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REVIEW ARTICLE



Rapid-acting antidepressants and the circadian clock

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A growing number of epidemiological and experimental studies has established that circadian disruption is strongly associated with psychiatric disorders, including major depressive disorder (MDD). This association is becoming increasingly relevant considering that modern lifestyles, social *zeitgebers* (time cues) and genetic variants contribute to disrupting circadian rhythms that may lead to psychiatric disorders. Circadian abnormalities associated with MDD include dysregulated rhythms of sleep, temperature, hormonal secretions, and mood which are modulated by the molecular clock. Rapid-acting antidepressants such as subanesthetic ketamine and sleep deprivation therapy can improve symptoms within 24 h in a subset of depressed patients, in striking contrast to conventional treatments, which generally require weeks for a full clinical response. Importantly, animal data show that sleep deprivation and ketamine have overlapping effects on clock gene expression. Furthermore, emerging data implicate the circadian system as a critical component involved in rapid antidepressant responses via several intracellular signaling pathways such as GSK3 β , mTOR, MAPK, and NOTCH to initiate synaptic plasticity. Future research on the relationship between depression and the circadian clock may contribute to the development of novel therapeutic strategies for depression-like symptoms. In this review we summarize recent evidence describing: (1) how the circadian clock is implicated in depression, (2) how clock genes may contribute to fast-acting antidepressants, and (3) the mechanistic links between the clock genes driving circadian rhythms and neuroplasticity.

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INTRODUCTION

Major depressive disorder (MDD) is one of the most serious psychiatric disorders. Worldwide, depression affects over 300 million people of all ages and is the leading cause of lifetime disability out of all medical disorders according to the World Health Organization (WHO) [1, 2]. Approximately 800,000 individuals die from suicide each year, many of which are associated with MDD [2, 3]. In the United States, the burden of MDD increased substantially over the past decade in terms of prevalence, the stress associated with COVID-19, rising economic costs and importantly, the limited efficacy of standard antidepressants [4]. Fast-acting interventions such as subanesthetic ketamine or sleep deprivation therapy (SDT) (e.g., 36 h of continuous wakefulness [5]) can effectively decrease suicidality within hours [6], thereby potentially saving many lives. The therapeutic limitation of classic antidepressants including limited efficacy (~50%), low remission rates (~30–40%) in addition to the prolonged response delay of several weeks [7] suggests that additional mechanistic factors may contribute to the pathophysiology of MDD.

Emerging evidence supports a circadian hypothesis of depression based, in part, on data showing that a subgroup of depressed patients (20–30%) has dysregulated 24 h rhythms including sleep,

core body temperature, hormonal secretions (i.e., cortisol, melatonin) and mood. Moreover, rhythms may normalize as symptoms remit [8–14]. Diurnal fluctuations in mood in a subgroup of depressed patients include a pattern of depressive symptoms that are significantly worse in the morning and dramatically improve by evening [6]. Perhaps the strongest and most direct evidence for a circadian defect in depression comes from a study of postmortem 24 h sinusoidal gene expression rhythms across six regions of human brain showing a dramatic dysregulation of circadian genes in MDD compared to controls [15]. The analysis supports the hypothesis that the disruption of the circadian expression of the essential genes running the circadian clock (i.e., core-clock genes) and the genes that they control (clock-controlled genes- CCGs) have an impact on the functional regulation of numerous neuronal processes and behaviors including mood [15].

The circadian clock, in addition to its canonical role in the regulation of circadian rhythms, participates in the control of diverse brain functions, including memory formation, astrocyte-mediated circadian behavior, sleep homeostasis, and energy balance [16–20]. More than 90% of depressed patients report disruptions in sleep including insomnia and early morning awakening. These patients tend to have more severe forms of

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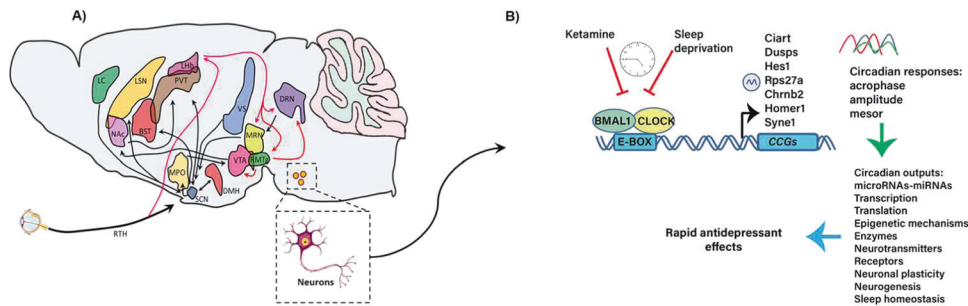


Fig. 1 Organization of the circadian clock. **A** Representative schema depicting efferent and afferent signaling to the suprachiasmatic nucleus (SCN) (black arrows). These include limbic structures including the infralimbic cortex (LC), lateral septal nucleus (LSN), basal forebrain of the stria terminalis (BST), ventral subiculum (VS), paraventricular thalamic nuclei (PVT), nucleus accumbens (NAc), ventral tegmental area (VTA), medial preoptic nucleus (MPO), dorsal raphe nucleus (DRN), median raphe nucleus (MRN) and hypothalamic nuclei [i.e., dorsomedial hypothalamus (DMH), and the retino-hypothalamic tract (RHT)] [28, 30]. The lateral habenula (LHb) efferent and afferent connections are shown (red arrows), ventral lateral geniculate (Vlgn), intergeniculate leaflet (IGL), rostromedial tegmental nucleus (RMTg) [25, 28, 34, 116, 220]. **B** A predictive model in which ketamine and sleep deprivation elicit common transcriptional responses by blocking BMAL1/CLOCK function at specific times of the day (Zeitgebers-ZTs) associated with neuronal and behavioral responses [94, 95, 219]. Changes in the acrophase and/or amplitude of the CCGs participating at different regulatory levels could affect mood. The 7 clock-controlled genes represent potential components of rapid antidepressant actions of ketamine and sleep deprivation.

