



A Pattern to Link Adenosine Signaling, Circadian System, and Potential Final Common Pathway in the Pathogenesis of Major Depressive Disorder

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Abstract

Several studies have reported separate roles of adenosine receptors and circadian clockwork in major depressive disorder. While less evidence exists for regulation of the circadian clock by adenosine signaling, a small number of studies have linked the adenosinergic system, the molecular circadian clock, and mood regulation. In this article, we review relevant advances and propose that adenosine receptor signaling, including canonical and other alternative downstream cellular pathways, regulates circadian gene expression, which in turn may underlie the pathogenesis of mood disorders. Moreover, we summarize the convergent point of these signaling pathways and put forward a pattern by which *Homer1a* expression, regulated by both cAMP-response element binding protein (CREB) and circadian clock genes, may be the final common pathogenetic mechanism in depression.

Keywords Adenosine receptors · Circadian genes · Depression · *Homer1a* · CREB

Introduction

Major depressive disorder (MDD) is one of the most prevalent forms of mental illness. It is a complex and heterogeneous disorder associated with high individual suffering,

increased risk of suicide, and a severe economic burden for society [1]. Several lines of evidence from animal and human studies have shown that disturbances of circadian clockwork are associated with the development of depression. Moreover, different chronotherapies, a variety of strategies that modulate biological clock, such as sleep deprivation and light therapy, are considered as alternative treatments for depression [2]. However, how the circadian clock influences pathophysiology of mood disorders, as well as the molecular and cellular mechanisms of action of the therapeutic interventions targeting circadian rhythm, is not well understood. The identification of the neurobiological substrates mediating the crosstalk between the circadian clock and mood regulation may lead to the development of new strategies for prevention and treatment of depression.

Numerous studies have demonstrated a role of adenosine receptors in the development of depression and antidepressant therapies [3–5]. Moreover, adenosinergic signaling is implicated in the regulation of different aspects of the circadian clock [6, 7]. However, the detailed mechanism has not been completely clarified. Recently, we found that the canonical circadian clock genes *Per1* and *Per2* were involved in the antidepressant action of an adenosine A₁ receptor (A₁R) agonist [8]. In addition, it has been shown that the expression of the synaptic plasticity protein *Homer1a*,

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proposed by our group as an important element mediating antidepressant effects and also a downstream target of adenosine receptor signaling [9–12], is directly regulated by the circadian clock [13].

In the present article, we review relevant recent advances linking adenosine receptors, circadian clock, and mood and propose that adenosine signaling regulates circadian clockwork and Homer1a, which may be a potential final common mechanism involved in the neurobiology and treatment of depression.

Adenosine Signaling and Mood

There are numerous studies on adenosine signaling and depression, which have been recently reviewed extensively by others [3–5]. The cellular effects of adenosine are mediated by four subtypes of G-protein coupled receptors: A₁R, A_{2A}R, A_{2B}R, and A₃R. In general, it was proposed that A₁Rs promote antidepressant-like effects, while A_{2A}Rs' activation enhances depression-like behaviors in rodents [3]. As for the A_{2B} and A₃ receptors, at present, we could not find any reports on their role in mood disorders [14, 15].

Several non-pharmacological antidepressant treatments including sleep deprivation (SD), electroconvulsive therapy (ECT), and deep brain stimulation (DBS) enhance A₁R signaling [9]. Hines et al. was first to demonstrate that A₁Rs are necessary for the antidepressant action of SD and that their activation leads to rapid antidepressant-like effects [16]. Our group utilized a line of transgenic mice conditionally overexpressing A₁R in calcium/calmodulin-dependent protein kinase type II (CaMKII) forebrain neurons [9, 11, 17]. Upregulating A₁R led to pronounced acute and chronic resilience toward depressive-like behavior in various tests, while A₁R knockout mice displayed an increased depressive-like behavior and were resistant to the antidepressant effects of SD [9]. Furthermore, we have shown that the antidepressant effects of A₁R activation are mediated by the synaptic plasticity protein Homer1a, which is upregulated by various antidepressant treatments such as SD, imipramine, ketamine, and A₁R activation [9, 12]. Using a different transgenic mouse lines with overexpression of A₁R in the cortex and hippocampus, we found that depending on the brain region of A₁R upregulation, the mice show different resistance to depression-like behavior, and that enhanced Homer1a expression in the hippocampus increases stress vulnerability [11].

