REVIEW

Regulation of Circadian Genes by the MAPK Pathway: Implications for Rapid Antidepressant Action

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Abstract Accumulating evidence suggests that the circadian rhythm plays a critical role in mood regulation, and circadian disturbances are often found in patients with major depressive disorder (MDD). The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway is involved in mediating entrainment of the circadian system. Furthermore, the MAPK/ERK signaling pathway has been shown to be involved in the pathogenesis of MDD and the rapid onset of action of antidepressant therapies, both pharmaceutical and non-pharmaceutical. This review provides an overview of the

involvement of the MAPK/ERK pathway in modulating the circadian system in the rapid action of antidepressant therapies. This pathway holds much promise for the development of novel, rapid-onset-of-action therapeutics for MDD.

Keywords Major depressive disorder · MAPK pathway · Circadian system · Rapid antidepressant therapy

Introduction

Rapid-onset antidepressant therapies have been shown to be related to the circadian rhythm, but the specific molecular pathways have not been clarified [1–3]. The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway is involved in major depressive disorder (MDD), but such an involvement has not been interpreted from the perspective of the circadian system [4]. The regulation of circadian genes by the MAPK/ERK pathway has been demonstrated elsewhere but not linked specifically to depression [5, 6]. In this review, we propose that rapid-onset pharmaceutical and non-pharmaceutical antidepressant therapies may modulate the circadian rhythm through the MAPK pathway.

Circadian Rhythm and Its Effect on Mood

The circadian rhythm in mammals is controlled by the suprachiasmatic nucleus (SCN), which is often referred to as the central circadian clock. It synchronizes the peripheral clock in various cells throughout the body. The molecular machinery of the circadian clock consists of

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Fig. 1 Circadian feedback loops in mammalian cells. The loops contain the classical core feedback loop (including BMAL1/CLOCK and PER/CRY proteins), an REV-ERB/ROR loop, and a *Dec* loop, which interlocks with the classical core loop. CLOCK and BMAL1 form heterodimers that activate the transcription of *Cry* and *Per* genes. PER dimerizes with CRY to inhibit CLOCK–BMAL1-mediated transcription. Rora activates the expression of BMAL1, and Rev-erb α inhibits it, forming a feedback loop. The CLOCK and

BMAL1 complexes activate transcription of the *Dec1* and *Dec2* genes, whereas the PER and CRY complexes inhibit them. In addition, DECs self-regulate to inhibit the transcription of their own genes. This forms another loop. These loops are interlocked. CK1 ϵ/δ , casein kinase 1 ϵ/δ ; CRY, cryptochrome; DEC, differentiated embryo chondrocyte; E-box, enhancer-box; PER, period; ROR, retinoic acid-related orphan receptor; P, phosphorylation.

interlocked molecular feedback loops [2, 7–9]. The core circadian loop consists of positive and negative branches. The positive branch consists of circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1) proteins, which heterodimerize and bind to the Enhancer Box of the period and cryptochrome genes to activate their transcription. The period (PER) and cryptochrome (CRY) proteins then heterodimerize in the cytoplasm and are phosphorylated by glycogen synthase kinase-3 and casein kinase I ϵ . Afterward, they shuttle back into the nucleus to inhibit the transcription of *Clock* and *Bmal1* genes. Lastly, the PER and CRY proteins are degraded in the cytoplasm and release the inhibition of transcription. This process lasts about 24 h.

In addition to the core circadian feedback loop, interlocking feedback loops have also been explored with regard to their modulation of the circadian rhythm. The other feedback loop contains Rora and Rev-erb α , which regulate BMAL1 expression [10–13]. Rora activates the expression of BMAL1, and Rev-erb α inhibits it, which reinforces the oscillations. Another loop consists of *Dec1* and *Dec2*, which negatively regulate circadian rhythms [14]. The CLOCK and BMAL1 complexes activate the transcription of the *Dec1* and *Dec2* genes, whereas the PER and CRY complexes inhibit them. In addition, differentiated embryo chondrocytes self-regulate to inhibit the transcription of their own genes. They also inhibit

transcription of the *Per* and *Cry* genes [15]. These form multiple interlocked molecular feedback loops that provide stability and fine regulation of the circadian machinery (Fig. 1).