MDD, are less likely to have full clinical responses to standardized treatments and may be at an increased risk for suicidal ideation and suicidal behaviors (for review, [21]).

Genetic and transcriptomic data provide convincing evidence linking circadian gene polymorphisms with an increased risk for depression [15, 22, 23]. Studies in rodent models of depressive-like behaviors highlight the complex interactions of the circadian system in mediating rapid antidepressant responses [24–26]. In this review, we summarize the rapid-acting mechanisms of action of subanesthetic ketamine and sleep deprivation and their effects on clock function, neuronal plasticity, sleep homeostasis, and neurogenesis.

THE CIRCADIAN CLOCK

Circadian rhythms control virtually all physiological, behavioral, and metabolic processes. In mammals, the suprachiasmatic nucleus (SCN) located in the hypothalamus serves as the central pacemaker, which is synchronized daily by light cycles via input from the retino-hypothalamic tract. The SCN in turn synchronizes peripheral clocks in other brain areas and peripheral organs to orchestrate circadian rhythms, through synaptic connections, autonomic innervations, and endocrine signaling [27]. The SCN can also be influenced by non-photic inputs including behavior, nutritional intake, exercise and social contact [27]. Moreover, on an anatomical level, the SCN is capable of receiving, integrating and sending information to an estimated 85 brain areas, resulting in the regulation of higher brain function [28] (Fig. 1A). Viral transneuronal labeling techniques in rats identified six afferent projections to the SCN including the retina, limbic system, hypothalamus, raphe nuclei, paraventricular thalamus, and extra retinal visual system [29]. Importantly, interactions between the SCN and limbic structures including the infralimbic cortex, lateral septal nucleus, bed nucleus of the stria terminalis, ventral subiculum, paraventricular thalamic nucleus, dorsal raphe nucleus (DRN) median raphe nucleus and lateral habenula (LHb), comprise critical circuitries that impact higher brain function [30]. Additionally, the peri-habenular nucleus, a recently identified region, serves as a link between intrinsically photosensitive retinal ganglion cells (ipRGCs) (expressing the photopigment melanopsin) and an SCN-independent pathway, to regulate affective behavior [31]. LHb neurons show daily firing-activity patterns, suggesting that the LHb likely relays circadian outputs through efferent projections to forebrain and midbrain aminergic nuclei [32–34]. The LHb is not considered an autonomous pacemaker since it depends on SCN innervation and light information to

maintain synchrony [35]. Light/dark environmental signals can trigger changes in circadian rhythmicity related to antidepressant efficacy of light therapy as demonstrated by light-mediated induction of *Per1* in the LHb. In contrast, long-term exposure to dark can transiently desynchronize SCN and habenular rhythms (dark-associated depressive-like symptoms are reversible by antidepressants) [36].

At the molecular level, the circadian clock consists of a network of interlocked transcriptional-translational feedback loops (TTFL). The core proteins within the TTFL are the transcription factors, Circadian Locomotor Output Cycles Kaput (CLOCK), and BMAL1. These transcription activators heterodimerize and rhythmically bind to E-box promoter elements and activate the clock-controlled genes (CCGs) (Fig. 1B). Among the CCGs, PERIOD 1–3 (PER 1–3), and CRYPTOCHROME 1 and 2 (CRY1 and 2) repress the transcriptional activity driven by CLOCK/BMAL1, and inhibit their own expression through a negative autoregulatory feedback loop that cycles in ~24 h [27, 37]. The CCGs encode transcriptional regulators, including the D-box binding protein (DBP), thyrotroph embryonic factor (TEF), retinoic acid-related orphan receptor $\alpha/\beta/\gamma$ (ROR $\alpha/\beta/\gamma$) and REV-ERB α/β (reverse erythroblastosis virus α/β). DBP and TEF bind to D-boxes, while ROR $\alpha/\beta/\gamma$ and REV-ERB α/β bind to REV-ERB/ROR promoter elements, in turn, inducing additional circadian waves in the expression of downstream genes. It is estimated that the circadian machinery controls the cyclic expression of about 10–30% of genes in any given cell [27, 37], although recent estimates indicate that many more genes may exhibit robust oscillations in response to nutritional and metabolic inputs to modulate the organization of circadian physiology [27, 38].

Moreover, neurotransmitters, hormones, metabolites, nutrients, humoral and environmental inputs interconnect cellular signals with the molecular clock [39–41]. For example, synchronous astrocytes have the capability of entraining rhythmicity in neurons via GABA signaling [42]. When rhythms are disrupted, (e.g., varied light/dark cycles, jet lag) interference with central and peripheral clock function can lead to abnormal clock gene rhythms [43] and increase the risk for physical and psychiatric disorders including depression [6, 13, 15, 44, 45].

Sleep deprivation therapy (SDT) and subanesthetic ketamine: clinical data and circadian mechanisms

Sleep deprivation therapy (SDT). SDT has been recognized as an effective treatment for depression [46, 47]. Its rate of efficacy, estimated to be at 40–60% efficacy is comparable to that of monoaminergic drugs but with a much faster onset (within 24 h).