However, activation of A₁R may elicit also manic or hypomanic episodes in patients with bipolar disorder [18]. It has been reported that peripheral adenosine levels were negatively correlated to the severity of depressive symptoms of bipolar disorder patients [19]. Therefore, peripheral adenosine levels may have a positive relationship with

mood, demonstrating the pivotal role of adenosine in mood regulation.

In contrast, it has been reported that rats with A_{2A}R overexpression in hippocampus, cortex, and striatum show increased depression-like behavior [20]. Vice versa, A_{2A}R KO mice exhibit reduced depression-like behaviors, such as decreases in the immobility time in forced swimming test and tail suspension test [21, 22]. The A_{2A}R antagonist istradefylline (KW6002) showed an antidepressant-like action on learned helplessness model rats [23]. However, some contradictory results of relationship between A_{2A}R and mood have also been released. Tsai et al. reported that they did not find any association of A_{2A}R (1976C > T) genetic polymorphism with mood disorders [24]. However, this does preclude the possibility of a role of A_{2A}R in the pathogenesis of mood disorders; rather, other A_{2A}R variants must also be extensively studied. Moreover, A_{2A}Rs have also been linked with depression, suicidal behavior, and impulsivity based on indirect evidence at a statistical association level [25]. For instance, Lucas et al. reported a negative association between caffeine consumption and risk of suicide based on cohort studies [26]. The actions of adenosine receptors on depression are summarized below (Table 1).

Circadian Clock and Mood Regulation

Circadian clocks govern a wide range of biochemical, physiological, and behavioral processes. In mammals, the circadian master pacemaker is located in the suprachiasmatic nucleus (SCN) [27]. The circadian oscillation of the intracellular clock is driven by transcription/translation-based feedback/feedforward loops, consisting of a set of clock genes. Positive regulatory elements are brain and muscle ARNT-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), which form heterodimers and induce the rhythmic transcription of *Period* (*Per1* & *Per2*) and *Cryptochrome* (*Cry1* & *Cry2*) genes. The PER and CRY proteins interact and translocate to the nucleus, where they act as negative regulators inhibiting CLOCK/BMAL1 transcription [28]. An additional loop including both activating and repressing regulatory elements is formed by retinoic acid receptor-related orphan receptors (ROR α , β , and γ) and nuclear receptors REV-ERB (α & β) [29, 30].

Table 1 Effects of adenosine receptors on depression or depression-like behavior

Receptors	Effect of activation	References
A ₁ R	Antidepressant like effect	[3, 8, 9, 11, 16, 139]
A _{2A} R	Pro-depressive like effect	[3, 20–23, 25, 26, 139, 140]

A large number of studies have demonstrated the relationship between the circadian clock and depression [31–39], with a great many reviews to refer to [31, 32, 34, 36, 40–45]. Most of these reports have shown correlation between genes, RNAs, proteins, and single nucleotide polymorphisms with the symptoms of MDD or depression-like behaviors [33, 38, 39, 46–48]. For example, variants of circadian genes, such as *CLOCK*, *BMAL1*, *NPAS2*, *Per3*, and *NR1D1*, play a role in mood disorders, mainly based on statistical analyses [49–53]. In addition, transgenic mice with mutations in certain clock genes have been characterized with depressive-like behavior. However, each mouse model shows a distinct mood/rhythm combination phenotype: similar mood characteristics occur with opposite changes of circadian period, and reduced circadian amplitude leads to different changes in mood behavior, which hinders a clear conclusion/hypothesis [54].