Previous studies have shown that daily rhythms are prominent in every aspect of bodily function, such as sleep/wake periods, core body temperature, blood pressure, hormone secretion, cognition, and mood [16, 17]. Disturbances of the circadian rhythm may be related to mental disorders. For example, since the 1950s, circadian disturbances have been reported in patients with mood disorders [18]. Circadian clinical manifestations in MDD patients include social activity rhythm disorder, sleep/wake cycle disorder, blood pressure rhythm disorder, and hormone secretion rhythm disorder [19]. In the late 1980s, the Social Zeitgeber Theory of mood disorders proposed that stress leads to alterations of the circadian rhythms in susceptible individuals, resulting in depressive or manic episodes [20]. Research on patients with first-episode MDD has shown disturbances in circadian rhythms of the expression of PERIOD1, PERIOD2, CRY1, BMAL1, NPAS2, and GSK-3 β , as well as abnormalities in the circadian rhythms of the secretion of melatonin, vasoactive intestinal peptide, cortisol, adrenocorticotrophic hormone, insulin growth factor-1, and growth hormone [21]. And these abnormalities are correlated with the severity of depressive symptoms. Some studies have also reported that mood symptoms are

alleviated along with the resumption of circadian rhythms with treatment [18, 19]. All therapeutic strategies that are employed for mood disorders alter or steady circadian rhythms [3]. Nevertheless, the mechanisms that underlie circadian rhythm disturbances that might induce mood alterations have not been clarified. Logan *et al.* found that chronic unpredictable mild stress (CUMS), a widely used animal model of depression, significantly reduces the rhythmic amplitude of activity and body temperature in mice [22]. These alterations of biological rhythms are directly correlated with depressive-like behaviors. Expression of the amplitude of the clock gene *per2* rhythm is decreased in the SCN and increased in the nucleus accumbens (NAc) of CUMS mice. Molecular circadian changes in the SCN and NAc are directly correlated with mood-related behaviors [22]. CUMS also causes disturbances in the circadian rhythms of plasma corticosterone, melatonin, and vasoactive intestinal peptide in rats [23]. The functions of daily rhythms of the hypothalamus-pituitary-thyroid (HPT) axis are also reduced in rats exposed to CUMS [24]. In addition, CUMS induces alterations of the *rPER2* rhythm in the rat SCN [25]. The hippocampal *CLOCK* protein has been shown to play an important part in the continuance of the depressive-like behaviors induced by CUMS [26].

Clock gene variants have often been associated with diurnal preference [19] and have been explored with regard to the mechanisms of mood disorders [27]. Preclinical and clinical reports suggest that mutations of both *Clock* [28, 29] and *Per* [30, 31] are associated with mood disorders. Previous research on circadian regulation has impressively exhibited its predictive value for the initiation of depression. Spulber *et al.* [32] studied the long-term behavioral changes induced by prenatal exposure to excessive glucocorticoids. They found that progressive changes in circadian entrainment precede depression. Circadian oscillations in *clock* gene mRNA expression are also diminished in skin fibroblasts before the initiation of depression. These results indicate that changes in the circadian entrainment of spontaneous activity and possibly *clock* gene expression in fibroblasts signal the development of depression. Other researchers have suggested that circadian disturbances might be the origin of mood disorders rather than their consequence [2].

Circadian rhythm disorders might be a part of the pathogenesis of mood disorders. However, detailed mechanisms, such as the cellular signaling pathways, have not been sufficiently clarified.

Regulation of the Circadian System by the MAPK Pathway

Light is known to be the strongest stimulus (zeitgeber) for entrainment of the circadian pacemaker [33, 34]. The retinohypothalamic tract (RHT) is located between the retina and the SCN in mammals. Even very dim light has been shown to entrain the circadian pacemaker [35–37]. However, non-photic stimuli have also been shown to exert weak but independent effects on the SCN. That is, other zeitgebers besides light can entrain the circadian pacemaker.

The MAPK signaling pathway may act as a critical common mediator of the circadian rhythm in the SCN, the periphery, and cultured cells, and circadian entrainment by photic and non-photic stimuli may be impacted by similar molecular mechanisms [38] (Fig. 2).