In Europe SDT is often used as a first line treatment but less frequently in the United States [48]. Although high relapse rates (return of depressive symptoms following a night of recovery sleep) are a major limitation, improvement can be sustained for several weeks with the administration of non-pharmacological circadian interventions of bright light therapy, and sleep phase advance [49, 50]. While the mechanism of SDT remains largely unknown, the sleep homeostasis hypothesis proposes that sleep is associated with synaptic downscaling, a weakening of synaptic strength thought to involve metabotropic glutamate receptors, while wakefulness facilitates synaptic potentiation [51, 52]. Moreover, in vivo two-photon imaging show that dendritic spine morphology is constantly changing during both wakefulness and sleep as demonstrated in rat pyramidal cells of the sensorimotor cortex [53]. Therefore, it is conceivable that extended wakefulness contributes to the antidepressant effects of SDT by promoting synaptogenesis.

Sleep is regulated by circadian (diurnal timing of sleep) and homeostasis (sleep pressure) processes. Circadian regulation of sleep is reported to be independent of prior wakefulness, differentiating it from homeostasis, although data in humans and rodents suggest an interaction. Insomnia affecting about 90% of depressed patients, is characterized by difficulty in falling asleep, staying asleep, early morning awakening and/or shortened rapid eye movement (REM) latency—symptoms compatible with a shift in circadian phase. Chronic insomnia is associated with an increased risk for recurrent depressive episodes as well as suicidality while normalization of sleep patterns may be an early predictor of antidepressant response [6, 21].

Clinical research has implicated the response to sleep deprivation associated with variants in serotonin-related pathways, (5HT2A, rs6313, 5HTTLPR) [54, 55], the serine-threonine kinase GSK3 β [56] and the core-clock gene *Per3* [57]. A genome-wide study of SDT in MDD and BP patients [58] showed post-SDT alterations in circadian genes (*Bmal1*, *Per2*, *Per3*, and *Nr1d1*) [58]. Of potential relevance is that we found that this subset of genes were abnormally expressed in MDDs across six brain areas compared to controls [15].

Studies in rodents suggest that astrocytes a subtype of glial cell are an important contributor to antidepressant actions of sleep deprivation specifically involving the adenosine receptor, A1 (A1R) [59, 60]. Importantly, astrocytes are key contributors to sleep homeostasis. When sleep need is high, astrocytes release chemical transmitters such as adenosine, that presynaptically inhibit excitatory transmission and induce slow-wave activity in rodent brain [61–63]. Furthermore, in the SCN, astrocytes contribute to pacemaker properties by relaying glutamatergic and ATP signals to neurons at night [64]. For example, astrocytic expression of clock genes modulate broad network fluctuations in glutamate in the sleep/wake network [65].

Ketamine. Subanesthetic ketamine administered intravenously dramatically decreases symptoms within 2–4 h with an efficacy of 70–80% [66–69]. Maintaining improvement longer than 1 week post-infusion has motivated strategies for sustaining responses including administering repeated doses [70] and adding adjunctive treatments [71]. Subanesthetic ketamine is also shown to decrease suicidal ideation as reported in double-blind studies in depressed patients [72, 73]. The moderate hour-long psychotomimetic side effects of ketamine are transient and may include hallucinations, dreamlike states, confusion, gaps in memory and out of body experiences. Ketamine has two enantiomers, (S) and (R); intranasal esketamine (S-ketamine) has been recently approved by the FDA [74].

Ketamine is a noncompetitive high-affinity N-methyl-D-aspartate receptor (NMDAR) antagonist, selectively blocks GluN2B-containing NMDAR on inhibitory GABAergic interneurons. This allows the disinhibition of glutamatergic transmission, which

in turn activates postsynaptic AMPA receptors and intracellular signaling pathways inducing plasticity [68, 75–79]. When the AMPA antagonist NBQX (2,3-dioxo-6-nitro-7-sulfamoyl-benzo[f]quinoxaline) is administered prior to ketamine injection (i.p.), the ability of ketamine to decrease depressive-like behavior in rodents is blocked [68, 80]. It is also postulated that ketamine could block the GluN2B component of the NMDA, thereby reducing the activation of the elongation factor-2 kinase (eEF2K) to prevent the phosphorylation of eEF2, thus inducing the translation of BDNF [76]. The BDNF–TRKB pathway activates the mammalian target of rapamycin complex 1 (mTOR1) [81–83]. mTOR, a signal integrator and neuronal response regulator, modulates the production of proteins required for the formation of spines and synapses [81]. This process underscores another intriguing interplay: mTOR signaling is controlled by the circadian clock, leading to the cyclic regulation of protein synthesis [84, 85]. In the SCN, mTOR participates in the light-induced translation of the core-clock and CCGs including *PER1-2* and *VIP* (vasoactive intestinal peptide). This is achieved by phosphorylating and inhibiting the translation repressor eIF4E binding protein (4E-BP), releasing the translation initiation factor 4E (eIF4E), and by activating translational effectors such as ribosomal proteins including S6 kinases [86]. Strikingly, the core-clock protein *BMAL1* acts as a translation factor by interacting with the translational machinery and promoting protein synthesis, and this mechanism is modulated by mTOR via phosphorylation of *BMAL1* at Ser42 [87].

The BDNF–TRKB pathway is induced by both classic monoaminergic antidepressants and fast-acting ketamine, by directly binding to TrkB [88], implying that classic, and glutamatergic antidepressants may share some common mechanisms. For instance, the *TrkB* gene is expressed in a circadian manner, which could be controlled directly by *BMAL1/CLOCK*, as suggested by the presence of E-box sites within its promoter [89]. Moreover, the melatonin precursor N-acetylserotonin (NAS) activates the *TrkB* pathway resulting in antidepressant-like effects in rodents [90]. Furthermore, daily *TrkB* activity follows a circadian pattern [90], suggesting that the circadian clock further modulates the *TrkB* pathway via neuronal plasticity.

