



Review Article

Molecular basis for the association between depression and circadian rhythm

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ABSTRACT

Depression is a life-threatening psychiatric disorder and a major public health concern worldwide with an incidence of 5% and a lifetime prevalence of 15%–20%. It is related with the social disability, decreased quality of life, and a high incidence of suicide. Along with increased depressive cases, health care cost in treating patients suffering from depression has also surged. Previous evidence have reported that depressed patients often exhibit altered circadian rhythms. Circadian rhythm involves physical, mental, and behavioral changes in a daily cycle, and is controlled by the suprachiasmatic nucleus of the hypothalamus in responding to light and darkness in an environment. Circadian rhythm disturbance in depressive patients causes early morning waking, sleep disturbances, diurnal mood variation, changes of the mean core temperature, endocrine release, and metabolic functions. Many medical interventions have been used to treat depression; however, several adverse effects are noted. This article reviews the types, causes of depression, mechanism of circadian rhythm, and the relationship between circadian rhythm disturbance with depression. Pharmaceutical and alternative interventions used to treat depressed patients are also discussed.

KEYWORDS: *Antidepressants, Chronotherapy, Circadian rhythm, Clock genes, Depression*

INTRODUCTION

Definition and prevalence of depression

The World Health Organization (WHO) has defined depression as a common mental disorder, characterized by sadness, loss of interest or pleasure, feeling of guilt or low self-worth, poor concentration, inability to carry out daily activities, disturbed sleep, and loss of appetite. Severe depression even leads to suicide. Around 2%–9% of people who die by committing suicide had histories of suffering from symptoms of major depression. Suicide is the second leading cause of death in the population of the age between 15 and 29 years in low- and middle-income countries of the Eastern Mediterranean, American Regions, African, European, and South-East Asian Regions [1]. According to the report of Minister of Health and Welfare of Taiwan in 2017, the suicide rate of Taiwanese is 16/100,000 population, which is increased and higher than the rate of 15.7/100,000 in 2015 [2]. Major depressive disorder (MDD) is one of the suicidal causes in Taiwan [3]. There are 322 million people affected with depression worldwide in 2015 that is around 4.4% of global population. The total number of people living with depression increased by 18.4% between the years 2005 and 2015. Nearly half of these people live in the South-East Asian Regions and the Western Pacific Regions. The Gender difference is observed in patients suffering from depression. The incidence

in females (5.1%) is higher than that in males (3.6%). Besides, the prevalence of depression varies by age, peaking in older adulthood of age between 55 and 74 years. Although with a lower incidence than older age groups, depression also occurs in children and adolescents younger than 15 years old [4].

Classification of depression

According to the International Classification for Disease and Related Disorder-10 published by the WHO, depression disorders are divided into two main subcategories MDD and depressive episode and dysthymia [5]. MDD, also known as unipolar depressive disorder which is characterized by depressed mood, loss of interest and enjoyment, and decreased energy. Levels of the depressive episode can be categorized from mild, moderate, to severe [1], which often lasts more than 2 weeks and years in some cases. If the patient does not receive appropriate treatment, the risk of recurrent depressive episodes and dysthymia increased. Dysthymia is characterized as a persistent or chronic form of mild depression in which the symptoms are similar to MDD but last longer, at least 2 years, sometimes decades [4,5].

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Pathophysiology of depression

Many factors are involved in the pathophysiology of depression including genetics [6,7], changes in the expression of inflammatory cytokines and stress hormones [8,9], abnormal release or low function of neurotransmitters such as serotonin [10], norepinephrine, dopamine (DA) [11], glutamate, and gamma-aminobutyric acid (GABA) [12], and disturbances of circadian rhythm [13,14]. Sleep disturbance, the major circadian rhythm change, is considered to be important diagnostic criteria for MDD. Around 90% of depressed patients have difficulty falling asleep and maintaining good quality of sleep. Depressive patients have shorter latency between sleep onset and the first episode of rapid eye movement (REM) sleep than healthy people. They also exhibit increased duration and times of eye movements during REM sleep and decreased slow-wave sleep [15,16]. Circadian rhythms are also disturbed in patients affected with mood disorder. They express positive symptoms including over-enthusiasm, happiness, activeness, and alertness, or negative symptoms including distress, fear, anger, guilt, and disgust [17].

