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Synchronized Time Keeping is Key to Healthy Mood Regulation

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Abstract

It has long been known that patients suffering from mood disorders such as major depression exhibit disrupted circadian rhythms. Given that circadian clocks are localized throughout the brain and body, an important open question is how the local clocks in the brain areas that regulate mood contribute to mental health. Recent data from Landgraf and colleagues found that clock gene expression rhythms in the brain regions of individual ‘helpless’ mice were dampened compared to those of ‘resilient’ mice, suggesting that stronger clocks in brain regions controlling mood lead to better mental health. Moreover, these dampened rhythms in the nucleus accumbens and periaqueductal gray were due to phase desynchrony of individual cells. However, the finding that clock gene expression in individual neurons was still rhythmic suggests future therapeutic strategies may be aimed at re-synchronizing these neurons.

Keywords

mood disorder; circadian rhythm; clock genes; depression

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BP), are relatively common disorders, affecting up to 20% of the adult population. However, despite the frequency of these disorders, there is much that we still do not understand about the physiological mechanism of these diseases. The difficulty in understanding the cause of these psychiatric diseases stems from the inherent complexity of the human brain. Since regions of the brain have varied and intertwined functions, it can be difficult to tease apart the pieces to determine where exactly something has gone wrong. However, an article recently published in EJN attempted to do just that by focusing on whether a broken internal biological clock in the brain leads to susceptibility of developing depression. Landgraf et al. examined two groups of mice that developed either ‘helpless’ behavior (approximating depressed mood) or ‘resilient’ behavior in response to a stressor. The researchers then measured a real-time readout of the brain’s clock in these mice by measuring the activity of *Period2* (or *Per2* for short)- one of the major genetic components of the circadian clock - fused with the firefly *Luciferase* gene, so that the brain cells glow in these mutant mice when this clock gene is turned on. By examining the disruption of the circadian clock in the brain

areas that regulate mood, Landgraf et al. hoped to link this disrupted brain function to depressive behavior (Landgraf *et al.*, 2015).

Circadian rhythms are intrinsic, ~24 hour rhythms in the body, including intricate processes such as protein levels within an individual cell, or whole body physiology like body temperature, blood pressure, and mood. These cycles are driven by a primary circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, which coordinates secondary clocks in peripheral tissues and other areas of the brain (Moore, 2013). It has long been known that patients suffering from MDD exhibit disrupted circadian rhythms, with altered sleep/wake cycles as well as irregular temperature cycles (Boyce & Barriball, 2010). But how local clocks in the brain areas that regulate mood contribute to mental health remains a mystery. Landgraf et al. found that the *Per2* expression rhythms in the brain regions of individual ‘helpless’ mice were dampened compared to those of ‘resilient’ mice, suggesting that stronger clocks in brain regions controlling mood lead to better mental health. The most interesting finding was that the dampened rhythms in some brain regions (e.g., the nucleus accumbens and periaqueductal gray) were actually due to individual cells being out of time with each other so that there was no overall rhythm in the larger ensemble of neurons. The fact that individual neurons were still capable of keeping time individually is encouraging since therapeutic drugs may be able to re-synchronize these neurons so that they are all keeping time together. While the results of this study strengthen the link between circadian rhythms and mood disorders, there are still many mechanistic pieces to put in to place.

Another mood disorder often linked to circadian abnormalities is bipolar disorder (BP). Bipolar disorder is characterized by bouts of mania and depression and affects around 2% of the population. BP has been linked to circadian rhythms via altered sleep/wake patterns, blood pressure, and abnormal hormone signaling (McClung, 2013). Melatonin, a common circadian hormone with a rhythm that is highly sensitive to light signals and can be disrupted in BP patients, can affect cAMP-CREB signaling in the brain which impacts signal transduction as well as plasticity (Gaspar *et al.*, 2014). Culturing neurons directly from BP patients is not a feasible option, and therefore, researchers have developed alternative methods of gathering data from cells that are easier to access. Various non-neuronal cell types extracted from patients have been cultured and used to examine the cellular differences in BP and normal patients (Viswanath *et al.*, 2015). In addition to altered circadian rhythms, the most replicated findings from subjects with BP involved alterations in calcium signaling, endoplasmic reticulum stress response, membrane ion channels, and apoptosis genes. Interestingly, many of these effects were reversed by treatment with lithium, which is commonly used to treat both depression and BP.

A primary target of lithium is glycogen synthase kinase 3 (GSK3) (Jope, 2011)-an enzyme that targets many proteins in the body, including several of the clock genes. The activation state of GSK3 varies over the circadian cycle in the SCN (Besing *et al.*, 2015), and chronic activation of GSK3 reduces the amplitude of circadian behavioral rhythms as well as increases excitability of SCN neurons specifically at night (Paul *et al.*, 2012). Interestingly, these mice with chronic GSK3 activation also serve as a model for BP (Polter *et al.*, 2010). Consistent with the idea that GSK3 may provide a link between impaired circadian rhythmicity and mood disorders, BP patients have ~35% lower inactivation

(phosphorylation) of GSK3 in blood samples than controls, even though total levels of GSK3 were the same in both groups (Polter *et al.*, 2010). In addition, certain human genetic variations in the GSK3 gene are associated with whether or not a patient will be responsive to lithium. In fact, the Welsh laboratory recently showed that lithium application rescues the impaired circadian rhythmicity of *Per2* expression in cultured skin cells from bipolar patients (McCarthy *et al.*, 2013).

Taken together, these findings present many interesting pieces to the puzzle of mood disorders. As shown in the Landgraf paper, a lack of synchronization among different brain regions or among individual cells within a brain region could underlie depressive-like behavior in mice.

Future research is needed to better understand how mood stabilizing targets such as GSK3 impact the synchronization of circadian clocks in various brain regions important in controlling mood. Given that many of these targets vary over the 24-h day, timed delivery of therapeutic drugs – the goal of chronopharmacology – is an important consideration in the treatment of MDD and BD.

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