Several brain regions relevant to psychopathology of depression, including the prefrontal cortex, hippocampus, amygdala, lateral habenula (LHb), and nucleus accumbens (NAc), possess an oscillating molecular clock [55–57]. Increasing evidence from human and rodents suggests that these region-specific oscillators in limbic areas are instrumental regulators of mood. Indeed, a microarray study demonstrated that the circadian patterns of gene expression in six brain regions (including amygdala, prefrontal cortex, hippocampus, and NAc) are significantly altered in human post-mortem subjects with MDD [48]. Moreover, many chronic stress-based animal models of depression show dysregulated circadian rhythms of locomotor activity, body temperature, and corticosterone levels [58], as well as reduced circadian expression amplitude of several canonical circadian clock genes in the SCN and amygdala, but increased amplitude in the NAc [55, 56, 59]. For instance, Christiansen et al. demonstrate effects of chronic mild stress on core circadian genes in rats [46]—the mean peak times of *Per2* and *Bmal1* expressions in SCN were either phase-delayed or phase-advanced in the chronic stress group. Taken together, these reports suggest that stress and/or MDD might differently affect the circadian clockwork in particular brain areas and that further investigation on region-specific circadian mechanisms are needed.

A potential role has been recently proposed for the circadian clock in the mechanism of rapid antidepressant treatments, like SD and ketamine [60]. Duncan et al. revealed an association between ketamine's clinical antidepressant response and circadian-related wrist-activity parameters [39], finding that responders showed a phase-advanced activity rhythm and a decreased measure compared with nonresponders at baseline. Orozco-Solis et al. showed downregulation of several canonical clock genes, including *Per1*, *Per2* and *Cry2*, by rapid antidepressant therapies SD and low-dose ketamine, using comparative transcriptomics

analyses [38]. Furthermore, ketamine usually takes its most robust effect on the next day of its treatment [61], a phenomenon probably related to the effect of ketamine on circadian system [43]. Preclinical studies reveal that both SD and ketamine downregulate circadian genes, probably through NMDAR, AMPAR, TrkB, MAPK, mTOR, GSK3 β , and CREB [38, 62–65], but the exact cellular pathway has not been confirmed and needs to be further investigated. Until now, only a few studies have revealed signaling pathways that act directly on the molecular circadian clock and mediate the pathogenesis of major depression or depression-like behaviors [8, 66].

The role of circadian rhythm in mood regulation is bidirectional, affecting both depression and mania [67–75]. For example, phase advance during manic episodes and phase delay during depressive episodes were found in the patients with bipolar disorder [76–79]. The *CLOCK* ^{Δ 19} and *Per2*^{Brdm1} mice exhibit hyperdopaminergic state and mania-like phenotypes [80–82], while in contrast, *Per1* knockout mice show depression-like behavior in forced swim test [83], directly demonstrating that the circadian clock influences monoamine oxidase A and mood. In addition, Olejniczak et al. revealed that light affects depression-like behavior through *Per1* in the LHb [83]. Therefore, our focus should not be restricted to only one axis of investigation. For instance, while A₁R agonism shows antidepressant-like effects, it may potentially induce manic or hypomanic episodes and vice versa [18, 84]. As a result, this side effect must be avoided when exploring novel antidepressants or mood stabilizers. Recently, Hinton et al. reported that administration of caffeine during adolescence in mice could induce circadian-dependent changes in mood fluctuations in adulthood, including depression and mania [85]. However, the exact cellular pathway underlying this phenomenon needs to be investigated further. In future, elucidation of the pathogenesis of trans-phase may be an important research field.

Taken together, these reports support a causal relationship between the circadian system and mood. However, alternative hypotheses have been proposed, and whether the disruption of circadian clocks are causes or consequences of mood disorders remains undetermined. Accordingly, Lazzarini Osprei et al. provide a model suggesting that mood may be an output of circadian rhythm by probability [86]. However, this hypothesis also needs to be further verified.

The Role of Adenosine Receptors in Circadian Clock Modulation

Light is the most potent resetting stimuli of the circadian clock. In addition to glutamate, adenosine appears to be a strong candidate for modulating SCN activity [87]. Indeed, application of adenosine attenuates light-induced phase

shifts, while A_1R antagonism can reverse this effect [88, 89]. Adenosine is known to increase during SD [90] and accordingly it has been shown in rodents and humans that SD also reduces the photic resetting of circadian activity [91, 92]. Likewise, in response to acute SD, a subset of circadian clock genes behave as immediate early genes and are transcriptionally responsive within hours of treatment [93, 94]. Conversely, longer SD suppresses 80% of rhythmic genes in the mouse brain [95, 96]. Moreover, the adenosine receptor antagonist caffeine modulates different aspects of the circadian rhythms including behavioral rhythm and the molecular clock [87, 97, 98]. It increases the light-entraining activity rhythm and lengthens the period of *hPer2* and *mBmal1* [97, 99]. In human-cultured cells, caffeine produced its effect on the circadian clock through adenosine receptor-cAMP signaling [100].

