Circadian Clocks and Mood-Related Behaviors

Urs Albrecht

Abstract Circadian clocks are present in nearly all tissues of an organism, including the brain. The brain is not only the site of the master coordinator of circadian rhythms located in the suprachiasmatic nuclei (SCN) but also contains SCN-independent oscillators that regulate various functions such as feeding and mood-related behavior. Understanding how clocks receive and integrate environmental information and in turn control physiology under normal conditions is of importance because chronic disturbance of circadian rhythmicity can lead to serious health problems. Genetic modifications leading to disruption of normal circadian gene functions have been linked to a variety of psychiatric conditions including depression, seasonal affective disorder, eating disorders, alcohol dependence, and addiction. It appears that clock genes play an important role in limbic regions of the brain and influence the development of drug addiction. Furthermore, analyses of clock gene polymorphisms in diseases of the central nervous system (CNS) suggest a direct or indirect influence of circadian clock genes on brain function. In this chapter, I will present evidence for a circadian basis of mood disorders and then discuss the involvement of clock genes in such disorders. The relationship between metabolism and mood disorders is highlighted followed by a discussion of how mood disorders may be treated by changing the circadian cycle.

Keywords Depression • Obesity • Light • Drugs

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1 Evidence for a Circadian Basis of Mood Disorders

Patients with depressive disorders appear to display abnormal circadian rhythmicity in a variety of body functions such as body temperature, plasma cortisol, noradrenaline, thyroid-stimulating hormone, blood pressure, and melatonin rhythms (Atkinson et al. 1975; Kripke et al. 1978; Souetre et al. 1989). Interestingly, treatment of patients with antidepressants or mood stabilizers normalizes these hampered rhythms. Furthermore, genetic alterations in casein kinases (Shirayama et al. 2003; Xu et al. 2005) modulating the circadian clock mechanism as well as polymorphisms found in clock genes have been found to associate with sleep disorders and depressive behavior [for a comprehensive list, see Kennaway (2010)]. However, most of these polymorphisms were not located in the coding region of clock genes.

Interestingly, nearly all individuals that suffer from mood disorders benefit from strict daily routines including strictly followed bedtime and rise in the morning (Frank et al. 2000). These routines probably help to maintain the circadian integrity of the body (Hlastala and Frank 2006). The effect of having a clock that is out of sync with the environment is evident to anyone who has experienced jet lag after traveling (Herxheimer 2005). Such changes in timing can cause in some individuals depressive or manic episodes. This has also been observed in shift workers where some individuals will develop mood disorders over time (Scott 2000). Recent work shows that a relationship between severity of bipolar depression and circadian misalignment is likely to exist (Emens et al. 2009; Hasler et al. 2010). Hence, the inability to properly adapt to environmental change appears to contribute to the development of mood disorders such as depression.

One of the most common disorders due to improper adaptation to changes in the environment is seasonal affective disorder (SAD). It is characterized by depressive symptoms that occur only during the winter months (Magnusson and Boivin 2003). It is hypothesized that melatonin, a circadian hormone secreted by the pineal gland, is involved in the development of SAD (Pandi-Perumal et al. 2006). Although it is clear that melatonin participates in the regulation of sleep and can be suppressed by light, it is still controversial whether a link between melatonin rhythms and SAD exists. Another equally controversial hypothesis to explain SAD is the circadian phase shift hypothesis, which is based on the observation that application of early morning bright light is effective in treating SAD (Lewy et al. 1998; Terman and Terman 2005) probably due to phase advancing the circadian system putting it back in sync with the sleep/wake cycle.

The mechanism underlying the association between circadian rhythms and mood disorders is unknown. It is conceivable, however, that molecular clock components may affect the expression of neurotransmitters and their receptors. It is of note that some of the major neurotransmitters, such as serotonin, noradrenaline, and dopamine, display a circadian rhythm in their levels (Weiner et al. 1992; Castaneda et al. 2004; Weber et al. 2004; Hampp et al. 2008). Also circadian rhythms in the expression and activity of several of the receptors for neurotransmitters have been

observed, suggesting that the entire circuits may be under circadian clock control (Kafka et al. 1983; Coon et al. 1997; Akhisaroglu et al. 2005). Therefore, it seems likely that disruption of the normal rhythms in neurotransmitter circuits may affect mood and mood-related behavior. How the clock modulates these circuits is still uncertain but emerging (Hampp et al. 2008).

