



Molecular Mechanisms in Mood Regulation Involving the Circadian Clock

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The circadian system coordinates activities and functions in cells and tissues in order to optimize body functions in anticipation to daily changes in the environment. Disruption of the circadian system, due to irregular lifestyle such as rotating shift work, frequent travel across time-zones, or chronic stress, is correlated with several diseases such as obesity, cancer, and neurological disorders. Molecular mechanisms linking the circadian clock with neurological functions have been uncovered suggesting that disruption of the clock may be critically involved in the development of mood disorders. In this mini-review, I will summarize molecular mechanisms in which clock components play a central role for mood regulation. Such mechanisms have been identified in the monoaminergic system, the HPA axis, and neurogenesis.

Keywords: clock genes, depression, monoamines, glucocorticoids, neurogenesis

A plethora of human genetic studies have identified polymorphisms in clock genes that associate with psychiatric disorders [reviewed in Ref. (1)]. This suggested that abnormalities in clock genes may be one of the causes for the development of mood disorders. At the cellular level, clock genes (*Bmal1*, *Clock*, *Per*, *Cry*, *Rev-erb*, and *Ror*) make up an autoregulatory transcriptional/translational feedback loop with a period of about 24 h (Figure 1, top gray circle) [reviewed in Ref. (2)]. These clock genes and their proteins not only self-promote their own temporally fluctuating transcription but they also regulate transcription of target genes (Figure 1) and/or modulate key molecular pathways via protein–protein interactions, such as the monoaminergic system, the HPA axis, or neurogenic pathways.

TRANSCRIPTIONAL REGULATION OF MONOAMINE SIGNALING BY CLOCK COMPONENTS

Neuroimaging studies in humans indicated that the monoaminergic system (dopamine, serotonin, and noradrenaline) was altered in subjects with mood disorders (3). This was further supported by optogenetic studies, in which control of neuronal activity of dopamine neurons in mice modulated mood, anxiety, and reward, confirming the importance of the monoaminergic system in mood-related behaviors (4, 5).

Interestingly, several studies described daily changes in dopamine, serotonin, and noradrenaline levels [reviewed in Ref. (6)]. Because these molecules modulate arousal, motivation, and reward, one would expect them to be targeted at the activity period of the day in order to avoid conflicts with sleep signals. Hence, monoaminergic signaling is likely to be regulated by the circadian clock, either directly or indirectly. In the last years, several investigations aimed at uncovering the role of circadian clock components in the direct transcriptional regulation of

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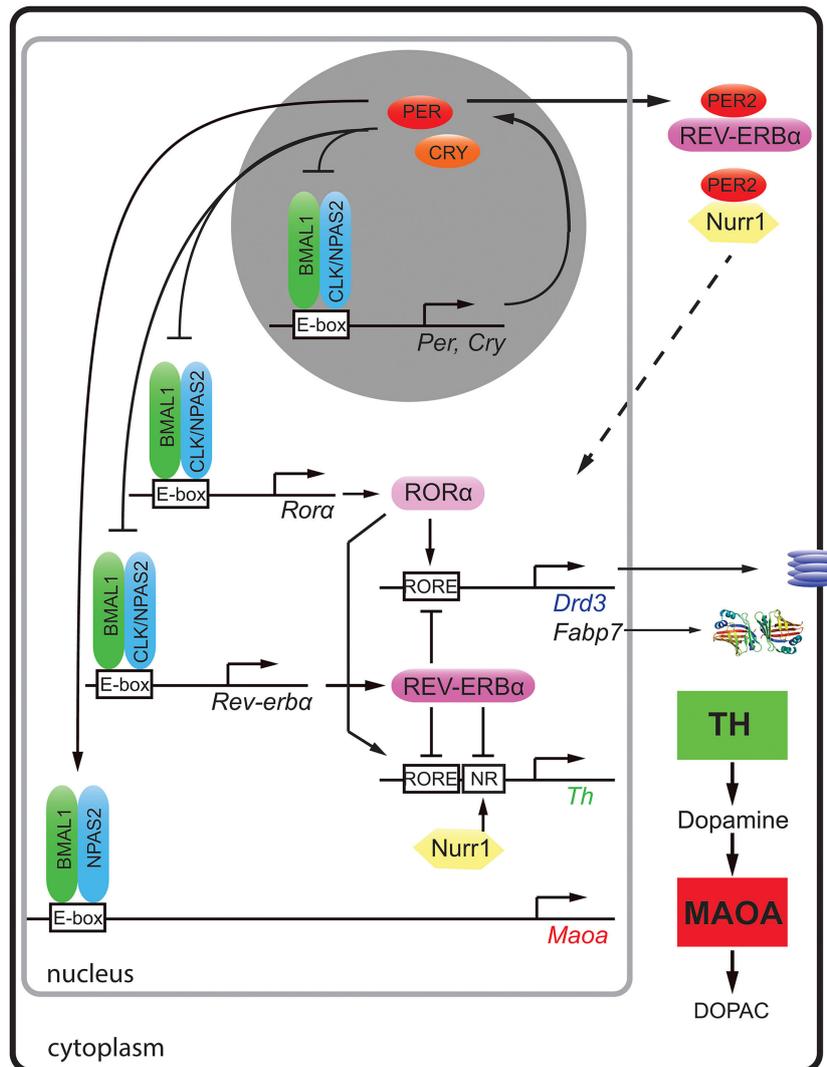