Adenosine A_1R and $A_{2A}R$ Signaling Pathways as Regulators of the Molecular Circadian Clock and Mood

In the following chapter, we will review and discuss A_1R and $A_{2A}R$ downstream signaling, including classical pathways and some alternative cascades, implicated in the regulation of the cellular circadian system and mood. Moreover, transcriptional factor CREB phosphorylation and induction of the synaptic protein Homer1a appear to be a convergent point of various pathways [101], and play a critical role both in the regulation of circadian rhythm [102, 103] and in the pathogenesis of depression [101].

Canonical Adenosine Signaling

ERK MAPK Pathway

A_1R activates the phospholipase C (PLC) β —inositol triphosphate (IP_3) pathway in order to induce the release of calcium from endoplasmic reticulum and subsequently activates extracellular regulated protein kinase (ERK) [10, 104]. After ERK is activated, it can consequently activate the downstream part of the MAPK signaling pathway. CREB is the endpoint of the pathway, which can enter the nucleus and bind to the CRE sites in the promoter regions of *Homer1a*, *Per1*, and *Per2* genes to regulate their transcription (Fig. 1) [10, 38, 44, 103, 105–107]. Moreover, it has been reported that adenosine A_1R -ERK1/2 signaling pathway in the prefrontal cortex and hippocampus region of mice was involved in the anti-menopausal depressant-like effect of Jiao-Tai-Wan [108]. Additionally, there have been numerous references showing that the ERK MAPK pathway plays a critical role in MDD [109–113]. Moreover, ERK-CREB signaling in the hippocampus and prefrontal

cortex was revealed as the downstream pathway of inosine to produce its antidepressant-like effect [114]. Thus, the ERK MAPK pathway is both important in circadian systems and mood regulation.

cAMP Signaling Pathway

cAMP is also a classical downstream signaling pathway of both A_1R and $A_{2A}R$ and plays a key role in the mammalian circadian clock [100, 105, 115]. The A_1R can suppress the cAMP pathway through inhibiting adenylate cyclase (AC) via its G_i ; contrarily, the adenosine A_{2A} receptor can stimulate cAMP pathway through activating AC via its G_s (Fig. 1) [3]. Burke et al. found that the intracellular mechanism of caffeine-induced regulation of the circadian rhythm is via the adenosine A_1 receptor-cAMP signaling pathway in human cells in vitro [100]. In addition, it was revealed that the cAMP-protein kinase A (PKA)-CREB pathway in rat hippocampal neurons was involved in the antidepressant-like effect of serum [116]. However, no interaction was identified of this pathway with circadian genes. As CREB is the endpoint of various cellular pathways, including the cAMP pathway, it has been suggested that CRE sites on the *Per1* or *Per2* genes might be the potential target (Fig. 1) [103, 105, 106]. Therefore, cAMP is another downstream signaling pathway that plays critical roles in both regulation of circadian genes and mood.

Ca^{2+} Signaling Pathway

Studies have revealed that both L-type calcium channels and calcium-induced calcium release can induce post-synaptic adenosine elevation [117] and that calcium signaling acts upon *Per1/2* genes directly via CREB in mammalian cells [103, 115, 118]. In addition, A_1R can also inhibit L-type calcium channels via its G_i [3]. Besides this, the ERK/MAPK signaling pathway is calcium-dependent. It has also been reported that the G_q - Ca^{2+} axis controls the circadian clock in the SCN [119], involved in both input and output of circadian systems [115, 120]. Furthermore, the cAMP/ Ca^{2+} signaling pathway determines properties of the circadian system, including phase, amplitude, and period; in turn, cAMP/ Ca^{2+} signaling is regulated by circadian system and rhythmically expressed [115].

