon GABA release was provided while showing that the selective activation of A_1Rs resulted in an inhibition of ischaemia-evoked GABA release in vivo, an action surprisingly also shared by agonists of A_{2A}Rs (O'Regan et al., 1992). One year later, another study reported absence of effect of locally perfused adenosine A_1R agonists upon veratridine or hypoxia-induced GABA release, while glutamate release was affected by similar treatment (Heron et al., 1993). Modifications of GABA release in situations where glutamatergic transmission is operative are of difficult interpretation since GABAergic neurons in the forebrain are interneurons. Therefore, direct actions on GABAergic nerve terminals from disynaptic changes through modification of glutamatergic inputs to GABAergic neurons are

Table 2
A2AR modulation of GABAergic transmission.

Brain area	Methodological details	Type of effect	Notes	Ref
Cortex	in vivo; electrophysiology	inhibition of neuronal firing	Blockade of the actions of the A_{2A}R agonist upon blockade of GABAergic transmission	Phillis (1998)
Cortex	astrocytes	Facilitation of GAT1- and GAT3-mediated GABA transport; gating of the facilitatory action of BDNF upon GAT1 trafficking	involvement of A_1R-A_{2A}R-A_1R-A_{2A}R tetramers	Vaz et al. (2011); Crisóvão-Ferreira et al. (2013)
Hippocampus	[^{3}H]GABA release from sinaptosomes	Enhancement of K^+-evoked GABA release	No effect of A_1R agonist	Cunha and Ribeiro (2000)
Hippocampus	slices, electrophysiology	Facilitation of GABAergic inputs from PV^+ interneurons to other interneurons, but not to pyramidal neurons. Promotes synchronous pyramidal cell firing under hyperexcitable conditions	highly selective synapse- and cell type specific influence of adenosine A_{2A}Rs at the hippocampus.	Rombo et al. (2015)
Hippocampus	synaptosomes	Facilitation of GAT1-mediated GABA transport	involvement of AC/cAMP/PKA to restrain inhibition by PKC	Cristóvão-Ferreira et al. (2009)
Hippocampus	prenatal exposure to caffeine or selective A_{2A}R agonist	Delayed migration and insertion of GABAergic neurons into the hippocampal circuitry during the first postnatal week	Offspring: increased neuronal network excitability and increased susceptibility to seizures in response to a seizure-inducing agent; cognitive deficits	Silva et al. (2013)
Hippocampus	Cultured neurones, electrophysiology	A_{2A}R activation is necessary and sufficient to stabilize GABAergic synapses even in the absence of $GABA_A$R signalling	A_{2A}Rs regulate elimination of inactive GABAergic synapses; Ca2+-calmodulin-dependent AC is involved	Gomez-Castro et al. (2021)
Hypothalamus	*ex vivo* slices, electrophysiology; in vivo, microdialysis	Enhanced firing rate of type-2 VLPO GABAergic neurones (*ex vivo*); increased GABA release in the TMN (in vivo)	postsynaptic action; highly selective cell type action (type-1 neurons not affected); increase in histamine release in MPO	Gallopin et al. (2005); Hong et al. (2005)
Brainsteam	in vivo; A_{2A}R agonist injected in NTS or 4th ventricle; CCR reflexes; phrenic activity; respiratory frequency	Inhibition of CCR reactivity; inhibition of centrally-controlled respiration	Blockade of A_{2A}R actions upon blockade of GABAergic transmission, thus compatible with A_{2A}R-mediated facilitation of GABAergic neuron activity	Minic et al. (2015); Wilson et al. (2004); Mayer et al. (2006); Duy et al. (2010)

Abbreviations – GAT: GABA transporter; BDNF: brain derived neurotrophic factor; PV: parvalbumin; VLPO: ventrolateral preoptic nucleus; TMN: tuberomammillary; NTS: *nucleus tractus solitarius*, CCR: cardiopulmonary chemoreflex; MPO: medial preoptic area.

hard to distinguish. In isolated hippocampal nerve terminals, A_1R agonists used in selective concentrations were devoid of effect upon GABA release (Cunha and Ribeiro, 2000).

Electrophysiological approaches also clearly reported absence of influence of adenosine A_1Rs upon GABAergic transmission (Kamiya, 1991; Lambert and Teyler, 1991; Yoon and Rothman, 1991). In all cases, adenosine was devoid of effect upon fast inhibitory postsynaptic currents (IPSCs), but inhibited excitatory postsynaptic currents (EPSCs). A_1R activation was also shown to be devoid of effect on spontaneous synaptic inhibitory inputs to either pyramidal glutamatergic neurons (I-E synapses) or GABAergic interneurons (I–I synapses), as assessed by recording mISPCs from both cell types in hippocampal slices in the presence of sodium channel and glutamate receptor blockers (Rombo et al., 2016).

Summarizing, in interneurons from the hippocampus phasic GABAergic transmission is resistant to A_1R-mediated inhibition (Kamiya, 1991; Lambert and Teyler, 1991; Yoon and Rothman, 1991; Rombo et al., 2016a). However, phasic GABAergic transmission to neurons that project into the hippocampus, as is the case of GABAergic inputs to stellate neurons, can be affected by presynaptic and post-synaptic A_1Rs (Li et al., 2011). Neuronal responsiveness in the amygdala is largely controlled by inhibitory processes, which are also presynaptically downregulated by adenosine A_1R activation (Heinbockel and Pape, 1999).

Though not directly influencing GABA release from hippocampal interneurons, adenosine A_1Rs are, however, likely present in their nerve terminals. Indeed, manipulation of A_1R activity affects the action of other neuromodulators, as vasoactive intestinal peptide (VIP) (Cunha-Reis et al., 2008) or cannabinoids (Sousa et al., 2011) upon GABA release. As we will detail below, A_1Rs might also be present in the soma of interneurons to affect tonic inhibition of a subset of interneurons (Rombo et al., 2016).

In the visual cortex, under condition of intense neuronal activity, adenosine A_1Rs postsynaptically upregulate phasic GABAergic transmission between somatostatin (SST)-expressing GABAergic neurons and pyramidal neurons (Henriques et al., 2022). Interestingly, such a mechanism involves the interplay with astrocytes, who respond to GABA released from SST interneurons upon intense stimulation. Released GABA activates $GABA_B$ receptors ($GABA_BRs$) in the astrocytes, with subsequent elevation of intracellular calcium, release of ATP and extracellular formation of adenosine that then, through A_1Rs, facilitates $GABA_AR$ activation in pyramidal neurons, and in such a way likely counterbalancing the inhibition of pyramidal neurons by released somatostatin (Henriques et al., 2022).

