For everything there is a season: biological rhythms in psychiatry

Mark Greener

A new study suggests that a circadian clock gene expressed in skeletal muscle may influence recovery from sleep deprivation, in mice at least. A greater understanding of such mechanisms may provide insights into one of the basic rhythms that rules our lives and disorders associated with disrupted sleep patterns.

The biology of almost every living thing changes over the course of a day. These ‘circadian rhythms’ control the way sunflowers track the sun. They influence the migration of butterflies and birds. And recent evidence underscores the intimate relationship between circadian and seasonal rhythms and psychiatric conditions. Indeed, a new study offers the first evidence that a biological clock in skeletal muscle in mice communicates with the brain to influence the most fundamental rhythms that rules our lives and disorders associated with disrupted sleep patterns.

At the end of a cue...

Circadian rhythms allow organisms to synchronise activities and behaviours with patterns of threats and opportunities in the environment, such as food availability, the risk of encountering predators and chances to mate. Indeed, almost every aspect of mammalian physiology shows circadian rhythms, including cardiovascular, nervous, digestive and urinary function. Circadian clocks also modulate oxidative stress, cell cycle and death, the response to DNA damage and gene expression. About 10% of the transcriptome (messenger RNA expressed from genes) shows circadian rhythms. Cues, such as light, (called zeitgebers) ‘entrain’ these endogenous circadian rhythms to track environmental changes. Without cues – such as living underground or during the Arctic winter – our biological clocks usually maintain a circadian rhythm of, on average, just over 24 hours. More rarely, circadian rhythms can become shorter or desynchronise (free-run). The endogenous pattern is genetically determined. People with long endogenous circadian periods tend to subjectively prefer the evening (owls), while those with short periods prefer the morning (larks).

Although light is the main zeitgeber, several other cues can entrain biological rhythms including sleep, social interactions, exercise and meal times.

Several reviews offer a detailed discussion of the networks that link zeitgebers and circadian patterns. Essentially, in one of the best characterised pathways, signals about light levels from the retina reach the suprachiasmatic nucleus (SCN), a small cluster of cells in the anterior hypothalamus. The SCN synchronises the body with the environmental light-dark cycle. For instance, the SCN stimulates synthesis and release of melatonin from the pineal gland during the night.

The SCN is remarkably sensitive. Single exposures to bright light lasting just 15 seconds and two minutes can alter circadian patterns (median phase shifts of –34.8 and –45.4 minutes respectively) compared with dim ambient light. Yet people in modern societies commonly experience light intensities between sunset and sleep that are more than twice as intense as natural light at the same time. In addition, many electronic devices emit monochromatic blue light. Photosensitive retinal ganglion cells, which transmit signals about ambient light to the SCN, are especially sensitive to these wave lengths. Even low levels of light from devices can, for example, delay sleep, reduce melatonin synthesis and impair next day alertness.

Not surprisingly, the increased light that is part of modern life generally disrupts sleep – such as delaying onset and shortening duration – and may increase the risk of some psychiatric disorders. Traditional Amish communities in rural Pennsylvania, for example, live without electric lights. The prevalence of seasonal affective disorder (SAD) is lower in Amish communities than in nearby Maryland: 0.84% and 4.3% respectively. The difference in subsyndromal SAD is even more marked: 1.75% and 13.5% respectively. Behavioural factors – such as the Amish’s greater exposure to natural patterns of outdoor light – presumably account for at least some of the difference.

A surprising finding

In addition to the SCN, organs and tissues throughout the body express ‘peripheral clocks’ that generate rhythms in, for example, body temperature, blood pressure, hormone secretion and metabolism. For example, a biological clock known as the ‘food-entrainable oscillator’...
triggers activities such as arousal, appetite, digestive secretions and metabolism 2–3 hours before a scheduled feed. The SCN helps synchronise the peripheral clocks and those taking their cues from light and food seem to interact, although the food-entrainable oscillator’s anatomical location is unknown.

Meanwhile, ‘core circadian clock genes’, expressed in the SCN and other peripheral tissues, also control central and peripheral clocks. These genes and their products form interconnected feedback loops. Polymorphisms (genetic variants) in circadian genes seem to influence susceptibility to several psychiatric disorders including bipolar disease, major depression and SAD.

Some peripheral clocks seem to influence sleep patterns. For example, a gene called Bmal1 encodes a transcription factor (a protein that controls gene expression). Genetically engineering mice that lack Bmal1 sleep for longer, show increased intensity of non-rapid eye movement sleep and recover from sleep deprivation more slowly than those with Bmal1.

Restoring Bmal1 in the brain had no effect on recovery after sleep deficits. Restoring Bmal1 in skeletal muscle, however, enabled mice to rebound from sleep deficits more quickly. For instance, researchers kept mice awake for almost 24 hours and used a genetic technique to add several copies of the Bmal1 gene to skeletal muscle cells. The mice, which had about six times the normal amount of Bmal1 in their skeletal muscle, were much less sleepy than controls without additional Bmal1. Mice with increased Bmal1 also slept substantially less during the 24 hours after sleep deprivation.

‘When we first saw the importance of the muscle, we were surprised,’ says senior author Ketema Paul, UCLA associate professor of integrative biology and physiology. ‘At first we didn’t believe it, so we repeated the experiment several times. We finally realised this is not a mistake; this is real. We show that not only is Bmal1 responsible for the ability to recover from sleep loss, but also that Bmal1 expression in the skeletal muscle is responsible for that process. When we increased Bmal1 in the skeletal muscle, the mice were able to tolerate more sleep loss. That suggests the skeletal muscle is directly communicating with the brain.’

