Adenosine receptor subtypes, first described 40 years ago, are known to regulate diverse biological functions and have a role in various conditions, such as cerebral and cardiac ischemia, immune and inflammatory disorders and cancer. In the brain, they limit potentially dangerous over excitation, but also regulate mechanisms essential in sleep and psychiatric disorders. In this review, we discuss the role of adenosine receptors in mood and anxiety disorders. Activation of A2A receptors is associated with increased depression-like symptoms, while increased A1 receptors signaling elicits rapid antidepressant effects. Indeed, several lines of evidence demonstrate that the therapeutic effects of different non-pharmacological treatments of depression, like sleep deprivation and electroconvulsive therapy are mediated by A1 receptor up-regulation or activation. In addition, A1 receptors may also play a role in the antidepressant effects of transcranial direct current stimulation and deep brain stimulation. As a potential downstream mechanism, which facilitates the antidepressant effects of A1 receptors, we propose a crosstalk between adenosinergic and glutamatergic systems mediated via synaptic plasticity protein Homer1a and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Moreover, adenosine receptors are also involved in the control of circadian rhythms, sleep homeostasis and some neuro-immunological mechanisms, all of them implicated in mood regulation. Antagonists of adenosine receptors such as caffeine have general anxiogenic effects. In particular, A2A receptors appear to have an important role in the pathophysiology of anxiety disorders. Taken together, the results discussed here indicate that the adenosinergic system is involved in both the etiology and the treatment of mood and anxiety disorders.

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Address correspondence and reprint requests to Dietrich van Calker, Department for Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg; Hauptstrasse 5, 79104 Freiburg, Germany. E-mail: dietrich-van-calker@uniklinik-freiburg.de

Dedicated to Bernd Hamprecht, senior author of the first reports on adenosine receptor subtypes (van Calker et al. 1978, 1979) at the event of his 80th birthday.

Abbreviations used: ADORA2A, adenosine A2 receptor gene; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATP, adenosine triphosphate; BDNF, brain derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase type II; cAMP, cyclic adenosine monophosphate; CBF, cerebral blood flow; CIART, circadian associated repressor of transcription; CMR, cerebral metabolic rate; CUS, chronic unpredictable mild stress; DBP, D-Box binding protein; DBS, deep brain stimulation; dnSNARE, dominant negative SNAP receptor; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; ECT, electroconvulsive therapy; ENT1, equilibrative nucleoside transporter 1; FKBP51, FK506 binding protein 51; GABA, gamma-aminobutyric acid; IL-1β, interleukin 1 beta; mPFC, medial prefrontal cortex; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin; NFkB, nuclear factor kappa B; NMDA, N-methyl-D-aspartate; NPAS4, neuronal PAS domain protein 4; PER2, period circadian regulator 2; PLC, phospholipase C; RORB, RAR related orphan receptor B; SD, sleep deprivation; shRNA, short hairpin ribonucleic acid; siRNA, small interfering ribonucleic acid; SNP, small nucleotide polymorphism; STAR*D, sequenced treatment alternatives to relieve depression; SWS, slow wave sleep; tDCS, transcranial direct current stimulation; TNF-α, tumor necrosis factor alpha; VC, ventral capsule; VEGF, vascular endothelial growth factor; VS, ventral striatum.
Mood disorders including unipolar depressive and bipolar disorders are heterogeneous illnesses, which cause high individual suffering and impose a severe economic burden on society. It is today believed that depression has a complex multifactorial origin in which psychosocial factors interact with neuropsychological factors and a hereditary burden to induce alterations in mechanisms such as neuroplasticity, neurogenesis, and neuroimmunological regulation, the relative impact of which may vary in different subtypes of depressive syndromes (Krishnan and Nestler, 2010). Modern biochemical hypotheses of depression include e.g., alterations in FK506-binding protein (FKBP) 51, a co-chaperone regulating the glucocorticoid receptor (Fries et al., 2017), the central expression of corticotrophin releasing factor (Waters et al., 2015) or alterations in immune parameters (Wohleb et al., 2016). In recent years, the potential role of glutamate signaling in depression has received particular attention since it appears to mediate the rapid antidepressant effects of ketamine (Murrough et al., 2017; van Calker et al., 2018). Glutamate dysfunction is suggested by genetic, post-mortem and in vivo neuroimaging data (Sanacora et al., 2008). On the other hand, facilitation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-dependent glutamate signaling appears to mediate in addition to those of ketamine also the effects of several other antidepressant measures. These include e.g., increased signaling via A1 receptors, sleep deprivation (SD) and of the muscarinic acetylcholine receptor antagonist scopolamine (Freudenberg et al., 2015; van Calker et al., 2018).

Depression is very often found comorbid with anxiety disorders. The sequenced treatment alternatives to relieve depression study discerned a prevalence of anxious depression of 46% (Fava et al., 2004), and a lower response to treatment in the comorbid group compared with the non-depression group has been identified (Fava et al., 2008; Domschke et al., 2010a). However, even when not comorbid with depression, anxiety disorders are among the most disabling conditions affecting up to 10% of the population (Craske and Stein, 2016) if not treated by pharmacotherapy (Koen and Stein, 2011) or psychotherapy (Otte, 2011). In the pathomechanism of anxiety disorders, both genetic (Gottschalk and Domschke, 2016) and psychological mechanisms such as childhood separation (Miltod et al., 2014) appear to be involved.

We have previously suggested a role of adenosine receptors in the regulation of mood (van Calker and Biber, 2005). However, reliable data indicating a potential role of the purines adenosine and adenosine triphosphate (ATP) in mental disorders have been obtained only recently (Yamada et al., 2014; Ortiz et al., 2015; Krugel, 2016; Cheffer et al., 2018). In this article, we will restrict our discussion to some selected aspects of adenosine receptor function in mood and anxiety disorders since the potential role of purine receptors in psychiatric illness in general has been comprehensively discussed recently (Krugel, 2016; Cheffer et al., 2018).

The adenosinergic system

Physiological effects of adenosine were first described by Drury and Szent-Gyorgyi (Drury and Szent-Gyorgyi, 1929) and later shown to be mediated by extracellular receptors (Degubareff and Sleator, 1965; Sattin and Rall, 1970). The existence of two different types of purine receptors for adenosine and for ATP, respectively, was first described by Burnstock (Burnstock, 1978), who suggested naming the receptors for adenosine as P1 and those for ATP as P2. In the same year, we first described the existence of two different types of receptors for adenosine which mediate the inhibition and stimulation of cyclic adenosine monophosphate accumulation and differ in their pharmacological properties (van Calker et al., 1978). Unaware of Burnstock’s nomenclature, we suggested the names A1 (inhibiting) and A2 (stimulating) for these receptors (van Calker et al., 1978, 1979). The coincidence and independence of these two discoveries led to a somewhat confusing twofold nomenclature (P1 receptors vs. A1 and A2 receptors). Almost at the same time Londos and coworkers (Londos et al., 1980) also detected two different types of adenosine receptors that regulated the adenylate cyclase in fat cells which they suggested to be called R1 (inhibiting) and R2 (activating). However, the nomenclature A1 and A2 is now established (Fredholm et al., 2001; Fredholm et al., 2011). The original definition of adenosine receptor subtypes by their effects on adenylate cyclase was soon substituted by a re-definition by means of efficacy of agonists and antagonists, since it became clear that adenosine receptors can have effects on various signal transducing systems. A2 receptors were later found to encompass two different types of receptors, the high affinity A2A and the low affinity A2B receptors, and an additional third adenosine receptor subtype (A3) was identified. These four adenosine receptor subtypes A1, A2A, A2B and A3 are coupled to G-proteins. A1 receptors typically act via the Gi/o
Adenosine receptors in depression and anxiety

family, whereas $A_{2A}$ and $A_{2B}$ receptors act via $G_i$. $A_{2B}$ receptors can also activate phospholipase C via $G_q$. $A_3$ receptors act via $G_i$-mediated inhibition of adenyl cyclase and $G_q$-mediated stimulation of phospholipase C (Fig. 1). The particular structure of these receptors is now ascertained by molecular cloning (Fredholm et al., 2001; Fredholm et al., 2011).

A general principle of adenosine’s action in the body is its activity as an ‘retaliatory metabolite’, which signals an disequilibrium between energy supply and demand and triggers counter-balancing measures such as increase in blood flow and/or diminished cellular activity by activation of adenosine receptors. Presently, adenosine receptors are known to fulfill important regulatory functions in many cells and tissues such as the kidney (Vallon et al., 2006), heart (Mubagwa and Flameng, 2001), lungs (Polosa and Blackburn, 2009) and gastrointestinal tract (Colgan et al., 2013) and have also an important role in several malignancies (Borea et al., 2016) such as respiratory disease (Caruso et al., 2013), inflammatory disease (Aherne et al., 2011) or cancer (Antonioli et al., 2013). However, perhaps the most important regulatory function of adenosine is in the brain. Here, $A_1$ receptors, which have high affinity for adenosine, are distributed both pre- and postsynaptically. Presynaptically, they inhibit the release of excitatory and inhibitory neurotransmitters, e.g., glutamate, dopamine, serotonin and acetylcholine. When situated postsynaptically $A_1$ receptors inhibit neuronal signaling by hyperpolarization and reduce excitability via regulation of potassium channels. $A_{2A}$ receptors are highly expressed on striatopallidal neurons with lower presence in other parts of the brain such as the cortex and hippocampus. They can form heteromers with $A_1$ receptors (Ciruela et al., 2006; Ferre et al., 2008; Cristovao-Ferreira et al., 2013) and with dopamine $D_2$ receptors (Fuxe et al., 2007), which enable adaptive responses in the regulation of synaptic plasticity (Fuxe et al., 2014). Adenosine $A_{2B}$ and $A_3$ receptors may play a protective role in brain ischemia (Pedata et al., 2016) and exitotoxicity (Moidunny et al., 2012).

Extracellular adenosine concentrations in the brain are determined by hydrolysis of ATP released from neurons or astrocytes and by transport through equilibrative nucleoside transporters (e.g., equilibrative nucleoside transporter 1) (King et al., 2006). Under neuropathological conditions (e.g., ischemia, trauma, excitotoxicity, neurodegeneration, neuroinflammation, epilepsy), the extracellular concentration of adenosine in the brain can rise rapidly from nanomolar to micromolar levels, which can have both beneficial and detrimental effects on the course of the illness (Lusardi, 2009; Gomes et al., 2011; Karmouty-Quintana et al., 2013; Melani et al., 2014; Burnstock, 2015; Eisenstein et al., 2015; Beamer et al., 2016; Boison, 2016; Stockwell et al., 2017). In mental illness, much less dramatic alteration in adenosine concentration is observed (Basheer et al., 2004).