MAPK Pathway Underlies Photic Entrainment of the Circadian System

The MAPK pathway [39] in mammals consists of ERK1/2, c-Jun N-terminal kinase (JNK), p38, and ERK5. The MAPK pathway has been suggested to be involved in entrainment of the circadian clock [38]. The potential involvement of Ras, part of the MAPK signaling pathway, in modulating the circadian rhythm has been proposed in several studies [40–48]. ERKs have also been shown to play a role in photic resetting of the clock in the rodent SCN [49, 50]. The role of the SCN clock as a master pacemaker is modulated by light *via* direct excitation from the eyes. Intrinsic photosensitive retinal ganglion cells detect light through melanopsin [51] and project directly to the SCN through the RHT. The terminals of the RHT release glutamate and pituitary adenylate cyclase-activating peptide (PACAP) in the SCN [52]. They are ligands for *N*-methyl-D-aspartate receptors (NMDARs) and Pac1 receptors, respectively, at postsynaptic neurons in the SCN. The activation of NMDARs is followed by an inflow of Ca^{2+} [53, 54], which stimulates Ca^{2+} -calmodulin kinase II that successively activates cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) [55, 56]. In parallel, the activation of NMDARs leads to the activation of Ras, with subsequent activation of the MAPK pathway. ERK1/2 phosphorylates p90 ribosomal S6 kinase, which successively phosphorylates CREB, which is indispensable for light-induced resetting of the circadian clock in the SCN [57, 58]. Pac1 receptors can be activated by both light and stress [59]. PACAP is a critical neurotransmitter that is released in stress transduction areas of the brain, including the paraventricular nucleus of the

Fig. 2 Photic- and non-photoc-responsive MAPK signaling pathways in the brain. In photic circadian clock entrainment, the neurotransmitters glutamate and PACAP are released onto SCN neurons *via* the eye and RHT. The activation of NMDA and Pac1 receptors in turn results in the activation of Ras and heterotrimeric G proteins, which successively activate ERK and CREB. Non-photoc stimulation by SD,

ECT, or DBS leads to the activation of adenosine A_1 receptors, which leads to the activation of ERK and CREB. Phosphorylated CREB is translocated to the nucleus and activates the transcription of immediate-early genes, including *Per1*. SD, sleep deprivation; ECT, electroconvulsive therapy; DBS, deep brain stimulation; P, phosphorylation; ER, endoplasmic reticulum; TSS, transcription start site.

hypothalamus, the amygdala, extended amygdala nuclei, and the prefrontal cortex (PFC).

A previous study provided strong evidence that CREB plays a vital role as an endpoint of the MAPK pathway in the regulation of the *mPer* (*mPer1* and *mPer2*) genes [58]. Additional studies suggested that the MAPK pathway mediates the photic input which is involved in immediate-early gene (e.g., *c-fos* and *Per1*) induction in the SCN [60–62]. *Per1* is a clock gene in the negative feedback loop of the circadian system, the activation of which is thought to be an important event in modulating the clock [63]. The MAPK pathway has a series of downstream effector molecules that control the expression of related genes, including circadian genes [64] (Fig. 2). Moreover, ERK

and MAPK interact with and phosphorylate CLOCK, BMAL1, CRY1, and CRY2 in the circadian system [6].

MAPK Pathway Underlies Non-photoc Entrainment of the Circadian System

In addition to light, non-photoc stimuli can also impact the circadian clock [65–67]. Numerous other stimuli have been shown to increase locomotor activity or arousal in animals, including injections of triazolam [68, 69] and morphine [70], confinement to a novel wheel [71, 72], social and sexual cues [73], and sleep deprivation [74]. Some research have also revealed that the circadian clock can be reset in

humans by modulating mealtime, exercise, sleep-wake schedule, and social stimuli [75].

The intracellular biochemical cascades that underlie non-photic phase-shifts have gradually been identified. A study [76] showed that dark pulses decrease the levels of phosphorylated ERK1/2 but do not affect the levels of phosphorylated Ets-like gene 1. Another study revealed the involvement of the ERK/MAPK pathway in phase-shifts in response to 3 h of sleep deprivation initiated at midday in Syrian hamsters [67]. Cultured NIH-3T3 fibroblasts treated with tissue plasminogen activator exhibit circadian oscillations of gene expression that are restrained by a MEK inhibitor, and sustained activation of the MAPK pathway is sufficient to activate circadian gene expression [38]. These results demonstrate that the MAPK pathway acts as a critical mediator of signaling pathways that are involved in circadian entrainment by non-photic stimuli.

