Of adenosine and the blues: The adenosinergic system in the pathophysiology and treatment of major depressive disorder

Joana I. Gomes [a,b,1], Miguel Farinha-Ferreira [a,b,1], Nádia Rei [a,b], Joana Gonçalves-Ribeiro [a,b], Joaquim A. Ribeiro [a,b], Ana M. Sebastião [a,b], Sandra H. Vaz [a,b,*]

[a] *Instituto de Farmacologia e Neurociências, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal*
[b] *Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal*

A B S T R A C T

Major depressive disorder (MDD) is the foremost cause of global disability, being responsible for enormous personal, societal, and economical costs. Importantly, existing pharmacological treatments for MDD are partially or totally ineffective in a large segment of patients. As such, the search for novel antidepressant drug targets, anchored on a clear understanding of the etiological and pathophysiological mechanisms underpinning MDD, becomes of the utmost importance.

The adenosinergic system, a highly conserved neuromodulatory system, appears as a promising novel target, given both its regulatory actions over many MDD-affected systems and processes. With this goal in mind, we herein review the evidence concerning the role of adenosine as a potential player in pathophysiology and treatment of MDD, combining data from both human and animal studies.

Altogether, evidence supports the assertions that the adenosinergic system is altered in both MDD patients and animal models, and that drugs targeting this system have considerable potential as putative antidepressants. Furthermore, evidence also suggests that modifications in adenosine signaling may have a key role in the effects of several pharmacological and non-pharmacological antidepressant treatments with demonstrated efficacy, such as electroconvulsive shock, sleep deprivation, and deep brain stimulation. Lastly, it becomes clear from the available literature that there is yet much to study regarding the role of the adenosinergic system in the pathophysiology and treatment of MDD, and we suggest several avenues of research that are likely to prove fruitful.

1. Introduction

Major Depressive Disorder (MDD) is a debilitating condition, affecting 246–286 million people worldwide [1], characterized by persistently depressed mood, inability to feel pleasure (anhedonia), motivational deficits, increased anxiety, somatic symptoms, cognitive impairments, sleep dysfunction, as well as suicidal thoughts and/or attempts [2,3]. The personal, societal, and economic burden of MDD is difficult to overstate. Indeed, MDD is the single greatest cause of global disability [4], representing a major burden upon public healthcare systems, and on the global economy at large. This impact is even greater when taking into account the fact that MDD is widely recognized major risk factor for other disabling conditions, such as substance abuse disorders [5], and cardiovascular disease [6].

The impact of MDD is largely amplified by the fact that the existing

treatments, which include psychotherapy [7], pharmacological treatment, and other non-pharmacological biological interventions, such as transcranial magnetic stimulation [8] or electroconvulsive therapy (ECT) [9], are often partially or totally ineffective. In fact, a 2006 large-scale research effort found that approximately 30 % of patients do not respond to any drug treatment [10]. Furthermore, even when effective, the existing antidepressants are often not well tolerated, causing a myriad of undesirable and often serious side-effects leading to treatment discontinuation [11], and seem to primarily target emotional symptoms. MDD-induced cognitive dysfunction has been much less targeted, despite its role in patient quality of life [12,13].

These problems underline the need of developing novel, effective, and safe antidepressant compounds. Unfortunately, research efforts have largely failed in this regard, likely due to a combination of factors. For one, MDD is characterized by an extremely diverse and complex

pathophysiology [3,4,14]. In fact, at the neurobiological level, in addition to monoaminergic dysfunctions [15], MDD is characterized by disruptions in glutamate [16,17], γ-amino-butyric-acid (GABA) [17,18], and endocannabinoid signaling [19], altered hypothalamic-pituitary-adrenal (HPA) axis activity [20,21], increased neuroinflammation [22,23], decreased neuro- and synaptogenesis [24–26], diminished brain-derived neurotrophic factor (BDNF) signaling [27,28], and impaired synaptic plasticity [29,30], among other numerous alterations. Furthermore, the etiology of MDD is not yet fully understood, with no individual, or group of, causative factors being capable of reliably predicting MDD diagnosis. Nonetheless, it is known that multiple factors play a role in the development of this disorder, including biological (e.g., genetic predisposition, hormonal imbalance, inflammatory or metabolic disease), environmental (e.g., early childhood adversity, acute trauma, chronic stress), and personal factors (e.g., personality traits, cognitive and coping styles, poor social relationships), often interacting with one another [31–36]. On the other hand, investment in neuropsychopharmaceutical development has continually decreased in the past decades [37], in part due to the poor investment-to-reward ratio that has characterized this field of drug development. Importantly, this has also likely influenced the type of drugs that have been developed, with most newly developed antidepressants being based upon the widely popular monoaminergic hypothesis of MDD, in essence being small improvements upon the commercially successful monoamine reuptake inhibitors. Indeed, in the last 10–20 years, less than a handful of compounds with partially or entirely monoamine-independent mechanisms of action [38–40] have been brought to market.

One as of yet largely unexplored target for antidepressant drug development is the adenosinergic system [41–43], here defined as the system that encompasses the enzymes responsible for the synthesis and catabolism of adenosine, the nucleoside transporters responsible for adenosine transport, and the P1 family of purinergic receptors. The inattention to the adenosinergic system as a target for MDD is somewhat surprising, considering that this ubiquitous neuromodulatory system has a modulatory role over most MDD-implicated dysfunctions. Indeed, the adenosinergic system has been demonstrated to have functional interactions with the monoaminergic [44,45], glutamatergic [46], GABAergic [47], and endocannabinoid systems [48,49], to modulate HPA axis [50] and neuroinflammatory activity [51], to be involved in the regulation of neuro- and synaptogenesis [52,53], as well as of BDNF signaling [54], and to impact synaptic plasticity [55,56]. Furthermore, adenosinergic drugs are already commercially available, and are known to be mostly safe. In fact, the most widely used psychoactive substance in the world – caffeine – exerts its effects through adenosine receptor antagonism [42]. Thus, the adenosinergic system appears as a prime target for the development of novel antidepressant drugs. Moreover, given its widespread interactions with multiple neurobiological systems and processes affected in MDD pathophysiology, understanding how changes in the adenosinergic system may cause, and/or be caused by depressive states would not only inform additional drug development, but also further increase our understanding of the pathophysiology of MDD.

As such, the aim of the present review is to provide a broad overview of adenosinergic system in relation to both the pathophysiology and treatment of MDD. Specifically, after an initial outline of the key elements in adenosinergic system, as well as of their distribution and functioning under physiological conditions, we will sequentially review the evidence regarding how each of those elements is affected in MDD conditions, including studies in MDD patients and in rodent models of MDD. Furthermore, we will review how manipulations of each of those elements of the adenosinergic system impact depressive symptoms and associated neurobiological dysfunctions. Lastly, we will provide a critical appraisal of the overall literature allowing suggestions for future research on this subject.

2. Overview of the adenosinergic system

Adenosine is one of the most ubiquitous and conserved neuromodulators in the central nervous system (CNS). In this section we will provide a brief overview of the receptors, transporters, and the enzymatic pathways responsible for the synthesis and breakdown of adenosine (see Fig. 1), so as to better contextualize the findings relating each of those constituents to the pathophysiology and treatment of MDD.

2.1. Adenosine synthesis, transport and catabolism

Extracellular adenosine levels in CNS are regulated by a complex machinery comprised of synthetic and degradative enzymes, as well as transporters. The relative relevance of each element depends on the cell metabolic state and, in the case of neuronal cells, their excitability status. Under basal conditions extracellular adenosine concentration is in the range of 25–250 nM [57], being sufficient for tonic activation of a substantial fraction of adenosine receptors. However, pathological situations involving abnormally high neuronal and astrocytic activity – such as hypoxia, ischemia, and seizures – result in markedly elevated extracellular concentrations of adenosine, largely due to an increase in the extracellular metabolism of adenine nucleotides to adenosine [57–59]. Congruently, many adenosine-mediated effects that are observed to a lesser extent under normal conditions (e.g. presynaptic inhibition of glutamate release), are greatly augmented during such pathological events, representing a neuroprotective mechanism [59–61].

Adenosine is synthetized both intra- and extracellularly. Intracellular adenosine synthesis occurs through the dephosphorylation of 5′-adenosine monophosphate (AMP) by the cytosolic enzyme 5′-nucleotidase, or through the hydrolysis of S-adenosil-homocysteine (SAH) by the enzyme SAH hydrolase. Two soluble 5′-nucleotidases have been identified: an inosine monophosphate (IMP)-selective cytosolic 5′-nucleotidase, and an AMP-selective cytosolic 5′-nucleotidase. The intracellular concentration of AMP under physiological conditions ($0.1-0.5$ mM) is much lower than the K_m values for AMP cytosolic-5′-nucleotidases ($1-14$ mM). As such, these enzymes only respond to abnormally high concentrations of AMP, which are primarily associated with increased metabolic activity. A small variation in adenosine triphosphate (ATP) catabolism can induce a large increase in AMP concentration, as the intracellular concentration of ATP is about 50 times higher than that of AMP [58]. This fact contributes to the proposal that the intracellular formation of adenosine from catabolism of cytosolic ATP is a highly sensitive signal of increased metabolic rate or metabolic stress [58,62]. Another source of adenosine is the transmethylation pathway, where adenosine results from SAH hydrolysis by SAH hydrolase (SAHH), which simultaneously produces l-homocysteine [63]. SAHH is involved in transmethylation mechanisms, since SAH results from transmethylase activity upon S-adenosylmethionine (SAM). Furthermore, SAM is a methyl donor in cells, and through SAM-dependent methyltransferases these methyl groups can be transferred to several types of substrates, such as nucleic acid, protein, phospholipids, and monoamine neurotransmitters, being deeply involved in epigenetic modifications [63,64].

SAH is able to inhibit SAM-dependent transmethylation reactions, with this inhibition being limited by the metabolic conversion of SAH to adenosine and l-homocysteine [63,64].

Brain SAHH expression is highest in the cortex and cerebellum, but under non-pathological conditions SAHH has low impact upon neuronal excitability [65]. This suggests a minor role for SAHH in the control of neuronal cytoplasmic adenosine levels, in contrast to what appears to occur in cardiac muscle cells [66].