Role of adenosine $A_{2A}$ receptors in depression

First evidence that $A_{2A}$ receptors are expressed in the hippocampus and inhibit the activity of $A_1$ receptors was reported already 1994 (Cunha et al., 1994). Later, evidence for an antidepressant-like effect of adenosine $A_{2A}$ antagonists and of $A_{2A}$ deficiency in rodents was provided by El Yacoubi et al (El Yacoubi et al., 2000; El Yacoubi et al., 2001), an effect later confirmed by various groups (El Yacoubi et al., 2003). Thus, over-expression of $A_{2A}$ receptors in forebrain neurons of transgenic rats is associated with increased depression-like behavior (Coelho et al., 2014) and anhedonia, one of the major pathological features of depression. In rodents, chronic unpredictable mild stress leads to an increase in depression-like behavior and is associated with a decrease in synaptic plasticity, a reduced density of synaptic proteins and an increase of $A_{2A}$ receptors in the striatum and in glutamatergic terminals in the hippocampus.
(Crema et al., 2013; Kaster et al., 2015). These behavioral and synaptic alterations induced by chronic unpredictable mild stress appear to be indeed mediated by an increase in adenosine $A_{2A}$ receptors, since they are prevented by caffeine (a non-selective adenosine antagonist for $A_1/A_{2A}$ receptors, which however elicits its effects on mood predominantly via antagonism at adenosine $A_{2A}$ receptors), by selective $A_{2A}$ receptor antagonists and by $A_{2A}$ receptor deletion in forebrain neurons (Kaster et al., 2015). Furthermore, $A_{2A}$ receptor antagonists evoke antidepressant-like effects in the forced swim test and the tail suspension test in rodents (Fig. 2) (Hodgson et al., 2009; Yamada et al., 2013). In particular, depression-associated psychomotor slowing, fatigue and anergia are improved by $A_{2A}$ receptor antagonists (Randall et al., 2011). This particular cluster of symptoms is also improved by modest doses of caffeine (Smith, 2009), apparently acting via antagonism at $A_{2A}$ receptors (Fig. 2) (Lopez-Cruz et al., 2018). Very recent evidence indicates that blockade of $A_{2A}$ receptors by a selective antagonist enhances the antidepressant-like activity of antidepressant medications such as tianeptine and agomelatine in mice behavioral despair tests (Szopa et al., 2019). Furthermore, $A_{2A}$ receptor blockade also reverts stress-induced hippocampal-related deficits induced by maternal separation (Batalha et al., 2013). At first sight, these antidepressant-like effects of $A_{2A}$ receptor antagonists appear to be inconsistent with the reported up-regulation by $A_{2A}$ receptor agonists of brain-derived neurotrophic factor (BDNF) expression in rat primary cortical neurons (Jeon et al., 2011), since BDNF has well documented antidepressant-like effects (Bjorkholm and Monteggia, 2016; van Calker et al., 2018). However, the effects of adenosine $A_{2A}$ receptor activation on BDNF appear to be complex (Rombo et al., 2016). Thus, e.g., in the hippocampus adenosine via $A_{2A}$ receptors influences BDNF actions on gamma-aminobutyric acid (GABA) transmission affecting both glutamatergic inputs to pyramidal neurons and cholinergic inputs to GABA-ergic interneurons. It can also affect $A_{2A}$ receptor-dependent facilitation of GABA uptake into astrocytes with consequent increase in GABA clearance from the synapses (Rombo et al., 2016). Furthermore, both anti-depressive-like and pro-depressive-like behaviors are associated with BDNF. To what extent one of these two opposite effects on behavior (anti-depressant or pro-depressant) dominates depends on the brain area and the brain cells in which these genes are activated (van Calker et al., 2018). How the predominant antidepressant-like effects of antagonism at $A_{2A}$ receptors are mediated is unknown. However, since $A_{2A}$ receptors are often found to inhibit the actions of $A_1$ receptors (Stockwell et al., 2017), one possible explanation for the antidepressant-like effects of $A_{2A}$ antagonists is the facilitation of activity of $A_1$ receptors (Fig. 2). Also genetic variations in the adenosine $A_2$ receptor gene were shown to modify the risk of depression (Gass et al., 2010). Thus, the TT genotype of an adenosine $A_2$ receptor gene small nucleotide polymorphism was associated with reduced risk for depression when compared to the CC/CT genotypes (Oliveira et al., 2019).

**Role of adenosine $A_1$ receptors in depression**

Antidepressant effects of activation of adenosine $A_1$ receptors were first suggested by our group (van Calker and Biber, 2005) and later experimentally confirmed by Hines et al. (Hines et al., 2013) and our group (Serchov et al., 2015). Our suggestion (van Calker and Biber, 2005) was based on findings indicating that the therapeutic effects of SD and electroconvulsive therapy (ECT) are closely related to changes in slow wave sleep, cerebral metabolic rate, and cerebral blood flow, parameters that are at least in part regulated by signaling through adenosine $A_1$ receptors. Hines et al. later indeed demonstrated a significant correlation between the ability of SD to both activate $A_1$ receptor signaling pathways and to promote antidepressant-like effects (Hines et al., 2013). They showed that $A_1$ receptors are required for the antidepressant effect of SD and that activation of $A_1$ receptors leads to sustained antidepressant-like behaviors. These authors also claimed that the antidepressant-like effect of SD is mediated by astrocytes, since the dominant-negative SNAP receptor (dnSNARE) transgene in astrocytes (SNARE proteins mediate fusion of vesicles with their target membrane, a process inhibited by dnSNARE) impaired the ability of SD to reduce immobility time in both the forced swim and tail suspension tests. However, these conclusions have been questioned on the grounds that expression of the dnSNARE transgene was not restricted to astrocytes but also found in cortical neurons (Fujita et al., 2014).

The fact that activation of adenosine $A_1$ receptors indeed evokes pronounced antidepressant effects was shown by our group in a line of transgenic mice in which an over-expression of $A_1$ receptors can be switched on and off (Serchov et al., 2015). This antidepressant effect of $A_1$ receptor activation is, mediated by neuronal $A_1$ receptors, since the $A_1$ transgene expression in these mice is restricted to calcium/calmodulin-dependent protein kinase type II forebrain neurons (Serchov et al., 2012; Serchov et al., 2015). Up-regulating $A_1$ receptors by activation of the transgene in these mice led to pronounced acute and chronic resilience toward depressive-like behavior in various tests. On the other hand, $A_1$ receptor knockout mice displayed an increased depressive-like behavior and were resistant to the antidepressant effects of SD, indicating that the antidepressant effects of SD are largely mediated by the up-regulation of adenosine $A_1$ receptors induced by SD (Fig. 2) (Serchov et al., 2015). Furthermore, we have shown that the antidepressant effects of $A_1$ receptor activation are mediated by the immediate early gene Homer1a, which is up-regulated by various antidepressant treatments such as SD, imipramine,
Ketamine as well as A1 receptor activation (Fig. 2). Indeed, small interfering ribonucleic acid knockdown of Homer1a in the medial prefrontal cortex (mPFC) enhanced depressive-like behavior and prevented the antidepressant effects of A1 receptor up-regulation, SD, imipramine and ketamine, while viral over-expression of Homer1a in the mPFC exerted antidepressant effects. Thus, Homer1a in the mPFC is a final common pathway mediating the antidepressant effects not only of adenosine A1 receptor activation but also of different other antidepressant treatments (Serchov et al., 2015; Serchov et al., 2016). Very recently, we have shown that this antidepressant effect of Homer1a activation is due to Homer1a induced constitutive agonist-independent mGluR5 activation, resulting in enhanced AMPA receptor-mediated synaptic transmission (Holz et al., 2019).

**Potential role of adenosine receptors in bipolar disorders**

The idea that adenosine receptors might be involved in the pathophysiology of bipolar disorder goes back to findings of an increased excretion of uric acid, a metabolite of adenosine, in manic patients (Machado-Vieira et al., 2002). Since then these findings have been confirmed by several groups suggesting a purinergic system dysfunction associated with manic phases of bipolar disorder (Machado-Vieira et al., 2002; De Berardis et al., 2008; Salvadore et al., 2010; Bartoli et al., 2016; Bartoli et al., 2017a; Bartoli et al., 2017b). This may also be related to the efficacy of allopurinol, which increases adenosine levels by inhibiting purine degradation (Marro et al., 2006; Schmidt et al., 2009), in treating acute mania when used adjunctively with lithium (Akhoundzadeh et al., 2006; Machado-Vieira et al., 2008) or valproate (Jahangard et al., 2014). This effect was, however, not evident when allopurinol was used in the absence of lithium or valproate (Weiser et al., 2014; Bartoli et al., 2017b). It is, however, still unclear, whether or not these findings, in the periphery, indeed indicate an adenosine dysfunction in bipolar disorder in the brain (Hirota and Kishi, 2013; Ortiz et al., 2015; Gubert et al., 2016). Evidence from association studies does not give any indication that genetically determined variation of the A1 receptor and its two promoters could play a major role in the development of bipolar affective disorder (Deckert et al., 1998a). Whether or not adenosine A1 receptors are also involved in manic-like behavior remains to be established. Indeed, SD, which up-regulates A1 receptors, not only has antidepressant effects but can also trigger symptoms of mania or hypomania in certain bipolar patients (Wehr, 1989; Lewis et al., 2017). Furthermore, there is evidence that carbamazepine, which is approved for the treatment of acute and dysphoric mania (Baldessarini et al., 2019) acts as a specific antagonist of adenosine A1 receptors (Van Calker et al., 1991). Via up-regulation of expression of A1 receptors carbamazepine may also induce a new quality of adenosine A1-receptor-mediated signal transduction in cells that initially express low basal A1-receptor numbers (Biber et al., 1996; Biber et al., 1999).
Role of adenosine A\textsubscript{1} and A\textsubscript{2A} receptors in anxiety disorders

In general, agonistic actions at A\textsubscript{1} receptors appear to promote anxiolytic effects (Jain et al., 1995; Florio et al., 1998; Vincenzi et al., 2016), whereas cyclopentyltheophylline, an A\textsubscript{1} antagonist, had anxiogenic properties (Florio et al., 1998). However, the investigation of other A\textsubscript{1} antagonists gave mixed results (Correa and Font, 2008). Unspecific antagonists of adenosine receptors appear to exert general anxiogenic effects. Thus, non-selective adenosine antagonists like caffeine, theophylline, theobromine (Charney et al., 1985; Lee et al., 1988; Kulkarni et al., 2007; Lopez-Cruz et al., 2014) and isobutylmethylxanthine (Florio et al., 1998) elicit anxiety related behavior. While the effects of caffeine on mood and memory (Kaster et al., 1997) as well as on wakefulness (Huang et al., 2005; Lazarus et al., 2011) appear to be mediated via antagonism at adenosine A\textsubscript{2A} receptors (see above), no definitive information is available about the adenosine receptor subtype mediating the anxiogenic effects of caffeine. At least in rodents, the anxiogenic effect of caffeine is not mimicked by selective A\textsubscript{2A} receptor antagonists (El Yacoubi et al., 2000), and increased anxiety-like behavior is observed not only in A\textsubscript{2A} (Ledent et al., 1997; Deckert, 1998) but also in A\textsubscript{1} (Johansson et al., 2001; Gimenez-Llort et al., 2002) receptor knockout mice. Thus, both adenosine receptors subtypes A\textsubscript{1} and A\textsubscript{2A} may play a role in anxiety at least in rodents.

The effects of A\textsubscript{2A} receptors in anxiety in rodents have been investigated in some detail: A\textsubscript{2A} receptor knock-out mice exhibit not only increased anxiety-like behavior but also increased c-Fos immunoactivity in the anterior cingulate cortex and the amygdala as compared to wild-type mice (Lopez-Cruz et al., 2017). However, the effects of A\textsubscript{2A} receptors on anxiety-like behavior in rodents are variable and highly dependent on the brain region. Thus, selective down-regulation of the A\textsubscript{2A} receptor in the basolateral complex of the amygdala by means of a lentivirus with a silencing short hairpin ribonucleic acid impaired fear acquisition as well as Pavlovian fear retrieval (Simoes et al., 2016). On the other hand, adult male rats over-expressing the human A\textsubscript{2A} receptor in forebrain neurons not only showed increased depressive-like behavior (see above) but also covered higher distances in the open field test and spent more time in the central zone than wild-type rats (Coelho et al., 2014). While this might indicate reduced anxiety-like behavior, the authors argue that there is a mutual influence between anxiety and locomotor activity even though locomotion and anxiety are differentially regulated by adenosine A\textsubscript{2A} receptors. Thus, the reason for the discrepancy between depressive-like behavior on the one hand and increased exploratory behavior on the other remains unexplained (Coelho et al., 2014).