Neuroimaging and postmortem studies have provided evidence about brain regions involved in depression. Regional brain imaging studies using magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography on depressed patients have shown a reduction of brain volume in the dorsal and medial prefrontal cortex, the dorsal and ventral anterior cingulate cortex, the orbital frontal cortex, and the insula [18]. The structural changes in these brain regions, especially dorsal and medial prefrontal cortex can cause reduction of problem-solving abilities, higher propensity to express negative emotions, and are associated with suicidal behavior [19].

Circadian rhythms and the underlying molecular mechanism

In mammals, the cyclic rhythmicity of a given molecular or biological process produced by oscillator within the 24-h dark-light cycle is called circadian rhythm or circadian clock [14]. The circadian rhythms are regulated by a central pacemaker, which is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [20]. Molecular mechanism of the circadian rhythm was discovered by Jeffrey C. Hall, Michael Rosbash, and Michael W. Young who received the Nobel Prize in Physiology or Medicine in 2017. Circadian rhythm is mediated by the transcriptional-translational feedback loop of core clock genes (TTLs), which includes the genes *Brain muscle ARNT-like1 (Bmal1)*, *Circadian locomotor output cycles kaput (CLOCK)*, *Period1 (PER1)*, *PER2*, *cryptochrome1 (CRY1)*, and *CRY2* [21]. BMAL1 and CLOCK proteins act in a positive feedback loop to regulate the expression of TTLs. They form a heterodimer and binds to enhancer box (E-box) elements, DNA response element with protein-binding site, within the promoter regions of *PER*, *CRY*, *reverse-related erythroblastoma (REV-ERB)*, and *retinoic acid receptor-related orphan receptor (RORs)* to activate their transcription during late night and early morning. Whereas, *PER* and *CRY* proteins constitute the negative feedback loop of regulating TTLs. They accumulate in the cytoplasm and form complexes that translocate back into the nucleus and inhibit BMAL1/CLOCK-mediated transcription

during late day and nighttime. The reactivation of BMAL1/CLOCK proteins occurs when *PER* and *CRY* are degraded by ubiquitination systems. In addition, *REV-ERB* and *ROR* nuclear receptor act in an auxiliary oscillatory feedback loop to regulate *Bmal1*, stabilizing core feedback loop. *REV-ERB* proteins exert a negative feedback by inhibiting *Bmal1* transcription, while *ROR* proteins are positive regulators of *Bmal1* transcription. *RORs* compete with *REV-ERB* for *ROR* element binding sites of *Bmal1* promoter [22].

Circadian rhythm disturbance in depressive patients

The circadian program regulates the daily rhythms of the brain and body. It is found in many organs and individual cells either in central or peripheral levels. In healthy people, the circadian clock involves in many aspects of our physiology including regulation of sleep pattern, feeding behavior, hormone release, blood pressure, and body temperature [23]. The disturbance of circadian rhythm for depressive patients is often indicated with abnormal sleep patterns including shortened latency of REM sleep, increased duration of the first REM period, increased times of eye movements during REM sleep, and decrease of total sleep time. Slow-wave activity, a marker of sleep homeostasis, shown on the electroencephalography (EEG) during non-REM sleep is usually decreased in patients affected with depression [24]. Besides, increased mean core temperature and decreased amplitude of the circadian changes are also found in depressed patients. The change of core temperature during night time is correlated with the release of hormones including thyroid stimulating hormone, norepinephrine, cortisol, and melatonin [25]. In addition, genetic mutations are known to be associated with circadian rhythm disturbance in depressive patients [26-28]. Circadian synchronization is critical for maintaining body homeostasis. Circadian synchronization for expression of clock genes is controlled by the natural light-dark rhythm within 24 h. The synchronization of circadian modulates the transcriptional-translational feedback loop of core CLOCK genes such as *BMAL1*, *CLOCK*, *PER*, *CRY*, *REV-ERB*, and *ROR*, which involve physical, mental, and behavior in mammals [29]. The desynchronization (loss of circadian rhythm) of clock genes expression is one pathophysiology of depressive disorder [30,31]. Understanding the factors that trigger desynchronization of core CLOCK genes in depression thus help develop more effective treatment than anti-depressants for patients affected with depressive disorders.