While phasic GABAergic transmission provides fast inhibitory inputs to the postsynaptic neuron, synchronically with the arrival of an action potential to the nerve ending, tonic GABAergic inhibition provides a sustained inhibitory tonus over the postsynaptic neuron. For this reason, tonic inhibition is a target of several anti-seizure medications. Adenosine A_1R activation reduce tonic inhibition of a subset of interneurons (Rombo et al., 2016a), the CB1/CCK (cholecystokinin) expressing interneurons (Fig. 1), which are involved in synchronous network oscillations (Klausberger et al., 2005). This may confer to adenosine an important modulatory action on hippocampal network oscillations that are the critical bases for hippocampal-dependent behaviour and cognitive processes. As discussed elsewhere (Semyanov et al., 2004), a selective action upon tonic inhibition without affecting phasic inhibition may also promote the control of neuronal gain without disrupting fidelity of synaptic GABAergic inhibition, which may prove relevant in the context of the role of A_1R in epilepsy.

The influence of A_1Rs upon tonic inhibition of hippocampal neurons is not restricted to the CB1/CCK expressing neurons, since A_1Rs also reduce tonic inhibition in pyramidal hippocampal neurons, as well as cause a global decrease in the expression of $GABA_AR$ δ-subunit (Rombo et al., 2016a), a key component of extrasynaptic receptors mediating tonic GABAergic currents. A decrease in tonic inhibition by adenosine A_1Rs may seem at odds with the anticonvulsant properties of adenosine. However, tonic GABAergic inhibition is more pronounced in interneurons than in pyramidal cells (Bai et al., 2001; Semyanov et al., 2003). Therefore, A_1Rs, by reducing tonic inhibition of interneurons, are

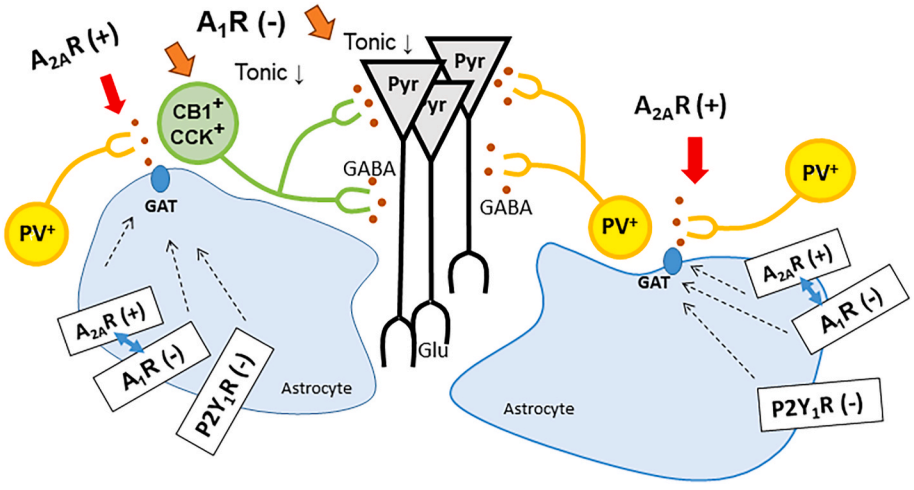

Fig. 1. Multiple points where A_1R and $A_{2A}R$ can interfere with GABAergic transmission in the hippocampus. Through A_1R adenosine inhibits tonic GABAergic inhibition upon CB1/CCK-positive interneurons (represented in green), thus disinhibiting these interneurons, therefore likely promoting their capacity to enhance greater inhibition of pyramidal neurons (represented in grey). A_1Rs also inhibit tonic inhibition of pyramidal neurons, but since tonic inhibition over these neurons is less intense that in GABAergic neurons, the disinhibition of CB1/CCK-positive interneurons likely prevails (see text and Rombo et al., 2016a for details and further discussion). Through $A_{2A}Rs$, adenosine enhances phasic GABAergic inputs to PV-positive interneurons, therefore inhibiting them and likely disinhibiting pyramidal neurons (see text and Rombo et al., 2015 for details and further discussion). At astrocytes, A_1R inhibit GABA uptake, therefore likely increasing the accessibility of GABA to extrasynaptic GABAergic receptors and as such promoting network inhibition. An opposite action is operated by $A_{2A}Rs$ that facilitate GABA uptake in astrocytes thus contributing to a reduction in GABA levels at the tripartite synapse. A_1Rs and $A_{2A}Rs$ heteromerize in astrocytes allowing a reciprocal control of GABA transport likely as a function of the levels of extracellular adenosine, which on the other hand, depends on the degree of neuronal activity, since it is known that high frequency of neuronal firing favour $A_{2A}R$ activation (see Cristóvão-Ferreira et al., 2013 for details and further discussion). $A_{2A}Rs$ also facilitate GABA uptake in nerve endings (not represented; see Cristóvão-Ferreira et al., 2009 and text above). ATP P2YR inhibit GABA transport in astrocytes (Jacob et al., 2014), therefore likely counteracting the action of $A_{2A}R$ under conditions of ATP release due to intense neuronal firing. Abbreviations: $CB1^+$: immunoreactive for cannabinoid receptor type 1 antibody; CCK^+: immunoreactive for cholecystokinin antibody; PV^+: immunoreactive for parvalbumin antibody; Pyr: pyramidal neuron; Glu: glutamate; GABA: Gama-aminobutyric acid; GAT: GABA transporter; $P2Y_1R$: peptide Y type 1 receptor; A_1R: adenosine A_1 receptor; $A_{2A}R$: adenosine A_{2A} receptor; (−): inhibition; (+): facilitation; tonic↓: tonic GABAergic current, the arrow pointing towards pyramidal or GABAergic neurons. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

disinhibiting them, and likely increasing inhibitory GABAergic signals to the hippocampal excitatory neurons, a mechanism that may contribute to the well-known anticonvulsant action of adenosine, whereas the decrease in tonic inhibition of pyramidal cells may avoid excessive inhibition of hippocampal output signalling.