Chronotherapeutics have gained traction as a strategy to increase antidepressant efficacy when treatment is administered in synchronicity with specific phases of the circadian clock. It is hypothesized that a novel mechanism of action of ketamine is to restore depression-related glial defects by modulating the density and distribution of cholesterol in the plasmalemma of astrocytes via interactions with cholesterol, BDNF and TrkB [88, 91, 92]. BDNF increases cholesterol signaling in neurons while cholesterol regulates *TrkB* signaling. Although biomarkers of cholesterol (i.e., lathosterol, mevalonate, squalene) have nocturnal peaks in expression, the absorption rates of cholesterol do not vary [93]. Nevertheless, further research can help determine whether the timing of ketamine administration as a function of peak cholesterol levels could increase antidepressant efficacy.

We demonstrated that ketamine represses circadian expression of clock genes *Bmal1*, *Per2*, *Cry1*, and *Dbp* in mouse fibroblast cell culture by decreasing binding of *CLOCK/BMAL1* to its target promoters. The binding capacity of *CLOCK/BMAL1* to its target promoter *DBP* was inhibited at circadian time 24 (CT24) 1 h posttreatment, paralleling its transcriptional inhibition. We estimated that the inhibitory effect lasted only a few hours as no effects were observed at other CTs [94].

Rodent and human data appear to be comparable in terms of timing of ketamine antidepressant actions. In rodents, ketamine was shown to reduce depressive-like behavior starting 30 min postinjection (paralleling changes in BDNF and mTOR levels in the hippocampus) with antidepressant effects lasting for several days [81, 83]. For MDD patients, the onset of improvement ranged between 40 and 120 min and was sustained from 2 h to 7 days [69].

Overlapping effects of ketamine and sleep deprivation

We hypothesized that SD and KT may share common mechanisms of action that converge on circadian-related processes to accelerate antidepressant responses. We analyzed the anterior cingulate (ACC) in mice treated with either 12 h sleep-deprived or 8 h post ketamine injection at a single time point (ZT13) and compared the results to a control group to determine which genes, if any, were shared between the two treatments in the ACC [95]. In support of a circadian role, we identified an overlapping downregulation of circadian genes including *Ciart*, *Per2*, *Npas4*, *Dbp*, and *Rorb* in both ketamine and sleep deprivation-treated mice [95]. Though the underlying mechanisms involved in the effects of ketamine and SDT as *zeitgebers* are unknown, data implicates the BDNF–TrkB pathway since both treatments act on this pathway across several brain areas [76, 88, 96–98]. Moreover, infusion of BDNF in the SCN induces phase advances in the circadian activity of rodents [99]. The BDNF–TrkB pathway also relays light inputs to the central clock [100]; specifically, the transcriptional repressor methyl-CPG binding protein 2 (MECP2 a BDNF regulator) is phosphorylated in response to light within the SCN via a CaMKII-dependent mechanism, allowing the expression of BDNF [101]. Lei et al. reported that the GluN2B antagonist MK-0657 (a component of the NMDA receptor), induces antidepressant effect by reducing BDNF expression and neuronal activity in the LHB [102]. Although not yet well understood, it is postulated that the actions of BDNF on mood or clock regulation is dependent on brain area and/or neuronal subtype [102].

Rapid antidepressant responses in treatment-resistant depressed patients suggest a mechanism that is linked to fast changes in synaptic function and plasticity as demonstrated with the restoration of spine density within hours of treatment with SDT or ketamine [79, 81, 103–105]. It is hypothesized that the induction of synaptogenesis reverses the loss of depression-associated synaptic connectivity and restores cognitive and emotional function. In contrast to ketamine and SDT, slower-acting antidepressants first target monoamines to promote synaptogenesis [79]. Ketamine has unique properties in its rapid acceleration of synaptic plasticity but may also have actions that overlap with molecular mechanisms that regulate homosynaptic scaling [106] while acute sleep deprivation induces rapid formation of hippocampal dendritic spines [104, 105].

Not surprisingly, ketamine also enhances the monoamine system, including serotonergic and dopaminergic neurotransmission [88, 107] while sleep deprivation primarily induces dopamine neurotransmission [108, 109]. Thus, both treatments alter the expression of genes related to the dopaminergic synapse, including the G-Protein Subunit Gamma 10 (*Gng10*, which is part of the heterotrimeric G proteins, involved in intracellular signaling) and the dopamine receptor 5 (D5R), among others [95]. Metabotropic glutamate (mGlu) are receptors coupled to G proteins and are important for glutamate binding, acting as glutamatergic agonists. Among the eight mGlu receptor subtypes, data supports the mGlu2/3 receptor as a potential therapeutic target for depression [110] although mGlu5 is thought to be essential for the rapid antidepressant actions of both sleep deprivation and ketamine [111]. LY341495, an antagonist of presynaptic mGlu2/3 activates VTA neuron firing via the mTOR pathway to increase dopaminergic tone [112]. LY341495 acts as a rapid-acting antidepressant in animal models of depression and is synergistic with ketamine [109, 113–115].

The LHB receives GABAergic inputs from the vLGN/IGL that are stimulated by light inputs from M4 type mRGCs, inducing antidepressant-like effects in mice [116]. As mentioned above, the LHB is involved in the circadian machinery and may play a role in antidepressant responses [33, 117–119]. This structure controls dopaminergic and serotonergic systems, integrating several brain functions, including motivation, reward and aversion, cognitive and circadian functions [34]. Interestingly, susceptible mice to

stress-induced depression exhibit blunted diurnal firing within cells projecting from the LHB to the DRN [120]. Moreover, enhanced bursting in the LHB has been linked to suppression of downstream aminergic reward centers. In a rodent model of depression, ketamine inhibits the burst-type firing in the LHB, consequently disinhibiting dopaminergic, serotonergic, and/or glutamatergic neurons of the reward system [119].