Indeed, deletion of A\textsubscript{2A} receptors in the forebrain rather inhibited fear conditioning, whereas deletion of A\textsubscript{2A} receptors in the striatum facilitated Pavlovian fear conditioning (Wei et al., 2014).

In humans, there is evidence from genetic studies for a potential role of the adenosine A\textsubscript{2A} receptor gene in anxiety disorders. The T allele of a silent polymorphism in exon 2 of the adenosine A\textsubscript{2A} receptor gene located on chromosome 22q11.23 (small nucleotide polymorphism rs5751876, 1976T>C, formerly 1083T>C, Tyr>Tyr) was consistently found associated with panic disorder (Deckert et al., 1998b; Hamilton et al., 2004; Rogers et al., 2010). However, no such association was discerned in populations of Asian descent (Yamada et al., 2001; Lam et al., 2005). This rs5751876 T risk allele – partly epistatically with another allele (2592 Tins/Tins genotype) – has furthermore been observed to significantly influence anxiety response after caffeine as well as amphetamine administration (Alsene et al., 2003; Hohoff et al., 2005; Childs et al., 2008). The mechanism by which this genotype (rs5751876 TT) may increase the risk for anxiety disorders was investigated in healthy probands. The TT genotype was found associated with increased connectivity between the insula and the prefrontal cortex along with heightened interoceptive accuracy (Geiger et al., 2016). Interoception denotes the sense of the internal state of the body as relayed from the body to specific subregions of the brain such as the brainstem, thalamus, insula, and anterior cingulate cortex. Increased interoception can lead to emotional distress, particularly in individuals with higher sensitivity for anxiety, and contribute to the predisposition to anxiety disorders (Domschke et al., 2010b). Furthermore, carriers of the risk genotype mentioned above (rs5751876 TT) showed the highest startle magnitudes after caffeine administration in response to unpleasant pictures in an emotion-potentiated startle paradigm, with this effect arising particularly from the female subgroup (Domschke et al., 2012a). In addition, female homozygous carriers of this genotype showed other distinctive features such as an impaired ability to selectively process very early information and to gate irrelevant sensory information as measured by the prepulse inhibition/facilitation paradigm (Gajewska et al., 2013). These findings in healthy probands could indicate that – under adverse life conditions – certain genotypes may confer an increased risk to develop one form of anxiety disorders. However, how these particular genotypes may lead to modifications in behavior is unclear, since they are not associated with changes of the amino-acid sequence of the A\textsubscript{2A} receptor. Hamilton and colleagues (Hamilton et al., 2004) discuss the possibility that these ‘silent’ variants may cause functional variation via codon preference during translation. Indeed, recent research has revealed mechanisms how “codon bias” can guide codon usage in translation and thereby alter the efficiency of protein production (Hanson and Coller, 2018).

Several other studies have revealed an interaction of the adenosinergic system with other systems pivotally involved...
in the pathogenesis of anxiety and panic disorder in particular such as the neuropeptide S system (Domschke et al., 2012b) or the dopaminergic system (Childs et al., 2008). A recent study implied that regular exercise exerts its anxiolytic effect by inhibiting A2A receptor function via enhancing serotonin 2A receptor signaling in the basolateral amygdala (Leem et al., 2019). In summary, there is converging multi-level evidence for an arousal-, attention- and anxiety-related role of the adenosinergic system (Geiger et al., 2016) suggesting further research into A2A receptors as promising pharmacological targets in the treatment of anxiety disorders (Yamada et al., 2014).

### Alteration of circadian rhythms in mood disorder: effect of adenosine receptors

Clock gene dysfunction has long been considered as one pathogenic factor in mood disorders (McCarthy and Welsh, 2012; Gonzalez, 2014; Landgraf et al., 2014; Landgraf et al., 2016; Beyer and Freund, 2017). Chronic stress exposure, a major cause for several psychiatric disorders, disrupts circadian rhythms (Zaki et al., 2019). Increasing evidence suggests that region-specific circadian oscillations in limbic regions are instrumental regulators of mood (Kim et al., 2015; Logan et al., 2015; Landgraf et al., 2016). Recent evidence indicates that intrinsically photosensitive retinal ganglion cells may be involved in mood regulation (Lazzerini Ospri et al., 2017). Purinergic signaling has been found important in the regulation of circadian rhythms (Reichert et al., 2016; Lindberg et al., 2018), and circadian regulation of clock genes is believed to be involved in the rapid antidepressant actions of ketamine and SD (Bunney et al., 2015). Both SD and ketamine modulate the activity of the clock gene machinery via effects on e.g., N-methyl-D-aspartate receptors, AMPA receptors and mammalian target of rapamycin (Bunney et al., 2015). Clock genes including circadian associated repressor of transcription, period circadian regulator 2, neuronal PAS domain protein 4, D-Box binding protein, and RAR related orphan receptor B are down-regulated in both ketamine- and SD-treated mice (Orozco-Solis et al., 2017). Since the antidepressant effect of SD is mediated by increased signaling via adenosine A1 receptors (Hines et al., 2013; Serchov et al., 2015), the down-regulation of clock genes by SD (Bunney et al., 2015; Orozco-Solis et al., 2017) is probably induced by activation of A1 receptors (Fig. 3). We have shown that the antidepressant effects of both SD and ketamine are finally mediated by an increase in Homer1a (Serchov et al., 2015). Among the compounds participating in the regulation of Homer1a (van Calker et al., 2018) particularly BDNF appears to be involved in clock gene regulation (Bunney et al., 2015; Bjorkholm and Monteggia, 2016; Serchov and Heumann, 2017), whereas little is known about a potential interaction of Homer1a with clock genes.

![Fig. 3 Adenosine receptors (AR) modulate sleep homeostasis and circadian clock and thus regulates mood.](image)

However, not only A1− but also A2A− receptors play an active role in the control of circadian rhythms which may be involved in the pathophysiology of mood disorders (Lindberg et al., 2018). Thus, adenosine signaling via A2A receptors was shown to regulate striatal cellular and behavioral circadian timing and activity level (Ruby et al., 2014). Both A1 receptors and particularly A2A receptors regulate sleep (Huang et al., 2005). However, while A1 receptors are known to mediate the antidepressant effects of SD (see above), little is known about the potential relationship between the function of A2A receptors in sleep and their role in depression or anxiety.

### Role of adenosine receptors in the effects of SD and chronic sleep restriction on mood and anxiety

As shortly mentioned above SD induces an increase in adenosine (Leenaars et al., 2018) and an up-regulation of adenosine A1 receptors in the brain (Porkka-Heiskanen et al., 1997; Elmenhorst et al., 2007; Elmenhorst et al., 2009; Elmenhorst et al., 2017), which elicits the sleepiness-inducing effects of prolonged wakefulness and mediates the antidepressant effects of SD (Fig. 3) (Hines et al., 2013; Serchov et al., 2015). The potential effects of SD on A2A receptors are much less clear. Initially, a down-regulation by SD (3 and 6 h) of A2A receptor messenger ribonucleic acid and receptor binding was found restricted to the olfactory tubercle (Basheer et al., 2001). Chronic sleep restriction was found to lead to A2A receptor down-regulation also only in the olfactory tubercle (Kim et al., 2015). Thus, the time course, brain area and the extent of
down-regulation of A2A receptors (if any) after SD is still unclear. Since A2A receptor activation induces depression-like behavior in rodents (see discussion above), down-regulation of A2A receptors may contribute to the antidepressant effects of SD and add to the antidepressant effects of increased A1 receptor signaling. However, presently no data are available that would support this hypothesis. The increased signaling via A1 receptors induced by SD leads to an enhanced formation of Homer1a in the mPFC, which mediates the antidepressant effects of SD (Serchov et al., 2015). However, SD in addition to its antidepressant effects also induces impairments in cognitive functions similar to those of ethanol which also induces an up-regulation of cerebral A1 adenosine receptors (Elmenhorst et al., 2018). In addition, SD in humans appears to increase state anxiety (Pires et al., 2016b), but may induce rather a decrease in anxiety-like behavior in preclinical models (Pires et al., 2016a). There are differences in the time courses for impairment of performance and recovery between acute and chronic sleep loss. While the acute up-regulation of A1 receptors induced by SD is accompanied by homeostatic increase in non-rapid eye movement sleep, slow-wave activity and adenosine-dependent inhibition of synaptic activity, prolonged sleep restriction (3 days) caused a reduction in these parameters by reducing the adenosine-tone and attenuated the response to acute sleep deprivation (Clasadonte et al., 2014). Similarly, whereas short time (12 h) SD elicited antidepressant effects, more extended SD (72 h) had no antidepressant-like effects in mice (Hines et al., 2013). Chronic exposure to sleep restriction is rather associated with an increased risk of depression (Baum et al., 2014; Conklin et al., 2018). Moreover, chronic sleep restriction induces long-lasting increase in A1R expression in several brain regions and a reduced adenosine A2A receptor density in one of the three brain areas analyzed (olfactory tubercle) (Kim et al., 2015), which may underlie the negative effects of chronic sleep restriction on mood regulation (Novati et al., 2008). Indeed, as already mentioned above, the consequences of A1 receptor up-regulation differ dependent on both the duration of sleep restriction and the particular part of the brain investigated. Chronic insufficient sleep duration equivalent to 5.6 h of sleep opportunity per 24 h impairs neurobehavioral performance even without extended wakefulness (McHill et al., 2018). Disturbed sleep also negatively affects the immune system (Irwin and Opp, 2017) and induces elevation in brain inflammatory molecules such as interleukin 1-β (IL-1β) and tumor necrosis factor-α (TNF-α) and inhibition of BDNF (Zielinski et al., 2014). These negative effects of chronic SD on cognitive performance (Elmenhorst et al., 2018) appear to be mediated via effects on both adenosine A1 and A2A receptors (Urry and Landolt, 2015) and are at least in part modified by heritable individual differences (Krause et al., 2017). Indeed, there is evidence that prolonged A1 receptor signaling and its cross-talk with A2A receptors may form the cellular basis for increased neurotoxicity in neurodegenerative disorders (Chen et al., 2014; Chen et al., 2016; Stockwell et al., 2017).