In conclusion, ERK MAPK, cAMP, and Ca^{2+} signaling pathways are the major downstream pathways of adenosine, which in parallel can regulate circadian molecular clock (Fig. 1). Pertinently, it has been demonstrated that levels of cAMP, Ca^{2+} , ERK, and CREB were decreased in postmortem patients with MDD [121]. Moreover, levels of these molecules were oppositely altered in patients with bipolar disorder treated with mood stabilizers compared to MDD

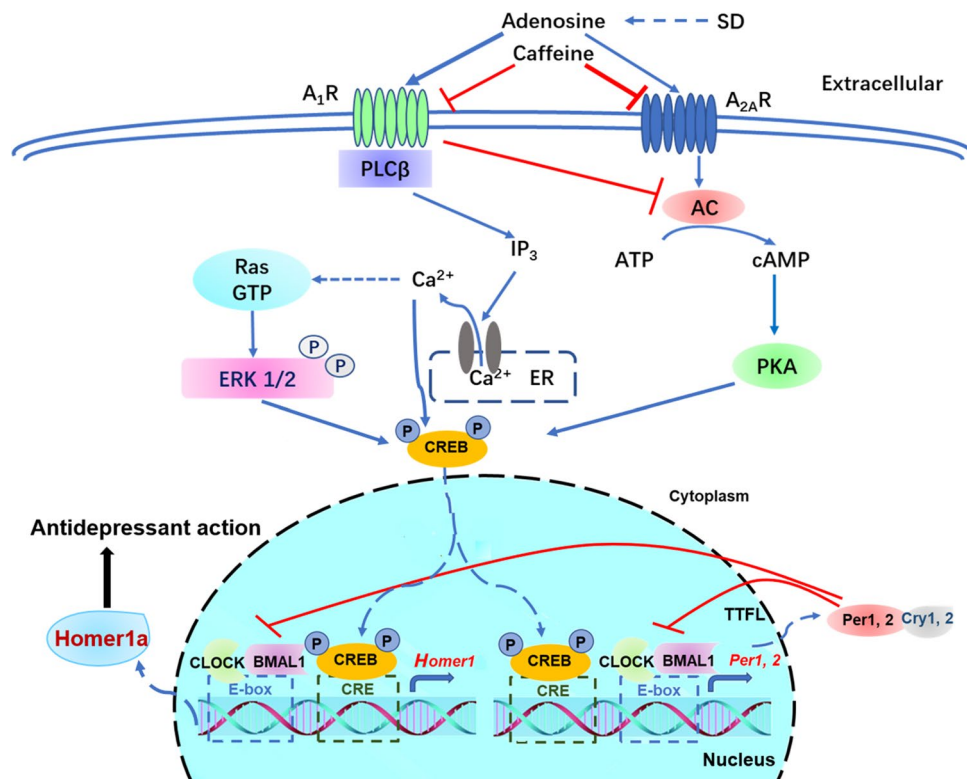


Fig. 1 Pattern of a potential final common mechanism of antidepressant action. Acute or chronic SD increases the adenosine levels in the brain and activates A_1R s and $A_{2A}R$ s. Subsequently, ARs act on various signaling pathways, including cAMP, PKA, Ca^{2+} , and MAPK in the cytoplasm, and converge on the phosphorylation of the transcriptional factor CREB. The phosphorylated CREB enters the nucleus and binds with the CRE sites on *Homer1* and *Per1/2* promoters to regulate their transcription. Simultaneously, these genes are transcriptionally regulated by CLOCK/BMAL1 via E-box elements on their promoters. Concurrently, PER form complexes with CRY in the cyto-

plasm, which in turn compete with CLOCK/BMAL1 complexes and block their transcription, as well as *Homer1a* expression. SD, sleep deprivation; AC, adenylate cyclase; PLC β , phospholipase C beta; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; IP3, inositol triphosphate; PKA, protein kinase A; ER, endoplasmic reticulum. Arrows indicate activation: the thicker arrow indicates that adenosine may have a preferential activation effect on A_1R during acute SD. In parallel, the red lines indicate inhibition, where the thicker line indicates greater inhibition of $A_{2A}R$ by caffeine

patients administered antidepressants [121], demonstrating their roles in mood regulation.

Other Potential Alternative Downstream Cellular Pathways of Adenosine Receptors

In addition to the canonical cellular pathways, there are also some recently explored downstream signaling pathways of A_1R , which have not been demonstrated to be involved in mood regulation but may suggest new further research directions.