A_1R-mediated decreases GABA-coupled chloride channel function (Concas et al., 1993) has also been shown to occur, and this may also seem at odds with the anti-seizure action of adenosine. However, one should keep in mind that control of $GABA_A$R activity may be particularly relevant during seizures, where GABAergic responses transiently switch from hyperpolarizing to depolarizing, therefore likely contributing to seizure progression. During seizures, the A_1R-dependent activation of potassium channels also has a shunting effect on $GABA_A$R-mediated currents, which could limit seizure activity (Concas et al., 1993). It is also important to highlight, however, that a positive interaction between adenosine and a $GABA_A$R agonist, through a mechanism also involving chloride channels in hippocampal neurons, was also reported (Akhondzadeh and Stone, 1994). The exact conditions and detailed mechanisms through which A_1Rs may facilitate or reduce chloride permeability of $GABA_A$Rs are yet unsolved. Also unknown is the nature of the $GABA_A$Rs (synaptic vs extrasynaptic) affected. It may happen that in some cells or circumstances (pathologic vs physiologic) A_1Rs reduce expression of extrasynaptic $GABA_A$Rs and/or chloride permeability (Concas et al., 1993), whereas in other conditions act synergistically with $GABA_A$R ligands to promote chloride influx (Akhondzadeh and Stone, 1994). Whether the facilitatory action of A_1Rs upon phasic GABAergic inputs from SST-expressing neurons to pyramidal neurons of the visual cortex (Henriques et al., 2022) involve alterations in $GABA_A$R permeability or in receptor number, is also unknown. Interestingly, $GABA_A$R number may also be affected by endogenous adenosine since chronic caffeine has been shown to alter the density of cortical benzodiazepine binding sites associated with $GABA_A$Rs (Shi et al., 1993), as it alters the density of A_1Rs but not A_{2A}Rs (Shi et al., 1993). Another study reported caffeine-induced changes in Cl channel binding sites but not of benzodiazepine binding sites (Lopez et al., 1989). Data on caffeine effects has to be interpreted with caution since chronic and acute caffeine effects may differ; the dose/concentration, the brain area and adenosine receptor involved also influence the final outcome of caffeine administration (Ribeiro and Sebastião, 2010).

Tonic inhibition by GABA is affected not only by changes in the number or properties of extrasynaptic $GABA_A$Rs, but also by the concentration of ambient GABA for which GABA transporters (GATs) have a determinant role. As such, modulation of GAT activity has important implications for the control of epilepsy (Conti et al., 2004; Schousboe et al., 2004). Indeed, seizure occurrence is in many cases effectively controlled by inhibitors GATs, which enhance extracellular GABA levels, prolong its inhibitory action and allow its spillover towards extrasynaptic sites, thus the availability of ambient GABA for extrasynaptic receptors, keeping neurons in a more hyperpolarized state. Adenosine A_1R activation did not affect the activity of the predominant GABA transporter in the nerve endings, GAT1 (Cristóvão-Ferreira et al., 2009), but inhibited GAT1 and GAT3 activity in astrocytes (Cristóvão-Ferreira et al., 2013). Absence of effect in nerve endings may leave unaffected fast replenishment of GABAergic vesicles in nerve terminals, whereas inhibition of astrocytic GATs may contribute to sustained neuronal hyperpolarization. GABA transport in nerve endings is, however affected by another family of purinergic receptors, those that respond to ATP, since activation of P2X7 receptors inhibit GAT activity through a mechanism that involve disruption of the sodium gradient required for GABA transport (Barros-Barbosa et al., 2015). ATP receptors in astrocytes, in this case the $P2Y_1$ receptor, also inhibit GAT activity through a similar mechanism (Jacob et al., 2014).

Hypoxia and ischaemia are well known triggers for adenosine release. The post-synaptic enhancement of inhibitory synaptic transmission that occurs in CA1 neurons for several hours after forebrain ischaemia in vivo involve activation of A_1Rs (Liang et al., 2009), a mechanism that may contribute to protect synapses from early excitotoxicity, thus adding to others that promote functional recovery after the insult (Sebastião et al., 2001). Interestingly, some redundancy between adenosine and GABA may exist to control excitatory synaptic transmission during hypoxia. Thus, a GABAergic contribution to the depression of synaptic transmission caused by hypoxia, can only be revealed when A_1R are blocked (Lucchi et al., 1996). A_1R-mediated disconnection of interneurons by adenosine released during hypoxia (Khazipov et al., 1995) may be involved, suggesting a higher sensitivity of E-I synapses than E-E synapses in what concerns the A_1R radiated control of glutamate release. On the other hand, endogenous GABA may also exert an inhibitory control over adenosine A_1R-mediated responses in the hippocampus (Fragata et al., 2006), which may represent an interrelated physiologic regulatory mechanism between the two inhibitory mediators.

Finally, one should consider differences between mature and immature neurons, since the influence of adenosine A_1Rs upon GABAergic transmission, in particular GABA release from immature or mature neurons may differ considerably. Thus, in immature neurons presynaptic A_1Rs affect GABA release probability, therefore likely affecting phasic GABAergic transmission, in clear contrast with what occurs in mature neurons. Indeed, in mechanically dissociated neurons from the hippocampus of P12-15 rats, but not from P30 rats, A_1R activation decreased the frequency of mIPSCs recorded in the presence of glutamate receptor blockers and tetrodotoxin (Jeong et al., 2003), thus precluding indirect actions through inhibition of excitatory inputs to GABAergic neurons. A presynaptic influence upon GABA release by endogenous A_1R activation has also been detected in neocortical layer I P5-7 neurons (Kirmse et al., 2008), a developmental stage where GABAergic activity can depolarize pyramidal neurons. This suggests that A_1R activation leads to reduced GABAergic excitatory drive to lower cortical layers, and consequently affecting neurodevelopmental regulation of excitatory glutamatergic synapse formation during a critical period of synaptogenesis.

2.2. Cerebellum

In the cerebellar network, A_1R activation, known to decrease the excitatory output of granule cells, also increases their excitability by reducing their GABAergic input; this A_1R action results both from presynaptic inhibition of phasic GABAergic inputs to granule cells, as well as from reduction of tonic GABAergic inhibition of granule cells (Courjaret et al., 2009). This ability of pre-synaptic A_1Rs to decrease GABA release in cerebellar neurons is in clear contrast with what occurs at the hippocampus (see above). Also contrasting with what has been reported to occur in the cortex (Shi et al., 1993), chronic caffeine does not alter the number of benzodiazepine binding sites in cerebellar membranes though markedly altering the number of adenosine receptor binding sites, likely of A_1R binding sites (Marangos et al., 1984),

Interestingly, adenosine A_1Rs and $GABA_B$Rs reciprocally compete for a limited number of adenylate cyclase catalytic units, and therefore the action of both receptors, if activated together, is non-addictive (Wojcik et al., 1985). On the other hand, adenosine release seems to be under control of $GABA_B$R activation (Klyuch et al., 2012). Interestingly A_1Rs at the cerebellum also inhibit adenosine release (Klyuch et al., 2012), suggesting that adenosine receptors can control the release of their ligand. A similar autocontrol of release occurs at the hippocampus (Pinto-Duarte et al., 2005) and at chromaffin cells (Delicado et al., 1990), but these cases are mediated by A_{2A}Rs.