2 Circadian Clock Genes and Mood Disorders

Studies in humans have begun to identify polymorphisms in certain circadian clock genes that associate with mood disorders. The T3111C SNP of the *CLOCK* gene associates with a higher recurrence rate of bipolar depression (Benedetti et al. 2003), and it associates with greater insomnia and decreased need for sleep in bipolar patients (Serretti et al. 2003). Two other members of the molecular clock, *BMAL1* and *PER3*, have been implicated in bipolar depression (Nievergelt et al. 2006; Benedetti et al. 2008). Recent studies suggest that SNPs of *PER2*, *NPAS2*, and *BMAL1* are associated with an increased risk for SAD (Partonen et al. 2007) and *Cry2* may be associated with depression (Lavebratt et al. 2010). All these clock genes appear to be associated with bipolar disorders (BD) and lithium response (McCarthy et al. 2012). Interestingly, associations of clock gene polymorphisms have been made with other psychiatric disorders such as schizophrenia and alcoholism, suggesting that clock genes are important in a range of psychiatric conditions (Spanagel et al. 2005; Mansour et al. 2006).

Animal studies support the role of circadian clock genes in mood regulation. Clock genes are expressed in many brain areas of the rewards system, which contributes to mood regulation. These areas include the ventral tegmental area (VTA), prefrontal cortex (PFC), amygdala (AMY), and the nucleus accumbens (NAc) (Fig. 1).

In these brain structures, 24-h oscillations of clock gene expression are not necessarily in the same phase but retain a specific phase relationship to one another [reviewed in Guilding and Piggins (2007)]. Mice carrying a mutation in the *Clock* gene [*Clock*Δ19 (Vitaterna et al. 1994; King et al. 1997)] display a behavior similar to human mania, and when treated with lithium, the majority of their behavioral responses are normalized toward those of wild-type mice (Roybal et al. 2007). Interestingly, transgenic mice overexpressing GSK3β show similarities to the phenotype of *Clock* mutant mice; they are hyperactive and have reduced immobility in the forced swim test (Prickaerts et al. 2006). This indicates that lithium, which inhibits GSK3β activity, acts at least partially via this kinase in *Clock* mutant mice normalizing their behavior. Reduced mobility in the forced swim test has also been observed in *Per2* mutant mice [$Per2^{Brdm1}$ (Zheng et al. 1999)], which is accompanied by elevated dopamine levels in the NAc (Hampp et al. 2008). Taken together, these findings may suggest that various mutations in circadian clock genes result in a similar manic phenotype. However, $Per1^{Brdm1}$ and $Per2^{Brdm1}$ mutant mice are not hyperactive like *Clock*Δ19 mice. $Per1^{Brdm1}$ mutant mice show

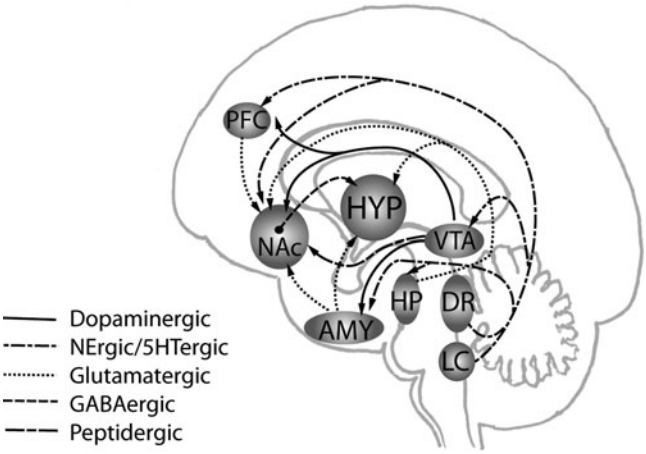

Fig. 1 Brain regions involved in mood regulation. Besides the hippocampus (HP) and the prefrontal cortex (PFC), several subcortical structures are involved in reward, fear, and motivation. These include the nucleus accumbens (NAc), amygdala (AMY), and hypothalamus (HYP). The figure shows only a subset of the many known interconnections between these various brain regions. The ventral tegmental area (VTA) provides dopaminergic input to the NAc, AMY, and PFC. *DR* dorsal raphe nuclei, *GABA* gamma-aminobutyric acid, *LC* locus coeruleus, *NE* norepinephrine, *5HT* serotonin