At the extracellular level, adenosine is produced by the conversion of released adenine nucleotides (especially ATP) via the ectonucleotidase pathway, and of cyclic adenosine monophosphate (cAMP) via the ecto-phosphodiesterase pathway. Specifically, ATP released as neurotransmitter, neuromodulator or gliotransmitter, by neurons and/or glial cells,
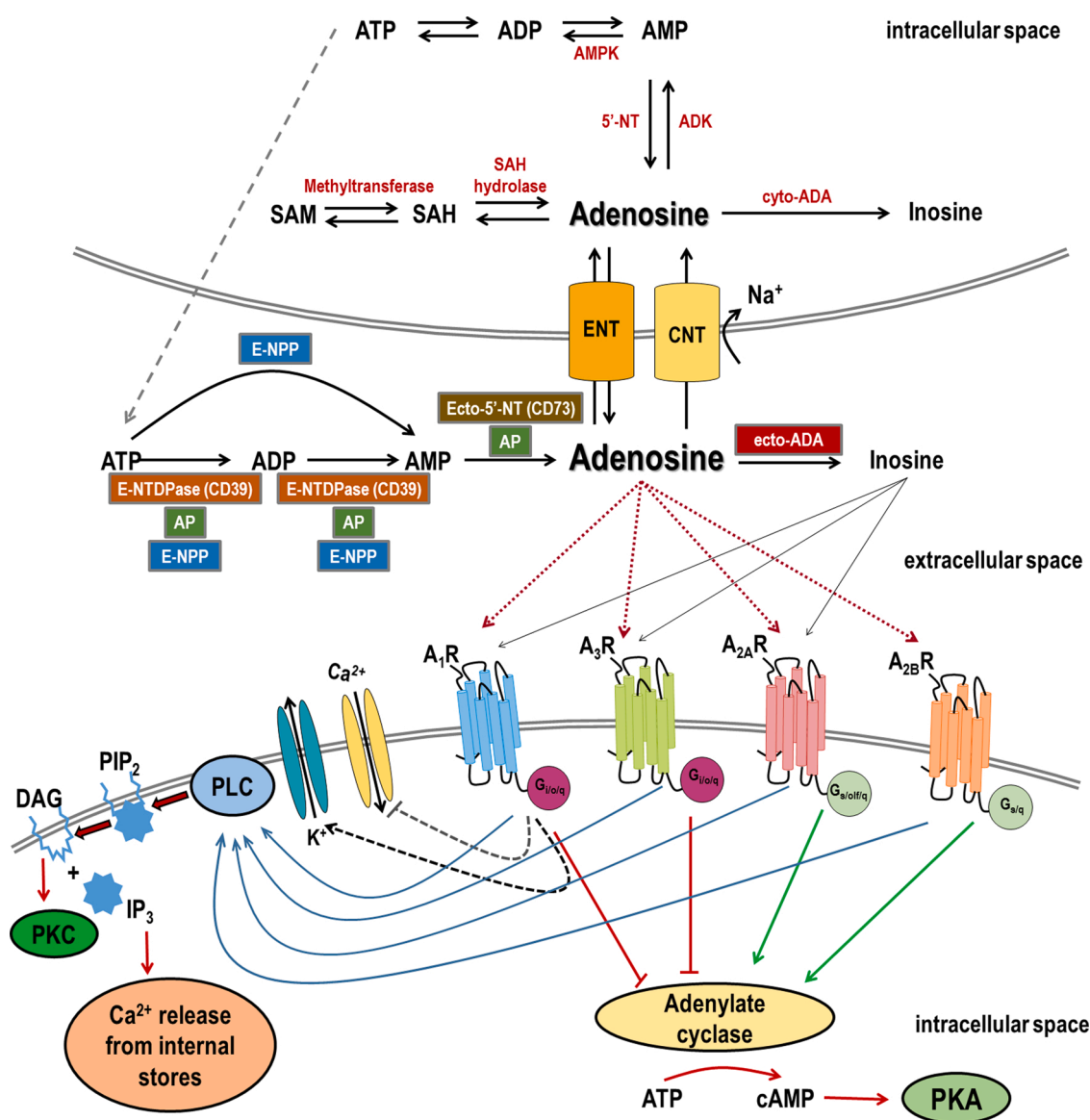
Fig. 1. Schematic representation of the adenosinergic system. Depending on energy requirements, intracellular ATP and adenosine are constantly recycled through a series of dephosphorylation and phosphorylation steps, mediated by enzymes such as 5′-nucleotidase (5′-NT), adenosine kinase (ADK), AMP kinase (AMPK), and S-adenosil-homocysteine (SAH) hydrolase. Extracellular adenosine is synthetized through the hydrolysis of ATP and ADP. Ecto-nucleotide pyrophos-phatase/phosphodiesterase (E-NPP) and alkaline phosphatase (AP) hydrolyse ATP to AMP. Ecto-nucleoside triphosphate diphosphydrolase (E-NTDPase/CD39) hydrolyses of ATP to ADP and ADP to AMP. AMP is further hydrolyzed by Ecto-5′NT/CD73 promoting the formation of adenosine, which can bind to four adenosine receptors. Canonically, activation of adenosine receptors either inhibits (A_1R and A_3R) or stimulates ($A_{2A}R$ and $A_{2B}R$) adenylate cyclase activity, and cyclic AMP (cAMP) production. Changes in phospholipase C (PLC) activity have been described after A_1R and A_3R activation, and it has also been shown that $A_{2A}R$, $A_{2B}R$ and A_3R can couple to G_q-protein. A_1R activation also leads to respective increases and decreases in K^+ and Ca^{2+} conductance, leading to neuronal hyperpolarization. Adenosine can be transported through the plasma membrane by two families of nucleoside transporters: the equilibrative nucleoside transporter (ENT) which allows bidirectional flux by diffusion, and the concentrative nucleoside transporter (CNT) which uses Na^+-coupling to transport adenosine to the intracellular space against the concentration gradient. Lastly, adenosine can be irreversibly deaminated into inosine by the adenosine deaminase (ADA), with inosine also being a bioactive molecule in brain, through A_1R, $A_{2A}R$ and A_3R binding.

Abbreviations: 5′-NT, 5′-nucleotidase; A_1R, adenosine A_1 receptor; $A_{2A}R$, adenosine A_{2A} receptor; $A_{2B}R$, adenosine A_{2B} receptor; A_3R, adenosine A_3 receptor; ADA, adenosine deaminase; ADK, adenosine kinase; ADP, adenosine diphosphate; AMP, adenosine monophosphate AMPK, AMP kinase; ATP, adenosine triphosphate; cAMP, cyclic AMP; CNT, concentrative nucleoside transporter; DAG, diacylglycerol; Ecto-5′NT/CD73, Ecto-5′nucleotidase/cluster of differentiation 73; E-NPP, Ecto-nucleotide pyrophosphatase/phosphodiesterase; ENT, equilibrative nucleoside transporter; E-NTDPase/CD39, Ecto-nucleoside triphosphate diphosphydrolase/ cluster of differentiation 39; IP3, inositol trisphosphate; PIP_2, Phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein, kinase C; PLC, phos-pholipase C; SHA, S-adenosil-homocysteine.

undergoes rapid enzymatic catabolism originating adenosine diphos-phate (ADP), AMP, and adenosine [67,68]. This catabolic process in-volves multiple ectonucleotidases such as E-NTPDases (ectonucleoside triphosphate diphosphohydrolases) – which include CD39, also known as NTPDase 1 or ecto-apyrase – E-NPPs (ectonucleotide pyrophospha-tase and/or phosphodiesterases), alkaline phosphatases (APs), and

ecto-5′-nucleotidase (CD73) [69,70]. These enzymes vary in several important aspects, most notably their specific substrates and end-products, but also in their coupling to the plasma membrane [70]. E-NTPDases, which possess transmembranar domains, are nucleotide-specific and hydrolyze nucleoside tri- and diphosphates, resulting in their respective monophosphates [69,70]. E-NPPs, the vast

majority of which also possess transmembrane domains, do not hydrolyze AMP, but do hydrolyze nucleoside tri- and diphosphates, in addition to also hydrolyzing ADP ribose, dinucleoside polyphosphates, and NAD$^+$ [69,70]. Conversely, both APs and CD73 are bound to the plasma membrane through glycosylphosphatidylinositol (GPI) anchoring, being primarily involved in local catalysis, and autocrine and paracrine signaling. CD73 is a plasma membrane-bound nucleotide-specific homodimer, found in both neuronal [71–76] and glial cells [77,78], which is primarily responsible for the conversion of extracellular AMP to adenosine. APs, on the other hand, are known to hydrolyze nucleoside tri-, di- and monophosphates, in addition to also hydrolyzing pyrophosphate. Furthermore, in addition to their membrane bound forms, soluble CD73 and AP forms do exist, being released by the breakdown of GPI anchors, extending the range of action of these enzymes [69,70].

As mentioned above, in addition to being synthetized extracellularly, adenosine is also synthetized intracellularly, after which it can be released to the extracellular space by bidirectional equilibrative nucleoside transporters (ENTs). The existing ENT subtypes (ENT1−4) transport both purine and pyrimidine nucleosides across the plasma membrane, in a concentration-gradient dependent manner, thus also being involved in the uptake of extracellular adenosine [79,80]. Radioligand binding studies, have reported ENT1 as being most expressed in the thalamus and superior colliculus, with reduced hippocampal, cortical and cerebellar expression [80–82]. However, it must be noted that studies using *in situ* hybridization have found evidence for marked ENT1 mRNA expression in both the hippocampus and the cerebellum of rats [83]. ENT2 expression extensively overlaps that of ENT1 [84], with mRNA expression being observed in cortical, striatal, thalamic, hippocampal, and cerebellar neurons [85]. Unlike ENTs 1 and 2, ENT3 is primarily located in the intracellular space, having an especially relevant role in lysosomal functioning [86]. Furthermore, while ENT3 has been reported to have CNS expression [87], it is thought to be most abundant in the placenta [86]. Lastly, ENT4 mRNA has been found to be expressed across the brain of multiple mammalian species [88–91], with studies finding ENT4 protein expression in the mouse cerebral cortex, hippocampus, basal ganglia, cerebellum, thalamus, and hypothalamus [91].

Contrastingly, concentrative nucleoside transporters (CNTs) – of which three known subtypes exist (CNT1-3) [79,80] – exclusively uptake extracellular nucleosides, using the force of the transmembrane Na$^+$ gradient. The highest CNT1 transcript levels were observed in the brain stem and cortex, with intermediate expression in the choroid plexus, hypothalamus, hippocampus, and cerebellum. On the other hand, CNR2 mRNA was found to be highly expressed in most brain regions [92], but in situ hybridization studies found evidence for greater expression in the dentate gyrus of the hippocampus, and the periaqueductal grey, with intermediate expression in the basal ganglia, hypothalamus, cortex and cerebellum [92,93]. Furthermore, while some evidence suggests that CNT2 may be expressed in astrocytes [94,95], in tissue sections it was exclusively found in neuronal cells [93]. Lastly, CNT3 expression has been found to be extremely reduced in rat and mouse neuronal cells [87], and to be absent, or below the detection threshold, in astrocytes [94].

The K_m values for adenosine vary between transporter subtypes (for a review see [79]), with CNTs having higher affinity than ENTs. Within ENTs, ENTs 1 and 2 can be considered of high affinity vis a vis ENTs 3 and 4 [79]. As such, the overall type of translocation processes implicated in adenosine transport (i.e., "concentrative" versus "equilibrative") will be contingent upon transporter distribution and affinity. Importantly, transport direction varies as a function of ENT activity and of the extra- and intracellular concentrations of adenosine, which depend on intra- and extracellular purine metabolism.

Adenosine can be catabolized in both extra- and intracellularly. Extracellularly, adenosine is primarily converted to inosine by adenosine deaminase (ADA), though ecto-ADA expression is usually relatively low. It is important to note that inosine, once believed to be an inert metabolite, is now known to be bioactive, with significant A$_1$R, A$_{2A}$R and A$_3$R interactions in the CNS [96–98].

Given the generally reduced expression of ecto-ADA, most extracellular adenosine is taken up by the aforementioned ENTs and CNTs, and then catabolized. This occurs mainly through phosphorylation into AMP by adenosine kinase (ADK), but also by conversion to inosine by intracellular ADA. Due to ENT activity, both ADK and intracellular ADA indirectly regulate extracellular adenosine concentration: studies in the hippocampus showed that extracellular adenosine concentrations increase with the inhibition of both ADK [65] and ADA [99,100]. However, it should be notated that basal adenosine concentrations depend not only on the activity of those enzymes, but also on adequate oxygen and/or glucose levels [100]. Furthermore, it is possible that the relative contribution of each particular enzyme to adenosine level oscillations may be cell-specific and, as referred, dependent upon the tissue microenvironment. Nevertheless, much remains to be determined regarding the factors contributing to the regulation of adenosine levels, despite attempts having already been made [101].