The mitogen-activated protein kinase (MAPK/ERK) pathway modulates synaptic plasticity and brain processes such as mood, learning and memory [121, 122]. Inhibition of the MAPK/ERK pathway blocks the antidepressant effects of several compounds including ketamine in mice [123]. In the mouse ACC, rapid-acting antidepressants ketamine and sleep deprivation down-regulate genes of the MAPK phosphatase family (MKPs, also known as DUSPs), which operate as the main negative regulators of MAPK signaling [124, 125]. DUSP1 undergoes fast turnover and functions in the spatiotemporal regulation of axonal organization [126]. Specifically, ketamine decreases *Dusp1*, *Dusp5*, *Dusp6*, and *Dusp8* gene expression, while SD represses *Dusp2* and *Dusp27* [95]. Accordingly, whole-genome expression profiling of postmortem brain tissue, demonstrates that DUSP1 is overexpressed in subjects with MDD while preclinical studies show that stress-induced depression in mice up-regulates *Dusp1* in the ACC [124, 127, 128]. Circadian transcriptome analysis has shown that these genes, with the exception of *Dusp8*, are expressed in a circadian manner across tissues [95]. Importantly, DUSP1 and PER1 promoters, share the cAMP-responsive element (CRE) and the E-box element, showing similar circadian expression profiles [129]. Of relevance is that binding of BMAL1, CLOCK, and NPAS2 to their target genes is also repressed during sleep deprivation in mice [130].

The circadian system plays a contributory role in mediating synaptic plasticity via GSK3 β , a kinase that operates as a potent inhibitor of mTOR. GSK3 β regulates multiple components of the circadian clock, including BMAL1 phosphorylation [131, 132] as well as modulating clock protein rhythms in the SCN [131, 133]. Inhibition of GSK3 β potentiates antidepressant responses to ketamine [134] in mice. GSK3 β also regulates the circadian expression of BMAL1 in hippocampal CA1, contributing to the modulation of diurnal changes in synaptic strength or long-term potentiation (LTP) and synaptic plasticity [132]. Clinically, a specific polymorphism of GSK3 β (rs334558C+) has been associated with severe insomnia in patients with major depressive episode [135]. Taken together, these observations support the notion that ketamine and sleep deprivation, at least in part, commonly act via neurotransmitter systems and interestingly through the circadian clock.

Circadian clock and neurogenesis

Mechanisms of action of sustained antidepressant responses lasting one or more weeks, are thought to be attributed to processes associated with neurogenesis rather than synaptogenesis [136, 137]. Since the half-life ($t_{1/2}$) of ketamine is about 3–4 h [69] and the integration of newly functional neurons takes several days, it is conceivable that ketamine stimulates neurogenesis which in turn could play a role in sustained antidepressant effects [138–141]. On the other hand, given that relapse often occurs on the night following SDT, the role of neurogenesis seems less clear although bright light is capable of promoting neurogenesis [142], which could, in part, explain the long-lasting effect of the combined therapies. For example, rats exposed to bright light (10,000lux, 30 min/day for 4 weeks) showed an increase in neurogenesis in the subgranular zone of the hippocampal dentate gyrus [142]. Conversely light deprivation in the Mongolian gerbil suppresses neurogenesis and induces depressive-like behavior [143].

Since its discovery in the 1960s, the presence of adult neurogenesis is still a matter of debate. However, growing evidence and the development of new technologies are allowing new insights of this process [144]. An in vivo imaging study confirmed that neural stem cells (NSCs) in adult mice can

