Published in "Annals of Medicine, 2010
doi: 10.3109/07853891003677432"
which should be cited to refer to this work.

Circadian clocks in mood-related behaviors

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Abstract
The circadian clock organizes biochemical and physiological processes of an organism in a temporal fashion. This temporal organization is crucial to avoid interference of processes that have adverse effects on each other. Thus, disruption of temporal organization can lead to health problems and behavioral disorders related to mood alterations. To alleviate the consequences of a disrupted temporal organization in the body, it is of importance to understand the processes involved in the synchronization of all body clocks and their phase relationship to the environmental day/night cycle at the mechanistic level. This review will focus on internal and external factors affecting synchronization and function of the circadian system and highlight connections to mood-related behavior.

Key words: *Depression, dopamine, light therapy, lithium, SAD, stress, synchronization*

Introduction

Rotation of the earth around its own axis leads to periodic exposure of its surface to the sun causing day and night. Life-forms on this planet adapted to the rhythmic light/dark exposure that has a period of about 24 hours. Since this rhythm is predictable, it was beneficial for organisms to develop an internal timer in order to predict daily recurring events, such as appearance of a food source. Additionally, this internal clock enables organization of metabolism and the cell cycle according to the time of day to avoid incompatible biochemical reactions to run at the same time and to allocate such reactions to the time of day when they are needed most (e.g. energy production during the activity phase, repair mechanisms during the rest phase). In order to assure a stable phase relationship between the natural light/dark cycle and the internal timing system of organisms, their clocks need to be reset daily, because the earth's orbit around the sun causes periodic seasonal alterations of day-length leading to short winter days and long summer days. The strongest cue for the synchronization between natural daily cycles and the internal clock of animals and humans is light (reviewed in (1)). It is perceived by the retina, where specialized retinal ganglion cells (RGCs) containing melanopsin project directly via the retinohypothalamic tract (RHT) to the suprachiasmatic nuclei (SCN), the main co-ordinator of the mammalian circadian system located in the ventral part of the hypothalamus (Figure 1). The SCN project to various brain regions involved in hormone secretion (e.g. paraventricular nucleus), sleep regulation (ventrolateral preoptic nucleus), thermoregulation (median preoptic region), and feeding/reward (e.g. dorsomedial hypothalamus) (reviewed in (2)).

Light perceived by RGCs causes release of glutamate at the synapses of the RHT and leads to activation of signaling pathways that converge on the phosphorylation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB). Phospho-CREB homodimers bind to the promoters of the clock genes *Per1* and *Per2* thereby activating their expression (Figure 2). As a consequence behavioral activity rhythms in mice and humans are phase advanced or delayed, depending on the time of noc-

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Key messages

- The circadian clock organizes biochemistry and physiology on a 24-hour time-scale. When this order is chronically disrupted health problems including mood disorders may occur.
- Environmental factors influence the circadian system and might be causative for biochemical and physiological disorganization of the body.

Abbreviations

BMAL1	brain and muscle aryl hydrocarbon receptor nuclear translocator-like factor 1
CCG	clock-controlled gene
CK1	casein kinase 1
CLOCK	circadian locomotor output cycles kaput
CREB	cAMP response element-binding protein
CRY	cryptochrome
DSPS	delayed sleep phase syndrome
FASPS	familial advanced sleep phase syndrome
GSK3β	glycogen synthase kinase 3β
IPSRT	interpersonal and social rhythm therapy
MAOA	monoamine oxidase A
NPAS2	neuronal PAS domain protein 2
NPY	neuropeptide Y
PER	period homolog
PK2	prokineticin 2
RGC	retinal ganglion cell
RHT	retinohypothalamic tract
SAD	seasonal affective disorder
SCN	suprachiasmatic nuclei
SD	sleep deprivation
VIP	vasoactive intestinal peptide
VTA	ventral tegmental area