opposite responses to conditioned cocaine preference compared to *Clock*Δ19 and *Per2*^{Brdm1} mutant mice (Hampp et al. 2008; Abarca et al. 2002), and they show no elevated alcohol preference compared to *Per2*^{Brdm1} mutants (Spanagel et al. 2005; Zghoul et al. 2007). However, in response to social defeat, *Per1*^{Brdm1} mutants increase alcohol consumption (Dong et al. 2011) indicating that the *Per1* gene is a nodal point in gene x environment interactions. A recent study also indicates that a *Per3* promoter polymorphism is associated with alcohol and stress response (Wang et al. 2012). Overall it seems that individual members of the circadian clock mechanism may have separate functions in regulating mood- and reward-related behaviors. These functions may be residing outside the central SCN pacemaker in specific brain structures (e.g., VTA, AMY, or NAc) or in peripheral clocks (e.g., liver, gut).

In this context, it is of interest to note that *Clock* is expressed in peripheral tissues (although low expression is observed in certain brain areas) in contrast to *Npas2*, a *Clock* homologue, which is strongly expressed in the brain (see Allen Brain Atlas, http://www.brain-map.org/). Accordingly, only peripheral circadian clocks require *Clock* (DeBruyne et al. 2007a), whereas in the SCN, *Npas2* can replace *Clock* function (DeBruyne et al. 2007b). Therefore, phenotypes observed in *Clock* mutant mice may also include effects derived from lack of this gene in peripheral tissues (see below section on Metabolism).

Dopamine, an important neurotransmitter in the reward system, displays daily rhythms in its levels in the NAc (Hampp et al. 2008; Hood et al. 2010) suggesting

that the entire reward circuit may be under circadian clock influence. Consistent with this view are the observations that proteins involved in dopamine metabolism and transmission display diurnal rhythms in their expression, including tyrosine hydroxylase (TH) (McClung et al. 2005), a rate-limiting enzyme in dopamine synthesis; monoamine oxidase A (MAOA) (Hampp et al. 2008), a rate-limiting enzyme in dopamine degradation; and dopamine receptors (Hampp et al. 2008; McClung et al. 2005). When *Clock* gene expression is knocked down in the VTA, which projects to the NAc via dopaminergic neurons, an increase in dopaminergic activity is observed (Mukherjee et al. 2010). This increased dopaminergic tone results in changes in dopamine receptor (DR) levels with both D1 and D2 type of DRs augmented (Spencer et al. 2012). Interestingly, a shift of the ratio of D1:D2 receptors in favor of D2 receptor signaling was observed leading to alterations in locomotor responses to D1- and D2-specific agonists (Spencer et al. 2012). In $Per2^{Brdm1}$ mutant mice, the dopamine levels in the NAc are elevated as evidenced by microdialysis (Hampp et al. 2008). This is associated with a decrease in MAOA activity in the VTA and NAc. Interestingly, the *Maoa* gene is directly regulated by BMAL1, NPAS2, and PER2, and hence, *Maoa* is a clock-controlled gene (CCG, Fig. 2). This directly links the clock with dopamine metabolism (Hampp et al. 2008). Of note is that SNPs for *BMAL1*, *NPAS2*, and *PER2* are associated with an increased risk for SAD in humans (Partonen et al. 2007) establishing a parallel between the findings in mouse and humans.

The behavioral phenotypes observed in $Per2^{Brdm1}$ mutant mice are probably only partially due to elevated dopamine levels, because these animals also show abnormally high glutamate levels in the striatum (Spanagel et al. 2005). Therefore the balance between dopaminergic and glutamatergic signaling in the striatum of these mice appears to be deregulated. This may lead to abnormal neural phase signaling, which is a putative coding mechanism through which the brain ties the activity of neurons across distributed brain areas to generate thoughts, percepts, and behaviors (Lisman and Buzsaki 2008). In *Clock*Δ19 mutant mice, this phase signaling seems to be disturbed and is accompanied by abnormal dendritic morphology and a reduction in the levels of glutamate receptor subunit GluR1 (Dzirasa et al. 2010). Mice lacking GluR1 show behaviors related to mood disorders and respond positively to lithium (Fitzgerald et al. 2010). These observations support the notion that alterations in the balance between dopaminergic and glutamatergic signaling are probably important in the regulation of mood state and that this may involve circadian clock components. However, research linking clock genes and mood disorders is still in the early stages, and more investigations are needed to understand how the circadian clock mechanism impinges on mood regulation and thus affects depression including major depression, bipolar disorder, and seasonal affective disorder.