Genes participate in both depression and circadian rhythm

Previous studies have found that several genes are involved in the pathology of depression. The study of whole blood transcriptome by Liliana Ciobanu in 2017 using the Weighted Gene Co-expression Analysis (WGCNA) constructs a network consisting of 29 modules. They demonstrate that two modules of WGCNA are associated with depression symptoms. There are 37 out of 82 genes in one module and 17 out of 64 genes in another module significantly associated with the phenotypes of depression. Among 37 protein-coding genes of the first module, 8 genes related to various translational, metabolic, and immune processes are also associated with depression, including the *PCYOX1 L*, *RPL14*, *MCTS1*, *GMAP7*, *NDUEB9*, *BOLA2*, *EIF3M*, and *RPL7A*. Among 17 protein-coding genes in the second module, 5 genes participate

in enzymatic, transcriptional, and translational regulation activities [28], are also associated with depression including the PRCP, POLR2J2, TAOK3, EIF2B5, and ATF4. Especially the activating transcription factor 4 (ATF4), or CREB2, is a transcription factor that plays a critical role in circadian rhythm by binding to the *Per2* gene [27]. About 50% to 90% of patients diagnosed with depression complain about bad sleep quality. The circadian rhythm change also contributes to the pathogenesis of winter depression. Evidence show that three circadian clock genes in gene-wise logistic regression analysis including the *Arntl*, *Npas2*, and *Per2* contribute to winter depression [26]. Another study also reported that the postmortem brains of MDD patients for whom at the recorded hour of death showed less synchronization of circadian rhythm genes between daytime and nighttime such as *BMAL1* (*ARNTL*), *PER1-2-3*, *NR1D1*(*REV-ERBa*), *DBP*, *BHLHE40* (*DEC1*), and *BHLHE41* (*DEC2*) (25). The study of a population-based sample of the Health 2000 dataset from Finland, including 384 depressed individuals and 1270 controls showed 113 single nucleotide polymorphisms (SNPs) of 18 genes of the circadian system in depressed patients. Moreover, the researcher found the SNPs of some circadian genes between female and male depressed patients are different. In female depression patients, 14 SNPs from 6 circadian-related genes including *TIMELESS*, *ARNTL*, *RORA*, nuclear factor, interleukin 3 regulated, *CSNK1E*, and *CRY2* were found. In males, 14 SNPs from 6 genes including *ARNTL*, aryl hydrocarbon receptor nuclear translocator-like 2 (*ARNTL2*), *RORA*, *NPAS2*, *TIPIN*, and period homolog 1 (*Drosophila*) (*PER1*) were identified [32]. Gender apparently is one important factor that affects the development of depression and abnormal circadian rhythm. Although the treatment of depression and circadian rhythm disturbance has been developed for seven decades, several side effects are still concerned. Therefore, studies on share molecules for depression and circadian rhythm disturbance might lead to alternative, novel therapeutic methods.