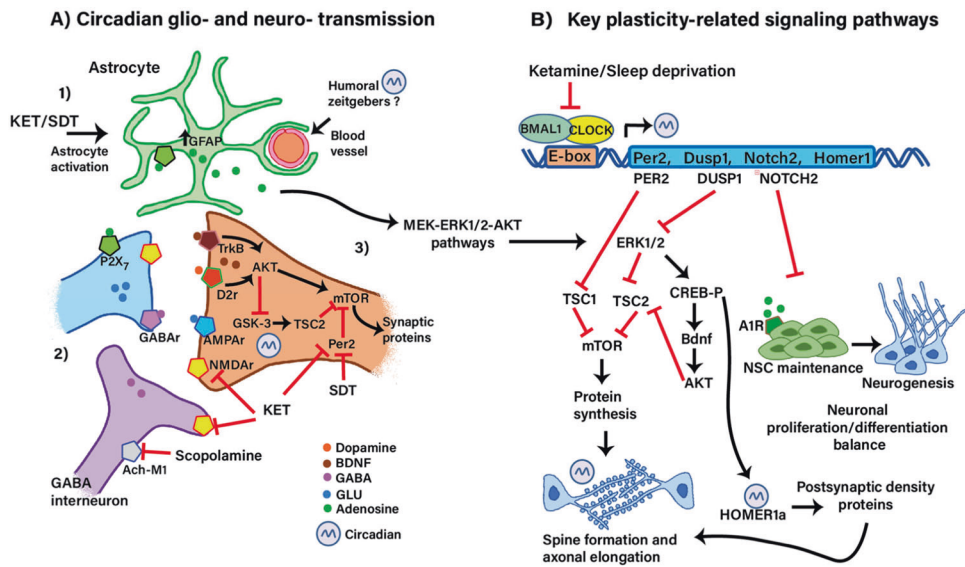


Fig. 2 Implication of the circadian clock in the regulation of neural signaling and behavior. **A** Proposed mechanisms of action of ketamine and sleep deprivation on the glutamatergic synapse. (1) ketamine and sleep deprivation activate astrocytes, which induces the exocytosis of adenosine, stimulating the $P2 \times 7$ (ATP-gated $P2X$ receptor cation channel family) receptor and releasing glutamate (GLU) into the intraneuronal space. Adenosine also binds A1R in NSCs inducing its proliferation via MEK/ERK-AKT pathways [59, 166–168]. Astrocytes might further receive humoral signals acting as zeitgebers from blood vessels thereby contributing to circadian neuronal activity [170, 221]. (2) Ketamine blocks NMDA receptors at the inhibitory GABAergic interneuron, leading to disinhibition of glutamatergic transmission [75]. (3) In turn, glutamate triggers the release of BDNF at postsynaptic neurons leading to stimulation of the TrkB-AKT-mTOR and subsequent synaptic protein synthesis [67, 78, 79]. Inhibition of GSK3 β (which is controlled by the circadian clock) contributes to the activation of mTOR [132, 222–225]. Dopamine also contributes to plasticity via the AKT-GSK3 pathway [226]. **B** Neuronal plasticity might be further enhanced by the inhibition (or phase-shift) of the BMAL1-CLOCK recruitment to Per2 Dusp1, Notch2, or Homer1 promoters [95]. Per2 functions as a scaffold to recruit TSC1, Raptor, and mTOR suppressing mTOR activity [227]. Dusp1 negatively regulates the MAPK pathway by dephosphorylation of ERK1/2 [127]. The transcriptional reduction of Dusp1 might disinhibit ERK1/2 which in turn blocks the TSC2 complex resulting in the induction of mTOR-mediated protein synthesis. Also, ERK1/2 activates the CREB-mediated transcription of *bdnf*, which indirectly induces protein synthesis by blocking the TSC2 complex via AKT. The transcriptional reduction of Notch1 promotes the neurogenesis involved in neural stem cell (NSC) maintenance [159]. Homer1 transcription is further modulated by CREB and participates in the synaptic plasticity-induced by sleep deprivation and ketamine [60, 228]. These mechanisms would be operating in different brain areas related to mood reward, and cognitive demanding tasks such as memory, attention, and decision-making such as the mPFC, hippocampus, striatum, ACC, and other brain regions.

differentiate into neurons and/or transit-amplifying progenitors, which in fact are capable of self-renewing and differentiating into neurons [145].

Several brain alterations have been related to neurogenesis. Reduced hippocampal neurogenesis is associated with psychiatric disease including schizophrenia and depression [140, 146–148]. Moreover, monoaminergic or glutamatergic antidepressants show significant effects on neurogenesis [140, 149].

The role of the circadian clock in the homeostasis of stem cells and in the regulation of cellular development including differentiation across tissue subtypes is supported by a number of studies [150–153]. Decreased BMAL1 in mice shows deficits in cognition [151, 154]. Reduced *Cry2* expression in the DG of adult mice is also associated with behavioral disorders of anxiety and depressive-like behavior [154]. The circadian clock has been implicated in controlling the expression of key regulators of neurodevelopment to help synchronize the differentiation of heterogeneous populations of cells. The signaling molecules within the NOTCH pathway, an important component of the neurodevelopmental signaling process [155], are under circadian clock control [156–158]. Interestingly both ketamine and SD alter the expression levels of transcripts of genes in the NOTCH pathway (Fig. 2B), particularly in the ACC of sleep deprivation- and ketamine-treated mice where Notch2 expression is reduced [95]. Importantly, as NOTCH2 preserves a state of latency on NSCs, its loss of function induces proliferation and increases neurogenesis in the hippocampus [159], as well as neuronal differentiation in NSC progenitors [160]. Moreover, the Notch2 gene is expressed in a circadian manner and contains an E-box within its promoter

[157]. Therefore, ketamine and SD would modulate neurogenesis by regulating the circadian expression of NOTCH pathway components. Accordingly, one night of SD in healthy human male subjects leads to epigenetic modifications in components of the NOTCH pathway, as observed in blood samples of the subjects [161].

Another circuitry of interest as mentioned above is the TrkB-dependent induction of the ERK pathway. It is hypothesized that ketamine could induce antidepressant effects through its enhancement of hippocampal neurogenesis acting via the ERK pathway and its components [138]. Supporting this hypothesis, ketamine increases neurogenesis in the dentate gyrus and in ventral hippocampus in both acute and chronically stressed mice, which can lead to depressive-like behavior. This was accompanied by an induction of GluN2B subunit of NMDAR, GluA1 subunit of AMPAR, as well as phosphorylation of mTOR [162, 163]. Likewise, sleep deprivation (12 h sleep deprivation in rodents) was shown to increase neurogenesis in the hippocampus [164, 165] and increase the levels of BDNF [96].

Further, the activation of the adenosine receptors A1R and A2B expressed in NSC, induce stem cell proliferation acting on MEK/ERK-AKT pathways [166]. Astrocytes participate in the antidepressant effects of both ketamine and SD in mice [59, 167, 168]. Ketamine, in a chronic unpredictable stress model in rats, acts on astrocytes by modulating glutamate transporter 1 (GLT1) expression, consequently increasing astrocyte plasticity via the BDNF-TrkB pathways and concomitantly decreasing apoptosis of astrocytes [169]. Importantly, evidence suggests that astrocytes, as a part of the neurovascular system [170], are capable of

computing peripheral signals and consequently receiving information from internal and external *zeitgebers* through their internal clocks, which then allows them to respond by modulating neuronal functions (Fig. 2A). Future studies may provide further details on the contributions of the astrocytic molecular clock on brain circadian synchronization/deregulation related to MDD.