Potential role of adenosine receptors in the antidepressant effects of electroconvulsive therapy

ECT is predominantly used to treat major depression but less frequently is also applied to treat schizophrenia, catatonia and acute mania (Payne and Prudic, 2009). The neurobiological mechanism of action of ECT is still unknown, but is related to the seizures induced by the treatment. Modern theories comprise e.g. neuroimmunological mechanisms such as low TNF-α (Sorri et al., 2018; Yrondi et al., 2018), alterations in BDNF and vascular endothelial growth factor (Minelli et al., 2011; Polyakova et al., 2015), neuroendocrine mechanisms (Hackett, 2014) and alterations in sortilin-derived propeptide (Roulot et al., 2018). We (van Calker and Biber, 2005) have first suggested a potential role of adenosine and A1 receptors in the mechanism of action of ECT based on the effects on slow wave sleep, cerebral metabolic rate and cerebral blood flow, since these effects are very similar to those of SD (see above) and a pronounced augmentation of adenosine and adenosine A1 receptors in the brain after ECT or seizures in general is well known (Lewin and Bleck, 1981; Newman et al., 1984; Gleiter et al., 1989; Boison, 2016). This increase in adenosine signaling evoked by ECT is most probably also responsible for the well-known ECT-induced increase in seizure threshold (Coffey et al., 1995; van Calker and Biber, 2005). In contrast to A1-receptors A2-receptors are rapidly down-regulated after ECT, perhaps contributing to the antidepressant effects (since A2 receptors rather increase depression, see above) (van Calker and Biber, 2005). Since increased signaling via adenosine A1 receptors has been shown to have pronounced antidepressant effects (Serchov et al., 2016), the ECT-induced increase in adenosine and A1 receptors is very likely at least partially responsible for ECT’s antidepressant activity. This conclusion is also corroborated by the other effects of ECT downstream to adenosine A1 receptor activation (Fig. 2). Indeed, similar to SD, which upregulates Homer1a via A1 receptor activation (Serchov et al., 2015), also ECT upregulates Homer1a expression levels in the cortex (Kato, 2009), most probably mediated by the increased A1 receptor signaling induced by ECT. Homer1a was therefore proposed to be instrumental for the therapeutic effect of ECT in depression (Kato, 2009; Serchov et al., 2016). In addition to adenosine and A1 receptors, also purinergic signaling through ATP via P2-receptors was suggested to play a role in ECT (Sadek et al., 2011).
Potential role of adenosine $A_1$ receptors in the antidepressant effects of transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a non-invasive technique of brain stimulation that modulates cortical excitability. It is used in humans in attempts to treat diverse neurological and neuropsychiatric disorders including e.g. Parkinson’s disease (Fregni et al., 2006), cerebrovascular events (Fregni et al., 2005), neuropathic pain (Mori et al., 2010), epilepsy (San-Juan et al., 2015) and depressive disorders (Meron et al., 2015; Moffa et al., 2018) including bipolar depression (Sampaio-Junior et al., 2018). In experimental animal models, it was shown that the modulation of cortical excitability induced by cathodal tDCS is mediated by adenosine $A_1$ receptors, since local microinjection of the adenosine $A_1$ receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine prevented the effects of cathodal tDCS (Marquez-Ruiz et al., 2012). Since activation of adenosine $A_1$ receptors elicits pronounced antidepressant-like effects (see previous paragraph) (Serchov et al., 2016), it is conceivable that the antidepressant effects of tDCS in some studies (Meron et al., 2015; Moffa et al., 2018) might be mediated by $A_1$ receptors (Fig. 2).

Potential role of adenosine $A_1$ receptors in the antidepressant effects of deep brain stimulation in treatment resistant depression

Deep brain stimulation (DBS) consists of implanting electrodes in specific brain areas followed by optimized stimulation settings. This technique has long been used for the treatment of a variety of neurological and neuropsychiatric disorders (Ward et al., 2010) including e.g., Parkinson’s disease and essential tremor (Benabid et al., 2009a; Benabid et al., 2009b), pain (Hamani et al., 2006; Levy et al., 2010) and obsessive compulsive disorder (Denys and Mantione, 2009). First evidence from small studies indicated that DBS might also improve treatment resistant depression (Mayberg et al., 2005; Giacobbe et al., 2009; Anderson et al., 2012; Berlim et al., 2014) including bipolar depression (Gippert et al., 2017). However, a recent controlled study could not demonstrate a significant effect of DBS in ventral capsule/ventral striatum, in chronic treatment resistant depression (Dougherty et al., 2015). Other recent controlled studies report limited antidepressant effects of DBS in other brain regions such as the ventral anterior limb of the internal capsule (Bergfeld et al., 2016) and the subcallosal cingulate gyrus (Merkel et al., 2018). Thus, one problem in the analysis of DBS in depression are the different anatomical targets affected by DBS in the various studies including e.g., ventral capsule/ventral striatum, subgenual cingulate cortex, medial forebrain bundle and the lateral habenula (Malone et al., 2009; Bewernick et al., 2010; Kennedy et al., 2011; Bewernick et al., 2012; Holtzheimer et al., 2012; Lozano et al., 2012; Berlim et al., 2014; Schlaepfer et al., 2014; Dougherty et al., 2015; Dandekar et al., 2018; Coenen et al., 2019). To complicate matters further, a potential role of glia in the mechanism of action of DBS appears possible (Anderson et al., 2012; Vedam-Mai et al., 2012; Fenoy et al., 2014; Etievant et al., 2015a; Etievant et al., 2015b; McIntyre and Anderson, 2016). The therapeutic effects of DBS in tremor (Bekar et al., 2008) and epilepsy (Miranda et al., 2014) were shown to be associated with a marked accumulation of adenosine, which mediated an activation of adenosine $A_1$ receptors. Similarly, also the action of DBS in depression could be due to activation of adenosine $A_1$ receptors (Fig. 2) (Tawfic et al., 2010; Etievant et al., 2013; Etievant et al., 2015a; Etievant et al., 2015b), in accordance with the pronounced antidepressant-like effects of $A_1$ receptor activation in mice (see above) (Serchov et al., 2016).

Regulation of adenosine receptor expression in mood disorders: Neuro-immunological mechanisms

In the preceding chapters, we have presented evidence that alteration of adenosine $A_{2A}$ and $A_1$ receptor expression and activity differentially influences mood in experimental animals, partly reflecting the $A_1$ receptor mediated antidepressant effects of SD and ECT in humans (Serchov et al., 2016). Thus it is important to examine how adenosine receptor expression is regulated in the brain under normal conditions and whether or not this regulation might be disturbed in mood disorders. There is very little information concerning the molecular mechanisms in the regulation of adenosine receptor expression, except for the role of nuclear factor (NF)-κB (Ramesh et al., 2007; Sheth et al., 2014). However, there is evidence that adenosine receptors interact with immunological mechanisms in the brain and that chemokines and cytokines such as IL-1β, IL-6, and TNF-α are altered in depressive disorder (Dantzer et al., 2008; Miller et al., 2009; Dowlatabadi et al., 2010; Young et al., 2014; Hodes et al., 2015; Bhattacharya et al., 2016; Slusarczyk et al., 2016; Wohleb et al., 2016; Kakeda et al., 2018; Kohler et al., 2018). Among these, alterations in IL-6 were found by cumulative meta-analyses to be the best documented (Haapakoski et al., 2015). We have shown that the expression of both adenosine $A_1$ and $A_2$ receptors in the brain and in neural cells in culture is regulated by interleukin-6 and other cytokines (Biber et al., 2001; Biber et al., 2008; Vazquez et al., 2008; Moidunny et al., 2010). On the other hand, adenosine stimulates via its receptor activation in mice (see above) (Serchov et al., 2016).
control the release of different cytokines in the brain (Rebola et al., 2011). Thus, there appears to exist a reciprocal interconnection between cytokines and adenosine receptors in the brain potentially important in the pathophysiology of depressive disorders. This crosstalk is particularly evident in retinal ganglion cells, where both adenosine A1 and A2A receptors interact with IL-6 to mediate cell survival and IL-6 modulates through the regulation of adenosine A1 and A2A receptor expression the level of BDNF (Perigolo-Vicente et al., 2013; Perigolo-Vicente et al., 2014), which has a well-documented role in depression (van Calker et al., 2018). Furthermore, A2A receptors are also involved in the regulation of the release of BDNF from activated microglia and in the proliferative role of BDNF (Gomes et al., 2013), in accord with the potential role of microglia in psychiatric disorders (Biber et al., 2016). Thus, there is reason to believe that adenosine via modulation of the effects of BDNF, IL-6 and perhaps other cytokines might improve the particular subtype(s) of depressive disorders that are regulated by neuroimmunological mechanisms (Wohleb et al., 2016).

Conclusions

As reviewed above, both A1 and A2A adenosine receptors are implicated in the etiology and treatment of mood and anxiety disorders. Thus activation of A1 and inhibition of A2A receptors elicit antidepressant effects (Fig. 2). The antidepressant effects of enhancement of A1 receptor signaling occurs through an increase of signaling via Homer1a which leads finally to a modulation of AMPA receptor functioning (Holz et al., 2019). How the antidepressant effects of inhibition of A2A receptors are mediated is still unknown. In addition to their role in mood disorders, adenosine A1 and A2A receptors also regulate anxiety-like behavior. In particular A2A receptors appear to be important in this regard. Adenosine receptors play an important role in sleep regulation and influence circadian clockwork. Indeed, circadian function and sleep regulation are consistently dysregulated in many mental diseases including depression and anxiety disorders (Fig. 3). Recent evidence has identified neuroimmunological mechanisms that both regulate and are regulated by adenosine receptors. As much as these mechanisms are involved in the pathophysiology of certain types of depression and perhaps also anxiety disorders they may present a promising field of future research. Preclinical studies have begun to assess antidepressant outcomes associated with adenosinergic modulators. Particularly, a therapeutic use of A2A receptor agonists has been suggested for autism-spectrum disorders and schizophrenia, while A2A receptor antagonists might carry some promise for Alzheimer’s disease, Parkinson’s disease, attention-deficit hyperactivity disorder, depression and anxiety (Domenici et al., 2019). Future research is, however, needed to explore the therapeutic potential of adenosine receptor modulators in clinical trials. With regard to translational research, the application of new technologies – for instance, epigenetics and proteomics – should be included in future studies. In therapeutic applications, more selective modulators of adenosine receptors should be developed and tested in mood and anxiety disorders.

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References

Abbraccio M. P. and Ceruti S. (2007) P1 receptors and cytokine secretion. *Purinergic Signal.* 3, 13–25.

Ahlene C. M., Kewley E. M. and Eltzschig H. K. (2011) The resurgence of A2B adenosine receptor signaling. *Biochem. Biophys. Acta.* 1808, 1329–1339.

Akhondzadeh S., Milajerdii M. R., Amini H. and Tehrani-Doost M. (2006) Allopurinol as an adjunct to lithium and haloperidol for treatment of patients with acute mania: a double-blind, randomized, placebo-controlled trial. *Bipolar Disord.* 8, 485–489.

Alsene K., Deckert J., Sand P. and de Wit H. (2003) Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 28, 1694–1702.

Anderson R. J., Frye M. A., Abulsouda O. A., Lee K. H., McGillivray J. A., Berk M. and Tye S. J. (2012) Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action. *Neurosci. Biobehav. Rev.* 36, 1920–1933.

Antonioli L., Blandizzi C., Pacher P. and Hasko G. (2013) Immunity, inflammation and cancer: a leading role for adenosine. *Nat. Rev. Cancer* 13, 842–857.

Baldessarini R. J., Tondo L. and Vazquez G. H. (2019) Pharmacological treatment of adult bipolar disorder. *Mol. Psychiatry* 24, 198–217.

Barfot F., Crocamo C., Mazza M. G., Clerici M. and Carra G. (2016) Uric acid levels in subjects with bipolar disorder: a comparative meta-analysis. *J. Psychiatr. Res.* 81, 133–139.

Barfot F., Crocamo C., Clerici M. and Carra G. (2017a) Allopurinol as add-on treatment for mania symptoms in bipolar disorder: systematic review and meta-analysis of randomised controlled trials. *Br. J. Psychiatry* 210, 10–15.

Barfot F., Crocamo C., Dakanalis A., Brosio E., Miottt A., Capuzzi E., Clerici M. and Carra G. (2017b) Purinergic system dysfunctions in subjects with bipolar disorder: a comparative cross-sectional study. *Compr. Psychiatry* 73, 1–6.

Basheer R., Halldner L., Alanko L., McCarley R. W., Fredholm B. B. and Porkka-Heiskanen T. (2001) Opposite changes in adenosine A1 and A2A receptor mRNA in the rat following sleep deprivation. *NeuroReport* 12, 1577–1580.
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Basheer R., Streeker R. E., Thakkar M. M. and McCarley R. W. (2004) Adenosine and sleep-wake regulation. Prog. Neurobiol. 73, 379–396.