turnal light exposure. At the molecular level the autoregulatory feedback loop mechanism of the clock is altered in its phase, most probably because the *Per* genes are induced by light in the SCN (3,4). PER (period homolog) and CRY (cryptochrome) proteins heterodimerize in the cytoplasm and enter the nucleus to inhibit the activation potential of the heterodimeric complex composed of BMAL1/CLOCK (brain and muscle aryl hydrocarbon receptor nuclear translocator-like factor 1/circadian locomotor output cycles kaput) (or BMAL1/NPAS2 (neuronal Per-Arnt-Sim [PAS] domain protein 2) in brain tissue) (Figure 2, reviewed in (5)). Otherwise this complex would activate transcription via binding to E-box elements present in the promoters of clock genes such as *Per*, *Cry*, *Dec*, and *Rev-erbα* or clock-controlled genes (CCGs) such as monoamine oxidase A (MAOA) (6). PER and CRY proteins inhibit their own transcription via the aforementioned inhibition of the BMAL1/CLOCK complex thereby establishing an autoregulatory feedback loop. REV-ERBα protein represses the transcription of BMAL1 thereby linking the PER/CRY feedback loop with BMAL1 expression (7). The half-life of these clock proteins is an important factor affecting the length of one feedback loop cycle. Casein kinase 1 ε/δ (CK1ε/δ) phosphorylates the PER proteins thereby targeting them for degradation by the 26S proteasome (8,9). *In vitro* studies suggest that the β-TrCP1 and FBXL3 E3 ubiquitin ligase complexes directly target PER (10,11) and CRY (12,13) proteins, respectively, for this degradation. Furthermore, SIRT1, an NAD^+-dependent deacetylase involved in transcriptional silencing, genome stability, and longevity (14), deacetylates PER2 which leads to its degradation (Figure 1) (15).

In mammals, daily rhythms can be observed in body temperature, the sleep/wake cycle, hormone levels, cognition, attention, and mood (16). The cycling of these physiological markers has a stable phase relationship with the natural light/dark cycle. A disruption of this stable phase relationship by external factors such as rotating shift-work may lead to health problems (e.g. obesity and mood disorders). Hence life-style is an important factor in the manifestation of mood disorders. However, some people are more prone than others to develop such disorders, indicating involvement of genetic (internal) factors. In addition to genes involved in metabolism and/or the cell cycle, alterations in clock genes and their promoters appear to predispose humans to development of mood disorders. This review will focus on the internal and external factors affecting synchronization and function of the circadian system and highlight connections to mood related behaviors.

External factors

Predictable events—light/dark cycle and sleep

Light is the most powerful synchronizer of the mammalian circadian system (see Introduction). It causes expression of PER genes in the SCN and a few peripheral oscillators like the pineal and adrenal glands (3,17–19) (Figure 1). From these relays other tissue clocks are co-ordinated via hormonal secretion, the autonomous nervous system, and indirectly