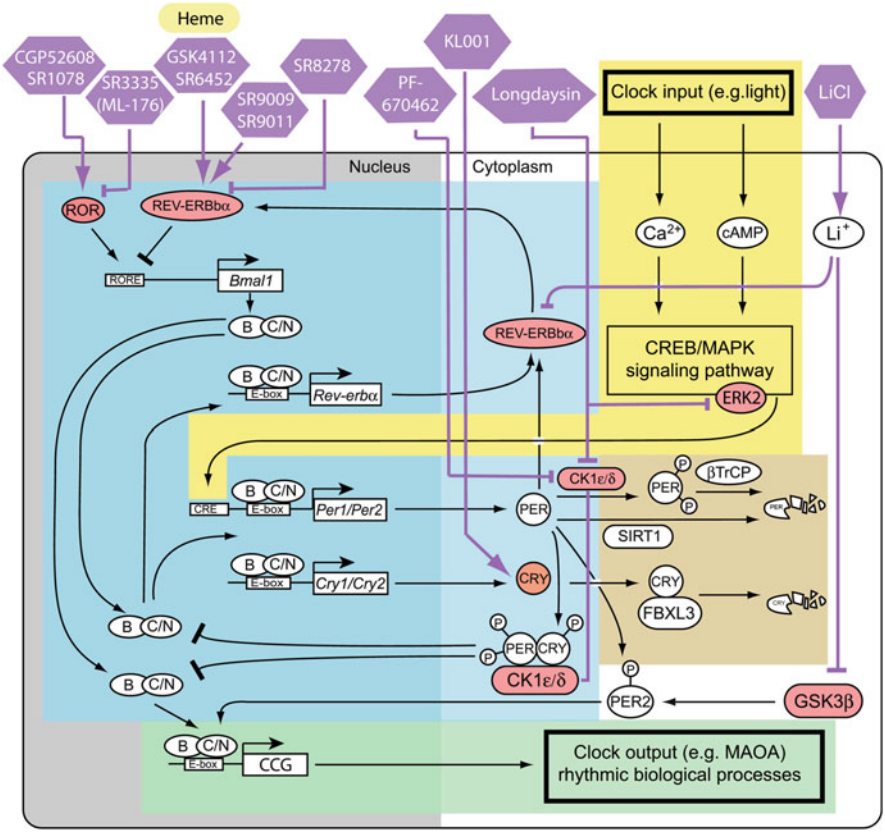

Fig. 2 Schematic representation of the mammalian circadian clock mechanism in a cell. The *blue* area depicts the autoregulatory transcriptional translational feedback loop. The transcription factors BMAL1 (B) and CLOCK (C) or NPAS2 (N) form a heterodimer which binds to E-box elements in the promoters of *Per1*/*Per2* and *Cry1*/*Cry2* genes. PER and CRY proteins are phosphorylated by CK1, and PER/CRY complexes may translocate to the nucleus to inhibit the action of the BC/N heterodimer, thereby inhibiting their own transcription. The *yellow* area depicts the clock input signaling pathways that converge on CREB, which binds to CRE elements in the *Per1* and *Per2* gene promoters and contributes to transcriptional activation, e.g., as a response to a light stimulus received by the retina. *Green* depicts the output pathway of the clock mechanism. BC/N binds to E-boxes in the promoter of a clock-controlled gene (CCG) transmitting time of day information to processes regulated by a CCG. An example of a CCG in the brain is monoamine oxidase A (MAO), which is involved in the degradation of catecholamines such as dopamine. The *brown-shaded* area shows the processes involved in the degradation of PER and CRY. *Purple hexagons* represent substances that influence the kinase and components of the clock mechanisms (*red*)

3 Metabolic Links Between Mood Disorders and the Clock

Mood disorders and their treatment are often associated with an increased risk of metabolic disorders, eating disorders, and obesity (McIntyre 2009). Interestingly, the *Clock*Δ19 mutant mice display in addition to the mania-like behavior also metabolic syndrome (Turek et al. 2005), and hence, a relationship between metabolism, mood, and the clock is apparent in this animal model. The peptides that regulate appetite and circulate in the bloodstream such as ghrelin, leptin, and orexin are altered in their expression in *Clock*Δ19 mutant mice (Turek et al. 2005). These peptides are produced in peripheral organs (ghrelin in the stomach, leptin in white adipose tissue) and bind to their receptors that are expressed in various areas of the brain including areas which are important in mood regulation such as the VTA. Therefore, feeding which affects the production and/or secretion of those peptides plays a role in the regulation of the reward system and hence in mood regulation.