Additional issues relevant to mood disorders, pathophysiology, and treatment

Circadian versus non-circadian factors underlying rapid antidepressant effects. Although this review focuses primarily on the circadian interactions involving ketamine and SDT, non-circadian factors are also considered important contributors to the acceleration of antidepressant actions. For example, subanesthetic ketamine alters the distribution of cholesterol within astrocytes resulting in the modulation of downstream glutamatergic processes thought to be important to ketamine's antidepressant effects (e.g., NMDA, AMPA, and mTOR [171]). Likewise, Reelin signaling has attracted attention as a putative mechanism of action of ketamine. In mice, genetic deletion of Reelin, a glycoprotein, was shown to block both ketamine-mediated depressive-like behavior and synaptic potentiation via modulation of the basal activity of the NMDA receptor [172]. Finally, micro-RNAs (mi-RNAs) in postmortem brains of MDDs and BP patients are reported to be down-regulated [173]. The importance of mi-RNAs is that they can exert a broad range of effects by binding to hundreds of target genes including those regulating synaptogenesis and neurotransmitters. Evidence that ketamine may exert its antidepressant actions via mi-RNAs comes from a study in a mouse model of depressive-like behavior whereby ketamine reversed the down-regulation of miR-98-5p in the hippocampus and prefrontal cortex, while an antagonist of miR-98-5 blocked ketamine's antidepressant effects [174].

Conventional antidepressants share mechanisms of action with ketamine and sleep deprivation but have a delayed response. Traditional antidepressants and anti-manic compounds (e.g., lithium, valproic acid) share overlapping mechanisms with ketamine and sleep deprivation by promoting neurogenesis and synaptic plasticity [11, 175–178]. In animal models of depression, antidepressant effects of ketamine and SDT can take place in a matter of minutes to hours [104, 105, 179]. It is not yet known whether other classes of antidepressants promote neurogenesis within a similar time-frame. Further, it might be predicted that melatonin agonists would have antidepressant properties as they phase-shift circadian rhythms and elicit depressive-like effects in mice. However, clinical data do not support melatonin as effective [180, 181] although the reason(s) for the lack of clinical response is not known.

Circadian interventions can decrease switches into hypomania/mania in BP following SDT. A relatively small percentage of bipolar patients are at risk for switches into hypomania (5.83%) and mania (4.85%) following SDT, comparable to the rate of switches associated with other classes of antidepressants [182]. Two strategies for decreasing switches is to administer bright light therapy following SDT in mid-day rather than early morning [183] and second, to block blue light [184]. It is suggested that mid-day bright light has a weaker effect on phase advancing melatonin rhythms than morning bright light [185, 186]. Blocking blue light (wavelength 400–500 nm associated with daylight, dampens ipRGCs signals [187]. Indeed, randomized placebo-controlled trials showed that blue-blocking sunglasses significantly decreased the incidence of switches [184, 188].

Relationship between circadian phase-specific phenotype and efficacy of rapid-acting antidepressants. To date, there is no consistent answer as to whether "circadian phase-specific" phenotypes show greater efficacy to fast-acting antidepressants

[21]. Although ketamine phase advances activity rhythms in ketamine responders, it is premature to infer that responders are phase-delayed [189]. There is much to be learned by measuring circadian parameters (e.g., rhythmic changes in metabolites, gene expression, activity, sleep, core body temperature, mood) as well as from questionnaires (e.g., Morningness-Eveningness (MEQ), Munich Chronotype (MCTQ)) to help clarify whether altered chronotypes are an essential factor in the therapeutic response to rapid-acting antidepressants. Predictive models incorporating circadian factors, as seen with ketamine, for example, could provide important insights [190]. Advances in machine learning offer unique opportunities to identify key variables relevant to treatment outcomes [191–193].

Altered circadian rhythms in responders vs. non-responders to ketamine and SDT. To date, identification of biological signatures and circadian patterns associated with response to rapid antidepressants is not yet known. To our knowledge there are no studies that address the efficacy of ketamine nor SDT as a function of circadian phenotypes (i.e., delayed or advanced rhythms, shorter or longer periods). Treatment-resistant depression (failure to respond to two or more traditional antidepressants) may define a particular circadian phenotype. The same may also be true for sleep deprivation responders although more research is needed. Moreover, there is little data differentiating circadian phenotypes of MDD and bipolar patients in terms of response to ketamine or SDT. More research is needed to further identify the circadian variables affecting biological rhythms.

Genome-wide association studies (GWAS). GWAS studies have identified variations in circadian rhythm phenotypes associated with either bipolar or MDD [194, 195]. In BP, none of the canonical clock genes were overrepresented [196]. In contrast, a GWAS study of rapid-cycling BP patients (European Americans and African Americans) showed SNP-based heritability and identified the SNP rs683813 (mapped close to BMAL2 (a paralog of BMAL1)) [197]. Data in MDD showed an association at the genome-wide levels for CRY1 (rs2287161), NPAS2 (rs11123857) with the strongest association in a SNP located near the CRY1 gene [198]. Additional molecular evidence from GWAS studies for circadian abnormalities is supported by genetic and transcriptomic data showing an association between circadian gene polymorphisms and MDD. These include CRY2 (rs10838524), VIPR2 (rs885861), TEF (rs738499), and SIRT1 (rs10997875) [22, 23, 198, 199]. Moreover, carriers of the CRY1 (rs2287161), NPAS2 (rs11123857), and VIPR2 (rs885861) SNPs are three times more likely to suffer from MDD [198].