2.2. Adenosine receptors

Currently, four different adenosine receptors have been identified and cloned, namely the A$_1$, A$_{2A}$, A$_{2B}$ and A$_3$ receptors (A$_1$R, A$_{2A}$R, A$_{2B}$R and A$_3$R, respectively) [102]. All four receptors are G protein-coupled receptors: A$_1$R and A$_3$R are negatively coupled to adenylyl cyclase through G$_{i/o}$ protein α-subunits, whereas A$_{2A}$R and A$_{2B}$R are positively coupled to adenylyl cyclase through G$_s$ proteins. Changes in the activity of phospholipase C activity have been described after A$_1$R [103,104] and A$_3$R [105] activation, and it has also been shown that A$_{2A}$R, A$_{2B}$R and A$_3$R can couple to G$_{q11}$ [102]. In the striatum, A$_{2A}$R are mainly coupled to G$_{olf}$ [106], a G-protein abundant in this brain area, that also activates adenylyl cyclase [107]. Adenosine receptors also have significantly different densities and affinities for adenosine: A$_1$R and A$_{2A}$R are widespread and have high affinity for adenosine, whereas A$_{2B}$R and A$_3$R, which are less expressed and have lower affinity [57,108]. However, it must be noted that the affinity of A$_3$R for adenosine is species-dependent, being high in humans and low in rodents [109].

Adenosine receptors are differentially expressed in different areas of CNS. A$_1$R is highly expressed in the cortex, cerebellum, hippocampus, and dorsal horn of spinal cord, whereas A$_{2A}$R is highly expressed in the striatum and olfactory bulb, being expressed to a lower extent in other brain regions [110], such as the amygdala, hippocampus or prefrontal cortex [111–113]. The overall modulatory role of adenosine in the CNS is mainly contingent upon on the balance between A$_1$R and A$_{2A}$R activity [59]. Both receptors can be present in the same synapse, with approximately 80 % of hippocampal nerve terminals expressing both A$_1$R and A$_{2A}$R [114]. Furthermore, in the hippocampus, neuronal A$_1$R and A$_{2A}$R expression is predominantly, but not exclusively, presynaptic [55, 114–118].

A$_1$R are most abundant in neurons, both pre- and postsynaptically [115,116,119], but are also expressed in glial cells, such in astrocytes [120] and microglia [121]. At the presynaptic level, A$_1$R activation decreases the release of several neurotransmitters, including glutamate, acetylcholine, serotonin (5-HT) and dopamine (DA), leading to the inhibition of synaptic transmission [122,123]. At the postsynaptic level, A$_1$R activation is associated with the inhibition of glutamate N-methyl-D-Aspartate receptor (NMDAR) mediated currents [124], inhibition of voltage sensitive Ca^{2+} channels [122], increased K$^+$ conductance [125], and disinhibition of inhibitory neurons through a decrease of GABA$_A$ receptor-mediated tonic inhibition [126]. These actions make it so that A$_1$R plays a key role in the regulation of synaptic transmission and plasticity, with its activation inhibiting hippocampal long-term potentiation (LTP), [127] and long-term depression (LTD) [128].

On the other hand, despite having relatively little hippocampal expression [111,129], A$_{2A}$R are readily activated by extracellularly generated adenosine, to facilitate neurotransmitter release [130], and

can have significant impact in hippocampal synaptic plasticity. Pre-synaptically, $A_{2A}R$ stimulation is triggers the release of several neurotransmitters, including glutamate [131,132], acetylcholine [133], DA [134], 5-HT [135], and GABA [131,136]. In addition, presynaptic $A_{2A}R$ play a critical role in supressing cannabinoid type 1 receptor- (CB_1R), and A_1R-mediated inhibition [137,138]. Postsynaptically, $A_{2A}R$ modulate the activation of NMDAR [118,139,140], CB_1R [141], metabotropic glutamate receptor 5 (mGluR5) [142], DA type 2 receptors (D_2R) [143]. Moreover, insofar postsynaptic $A_{2A}R$ are necessary for the co-activation of NMDAR [140], they are required for the maintenance of LTP [144]. Additionally, $A_{2A}R$ activity is known the facilitate the effects of BDNF upon synaptic transmission and plasticity [144–146].

As previously described, there are two major sources of extracellular adenosine. On the one hand, under rest or low-frequency stimulation, A_1R is primarily activated by ENT-released adenosine [147]. On the other hand, conditions of increased presynaptic stimulation favor the release of ATP, which is then metabolized to adenosine. This pathway leads to preferential $A_{2A}R$ activation [130,147]. Thus, adenosine induced suppression of neuronal activity, preservation of ATP stores, and neuroprotection [148] are mainly attributable to A_1R activation, while $A_{2A}R$ activation, may exacerbate excitotoxicity in several brain areas [149–152]. Importantly, however, despite $A_{2A}R$ being mainly associated with pathological situations, these receptors also gate the neuroprotective actions of some molecules, such as neurotrophic factors [145,146,153].

Unlike A_1R and $A_{2A}R$, $A_{2B}R$ has a low level of expression in the brain, being primarily expressed in peripheral tissues [154]. Lastly, A_3R is reported to have intermediate levels of expression in the human cerebellum and hippocampus, and low levels in most of the remaining regions [102]. Besides their reduced expression in the brain, $A_{2B}R$ and A_3R also have low-affinity for adenosine [155]. Nonetheless, these receptors might be activated during conditions of hypoxia or ischemia, in which extracellular adenosine levels rise [58,156–158].

Lastly it must be noted that, in addition to their neuronal expression, all four adenosine receptors are detected in astrocytes [159], and have been reported to be expressed in microglial cells or microglial cell lines [160,161].

3. The adenosinergic system in MDD pathophysiology and treatment

3.1. Adenosine synthesis

The impact of MDD-like conditions on the levels and activity of enzymes involved in adenosine synthesis have been investigated in multiple animal studies. ATPase, ADPase and CD73 activity were assessed in synaptosomes derived from the spinal cords of male and female Sprague-Dawley rats, that had undergone a chronic restraint stress procedure [162]. In this work, the authors found male-specific decreases and increases in ADPase and CD73 activity, respectively, with no changes in ATPase activity [162]. Interestingly, in this study no effects were observed in females [162], likely due to the effects of estradiol, as evidenced by a posterior study in ovariectomized female rats, where chronic restraint stress induced a decrease in spinal cord CD73 (but not ATPase or ADPase) activity, which was not observed in similarly stressed 17β-estradiol-treated animals [163].

In another study from these authors, neither ATPase, ADPase, nor CD73 activity were observed to be altered in synaptosomes derived from the hypothalamus and cortex derived of male Sprague-Dawley rats exposed to a similar chronic restraint stress protocol [164]. Moreover, in these animals, a decrease in blood serum ADPase activity was observed [164]. Furthermore, both 15- and 40-day restraint stress exposures were found to induce increased ATPase activity in hippocampal synaptosomes obtained from male Sprague-Dawley rats, without affecting ADPase or CD73 activity [165].

In recent years there has been an increase in the number of studies using zebrafish as model organism for the study of depression, and of putative treatments for it. This is likely due to the fact that not only do zebrafish allow rapid, low-cost, high throughput manipulation and testing, but also due to their remarkably high physiological and genetic homology to mammals [166,167]. Moreover, zebrafish models have been demonstrated to have considerable predictive value, in regards to detecting the effects of known antidepressant compounds [166,167]. Interestingly, a recent study with zebrafish exposed to an unpredictable chronic stress protocol, found no differences in the hydrolysis of either ATP, ADP or AMP, suggesting no changes in enzymatic activity [168]. However, it should be noted that, despite this lack of changes in the activity of hydrolytic enzymes, when ATP metabolism was measured directly, a significant increase in ATP-derived adenosine levels was observed in the brains of stress-exposed zebrafish [168].

A recent study found that chronic social defeat stress (CSDS) exposure resulted in increased hippocampal CD39 expression and activity, as well as a marked depressive-like state, as evidenced by increased immobility time in the tail suspension (TST) and forced swim tests (FST), and decreased sucrose intake in the sucrose preference test (SPT) [169] (for a brief overview of the most common behavioral tests used in the assessment of depressive- and anxiety-like behaviors see Table 1). Furthermore, it was also found that CSDS induces an equally strong anxiogenic effect in the elevated plus maze (EPM) and the Open Field Test (OFT) [169]. Most notably, these authors found that both pharmacological and genetic silencing of hippocampal CD39, resulted in a partial reversal of CSDS-induced depressive-like behaviors, and associated molecular alterations, including increased hippocampal neurogenesis, spinogenesis, and extracellular ATP level [169]. Congruently, administration of the CD39-analog apyrase resulted in CSDS-like increases in depressive-like behaviors [169]. Conversely, in non-CSDS-exposed mice, genetic or pharmacologic silencing of hippocampal CD39 resulted in antidepressant-like effects, with animals performing better than controls [169]. Thus, hippocampal CD39 seems to have a key role in the regulation of mood states, and may represent an important target for future drug-development. However, these results must be considered in light of the fact that CD39 silencing may imply other undesirable effects, as evidenced by the fact that CD39-KO mice have been reported to be highly seizure-prone [196]. Nonetheless, in agreement with the data of

Cui et al. [169], CD39-KO mice were reported to show decreased anxiety-like behavior in the EPM, without alterations of in the social interaction test (SIT), the OFT, or the fear conditioning paradigm [196].

On the other hand, the impact of CD73 manipulations was assessed in a pair of studies with CD73-KO mice. In the first of these studies, CD73-KO mice were found to have wild type (WT)-like performance in the EPM, OFT and the light-dark box test (LDBT), as well as in the FST, and the fear conditioning paradigm, thus suggesting unaltered emotional function [197]. In line with this data, another study reported the LDBT and OFT performance of CD73-KO mice to be similar to that of controls [198]. Intriguingly, regarding cognitive parameters known to be impacted in MDD, it was first reported that neither working memory, nor spatial memory and learning were affected in CD73-KO mice [197]. However, a subsequent study observed an improvement in working memory, assessed in the Spontaneous Alternation Y-Maze, in CD73-KO mice [198]. Furthermore, CD73-KO mice evidenced altered social behavior, with decreased social dominance, and preference for social novelty in the social motivation and social novelty test, despite presenting increased social activity [197].

Interestingly, there is some evidence that conventional antidepressants may significantly impact the enzymes involved in adenosine synthesis (see Table 2 for an overview of the effects of classical antidepressant treatments upon the adenosinergic system). In the blood serum, acute treatment with the tricyclic antidepressant (TCA) nortriptyline – but not the selective 5-HT re-uptake inhibitor (SSRI) fluoxetine – led to a decrease in ATP hydrolysis, without affecting ADP or AMP hydrolysis [199]. Similarly, acute nortriptyline, but not

Table 1
Overview of the most widely used behavioral tests for the assessment of anxiety- and depressive-like behaviors.