Batalha V. L., Pego J. M., Fontinha B. M., Costenla A. R., Valadas J. S., Basqi Y., Radijainia H., Muller C. E., Sebastiao A. M. and Lopes L. V. (2013) Adenosine A2A receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. Mol. Psychiatry 18, 320–331.

Baum K. T., Desai A., Field J., Miller L. E., Rausch J. and Beebe D. W. (2014) Sleep restriction worsens mood and emotion regulation in adolescents. J. Child Psychol. Psychiatry 55, 180–190.

Beamer E., Goloncser F., Horvath G., Beko K., Otrokoczi L., Kovanyi B. and Sperlugh B. (2016) Purinergic mechanisms in neuroinflammation: an update from molecules to behavior. Neuropharmacology 104, 94–104.

Bekar L., Libionka W., Tian G. F., et al. (2008) Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. Nat. Med. 14, 75–80.

Benabid A. L., Chabardes S., Mitrofanis J. and Pollak P. (2009a) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol. 8, 67–81.

Benabid A. L., Chabardes S., Torres N., Pfaltz B., Krack P., Fraix V. and Pollak P. (2009b) Functional neurosurgery for movement disorders: a historical perspective. Prog. Brain Res. 175, 379–391.

Bergfeld I. O., Mantione M., Hoogendoorn M. L., et al. (2016) Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 73, 456–464.

Berlim M. T., McGirr A., van Calker D., Serchov T., Normann C. and Biber K. (2018) Recent insights into antidepressant therapy: distinct pathways and potential common mechanisms in the treatment of depressive syndromes. Neurosci. Biobehav. Rev. 88, 63–72.

Bjorkholm C. and Monteggia L. M. (2016) BDNF as a multi-signalling guardian angel in human diseases: when, where and how does it exert its protective effects? Trends Pharmacol. Sci. 37, 419–434.

Bunney B. G., Li J. Z., Walsh D. M., et al. (2015) Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. Mol. Psychiatry 20, 48–55.

Burnstock G. (1978) A basis for distinguishing two types of purinergic receptor. Cell Membr. Recept. Drugs Horm. 107–118.

Burnstock G. (2015) Purinergic signalling and the autonomic nervous system in health and disease. Auton. Neurosci. 191, 1.

van Calker D. and Biber K. (2005) The role of glial adenosine receptors in neural resilience and the neurobiology of mood disorders. Neurochem. Res. 30, 1205–1217.

van Calker D., Muller M. and Hamprecht B. (1978) Adenosine inhibits the accumulation of cyclic AMP in cultured brain cells. Nature 276, 839–841.

van Calker D., Muller M. and Hamprecht B. (1979) Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. J. Neurochem. 33, 999–1005.

van Calker D., Serchow T., Normann C. and Biber K. (2018) Recent insights into antidepressant therapy: distinct pathways and potential common mechanisms in the treatment of depressive syndromes. Neurosci. Biobehav. Rev. 88, 63–72.

Caruso M., Alamò, Crisafulli E., Raciti C., Fischella A. and Polosa R. (2013) Adenosine signaling pathways as potential therapeutic targets in respiratory disease. Expert Opin. Ther. Targets 17, 761–772.

Charney D. S., Heninger G. R. and Jatlow P. I. (1985) Increased anxiogenic effects of caffeine in panic disorders. Arch. Gen. Psychiatry 42, 233–243.

Cheffer A., Castillo A. R. G., Correa-Velloso J., Goncalves M. C. B., Nauildij Y., Nascimento I. C., Burnstock G. and Ulrich H. (2018) Purinergic system in psychiatric diseases. Mol. Psychiatry 23, 94–106.

Chen Z., Xiong C., Pancyr C., Stockwell J., Walz W. and Cayababay F. S. (2014) Prolonged adenosine A1 receptor activation in hypoxia and pial vessel disruption focal cortical ischemia facilitates clathrin-mediated AMPA receptor endocytosis and long-lasting synaptic inhibition in rat hippocampal CA3-CA1 synapses: differential regulation of GluA2 and GluA1 subunits by p38 MAPK and JNK. J. Neurosci. 34, 9621–9643.

Chen Z., Stockwell J. and Cayababay F. S. (2016) Adenosine A1 receptor-mediated endocytosis of AMPA receptors contributes to impairments in long-term potentiation (LTP) in the middle-aged rat hippocampus. Neurochem. Res. 41, 1085–1097.

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

Chiu G. S., Stoeckell J. and Cayababay F. S. (2016) Adenosine A1 receptor-mediated endocytosis of AMPA receptors contributes to impairments in long-term potentiation (LTP) in the middle-aged rat hippocampus. Neurochem. Res. 41, 1085–1097.

Chiu G. S., Stoeckell J. and Cayababay F. S. (2016) Adenosine A1 receptor-mediated endocytosis of AMPA receptors contributes to impairments in long-term potentiation (LTP) in the middle-aged rat hippocampus. Neurochem. Res. 41, 1085–1097.
Ciruela F., Ferre S., Casado V., Cortes A., Cunha R. A., Lluis C. and Franco R. (2006) Heterodimeric adenosine receptors: a device to regulate neurotransmitter release. *Cell. Mol. Life Sci.* 63, 2427–2431.

Clasadonte J., McIver S. R., Schmitt L. I., Halassa M. M. and Haydon P. G. (2014) Chronic sleep restriction disrupts sleep homeostasis and behavioral sensitivity to alcohol by reducing the extracellular accumulation of adenosine. *J. Neurosci.* 34, 1879–1891.

Coelho J. E., Alves P., Canas P. M., et al. (2014) Overexpression of adenosine A2A receptors in rats: effects on depression, locomotion, and anxiety. *Front. Psychiatry.* 5, 67.

Coenen V. A., Bewernick B. H., Kayser S., et al. (2019) Superlateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial. *Neuropsychopharmacology* 44, 1224–1232.

Coffey C. E., Lucke J., Weiner R. D., Krystal A. D. and Aque M. (1995) Seizure threshold in electroconvulsive therapy (ECT) II. The anticonvulsant effect of ECT. *Biol. Psychiat.* 37, 777–788.

Colgan S. P., Fennimore B. and Ehrentraut S. F. (2013) Adenosine and gastrointestinal inflammation. *J. Mol. Med.* 91, 157–164.

Conklin A. I., Yao C. A. and Richardson C. G. (2018) Chronic sleep deprivation and gender-specific risk of depression in adolescents: a prospective population-based study. *BMC Public Health* 18, 724.

Correa M. and Font L. (2008) Is there a major role for adenosine A2A receptors in anxiety? *Front. Biosci.* 13, 4058–4070.

Craske M. G. and Stein M. B. (2016) Anxiety. *Lancet* 388, 3048–3059.

Crema L. M., Pettenazzo L. F., Schlabitz M., Diehl L., Hoppe J., Mestriner R., Laureano D., Salbego C., Dalmaz C. and Vendite D. (2013) The effect of unpredictable chronic mild stress on depressive-like behavior and on hippocampal A1 and striatal A2A adenosine receptors. *Physiol. Behav.* 109, 1–7.

Cristovao-Ferreira S., Navarro G., Brugarolas M., et al. (2013) AIR–A2AR heteromers coupled to Gs and Gi0 proteins modulate GABA transport into astrocytes. *Purinergic Signal.* 9, 433–449.

Cunha R. A., Johansson B., van der Ploeg I., Sebastiao A. M., Ribeiro J. A. and Fredholm B. B. (1994) Evidence for functionally important adenosine A2A receptors in the rat hippocampus. *Brain Res.* 649, 208–216.

Dandekar M. P., Fenoy A. J., Carvalho A. F., Soares J. C. and Quevedo J. (2018) Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. *Mol. Psychiatry* 23, 1094–1112.

Dantzer R., O’Connor J. C., Freund G. G., Johnson R. W. and Kelley K. W. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9, 46–56.

De Berardinis D., Conti C. M., Campanella D., et al. (2008) Evaluation of plasma antioxidant levels during different phases of illness in adult patients with bipolar disorder. *J. Biol. Regul. Homeost. Agents* 22, 195–200.

Deckert J. (1998) The adenosine A2A receptor knockout mouse: a model for anxiety? *Int. J. Neuropsychopharmacol.* 1, 187–190.

Deckert J., Nothen M. M., Albus M., et al. (1998a) Adenosine A1 receptor and bipolar affective disorder: systematic screening of the gene and association studies. *Am. J. Med. Genet.* 81, 18–23.

Deckert J., Nothen M. M., Franke P., Delmo C., Fritzje J., Knapp M., Maier W., Beckmann H. and Propping P. (1998b) Systematic mutation screening and association study of the A1 and A2a adenosine receptor genes in panic disorder suggest a contribution of the A2a gene to the development of disease. *Mol. Psychiatry* 3, 81–85.

Dégubareff T. and Sletor W., Jr (1965) Effects of caffeine on mammalian atrial muscle, and its interaction with adenosine and calcium. *J. Pharmacol. Exp. Ther.* 148, 202–214.

Denys D. and Mantine M. (2009) Deep brain stimulation in obsessive-compulsive disorder. *Prog. Brain Res.* 175, 419–427.

Domenici M. R., Ferrante A., Martire A., Chiodi V., Pepponi R., Tebano M. T. and Popoli P. (2019) Adenosine A2A receptor as potential therapeutic target in neuropsychiatric disorders. *Pharmacol. Res.* 147, 104338.

Domshke K., Deckert J., Arolt V. and Baune B. T. (2010a) Anxious versus non-anxious depression: difference in treatment outcome. *J. Psychopharmacol.* 24, 621–622.

Domshke K., Stevens S., Pfleiderer B. and Gerlach A. L. (2010b) Interceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. *Clin. Psychol. Rev.* 30, 1–11.

Domshke K., Gajewska A., Winter B., et al. (2012a) ADORA2A gene variation, caffeine, and emotional processing: a multi-level interaction on startle reflex. *Neuropsychopharmacology* 37, 759–769.

Domshke K., Klauke B., Winter B., et al. (2012b) Modification of caffeine effects on the affect-modulated startle by neuropsychiatric S receptor gene variation. *Psychopharmacology* 222, 533–541.

Dougherty D. D., Rezaï A. R., Carpenter L. I., et al. (2015) A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol. Psychiatry* 78, 240–248.

Dowlati Y., Hermann N., Swardflager W., Liu H., Sham L., Reim E. K. and Lancot K. L. (2010) A meta-analysis of cytokines in major depression. *Biol. Psychiatry* 67, 446–457.

Drury A. N. and Szent-Györgyi A. (1929) The physiological activity of adenosine compounds with especial reference to their action upon the mammalian heart. *J. Physiol.* 68, 213–237.

Eisenstein A., Patterson S. and Ravid K. (2015) The many faces of the A2b adenosine receptor in cardiovascular and metabolic diseases. *J. Cell. Physiol.* 230, 2891–2897.

El Yacoubi M., Ledent C., Parmentier M., Costentin J. and Vaugeois J. M. (2000) The anxiogenic-like effect of caffeine in two experimental procedures measuring anxiety in the mouse is not shared by selective A2A adenosine receptor antagonists. *Psychopharmacology* 148, 153–163.

El Yacoubi M., Ledent C., Parmentier M., Bertorelli R., Ongini E., Costentin J. and Vaugeois J. M. (2001) Adenosine A2A receptor antagonists are potential antidepressants: evidence based on pharmacology and A2A receptor knockout mice. *Br. J. Pharmacol.* 134, 68–77.

El Yacoubi M., Costentin J. and Vaugeois J. M. (2003) Adenosine A2A receptors and depression. *Neurology* 61, 882–87.