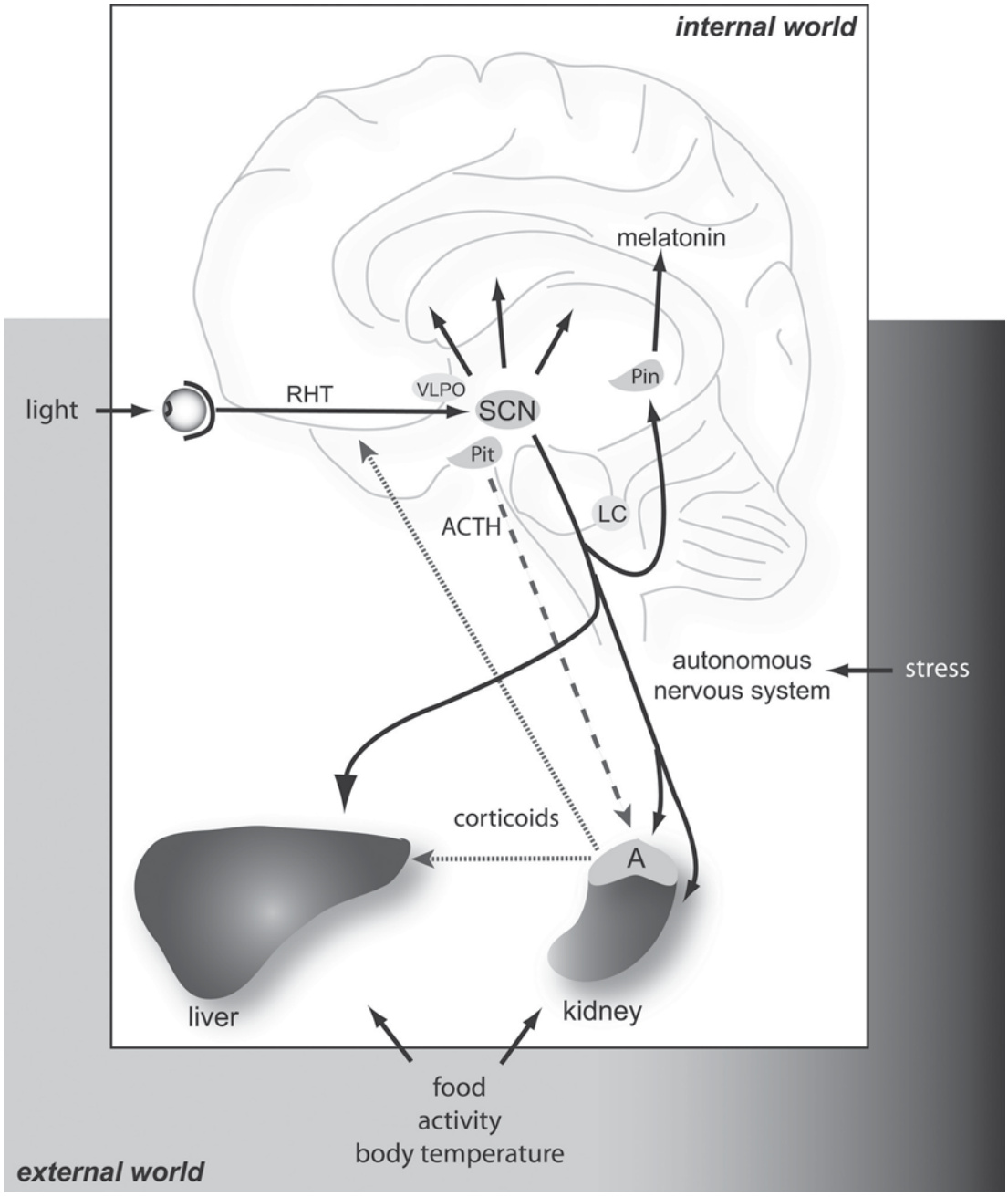

Figure 1. Pathways to synchronize the circadian system. The network of circadian clocks present in all cells and tissues is synchronized with external time via neuronal and humoral pathways. A light signal perceived by the retina is mediated via the retinohypothalamic tract (RHT) to the suprachiasmatic nuclei (SCN) and affects clock gene expression. From the SCN the sleep (ventrolateral preoptic nucleus (VLPO)) and arousal centers (locus coeruleus (LC)), endocrine tissues such as the pituitary (Pit) and the adrenal, and other peripheral tissues such as the kidneys and liver are synchronized via the autonomous nervous system. Rhythmically released hormones, ACTH from the pituitary (Pit), melatonin from the pineal (Pin), and corticoids from the adrenal (A), further contribute to the synchronization of the circadian system. Additionally, other external factors such as food, stress, and systemic cues affect the circadian system.

via the regulation of the rest/activity cycle and with it body temperature and metabolic activity (20,21) (Figure 1). Due to these consequences of light on physiology and behavior, irregular light exposure, as experienced in shift-work and jet lag, has strong implications on physiology and behavior which manifest as health problems such as cardiovascular disease, cancer, and mood disorders (22). Therefore, regular periodic exposure to light appears to be beneficial for health, because it synchronizes the circadian system to maintain biochemical and physiological order in the body. Interestingly, light therapy has been successfully used to treat mood disorders. This is especially true for seasonal affective disorder