Test	Description	Construct Modelled	Main Measures	Limitations/Biases	Key Refs.
Differential Reinforcement of Low-rate 72-s (DRL-72-s)	Animals are trained to acquire a stable pattern of operant behavior, whereby lever presses are only reinforced if performed at least 72 s after the last reinforcement.	Decreased motivation	Number of responses (index of depressive-like behavior) Number of reinforcers obtained (inverse index of depressive-like behavior) Cumulative inter-response time distribution (rightward shift = inverse index of depressive-like behavior)	Biased by impairments in learning processes;	[170]
Elevated Plus Maze (EPM)	Animals are placed in the center of an elevated maze shapes like a plus – with two open arms and two arms enclosed on three sides by high walls – and are left to explore for a defined period of time.	Generalized anxiety	Time spent and number of entries in the open arms (inverse indexes of anxiety-like behavior);	Biased by alterations in locomotor function; May not be an adequate measure of anxiety-like behavior; Limited predictive validity;	[171, 172]
Fear Conditioning Paradigm	Animals are conditioned to associate conditioned stimuli (cue) with an aversive unconditioned stimulus (shock), and emit a conditioned freezing response. Subsequently animals are exposed to the cue in a novel environment (cued fear conditioning), and/or to the context where original conditioning took place but in the absence of the cue itself (contextual fear conditioning).	Aversive associative memory (e.g., phobia)	Cue-evoked freezing responses (index of cued conditioned fear); Context-evoked freezing responses (index of contextual of conditioned fear);	Biased by alterations in nociception;	[173, 174]
Forced Swim Test (FST)	Animals are placed into a water filled cylinder from which they cannot escape for a single 6-minute session (mice) or for 2 sessions – lasting 15 and 5 min respectively – spaced 24 h apart (rats).	Impaired stress-coping	Time spent in immobility (index of depressive-like behavior); Time spent climbing (inverse index of depressive-like behavior); Time spent swimming (inverse index of depressive-like behavior);	Biased by alterations in locomotor function; Highly stress inducing;	[175, 176,177]
Light-Dark Box Test (LDBT)	Uses an apparatus composed by two chambers – one dark, and fully covered, the other open and brightly lit – connected by a small passage. Animals are placed in the dark chamber and allowed to freely explore the entire apparatus for a defined period of time.	Generalized anxiety	Latency to first entry in the light chamber (index of anxiety-like behavior); Time spent in the light chamber (inverse index of anxiety-like behavior);	Biased by alterations in locomotor function;	[178, 179]
Marble Burying Test (MBT)	Animals are placed in a cage with lightly tamped bedding, on top of which an array of glass marbles has been disposed, and left to explore/ interact for a defined period of time.	Unclear (anxiety, compulsion, neither?)	Number of marbled buried (index of anxiety-like behavior)	Interpretation is highly contentious;	[180, 181,182, 183,184]
Open Field Test (OFT)	Animals are placed in an enclosure whose center region is brightly lit, and are allowed to freely explored for a defined period of time.	Generalized anxiety	Time spent in a virtually defined center zone (inverse index of anxiety-like behavior); Locomotor measures (distance travelled, average speed);	Biased by alterations in locomotor function; May not be an adequate measure of anxiety-like behavior; Limited predictive validity;	[185, 186]
Shuttle Box Escape	Animals are first exposed to inescapable shocks on one of two compartments in a conditioning chamber, with no way to access the other compartment. After a defined period of time, animals are again placed in the shock-paired compartment, with open access to the remaining compartment, allowing them to escape shock exposure.	Apathy/learned helplessness	Number of shocks received when escape is possible (escape failures; index of depressive-like behavior); Latency to escape shock (inverse index of depressive-like behavior);	Biased by alterations in locomotion and nociception;	[187, 188,189]
Social Interaction Test (SIT)	Animals are placed in the open field with a unknown social partner of the same sex, weight and age, and allowed to freely explore and interact for a defined period of time.	Social anxiety	Time spent in active social interaction (inverse index of anxiety-like behavior);	Biased by alterations in locomotor function, and social motivation/reward; Limited predictive validity;	[190, 191]
Sucrose Preference Test (SPT)	Animals are allowed free access to two bottles – one containing water, and the other a low concentration sucrose solution – for a defined period of time.	Anhedonia	Relative sucrose preference (inverse index of depressive-like behavior); Sucrose intake (inverse index of depressive-like behavior);	Biased by alterations in gustatory perception;	[192, 193]
Tail Suspension Test (TST)	Mice are hung upside down by their tails for a defined period of time (typically 6 min), and behavior is scored.	Impaired stress-coping	Time spent in immobility (index of depressive-like behavior);	Biased by alterations in locomotor function;	[194, 195]

Table 2

Impact of pharmacological and non-pharmacological antidepressant treatments on adenosine synthesis, transport, catabolism, levels and P1 receptors.

	Adenosine Synthesis	Adenosine Transport	Adenosine Catabolism	Adenosine Levels	Receptors			
					A$_1$R	A$_{2A}$R	A$_{2B}$R	A$_3$R
DBS	–	–	–	↑hipp [A,B]	–	–	–	–
ECS/ECT	↓ Serum ADP/AMP hydrolysis [A] ↑ Serum & CSF ATP/ADP hydrolysis [C]	↑ Str density [A] ↔ Ctx, Hipp, Cbl density [A] ↔ Ctx, Hipp, Cbl, Str, density [C]	–	↑ whole-brain [A]	↑ Ctx density [C] ↔ Hipp, Cbl, Str density [C] ↔ Ctx, Hipp, Cbl, Str density [A]	↔ Ctx, Hipp, Cbl, Str density [A,C]	–	–
MAOI	–	–	–	–	–	–	–	–
MRA	–	–	–	–	–	–	–	–
NaSSA	–	–	–	–	–	–	–	–
NDRI	–	–	–	–	–	–	–	–
NMDAR-A	–	–	–	–	–	–	–	–
NRI	–	–	–	–	–	–	–	–
RIM-A	–	–	–	–	–	–	–	–
SARI	–	–	↓ ADA activity [E]	–	–	–	–	–
SD	–	–	–	↑BF [A]	↑ BF density [A,C,F] ↑ BF mRNA [A]	↓ OT density [C] ↓ OT mRNA [A]	–	–
SMS	–	–	–	–	–	–	–	–
SNRI	–	–	–	–	–	–	–	–
SSRI	↔ Serum ATP/ADP/AMP hydrolysis [A] ↓ Serum ATP/ADP/AMP hydrolysis [C] ↔ Hipp & Ctx ATP/ADP/AMP hydrolysis [A] ↓ Hipp ATP hydrolysys [C] ↔ Hipp ADP/AMP hydrolysis [C] ↑ Ctx ADP/AMP hydrolysis [C] ↓ Ctx ATP hydrolysis [C] ↓ Serum ADP hydrolysis [A] ↔ Serum ATP/AMP hydrolysis [A] ↓ Hipp & Ctx ATP hydrolysis [A] ↑ Hipp ADP hydrolysis [A] ↔ Hipp & Ctx AMP hydrolysis [A]	↑ whole-brain CNT2 mRNA [B] ↔ whole-brain ENT1−3, CNT3 mRNA [B]	↑ Serum ADA activity [C,F] ↔ whole-brain ADK mRNA [B]	↑ Plasma [A,C,F]	–	–	–	–
TCA	↓ Serum ATP/ADP/AMP hydrolysis [C] ↓ Hipp ATP hydrolysys [C] ↔ Hipp ADP/AMP hydrolysis [C] ↑ CTX ATP/ADP/AMP hydrolysis [C]	↓ activity [D]	↔ ADA & ADK activity [D]	–	–	–	–	–

Abbreviations: -, effects not studied; ↔ no effects; ↓ decrease; ↑ increase; A$_1$R, Adenosine A$_1$ receptor; A$_{2A}$R, Adenosine A$_{2A}$ receptor; A$_{2B}$R, Adenosine A$_{2B}$ receptor; A$_3$R, Adenosine A$_3$ receptor; ADA, adenosine deaminase; ADK, adenosine kinase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; BF, basal forebrain; Cbl, cerebellum; CNT, concentrative nucleoside transporter; CSF, cerebral spinal fluid; Ctx, Cortex; DBS, deep brain stimulation; ECS/ECT, electroconvulsive shock/therapy; ENT, equilibrative nucleoside transporter; Hipp, hippocampus; MAOI, monoamine oxidase inhibitor; MRA, melatonin receptor agonist; NaSSA, noradrenaline and serotonin specific antidepressant; NDRI, noradrenaline and dopamine reuptake inhibitor; NMDAR-A, NMDA receptor antagonist; NRI, noradrenaline reuptake inhibitor; OT, olfactory tubercle; RIM-A, reversible inhibitor of monoamine oxidase A; SARI, serotonin antagonist and reuptake inhibitor; SD, sleep deprivation; SMS, serotonin modulator and stimulator; SNRI, serotonin and noradrenaline reuptake inhibitor; Str, striatum; TCA, tricyclic antidepressant. a, acute administration; b, sub-chronic administration; c, chronic administration; d, cell line study; e, ex-vivo application; f, human MDD patients.

fluoxetine, treatment decreased hippocampal and cortical ATP hydrolysis, while also increasing ADP hydrolysis in the hippocampus [200]. However, chronic treatment with these compounds led to different results. In blood serum, both fluoxetine and nortriptyline-treatments led to a decrease ATP, ADP, and AMP hydrolysis [199]. On the other hand, the hippocampus, both compounds decreased ATP hydrolysis, without affecting ADP or AMP metabolism [200]. Moreover, in the cortex, fluoxetine treatment decreased ATP hydrolysis, while increasing ADP and AMP metabolism, whereas nortriptyline increased hydrolysis of both ATP, ADP and AMP [200]. However, it should be noted that another study found fluoxetine treatment to have no impact upon whole brain apyrase mRNA expression [201]. Relatedly, a recent study with zebrafish found that pre-treatment with the CD73 inhibitor AMPCP did not diminish or increase the antidepressant-like actions of the NMDAR

antagonist MK-801 [202].

Like classical antidepressant compounds, electroconvulsive shock (ECS) treatment has also been shown to modulate adenosine synthesis. In the short term, 12 h after a single ECS session, blood serum ADP and AMP hydrolysis was found to be decreased [203]. On the other hand, when similar assessments were performed 7 days after the last of an 8-session ECS treatment protocol, persistent increases in ATP and ADP hydrolysis were observed in both serum and cerebral spinal fluid samples, suggesting a role for increased adenosine synthesis in the antidepressant effects of ECS [203,204].

Finally, it must be noted that alterations in the intracellular adenosine precursor SAM, have been shown to translate into alterations in methyltransferase activity, resulting in abnormal methylation patterns. Importantly, such aberrant methylation patterns have been implicated

in the pathogenesis of multiple neuropsychiatric disorders, including MDD [64,205].

In sum, evidence appears to largely support the existence of an important role for altered adenosine synthesis in the emergence of MDD symptoms. Moreover, it seems to be the case that targeting those dysfunctions in adenosine synthesis has a significant beneficial effect over symptoms, and thus may hold significant therapeutic potential.

3.2. Adenosine transport

Given that sleep disruption and fatigue are common symptoms of MDD, and considering the role of adenosine in sleep regulation, a possible relationship between adenosinergic dysfunction and MDD-associated sleep disruption has been proposed. In line with this, a study assessed the association between a number of single nucleotide polymorphisms (SNPs) – in the genes coding for ADA, ADK, ENTs, CNTs, and CD73 – and MDD diagnosis with or without sleep disturbances, in patients of both sexes [206]. While in initial analyses these authors found multiple significant associations between specific SNPs and MDD, only one survived correction for multiple comparisons [206]. Specifically, a significant female-specific association was found between the SLC29A3 rs12256138 SNP and MDD diagnosis, suggesting a possible involvement between ENT3 alterations and this disorder [206].

The role of nucleoside transport in depressive-like symptoms in rodents has also been studied by both genetic and pharmacological approaches. Pharmacological studies found that administration of the non-specific transporter inhibitor papaverine, led to an anxiolytic-like effect in the EPM [207]. Similarly, microinjection of the specific ENT1 antagonist NBMPR into the amygdala, but not the caudate-putamen, of C57BL6 mice, resulted in an anxiolytic-like effect in both the EPM and the OFT [208]. Likewise, when male ENT1-KO mice were assessed, a significant decrease in anxiety-like behavior was observed in the EPM, OFT and LDBT [208,209], but not in the marble burying test (MBT) [209]. Moreover, female ENT1-KO mice tested in the OFT and the MBT, also evidenced decreased anxiety in those tests [209]. Furthermore, when ENT1-KO mice of both sexes were assessed for altered depressive-like behaviors in the FST, a significant antidepressant-like effect was observed, as evidence by reduced immobility time as compared with WT littermates [209].

