Review Article

Circadian System and Bipolar Disorder

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ABSTRACT

Bipolar disorder (BD) is a highly heritable neuropsychiatric disorder associated with disrupted circadian rhythms. In mammals, circadian rhythms are regulated endogenously by circadian clock genes. At cellular level, oscillation of various clock genes required for maintenance of biological rhythms to an approximate 24 hour cycle is generated by transcriptional autoregulatory feedback loops. Secondary to this, post-translational modifications like phosphorylation, SUMOylation, acetylation and methylation of clock proteins play a significant role in regulating circadian rhythms. Several single nucleotide polymorphism (SNP) association studies and genome-wide association studies (GWAS) have identified the involvement of clock gene variants in BD. The therapeutic efficacy of mood stabilizers and antidepressants used to treat BD can be partially explained by their action on molecules regulating circadian rhythms. This review details the biology of circadian rhythms, posttranslational modifications of clock proteins that regulate the rhythms, evidences of clock gene variants associated with BD and effects of treatment of BD on circadian clock.

Keywords: Bipolar disorder, Circadian rhythms, Clock genes.

INTRODUCTION

Bipolar disorder (BD) also known as manic-depressive illness is a chronic, heritable neuropsychiatric disorder with complex origins in gene-environment interactions. The characteristic features of BD are extreme shifts in mood, energy and functioning. The shifts in mood are not merely related to life events. Genetic, physiological, psychological and environmental factors contribute to the illness. The United States has the highest lifetime rate of BD at 4.4%, and India the lowest, with 0.1%.[1] BD is a polygenic disorder with heritability estimate at about 85%.[2] Disrupted circadian rhythm is shown to be associated with BD. Hence, the biology of circadian rhythm and association of polymorphism of circadian rhythm genes with development of BD has been elaborated.

Circadian Rhythms

The term "circadian" which derives from the Latin phrase "circa diem" meaning "about a day" refers to the biological processes that display rhythms during a period close to 24 hours. Circadian rhythms enable living beings to adapt to their periodically varying environment, through entrainment of rhythms. Entrainment refers to the process where the circadian pacemaker resets itself in response to light to maintain synchrony of the clock to the 24 hour day. A pacemaker is a functional entity capable of self-sustaining oscillations that synchronizes other rhythms. Circadian clocks are capable of functioning autonomously, although they are entrained by environmental signals like day/night cycles.[3] The light-dark cycle of the solar day plays a vital role in regulating circadian rhythms.[4] The conservation of circadian system is observed since the time plants diverged from the common lineage with animals and fungi.[5-7] The three major circadian pacemakers in mammals are the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, the retina and the pineal gland. The SCN is the dominant circadian pacemaker[8] which synchronizes to the environment by light input from melanopsin present in the ganglion cells of the retina[9] through the retinohypothalamic tract.[10] Clocks are also present in several other brain regions[11-13] and peripheral tissues (e.g., liver, kidneys, heart, muscle).[14,15] Although the peripheral clocks have the capability of generating oscillations independently, the SCN clock synchronizes them.[6,16] Circadian rhythms regulate behaviour and physiological functions like sleep-wake cycles, hormonal secretion, body temperature and metabolism.[17,18] Circadian rhythmicity is cell-autonomous, in both SCN neurons and non-SCN cells.[19,20] Genetic variants in clock and clock-related genes display abnormal circadian rhythms.[21,22] The circadian rhythms in SCN and peripheral tissues are regulated by the cellular circadian clocks involving transcription factors and their modulators.

Cellular Circadian Clock Network

The cellular circadian clock comprises of clock genes which regulate and are themselves regulated by transcription-translation feedback loops to adjust rhythms to an approximate 24 hour cycle.[23,24] The positive loop of the mammalian clock system comprises of circadian locomotor output cycles kaput (CLOCK) or Neuronal period-aryl hydrocarbon receptor nuclear translocator – single minded (PAS) domain protein 2 (NPAS2) and two aryl hydrocarbon receptor nuclear translocator-like (ARNTL/ARNTL2) proteins. These proteins are members of basic helix–loop–helix (bHLH)