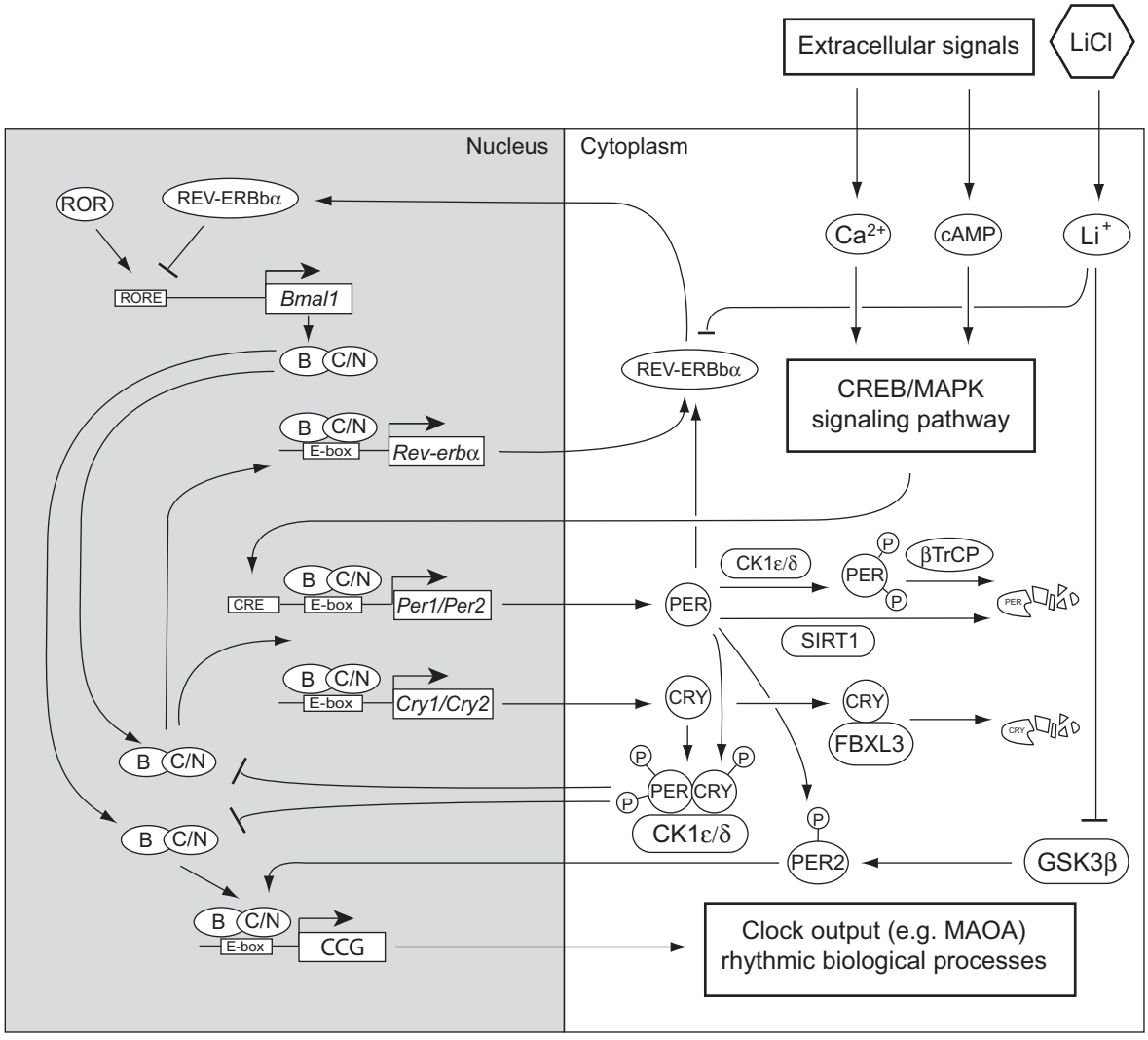

Figure 2. Transcriptional–translational feedback network constituting the mammalian circadian clock. A primary negative feedback loop involves the genes *Clock* (protein abbreviated with C) and its paralog neuronal PAS domain protein 2, *Npas2* (protein abbreviated with N), *Bmal1*, the period homologs *Per1*, *Per2*, and the cryptochromes *Cry1*, *Cry2*. The secondary feedback loop is composed of *Rev-erbα* and retinoic acid receptor related orphan receptor (ROR) whose gene products bind ROR response elements (ROREs) in the *Bmal1* promoter and repress or activate this gene, respectively. In addition to transcriptional activators and repressors, post-translational modification and degradation of circadian clock proteins are crucial steps for determining circadian periodicity. Key kinases for PER and CRY phosphorylation are casein kinase 1 ε (CK1ε) and CK1δ. Phosphorylation of PER and CRY proteins leads to facilitated nuclear transport or alternatively targets them for polyubiquitination and degradation by the 26S proteasomal pathway involving the β-TrCP1 and FBXL3 E3 ubiquitin ligase complexes. The output of this clock mechanism is the transcriptional regulation of clock-controlled genes (CCG) that mediate rhythmic biological processes. The autoregulatory feedback loop mechanism of the circadian clock can be adjusted to external events via activation of the CREB/MAPK (mitogen-activated protein kinase) signaling pathway that impinges on *Per* gene regulation. Pharmacological agents such as lithium ions (Li^+) can modulate clock protein stability and modulate the circadian cycle and associated biological processes.