2.3. Basal ganglia

Though most of the available information on purinergic modulation of basal ganglia activity is related to A_{2A}R function, adenosine A_1Rs also affect basal ganglia function, an action that does not only result from inhibition of the glutamatergic inputs to the striatum, but also from

interactions with D_1R signalling in medium spiny GABAergic neurons of the direct pathway, where A_1R and D_1R are co-localized. A_1Rs inhibit the facilitatory action of D_1Rs upon GABA release, an action detected both in dorsal (Ferré et al., 1996) and ventral (Mayfield et al., 1999) areas of the basal ganglia. That A_1Rs blunt dopamine D_1R-mediated facilitation of GABAergic inputs to *substantia nigra reticulata* neurons was also noticed several years ago (Mango et al., 2014). The antagonistic interaction between A_1R and D_1Rs in the basal ganglia may also occur through D_1R-A_1R heteromerization (Cortés et al., 2019) as well as at the level of the transducing system, since A_1Rs are negatively coupled and D_1R are positively coupled to adenylate cyclase. A relevant A_1R/D_1R antagonistic interaction that involves the cyclic AMP/PKA pathway and an orchestrated homeostatic cross-talk between neuronal excitability, microglia, A_1R and D_1R in GABAergic striatal neurons has been recently reported (Badimon et al., 2020). Enhanced excitability leads to release of ATP, activation of $P2Y_{12}$ receptors in microglia, enhanced expression of ectoenzymes at the microglia membrane to catabolize ATP into adenosine, enhanced activation of A1Rs colocalized with D1Rs in medium spiny GABAergic neurons, and a consequent decrease of the facilitatory action of D_1R activity in these neurons (Badimon et al., 2020). The lower activity of striatopallidal GABAergic neurons, allows enhanced activity of GABAergic neurons of the *globus pallidus internus* and *substantia nigra reticulata* neurons, thus enhanced inhibition of thalamic neurons with consequent decrease in the excitatory drive from the thalamus to the cortex. Indeed, this A_1R-mediated suppressive effect of microglia upon D_1R activity has a relevant role in the control of synchrony and firing frequency of striatal neurons (Badimon et al., 2020). Neuroinflammatory conditions, result in microglia inability to promote catabolism of ATP into adenosine, and thus to exacerbation of D1R-mediated responses, with increased susceptibility to D_1R agonist-induced seizures (Badimon et al., 2020). An antioscillatory action of adenosine, associated to a presynaptic A_1R-mediated suppression of inhibitory inputs to the thalamus has also been reported several years ago (Ulrich and Huguenard, 1995).

A presynaptic inhibition of the GABAergic inputs to the *substantia nigra reticulata* neurons has also been reported (Shen and Johnson, 1997), suggesting that besides the D_1R/A_1R interactions, A_1Rs are also likely present in the nerve endings of the D_1R/dynorphin-positive GABAergic neurons of the direct pathway (striatopallidal neurons). A_1Rs also might be present in the indirect pathway to promote presynaptic inhibition of both GABAergic and glutamatergic inputs to subthalamic nucleus neurons (Shen and Johnson, 2003).

Early presynaptic depression of IPSCs caused by oxygen/glucose deprivation in striatal slices results from adenosine release and activation of A_1Rs, thus suggestive of an ability to depress GABA release from striatal GABAergic nerve terminals (Centonze et al., 2001). Again, this is in clear contrast with the hippocampus where monosynaptic IPSCs are more resistant to hypoxia and to presynaptic modulation by adenosine A_1Rs (Goda et al., 1998).

GAT1–mediated GABA transport at the striatum is up-regulated by caffeine, an action reverted by A_1R agonists, suggesting that GABA transport is under control by adenosine A_1Rs, which may prove relevant under pathological conditions involving deficient GAT1 activity (Kubrusly et al., 2021).

2.4. Hypothalamus and midbrain

One of the most widely experienced action of caffeine is interference with sleep and, as well known, this is due to its ability to block both A_1R and A_2R, both being expressed in sleep controlling areas. As recently proposed, $A_{2A}Rs$ may provide sleep gating, allowing the brain to sleep, while the main function of A_1Rs is likely to modulate sleep function (Lazarus et al., 2019). Some of these modulatory actions occur through the control of GABAergic inputs to different types the hypothalamic neurons. Activation of presynaptic A_1R has been shown to decrease spontaneous GABAergic transmission onto tuberomammillary neurons (TMN) of the hypothalamus (Yum et al., 2008). As discussed (Yum et al., 2008), such an action would likely contribute to disinhibition of TMN neurons, therefore to arousal. This may suggest that inhibitory A1Rs in GABAergic terminals that project to TMN neurons is to prevent over-inhibition of TMN neurons, thus fine-tuning the sleep-wakefulness cycle (Yum et al., 2008). Functional adenosine A_1Rs are also present in GABAergic nerve terminals projecting to hypothalamic hypocretin neurons, which again, was interpreted as a mechanism to prevent over-inhibition of hypocretin neurons and as such to finely-tune sleep (Xia et al., 2012). Disinhibition of sleep promoting neurons of the ventrolateral preoptic area of the hypothalamus by presynaptic A_1R located in GABAergic neurons has also been reported (Morairty et al., 2004).

Adenosine, via A_1R, inhibits synaptic GABAergic inputs to the cell body of magnocellular cells located at supraoptic nucleus of the hypothalamus (Oliet and Poulain, 1999), thus with a likely impact upon hormone secretion and fluid homeostasis since magnocellular neurons of the hypothalamus project to neurohypophysis.

Presynaptic A_1Rs inhibit phasic GABAergic inputs to neurons of the paraventricular nucleus of the hypothalamus (Han et al., 2011) and to midbrain periaqueductal grey neurons (Bagley et al., 1999), in line with evidence that adenosine, through control of GABAergic transmission, acts as an important neuromodulator of the centrally mediated cardiovascular regulation (Thomas, and Spyer, 1999).

In cultured neurons of the arcuate nucleus and of the suprachiasmatic nucleus of the hypothalamus, the centre for control of mammalian circadian rhythms, adenosine inhibits synaptic GABA release, an action that may involve not only A_1R but also $A_{2A}R$ (Chen and van den Pol, 1997).