Elmenhorst D., Meyer P. T., Witz O. H., Nauts C. H., Ermert J., Coenen V. A., Bewernick B. H., Kayser S., et al. (2003) Adenosine A2A receptors in rats: effects on depression, locomotion, and anxiety. *Front. Psychiatry.* 5, 67.

Elmenhorst E. M., Elmenhorst D., Benderoth S., Kroll T., Bauer A. and Aeschbach D. (2018) Cognitive impairments by alcohol and sleep deprivation increases A1 adenosine receptor binding in the human brain: a positron emission tomography study. *J. Neurosci.* 28, 2410–2415.

Elmenhorst D., Basheer R., Bauer A. and Ermert J., Coenen V. A., Bewernick B. H., Kayser S., et al. (2003) Adenosine A2A receptors and bipolar affective disorder: systematic screening of the gene and association studies. *Am. J. Med. Genet.* 81, 18–23.

Elmenhorst D., Nothen M. M., Franke P., Delmo C., Fritzje J., Knapp M., Maier W., Beckmann H. and Propping P. (1998b) Systematic mutation screening and association study of the A1 and A2a adenosine receptor genes in panic disorder suggest a contribution of the A2a gene to the development of disease. *Mol. Psychiatry* 3, 81–85.

El Yacoubi M., Costentin J. and Vaugeois J. M. (2003) Adenosine A2A receptors and depression. *Neurology* 61, 882–87.
treatment of major depression? *Curr. Drug Targets* **14**, 1295–1307.

Etevant A., Lucas G., Dkhissi-Benyahya O. and Haddjeri N. (2015a) The role of astroglia in the antidepressant action of deep brain stimulation. *Front. Cell. Neurosci.* **9**, 509.

Etevant A., Oosterhof C., Betty C., et al. (2015b) Astroglial control of the antidepressant-like effects of prefrontal cortex deep brain stimulation. *EBioMedicine* **2**, 898–908.

Fava M., Alpert J. E., Carmin C. N., et al. (2004) Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol. Med.* **34**, 1299–1308.

Fava M., Rush A. J., Alpert J. E., et al. (2008) Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am. J. Psychiatry* **165**, 342–351.

Fenoy A. J., Goetz L., Chabardes S. and Xia Y. (2014) Deep brain stimulation: are astrocytes a key driver behind the scene? *CNS Neurosci. Ther.* **20**, 191–201.

Ferre S., Ciruela F., Borycz J., et al. (2008) Adenosine A1–A2A receptor heteromers: new targets for caffeine in the brain. *Front. Biosci.* **13**, 2391–2399.

Fiebich B. L., Biber K., Gyufko K., Berger M., Bauer J. and van Calker D. (1996) Adenosine A2b receptors mediate an increase in interleukin (IL)-6 mRNA and IL-6 protein synthesis in human astroglia cells. *J. Neurochem.* **66**, 1426–1431.

Fiebich B. L., Akundi R. S., Biber K., Hamke M., Schmidt C., Butcher R. D., van Calker D. and Willnroth F. (2005) IL-6 expression induced by adenosine A2b receptor stimulation in U373 MG cells depends on p38 mitogen activated kinase and protein kinase C. *Neurochem. Int.* **46**, 501–512.

Florio C., Prezioso A., Papaioannou A. and Vertua R. (1998) Adenosine A1 receptors modulate anxiety in CD1 mice. *Psychopharmacology* **136**, 311–319.

Fredholm B. B., Izzerman A.P., Jacobson K.A., Klotz K.N. and Linden J. (2001) International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol. Rev.* **53**, 527–552.

Fredholm B. B., Izzerman A. P., Jacobson K. A., Linden J. and Muller C. E. (2011) International Union of Basic and Clinical Pharmacology, LXXXI. Nomenclature and classification of adenosine receptors—an update. *Pharmacol. Rev.* **63**, 1–34.

Fregni F., Boggio P. S., Mansur C. G., et al. (2005) Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *NeuroReport* **16**, 1551–1555.

Fregni F., Boggio P. S., Santos M. C., Lima M., Vieira A. L., Rigonatti S. P., Silva M. T., Barbosa E. R., Nitsche M. A. and Pascual-Leone A. (2006) Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Mov. Disord.* **21**, 1693–1702.

Freudenberg F., Celikel T. and Reif A. (2015) The role of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in depression: central mediators of pathophysiology and antidepressant activity? *Neurosci. Biobehav. Rev.* **52**, 193–206.

Fries G., Gassen N. and Rein T. (2017) The FKBPs1 glucocorticoid receptor co-chaperone: regulation, function, and implications in health and disease. *Int. J. Mol. Sci.* **18**, E2614.

Fujita T., Chen M. J., Li B., et al. (2014) Neuronal transient expression in dominant-negative SNARE mice. *J. Neurosci.* **34**, 16594–16604.

Fuxe K., Ferre S., Genedani S., Franco R. and Agnati L. F. (2007) Adenosine receptor-dopamine receptor interactions in the basal ganglia and their relevance for brain function. *Physiol. Behav.* **92**, 210–217.

Fuxe K., Agnati L. F. and Borroto-Escuela D. O. (2014) The impact of receptor-receptor interactions in heteroreceptor complexes on brain plasticity. *Expert Rev. Neurother.* **14**, 719–721.

Gajewska A., Blumenthal T. D., Winter B., et al. (2013) Effects of ADORA2A gene variation and caffeine on prepuise inhibition: a multi-level risk model of anxiety. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **40**, 115–121.

Gass N., Ollila H. M., Utge S., Partonen T., Kronholm E., Pirkola S., Suhonen J., Silander J., Porkka-Heiskanen T. and Paunio T. (2010) Contribution of adenosine related genes to the risk of depression with disturbed sleep. *J. Affect. Disord.* **126**, 134–139.

Geiger M. J., Domshke K., Holmola G. A., Schulz S. M., Nowak J., Akhri A., Pauli P., Deckert J. and Neufang S. (2016) ADORA2A genotype modulates interleukin and antiinflammatory processing in a fronto-insular network. *Eur. Neuropsychopharmacol.* **26**, 1274–1285.

Giacobbe P., Mayberg H. S. and Lozano A. M. (2009) Treatment resistant depression as a failure of brain homeostatic mechanisms: implications for deep brain stimulation. *Exp. Neurol.* **219**, 44–52.

Gimenez-Lliort L., Fernandez-Teruel A., Escorihuela R. M., Fredholm B. H., Tobena A., Pekny M. and Johansson B. (2002) Mice lacking the adenosine A1 receptor are anxious and aggressive, but are normal learners with reduced muscle strength and survival rate. *Eur. J. Neurosci.* **16**, 547–550.

Gippert S. M., Switala C., Bewernick B. H., Kayser S., Brauer A., Coenen V. A. and Schlaepfer T. E. (2017) Deep brain stimulation for bipolar disorder-review and outlook. *CNS Spectr.* **22**, 254–257.

Gleiter C. H., Deckert J., Nutt D. J. and Marangos P. J. (1989) Electroconvulsive shock (ECS) and the adenosine neuromodulatory system: effect of single and repeated ECS on the adenosine A1 and A2 receptors, adenylyl cyclase, and the adenosine uptake site. *J. Neurochem.* **52**, 641–646.

Gomes C. V., Kaster M. P., Tome A. R., Agostinho P. M. and Cunha R. A. (2011) Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. *Biochem. Biophys. Acta.* **1808**, 1380–1399.

Gomes C., Ferreira R., George J., Sanches R., Rodrigues D. I., Goncalves N. and Cunha R. A. (2013) Activation of microglial cells triggers a release of brain-derived neurotrophic factor (BDNF) inducing their proliferation in an adenosine A2A receptor-dependent manner: A2A receptor blockade prevents BDNF release and proliferation of microglia. *J. Neuroinflammation* **10**, 16.

Gonzalez R. (2014) The relationship between bipolar disorder and biological rhythms. *J. Clin. Psychiatry* **75**, e322–331.

Gottschalk M. G. and Domschke K. (2016) Novel developments in genetic and epigenetic mechanisms of anxiety. *Curr. Opin. Psychiatry* **29**, 32–38.

Gubert C., Jacintho Moritz C. E., Vasconcelos-Moreno M. P., Quadros Dos Santos B. T. M., Sartori I., Fijtman A., Kauer-Sant’Anna M., Kapczinski F., Battistini A. M. O. and Magalhaes P. (2016) Peripheral adenosine levels in euthymic patients with bipolar disorder. *Psychiatry Res.* **246**, 421–426.

Haapakoski R., Mathieu J., Ebmeier K. P., Alenius H. and Kivimaki M. (2013) Evidence for genetic linkage between a polymorphism in the adenosine A2A receptor gene and severity of depressive symptoms in patients with bipolar disorder. *Eur. Neuropsychopharmacol.* **23**, 196–205.

Hamani C., Schwartz J. M., Rezaei A. R., Dostrovsky J. O., Davis K. D. and Lozano A. M. (2006) Deep brain stimulation for chronic neuropathic pain: long-term outcome and the incidence of insertionional effect. *Pain* **125**, 188–196.

Hamilton S. P., Slager S. L., De Leon A. B., Heiman G. A., Klein D. F., Hodge S. E., Weissman M. M., Fyer A. J. and Knowles J. A. (2004) Evidence for genetic linkage between a polymorphism in

© 2019 International Society for Neurochemistry, *J. Neurochem.* (2019) **151**, 11–27.
the adenosine 2A receptor and panic disorder. *Neuropsychopharmacology* **29**, 558–565.

Hanson G. and Coller J. (2018) Codon optimality, bias and usage in translation and mRNA decay. *Nat. Rev. Mol. Cell Biol.* **19**, 20–30.

Haskell R. F. (2014) Electroconvulsive therapy's mechanism of action: neuroendocrine hypotheses. *J. ECT* **30**, 107–110.

Hasko G., Pacher P., Vizi E. S. and Illes P. (2005) Adenosine receptor signaling in the brain immune system. *Trends Pharmacol. Sci.* **26**, 511–516.

Hines D. J., Schmitt L. I., Hines R. M., Moss S. J. and Haydon P. G. (2013) Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. *Transl. Psychiatry* **3**, e212.

Hirata T. and Kishi T. (2013) Adenosine hypothesis in schizophrenia and bipolar disorder: a systematic review and meta-analysis of randomized controlled trial of adjuvant purinergic modulators. *Schizophr. Res.* **149**, 88–95.

Hodes G. E., Kana V., Menard C., Merad M. and Russo S. J. (2015) Neuroimmune mechanisms of depression. *Nat. Neurosci.* **18**, 1386–1393.

Hodgson R. A., Bertorelli R., Varty G. B., Hodes G. E., Kana V., Menard C., Merad M. and Russo S. J. (2015) Adenosine hypothesis in schizophrenia and bipolar disorder: implications for ischaemia reperfusion injury. *Pflugers Arch.* **468**, 674–682.

Koen N. and Stein D. J. (2011) Pharmacotherapy of anxiety disorders: a critical review. *Dialogues Clin. Neurosci.* **13**, 423–437.

Kohler C. A., Freitas T. H., Stubbs B., et al. (2018) Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: systematic review and meta-analysis. *Mol. Neurobiol.* **55**, 4195–4206.

Krause A. J., Simon E. B., Mander B. A., Greer S. M., Saletin J. M., Goldstein-Piekarski A. N. and Walker M. P. (2017) The sleep-deprived human brain. *Nat. Rev. Neurosci.* **18**, 404–418.

Kumar S., Shastri A., Kumar A. and Cao Q. (2018) Enhanced mGlu5 signaling in excitatory neurons promotes rapid antidepressant effects via AMPA receptor activation. *Neuropharmacology* **1386**, 907–916.