(SAD) (23), also known as winter depression. SAD is a mood disorder in which people have normal mental health throughout most of the year, but experience depressive symptoms in winter or, less frequently, in other seasons, repeatedly, year after year. SAD is more prevalent in countries of higher latitude (e.g. Scandinavia, Canada) correlating with the extremely shortened daily light period during the winter season. SAD can be successfully treated in some cases with melatonin or by exposure to bright light; especially early morning light appears to be effective resulting in a phase advance of behavioral and endocrine rhythms (24,25).

Light therapy is more and more frequently used in non-seasonal depression and bipolar disorder (26–28), either exclusively or in combination with other conventional treatments. A few data exist on the efficacy of light exposure on schizophrenic patients. For example, irregular natural light exposure correlates with disease severity (29), and light treatment, especially in the blue wavelength range that activates melanopsin-containing RGCs (see Introduction),

can re-establish normal endocrine function in schizophrenic patients (30). This is probably due to direct regulation of the SCN, which transmits the light signal to activate the adrenals (18) (Figure 1). Corticosteroids from the adrenal have a strong feedback effect on neurophysiological functions in the central nervous system (CNS) (31). However, the molecular mechanisms through which light causes the alleviating effects on mood disorders are not understood.

Recent findings indicate that light-mediated signaling involving the clock gene *Per2* affects synaptic efficiency in mice by regulating the presence of vesicular glutamate transporter 1 on a defined vesicular pool (32,33). The light-regulated membrane traffic of neurotransmitter transporters may allow the presynaptic terminals to replenish during physiological rest periods and to avoid prolonged or repeated periods of enhanced stimulation. This is probably one of several reasons why mice bearing a mutation in the *Per2* gene show alterations in mood-related behaviors (6,34,35). Proteomic analysis revealed that synaptic vesicle cycling itself is probably important for sustaining the circadian clock in the SCN (36). This is supported by the finding that mice with a mutation in the GTPase Rab3, a regulator of synaptic vesicle transport and Ca^{2+}-triggered vesicle release probability, accelerates the clock by about 2 hours (37). Taken together synaptic vesicles appear to play an important role in light-mediated effects on the circadian clock and its neurophysiological outputs.

Mood disorders are strongly associated with sleep disturbance (38–41). Sleep is regulated by two different mechanisms, a homeostatic one that accumulates the need for sleep depending on the time spent awake (like an hour-glass counter), and a rhythmic one controlled by the circadian clock in the SCN that under normal conditions confines sleep to the night in humans (or day in nocturnal animals like mice) (42). Therefore, it is reasonable to assume that the circadian clock, the sleep/wake cycle, and the interaction between the two may play a role in the pathophysiology of mood disorders. In support of this view is the finding that sleep deprivation (SD) can have antidepressant effects and, in susceptible patients, precipitate mania (43). Hence it appears that sleep/wake disruption can play a causal role in mood disorders. If the protocol for SD is stopped, relapse of depressive symptoms is observed. SD serves as a strong external signal, which might lead to synchronization of various oscillators. If SD is not maintained, gradually desynchronization of various, weakly coupled oscillators in different brain regions can occur, ultimately contributing to depressive symptoms. At the cellular level temporal synchronization of the circadian clock in fibroblasts is achieved *in vitro* by a serum shock or the glucocorticoid analog dexamethasone (44,45). Omission of these external signals for the cell culture leads to a gradual desynchronization of the circadian clocks in the individual cells. Similar to a serum shock inducing synchronized rhythmic clock gene expression in fibroblasts, SD can temporally stabilize rhythmic cortisol release from the adrenal in depressive patients but has no effect in the control group (46). However, it is not clear whether SD directly acts on the clock mechanism as a synchronizing signal. Metabolism and/or the cell cycle, which both are intimately linked to the clock (Figure 3), might be affected by SD. Hence, SD would act on mood either via modulation of the circadian clock and/or via metabolism and the cell cycle.