2.5. Retina

As in the hippocampus, in retinal neurons the exocytotic release of GABA does not seem to be directly affected by A_1R activation (Santos et al., 2000). A_1Rs may however inhibit GABA release mediated by reversal of the GABA transporters since A_1R antagonists and caffeine potentiate GAT1 mediated GABA release (Ferreira et al., 2014). Interestingly acute and chronic caffeine may have opposite effects upon GABA transport, the acute being due to A_1R blockade and the chronic action being related to upregulation of retinal A_1Rs, which have impact in retinal development (Ferreira et al., 2014; Borges-Martins et al., 2019).

Interestingly, A_1Rs may modulate the developmental shift of GABAergic transmission since exposure to caffeine during the synaptogenesis period of the retina, decreased the expression of the chloride cotransporter KCC2, an action mediated by A_1Rs and not $A_{2A}Rs$ (Pereira-Figueiredo et al., 2020). A delay in the developmental shift of GABAergic transmission may favour membrane depolarization and NMDA receptor activity and calcium signalling. As mentioned below, in forebrain immature neurons, $A_{2A}Rs$ and $GABA_ARs$ converge to increase intracellular calcium and stabilize GABAergic synapses (Gomez-Castro et al., 2021). Weather A_1R and $A_{2A}R$ may converge to control neuronal network stabilization in the retina deserves further analysis.

3. Modulation by A_{2A} receptors

The modulatory action of adenosine $A_{2A}Rs$ upon dopaminergic D_2R inputs to striatal-pallidal GABAergic medium spiny neurons is one of the most known actions of adenosine $A_{2A}Rs$. The physiologic and pathophysiologic implications of that action have been matter of several recent reviews (Ferré, 2016; Borroto-Escuela et al., 2021) and therefore, will not be addressed here. It is also well known that $A_{2A}Rs$ can heteromerize with other receptors, namely with D_2Rs and A_1Rs and as such control inputs to GABAergic striatal neurons. This has also been a matter of very recent reviews (Franco et al., 2021; Ferré et al., 2023) and thus, not discussed here too.

3.1. Forebrain

Early evidence for a relevant facilitatory action of A_{2A}Rs upon GABAergic transmission was provided by John Phillis, who showed that an A_{2A}R-mediated inhibitory action on spontaneous neuronal firing in vivo was prevented upon blockade of $GABA_A$Rs (Phillis, 1998). This clearly suggested that the predominant action of A_{2A}R in the cerebral cortex was over GABAergic rather than glutamatergic transmission. By using isolated nerve terminals of the rat hippocampus, it was also shown that A_{2A}R activation facilitates evoked GABA release, while selective concentrations of an A_1R agonist were devoid of effect upon GABA release (Cunha and Ribeiro, 2000). More recently (Rombo et al., 2015), evidence has been provided for the presence of adenosine A_{2A}Rs in a subpopulation of hippocampal interneurons, the parvalbumin positive (PV^+) neurons (Fig. 1), presynaptically facilitating GABAergic inputs to other interneurons and, in such a way, contributing to disinhibition of pyramidal neurons. Interestingly, A_{2A}Rs do not affect GABAergic inputs to excitatory neurons, as they also do not influence glutamatergic inputs to GABAergic neurons (Rombo et al., 2015) but, as expected, A_{2A}R enhance glutamatergic inputs to glutamatergic neurons (Rombo et al., 2015). Importantly, PV^+ neurons are responsible for hippocampal network synchronization (Cobb et al., 1995). Altogether, the highly selective synapse- and cell type specific influence of adenosine A_{2A}Rs at the hippocampus, suggests an influence of these adenosine receptors upon synchronous pyramidal cell firing in hyperexcitable conditions. Accordingly, an A_{2A}R antagonist suppresses spontaneous firing in an *ex vivo* model of epilepsy (Rombo et al., 2015).

GABA transport into nerve endings is facilitated by A_{2A}R, through a mechanism that involves activation of the adenylate cyclase/cAMP/PKA transducing pathway to restrain inhibition of GAT1 by PKC (Cristóvão-Ferreira et al., 2009). In astrocytes, A_{2A}Rs also facilitate GABA uptake (Cristóvão-Ferreira et al., 2013) and gate the facilitatory action of brain-derived neurotrophic (BDNF) upon GAT1 mediated GABA transport (Vaz et al., 2011). Interestingly, A_{2A}R and A_1R in the astrocytes form A_1R-A_{2A}R-A_1R-A_{2A}R tetramers, so that blockade of one of the protomers reciprocally prevents the ability the other to affect uptake (Cristóvão-Ferreira et al., 2013). This regulation of GABA transport in astrocytes through A_1R-A_{2A}R-A_1R-A_{2A}R tetramers operate via G_s and $G_{i/0}$ to either enhance (A_{2A}R) or inhibit (A_1R) GABA uptake. Inhibition requires lower adenosine concentrations, but slight increases in concentration are enough to engage an opposite modulation of GABA uptake (Cristóvão-Ferreira et al., 2013), highly suggestive that subtle changes in the levels of extracellular adenosine at the tripartite synapse, which may finely affect tonic GABAergic inhibition and thus network excitability. One may thus speculate that A_1R-A_{2A}R-A_1R-A_{2A}R tetramers in astrocytes, by regulating GABA transport, behave as dual amplifiers, facilitating excitation at intense astrocytic to neuronal signalling (due to A_{2A}R-mediated decreases of extracellular GABA), and increasing inhibition at low neuronal firing rates (due to increases in extracellular GABA). Importantly, however, overstimulation of just one of the protomers leads to internalization of the whole complex (Cristóvão-Ferreira et al., 2013) and in such a way likely avoiding sudden switching from excitation to inhibition that could occur if only of the receptors would be internalized. The main advantage of heteromerization may well be to act in a concerted way to modulate neuronal function.

In contrast to what occurs in the hippocampus (Cristóvão-Ferreira et al., 2009, 2013), in slices of the rat *globus pallidus* GAT1-mediated GABA transport is inhibited by adenosine A_{2A}R activation, and interestingly, this also occurs through a PKA-dependent mechanism (Gonzalez et al., 2006). Whether GABA transporters are regulated by PKA-mediated phosphorylation in opposite ways in the hippocampus and in the *globus pallidus* remains to be determined.