TREATMENT FOR CIRCADIAN RHYTHM DISTURBANCE AND DEPRESSION

Antidepressant treatment

Several neurotransmitters including DA, GABA, serotonin, norepinephrine, as well as melatonin, are involved in

pathophysiology of depression [10-12]. Antidepressants are commonly prescribed to patients as treatments for clinical depression or to prevent recurrence. Several antidepressants also appear to be effective in treating disturbance of circadian rhythm, particularly on sleep disorder. However, aversive side effects including headaches, nausea, fatigue, sexual dysfunction, weight changes, and loss or increase of appetite are noted in Table 1.

Chronotherapies

Chronotherapy is a series of nonpharmaceutical and biologically-based clinical interventions including sleep deprivation (also known as wake therapy), sleep phase advance, light and dark therapy [52]. In 1971, the first experiment of chronotherapies was developed in European countries to treat depressed patients with severe insomnia [53]. This technique is in clinical use as antidepressant treatment by controlling sleep rhythm of patients. This treatment has found to be highly effective and causes minimum side effect in depressive patients [54]. Chronotherapy is also reported to be effective on two adolescent patients affected with depression but resistant to antidepressants [55]. Although it appears to be promising, the effect of chronotherapy is transient. Patients would return to abnormal sleep pattern again after the treatment stops for 1 or 2 days [56]. Several studies have reported that sleep phase advance and bright light therapy can improve depressive symptoms and prevent the depression relapsing after sleep deprivation [57,58]. Therefore, chronotherapy has been modified to "adjunctive triple chronotherapy," which combines wake therapy, sleep phase advance and bright light therapy. The adjunctive triple chronotherapy is practicable and tolerable in acutely suicidal and depressive inpatients [59]. Adjunctive triple chronotherapy combined with antidepressant treatment is reported to prolong the therapeutic effect for about 9 weeks [57].

Animal model for depression and circadian rhythm disturbance

Depression with circadian rhythm change in patients is usually found in clinical observation. Understanding the shared molecular mechanisms underlying these two symptoms are an important theme. However, the study of molecular, biochemical, physiological, and behavioral changes in human are not feasible.

Table 1: The properties and side effects of antidepressants that are effective in treating both depression and circadian rhythm disturbance

Drug	Properties	Side effects	References
Trimipramine	TCAs	Sedation, weight gain, dry mouth, constipation, and orthostatic hypotension	[33-36]
Doxepin	Inhibit reuptake of serotonin, norepinephrine, and dopamine		
Amitriptyline	Insomnia treatment: Trimipramine (50-200 mg), doxepin (3-6 mg), and amitriptyline (10-100 mg)		
Paroxetine	SSRIs	Sexual functioning, sleepiness, weight gain, agitation, dizziness, dry mouth, nausea, nervousness, headache, vomiting, diarrhea	[37-40]
Fluvoxamine	Selectively inhibit reuptake of serotonin Insomnia treatment: Paroxetine (20 mg), fluvoxamine (50 mg)		
Mirtazapine	Atypical antidepressants	Headache, agitation, insomnia, loss or increase of appetite, weight loss or gain, sweating, sedation, nausea, diarrhea, dizziness	[41-43]
Trazodone	Mixed effects on dopamine, serotonin, or norepinephrine Insomnia treatment: Mirtazapine (15-45 mg), Trazodone (150-400 mg)		
Agomelatine	It act on both melatonin and serotonin receptors Insomnia treatment: Without causing daytime sedation (25-50 mg)	Headache, nausea, dizziness, insomnia, somnolence, constipation, and abdominal pain	[44-51]