Recently, Jagannath et al. revealed that adenosine could regulate the circadian clock through activating the adenosine A_1/A_{2A} receptor, and their downstream Ca^{2+} -ERK-AP-1 and CREB/cAMP-regulated transcriptional coactivators (CRTC1)-CRE signaling pathways to modulate the expression of *Per1* and *Per2* genes in mice [122]. They found that these signaling pathways were also stimulated by light [122]. Thus, adenosine can alter the circadian time by integrating

signals from light and sleep. Furthermore, Trautmann et al. showed that caffeine acts on mood through the elevation of phosphorylated Thr75-DARPP-32, which can bind to CLOCK and inhibit the CLOCK/BMAL1 complex interaction, consequently modulating the expression of circadian genes and potentially linking adenosine, circadian systems, and mood [66].

Adenosine receptors are also involved in the modulation of other neurotransmitter systems. For example, the $A_{2A}R$ is colocalized postsynaptically in dopamine areas, including the striatum and NAC [123]. Indeed, it has been demonstrated that there is a functional interaction between dopamine D2Rs and $A_{2A}R$ s, which converge on the same signal transduction pathways in an antagonistic way [124]. Likewise, A_1R and D1Rs antagonistically interact [125]. The dopaminergic system plays an important role in the control of reward and motivation-oriented behavior, which is severely affected in MDD. Since dopamine synthesis and particularly its limiting enzyme tyrosine hydroxylase (TH)

are under circadian regulation, this interaction between adenosinergic and dopaminergic system represents another potential signaling pathway involved in mood regulation [126].

Convergent Points of Adenosine Receptor Signaling

CREB

CREB is a convergent point of various pathways in the pathogenesis of MDD and is the downstream effector molecule of adenosine signaling [101]. The role of CREB in MDD varies with different brain regions [101]. For example, overexpression of CREB in the dentate gyrus of the hippocampus produced an antidepressant-like effect in rats [127], while overexpression of CREB in either the CA1 pyramidal cell layer of the hippocampus or the prefrontal cortex did not show this effect [127]. Conversely, overexpression of CREB in the basolateral amygdala or in the NAc produced a pro-depressive-like effect [128, 129]. Meanwhile, the acting points of CREB on the circadian genes *Per1/2* have been elucidated (Fig. 1) [8, 106, 122]. Phosphorylated CREB is one of the transcriptional factors regulating *Per1/2*. Besides this, AP-1 is another transcriptional factor that can also bind with AP-1 sites in the promoter regions of *Per* genes. In the *Per2* gene, AP-1 REs are putative and conserved, while in contrast are not well conserved in *Per1* [122]. Moreover, it has been reported that the sequences of CRE (TGACGTCA) and 12-O-tetradecanoylphorbol-13-acetate-responsive element (TRE) (TGACTCA) are very similar, and that the nuclear factors of CREB, CRE modulator (CREM), and Jun were also very similar in structure [130, 131]. This may lead to transcriptional cross-talk and potential competitive effects. Therefore, we deduce that this physiological process may be involved in the interaction between *Per1*, *Per2*, and *Homer1a* genes, and may play a key role in supplement to the traditional feedback loops of the molecular circadian clock.

CREB conduction signals can also be regarded as an intrinsic part of clock oscillations, modulating acute alterations in the circadian clock and transcription-translation feedback loops [118, 132].

Apart from circadian genes *Per1/2*, there are hundreds of genes that have CRE sequences in their promoter regions that can be bound with pCREB/CREB. Therefore, *Per1/2* might not be the only final common targets of antidepressants and other genes, such as *Homer1a*, might have an interaction with these circadian genes (see below).