Mechanistic links between the circadian clock and MDD: key strategies. Homeostasis requires an integration of circadian signaling across cells, tissues and organs achieved through direct and indirect transcriptional processes. Though the core-clock genes are ubiquitously rhythmic, transcripts are tissue-specific to biological processes [200]. In cortex, synaptic structure and function is driven by two waves of daily oscillations in synchrony with the sleep–wake cycle. Transcriptomic analyses of mouse forebrain synaptoneuroosomes showed that transcripts and proteins accumulate in anticipation of the rodent active phase (dark) whereas mRNAs associated with metabolism, intracellular signaling and translation precede the resting phase (light). When sleep pressure is high as with sleep deprivation a major portion of the circadian proteome is eradicated [201]. In parallel, loss of sleep, dynamically induces a dampening of synaptic strength in forebrain via phosphorylation [202]. Taken together, these studies provide further support for a role of cortical synaptic remodeling as a mode of action for the antidepressant effects of sleep deprivation. As reviewed above, ketamine can induce rapid changes in synaptic remodeling, possibly through glutamatergic

interactions [81, 103, 106, 111]. A strategy would be to stabilize the modifications in synaptic remodeling with additional treatments to prolong the antidepressant responses associated with rapid-acting antidepressants. To our knowledge there are no studies that have applied bright light therapy and sleep phase advance to ketamine responders. Additionally, it is not known whether administration of subanesthetic ketamine would help stabilize responses to SDT. If these two interventions converge on similar synaptogenic signaling pathways, the combined effect might help sustain improvement beyond weeks to months.

Rhythmic signals from single cells to synchronization of tissue involve the coupling of period and phase between individual oscillators. The coupling of cellular oscillators (“tissue clock”) with tissue oscillators comprise an organismal clock [39, 203] that is essential to maintaining physiological homeostasis. This also encompasses entrainment to intrinsic and extrinsic signaling (e.g., neurotransmitters, metabolites, nutrients, humoral, and environmental factors [39–41]). This can be achieved by multiple molecular regulatory systems including circadian control on mi-RNAs [204], epigenetic chromatin remodeling [205], transcriptional [206], post-transcriptional [200], translational, and posttranslational modifications that impinge at cellular, tissue, and system levels. Especially advantageous are the “omic” technologies (e.g., transcriptomics, proteomics, metabolomics) [207], which are currently being applied to circadian research [200, 208–210]. Studies of the circadian proteome have helped to characterize rhythmic signaling pathways [211]. Thus, analyzing the circadian variations (acrophase, amplitude and mesor) and their effects on various biological processes, could help identify processes linking the circadian clock to rapid-acting antidepressants. Additionally, they could provide insight to understand how rapid-acting antidepressants can modulate those rhythmic processes involved to mood regulation at molecular, cellular, physiological and behavioral levels (Fig. 1B). The integration of several lines of research could help identify a biological signature to evaluate homeostasis and to assist clinicians in determining optimal treatments.

Gender-relevant circadian phenotypes. An estimated 20–30% of MDD patients are hypothesized to have a “circadian rhythm depression” disorder. Gender differences in this subgroup show that females have shorter intrinsic circadian periods and higher plasma melatonin and cortisol levels [212]. Gender differences were also identified in postmortem nonpsychiatric brain tissue showing that males had almost twice as many significant rhythmic transcripts in the DLPFC while females had nearly four times as many rhythmic transcripts in the anterior cingulate (ACC) [213]. The significance of these findings is not yet known although gender-specific machine learning models are being applied to predict responses to SSRI classes of antidepressants [214].

CONCLUDING REMARKS

Despite the widespread use of traditional antidepressants, suicide rates in the US have significantly increased from 30,000 to 46,000 deaths per year from 1999 to 2017 [215] and increased to 48,344 in 2020 [216], reflecting the limitations of monoaminergic-based treatments. Epidemiological, clinical and experimental evidence over the past 50 years has clearly established a causal link between circadian disruptions including sleep disturbances, hormonal secretions, core body temperature and mood in a subset of MDD and BPD patients [6, 8–13]. This coincides with modern lifestyle “social zeitgebers” which are frequently associated with sleep disorders, increased stress, and circadian disruptions [27, 217]. Considering that maladaptation to the environment may increase the risk for psychiatric disorders [218], it is conceivable that these disorders could be associated with circadian desynchronization affecting high brain function and mood [25]. The antidepressant actions of non-pharmacological chronotherapies

such as bright light therapy, sleep phase advance, and SDT support a circadian hypothesis as do emerging findings on the modulation of the circadian clock and its pathways by the pharmacological actions of ketamine (Fig. 2) [94, 95, 219]. It is not yet known whether depressed patients with dysregulated circadian rhythms are more likely to respond to fast-acting antidepressants such as ketamine or to SDT.

A limitation to the circadian hypothesis is that there are no definitive genes and/or pathways that are known to be directly correlated with a rapid response to sleep deprivation or to ketamine. Rather, most of the data is inferred, based upon a relatively large number of studies in rodent models of depressive-like behavior that are predominantly focused on ketamine and less so, on sleep deprivation. The animal data and clinical observations should motivate researchers to continue to obtain information relevant to this investigative area. Finally, this is an exciting time for the scientific community to understand in greater depth the pathophysiological basis of depressive illness and to consequently, improve prophylactic and therapeutic treatments.

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AUTHOR CONTRIBUTIONS

BB, WB, EB, PSC and ROS conceptualized and wrote the paper. SS and LMV contributed with critical suggestions. All authors edited the paper.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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