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Sleep and Mood: Chicken or Egg?

q1 **Louis J. Ptáček, Ying-Hui Fu, and Andrew D. Krystal**

It has long been recognized that there is an association between sleep and mood. Both of these phenomena are light-sensitive; light entrains the circadian clock, and too little light predisposes a significant portion of the population to seasonal affective disorder. Sleep deprivation can precipitate mania in patients with bipolar disease (1) but can also be an effective treatment for “breaking” a bout of pharmacologically refractory depression (2). Glycogen synthase kinase 3 beta has been shown to be a circadian gene in flies (3) and mammals (4) and is a target of lithium therapy, which is useful in many patients with bipolar disease. Some mice with mutations causing circadian phenotypes show mood-like behaviors. However, people with mood disorders frequently experience difficulty falling and staying asleep and can manifest circadian phenotypes (e.g., early morning awakening and diurnal mood variation of severe depression) (5). Genetic variants in the circadian gene *PER3* were recently shown to cause a human circadian phenotype associated with seasonal affective disorder (6). Given this remarkable list of associations between sleep/circadian function and mood, one is left asking: “Which came first, the chicken or the egg?”

Evidence from previous studies suggests that sleep/circadian system modifications have mood effects. This includes alterations of light schedules or lesioning of the suprachiasmatic nuclei (SCN, the master circadian regulator in the brain), which can lead to phenotypes that are thought to mimic psychiatric disorders seen in humans. However, altering light schedules and lesioning of the SCN may have pleiotropic effects separate from central circadian dysregulation that complicate interpretations of these results.

In the article by Landgraf *et al.* (7), the authors show that circadian disruption resulting from knocking down expression of a gene (*BMAL1*, an essential positive regulator of circadian rhythmicity) in SCN leads to helplessness-like, behavioral despair-like, and depression-like behavior in mice. This is the best evidence to date suggesting that disturbance of the circadian system may, indeed, precipitate mood dysfunction.

Still, the issue of causality remains far from resolved. It is worth noting that there are complex interactions between behavioral phenotypes, circadian function, and sleep. It is also important to note that circadian function (i.e., rhythmicity) is distinct from sleep homeostasis. Clock genes in cells lead to cell autonomous oscillatory behavior of transcription, translation, and the posttranslational function of many genes and proteins. Therefore, circadian disruption itself may inevitably have behavioral consequences, and some behavioral phenotypes might result from altered sleep. Shift workers often do not fully synchronize to the “new” time schedule and this, in turn, can lead to sleep deprivation. We must therefore

consider separate contributions of circadian alterations and resulting sleep deprivation in thinking about behavioral consequences in humans where it is impossible to regulate the light environment and manipulate circadian function as easily as we can in model organisms. The fact that disruption of rhythms can lead to mice with features of human behavioral disorders is not mutually exclusive from the converse.

It is important to exploit opportunities that are possible in each system (including *Homo sapiens*!) while being cognizant of limitations that exist. Many researchers use *Mus musculus* and other model organisms because they afford genetic and other tools that are not possible in humans. Landgraf *et al.* (7) inject a viral vector encoding a short hairpin RNA to knock down expression of the clock gene *BMAL1*. This is a powerful tool that leads to circadian disruption without changing the lighting schedule or creating an ablation that leads to neuronal loss in SCN and disruption of light-sensing inputs and physiological outputs of the master clock. However, there are also inherent challenges in behavioral phenotyping of mice. It is impossible to really determine whether a mouse is depressed or anxious. The authors use available assays for measuring several mouse behaviors and show differences between experimental and control mice. For example, the mice with disrupted circadian function show increased depression-like behavior. They interpret this to suggest that depression can result from circadian disruption, but are careful to note important caveats in extending behavioral assessments from mice to humans.

Another important question is whether the converse is true. Is it possible for a primary behavioral phenotype like depression to lead to circadian dysregulation? Although it is clear that affect is (in part) genetically determined, genes or mutations causing affective disorders have been elusive. Once we have better understanding of the genetics underlying affective disorder, it will be possible to begin thinking about how to test this question. However, an inherent problem is the fact that affect is almost certainly a distributed network property of the brain. While it is possible to disrupt circadian function by knocking down an essential circadian gene in the SCN, there is no recognized locus in the central nervous system whose disruption will give rise to depression. Therefore, expression of a “depression mutation” may have systemic effects that could preclude strong conclusions regarding depression causing a circadian phenotype. Given the complex interactions of circadian function/sleep, mood, and other behaviors, it would not be surprising if the causal relationship between circadian/sleep and mood phenotypes is bidirectional. Several observations in humans suggest—but do not prove—that this may be the case (8–10). In the end, it may not be a question of “chicken versus egg” as much as one of “chicken AND egg.”

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