TCAs: Tricyclic antidepressant, SSRIs: Selective serotonin reuptake inhibitors

Therefore, animal models have been widely used to study and help us understand the pathophysiological mechanism of the disorders and to develop treatments. There are many animal models of depression which also show circadian rhythm changes. Li *et al.* reported that wild type female mice induced by forced swim test as an acute stress model of depression showed circadian rhythm change in the night phase when compared to male mice [60]. Mice immobilized in the tail suspension test to induce depression exhibiting sleep-wakefulness alterations, which are also observed in depressed patients [61]. Another depression model, the chronic social defeat stress (CSDS) paradigm, is used to study the effects of acute and chronic stresses in mice [62]. This model involves an ethological form of stress related to territorial aggression of mice. For 10 consecutive days, wild-type mice were placed in a cage containing CD1 mice that had been previously screened for aggressive behavior. After that, mice were tested with electroencephalography (EEG), electromyography, body temperature, and locomotor activity. Results show that mice went through CSDS exhibiting persistent sleep deprivation and circadian rhythm change that similarly appear in humans [63]. Genetic manipulation is also used to create the model of depression and circadian rhythm disturbance including the SCN-specific *Bmal1*-knockdown mice [64], *Per2* knockout mice [65], and *Per3* knockout mice [66].

CONCLUSION

Several evidence have suggested that circadian rhythm disturbance may play a major role in the pathophysiology of

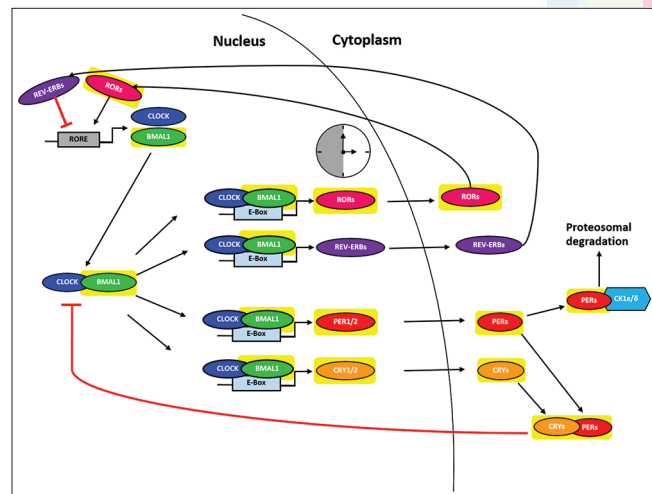


Figure 1: The transcriptional regulation circuit of clock genes in mammal. Circadian rhythm is mediated by the genes *Brain muscle ARNT-like 1* and *circadian locomotor output cycles kaput* act in a positive feedback loop to regulate expression of the transcriptional-translational feedback loop of core clock genes during late night and early morning. They form a heterodimer and binds to enhancer box elements, DNA response element with protein-binding site, within the promoter regions of *Period*, *CRY*, *REV-ERB*, and *RORs*. *Period* and *CRY* accumulate in the cytoplasm and form complexes that translocate back into the nucleus and inhibit brain muscle ARNT-like1/circadian locomotor output cycles kaput-mediated transcription during late day and nighttime. In addition, reverse-related erythroblastoma proteins exert a negative feedback by inhibiting *Bmal1* transcription, while related orphan receptor proteins are positive regulators of *Bmal1* transcription. Related orphan receptors compete with reverse-related erythroblastoma for related orphan receptor element binding sites of *Bmal1* promoter. The genes highlighted in yellow are also involved in depression, however, the pathway that links depression and circadian rhythm disturbance is not delineated yet

depression. The molecular, biochemical, physiological, and behavioral changes link circadian rhythm disturbance with depression. The molecules involved in circadian rhythm disturbance and depression have been well studied, however, pathways that link the two disorders are not clear yet. The transcriptional regulation circuit of clock genes in mammals is illustrated in Figure 1. Among them, we labeled those genes also known to be involved in depression with yellow background. They may play important roles in linking depression and circadian rhythm.

Both pharmaceutical and nonpharmaceutical interventions for circadian rhythm disturbance are effective in treating some depressive patients, however, aversive side effects are noted and 10%–30% of patients are not responsive to the drugs in the market. Researches to delineate molecular pathway(s) that link the two disorders thus become an urgent theme for the development of novel drug target and new therapeutic treatment.

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Conflicts of interest

There are no conflicts of interest.

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