Research on the mechanisms that underlie physical therapy have revealed that sleep deprivation, electroconvulsive therapy (ECT), and deep brain stimulation (DBS) are associated with an increase in adenosinergic signaling [77–80]. Sleep deprivation increases the secretion of adenosine in the brain and upregulates adenosine A₁ receptors in humans and rodents [81–83]. Two physical therapies for depression, ECT and DBS, increase the levels of adenosine and stimulate A₁ receptors [77, 79, 84, 85]. Previous studies have shown that A₁ receptors regulate phospholipase C [86–89] and the ERK pathway [90, 91] in cells where they are highly expressed (e.g., neurons and smooth muscle cells). The MAPK pathway is an important component of the circadian clock [6] and mediates the regulation of the circadian rhythm. Evidence suggests that A₁ receptors mediate the circadian rhythm through the MAPK pathway and downstream CREB (Fig. 2).

To summarize, these investigations indicate that the MAPK pathway acts as a critical common mediator in the signaling pathways that regulate the circadian rhythm which is induced by both photic and non-photic stimuli. Regulation of the circadian system by the MAPK pathway may also play a critical role in depression.

MAPK Pathway in Depression

The MAPK/ERK pathway has been shown to play a critical role in MDD [92, 93] and in the actions of antidepressants [4, 94, 95]. Elements of the MAPK/ERK signaling pathway, including MEK1, MEK2, and Rap1, are reduced in the frontal cortex in MDD patients [96]. The levels of CREB cAMP and Ca²⁺ signaling also reduced in MDD [96]. Evidence also suggests decreases in ERK1/2, ERK5, MEK1, and CREB in the hippocampus [97, 98] and Rap1 activity in the PFC and hippocampus [99] in depressed

suicidal individuals. Postmortem investigations have reported that the mRNA and protein levels of ERK1/2 in prefrontal cortical areas and the hippocampus are significantly reduced in depressive suicide individuals [96, 99, 100]. MAPK-phosphatase 1 (MKP-1), a negative modulator of the MAPK pathway, is increased in the hippocampus of MDD patients [93]. The overexpression of MKP-1 is sufficient to induce depressive-like behavior in rodent models [93, 101]. The MAPK pathway has been suggested to play a vital role in the development of depression [95, 102].

Activity of the MAPK pathway is inhibited by chronic stress and restored by antidepressant treatment [103]. Inhibition of the MAPK pathway induces depressive- and anxiety-like behaviors [104]. Duman and colleagues demonstrated that inhibition of the MAPK pathway leads to depressive-like behaviors and blocks the behavioral actions of antidepressants on rodents [4]. Furthermore, depressive-like behavior is positively associated with a reduction of pERK in a rat model of depression [105]. Inhibition of the ERK pathway produces depressive-like behavior and blocks the antidepressant effects of ketamine [106]. Moreover, Pochwat *et al.* reported that ERK activation is crucial for both the short- and long-term antidepressant-like actions of NMDAR antagonists in the forced swim test in rats [107]. Recently, Labonté and colleagues reported that an increase in ERK signaling in glutamatergic pyramidal neurons in the ventromedial PFC (vmPFC) specifically increases the susceptibility of female rats to stress [108]. However, these results are in sharp contrast to those of previous studies in rodents [109–111] and postmortem human brains [96]. The study by Labonté and colleagues investigated the vmPFC, whereas most other previous studies focused on other cortical regions or the NAc. This may be the main reason for the discrepant findings. Further work is needed to illustrate why an increase in ERK signaling in the female vmPFC results in depressive-like behavior, while the same change in the male vmPFC has diverse outcomes.

In summary, abundant evidence indicates that the MAPK/ERK pathway is involved in the pathogenesis of depression and may be an attractive target for the development of new therapeutic strategies for MDD.

Regulation of the Circadian System by the MAPK Pathway: Involvement in Rapid Antidepressant Effects

Accumulating evidence suggests that MDD is a circadian-related disorder. Almost all patients with MDD suffer from alterations of diurnal rhythmicity (e.g., temperature, sleep, hormone secretion, and mood) during depressive episodes

[3]. A review showed that both low-dose ketamine and sleep deprivation therapy (SDT) modulate the circadian rhythm in humans, animals, and neuronal cells [3]. The fact that both therapies impact sleep homeostasis and the circadian rhythm indicates that the circadian and sleep-wake systems and their interactions are related to rapid antidepressant effects.