Homer1a

Homer1a is a member of the Homer family of postsynaptic scaffolding proteins, which is rhythmically expressed and

acts as neuronal activity-inducible modulator of glutamatergic signaling [10, 13, 133]. It has been shown that Homer1a induction, as a downstream effect of A₁R signaling, may be a convergent point of several non-pharmaceutical treatments of MDD [9–11, 133]. Homer1a has been subsequently proposed as a final common pathway of various antidepressant therapies, including ECT, TMS, SD, and ketamine, as well as for classical treatments, such as imipramine and fluoxetine [10]. In addition, it has been shown that metabotropic glutamate receptor 5 (mGlu5) and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA) might be the potential targets for Homer1a to act and exhibit its antidepressant effect [12]. Recently, Sato et al. revealed that the *Homer1* gene is bimodally regulated by CREB via the CRE site and by the CLOCK/BMAL1 complex via E-box, demonstrating an important crosstalk between CREB and the circadian clock, and thus showing a pivotal role of Homer1a in integrating signals from both adenosine signaling and circadian rhythms [13]. Therefore, this may be the most promising final common pattern in the pathogenesis of depression and the mechanism of antidepressants. Thus, we propose that *Homer1* and *Per* genes, receiving signals from both CREB and the CLOCK/BMAL1 complex, which is inhibited by PERs, may be a potential common mechanism of various antidepressant therapies (Fig. 1).

Conclusions and Future Directions

Acute SD is known to elicit rapid antidepressant effects, while chronic sleep restriction is considered as a risk factor for depression [134]. However, adenosine is accumulated in the brain after both acute and chronic sleep loss and acts as modulatory neurotransmitter regulating brain homeostasis via modulation of sleep and homeostatic plasticity, circadian clockwork, and mood [3, 9, 135–138].

We deduce that, on one hand, this conflicting effect of adenosine might be due to the preferential activation of its receptors, since A₁R and A_{2A}R signaling have contrasting effects on mood. Perhaps during the acute SD phase, adenosine has a greater effect on A₁R [9], whereas, during chronic sleep loss, there may be a counterbalancing effect and possibly more action on the A_{2A}R with an opposing effect on downstream signaling (Serchov et. 2020). At the same time, caffeine, an antagonist of adenosine receptors, may have a stronger antagonistic effect on A_{2A}R than A₁R, resulting in an antidepressant effect [21, 22, 139]. On the other hand, pCREB may also have a biased or counterbalancing effect on *Homer1* and *Per* genes, and the final Homer1a protein expression level may depend on the probability of circadian output, which may match the alternative hypothesis model provided by Lazzerini Ospri et al. [86].

As discussed above, circadian gene expression is differentially affected by chronic stress, depression, or antidepressant treatments in different brain regions. Thus, the different effects of adenosine signaling on the circadian clock, Homer1a expression, and mood might also be brain region-specific [11, 133].

Taken together, we summarize that adenosine A₁R/A_{2A}R signaling converges on the transcriptional factor CREB. After CREB is activated, it can bind to both CRE/AP-1 sites on *Per1/2* gene promoters, or the CRE site on the *Homer1* promoter, thus modulating their expression. In turn, *Per/Cry* complexes translocate to the nucleus and inhibit BMAL1 activity. Since *Homer1* expression is bimodally regulated by BMAL1 and CREB, we deduce that *Homer1a* expression might be inhibited by *Per* indirectly (Fig. 1). Thus, *Homer1a* is potentially a final common pathway in the pathogenesis and treatment of depression, which links adenosine signaling, circadian clock, and neuro-plasticity together, mediating both the antidepressant effects of acute SD and the detrimental action on mood of chronic sleep loss.

Additionally, the synthesis of dopamine is also regulated in a circadian manner, through the time-dependent expression of TH by promoter occupancy of CLOCK, NAD⁺-dependent sirtuin 1 (SIRT1), and CREB [107]. This pathway links the metabolic system, circadian rhythms, and neurotransmitter system together, important in the regulation of many physiological processes and psychiatric diseases. In the future, we shall investigate this common mechanism from several other perspectives: neuro-inflammation, systems of monoamine and glutamatergic signaling, the hypothalamic–pituitary–adrenal (HPA) axis, brain-gut axis, metabolic peptide signal transduction, and mitochondrial function, with the aim of exploring the common pathophysiology of depression from a cellular to systemic level.

Above all, identification of the common pathogenesis of MDD will help us to better understand the underlying pathogenesis of mood disorders and to explore novel antidepressants or mood stabilizers with fewer side effects.

Author Contribution All authors contributed to the study conception and design. The first draft of the manuscript was written by Xing-Ling Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interests Tsvetan Serchov has honoraria consulting Prime-time Life Sciences, LLC. All other authors declare that they have no relevant financial or non-financial interests to disclose.

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