Period-Arnt-Single-minded (PAS) domain transcription factor family.[25] The circadian rhythm cycle begins when the transcription activator CLOCK dimerizes with ARNTL to initiate the cellular circadian oscillation. CLOCK and ARNTL heterodimerize and bind to DNA elements called E-boxes (CACGTG), E^1-boxes (CACGTT)[26-29] Noncanonical E-box (CATGTG)[30] and EL-box (CACGAG)[31] in the promoter of their target genes such as the clock genes *PERIOD* (isoforms *PER*1, *PER*2, and *PER*3) and *CRYPTOCHROME* (isoforms *CRY*1 and *CRY*2) to activate their transcription during the daytime. Their protein products PER and CRY form a dimer in the cytoplasm and translocate into the nucleus at night, where they interact directly with CLOCK-ARNTL to repress their own transcription.[5,32-36] Consequently, PER and CRY levels fall as the PER-CRY repressor complex is targeted for degradation by specific E3 ubiquitin ligase complexes[37-39] and the negative repression is relieved resulting in CLOCK-ARNTL activating a new round of transcription to begin the circadian cycle anew. This cell autonomous, auto regulatory transcriptional feedback loop takes about 24 hours to complete and forms the core mechanism of the circadian clock in mammals.[40]

The primary loop of circadian cycle is accompanied by two adjoining loops. The first adjoining loop involves *Rev-erbα/β* or *NR*1D1/2 and *RORα/β* genes which encodes for orphan nuclear receptor. NR1D1/2 protein binds to retinoic acid-related orphan receptor element (RORE) within the promoter region of *ARNTL* gene and represses its transcription whereas ROR proteins compete for the same site and activate its transcription.[41,42] Similar to *CRY* and *PER* genes, transcription of *Rev-erb α/β* and *ROR α/β* genes is activated by CLOCK/ARNTL heterodimers acting through E-box enhancers in their promoters. Unlike CRY/PER complexes which repress their own expression by acting directly on CLOCK/ARNTL heterodimers, REV-ERBα inhibits its own transcription in an indirect manner by repressing transcription of its activator, ARNTL. Furthermore, as a target of CLOCK/ARNTL-mediated activation, *Rev-erbα* transcription is also repressed by the inhibitory action of CRY/PER complexes on CLOCK/ARNTL.[41] Together these processes terminate REV-ERBα-mediated inhibition of ARNTL expression such that ARNTL accumulates at the proper time to heterodimerize with CLOCK, translocate to the nucleus, and initiate a new round of transcription as CRY-PER levels decline. Indeed, appropriately timed circadian nuclear accumulation of CLOCK/ARNTL is mainly ARNTL-dependent.[41,42]

The second adjoining loop of circadian cycle involves the proline and acidic amino acid-rich domain basic leucine zipper (PAR bZip) transcription factors like, D-site of albumin promoter binding protein (DBP), thyrotroph embryonic factor (TEF), hepatic leukemia factor (HLF), the bZip protein, nuclear factor interleukin-3-regulated gene (*NFIL3*, also known as *E4BP4*), DEC1 [basic helix loop helix (BHLHE40) protein] and DEC2 (BHLHE41), all of which are transcriptional targets of CLOCK-ARNTL.[6,24,43] These factors bind to the D-box element of circadian clock genes and regulate their transcription.[44] In general, the transcription of these gene families is driven by ARNTL/CLOCK via E-box sequences. The D-box activators then further drive the transcription of *PER*, *Rev-erbα/β* and *RORα/β*. Activation of the RRE by *RORα/β* feeds back to drive the transcription of ARNTL/CLOCK, as well as the transcription of the E4BP4. E4BP4 is a transcriptional repressor that binds at the D-box sequence and may further regulate PER and CRY proteins. It is speculated that a particular target gene can alternatively bind PAR bZip transcription factors or the repressor E4BP4, allowing its precise transcriptional regulation.The genes in the D-box loops enable the circadian oscillations to be more robust and add precision to the period.[42,45] The three binding elements namely E-box in the morning, D-box in the day, and RRE elements in the evening together provide the necessary delay to cycle at near 24 hour.[46,47]

Post-Translational Modifications of Clock Proteins

The "core" circadian clock consists of 18 genes namely *ARNTL1/2, CLOCK, NPAS2, PER1/2/3, CRY1/2, NR1D1/2, RORA/B/C, DEC1/2,* casein kinases-1δ/ε (*CK1D/E*)[28] and about 343 genes modulate circadian rhythms.[48] Several clock controlled genes oscillate rhythmically in some tissues. In addition to these core transcriptional mechanisms, circadian rhythms are regulated by post-translational modifications of clock proteins.