Sleep Deprivation Therapy and Other Non-pharmaceutical Treatments

The advent SDT was a major revolution when considering its rapid remission of depressive manifestations [112]. SDT generally refers to keeping patients awake for ~36 h. The mechanism underlying the effects of SDT has been investigated for many years, but no mechanism has yet been demonstrated. Bunney *et al.* proposed that abnormal circadian clock genes which control rhythms are altered by a change of the sleep-wake cycle [7, 16]. SDT responders present distinct activation of circadian genes (*Rora*, *Dec2*, and *Per1*) after SDT, whereas non-responders present notable reductions in the expression of these genes afterwards [7]. A few studies of clock genes in mice showed that a subset of circadian clock genes (e.g., *Per1* and *Per2*) appear to behave as immediate-early genes and are transcriptionally responsive within hours after sleep deprivation [113–116]. Depriving mice of sleep inhibits ~80% of rhythmic genes [114, 117].

The MAPK/ERK signaling pathway has been shown to be involved in the mechanism of action of SDT [118]. The diurnal activation of ERK in the dorsomedial SCN (i.e. the “shell”) is suppressed following sleep deprivation. A previous study indicated that adenosine A₁ receptors are important for the antidepressant effects of sleep deprivation [119, 120]. Two other rapid-onset non-pharmaceutical therapies for depression, ECT and DBS, are also associated with an increase in the release of adenosine and the activation of A₁ receptors [77, 79, 84]. Interestingly, A₁ receptors regulate the ERK pathway [90, 91]. These studies suggest that the rapid-onset non-pharmaceutical treatments for depression exert their antidepressant effects by stimulating A₁ receptor-ERK1/2 signaling (Fig. 2).

Besides, light therapy can also produce a rapid antidepressant effect. However, the parameters of light therapy varied among different clinical trials, so the results were different [121, 122]. Currently, there is no uniform procedure for light therapy. Above, we discussed the involvement of the MAPK/ERK pathway in both photic and non-photoc entrainment of the circadian system. We propose that rapid-onset-of-action non-pharmaceutical treatments for depression exert their antidepressant effects by activating MAPK/ERK signaling, which mediates

resetting of the circadian system, although no direct evidence is yet available to support our viewpoint.

Low-Dose Ketamine

Several studies indicate that the rapid antidepressant effects of low-dose ketamine are closely related to the regulation of circadian systems. Duncan *et al.* [123] found an association between the clinical antidepressant effects of ketamine and circadian timekeeping (i.e., amplitude and timing) using wrist-activity monitors in MDD patients. Bellet *et al.* [124] found that ketamine affects molecules associated with the central circadian clock. Specifically, ketamine decreases the amplitude of circadian transcription of the *Bmal1*, *Per2*, and *Cry1* genes in a dose-dependent manner. Ma *et al.* [125] reported that ketamine accelerates the differentiation of double cortin-positive adult hippocampal neural progenitors into functionally mature neurons. This process requires activation of the tyrosine kinase receptor B (TrkB)-dependent ERK pathway. TrkB-dependent neuronal differentiation is related to the sustained antidepressant effects of ketamine. Moreover, another study reported that acute inhibition of the MAPK pathway produces depressive-like behavior and blocks the antidepressant effect of ketamine [106]. Recently, Yang *et al.* found that (*R*)-ketamine significantly attenuates the decrease in ERK phosphorylation and its upstream effector MAPK/ERK in the PFC and hippocampal dentate gyrus in susceptible mice following chronic social defeat stress [126]. Based on this evidence, we speculate that low-dose ketamine produces its rapid antidepressant effects through the MAPK pathway to regulate the circadian system.

Overall, these results suggest that both SDT and ketamine act on circadian genes through the ERK/MAPK pathway, which phosphorylates CREB to produce a rapid antidepressant response. Using comparative transcriptomics analyses, Orozco-Solis *et al.* found that both SDT and ketamine act on the circadian clock *via* the MAPK/ERK pathway in the anterior cingulate cortex [127]. These findings suggest that the mediation of entrainment of the circadian system by the MAPK/ERK pathway may be involved in neuropathological processes that are associated with depression and antidepressant therapy, although further studies are needed to test this possibility (Fig. 3).