FIGURE 1 | Molecular regulation of clock and clock-controlled genes of the monoaminergic system and neurogenesis. The clock proteins BMAL1 (green), CLOCK (blue), and NPAS2 (blue) bind to E-box elements present in the promoters of clock genes (*Per*, *Cry*, *Rora*, and *Rev-erba*) and the clock-controlled gene for monoamine oxidase A (*Maoa*). PER (red) and cryptochrome (CRY, orange) proteins inhibit the action of BMAL1/CLOCK and BMAL1/NPAS2 heterodimers, respectively. The nuclear receptors [retinoic orphan receptor α (ROR α , rose)] and REV-ERB α (purple) both bind to RORE elements of dopamine receptor 3 (*Drd3*), fatty acid binding protein 7 (*Fabp7*), and tyrosine hydroxylase (*Th*) in a competitive manner and activate or inhibit their expression, respectively. The nuclear receptor Nurr1 (yellow) regulates *Th* via its NR promoter element. Via protein-protein interactions, PER2 can modulate the actions of REV-ERB α and Nurr1 (hatched arrow). This regulation results in temporally regulated expression of the dopamine synthesizing (TH, green square) and degrading enzymes (MAOA, red square) leading to fluctuating levels of dopamine in the striatum.

elements important for monoaminergic signaling, such as the enzymes monoamine oxidase (MAO) and tyrosine hydroxylase (TH) both key enzymes for the degradation and synthesis of dopamine, respectively.

Dopamine degradation is under clock control. This was first suggested by the observation that the clock components BMAL1 and NPAS2 transcriptionally activated a luciferase reporter driven by the murine monoamine oxidase A (*Maoa*) promoter in a circadian fashion. This indicated that these two clock components directly regulated *Maoa* transcription (Figure 1). This notion was further strengthened by the observation that

BMAL1 protein was recruited to the *Maoa* promoter in brain tissue (7). Interestingly, the regulation by BMAL1/NPAS2 was modulated by PER2 in a positive fashion, but not in the predicted negative manner (Figure 1). This led to increased *Maoa* mRNA levels (7). This finding suggested potential tissue specific regulatory factors that turned PER2 into a positive regulator of BMAL1/NPAS2-driven transcriptional regulation in the striatum. As a consequence of lack of PER2, not only *Maoa* mRNA but also MAOA protein levels were decreased. Hence, dopamine degradation was reduced, and dopamine levels in the nucleus accumbens were increased. This was paralleled by

a depression-resistant-like phenotype and changes in neuronal activity in response to MAO inhibitors in mice (7). These findings strongly suggested that the degradation of monoamines was clock modulated. It is very likely that the described clock-mediated regulation of monoamines is relevant for humans, because single-nucleotide polymorphisms in *Per2*, *Bmal1*, and *Npas2* associated in an additive fashion with seasonal affective disorder or winter depression (8).

A recent study showed that not only dopamine degradation but also dopamine synthesis is under clock influence. The mouse, rat, and human *Th* promoters were repressed by REV-ERB α , and they were activated by retinoic orphan receptor α (ROR α) and nuclear receptor-related protein 1 (NURR1) (9). Chromatin immunoprecipitation experiments revealed that REV-ERB α and NURR1 were binding to the *Th* promoter in an antagonistic manner (9). In accordance with this mechanism (Figure 1), *Rev-erb α* knock-out mice displayed elevated *Th* mRNA and protein levels leading to increased dopamine amounts and firing rate in the striatum (9, 10). As a consequence, these animals showed less depression-like and anxiety-like behavior compared to wild-type animals (9). The temporal regulation of TH may be further modulated through protein–protein interactions. For example, PER2 has the potential to interact with both REV-ERB α and NURR1 proteins (11), which would allow temporal synchronization of the action of these two nuclear receptors (Figure 1, top right, hatched arrow). This is, however, a speculation and needs verification.