Unpredictable events—social and non-social stress

The circadian clock's function is to maintain a stable phase relationship between endogenous rhythms

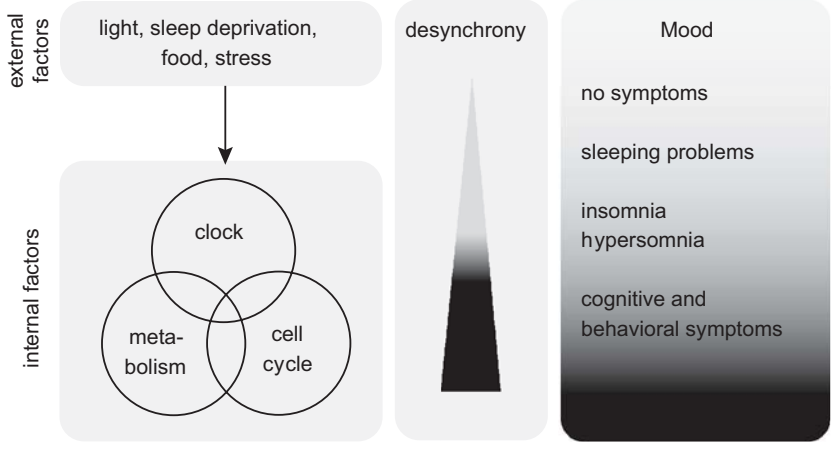

Figure 3. Model illustrating the relationship between internal/external factors and mood status according to the degree of desynchronization between the internal and external worlds.

and the predictable light/dark cycle and is an adaptation to predictable aspects of the environment (see Introduction). However, the stress system that acts on the autonomous nervous system is an adaptation to unpredictable aspects of the environment (47). Experiments in rodents illustrate that social as well as non-social stress alter the shape and amplitude of a circadian rhythm but do not perturb the central oscillator in the SCN. In line with these findings are experiments showing that manipulation of the main neuroendocrine components of the stress system does not have any major effect on the circadian clock (reviewed in (48)). However, circadian rhythms at the output level are strongly affected by stress. For example, the synthetic glucocorticoid dexamethasone alters rhythmic gene expression in cell cultures from liver, kidney, and heart tissue, even though it does not affect gene expression in neurons of the SCN (45). However, *in vivo* glucocorticoid treatment does not have a strong effect on free-running temperature and activity rhythms (49,50), but it cannot be excluded that glucocorticoids affect other rhythms that are under partial control of sub-oscillators. It may also be that such sub-oscillators in peripheral tissues are affected by stress factors other than glucocorticoids. It may be speculated that certain stress factors affect oscillators in peripheral tissues such as the liver and kidney (Figure 1), temporarily disturbing their control by the central pace-maker clock in the SCN, which may then be partly responsible for disturbed overt rhythms seen, for instance, after social defeat stress. Chronic stress might lead to a permanent desynchronization of the light-sensitive pace-maker in the SCN and the clocks in peripheral tissues, rendering the organism susceptible to the development of diseases affecting mood.

Stress-mediated desynchronization of peripheral clocks in patients with bipolar disorder can be successfully treated with interpersonal and social rhythm therapy (IPSRT) along with pharmacological treatment (reviewed in (51)). This therapy helps patients to see how psycho-social stressors and social role transitions can disrupt the daily routines that are important to maintain the circadian integrity of the body. Hence, IPSRT reduces stress influence via the autonomic nervous system and reinforces daily routine. As a result peripheral clocks are probably aligned with the day/night cycle and the central clock in the SCN, increasing biochemical and physiological order in the entire organism.

The 24-hour society, as we know it today, is strongly influenced by the aberrant occurrence of the external parameters light, sleep deprivation, and stress. Due to the constant access to electricity and hence artificial light, the activity of individuals has gradually shifted into the night period that naturally would be used for rest and sleep (52). The consequence is accumulation of a sleep deficit, forcing people to sleep at unusual times. This may lead to deprivation of naturally occurring external signals, further enhancing desynchronization between the organism and nature. The result is a 'social jet lag'. Since natural external signals still can influence the desynchronized organism, at certain times a permanent adaptation is the consequence, with the organism permanently trying to align the internal and external worlds. The constant access to light also affects interpersonal relationships and social roles due to work and stress at unusual times, which leads to a desynchronization of peripheral clocks. Primed by such desynchronization the organism becomes hypersensitive to stressful life events, such as death of a beloved person or other traumatic incidents, triggering development of mood disorders (53). Hence, several incidents accumulate and together increase the amount of desynchrony ultimately affecting the degree of a mood disorder (Figure 3) (54).

Internal factors—clock components impinging on mood

Neurological and behavioral phenotypes of clock gene mutations in rodents

Given the fact that clock genes are expressed in various brain areas with different phases (55), an impact of clock genes on brain function can be expected. Deficits in brain function could be due to a disturbance in SCN oscillator function or hampered oscillator function in discrete brain areas; alternatively, they might be a secondary consequence of neuronal dysfunction.