One interesting discrepancy, however, comes from the fact that acute administration of the ENT inhibitor NBTI resulted in a dose-dependent impairment in shuttle box escape performance, similar to that observed after inescapable shock exposure [210], suggesting a prodepressant impact of transporter blockade. Moreover, when NBTI was combined with a sub-effective shock exposure, a synergistic effect was observed [210].

A few studies have assessed how adenosine transporters are impacted and impact antidepressant treatment. Specifically, 3-day fluoxetine treatment led to an increase in whole-brain CNT2 mRNA expression, without altering that of ENT1−3, CNT3, or ADK [201]. Furthermore, there is some evidence that the TCA amitriptyline may inhibit adenosine transport [211]. Interestingly, while it has been demonstrated that a single ECS exposure rapidly (30 min) induces marked increases in striatal adenosine uptake, these appear to be short-lasting, not being detectable 24 h later [212]. Similarly, repeated ECS treatment had no significant effect upon adenosine uptake – in either the striatum, the cortex, the hippocampus, or the cerebellum – when measurements were performed 24 h after the last session [212].

Lastly, recent study with zebrafish found that NBTI co-treatment had no impact upon the antidepressant-like action of the NMDAR antagonist MK-801 [202], but in contrast, dipyridamole, a non-specific nucleoside transport inhibitor, synergistically acted with MK-801, increasing its antidepressant-like effects [202]. Accordingly, acute dipyridamole administration potentiated the antidepressant-like effect of sub-effective zinc chloride doses, in the FST [213].

Altogether, the presently available evidence cannot firmly support a conclusion regarding the possible involvement of adenosine transporters in the pathophysiology of MDD, nor the possible relevance of nucleoside transport inhibitors in MDD therapeutics. The differences between acute and prolonged administration of nucleoside inhibitors, the short-lasting influence of intense neuronal activity upon extracellular levels of adenosine, and the different responses to selective and non-selective nucleoside inhibitors are indicative of a strong capability of the nucleoside transporters to adapt to changes in the extracellular levels of adenosine and to drug manipulations. Whether this might explain some of the apparent contradictory findings on the role of the transporters on depression or the action of antidepressant drugs awaits further studies. It is also important to keep in mind that ENTs are bidirectional and therefore take up or release adenosine as a function of the relative intra- and extracellular concentrations of the nucleoside. As such, ENTs inhibitors may lead to either increases or decreases in the extracellular concentrations of adenosine as a function of the neuronal activity and metabolic state of neuronal cells, including neurons, astrocytes and microglia.

3.3. Adenosine catabolism

To the best of our knowledge, all the published work regarding the association between MDD and altered adenosine catabolism, focused on ADA, with results being somewhat contradictory.

In the blood serum of rats exposed sub-chronic (3-day) restraint stress, an increase was observed in ADA activity, which was not observed after a single restraint session [214]. Similarly, in a study with MDD patients, blood ADA activity was found to be increased in the MDD group [215]. Contrastingly, however, a previous in a previous study with MDD patients, an association was observed between decreased – rather than increased – blood serum ADA activity and MDD diagnosis [216]. In line with this, a recent paper using zebrafish exposed to a unpredictable chronic stress protocol, found a decrease in the activity of brain ecto-ADA activity, but not in that of cytosolic ADA [168]. Moreover, these authors assessed how chronic stress impacted the expression of several ADA genes, and found no significant alterations [168].

Regarding ADA manipulations, a recent study assessed the impact of ADA abolishment on behavioral outcomes [217]. These authors found that ADA-KO mice presented increased anxiety-like behaviors in the OFT and LDBT [217]. Results in the OFT have, however, to be evaluated in light of the fact that these animals also presented clear signs of locomotor hypoactivity [217]. Importantly, enzyme replacement therapy had no effect upon these behavioral alterations [217].

Interestingly, pharmacological inhibition of ADA has been contradictorily reported to induce both pro- and antidepressant-like effects. Specifically, a 1998 study showed that acute intracerebroventricular administration of EHNA induced escape deficits – similar to those observed after exposure to inescapable shocks – in the shuttle box escape paradigm [218]. Furthermore, a sub-active EHNA dose, in combination with sub-effective shock exposure, resulted in escape deficits similar to those observed by active dose EHNA or effective shock exposure, suggesting a synergistic interaction [218]. Conversely, in a more recent study, acute intraperitoneal EHNA administration, resulted in dose-dependent decreases in FST immobility time – suggesting an antidepressant-like effect – without altering OFT performance [219].

The effects of ADK manipulation were assessed in a single study, where a transgenic mouse line overexpressing ADK (Adk-tg) was assessed for alterations in anxiety-like behaviors, and fear conditioning, as well as working-, and reference memory [220]. Performance in the EPM was found to be WT-like, suggesting normal anxiety-like behavior [220]. On the other hand, in the fear conditioning, Adk-tg mice presented impaired acquisition and expression of the response to conditioned stimuli [220]. Furthermore, these animals evidenced severe deficits in both working and reference memory [220].

The effects of antidepressant treatment on the enzymes involved in adenosine catabolism were first assessed in 1985 paper, which found

that the serotonin antagonist and reuptake inhibitior (SARI) trazodone acted as an inhibitor of brain ADA [221]. On the other hand, a subsequent in vitro study, where amitriptyline was found to not impact the activity of either ADK or ADA [211]. In contrast, two subsequent studies have found that in both MDD and panic disorder patients, 8-week SSRI treatment was associated with significant increases in blood ADA activity [215,222]. Curiously, a recent study found that sub-chronic (3-day) fluoxetine administration had no impact upon whole-brain ADK mRNA expression [201]. Finally, in zebrafish, acute EHNA pre-treatment did not significantly alter the antidepressant-like effects of MK-801 administration [202].

Overall, ADA alterations have been consistently observed to be related to depressive and anxious symptomatology, and may represent fruitful targets for future development. However, it is important to keep in mind that ADA manipulations are likely to have markedly unselective and widespread effects, some of which may be undesirable. On the other hand, there is a clear dearth of research on the role of ADK in the pathophysiology and/or treatment of MDD symptoms, which is surprising given the key role of this enzyme in the regulation of intra- and extracellular adenosine levels (see section 2.1), and its relevance as a therapeutic target multiple other pathologies [223], including neuropsychiatric ones [224]. This is, thus, an area which undoubtedly deserves future research.

3.4. Adenosine levels

Changes in adenosine synthesis, transport and catabolism, found in MDD patients and/or animal models, are likely to impact adenosine levels, resulting in the non-selective changes in the activation state of adenosine receptors. However, to the best of our knowledge, no published work has assessed the possibility that adenosine levels may be altered in MDD patients or animal models. Nonetheless, a few studies have assessed the impact of manipulations aimed at altering adenosine levels.

Acute intraperitoneal administration of adenosine was reported to induce marked increases in FST immobility time, which were prevented by co-administration of caffeine, theophylline, and some – albeit not all – classical antidepressant compounds [225]. In a subsequent study, acute intraperitoneal administration of the non-selective adenosine receptor agonist NECA, resulted in a dose-dependent impairment of escape behavior in the shuttle escape paradigm, similar to that induced by inescapable shock [226].

However, more recent publications have reported adenosine administration to induce markedly different effects than those originally reported. Indeed, acute adenosine administration has been consistently shown to induce reductions in immobility time in both the FST and the TST, without altering locomotor activity [227–232]. Furthermore, this effect has been demonstrated to be reliant on a number of interactions with other – non-adenosinergic – targets, including the nitric oxide–cGMP pathway [228], the 5-HT type 1A [231] and NMDA [227] receptors, K^+ channels [230], and the opioid system [229]. One possible explanation for the discrepancy of results vis a vis those originally reported, related to the differences adenosine doses used [225]. Specifically, whereas antidepressant effects are observed at doses of $1-10$ mg/kg [227–232], the report finding a prodepressant effect of adenosine, administered a 100 mg/kg dose [225], which is likely to induce a strong sedating and/or locomotion impairing effect. Nonetheless, it must be noted that in a recent study with rats submitted to bilateral olfactory bulbectomy (OBX), 14-day adenosine treatment had no effect upon altered FST, OFT or SPT performance [233].

The impact of antidepressant drug treatment upon adenosine levels has been assessed in a single study, where MDD patients underwent a 40-day treatment with daily doses of the SSRI citalopram, and plasma adenosine and 5-HT levels were assessed at multiple time-points [234]. As expected, plasma levels of 5-HT increased soon after citalopram administration, peaking after 12 h, and then gradually decreased [234].

This temporal progression remained stable across the 40-day treatment, but there was evidence of an increase in the magnitude of the effect, in response to prolonged treatment. Interestingly, adenosine levels consistently followed the same temporal progression, with a statistically significant association being observed [234]. Given this, it is curious that the co-administration of adenosine either with the SSRI fluoxetine, or the antipsychotic 5-HT type 2A receptor antagonist ketanserin, did not lead to a synergistic effect in the FST [231]. On the other hand, a synergistic antidepressant effect was observed after co-administration of adenosine and the TCA imipramine [227]. Likewise, sub-active – but not active – doses of adenosine and the NMDAR antagonists ketamine and MK-801, resulted in a synergistic antidepressant-like effect in the FST [227].

Concluding, evidence supports the notion that increasing adenosine levels may have a significantly beneficial impact upon depressive and anxious symptomatology. This is fully in line with the therapeutic effects reported while targeting adenosine synthesis, catabolism, and transport, all of which can lead to a similar increase in adenosine levels.

3.5. Adenosine receptors

3.5.1. A_1R

Given the known role of A_1R in the regulation of sleep, and the relation between altered sleep and MDD, it is interesting to note that in a study assessing the association of multiple SNPs in genes coding for elements of the adenosinergic system, no significant effects were found for *ADORA1* polymorphisms [206]. Furthermore, to the best of our knowledge there are no published reports assessing changes in A_1R levels in the brains of human MDD patients.

Interestingly, in animal studies, chronic stress exposure has been shown to impact hippocampal A_1R expression, albeit with contradictory results. Specifically, it has been shown that sub-chronic restraint stress exposure results in a decrease in hippocampal A_1R binding and protein levels [235]. Contrastingly, however, a subsequent study using rats exposed to either chronic restraint stress or chronic mild stress protocols, showed the opposite effect, whereby both protocols resulted in an increase – rather than a decrease – in hippocampal A_1R binding/protein levels [236].

Pharmacological studies with A_1R agonists have largely consistent findings. Specifically, it was found that acute administration of the A_1R agonist CHA led to a decrease in FST immobility times [232]. Likewise, another report found weekly CHA administration to have antidepressant-like effects in the differential reinforcement of low rate 72-s (DRL-72 s) schedule assay [237]. Moreover, in addition to decreasing FST immobility, acute CCPA administration was also shown to lead to a sustained (36 h) reduction of anhedonic-like behavior in the SPT [238]. Relatedly, in a recent study, the selective A_1R agonist MRS5474 was shown to acutely decrease FST immobility times for non-stressed mice, as well as to decrease TST immobility in mice exposed to a repeated swim stress protocol [239]. Importantly, an early study suggested that acute administration of the A_1R agonist R-PIA mimicked the effects of pre-exposure to inescapable shock on escape shuttle performance [226]. However, it must be noted that these authors did not control for the possibility that this decrease in performance may be attributable to possible hypolocomotion-inducing effects of A_1R agonists, rather than a true prodepressant-like effect, despite reporting visual evidence of such possible effects. Finally, it must be noted that in one study no evidence was found for an antidepressant-like effect of acute CHA administration in the FST [213].