3.2. Hypothalamus, midbrain and brainsteam

GABAergic innervation from the ventrolateral preoptic nucleus (VLPO) to the TMN histaminergic neurons plays pivotal roles in the regulation of sleep-wakefulness (Sherin et al., 1998). As mentioned above, A_1R decreases spontaneous GABAergic transmission onto TMN neurons, an action that may contribute to fine-tune control of the sleep-wakefulness cycle. In contrast, A_{2A}Rs postsynaptically stimulate a subpopulation of VLPO GABAergic neurons, the type-2 neurons, mostly involved in sleep promotion (Gallopin et al., 2005). In freely moving rats, application of an A_{2A}R agonist, CGS 21680, to the subarachnoid space underlying the rostral basal forebrain significantly promoted sleep and inhibited histamine release in the frontal cortex and pre-optic area (Hong et al., 2005). Importantly, CGS 21680 increased GABA release specifically in the histaminergic TNM neurons, as well as increased histamine release in the medial preoptic area (MPO) (Hong et al., 2005). These actions are compatible with the *ex vivo* finding that A_{2A}Rs stimulate GABAergic VLPO neurons that project into histaminergic TMN neurons (Gallopin et al., 2005). Altogether, these studies show that one of the mechanisms through which A_{2A}Rs promote sleep is by enhancing GABA-mediated inhibition of the wakefulness-promoting histaminergic neurons at the level of the hypothalamus.

In the *nucleus tractus solitarius* (NTS), both A_1R and A_{2A}R subtypes attenuate cardiopulmonary chemoreflex (CCR), sympathoinhibition of renal, adrenal, and lumbar sympathetic nerve activity and attenuate reflex decreases in arterial pressure and heart rate (Spyer and Thomas, 2000; Burnstock, 2007). While A_1Rs operate through a glutamatergic mechanism, the inhibition of the CCR that results from activation of A_{2A}Rs in the NTS involves a GABAergic mechanism, with a dominant role of $GABA_A$ compared with $GABA_B$Rs (Minic et al., 2015).

A_{2A}R mRNAs are present in GABAergic neurons of brainstem areas involved in the central control of respiration, including bulbospinal GABAergic neurons projecting to the phrenic motor nuclei (Zaidi et al., 2006). During early development, adenosine promotes respiratory depression and contributes to recurrent apnea, an action that results from an interaction with GABAergic circuits since it is abolished upon blockade of GABAergic transmission (Wilson et al., 2004). In infant (14–16 days after birth), but not in adult rats, the intracerebroventricular injection of an A_{2A}R agonist decreases the respiratory drive, an action prevented by prior $GABA_A$R blockade (Mayer et al., 2006), thus also suggesting that adenosine A_{2A}Rs affect GABAergic neurons to centrally control respiration. A_{2A}R-mediated amplification of GABAergic mechanisms in the nucleus *tractus solitarius* with implications for reflex respiratory control has also been demonstrated (Duy et al., 2010). Interestingly, adenosine, through excitatory A_{2A}R and A_{2B}R located at the carotid body, mediate an increase in carotid sinus nerve firing frequency and an increase in the respiratory drive in response to hypoxia and hypercapnia (McQueen and Ribeiro, 1983, 1986; Conde et al., 2006, 2009; Livermore and Nurse, 2013; Sacramento et al., 2018), but the involvement of GABAergic transmission in these facilitatory actions of adenosine on the carotid body is unknown.

3.3. Modulation of GABAergic neuronal maturation

Dysfunction of GABAergic signalling and in particular in the maturation of GABAergic synapses, leads to severe neurodevelopmental diseases, which may express as drug-resistant forms of epilepsy, cognitive impairment and, often, mental retardation or even premature death (Trinchero et al., 2021; Virtanen et al., 2021). In offspring of dams treated with an A_{2A}R antagonist or caffeine, there is a delay in the migration and insertion of GABAergic neurons into the hippocampal circuitry during the first postnatal week (Silva et al., 2013), which suggests that A_{2A}Rs play a role in the migration of GABAergic neurons. Delayed maturation of GABAergic neurons is related to alterations in the relative expression of NKCC1 and KCC2 chloride transporters (Ben-Ari, 2014; Szymanski and Minichiello, 2022). Prenatal administration of caffeine, through upregulation of A_1Rs, decreases the expression of KCC2 and delays maturation of GABAergic retinal neurones with impact in retinal development (Pereira-Figueiredo et al., 2020). Whether A_{2A}R

also control the expression of chloride transporters remains to be studied.

An elegant and detailed study (Gomez-Castro et al., 2021) recently showed that the loss of GABAergic synapses due to neuronal inactivity could be prevented by $A_{2A}R$ activation and importantly, that $A_{2A}R$ activation proved sufficient to stabilize GABAergic synapses even in the absence of $GABA_AR$ signalling. Therefore, as highlighted in a commentary (Sebastião, 2022), $A_{2A}R$ play a maestro role in GABAergic synapses stabilization. That $A_{2A}R$ expression in different brain areas is not constant during brain development is known for a long time (Weaver, 1993), but interestingly, their expression is particularly high at the time window of GABAergic synapse maturation (Gomez-Castro et al., 2021). The convergence of $GABA_AR$ and A $_{2A}R$ pathways on the stabilization of GABAergic synapses relies on the rises of intracellular calcium, Ca^{2+}-calmodulin dependent activation of adenylate cyclase and cAMP production (Gomes-Castro el al, 2021), which in immature neurons is favoured by the depolarizing action of $GABA_ARs$ (Ben-Ari, 2014).

Interfering with $A_{2A}Rs$ *in utero* or in vivo during the peak of the postnatal synaptogenesis not only led impaired migration of GABAergic neurons and loss of GABAergic synapses, but also has long term consequences, as behavioural impairment during adulthood (Silva et al., 2013; Gomez-Castro et al., 2021). However, blockade of $A_{2A}R$ during development likely affects in other types of neurons, than just in GABAergic synapses, since $A_{2A}Rs$ play a role in synaptic plasticity, even in young animals (Dias et al., 2013; Mouro et al., 2018; Martins et al., 2020), facilitate synaptic actions of neurotrophins in glutamatergic as well as in GABAergic transmission (Diógenes et al., 2004; Fontinha et al., 2008; Colino-Oliveira et al., 2016) and facilitate neurotrophin-mediated increases in cell proliferation and neuronal differentiation (Ribeiro et al., 2021). Dysregulation of adenosine-neurotrophin interactions during neurodevelopmental stages leads to brain dysfunction and epilepsy (Diógenes et al., 2014; Sandau et al., 2016). Adenosine, through $A_{2A}R$, promotes neurogenesis (Ribeiro et al., 2021), axonal polarization (Alçada-Morais et al., 2021), axonal elongation (Ribeiro et al., 2016a) neuronal migration (Silva et al., 2013; Alçada-Morais et al., 2021), as well as synaptic pruning (Nadal et al., 2016a, 2016b). Altogether these findings indicate that one of the most relevant physiological roles for $A_{2A}R$ occurs very early in life, in clear contrast with what is known to occur upon aging, where $A_{2A}R$ are clearly involved in neurodegeneration by exacerbating excitotoxicity (Ribeiro et al., 2016b). As highlighted (Sebastião, 2022), the biological basis for the 'angel-to-demon' shift played by $A_{2A}R$ throughout life is largely unknown, but time windows and interplay with specific proteins at critical time points is likely involved.