Kulkarni S. K., Singh K. and Bishnoi M. (2007) Involvement of adenosine A2A receptor. *Neuropharmacology* **45**, 2127–2133.

Karmouy-Quintana H., Xia Y. and Blackburn M. R. (2013) Adenosine signaling during acute and chronic disease states. *J. Mol. Med.* **91**, 173–181.

Kaster M. P., Machado N. J., Silva H. B., et al. (2015) Caffeine acts through neuronal adenosine A2A receptors to prevent mood and memory dysfunction triggered by chronic stress. *Proc. Natl Acad. Sci. USA* **112**, 7833–7838.

Kato N. (2009) Neurophysiological mechanisms of electroconvulsive therapy for depression. *Neurosci. Res.* **64**, 3–11.

Kenny S. H., Giacobbe P., Rizvi S. J., Placenza F. M., Nishikawa Y., Mayberg H. S. and Lozano A. M. (2011) Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *Am. J. Psychiatry* **168**, 502–510.

Kim Y., Elmenhorst D., Weisshaupt A., Wedekind F., Kroll T., McCarley R. W., Strecker R. E. and Bauer A. (2015) Chronic sleep restriction induces long-lasting changes in adenosine and noradrenergic receptor density in the rat brain. *J. Sleep Res.* **24**, 549–558.

King N., Lin H., McGivan J. D. and Suleiman M. S. (2006) Expression and activity of the glutamate transporter EAAT2 in cardiac hypertrophy: implications for ischaemia reperfusion injury. *Pflugers Arch.* **452**, 674–682.

Krugel U. (2016) Purinergic receptors in psychiatric disorders. *Neuropsychopharmacology* **104**, 212–225.

Kulkarni S. K., Singh K. and Bishnoi M. (2007) Involvement of adenosine receptors in treatment-resistant unipolar and bipolar depression. *Arch. Gen. Psychiatry* **64**, 150–158.

Holz A., Mülch F., Schwarz M. K., et al. (2019) Enhanced mGlu5 signaling in excitatory neurons promotes rapid antidepressant effects via AMPA receptor activation. *Neuron*. Published online August 13, 2019. doi: 10.1016/j.neuron.2019.07.011.

Huang Z. L., Qu W. M., Eguchi N., Chen J. F., Schwarzschild M. A., Fredholm B. B., Urade Y. and Hayashi O. (2005) Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. *Nat. Neurosci.* **8**, 858–859.

Irwin M. R. and Opp M. R. (2017) Sleep health: reciprocal regulation of sleep and innate immunity. *Neuropsychopharmacology* **42**, 129–155.

Jahangard L., Soroush S., Haghighi M., Ghaleiha A., Bajoghli H., Holsboer-Trachsel E. and Brand S. (2014) In a double-blind, randomized and placebo-controlled trial, adjuvant allopurinol improved symptoms of mania in in-patients suffering from bipolar disorder. *Eur. Neuropsychopharmacol.* **24**, 1210–1221.

Jain N., Kemn N., Adeyemo O., Buchanan P. and Stone T. W. (1995) Anxiolytic activity of adenosine receptor activation in mice. *Br. J. Pharmacol.* **116**, 2127–2133.

Jeon S. J., Rhee S. Y., Ryu J. H., et al. (2011) Activation of adenosine A2A receptor up-regulates BDNF expression in rat primary cortical neurons. *Neurochem. Res.* **36**, 2259–2269.

Johansson B., Hallnér L., Dunnwiddie T. V., et al. (2001) Hyperalgesia, anxiety, and decreased hypoxic neuroprotection in mice lacking the adenosine A1 receptor. *Proc. Natl Acad. Sci. USA* **98**, 9407–9412.

Kakuda S., Watapake K., Katsuki A., Sugimoto K., Igata N., Ueda I., Igata R., Abe O., Yoshimura R. and Korogi Y. (2018) Relationship between interleukin (IL)-6 and brain morphology in drug-naive, first-episode major depressive disorder using surface-based morphometry. *Sci. Rep.* **8**, 10054.
Leem Y. H., Jang J. H., Park J. S. and Kim H. S. (2019) Exercise exerts an anxiolytic effect against repeated restraint stress through 5-HT2A-mediated suppression of the adenosine A2A receptor in the basolateral amygdala. *Psychoneuroendocrinology*. https://doi.org/10.1016/j.psyneuen.2019.06.005 [Epub ahead of print].

Leenaars C. H. C., Saveliev S. A., Van der Mieren S., Joosten R., Dematteis M., Porka-Heiskanen T. and Feenstra M. G. P. (2018) Intracerebral adenosine during sleep deprivation: a meta-analysis and new experimental data. *J. Circadian Rhythms* 16, 11.

Levy R., Deer T. R. and Henderson J. (2010) Intracranial neurostimulation for pain control: a review. *Pain physician* 13, 157–165.

Lewin E. and Bleck V. (1981) Electrocoshock seizures in mice: effect on brain adenosine and its metabolites. *Epilepsia* 22, 577–581.

Lewis K. S., Gordon-Smith K., Forty L., Di Florio A., Craddock N., Jones L. and Jones I. (2017) Sleep loss as a trigger of mood episodes in bipolar disorder: individual differences based on diagnostic subtype and gender. *Br. J. Psychiatry* 211, 169–174.

Lindberg D., Andres-Beck L., Jia Y. F., Kang S. and Choi D. S. (2017) Adenosine A2A receptor deletion affects social behaviors and anxiety in mice: differences between the nonselective adenosine receptor antagonists caffeine and theophylline in motor and mood effects: studies using medium to high doses in animal models. *Behav. Brain Res.* 321, 8–17.

Lindberg D., Carbo-Gas M., Pardo M., Bayarri P., Valverde O., Ledent C., Salamone J. D. and Correa M. (2018) Purinergic signaling in neuron-astrocyte interactions, circadian rhythms, and alcohol use disorder. *Front. Physiol.* 9, 9.

Logan R. W., Edgar N., Gillman A. G., Hoffman D., Zhu X. and McClung C. A. (2015) Chronic stress induces brain region-specific alterations of molecular rhythms that correlate with depression-like behavior in mice. *Biol. Psychiat.* 78, 249–258.

Londo P., Cooper D. M. and Wolff J. (1980) Subclasses of external adenosine receptors. *Proc. Natl Acad. Sci. USA* 77, 2551–2554.

Lopez-Cruz L., Pardo M., Salamone J. D. and Correa M. (2018) Differences between the nonselective adenosine receptor antagonists caffeine and theophylline in motor and mood effects: studies using medium to high doses in animal models. *Behav. Brain Res.* 270, 213–222.

Lopez-Cruz L., Carbo-Gas M., Pardo M., Bayarri P., Valverde O., Ledent C., Salamone J. D. and Correa M. (2017) Adenosine A2A receptor deletion affects social behaviors and anxiety in mice: involvement of anterior cingulate cortex and amygdala. *Behav. Brain Res.* 321, 8–17.

Lopez-Cruz L., Salamone J. D. and Correa M. (2018) Caffeine and selective adenosine receptor antagonists as new therapeutic tools for the motivational symptoms of depression. *Front. Pharmacol.* 9, 526.

Lozano A. M., Giacobbe P., Hamani C., et al. (2012) A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *J. Neurosurg.* 116, 315–322.

Lusardi T. A. (2009) Adenosine neuromodulation and traumatic brain injury. *Curr. Neuropharmacol.* 7, 228–237.

Machado-Vieira R., Lara D. R., Souza D. O. and Kapczinski F. (2002) Purinergic dysfunction in mania: an integrative model. *Neurosci. Biobehav. Rev.* 26, 297–304.

Machado-Vieira R., Soares J. C., Lara D. R., Luckenbaugh D. A., Busnello J. V., Marca G., Cunha A., Souza D. O., Zarate C. A., Jr and Kapczinski F. (2008) A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and diprydiamole adjunctive to lithium in acute bipolar mania. *J. Clin. Psychiatry* 69, 1237–1245.

Malone D. A., Jr, Dougherty D. D., Rezai A. R., et al. (2009) Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol. Psychiatry* 65, 267–275.

Martinez-Mozos R., Leal-Cantero R., Sanchez-Campusano R., Molaei-Ardekanl B., Wendling F., Miranda P. C., Ruffini G., Gruart A. and Delgado-Garcia J. M. (2012) Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proc. Natl Acad. Sci. USA* 109, 6710–6715.

Marro P. J., Mishra O. P. and Delivoria-Papadopoulos M. (2006) Effect of allopurinol on brain adenosine levels during hypoxia in newborn piglets. *Brain Res.* 1073–1074, 444–450.

Mayberg H. S., Lozano A. M., Voon V., McNeely E. H., Seminowicz D., Hamani C., Schwab J. M. and Kennedy S. H. (2005) Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.

McCarthy M. J. and Welsh D. K. (2012) Cellular circadian clocks in mood disorders. *J. Biol. Rhythms* 27, 339–352.

McHill A. W., Hull J. T., Wang W., Cziesler C. A. and Klerman E. B. (2018) Chronic sleep curtailment, even without extended (>16-h) wakefulness, degrades human vigilance performance. *Proc. Natl Acad. Sci. USA* 115, 6070–6075.

McIntyre R. C. and Anderson R. W. (2016) Deep brain stimulation mechanisms: the control of network activity via neurochemical modulation. *J. Neurochem.* 139(Suppl 1), 338–345.

Melani A., Pugliesi A. M. and Pedata F. (2014) Adenosine receptors in cerebral ischemia. *Int. Rev. Neurobiol.* 119, 309–348.

Merkl A., Aust S., Schneider G. H., Visser-Vandewalle V., Horn A., Kuhn A., Kuhn J. and Bajbouj M. (2018) Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a double-blinded randomized controlled study and long-term follow-up in eight patients. *J. Affect. Disord.* 227, 521–529.

Meron D., Hogner N., Garner M. and Baldwin D. S. (2015) Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. *Neurosci. Biobehav. Rev.* 57, 46–62.

Miller A. H., Maletic V. and Raison C. L. (2009) Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol. Psychiat.* 65, 732–741.

Miltiadou D., Markowitz J. C., Gerber A. J., Cyranowski J., Alternus M., Shapiro T., Hofer M. and Glatt C. (2014) Childhood separation anxiety and the pathogenesis and treatment of adult anxiety. *Am. J. Psychiatry* 171, 34–43.

Minelli A., Zanardini R., Abarre M., Bortolomasi M., Gennarelli M. and Bocchio-Chiavetto L. (2011) Vascular endothelial growth factor (VEGF) serum concentration during electroconvulsive therapy (ECT) in treatment resistant depressed patients. *Prog. Neuropsychopharmacol. Biol. Psychiat.* 35, 1322–1325.

Miranda M. F., Hamani C., de Almeida A. C., et al. (2014) Role of adenosine in the antiepileptic effects of deep brain stimulation. *Front. Cell. Neurosci.* 8, 312.

Moffa A. H., Brunoni A. R., Nikolin S. and Loo C. K. (2018) Transcranial direct current stimulation in psychiatric disorders: a comprehensive review. *Psychiatr. Clin North Am.* 41, 447–463.

Moidunny S., Dias R. B., Wesseling E., Sekino Y., Boddeke H. W., Sebastiao A. M. and Biber K. (2010) Interleukin-6-type cytokines in neuroprotection and neuromodulation: oncostatin M, but not leukemia inhibitory factor, requires neuronal adenosine A1 receptor function. *J. Neurochem.* 114, 1667–1677.