Interestingly, in addition to having antidepressant-like effects A_1R agonists also appear to have remarkable potential as drugs to control symptoms of anxiety, which often co-occur with MDD. Indeed, an early study found that acute administration of the A_1R agonist CPA had an anxiolytic-like effect in the EPM [240]. Interestingly, these results were not observed in a subsequent study [241]. Nonetheless, another study found that acute administration of the A_1R agonist CCPA had a

significant anxiolytic-like effect not just in the EPM, but in the LDBT as well, albeit not at all the doses tested, suggesting the possibility that the anxiolytic-like effects of this compound may not increase linearly with dose [242]. Lastly, ethanol withdrawal is known to have marked anxiogenic-like effects in rodents. Interestingly, a report found that acute CCPA administration 18 h after ethanol challenge, prevented that increase in anxiety, again suggesting an anxiolytic-like effect of A_1R activation [243]. One important caveat to these results is that, with one exception [243], none of the above mentioned studies controlled for the possibility that the apparent anxiolytic-like effects of A_1R agonists may actually derive from locomotor impairing and/or sedating actions of these compounds.

The potential of A_1R agonists as add-on drugs to antidepressant drug treatment has been explored in a few studies. In this line of research it was reported the A_1R agonist CHA acutely potentiated the antidepressant-like effects of sub-active doses of zinc in the FST [213]. However, the same compound was ineffective in potentiating the action of the NMDAR antagonist MK-801 in a zebrafish study [202].

More recently, attention has been focusing on allosteric modulators of A_1R, rather than on agonists per se, since allosteric modulators are expected to have less side effects and induce less compensatory changes in the receptors than those caused by agonists. In this regard, a recent study using the novel A_1R positive allosteric modulator TRR469 reported acute anxiolytic-like effects in the EPM, LDBT, OFT and MBT, that were comparable to those of diazepam [244]. Furthermore, this compound did not share the ethanol potentiating properties of diazepam, nor did it induce significant locomotor alterations [244]. Most importantly, these effects were associated with increased CCPA binding in the hippocampus, amygdala and prefrontal cortex, and were fully antagonized by DPCPX pre-treatment, both of which suggest increased A_1R signaling as the mechanistic underpinning of the effects of TRR469 [244].

In addition to studies with A_1R agonists, there has also been considerable research focusing the effects of A_1R antagonists upon depressive- and anxiety-like behaviors. Indeed, acute administration of the A_1R antagonist DPCPX did not significantly impact FST immobility times, but did block the antidepressant-like effects of adenosine [232]. These findings have been replicated by multiple subsequent studies, with both the TST and FST [213,245,246]. Similarly, other studies found that the same compound had no significant impact on DRL-72 s performance after weekly administration [237], nor did it acutely alter shuttle-escape performance deficits induced by inescapable shock exposure [210], or reserpine-induced FST impairments [247], altogether suggesting no effect of A_1R antagonism upon depressive-like behaviors. However, a recent study did report acute DPCPX administration to induce a significant antidepressant-like effect in both the FST and TST [248].

Regarding anxiety, Yacoubi et al. found that acute administration of the A_1R antagonist DPCPX had no effect upon anxiety-like behavior in the EPM [241], replicating a similar finding previously obtained by Jain et al. with the A_1R antagonist CPX [240]. Likewise, acute DPCPX administration did not significantly impact ethanol withdrawal-induced increases in anxiety in either direction [243]. However a previous study reported that the A_1R antagonist CPT had a marked anxiogenic-like effect in both the LDBT and EPM after acute administration [242]. Remarkably, a recent study found that chronic exposure to the same antagonist resulted in an increase in time spent in the center zone of the OFT, suggesting an anxiolytic-like effect of A_1R antagonism [249], and highlighting that chronic and acute administration of A_1R antagonists may have quite distinct, if not entirely opposite effects. Such differences are expected from a pharmacological point of view, and has been documented several times in relation to other A1R-mediated effects of the antagonists [56,61,250]. Moreover, different outcomes as a function of the tests used are also expected. Indeed, it has been reported that while acute administration of the highly selective A_1R antagonist FR194921 does not significantly impact FST immobility, it does show

significant anxiolytic like effect in the SIT and the EPM, while also reversing scopolamine-induced deficits in passive place avoidance [251].

In zebrafish, acute DPCPX administration was associated with an increased in anxiety-like behavior in the scototaxis test, in addition to leading to increased autonomic arousal [252].

In addition to their standalone effects, the potential of A_1R antagonists as adjunct to antidepressant drug treatments has also been assessed. It has been recently demonstrated that while DPCPX acutely enhances the antidepressant-like effect of sub-active doses of imipramine, escitalopram, and reboxetine [248], it does not have a similar interaction with the atypical antidepressants agomelatine and tianeptine [246]. Furthermore, another study reported a similar acute DPCPX-induced potentiation of the antidepressant-like effects of mocloblemide and bupropion in both the FST and TST, and of venlafaxine in the FST alone [245]. On the other hand, acute administration of the same compound effectively abolished the antidepressant-like effect of zinc administration in the mouse FST [213], as well as the antidepressant-like effects of the NMDAR antagonist MK-801 in zebrafish [202].

One of the most puzzling treatments to have demonstrated antidepressant efficacy is acute sleep deprivation [253]. In fact, while the entire mechanism by which this intervention leads to a reduction in depressive symptomatology is not understood, it has been suggested that increased adenosine levels leading to an increase in A_1R signaling play a fundamental role in those effects [43,254]. Indeed, adenosine levels are known to increase in response to sleep deprivation [254]. Moreover, it has been recently demonstrated that astroglial A_1R activation is necessary for the sustained antidepressant-like effects following 12, but not 72, hours of sleep deprivation, such that these effects are absent in A_1R KO mice [238,239]. Furthermore, in line with this, there is evidence that sleep deprivation leads to a rapid upregulation of A_1R, in both humans [255] and animals [256–258].

Like sleep deprivation, ECT is known to have rapid and pronounced antidepressant effects. Moreover, similarly as to what is the case for sleep deprivation, ECT has been shown to both increase brain adenosine levels [259], as well as to upregulate A_1R [212,260]. Furthermore, it has been proposed that, insofar NMDAR antagonists are antidepressant, and A_1R signaling restrains NMDAR activation, this may play a role in the antidepressant effects of ECT [161,204].

Transcranial direct current stimulation (tDCS) is a non-invasive technique of brain stimulation that modulates cortical excitability, and has shown some promise in the treatment of MDD [261,262]. While, to the best of our knowledge, there is no study determining whether the antidepressant-like effects of tDCS are A_1R-dependent, it must be noted that, in rabbits, tDCS-induced modulation of cortical excitability appears to rely on A_1R activation, as shown by the fact that local application of an A_1R antagonist prevented the antidepressant-like effects of tDCS [263].

Similarly to tDCS, deep brain stimulation (DBS) has recently been the focus of increasing study as a putative therapy for MDD [264]. It is known that the therapeutic effects of DBS in both epilepsy [265] and the control of tremors [266] are associated with a marked accumulation of adenosine, resulting in increased A_1R activation. Thus, it has been proposed that this mechanism may also underpin the antidepressant-actions of DBS [43,267].

The involvement of A_1R in MDD has further been probed by genetic manipulation studies in animals, the majority of which have focused on the KO of A_1R. While assessing A_1R KO mice in both the FST and TST, no significant performance differences were observed relative to WT levels [238]. However, a subsequent study found that A_1R deletion resulted in a significant increase in susceptibility to the deleterious effects of a repeated swim stress protocol, behavioral signs of depressive-like behavior developed more rapidly and pronouncedly than in WT animals [239]. Congruently, when tested in the TST and the SPT, A_1R KO mice presented marked increases in depressive-like behaviors [239].

In addition, a few studies have assessed parameters related to anxiety-like behavior. It was found that A_1R KO mice have increased anxiety-like behavior in the LDBT [268,269], as well as in the OFT, EPM, and holeboard tests, while also being significantly more aggressive than their WT counterparts in the resident-intruder test [269]. However, a subsequent study found A_1R KO mice to have almost entirely WT-like performance in a battery of tests of anxiety-like behavior, with no differences being found either in the LDBT, the OFT, or the O-Maze, and only a small increase in anxiety-like behavior observed in the emergence test [270]. In addition, at the neurochemical level, it has been reported that despite having normal corticosterone responses to acute restraint stress, A_1R KO mice evidenced abnormally high adrenaline – but not noradrenaline (NA) – levels after that stress exposure [271]. Furthermore, after chronic restraint stress, no differences were observed between WT and A_1R KO mice, in any of the aforementioned neurochemical parameters [271].

Lastly, there have been two studies assessing how increasing A_1R signaling via its overexpression impact depressive-like behaviors. In line with the apparent antidepressant-like effects of A_1R agonists, A_1R overexpression has been shown to result in decreased immobility in both the FST and the TST [239]. Furthermore, by selectively turning A_1R overexpression on or off during repeated swim stress exposure, as well as after its end, it was concluded A_1R overexpression increased resilience to the deleterious effects of stress, but that this resilience only translated into reduced TST and FST immobility times, and increased sucrose preference, if overexpression was maintained after the end of stress exposure [239]. Moreover, increasing A_1R overexpression exclusively after the end of repeated swim stress, had a significant antidepressant-like effect in the above mentioned tests [239]. Curiously, in a recent study, the same authors observed that the effects of A_1R overexpression may be contingent upon the brain regions in which such overexpression occurs. Indeed, by comparing the behavioral profiles of two strains overexpressing A_1R in forebrain neurons, one of which also had hippocampal A_1R overexpression, a clear difference emerged [272]. Specifically, forebrain-only A_1R overexpression resulted in a similar resilience-promoting and antidepressant-like effect as that previously reported, in addition to also resulting in anxiolytic-like effects in the EPM, OFT, and LDBT [272]. Contrastingly, while combined forebrain and hippocampal A_1R overexpression also lead to decreased TST and FST immobility, and anxiolytic-like effects in the EPM, OFT, and LDBT, without previous stress exposure, it did result in a decrease in resilience to the effects of repeated swim stress, and in an increase anhedonic-like behavior in the SPT [272]. As such, it seems to be the case that hippocampal A_1R expression is a key regulator of resilience to the prodepressant effects of stress [272].

In sum, there is considerable evidence to suggest that A_1R play a key role in the modulation of depressive and anxious behaviors, and may represent an important target for future drug development. Indeed, A_1R activation was almost entirely reported to produce therapeutic effects, and is a likely mechanism for the antidepressant actions of multiple existing non-pharmacological treatments. As such, future research should focus on better understanding the specific pathways and mechanisms underpinning the antidepressant effects of A_1R agonists, as well as in studying the interaction between this receptor and the $A_{2A}R$. Furthermore, it would be interesting to perform studies that more accurately determine the role of A_1R in the antidepressant-like effects of non-pharmacological interventions such as ECT, tDCS, and DBS.

3.5.2. $A_{2A}R$

Given its widely described role as a regulator of synaptic activity, plasticity, and function, it is unsurprising that considerable research has been performed aiming at understanding how $A_{2A}R$ is altered in the context of MDD, and how manipulations targeting it change depressive symptomatology.

In a small study, MDD patients showed a lower change of platelet intracellular Ca^{2+} in response to different doses of $A_{2A}R$ agonist

CGS21680, relative to controls [273]. Interestingly, another cross study of 1253 individuals from Brazil demonstrated that a TT genotype on the rs2298383 SNP in the *ADORA2A* gene, encoding $A_{2A}R$, is associated with higher resilience to depression, as well as disturbances in sleep and attention, which are common symptoms of MDD [274]. Moreover, there is evidence for an association between specific *ADORA2A* polymorphisms and panic disorders [275,276]. On the other hand, a study focusing on the rs5751876 SNP, in an Asian population that included 192 subjects with mood disorders patients and 216 control subjects, did not observe any correlation between this SNP and MDD [277].