Mutations in the genes *Clock*, *Bmal1*, *Cry1*, and *Cry2* result in altered sleep time, sleep fragmentation, and atypical responses after sleep deprivation in mice (56–58). Elements of sleep homeostasis are also affected in mice mutant in a number of other clock-related genes including *Npas2*, *Dec2*, *Dbp*, and *Pk2* (59–62). However, evidence exists for a functional segregation of circadian and homeostatic parameters of sleep, because mutations in *Per1* and *Per2* cause no effects on the sleep homeostatic mechanism, although robust rhythms of sleep and wakefulness are affected under constant conditions (63,64). Taken together, these data indicate that clock genes have an effect on allocation of sleep time; however, only a subset of clock genes appears to affect the homeostat. This is probably due to indirect effects of clock genes on metabolism and neuronal function.

As already discussed above, a desynchronized circadian system affects emotional behavior. Mice mutant in the gene *Clock* expressing a dominant negative version of the CLOCK protein exhibit a spectrum of behavioral abnormalities, including low anxiety, mania, and hyperactivity (65,66). Furthermore, deregulation of important neurotransmitters such as neuropeptide Y (NPY) or vasoactive intestinal peptide (VIP), which are involved in signaling to and within the SCN, leads to alterations in anxiety-like behavior and aggression (67–69). Lithium, a mood-stabilizing agent, can reverse behavioral disturbances observed in *Clock*-mutant mice (66), indicating that the therapeutic effects of lithium may be partly mediated via the circadian system. This hypothesis is bolstered by the finding that lithium is a potent inhibitor of glycogen synthase kinase 3β (GSK3β), a kinase that influences the nuclear expression and stability of a number of transcription factors and circadian clock proteins including REV-ERBα and PER2 (70–72) (Figure 2). However, it is unclear whether the lithium doses used for therapeutic treatment in humans are sufficient to inhibit human GSK3β. In mice, the clock proteins BMAL1, NPAS2, and PER2 regulate the expression levels and activity of monoamine oxidase A (MAOA), an enzyme important in the degradation of dopamine (and other catecholamines) (6). In this mechanism PER2 acts as a co-activator and modulates dopamine levels in the mesolimbic dopaminergic system. This has an impact on mood-related behavior in mice, leading to the conclusion that the clock can influence mood. In support of this view is that SAD in humans correlates with the frequency of specific single-nucleotide polymorphisms in *BMAL1*, *NPAS2*, and *PER2* (73). Based on the finding that the circadian clock regulates dopamine metabolism and in view of the fact that PER2 interacts with GSK3β (70), it was proposed that PER2 phosphorylation by GSK3β favors accumulation of PER2 in the nucleus where it enhances the NPAS2:BMAL1-mediated transcription of monoamine oxidase A (*Maoa*) (74). As a consequence more MAOA enzyme would be generated and translocated to the inner mitochondrial membrane. There, MAOA degrades dopamine, producing 3,4-dihydroxyacetaldehyde, peroxide, and ammonia. Increased levels of PER2 might therefore lead to less dopamine and a more depressed mood state (75,76). The mood stabilizer lithium inhibits the action of GSK3β, and less PER2 would be phosphorylated (70). As a consequence, PER2 would become less abundant in the nucleus, which would lead to less MAOA production. Consequently, dopamine would rise and improve mood status. This might be a potential mechanism explaining the beneficial effects of lithium on mood. In line with the notion that clock genes influence mood through modulation of dopamine are the observations that *Clock*-mutant mice display an increase in dopaminergic activity in the ventral tegmental area (VTA) and that restoration of *Clock* expression in the VTA rescues some of the mood-related behavioral abnormalities (66,77). Of note is, however, that more dopamine (or dopaminergic activity) does not always correlate with an improvement of mood status. Mice that have been subjected to a chronic social defeat paradigm, which leads to a strong depression-like state, show an increase in dopaminergic activity in the VTA, while mice resistant to this paradigm display no change (78).

An alternative to lithium in treating depression is bright light therapy (see above), which has been successfully used for recurrent winter depression or SAD (23). Clock genes, especially *Per1* and *Per2*, are inducible by light in the SCN (4). However, it is not known how this might relate to the relief of depressive episodes. One possibility is that light affects the habenula, which receives direct light input from the retina (79). The clock genes *Per1* and *Per2* in the habenula might be induced by light leading to alterations in the function of the mesolimbic dopaminergic system, thought to be modulated by this brain region (80). Interestingly, a recent study in *Drosophila* shows that dopamine plays an important role in circadian entrainment reinforcing a connection between light signaling to the clock and dopamine (81).