Interestingly, REV-ERB α and ROR α were described to regulate the expression of the dopamine D3 receptor gene (*Drd3*) in an antagonistic manner (12) (Figure 1). This provided a molecular explanation why this receptor was expressed in a diurnal manner in the striatum (13). DRD3 inhibits adenylyl cyclase through inhibitory G-proteins [reviewed in Ref. (14)] and mutation of DRD3 in mice suggested an involvement of this receptor in mediating emotional behavior and depression in mice (15). A role of NPAS2 in the regulation of *Drd3* has also been suggested (16), although it is unclear how NPAS2 would regulate the *Drd3* promoter. Taken together, it appears that REV-ERB α and ROR α synchronize dopamine production and the expression of DRD3 in the striatum probably to optimally restrict dopamine signaling in the striatum to a particular time window. This implies that the targeting of DRD3 and/or REV-ERB α /ROR α by pharmacological agents may benefit from timed application. This would reduce dosage and diminish side effects such as weight gain, which is observed often in patients treated for mood disorders.

MOLECULAR REGULATION OF COMPONENTS OF THE HPA AXIS BY CLOCK PROTEINS

Epidemiological studies suggested that stressful life events play a role in the etiology of depression (17), and hypercortisolemia was observed in a subset of patients with depression [reviewed in Ref. (18)]. Furthermore, antidepressant treatment appeared to stabilize the function of the HPA axis *via* the serotonergic

system (19), suggesting an involvement of the HPA axis and glucocorticoids in mood regulation [reviewed in Ref. (20)].

Conditional mutagenesis in mice of the glucocorticoid receptor (GR) in the nervous system provided evidence for the importance of GR signaling in emotional behavior (21). Overexpression of GR lead to depressive-like behavior, and these mice showed enhanced sensitization to cocaine (22), consistent with observations that GR may be a potential target to reduce cocaine abuse (23). Interestingly, GR bound to NURR1 thereby increasing the transcriptional potential of NURR1 to induce TH (24) (Figure 1). Hence, the amount of nuclear GR appeared to be important for this function. Although glucocorticoids displayed circadian rhythmicity [reviewed in Ref. (25)], GR expression was constant over 24 h in the liver, which applies most likely to the brain as well. However, GR nuclear localization appeared to be gated by REV-ERB α in the liver with nuclear GR levels high at zeitgeber time 20 (activity period of mice) (26). If this would apply to the brain, REV-ERB α would gate binding of GR to NURR1 for induction of the *Th* promoter (Figure 2). As illustrated above, mood-related behavior and dopamine levels were changed in *Rev-erb α* ^{-/-} mice, and this may also involve GR, which regulates catechol-*O*-methyltransferase (26), an enzyme degrading the MAOA product 3,4-dihydroxyphenylacetic acid to homovanillic acid. Therefore, it is likely that the monoaminergic system and the glucocorticoid pathway are linked *via* GR.

The cryptochrome (CRY) proteins interact with GR in a ligand-dependent manner in mouse liver leading to rhythmic repression of GR activity (27). Additionally, the CRY proteins participate in glucocorticoid-dependent suppression of the HPA axis and the production of endogenous glucocorticoids (27). Mice

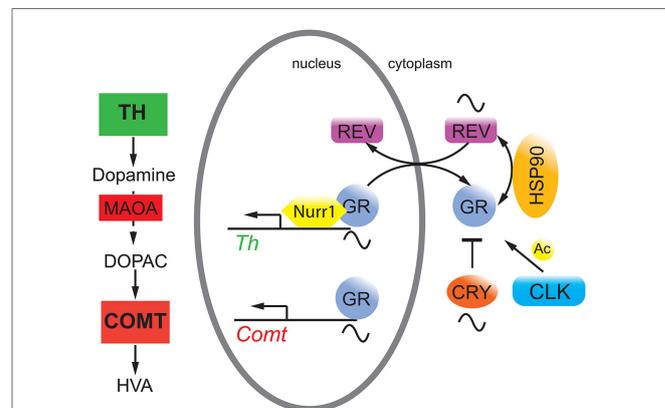


FIGURE 2 | Hypothetical model on the interaction of circadian clock proteins with the glucocorticoid receptor (GR). REV-ERB α (REV, purple) gates nuclear localization of the GR (gray) *via* an unknown mechanism probably involving heat shock protein 90 (HSP90, yellow). GR function is inhibited by cryptochrome (CRY, orange) proteins and is modulated by CLOCK (blue) *via* acetylation (Ac), although it is unclear whether this happens in the cytoplasm and/or the nucleus. GR regulates target genes such as catechol-*O*-methyltransferase (*Comt*) whose protein is an enzyme (COMT, red square) that degrades 3,4-dihydroxyphenylacetic acid (DOPAC) to homovanillic acid (HVA). GR may also interact with Nurr1 to modulate tyrosine hydroxylase (*Th*) expression thereby influencing dopamine production.

lacking *Cry1* showed depression-like behavior combined with reduced levels of dopamine in the striatum (28). This phenotype was most likely the result of the effects of CRY on both pathways illustrated in **Figures 1** and **2**. Furthermore, GR was acetylated by CLOCK, which lead to decreased sensitivity to glucocorticoids in the morning in humans and to an increased sensitivity at night when acetylation was reversed (29).