4. Adenosine and GABA under disease conditions

Among the most well-known actions of adenosine under abnormal brain conditions are during seizures, ischaemia and pain control. In all these, GABA also plays a role, and evidence for convergence among them do exist.

Activation of adenosine A_1R restrains seizure-like activity in the hippocampus, not only due to its well-known inhibitory actions upon glutamatergic signalling (Etherington and Frenguelli, 2004; Fedele et al., 2006; Li et al., 2007), but also by directly influencing GABAergic transmission (Concas et al., 1993). The finding that adenosine was not effective to restrain bicuculline-induced seizures, while being effective against seizures induced by a non-$GABA_AR$ agonist lead to the proposal that allosteric modification upon the $GABA_AR$ could be involved, at least in part, in the action of adenosine A_1R agonists to control hiperexcitability (Petersen, 1991). Indeed, some authors document an interference of adenosine analogues on $GABA_AR$ number and binding properties (Skolnick et al., 1980; Davies, 1985).

During seizure activity, when $GABA_AR$ responses transiently switch from hyperpolarizing to depolarizing and excitatory, activation of A_1R by endogenously released adenosine efficiently attenuates $GABA_AR$-mediated depolarization (Ilie et al., 2012). This results from A_1R-dependent activation of K^+ channels that increases membrane conductance and shunts the GABA-mediated excitatory drive (Ilie et al., 2012). The inhibition of GABA-mediated depolarizing responses by A_1R restrain excitability during the seizure event period, likely leaving synaptic inhibition functional after neuronal recovery, when GABA-mediated hyperpolarization is again of value. A_1R activation also supresses the high frequency oscillations recorded when disrupting tonic inhibitory inputs from enthorinal cortex to hippocampus (Ortiz and Gutiérrez, 2015). These results strongly suggest that A_1Rs exert a strong control of the GABAergic circuitry during epileptiform activity. As mentioned above, A_1R-mediated disinhibition of interneurons by affecting tonic inhibition and extrasynaptic $GABA_AR$ expression (Rombo et al., 2016a) as well as by inhibition of GATs in astrocytes (Cristóvão-Ferreira et al., 2013) may also contribute to the anti-seizure action of adenosine.

The technique of membrane microtransplantation of *Xenopus oocytes* with resected tissue has been proving as a very useful tool of investigation in the field of neurophysiology. It allows testing access changes in neurotransmitter responses due to pathologic states and even comparing changes in animal models of disease with those detected in diseased human tissue from autopsies or surgeries in quantities that would not permit other kind of functional studies (Ruffolo et al., 2020). Endogenous adenosine increases frequency-dependent $GABA_A$ currents rundown, thus likely, $GABA_AR$ instability (Roseti et al., 2008). These actions were confirmed in rodent as well as in human epileptic tissue and it was shown that the complete blockade of adenosine receptors is able to reduce $GABA_AR$ rundown and improve the receptor stability (Roseti et al., 2008). These actions are mostly mediated by $A_{2A}R$, and not influenced by A_1R manipulation. Both $A_{2B}R$ and A_3R are also involved in the control of $GABA_AR$ stability and act in the opposite direction of $A_{2A}R$ but with much less physiological relevance (Roseti et al., 2008, 2009). Interestingly, an increase of the extracellular levels of adenosine through reduced expression of adenosine kinase leads to increased rundown of $GABA_AR$ currents upon repetitive stimulation, an action mimicked by a selective $A_{2A}R$ agonist (Diógenes et al., 2014). Overactivation of $A_{2A}Rs$ due to prolonged adenosine overload may also promote epileptogenesis by promoting dysfunctional plasticity and circuit rewiring due to $A_{2A}R$-mediated gating of BDNF actions (Diógenes et al., 2014). As mentioned above, disinhibiton of pyramidal neurons by facilitating GABAergic inputs from PV^+ GABAergic neurons towards other interneurons (Rombo et al., 2015), in conjunction with a facilitatory action upon GAT activity (Cristóvão-Ferreira et al., 2009; 2013) may also contribute to the pro-convulsant action of $A_{2A}Rs$ (Rombo et al., 2015). Together, these data suggest that the putative therapeutic use of adenosine based therapies for the control of epileptiform activity (Świąder et al., 2014; Boison, 2016; Vezzani et al., 2022) may benefit from a simultaneous inhibition of $A_{2A}Rs$ with consequent reduction of $GABA_AR$ instability, maladaptative BDNF signalling and neuronal hyperexcitation (Roseti et al., 2008; Shinohara et al., 2013; Diógenes et al., 2014; Rombo et al., 2015; Sandau et al., 2016). Recent evidence also showed that $A_{2A}R$ contribute to epilepsy-related mousy fibre sprouting, most likely through the reactivation of the ability of $A_{2A}R$ to control axon formation/outgrowth (Xu et al., 2022).

The levels of extracellular adenosine increase in low oxygen or glucose supply circumstances (Frenguelli et al., 2007; Martín et al., 2007). Under these conditions adenosine reduces neuronal damage and prevents excitotoxicity (Pedata et al., 2016; Ribeiro et al., 2016b), thus facilitating synaptic recovery (Johansson et al., 2001; Sebastião et al., 2001). Although most of the changes in neuronal activity that occur after an ischemic insult result from the enhancement of glutamate release leading excitotoxicity, alterations in GABAergic transmission also occur, which may contribute to neuronal death. Four hours after a transient ischaemic episode, it was detected a postsynaptically-mediated decrease in phasic GABAergic inputs to pyramidal neurons (but not to interneurons) (Zhan et al., 2006), thus likely contributing to