In animal studies, sub-chronic restrain stress has been shown to lead to an increase in hippocampal $A_{2A}R$ expression [235], whereas exposure to a chronic mild stress paradigm was shown to result in the upregulation of striatal $A_{2A}R$ binding [236]. Likewise, in the helpless mouse (HM) mouse model of MDD, an increase in hippocampal $A_{2A}R$ density was reported [278]. Interestingly, while not an animal model of MDD, it was demonstrated that adult rats, submitted to hyperthermia-induced seizures during the neonatal period, displayed a depressive like behavior accompanied by an upregulation of cortical $A_{2A}R$ receptors as well as an increase in its functionality [279]

In addition, there is a considerable number of studies reporting the impact of pharmacologically targeting $A_{2A}R$ on depressive-like symptomatology.

It has been reported that acute treatment with the $A_{2A}R$ agonist DPMA, had no effects on anxiety-like behaviors in mice [240]. Furthermore, combined administration of DPMA and the selective A_1R agonist CPA, prevent the anxiolytic-like effect of the latter [240]. Interestingly, CGS21680, another $A_{2A}R$ selective agonist, when acutely infused into the nucleus accumbens (NAc) of normal rats, led to an identical deficit to that induced by inescapable electric shock stress, in the learned helplessness paradigm [280]. Accordingly, a recent study demonstrated that acute CGS21680 treatment induced an anxiogenic-like effect in normal mice [281]. Curiously, however, these results may need to be considered in light of the fact that CGS21680 administration has been shown to induce reductions in locomotor activity, which may underpin its apparent anxiogenic-like effect in the EPM [282]. Nonetheless, it should be noted that – despite the apparent prodepressant effects of $A_{2A}R$ activation – co-administration of DPMA potentiated the antidepressant-like effect of sub-effective doses of zinc in the mouse FST [213].

Congruently with the above described evidence of an apparent prodepressant-like impact of $A_{2A}R$ activation, $A_{2A}R$ antagonists have been overwhelmingly shown (but see ref [283]) to exert significant antidepressant-like [284], but not anxiolytic-like effects [240,282,283]. Indeed, the $A_{2A}R$ antagonists SCH58261, SCH412348, preladenant, DMPX and istradefylline (KW6002) have all be shown to acutely reduce immobility in the FST and TST [285–288]. However, it must be noted that in two of these studies a drug-induced increase in spontaneous locomotor activity was also observed, complicating the interpretation of FST and TST results [285,287]. Likewise, a study assessing the antidepressant and anxiolytic potential of a series of novel $A_{2A}R$ antagonists (KD66, KD167 and KD206), found that while only KD66 appeared to have anxiolytic-like effects, all three compounds reduced immobility time in the FST and the TST after both acute and chronic treatment [289]. Remarkably, this effect was observed, despite spontaneous locomotor activity being unaltered or, in some instances, actually reduced by drug treatment [289]. Moreover, chronic KW6002 administration improved the inescapable shock-induced escape deficit in a rat learned helplessness model, with an effect comparable to that of desipramine and fluoxetine [280]. In accordance, it was reported that chronic KW6002 treatment had a protective effect over chronic stress-induced impairments in behavioral tests of memory, as well as in the FST and TST [290]. Similarly, it was observed that acute administration of the $A_{2A}R$ antagonists CSC and DMPX could revert the prodepressant effects of reserpine and interleukin 1β administration [247,291]. Additionally, in OBX rats, 14-day treatment with the $A_{2A}R$ antagonist ZM241385 was

decreased immobility in the FST, normalized indexes of anxiety-like behavior in the OFT, and reversed anhedonic-like behavior in the SPT [233].

The capacity of $A_{2A}R$ antagonists to prevent/reverse behavioral alterations associated with depressive-like phenotypes has been shown to be correlated to additional neurobiological effects. Indeed, concomitant SCH58261 administration was shown to prevent early hippocampal modifications induced by sub-chronic restraint stress exposure [235]. Likewise, chronic KW6002 treatment reversed stress-mediated hippocampal deficits in the maternal separation model of MDD [151]

In addition to their standalone effects, $A_{2A}R$ antagonists have shown remarkable promise as putative add-on therapies for existing antidepressant compounds. Indeed, $A_{2A}R$ antagonists have been shown to acutely potentiate the therapeutic effects of antidepressants spanning multiple classes and mechanisms of action, such as fluoxetine [286], paroxetine [286], escitalopram [288], imipramine [288], deprenyl [286], mocloblemide [245], venlafaxine [245], reboxetine [288], bupropion [245], tianeptine [246], and agomelatine [246]. Curiously, but in agreement with what has been reported for $A_{2A}R$ agonists, co-administration of the $A_{2A}R$ antagonist ZM241385 with zinc, reduced the antidepressant-like effects of the latter [213].

One interesting niche application of $A_{2A}R$ antagonists is in the mood symptoms associated with Parkinson's disease (PD). Indeed, not only is KW6002 already approved for PD pharmacotherapy, as an adjunct to L-Dopa/Carbidopa treatment, but there is some tentative evidence that it may reduce depressive symptomatology in these patients. Specifically, two open label studies with PD patients reported that KW6002 led to significant reductions in depressive, anhedonic, and apathy symptomatology [292,293]

Congruently, in a recent study, a newly developed $A_{2A}R$ antagonist (compound 33), acutely administered to PD rat models, had significant beneficial effect in the FST and TST [294]. Likewise, Lu AA47070A, another $A_{2A}R$ antagonist, acutely improved the results of PD rat models, in effort-related choice behavior measures, suggesting possible usefulness in the motivational symptoms of MDD [295]. Interestingly, these effects of $A_{2A}R$ antagonists may be also associated with the modulation of DAergic transmission, since $A_{2A}R$ are known to directly interact with D_2R, decreasing their activity [296–298]. Accordingly, acute administration of the $A_{2A}R$ antagonists MSX-3 or KW6002, or of the MSX-2 prodrug MSX-4, reversed the decreased in effort-related behaviors induced by D_2R antagonist administration [299–301]. Furthermore, it has been suggested that this interaction may also hold functional significance for the remaining antidepressant-like effects of $A_{2A}R$ antagonists, such as decreased FST/TST immobility [285,286].

While the effects of sleep deprivation are thought to be primarily mediated by A_1R signaling, it is notable that 3–6 h sleep deprivation episodes were found to downregulate olfactory tubercle $A_{2A}R$ [256,302]. Thus, considering that $A_{2A}R$ stimulation inhibits A_1R activity [303] it is compelling to speculate that $A_{2A}R$ downregulation may be involved with the antidepressant effects of sleep deprivation mediated by A_1R.

Work concerning genetic manipulation of $A_{2A}R$ expression has largely confirmed the pharmacological findings. Specifically, in line with the notion that $A_{2A}R$ activation has a prodepressant-like impact, it has been reported that adult rats overexpressing human $A_{2A}R$ in neurons present with a depressive-like phenotype, as evidenced by increased FST immobility, decreased sucrose preference in the SPT, in addition to presenting hyperlocomotion [304]. Conversely, and again in agreement with $A_{2A}R$ antagonist studies, $A_{2A}R$ knockout mice show increased decreased immobility in the FST/TST [305]. Furthermore, these animals show increased resilience to the deleterious effects of chronic stress exposure at the behavioral, neurochemical and synaptic plasticity levels [290].

In summary, there is considerable evidence to support the notion that $A_{2A}R$ plays an important role in the pathophysiology and treatment of MDD. Indeed, evidence suggests that increased $A_{2A}R$ signaling –

which can be triggered by stress exposure – has largely prodepressant effects, which can be prevented or reversed by treatment with $A_{2A}R$ antagonists. Importantly, it should be noted that insofar $A_{2A}R$ antagonists are known to increase locomotor activity, data derived from tests vulnerable to being biased by locomotor changes (e.g., FST, TST) have to be interpreted cautiously. Nonetheless, congruent $A_{2A}R$ antagonist-induced antidepressant-like effects were found in tests not reliant on locomotor measures, such as the SPT, and these treatments also appeared to have beneficial effects on the motivational symptoms of MDD as well. As such, future studies should focus on determining the specific mechanisms underpinning the antidepressant actions of $A_{2A}R$ antagonists (e.g., interactions with A_1R and/or D_2R), as well as on exploring the role played by this receptor in the pathophysiology of MDD.

3.5.2.1. Caffeine. Caffeine is by far the most widely consumed psychoactive substance in the world, being used for its positive effects on mood and alertness. Importantly, while caffeine is a non-selective adenosine receptor antagonist, it is commonly thought that the majority of its therapeutic and neuroprotective effects primarily derive from $A_{2A}R$ antagonism.

Human epidemiological data has consistently shown that caffeine intake is associated with a decreased risk of MDD diagnosis. A 10-year prospective study of over 50,000 US women free from MDD at baseline, found those individuals consuming 2–3 cups of coffee a day were at a decreased risk of being diagnosed with MDD, in relation to those consuming 1 or less cups a day [306]. Similarly, a subsequent meta-analysis of observational studies found evidence for a dose-dependent protective effect of coffee – but not tea – over depressive symptoms [307]. Largely in agreement, another meta-analysis found a similar dose-dependent effect, hereby MDD risk decrease by approximately 8% for each daily cup consumed [308]. Furthermore, these authors found that the beneficial effects of caffeine did not follow a linear progression, but were greater at 68−509 mg/day [308].

In line with this, multiple animal studies have reported that acute administration of caffeine induces a significant antidepressant-like effect, as evidenced by decreased immobility time in both the FST and the TST [309–311] (but see reference [225]), and by improved escape behavior in the escape shuttle paradigm [312]. In fact, this was the case even after animals had been previously exposed to an chronic unpredictable stress protocol, as shown by an acute dose-dependent caffeine-induced decrease in FST immobility time [313]. Similarly, a single administration of caffeine was enough to rescue reserpine-induced increases in FST immobility time, suggesting an antidepressant effect [247]. However, it must be noted that while this latter study did not control for the possible locomotor effects of caffeine [247], in the former work a significant increase in spontaneous locomotor activity was observed after caffeine treatment [313], which may have led to the effects observed in the FST.

Like acute treatment, chronic caffeine treatment seems to have a significant antidepressant effect, which may result from the fact that $A_{2A}R$, unlike A_1R, are less prone to adapt while chronically manipulated. Indeed, it has been reported that 2-week daily caffeine treatment, starting after a 4-week chronic unpredictable stress protocol, had a protective effect [314]. Specifically, these authors observed that, despite caffeine inducing anxiogenic-like effects in control animals, in stress-exposed subjects it had anxiolytic- and antidepressant-like effects, in the EPM, as well as the FST and the SPT, respectively [314]. Moreover, not only did caffeine treatment prevent the stress-induced decrease in hippocampal 5-HT and DA levels, it actually raised them above control-levels [314].

Furthermore, in addition to treating already present depressive-like deficits – and in line with the human data reported above – there is evidence to support the notion that chronic caffeine treatment may have a prophylactic effect against the deleterious effects of stress. Indeed, a

recent study demonstrated that 3-week caffeine exposure prior to the onset of a chronic unpredictable stress protocol, largely prevented the development of increased anxiety- and depressive-like behaviors, of cognitive impairments, and of several MDD-associated neurobiological alterations, such as increased corticosterone levels, astrogliosis, and loss of synaptic markers [290]. In line with this, a recent study reported that chronic (14 day) pre-treatment with caffeine protected mice against the prodepressant and anxiogenic effects of a CSDS protocol, as assessed in the OFT, SIT and SPT [315]. Intriguingly, however, similar effects were not observed if chronic treatment started at the same time, or after the end of, CSDS exposure [315]. Likewise, acute treatment, irrespectively of whether performed before the onset of CSDS or after its end, had no protective effect [315]. Curiously, these authors also found that in non-CSDS-exposed animals, chronic caffeine treatment had no impact on baseline FST, TST or OFT performance [315]. Similarly, in a study using HM, while chronic caffeine intake reversed memory deficits and the loss of hippocampal synaptic markers – possibly due to antagonism of upregulated hippocampal $A_{2A}R$ – it had no effect on depressive- or anxiety-like behaviors [278].