Polymorphisms in genes of the circadian clock and mood disorders in humans

In many CNS disorders, disturbance of circadian rhythms and sleep is part of the clinical characterization of the disease. Such clock and sleep disruptions are probably secondary to compromised neuronal circuitry when brain regions regulating output rhythms are affected. In any case, it is difficult to dissect whether disruptions in the circadian clock are a cause or a consequence of CNS disorders. However, it is very likely that disruption of circadian oscillators can at least modify disease severity and that, in some cases, it might play a more primary role in disease etiology.

Mice mutant in clock genes often display alterations in the period length of the circadian rhythm leading to alterations in sleep onset. Therefore, one would predict that also in the human population such alterations in period length would be associated with sleep onset caused by variants of genes involved in the circadian clock mechanism. So far, the best understood familial syndrome hinting at a direct involvement of the circadian clock in early sleep

onset is the familial advanced sleep phase syndrome (FASPS). This disorder is characterized by very early sleep on- and offset. Affected individuals show a profound phase advance of melatonin and temperature rhythms associated with a very short period length and variable degrees of depression (82). Since the trait segregates in an autosomal dominant manner with high penetrance, the genes affected in such families could be identified. In one family, the casein kinase 1 ε (CK1ε) binding site in the gene product of *PER2* was mutated, which causes hypophosphorylation of the PER2 protein (83). A missense mutation in *CK1δ* that decreases the enzymatic activity of CK1δ also leads to hypophosphorylation of PER2 (Figure 2) and FASPS (84).

To identify associations between the circadian clock and human disease, clock gene polymorphisms were studied in patients and healthy people. A polymorphism in the *Clock* gene did associate with delayed sleep phase syndrome (DSPS) (85). A silent polymorphism in the *PER1* gene did associate with extreme diurnal preference (86), as did a structural polymorphism in the *PER3* gene (87). A shorter 4-repeat allele of a 54-base-pair coding-region polymorphism in *PER3* appears to be associated with DSPS (88), and this polymorphism predicts sleep structure and waking performance (89). Interestingly, polymorphisms in various clock genes do not only affect sleep-associated phenotypes. A single nucleotide polymorphism in *CLOCK* appears to bias neural correlates of moral valence decision in depressed patients (90), and other genetic variants of this gene are associated with individual susceptibility to obesity (91). The *NPAS2* gene has been associated with seasonal affective disorder (92) as well as the genes *BMAL1* and *PER2* (73). Furthermore, *BMAL1* variants appear to be associated with susceptibility to hypertension and type 2 diabetes (93), and *PER2* variation is associated with depression vulnerability (94). There is also evidence that single nucleotide polymorphisms in retinoic acid receptor-related orphan receptor (ROR) beta are associated with bipolar disorder (95). For *CRY1*, an involvement in schizophrenia has been suggested, because it is close to a linkage hot spot of this disease and interacts with antipsychotic drugs and the dopamine system (96). However, *CRY1* appears not to be involved in bipolar disorder (97).

The association of clock gene polymorphisms with mood disorders strongly suggests that clock genes may be important candidates in the search for the molecular basis of mood disorders. In the future, systematic studies in both humans and animals will uncover the contribution of clock gene variants to the onset and severity of mood disorders.

Conclusions

The influence of external (light, SD, stress) and internal factors (genetic alterations) on mood-related behaviors has been extensively studied. The interplay between external and internal factors and their concerted action in relation to mood is, however, poorly understood. Therefore, future studies need to aim at the elucidation of mechanisms that connect the effects of external factors on internal mechanisms to understand, for example, how light or lithium therapy is beneficial for certain mood disorders at the mechanistic level. These studies will have the potential to suggest novel therapeutic approaches, both pharmacological and non-pharmacological. This provides one of the best opportunities in psychiatry today for translational, bench-to-bedside research.

Acknowledgements

The author wishes to thank I. Schmutz and Dr J. Ripperger for critical reading of the manuscript. Support for the author's laboratory by the Swiss National Science Foundation, the 6th EU research program EUCLOCK and the State of Fribourg is acknowledged.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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