Phosphorylation

Phosphorylation of clock proteins by CK1δ/ε and glycogen synthase kinase 3 beta (GSK3β) proteins are necessary to maintain the stability, activity, binding partners, and subcellular localization of clock proteins.[49] GSK3β phosphorylates timeless (TIM),[50,51] CRY2,[52,53] PER2[54] and NR1D1.[54] The importance of the post-translational regulation within the core mechanism of the circadian clock is supported by the fact that mutations in CK1δ/ε result in altered kinase activities and cause shorter circadian periods in mammals. Phosphorylation of PER and CRY proteins by CK1δ/ε and GSK3β leads to its ubiquitination and proteasomal degradation.[52,55-58] In particular, the role for CKIε in PER protein phosphorylation, nuclear entry, and turnover has been clearly demonstrated.[56] Degradation of the negative limb proteins PER and CRY is required to terminate the repression phase and restart a new cycle of transcription. Hence, stability/degradation rate of the PER and CRY proteins is crucial in determining the period of the clock. Apart from PER and CRY proteins, recent studies suggest the involvement of phosphorylation of CLOCK and ARNTL in regulating circadian rhythms. GSK3β phosphorylates ARNTL which controls the stability of the protein and the amplitude of circadian oscillation.[59] ARNTL was shown to be a substrate for CK1ε[56] and dimerization of ARNTL with CLOCK through the PAS domains is required for these phosphorylation events and for subsequent transactivation.[23] Phosphorylation by the same kinase has opposite effects for different clock substrates (For

example, phosphorylation by CK1 δ/ε leads to degradation of PER but stabilization of ARNTL). In agreement with the model outlined above, ARNTL phosphorylation may enhance transactivation at E-box sites.[56] This model is also supported by the fact that phosphorylated forms of ARNTL are predominantly found in the nucleus at the time of maximal transcriptional activity of CLOCK/ARNTL.[35,55,60,61] In addition it has been found that, negative loop protein CRY can blunt the phosphorylation of ARNTL and shift the ratio of phosphorylated/unphosphorylated forms of ARNTL towards a predominance of unphosphorylated (transcriptionally inactive) form. Through this action, CRY may interfere with the transactivation of CLOCK/ARNTL. CRY represses the activity of CLOCK-ARNTL to maintain the circadian rhythmicity which indicates that transcriptional feedback is required for mammalian clock function.[62]

Sumoylation

The process of tagging small ubiquitin-related modifier protein (SUMO) to lysine residues of ARNTL called as SUMOylation is a reversible posttranslational modification controlled by an enzymatic pathway which is essential to maintain the rhythmicity of the clock. ARNTL is sumoylated on a highly conserved lysine residue (Lys^{259}). SUMOylation of ARNTL requires and is induced by CLOCK.[60]

Acetylation

Acetylation of proteins is another essential phenomenon in regulating the clock. CLOCK acetylates non-histone substrate, like its own binding protein ARNTL at a highly conserved Lys537 residue. CLOCK-ARNTL dimerization is essential for this process. ARNTL acetylation facilitates binding of CRY1 to CLOCK–ARNTL complex and promotes transcriptional repression.[63] The chromatin remodeling necessary for cyclic transcriptional activity exerted by CLOCK-ARNTL is achieved by rhythmic acetylation/deacetylation of histones (H3 and H4) at multiple clock target genes.[27,64] Histone acetyltransferases (HATs) proteins acetylate histones to enable the chromatin to open up. Histone deacetylases (HDACs) deacetylate histones, locking the chromatin such that it is not accessible to the transcriptional machinery. The CLOCK protein itself possesses a HAT domain. This suggests that CLOCK may be both necessary and sufficient for histone acetylation. HAT activity of the CLOCK and chromatin remodelling are essential for the core clock mechanism.[65] Further, ARNTL enhances HAT function of CLOCK.