Recently, CHRONO, a protein that acts as a repressor in the circadian clock mechanism similar to CRY2 appeared to have the potential to interact with GR as well (30). Interestingly, *Chrono* mRNA was induced in the hypothalamus after stress stimulation whereas *Cry2* mRNA was not. This suggested that CHRONO may be a stress-inducible repressor of the circadian clock coupling the clock with the HPA axis (30). However, it is not known whether *Chrono* knock-out mice display alterations in mood-related behaviors.

TRANSCRIPTIONAL REGULATION OF NEUROGENESIS BY CLOCK PROTEINS

Adult neurogenesis is an important process to replace lost or dysfunctional neurons with new neurons produced from neuronal stem cells. Most of them are found in the subventricular zone lining the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus. Environmental stimuli, such as stress, physical activity, sleep deprivation, enriched living conditions, and jet-lag, can influence adult hippocampal neurogenesis in mammals (31–35). These environmental stimuli directly affect the circadian clock as well [reviewed in Ref. (36)], suggesting that the clock plays a mediator role between environmental change and neurogenesis. Animal studies showed that chronic stress and depression-inducing behavior reduced hippocampal neurogenesis while antidepressants enhanced it (37), suggesting a connection between neurogenesis and depressive behavior (38). Hence, change of the clock by environmental stimuli may affect neurogenesis, which in turn affects mood-related behaviors. Interestingly, neurogenesis varied over the day (39–42), and mutations in clock genes affected adult hippocampal neurogenesis (28, 43–46). The effect of the clock on this process was at least in part due to the control of the timing of cell-cycle entry and exit of quiescent neural progenitor cells (QNPCs) (47). For example, absence of *Per2* abolished the gating of cell-cycle entrance of QNPCs (43, 47), whereas lack of *Bmal1* resulted in constitutively high levels of proliferation and delayed cell-cycle exit (46, 47).

On the molecular level evidence of direct clock gene-mediated regulation of neurogenesis is scarce. The mechanism of

Clock- and *Bmal1*-mediated neuronal differentiation appeared to be associated with the neurogenic transcription factor NeuroD1 (48), although a direct regulation of its promoter by clock genes was not shown. In contrast, the regulation of fatty acid binding protein 7 (*Fabp7*), also termed brain lipid-binding protein, by the clock component REV-ERB α has been elucidated (44). FABP7 facilitates the solubility of long-chain fatty acids and is implicated in cell growth and differentiation (49). It affects neuronal differentiation (50) and is a marker for neuronal progenitor cells (51, 52). The promoter of the *Fabp7* gene was directly suppressed by REV-ERB α , and this suppression was relieved by ROR α , a positive competitor of REV-ERB α (**Figure 1**) (44). Mice lacking *Rev-erba* displayed increased levels of FABP7, which was associated with alterations in mood-related behaviors, changes in hippocampus-dependent cognitive performance, and increased hippocampal neurogenesis (44).

Taken together, this overview illustrates multiple levels of molecular mood regulation with REV-ERB α (and PER2 as REV-ERB α modulator) being involved in all of the processes described; regulation of the monoaminergic system, the HPA axis, and neurogenesis.

In the future, a better understanding of the hypothetical molecular processes illustrated in **Figure 2** will be of great importance, because it is unknown whether CRY and CLOCK affect GR function in the nucleus or the cytoplasm. This would distinguish whether the influence of these two clock components is directly on transcription or on modulation of GR protein stability and transport, which would influence GR-mediated transcription in an indirect manner. Furthermore, the posttranslational regulation of REV-ERB α is poorly understood with the exception of its residues S55/S59, which are phosphorylated by GSK3 β and may mediate cellular sensitivity to lithium (53). Time-of-day-dependent phosphorylation sites on REV-ERB α and GR (54) may contribute to the gated regulation of nuclear presence of these two receptors and hence on the regulation of metabolism and mood-related behaviors.

AUTHOR CONTRIBUTIONS

UA wrote the manuscript and prepared the figures.

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