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REVIEW

The role of adenosine receptors in mood and anxiety disorders

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Abstract

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 A_{2A} receptors is associated with increased depression-like symptoms, while increased A_1 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 A_1 receptor up-regulation or activation. In addition, A_1 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 A_1 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 neuroimmunological mechanisms, all of them implicated in mood regulation. Antagonists of adenosine receptors such as caffeine have general anxiogenic effects. In particular, A_{2A} 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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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 A_2 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; NFκB, 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.

Keywords: circadian rhythm, deep brain stimulation, electroconvulsive therapy, sleep deprivation, transcranial direct current stimulation.

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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 in depression 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 A_1 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 (Milrod *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 A_1 (inhibiting) and A_2 (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. A_1 and A_2 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 R_i (inhibiting) and R_a (activating). However, the nomenclature A_1 and A_2 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. A_2 receptors were later found to encompass two different types of receptors, the high affinity A_{2A} and the low affinity A_{2B} receptors, and an additional third adenosine receptor subtype (A_3) was identified. These four adenosine receptor subtypes A_1, A_{2A}, A_{2B} and A_3 are coupled to G-proteins. A_1 receptors typically act via the $G_{i/o}$

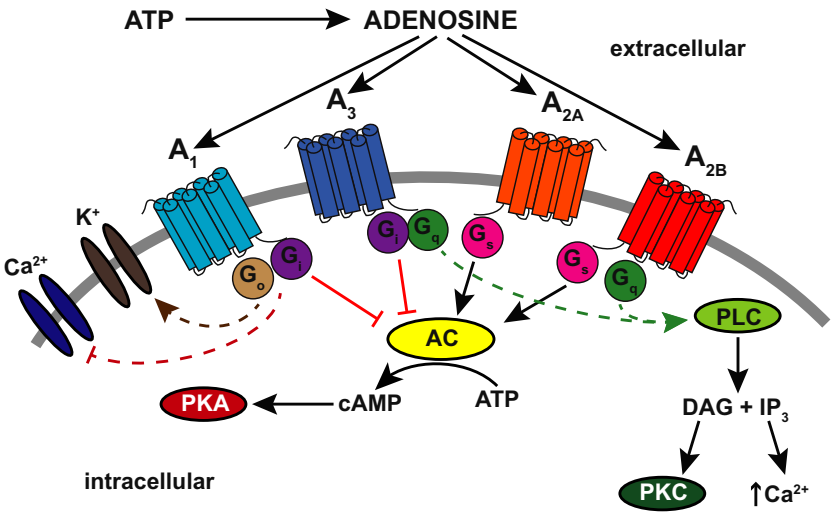

Fig. 1 Four subtypes of adenosine receptors and their intracellular signaling. AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; G, G protein; IP_3, inositol triphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

family, whereas A_{2A} and A_{2B} receptors act via G_s. A_{2B} receptors can also activate phospholipase C via G_q. A_3 receptors act via G_i-mediated inhibition of adenylyl 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 effects 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 overexpression 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,