Methylation

Methylation could be another histone modification which is important for clock function.[66-68] The CLOCK-ARNTL complex recruits the methyl transferase called MLL1 to cyclically methylated histone H3 and HDAC inhibitor ARID domain - containing histone lysine demethylase 1α (JARID1α) to facilitate transcriptional activation.[67,68]

Circadian rhythms and BD

The role of circadian system in BD is substantiated by several studies. Disruption in circadian rhythms leads to increased incidence of many diseases, such as cancer and mental illness.[69] Disrupted circadian rhythms could contribute directly to the pathophysiology of BD.[70-73] BD patients exhibit cyclicity of mood and sleep disturbances suggesting the possibility of clock dysfunction.[73-75] There are abnormalities in circadian alignments in BD patients.[76] Mutations in circadian clock genes alter circadian rhythms, rest-activity cycles and sleep patterns.[77-79] Circadian rhythm abnormalities in the sleep wake-cycle (excessive sleep in the depressive phase and reduced need for sleep in the manic phase) are confirmed in BD.[80] The sleep-wake cycle is altered by variants in clock genes like, *PER*1,[81] *PER*2,[82,83] *PER*3,[84-86] *TIM*[87] and *CSK*1*ε*.[88] Circadian rhythmicity of clock genes also regulate energy metabolism.[89] Mutant mouse models of clock genes such as *ARNTL*, *CLOCK*, *NPAS*2, *CRY*1 and *CRY*2 also have alterations in homeostasis along with sleep abnormalities.[90-92]

Circadian functions like variation in mood, body temperature and secretion of hormones like cortisol, norepinephrine, thyroid stimulating hormone and melatonin are disrupted in BD subjects.[93-96] Melatonin regulates sleep and other cyclical bodily functions and its synthesis is inhibited by light.[97] Melatonin levels were significantly lowered in BD patients compared to controls.[98-100] A phase advance of melatonin levels was found in manic patients[101] and a delayed peak melatonin time was reported in euthymic bipolar patients.[100] Bright light and melatonin are used to treat circadian rhythm disorders[102] and melatonin is the only option to treat blind people with bipolar disorder.[103]

BD with seasonal pattern (mania during spring and summer, depression during fall and winter) referred to as seasonal affective disorder (SAD) is associated with disrupted circadian rhythms.[104] Patients with SAD generate a biological signal towards change of season that is absent in healthy volunteers. The duration of nocturnal period of active melatonin secretion is shorter in summer than in winter.[105] The clock gene variants hinder the ability of BD subjects to appropriately adapt their circadian rhythms to their environment and subject them to sleep disturbances.[106] Life stress affects sleep-wake and social rhythms, leading to circadian clock disruption and subsequent mood episodes.[107,108] The social zeitgeber theory states that stress in life results in mood episodes which disrupts the social routines and thereby the biological rhythms.[109]

Evidences for Association of Circadian Clock Genes in BD and SAD

Convergent Functional Genomics (GFG), an approach that identifies a gene based on its position on a chromosome and its function is emerging as a tool to identify the potential candidate genes associated with BD. CFG

approach identified *DBP*,[110] *ARNTL*,[111] *GSK3β* and *RORα/β* genes[112] as potential BD candidate genes. A single nucleotide polymorphism (SNP) in *CLOCK* gene (T3111C; rs1801260) is associated with decreased need for sleep in bipolar patients.[113,114] *CLOCK* gene variant is associated with human diurnal preference.[115] *NPAS2* gene mutant mice[78] and *CLOCK* gene mutant mice display a behavioural profile that is similar to human mania.[116] Mice with mutant *CLOCK* gene have a lengthened circadian period.[117] Reduced activity is observed in mice with *ARNTL* gene knockout which reverts to normal by replacing ARNTL function in muscle.[118] *DBP* gene was identified as potential candidate for BD in gene expression studies.[110] *DBP* gene knock-out mice display a bipolar-like phenotype.[112] A decrease in expression of *ARNTL*, *DBP* and *NR1D1* genes is seen in fibroblasts from bipolar subjects.[119] An increase in *ARNTL* gene expression is observed in post-mortem brains of BD subjects.[120] *PER2* gene variation is associated with depression.[121] *CRY2* gene variant is associated with winter depression and lowered *CRY2* gene levels is associated with depression in BD.[122] *TIM* gene variants are also associated with depression and sleep disturbance.[87]

SNP association studies[123-145] and GWAS with evidences from gene expression and genetic data from human and animal model studies[146] implicated variants in several clock genes in BD (Table 1). SNP association studies[122,124,147] have implicated variants in clock genes in SAD (Table 1).