Moidunny S., Vinet J., Wesseling E., Bijzet J., Shieh C. H., van IJzendoorn S. C., Bezzi P., Boddeke H. W. and Biber K. (2012) Adenosine A2B receptor-mediated leukemia inhibitory factor release from astrocytes protects cortical neurons against excitotoxicity. *J. Neuroinflammation* 9, 198.

Mori F., Codeca C., Kusayangai H., Montealeone F., Buttari F., Fiore S., Bernardi G., Koch G. and Centonze D. (2010) Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *J. Pain* 11, 436–442.

Mubagwa K. and Flameng W. (2001) Adenosine, adenosine receptors and myocardial protection: an updated overview. *Cardiovasc. Res.* 52, 25–39.
Murrough J. W., Abdallah C. G. and Mathew S. J. (2017) Targeting glutamate signalling in depression: progress and prospects. Nat. Rev. Drug Discovery 16, 472–486.

Newman M., Zohar J., Kailan M. and Belmaker R. H. (1984) The effects of chronic lithium and ECT on A1 and A2 adenosine receptors in rat brain. Brain Res. 291, 188–192.

Ng A., Tam W. W., Zhang M. W., Ho C. S., Husain S. F., McIntyre R. S. and Ho R. C. (2018) IL-1beta, IL-6, TNF- alpha and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. Sci. Rep. 8, 12050.

Novati A., Roman V., Cerini S., Hagemow R., den Boer J. A., Luiten P. G. and Meerlo P. (2008) Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. Sleep 31, 1579–1585.

Oliveira S., Ardais A. P., Bastos C. R., Gazal M., Jansen K., de Mattos A., Roman V., Cetin T., Hagewoud R., den Boer J. A., Luiten P. G., Novati A., Roman V., Cetin T., Hagewoud R., den Boer J. A., Luiten P. G. and Meerlo P. (2008) IL-6, A1 and A2aR: a crosstalk that modulates BDNF and neurotrophic factor and antidepressive effect of electroconvulsive therapy: Part I. A state of the evidence. J. Neurochem. 100, 1351–1363.

Randall P. A., Nunes E. L., Janniere S. L., Stopper C. M., Farrar A. M., Sager T. N., Baqi Y., Hockemeyer J., Mullings E. L., Max P. J., Hershfield M. S. and Andersen M. L. (2016a) Effects of acute sleep deprivation on anxiety-like behavior in rats. Sleep Med. 24, 109–118.

Rogers P. J., Hohoff C., Heathery S. V., Mullings E. L., Maxfield P. J., Evershed R. P., Deckert J. and Nutt D. J. (2010) Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. Neuropsychopharmacology 35, 1973–1983.

Rombo D. M., Ribeiro I. A. and Sebastiao A. M. (2016) Hippocampal GABAergic transmission: a new target for adenosine control of excitability. J. Neurochem. 139, 1056–1070.

Roulot M., Minelli A., Bortolomasi M., Maffioletti E., Gennarelli M., Borsotto M., Heutteaux C. and Mazella J. (2018) Increased serum levels of sortilin-derived propeptide after electroconvulsive therapy in treatment-resistant depressed patients. Neuropsychiatr. Dis. Treat. 14, 2307–2312.

Ruby C. L., Vaidie C. A., Hinton D. J., Abulseoud O. A., Walker D. L., O’Connor K. M., Noterman M. F. and Choi D. S. (2014) Adenosinergic regulation of striatal clock gene expression and ethanol intake during constant light. Neuropsychopharmacology 39, 2342–2440.

Sadek A. R., Knight G. E. and Burnstock G. (2011) Electroconvulsive therapy: a novel hypothesis for the involvement of purinergic signalling. Purinerg. Signal. 7, 447–452.

Salvadore G., Viale C. I., Luckenbaugh D. A., San-Juan D., Morales-Quezada L., Orozco Garduno A. J., Alonso-Sampaio-Junior B., Tortella G., Borrione L., Sadek A. R., Knight G. E. and Burnstock G. (2011) Electroconvulsive therapy: a novel hypothesis for the involvement of purinergic signalling. Purinerg. Signal. 7, 447–452.

Sanacora G., Zarets C. A., Krystal J. H. and Manji H. K. (2008) Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat. Rev. Drug Discovery 7, 426–437.

Sattin A. and Rall T. W. (1970) The effect of adenosine and adenine nucleotides on the cyclic adenosine 3′, 5′-phosphate content of guinea pig cerebral cortex slices. Mol. Pharmacol. 6, 13–23.

Schlaepfer T. E., Bewernick B. H., Kayser S., Hurleran R. and Coenen V. A. (2014) Deep brain stimulation of the human reward system of the sleep-inducing effects of prolonged wakefulness. Science 276, 1265–1268.

Ramesh V., Thatte H. S., McCarley R. W. and Basheer R. (2007) Adenosine and sleep deprivation promote NF-kappaB nuclear translocation in cholinergic basal forebrain. J. Neurochem. 100, 1351–1363.

© 2019 International Society for Neurochemistry. J. Neurochem. (2019) 151, 11–27.
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for major depression—rational, outcomes and outlook. Neuropsychopharmacology 39, 1303–1314.

Schmidt A. P., Bohmer A. E., Antunes C., Schallengerberger C., Porciuncula L. O., Elisabetsky E., Lara D. R. and Souza D. O. (2009) Anti-nociceptive properties of the xanthine oxidase inhibitor allopurinol in mice: role of A1 adenosine receptors. Br. J. Pharmacol. 156, 163–172.

Schwaninger M., Neher M., Viegas E., Schneider A., Serchov T., Atas H. C., Normann C., van Calker D. and Biber K. (2012) Ras activity tunes the period and modulation of the entrainment of the suprachiasmatic clock. Front. Neurol. 8, 264.

Serchov T., Atas H. C., Normann C., van Calker D. and Biber K. (2012) Genetically controlled upregulation of adenosine A1 receptor expression enhances the survival of primary cortical neurons. Mol. Neurobiol. 46, 535–544.

Serchov T., Clement H. W., Schwarz M. K., Vallon V., Muhlbauer B. and Osswald H. (2006) Adenosine and kidney disorder. Brain Behav. Pharmacol. Biochem. Behav. 837, 549–562.

Serchov T., Heumann R. (2017) Ras activity tunes the period and modulates the entrainment of the suprachiasmatic clock. Front. Neurol. 8, 264.

Serchov T., Atas H. C., Normann C., van Calker D. and Biber K. (2012) Genetically controlled upregulation of adenosine A1 receptor expression enhances the survival of primary cortical neurons. Mol. Neurobiol. 46, 535–544.

Serchov T., Clement H. W., Schwarz M. K., et al. (2015) Increased signaling via adenosine A1 receptors, sleep deprivation, imipramine, and ketamine inhibit depressive-like behavior via induction of Homer1a. Neurosci. 57, 535–544.

Serchov T., Heumann R., van Calker D. and Biber K. (2016) Signaling pathways regulating Homer1a expression: implications for antidepressant therapy. Biol. Chem. 397, 207–214.

Sheth S., Brito R., Mukherjea D., Rybak L. P. and Ramkumar V. (2014) Adenosine receptors: expression, function and regulation. Int. J. Mol. Sci. 15, 2024–2052.

Simoes A. P., Machado N. J., Goncalves N., Simoes A. T., Nunes A., Pereira de Almeida L., Goosens K. A., Rial D. and Cunha R. A. (2016) Adenosine A2A receptors in the amygdala control synaptic plasticity and contextual fear memory. Curr. Top. Behav. Neurosci. 25, 119–131.

Simoes A. P., Machado N. J., Goncalves N., Kaster M. P., Neher M. and Serchov T. (2017) Stimulation of interleukin-6 secretion and gene transcription in primary astrocytes by adenosine. J. Neurochem. 69, 1145–1150.

Stockwell J., Jakova E. and Cayabyab F. S. (2017). Adenosine A1 and A2A receptors in the brain: current research and their role in neurodegeneration. Molecules 22, E676.

Eur. J. Pharmacol. 206, 285–290.

Vazquez J. F., Clement H. W., Sommer O., Schulz E. and van Calker D. (2008) Local stimulation of the adenosine A2B receptors induces an increased release of IL-6 in mouse striatum: an in vivo microdialysis study. J. Neurochem. 105, 904–909.

Vedam-Mai V., van Battum E. Y., Kastens W., Feenstra M. G., Denys D., Reynolds B. A., Okun M. S. and Hol E. M. (2012) Deep brain stimulation and the role of astrocytes. Mol. Psychiatry 17(124–131), 115.

Vincenzi F., Ravani A., Pasquini S., Merighi S., Gessi S., Romagnoli R., Balardi P. G., Borea P. A. and Varani K. (2016) Positive allosteric modulation of A1 adenosine receptors as a novel and promising therapeutic strategy for anxiety. Neuropharmacology 111, 283–292.

Ward H. E., Hwynn N. and Okun M. S. (2010) Update on deep brain stimulation for neuropsychiatric disorders. Neurobiol. Dis. 38, 346–353.

Waters R. P., Rivalan M., Bangasser D. A., Deussing J. M., Ising M., Wood S. K., Holsboer F. and Summers C. H. (2015) Evidence for the role of corticotropin-releasing factor in major depressive disorder. Neurosci. Biobehav. Rev. 58, 63–78.

Wehr T. A. (1989). Sleep loss: a preventable cause of mania and other excited states. J. Clin. Psychiatry 50(Suppl), 8–16; discussion 45–17.

Wei C. J., Augusto E., Gomes C. A., Singer P., Wang Y., Boison D., Cunha R. A., Yee B. K. and Chen J. F. (2014) Regulation of fear responses by striatal and extrastriatal adenosine A2A receptors in forebrain. Biol. Psychiat. 75, 855–863.

Weiser M., Burshtein S., Gershon A. A., Marian G., Vlad N., Greuc I. G., Tocari E., Tiugan A., Hotineau M. and Davis J. M. (2014) Allopurinol for mania: a randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. Bipolar Disord. 16, 441–447.

Wohleb E. S., Franklin T., Iwata M. and Duman R. S. (2016) Integrating neuroimmune systems in the neurobiology of depression. Nat. Rev. Neurosci. 17, 497–511.

Yamada K., Hattori E., Shimizu M., Sugaya A., Shibuya H. and Yoshikawa T. (2001) Association studies of the cholecystokinin B receptor and A2a adenosine receptor genes in panic disorder. J. Neural. Transm. 108, 837–848.

Yamada K., Kobayashi M., Mori A., Jenner P. and Kanda T. (2013) Antidepressant-like activity of the adenosine A2A receptor antagonist, ifradefylline (KW-6002), in the forced swim test and the tail suspension test in rodents. Pharmacol. Biochem. Behav. 114–115, 23–30.

Yamada K., Kobayashi M. and Kanda T. (2014) Involvement of adenosine A2A receptors in depression and anxiety. Int. Rev. Neurobiol. 119, 373–393.

Young J. J., Bruno D. and Pomara N. (2014) A review of the relationship between proinflammatory cytokines and major depressive disorder. J. Affect. Disord. 169, 15–20.

Yroni A., Sporer M., Peran P., Schmitt L., Arbuz C. and Sauvaget A. (2018) Electrocortical convulsive therapy, depression, the immune system and inflammation: a systematic review. Brain Stimul. 11, 29–51.

Zaki N. F. W., Spence D. W., BaHammam A. S., Pandi-Perumal S. R., Cardinali D. P. and Brown G. M. (2019) Sleep and circadian rhythms in health and disease: a complex interplay. Eur. Arch. Psychiatry Clin. Neurosci. 269, 365–366.

Zielinski M. R., Kim Y., Karpova S. A., McCarley R. W., Strecker R. E. and Gerashchenko D. (2014) Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression. Neurosci. Lett. 580, 27–31.