Energy uptake and expenditure also impact on the circadian clock mechanism. Binding of the BMAL1/CLOCK or BMAL1/NPAS2 heterodimer to their cognate E-box sequence in clock gene or clock-controlled gene (CCG) promoters (Fig. 2) is sensitive to the $NAD(P)^+/NAD(P)H$ ratio (Rutter et al. 2001) that is determined by metabolic status. Because nicotinamide phosphoribosyltransferase (NAMPT, the rate-limiting enzyme in the NAD^+ salvage pathway) is transcriptionally regulated by the circadian clock, NAD^+ levels oscillate in the cytosol and probably also in the nucleus in a daily fashion (Nakahata et al. 2009; Ramsey et al. 2009). Disruption of the NAD^+ oscillation by mutating the NAD^+ hydrolase CD38 altered behavioral and metabolic circadian rhythms (Sahar et al. 2011). CD38 deficient mice showed a shortened circadian period and alterations in plasma amino acid levels. This may contribute to abnormal brain function, because many amino acids including tryptophan, tyrosine, and glutamate are precursors of neurotransmitters or are neurotransmitters, respectively.

Nuclear receptors regulate various aspects of metabolism affecting various tissues including the brain. Many nuclear receptors display circadian mRNA expression patterns including REV-ERB (NR1D), ROR (NR1F), and PPAR (NR1C) (Yang et al. 2006). Some of them like the REV-ERBs and RORs are directly involved in the circadian clock mechanism (Fig. 2). A number of nuclear receptors have the potential to interact with the clock component PER2 (Schmutz et al. 2010) linking the clock with metabolism at the posttranslational level.

These observations reinforce the relationship between metabolism, circadian clock, and brain function. Therefore it is tempting to speculate that abnormal metabolism induced by improper eating habits and/or improper sleeping behavior may contribute to the development of mood disorders. This may occur indirectly via alteration of amino acid metabolism and/or synthesis and release of appetite-regulating peptides such as ghrelin and leptin.

4 Treatment of Mood Disorders Changing the Circadian Cycle

Sleep deprivation (SD), bright light therapy, and pharmacological treatments have been successfully used to attenuate depression [reviewed in McClung (2007)]. SD improves depressive symptoms in 40–60 % of patients (Wirz-Justice and Van den Hoofdakker 1999) probably via activation of limbic dopaminergic pathways (Ebert and Berger 1998) and shifting clock phase. In rodents SD decreases immobility in the forced swim test (Lopez-Rodriguez et al. 2004) and stimulates hippocampal neurogenesis (Grassi Zucconi et al. 2006), which is similar to the actions of antidepressant drugs. Furthermore, SD affects phase shifts of the clock in rodents (Challet et al. 2001).

Bright light therapy appears to be effective for several mood disorders including depression (Terman and Terman 2005). Its efficiency is probably rooted in the ability of light to advance clock phase. Similarly to antidepressant drug treatment, it generally takes 2–4 weeks until beneficial effects on mood are seen. Interestingly, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine produce phase advances in firing of SCN neurons in rat slice cultures (Ehlen et al. 2001; Sprouse et al. 2006). Similarly, agomelatine, which is a melatonin receptor agonist and antagonist of some serotonin receptor isoforms, can cause phase advances in both mice and hamsters (Van Reeth et al. 1997). Long-term antidepressant responses can be induced in bipolar patients applying a combination of SD, morning bright light therapy, and sleep phase advances as a replacement of pharmacological treatment (Wu et al. 2009). Taken together, it appears that phase advancing circadian clock phase elicits antidepressant effects that may involve modulation of SCN activity as well as the serotonergic and melatonin systems.

The mood stabilizer lithium is commonly used for treatment of depressive patients and lengthens the circadian period (Johnsson et al. 1983; Hafen and Wollnik 1994), likely involving the inhibition of GSK3β, which phosphorylates the molecular components PER2 and REV-ERBα of the circadian clock (Iitaka et al. 2005; Yin et al. 2006) (Fig. 2). It produces strong phase delays in circadian rhythms in a variety of organisms, including humans (Atkinson et al. 1975; Johnsson et al. 1983; Klemfuss 1992) and impacts on amplitude and period of the molecular circadian clockwork (Li et al. 2012). Since the strongest effects of lithium are as an antimanic agent, it is interesting that it is acting in an opposite way on circadian period compared to antidepressant treatments (see above).