Table 1: Studies with evidences for clock gene variants significantly associated with BD and SAD

Gene	BD	SAD
ADCYAP1C	rs1610037[139]	-
ARNTL	rs1982350[125,126,139] rs969486[125,139] rs1481892; rs7107287; rs4757142; rs895682[125, 126] rs2896635; rs2290035;rs2279287[126] rs7126303[135] rs2278749[126, 127, 139] rs3789327[127, 139] rs4757141; rs4757138; rs3816360; rs11022781[146] rs969485[139] rs747601[141]	rs2290035[124] rs2279287[149]
ARNTL2	rs10842905; rs11610949; rs10506018; rs2970844; rs11048994; rs4964060; rs35878285[139]	-
BHLHE40	rs1537720; rs10982664[141]	-
BHLHE41	rs4963954[139]	-
CLOCK	rs10462028; rs2070062[139] rs1801260[123,133,139] rs12504300[132, 139]	-
	rs3805148; rs3736544; rs4864542; rs12648271[132] rs6850524[131, 132] rs4340844[131] rs2412646[137]	
CRY1	rs2287161[139]	-
CRY2	rs1554338[135] rs10838524[138]	rs10838524[122] rs1554338[143]
CSK1δ	rs4510078[132]	-
CSK1ε	rs1997644[135, 139] rs1534891[142]	-
EGR3	rs1996147[135]	-
GSK3 β	rs17811013; rs17810235; rs6438552[146] SNP T-50C[128]	-
NPAS2	rs7581886; rs4851392; rs17662394[139] rs11123857 [135,139] rs13025524; rs17025005[135] rs1562313[132]	rs11541353[124, 147] rs6738097[143]
NR1D1	rs2314339; rs2071427; rs2269457[132] rs939347[130,134] rs12941497[134]	-
PER1	rs2585405[132]	-
PER2	rs4663868; rs2304672; rs2304669[132]	rs2304674; rs56013859[147]
PER3	rs228642[127, 139] rs2859387[125, 126] rs228666; rs2859388; rs228729[127] rs228697 [127, 132] (VNTR) [129, 140, 144]	-
PPARGC1B	rs7732671[132]	-
RORA	rs4774370[139]	-
RORB	rs10491929; rs17691363; rs10217594[135] rs10869435[141, 146] rs1327837[146] rs7022435; rs3750420; rs1157358; rs3903529[136]	-
THRA	rs939348[132]	-
TIM	rs2291738[125, 126] rs2279665; rs774026; rs2291739[126]	-
3-gene interaction (*TMEM165; BHLHE40; CSK1 ε*)	rs534654; rs6442925; rs1534891[131]	-
VIP	rs17083008; rs688136[139]	-
VIPR2	rs885861; rs12670064; rs3793227[139]	-

Effects of Treatment of BD on Circadian Clock

BD treatment studies provide indirect evidences for the involvement of clock genes in BD. Mood stabilizers such as lithium and valproate and antidepressants used to treat BD exert their action through molecules associated with the regulation of circadian rhythms.[72,148,149] Mood stabilisers modulate circadian function.[116,150-153] Mice with mutant *CLOCK* gene display a human mania-like behavioural profile that reverts to almost normal with chronic administration of lithium. Lithium treatment in cells results in rapid proteosomal degradation of *NR1D1* gene and activation of clock gene *ARNTL*.[53] Lithium inhibits GSK3β[154] and regulates circadian rhythms of BD patients and model organisms[148-156] and shortens period in mammalian cells.[157,158] Lithium increases the amplitude of *PER2* and *CRY1* genes and reduces the amplitude of *PER3*, *CRY2*, *ARNTL*, *E4BP4* and *NR1D1* genes and alters the period of *PER2* gene in serum shocked cultured murine fibroblasts.[159] Lithium regulates the circadian system by phosphorylating the clock proteins CRY2,[50] PER2[52] and NR1D1[53] and ARNTL[57] and delaying the *PER2* gene transcription.[160] Lithium salts and valproate reduce the suppression of melatonin by light in healthy controls as well as in BD patients.[100,161,162] Lithium alters clock gene expression and delays circadian rhythms in rodents, monkeys and humans.[163-166] Phosphorylation of clock proteins by GSK3β plays a vital role in mood stabilization.[167] Valproate also regulates circadian rhythms by acting on GSK3β.[168] Non-pharmacological techniques such as bright light therapy and total sleep deprivation are used to treat BD by resetting the circadian clock.

BD patients benefit by a strict sleep-wake cycle which regulates circadian rhythms.[169,170]

CONCLUSION

BD is a highly heritable psychiatric disorder. There is considerable advancement in studies associating polymorphisms in circadian clock genes with the pathophysiology of BD. Studies relating post-translational modifications of clock proteins and BD could be an area of focus in future research.

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