On the other hand, it has been reported that simultaneous chronic daily exposure to restraint stress and caffeine, resulted in a male-specific decreases and increases in plasma corticosterone, and hippocampal DNA damage [316]. Furthermore, these authors found that caffeine – both with and without concomitant restraint stress exposure – also induced male-specific increases in anxiety-like behavior, in the EPM [316].

Finally, one consistent finding relates to the synergistic effect of caffeine with conventional antidepressant treatments. Indeed, it has been consistently demonstrated that a sub-active dose of caffeine is capable of significantly increasing the antidepressant-like effects of conventional antidepressant compounds belonging to multiple classes, including SSRIs [311], TCAs [311], 5-HT and NA reuptake inhibitors [310,317], NA and DA reuptake inhibitors [310,317], reversible monoamine oxidase A inhibitors [317], NAergic and specific 5-HTergic antidepressants [318], melatonin receptor agonists [318], NMDAR antagonists [309]. Remarkably, this potential as an effective add-on treatment to antidepressant drugs has also been demonstrated in human MDD patients, taking the SSRI escitalopram [319]. However, it must be noted that while caffeine may potentiate the effects of antidepressant compounds, caffeine withdrawal may have the opposite result. Indeed, a recent study with rats exposed to caffeine for 14-days found that, whereas caffeine-maintained animals showed an increased antidepressant-like response to sub-effective SSRI treatment, in animals undergoing caffeine withdrawal the opposite was observed [311].

Altogether, data derived from caffeine studies not only reinforces the potential of $A_{2A}R$ antagonism as a highly viable strategy for the treatment of MDD, but also highlights a highly interesting potential application of caffeine: that of a magnifier of the effects conventional antidepressant drugs. Indeed, it would be extremely interest to analyze existing data from antidepressant drug trials, and determine what – if any – is the impact of caffeine use upon the success of drug therapy. Furthermore, it would be highly relevant to study the specific mechanisms which underpin this apparent caffeine-induced potentiation of antidepressant drug effects.

3.5.3. $A_{2B}R$

To the best of our knowledge there are no published reports assessing if/how $A_{2B}R$ are altered either in MDD patients, or animal models of MDD, nor tying *ADORA2B* polymorphisms to MDD.

Congruently with this lack of data, and despite the apparent role played by $A_{2B}R$ in neuroinflammatory activity [157,320], and the relationship between neuroinflammation and depressive-like states [22, 23], very few reports have actually assessed how $A_{2B}R$-targetted manipulations impact emotional behavior. Specifically, a 2015 study using reserpinized rats found that acute treatment with the selective $A_{2B}R$ antagonist alloxazine had no effect upon the reserpine-induced increases in immobility time in the FST [247]. Curiously, a study with $A_{2B}R$

knockout mice, found them to present a slightly altered anxiety-like behavior profile: while $A_{2B}R$-KO mice did not present changes in anxiety-like behavior, they did spend more time than WT littermates in the center zone of the EPM [321]. Furthermore, these authors reported altered Y-Maze behavior in $A_{2B}R$-KO mice, which they interpreted as indicating an increased exploratory drive [321]. Finally, it has been reported that, while fluoxetine does not directly target $A_{2B}R$, it leads to an increase in BDNF levels – which is known to be associated to antidepressant-like effects – through a mechanism relying on ATP-derived adenosine activating astroglial $A_{2B}R$ [322].

Concluding, there is not enough data to confidently postulate a role for $A_{2B}R$ in the pathophysiology and treatment of MDD. However, in our opinion, this topic should be investigated in future research.

3.5.4. A_3R

There appear to be no published reports assessing A_3R alterations in MDD patients, or animal models. Likewise, we found no reports relating *ADORA3* polymorphisms to MDD. It should be noted, however, that specific *ADORA3* polymorphisms have been associated to altered 5-HT transporter (SERT) function [323]. While these alterations have been exclusively associated to autism spectrum disorders, it is possible – given the role of 5-HT dysfunction in the pathophysiology of MDD, and of 5-HT reuptake inhibition in its treatment – that these *ADORA3* polymorphisms may hold relevance for MDD.

Indeed, despite the fact that A_3R has been shown to directly interact and regulate SERT function [45,323,324], to the best of our knowledge, the effects of A_3R receptor manipulation were only assessed in a single study. Specifically, behavioral phenotyping of A_3R-KO mice revealed no differences from WT littermates regarding anxiety-like behavior, assessed in the EPM and the LDBT [325]. On the other hand, in the FST and the TST, A_3R-KO mice spent significantly more time immobile than WT mice, despite evidencing increased locomotor activity, suggesting an increase in depression-like behavior [325]. Finally, when these animals were exposed to a fear conditioning paradigm, no differences were observed vis a vis WT controls [325].

Similarly to what is the case with $A_{2B}R$, there is not nearly enough evidence to confidently assert the relevance of A_3R as a target for the treatment of MDD, nor as a player in the pathophysiology of the disorder. However, even more than $A_{2B}R$, A_3R may prove to be a highly interesting and fruitful object of MDD research, given its relation with SERT, and is clearly deserving of further study.

4. Concluding remarks

In this work, we aimed at reviewing the available evidence implicating adenosine in the pathophysiology of MDD, as well as the evidence regarding the consequences of manipulating this neuromodulatory system on depressive and anxious symptoms (summarized in Table 3).

Altogether, we believe there is enough evidence to confidently assert that MDD significantly impacts the expression and functioning of the adenosinergic system, with data being most robust regarding A_1R and $A_{2A}R$. Moreover, in our review of the data, we consistently found that increasing adenosine levels – be it through pharmacological or non-pharmacological means – leads to reliable antidepressant and anxiolytic effects. Furthermore, it seems to be the case that these beneficial effects of adenosine, are primarily related to A_1R activation – which was consistently shown to have desirable antidepressant and anxiolytic properties – but not $A_{2A}R$ activation. Indeed, the functional opposition between A_1R and $A_{2A}R$ clearly manifests in the reviewed data: whereas A_1R agonism is antidepressant, $A_{2A}R$ agonism is not. Conversely, whereas A_1R antagonism does not induce desirable effects, $A_{2A}R$ antagonism consistently evokes antidepressant-like effects. As such, it would be interesting to determine whether this functional opposition can be better exploited for therapeutic means, by – for example – combining selective A_1R agonists and $A_{2A}R$ antagonists.

In fact, this is only one of many possible future avenues of research

Table 3

Impact of adenosinergic system manipulations upon anxiety- (A) and depressive-like (D) behaviors.

	Synthetic Enzymes		Transporters		Degradative Enzymes		Receptors			
	CD39	CD73	ENTs	CNTs	ADA	ADK	A_1R	$A_{2A}R$	$A_{2B}R$	A_3R
Agonism	–	–	–	–	–	–	A: ↑ D: ↑	A: ↓/↔ D: ↓	D: ↔	–
Antagonism/Inhibition	A: ↑ D: ↑	–	A: ↑	A: ↑	A: ↑/↓	–	A: ↑/↓/↔ D: ↔	A: ↑ D: ↑	–	–
PAM	–	–	–	–	–	–	A: ↑	–	–	–
Gene Knockout	A: ↑ D: ↑	A: ↔ D: ↔	A: ↑ D: ↑	–	A: ↔	–	A: ↓/↔ D: ↓	A: ↑ D: ↑	A: ↔ D: ↔	A: ↔ D: ↓
Gene Overexpression	–	–	–	–	–	A: ↔	A: ↑ D: ↑	D: ↓	–	–

A_1R, adenosine A_1 receptor; $A_{2A}R$, adenosine A_{2A} receptor; $A_{2B}R$, adenosine A_{2B} receptor; A_3R, adenosine A_3 receptor; ADA, adenosine deaminase; ADK, adenosine kinase; CD39, cluster of differentiation 39; CD73, cluster of differentiation 73; CNTs, concentrative nucleoside transporters; ENTs, equilibrative nucleoside transporters; PAM, positive allosteric modulation; ↑, therapeutic effects; ↓, deleterious effects; ↔, no effects; -, effects not studied.

that we have observed, many of which we have evidenced across the present work. Indeed, despite the apparent promise of the adenosinergic system as a target for the development of novel antidepressant treatments, there are still significant gaps in the already existing literature, as well as important unexplored avenues of research.

For one, there is a clear dearth of studies using models of MDD – that is manipulations purporting to replicate the pathophysiological features of MDD, such as the chronic mild stress model, rather than just a specific endophenotype of it (e.g., FST) [326]. These models are key for a better understanding of how the adenosinergic system itself is first impacted by depressive-like deficits. But more importantly than that, by actually inducing MDD-like neurobiological changes in the animals, these models allow for a more realistic – and, therefore, more likely to have translational success – test of the therapeutic potential of novel adenosinergic compounds.

Likewise, another important gap pertains to the considerable lack of work concerning the $A_{2B}R$ and A_3R, as well as the enzymes and transporters that constitute the adenosinergic system. In fact, given the role of dysfunctional 5-HT signaling and neuroinflammation in the pathophysiology of MDD [15,22,23], the A_3R seems like a prime target for investigation as both a stand-alone and a possible add-on treatment.

On the other hand, we believe that better exploring the possibility that drugs preferentially targeting different A_1R and $A_{2A}R$ populations (e.g., pre- vs. post-synaptic) would also be highly interesting. In fact, it has been shown that the effects of certain compounds are primarily attributable to the activation of receptors located in specific cellular localizations, rather than to the activation of all receptors [49,327]. Similarly, more hypothesis-driven, mechanistic and focused work regarding the specific cellular populations and signaling pathways involved in the effects of adenosinergic drugs – by themselves or in combination with other antidepressant compounds – would be highly desirable. Indeed, one of the most consistently reported findings here reviewed, pertained to the synergistic effect of caffeine and antidepressants [328]. While this combination might not be a true breakthrough in terms of therapeutic effectiveness, it does represent a possibly easy, safe, and affordable way of maximizing the therapeutic benefit of these compounds while also reducing their side-effects by – for example – allowing the use of lower doses.

Lastly, the role played by adenosine receptor heteromers in the pathophysiology and treatment of MDD remains a wholly unexplored field. While this is not entirely surprising, considering how relatively recent the evidence of functional heteromers is, it is the most significant gap in the literature and one that might hold considerable interest. This is all the more surprising when considering that adenosine receptors are known to form functional heteromers not just with one another (e.g., A_1-$A_{2A}R$ [329]), but also with receptors from other systems deeply impacted by MDD [49,330–333]. Moreover, these heteromers have been shown to be involved in the regulation of important processes, whose dysfunction may be key in the development and/or treatment of this

disorder [334]. Critically, the payoff from such research may come in the form not just of a novel and more profound understanding of the pathophysiology of MDD, but also in the form of novel primary or add-on treatments to either increase antidepressant efficacy, or decrease undesirable effects. Indeed, this has already been shown to some extent, as demonstrated by the fact that the deleterious effects of CB_1R agonists can be mitigated through interaction with $A_{2A}R$-CB_1R heteromers [49].

Thus, concluding, we believe that there is ample evidence to support the notion that adenosine and the adenosinergic system is an important player in the pathophysiology of MDD, and represents a prime target for the development of novel drugs for the treatment of this disorder.

Declaration of Competing Interest

The authors report no declarations of interest.

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