Other kinases besides GSK3β that may serve as a pharmacological entry points to alter the circadian clock are the casein kinases 1ε and δ (CK1ε/δ). Application of a CKIδ inhibitor (PF-670462) (Fig. 2) to wild-type mice lengthened circadian period accompanied by nuclear retention of the clock protein PER2 (Meng et al. 2010). Interestingly, selective inhibition of CK1ε by PF-4800567 minimally alters circadian clock period (Walton et al. 2009). However, whether these compounds affect mood-related behavior remains to be investigated. Recently, longdaysin, a molecule that targets three kinases, CKIα, CKIδ, and ERK2 was discovered in a large-scale chemical screen (Hirota et al. 2010) (Fig. 2). CKIα inhibition by

longdaysin reduced PER1 phosphorylation and its subsequent degradation. As a consequence, the period in human cells became longer than normal. In vivo, zebra fish embryos displayed a longer clock period after longdaysin administration illustrating the potential of longdaysin to manipulate the circadian clock (Hirota et al. 2010).

Another way of pharmacologically targeting the circadian clock is delivery of substances that activate or inhibit the nuclear receptors of the ROR (NR1F) and REV-ERB (NR1D) families (Fig. 2). Heme seems to be an important ligand influencing REV-ERB transcriptional potential (Yin et al. 2007), and the synthetic agonist GSK4112 (SR6452) (Grant et al. 2010) can compete with heme allowing to start to decipher REV-ERB function. Because REV-ERBs play an important role in adipogenesis, application of heme and GSK4112 (SR6452) has been tested in the regulation of this process. It appears that they are effective modulators of adipogenesis and hence may be useful in the treatment of metabolic disease (Kumar et al. 2010). To which extent the circadian clock is affected by GSK4112 and how mood-related behavior is modulated remain to be tested, although this may be difficult since GSK4112 exhibits no plasma exposure (Kojetin et al. 2011). Recently, a synthetic antagonist for the REV-ERB nuclear receptors was identified (Kojetin et al. 2011), and two REV-ERB agonists with in vivo activity were described which display good plasma exposure (Solt et al. 2012). Administration of these two agonists (SR-9011 and SR9009) altered circadian behavior and clock gene expression in the hypothalamus as well as in the liver, skeletal muscle, and adipose tissue of mice. This resulted in increased energy expenditure. Treatment with these two agonists decreased obesity by reduction of fat mass in diet-induced obese mice, improving dyslipidemia and hyperglycemia (Solt et al. 2012). Hence, it appears that synthetic agonists for REV-ERB may be beneficial in the treatment of sleep and metabolic disorders. Synthetic molecules that bind to the ROR family members have also been identified. SR1078 is an agonist for RORα and RORγ (Wang et al. 2010), whereas SR3335 (ML-176) appears to be a RORα selective inverse agonist (Kumar et al. 2011) (Fig. 2). Future experiments will show how useful these molecules will be in the treatment of metabolic and mood disorders and how they modulate circadian clock function.

Recently, small molecule activators of cryptochrome (CRY) were identified (Hirota et al. 2012). KL001, a carbazole derivative, lengthened circadian period in vitro by preventing ubiquitin-dependent degradation of CRY. It appears that KL001 specifically binds to the FAD binding pocket of CRY and stabilizes it in the nucleus. KL001 repressed glucagon-dependent induction of *Pck1* and *G6pc* genes inhibiting glucagon-mediated activation of glucose production, and therefore, this molecule may provide the basis for a therapeutic approach for diabetes. Since CRY proteins have been implicated in mood disorders (see above), KL001 may also be useful in the development of novel drugs to treat neuropsychiatric disorders.

Taken together, the experimental data in humans and mice suggest that there are two major ways in modulating the circadian clock and clock-related physiological processes. First, environmental factors such as light and food uptake can affect the clock in a long-term manner. Changes in the environment will have to be

continuously present to alter the circadian clock and physiology. Second, pharmacological treatment will allow modulation of the circadian clock in a fast way; however, also this type of treatment will need to have some continuity; otherwise, stop-and-go cycles of circadian timing will stress metabolism and brain function in an unhealthy way. Circadian pharmacology has just seen its dawn, and the future will show how promising the newly discovered agents really are.

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