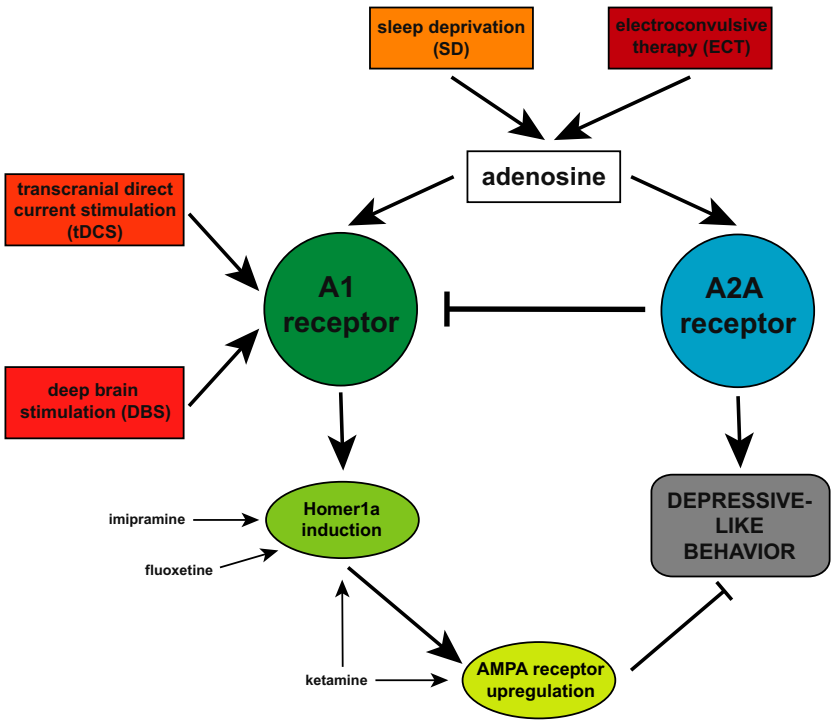

Fig. 2 Interaction between adenosine A1 and A2A receptors in the regulation of depressive-like behaviour.

ketamine as well as A_1 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 A_1 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 A_1 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 (Akhondzadeh *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 A_1 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 A_1 receptors are also involved in manic-like behavior remains to be established. Indeed, SD, which up-regulates A_1 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 A_1 receptors (Van Calker *et al.,* 1991). Via up-regulation of expression of A_1 receptors carbamazepine may also induce a new quality of adenosine A_1-receptor-mediated signal transduction in cells that initially express low basal A_1-receptor numbers (Biber *et al.,* 1996; Biber *et al.,* 1999).

Role of adenosine A_1 and A_{2A} receptors in anxiety disorders

In general, agonistic actions at A_1 receptors appear to promote anxiolytic effects (Jain *et al.,* 1995; Florio *et al.,* 1998; Vincenzi *et al.,* 2016), whereas cyclopentyltheophylline, an A_1 antagonist, had anxiogenic properties (Florio *et al.,* 1998). However, the investigation of other A_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.,* 2015) as well as on wakefulness (Huang *et al.,* 2005; Lazarus *et al.,* 2011) appear to be mediated via antagonism at adenosine A_{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_{2A} receptor antagonists (El Yacoubi *et al.,* 2000), and increased anxiety-like behavior is observed not only in A_{2A} (Ledent *et al.,* 1997; Deckert, 1998) but also in A_1 (Johansson *et al.,* 2001; Gimenez-Llort *et al.,* 2002) receptor knockout mice. Thus, both adenosine receptors subtypes A_1 and A_{2A} may play a role in anxiety at least in rodents.

The effects of A_{2A} receptors in anxiety in rodents have been investigated in some detail: A_{2A} receptor knock-out mice exhibit not only increased anxiety-like behavior but also increased c-Fos immunoreactivity in the anterior cingulate cortex and the amygdala as compared to wild-type mice (Lopez-Cruz *et al.,* 2017). However, the effects of A_{2A} receptors on anxiety-like behavior in rodents are variable and highly dependent on the brain region. Thus, selective down-regulation of the A_{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_{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_{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_{2A} receptors in the forebrain rather inhibited fear conditioning, whereas deletion of A_{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_{2A} receptor gene in anxiety disorders. The T allele of a silent polymorphism in exon 2 of the adenosine A_{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_{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 A_{2A} 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 A_{2A} 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 A_1 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 A_1 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.