hyperexcitability during reperfusion. Interestingly, 12 h after transient ischaemia, there is an increase in GABAergic currents, which is prevented by blockade of adenosine A_1Rs (Liang et al., 2009). It is worthwhile to note that *during* an hypoxic episode, A_1R activation may mask $GABA_A$R-mediated responses (Lucchi et al., 1996). One may thus speculate that during an ischaemic or hypoxic insult, adenosine may be more relevant than GABA to protect from excitotoxicity, likely due to a disconnection of the GABAergic interneurons from their excitatory inputs (Lucchi et al., 1996). Early after reoxigenation, A_1Rs (Lee et al., 1986) and pyramidal $GABA_A$Rs (Zhan et al., 2006) are downregulated, this being thus a period where promoting GABAergic transmission may be relevant. Indeed, diazepam, given shortly after ischaemia, but not immediately after the acute insult (Sternau et al., 1989) has neuroprotective actions (Schwartz et al., 1995). Later during reoxigenation, A_1R activation by released adenosine boosts GABAergic responses by a yet unknown mechanism, and may afford additional neuroprotection. On the other hand, benzodiazepines inhibit adenosine transporters and potentiate the inhibitory action of adenosine at synapses (Phillis et al., 1981; De Mendonça and Ribeiro, 1989), which may further contribute to their neuroprotective actions.

Angelman syndrome (AS) is a neurogenetic disorder involving ataxia and motor dysfunction and synaptic alterations that include upregulation of vesicular GABA transporters in the cerebellum and its down regulation in the striatum. Notably, these alterations as well as motor dysfunction and striatal synaptic dysfunction were attenuated by chronic administration of an A_{2A}R antagonist (Moreira-de-Sá et al., 2021), suggesting a relevant influence of A_{2A}Rs in the pathophysiology of AS. The molecular and cellular mechanisms involved in it certainly deserves further attention.

GABAergic transmission in the spinal cord plays a major role in nociception and pain processing mechanisms. Adenosine is also known as an antinociceptive molecule (Sawynok et al., 1990; Sawynok, 2007), an action that involve, besides other mechanisms (Shaw et al., 2020), A_1Rs located at peripheral, spinal, and supraspinal sites (Vincenzi et al., 2020). Convergence between the action of adenosine A_1Rs and GABA to induce antinoception was early identified (Sabetkasai and Zarrindast, 1993). This interaction not only impacts upon pain processing but also likely upon synaptic plasticity during overstimulation, thus, sensitization of pain pathways (Hu and Li, 1997). Indeed, convergent and activity-dependent inhibition of GABA release by A_1R and $GABA_B$ autoreceptors have been shown to occur in dorsal horn neurons of the spinal cord, suggestive of a modulation of the integrative properties of these neurons under physiological conditions and/or during the development of pathological pain states (Hugel and Schlichter, 2003). GABAergic and glycinergic transmission in *substantia gelatinosa* neurons is suppressed by activation of presynaptic A_1R, an action that may also contribute to the modulation of pain transmission (Yang et al., 2004). Visceral pain may also be modulated by A_1Rs that postsynaptically suppress GABA-induced Cl^- currents in neurons from the sacral dorsal commissural nucleus of the spinal cord (Li et al., 2004). Similar post-synaptic actions of A_1R have been detected in the superficial laminae (laminae I and II) of the rat spinal dorsal horn (Wu et al., 2003). Adenosine A_1Rs also exert a modulatory effect on the GABA-induced presynaptic inhibition in primary sensory transmission (Hu and Li, 1997).

Adenosine A_3AR agonists reduce spinal cord pain processing producing selective alleviation of persistent neuropathic pain states (Little et al., 2015). Interestingly, A_3Rs do so by enhancing GABA bioavailability within the synaptic cleft as a consequence of inhibition of GAT activity, while also enhancing GABAergic efficacy by potentiating the activity of the chloride transporter, KCC2 (Ford et al., 2015), which extrudes chloride to the extracellular space, thus contributing to a more negative equilibrium potential for GABA. Due to the absence of influence of A_3Rs on the cardiovascular system, the use of A_3R agonists against neuropathic pain represent a unique opportunity to take advantage of two important inhibitory pain pathways, adenosine and GABA, without side effects that are usually associated while trying to modulate each of these pathways with drugs so far available.

5. Concluding remarks

Several years ago, we (Sebastiao and Ribeiro, 2009) pointed out that "*In addition to its direct pre- and post-synaptic actions on neurones, adenosine is rich in nuances of priming, triggering and inhibiting the action of several neurotransmitters and neuromodulators* (…) *The harmonic way adenosine builds its influence at synapses to control neuronal communication is operated through fine-tuning, 'synchronizing' or 'desynchronizing' receptor activation* …". Adenosine is known to play a crucial role to the effects of deep brain stimulation (Bekar et al., 2008), which mainly aims to affect neuronal synchronization and therefore influence several psychiatric and neurodegenerative diseases. Indeed, adenosine is known to control the release and actions of many synaptic mediators from neurons and glial cells. As highlighted in this review, it also does so by interplaying with GABAergic system, which has a pivotal role in the primary generation of high-frequency oscillations and local synchronization, regulating the strength of glutamatergic connections (see e.g. Uhlhaas and Singer, 2006). Abnormal neural synchronization is central for several neurological diseases, including neurodevelopmental ones as well those that appear throughout the lifespan or that are more related to ageing (e.g. epilepsy, schizophrenia, autism, Alzheimer's, and Parkinson's diseases). Being adenosine also involved in those diseases, the understanding of its ability to crosstalk with the GABAergic signalling offers novel opportunities to the development of novel safe, selective, and effective therapeutics that may target ARs or adenosine levels to correct brain function.

Also of high importance, is the knowledge that there are specific time windows for the action of adenosine receptors throughout life. As mentioned above, adenosine A_{2A}Rs by interfering with GABAergic transmission play a critical role during neuronal development. However, under pathologic conditions associated to ageing, A_{2A}Rs shift towards an excitotoxic role, exacerbating the dysregulation of glutamatergic signalling. Little is yet known about the mechanisms that determine these time windows, but it is becoming clear that modifications in signalling cascades and in protein-protein interactions at specific time points do play an important role. After all, protein partnership, like human friendship, may critically determine destiny. It is the role of science and of scientists to shape the destiny of adenosine - a sort of "universal modulator" or a "maestro" that provides adequate control of neuronal signalling – and to take advantage of it whenever corrections of neuronal signalling are needed.

Declaration of competing interest

None

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors research unit has been receiving support by European Union's Horizon 2020(H2020)-WIDESPREAD-05-2017-Twinning (Epi-Epinet) under grant agreement No. 952455, and Fundação para a Ciência e a Tecnologia (FCT) (Projects number PTDC/MED-FAR/30933/2017 and PTDC/MED-FAR/4834/2021.

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