Future research may uncover the pathways that allow the skeletal muscle to communicate with the brain and identify genes controlled by Bmal1. In addition, pharmacologically increasing levels of Bmal1 or modulating the pathways to the SCN might offer new treatments for sleep disturbances. ‘We have a few candidates that we’re studying,’ Professor Pauls says.

Ignoring the clock can damage your health

As Foster and Kreitzman point out: ‘Being forced to live against one’s circadian clock’ can damage your health. Disrupted circadian patterns seem to be associated with, for instance, lowered alertness and performance, and an increased risk of obesity, cardiovascular, sleep-wake, psychiatric, immunological and metabolic disorders as well as certain cancers. Indeed, sleep deprivation associated with the transition from day to night shifts can impair performance more than the legal blood alcohol limit.

‘Social jet lag’, for example, refers to the difference between the time that your alarm makes you crawl out of bed and your natural jet wake time. Every hour of social jet lag increases the risk of being obese or overweight by 30%. Moreover, a study that enrolled 13 464 people from England in 1998–2000 found that those who napped during the daytime were 30% more likely to develop diabetes by July 2006 than those who did not after adjusting for cofounders. Compared with people who slept for six to eight hours, sleeping for less than six and more than eight hours increased the risk of diabetes by 46% and 64% respectively. Indeed, people who slept for less than six hours and who napped during the day were almost three times (odds ratio 2.57) more likely to develop diabetes.

In addition, about 70% of depressed outpatients report difficulty falling asleep, frequent wakening, early morning waking, daytime tiredness and other sleep problems. Some patients even regard depression as predominantly a sleep disorder rather than a mood disorder.

Other clinical observations support the intimate association between psychiatric conditions and disrupted circadian patterns. One study found that the more time zones a person who is prone to mental illness crossed, the greater their risk of admission to a psychiatric hospital. In addition, patients with sun-down syndrome (nocturnal delirium) show worsening of behaviours such as agitation, aggression, restlessness and delirium during the late afternoon and early evening.

Furthermore, patients with mood disorders (including major depression, bipolar disorder and SAD) often display abnormal rhythms of body temperature, levels of cortisol, melatonin and some other hormones, blood pressure and sleep-wake cycles. For instance, a manic episode seems to reduce the need for sleep, while sleep deprivation for a night can produce an antidepressant effect, often within hours.

Animal studies are beginning to uncover the pathways that link circadian genes, such as the aptly named Clock genes, and mood. For instance,
a strain of mice with mutated Clock genes exhibit behavioural patterns similar to the manic phase of bipolar disease, including hyperactivity, increased cocaine sensitisation and anxiety-like behaviours, decreased depression and shorter sleep latency. Delivering a functional Clock gene into the ventral tegmental area (VTA) improves these mania-like behaviours.10

The VTA is one of several brain regions other than the SCN that express a biological clock and the electrophysiological activity of this area shows a ‘robust’ circadian pattern.10 Mice with mutated Clock genes showed enhanced activity of dopaminergic cells in the VTA, some of which innervate the mesocorticolimbic pathway. In turn, the mesocorticolimbic pathway seems to modulate motivation, emotion and reward. Abnormalities in this pathway seem to be linked to addiction, affective disorders, schizophrenia and attention-deficit hyperactivity disorder (ADHD).10

Seasonal changes
Circadian rhythms also help synchronise seasonal activity, reflecting, for instance, the changing day length. Indeed, the activity of about a quarter of our genes changes over the year. As a result, researchers have found numerous ‘indications of annual cycles’.1 For example, reproduction, mood, energy, performance, aggression, feeding, metabolism, thermoregulation, autonomic function, levels of certain neurotransmitters and hormones, and the composition of fat and blood all show seasonal variations.1,3,5,11 The immune system has a ‘profound pro-inflammatory’ profile in winter.11

The endogenous circadian period is shorter in spring and autumn than in summer and winter. The Swiss survey, for example, found that sleep was 24 minutes longer in winter than during the summer. Meanwhile, most studies report more episodes of mania during spring and summer. Further studies need to ascertain which people are especially susceptible to the clinical effects of these seasonal changes.9

SAD, the archetypal seasonal psychiatric condition, was characterised as a specific condition in 1984. With the benefit of hindsight, however, ancient texts described the disease. Indeed, the Swiss study suggests that mood, social contacts and energy tend to be higher in the spring and summer than the autumn or winter, even among people who do not meet the criteria for full or subsyndromal SAD.9

A recent review noted, however, that the pathophysiology of SAD remains poorly understood.9 For example, researchers have not fully explained SAD pathogenesis in terms of abnormal melatonin secretion, disturbed circadian phase relationships or both. Moreover, SAD patients show similar serotoninergic and catecholaminergic dysfunctions as people with major depression. Indeed, levels of monoamine neurotransmitters, such as serotonin and dopamine, in the brain show seasonal variations.9

To complicate matters further, genetic and behavioural factors can influence SAD. So between 1.4% and 9.7% of people in North America, 1.3–3% in Europe and up to 0.9% in Asia develop SAD. As this suggests, SAD becomes more common in northern latitudes. However, native populations living in the same areas – such as Lapps in Finland or Icelanders in Canada – do not seem to be at increased risk of SAD.9

Perhaps because of the pathogenic uncertainty, lights’ mode of action in SAD remains unclear. However, bright sunlight seems to directly influence serotonin turnover in the brain. Moreover, bright light may effectively treat some people with non-seasonal major depression and bipolar disease, and could find a role in, for example, managing premenstrual and postnatal depression and the sleep problems associated with ADHD, schizophrenia, renal transplants and cirrhosis.9

These examples barely scratch the surface of recent research into our circadian and seasonal rhythms. Yet numerous questions remain unanswered. Most fundamentally, it’s still not fully clear why we sleep. We still have so much to learn about our enigmatic circadian rhythms.

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References