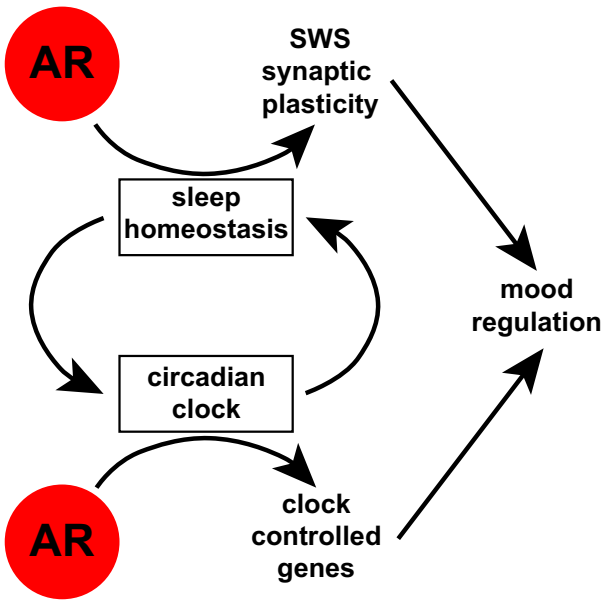

Fig. 3 Adenosine receptors (AR) modulate sleep homeostasis and circadian clock and thus regulates mood.

However, not only A_1– but also A_{2A}– 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 A_{2A} receptors was shown to regulate striatal cellular and behavioral circadian timing and activity level (Ruby *et al.,* 2014). Both A_1 receptors and particularly A_{2A} receptors regulate sleep (Huang *et al.,* 2005). However, while A_1 receptors are known to mediate the antidepressant effects of SD (see above), little is known about the potential relationship between the function of A_{2A} 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 A_1 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 A_{2A} receptors are much less clear. Initially, a down-regulation by SD (3 and 6 h) of A_{2A} 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 A_{2A} 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 A_{2A} receptors (if any) after SD is still unclear. Since A_{2A} receptor activation induces depression-like behavior in rodents (see discussion above), down-regulation of A_{2A} receptors may contribute to the antidepressant effects of SD and add to the antidepressant effects of increased A_1 receptor signaling. However, presently no data are available that would support this hypothesis. The increased signaling via A_1 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 A_1 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 A_1 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 A_1R expression in several brain regions and a reduced adenosine A_{2A} 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 A_1 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 A_1 and A_{2A} 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 A_1 receptor signaling and its cross-talk with A_{2A} 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 (Haskett, 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 A_1 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 A_1 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 A_1-receptors A_2-receptors are rapidly down-regulated after ECT, perhaps contributing to the antidepressant effects (since A_2 receptors rather increase depression, see above) (van Calker and Biber, 2005). Since increased signaling via adenosine A_1 receptors has been shown to have pronounced antidepressant effects (Serchov *et al.,* 2016), the ECT-induced increase in adenosine and A_1 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 A_1 receptor activation (Fig. 2). Indeed, similar to SD, which upregulates Homer1a via A_1 receptor activation (Serchov *et al.,* 2015), also ECT upregulates Homer1a expression levels in the cortex (Kato, 2009), most probably mediated by the increased A_1 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 A_1 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 (Merkl *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) (Tawfik *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; Dowlati *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 A_{2B}- and A_{2A} receptors excretion of IL-6 (Fiebich *et al.,* 1996; Schwaninger *et al.,* 1997; Schwaninger *et al.,* 2000; Fiebich *et al.,* 2005) and IL-1β (Chiu *et al.,* 2014), both found increased in depression (Ng *et al.,* 2018), and regulates immune functions in the brain (Hasko *et al.,* 2005; Abbracchio and Ceruti, 2007; Chiu and Freund, 2014). Furthermore, there is very robust evidence showing that A_{2A} receptors

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 A_1 and A_{2A} receptors interact with IL-6 to mediate cell survival and IL-6 modulates through the regulation of adenosine A_1 and A_{2A} 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, A_{2A} 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 A_1 and A_{2A} adenosine receptors are implicated in the etiology and treatment of mood and anxiety disorders. Thus activation of A_1 and inhibition of A_{2A} receptors elicit antidepressant effects (Fig. 2). The antidepressant effects of enhancement of A_1 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 A_{2A} receptors are mediated is still unknown. In addition to their role in mood disorders, adenosine A_1 and A_{2A} receptors also regulate anxiety-like behavior. In particular A_{2A} 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 A_{2A} receptor agonists has been suggested for autism-spectrum disorders and schizophrenia, while A_{2A} 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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