At present, most of the commonly-used first-line antidepressants target monoamine neurotransmitters, such as the selective serotonin reuptake inhibitors. Although the MAPK signaling pathway is involved in almost all of their mechanisms, they do not directly target this signaling pathway, so the onset of their action takes a relatively long

Fig. 3 Low-dose ketamine and non-pharmaceutical treatments, including SD, DBS, and ECT, regulate the circadian system through the MAPK pathway, which phosphorylates CREB to produce a rapid antidepressant response. Phosphorylated CREB directly binds to the CRE sequence of the *per1* and *per2* genes and regulates their transcription. ERK/MAPK interacts with and phosphorylates CLOCK, BMAL1, CRY1, and CRY2 in the circadian system, leading to a rapid antidepressant effect. SD, sleep deprivation; ECT, electroconvulsive therapy; DBS, deep brain stimulation.

time. Sleep deprivation can have a rapid antidepressant action but this only lasts for a short period and is easy to reverse. Depressive symptoms can recur as sleep recovers. However, the other rapid antidepressant methods, such as DBS, modified ECT, and low-dose of ketamine, whose mechanisms of action are still in the exploratory stage, are not well established. So we cannot provide the long-term outcomes of the currently available interventions targeting the MAPK pathway for antidepressant effects.

Conclusions and Future Directions

To date, accumulating evidence has indicated that the MAPK/ERK pathway is involved in the pathogenesis of depression and the mechanism of action of both pharmaceutical and non-pharmaceutical antidepressant therapies. Increasing evidence also demonstrates the mediation of entrainment of the circadian system by the MAPK/ERK pathway. However, little evidence links these systems to depression. To our knowledge, only one study has directly demonstrated such a mechanism in depression [127] using comparative transcriptomics analyses. Future studies are needed to test this hypothesis using various models, including behavioral tests, western blot, virus microinjection into specific brain areas, and conditioned intervention genes in animals.

Some basic questions still need to be answered. First, does the circadian system play an important or indispensable role in the pathogenesis of depression? Second, do

other pathways mediate entrainment of the circadian system? Third, how do these pathways interact with and affect the circadian system? These are critical questions that need to be explored. The MAPK pathway is a promising target for novel therapeutics with a rapid onset of action for the long-term treatment of severe, refractory MDD.

Based on previous studies, we propose that the regulation of circadian genes by the MAPK pathway is involved in the mechanism of depression. Nonetheless, direct evidence is needed to demonstrate that the rapid antidepressant effects of non-pharmaceutical and pharmaceutical therapies occur through entrainment of the circadian system mediated by the MAPK/ERK pathway. In fact, not all MDD patients respond to one kind of rapid antidepressant therapy, such as sleep deprivation, DBS or low-dose ketamine. This indicates that the mechanism underlying depression differs in different individuals. Nevertheless, the circadian rhythm involvement in depression and antidepressant therapy may also be complicated. Lazzerini Ospri *et al.* argued that circadian rhythms and mood could have synergistic effects but not be causally linked [128]. They proposed that mood could be affected by a comparison of the incidental properties of the output of circadian oscillators. Nevertheless, direct evidence or detailed mechanisms have not been provided. Above all, we need to explore the mechanism underlying this phenomenon. The MAPK pathway is important for mood regulation and clock entrainment, but the existing evidence cannot explain this complicated phenomenon.

In conclusion, most researchers in this field support the idea that circadian rhythm and mood are closely related, and some believe that there may be a causal link between them. However, so far there is no direct evidence of such a link. In this review, we propose that rapid-onset antidepressant therapies, both pharmaceutical and non-pharmaceutical, may regulate the circadian rhythm through the MAPK pathway. As far as we know, this is the first review to link the MAPK pathway, the circadian system, and antidepressant action, and only one report supports this link. Hence, in the future, we need use various animal models, specific gene interventions, virus microinjection into specific brain areas, or conditioned intervention genes in animals to test this hypothesis. And this may provide strong support for the Social Zeitgeber Theory of mood disorder.

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