BY SALLY POBOJEWSKI • PHOTOS BY MARTIN VLOET

THE RHYTHM OF LIFE

MAINTAINING BALANCE IN BODY RHYTHMS IS KEY TO GOOD HEALTH

Life on Earth is connected to the daily rhythm of the rising and setting sun. This ancient cycle of light and dark is so familiar it's easy to forget how much it influences our body, our behavior, and even our health.

Like all animals, human beings have rhythmic patterns of activity that affect every aspect of our daily lives. They control when we wake and when we sleep, when we work and when we rest, when we want to eat and when we want to have sex.

Scientists call them circadian rhythms — changes in physical activity, metabolism, hormone production, cell activity, organ function and body temperature — that rise and fall at fixed intervals over roughly a 24-hour period.

Everyone has an individual pattern of circadian rhythms. It develops during the first six months of life and, once established, is not easy to change. Morning larks will always be awake and alert at dawn, while night owls won't come to life until hours later.

If we have to work the night shift, care for a new baby or cram for an exam, we can ignore our circadian rhythms for a little while. But over the long term, messing with the biological clock can have serious consequences for us and for society.

The 24-hour/7-day-a-week pace of today's industrialized society — with its long-distance travel, fast food, television, computers and artificial lighting — requires many of us to fight against our natural circadian rhythms. U-M scientists say researchers are just beginning to understand the public health implications of the way we live.

Heart attacks, strokes, high blood pressure, depression, cancer, insomnia, obesity, diabetes, dementia, migraines and accidents all have been linked to disruptions in circadian rhythms. Clinical studies of nurses, police officers, factory workers and medical residents have found a much higher incidence of accidents, chronic sleep disturbances, depression and other diseases in people who work nights or, even worse, switch back and forth between day and night shifts. ➤

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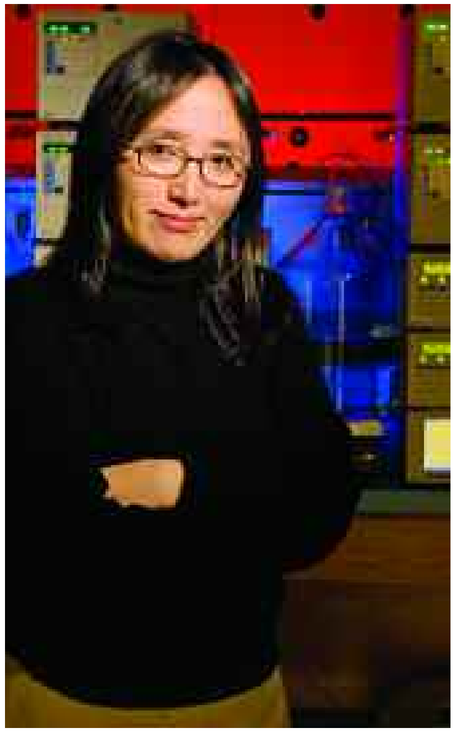
"We feel like we're so invincible, we can pull an all-nighter and we'll be fine. But no one really knows the long-term consequences of doing such things repeatedly," says Jimo Borjigin, Ph.D., an assistant professor of molecular and integrative physiology and a Biological Sciences Scholar in the U-M Medical School. "Many things we don't consider to be circadian functions are affected when circadian systems are disrupted."

THE MASTER CLOCK AND MELATONIN

To appreciate the complexity of circadian rhythms, consider what happens to your body before you wake every morning. All night long, the pineal gland at the base of your brain has been secreting a hormone called melatonin. An hour or so before you wake, melatonin production shuts down, while production of a stress hormone called cortisol skyrockets. Body temperature increases, the gastrointestinal tract starts moving again, and cellular metabolism revs up to provide energy to support the day's activity. By the time you open your eyes and stretch, the cells and organs in your body are already at work and ready to start the day.

All this activity is regulated by the body's master clock — two small clusters of neurons called the suprachiasmatic nucleus, or SCN, located deep within the mammalian brain. The SCN is ultra-sensitive to light. When light hits cells in the retina at the back of the eye, it stimulates the SCN to turn on genes that send wake-up signals throughout the human body.

Scientists have known for decades that the SCN is the body's master clock. But several years ago, they discovered that it's not the body's only clock. They now know that many cells in the body have an internal clock to regulate activity within the cell. Scientists believe that one of the SCN's most important jobs is to coordinate the activity of these individual cellular clocks so everything stays in sync with the outside environment.



Jimo Borjigin

"It's really mind-boggling, and not well understood, how this tiny bit of tissue in the brain has so much control," Borjigin says.

One way to study how the SCN coordinates the body's circadian activity is to take away the clock's light/dark cues and see what happens. Suppose you put a laboratory rat in a totally dark room for several days with lots of food and water and let it sleep and eat whenever it wants. U-M scientists who study circadian rhythms have done this many times with different types of animals. It's called free-running.

Experiments conducted under free-running conditions have led to the discovery that the natural circadian period varies depending on species, gender and the individual animal.

In humans, the average circadian period is close to 24.5 hours, according to Borjigin. Most rats have a slightly longer than 24-hour cycle, while most mice run slightly shorter than 24 hours. Scientists don't know how these differences affect an animal's ability to cope with disruptions in circadian rhythms.

Another mystery is how the SCN manages to fit an animal's natural circadian period, which is longer or shorter than 24 hours, into a fixed 24-hour daily cycle. How does the clock adjust to match gradual changes in the relative amounts of light and darkness that occur as seasons change? How does it deal with sudden changes like switching to daylight-saving time or traveling across multiple time zones?

The ability of the master clock to compress or expand internal circadian cycles to match changes in the external environment, like changing time zones, is called entrainment. It is one of the most important issues being studied in the circadian field.

Borjigin focuses on the hormone melatonin, because it provides an important key to understanding how the master clock manipulates the timing of circadian rhythms to fit within a 24-hour cycle. By monitoring changes in the onset and offset of melatonin production under various light conditions, Borjigin hopes to figure out how the SCN shifts the body's circadian cycle to match the solar cycle.

To study how melatonin interacts with the biological clock, Borjigin developed a technique that allows her to monitor the amount and timing of melatonin production in the brain of a living rat.

The key to the technique's success is a micro-dialysis probe that is surgically implanted directly into the rat's pineal gland. After the rat recovers from surgery, it goes about its daily activities while the probe collects fluid around the pineal gland. Every 10 minutes, a sample of fluid is sent automatically to a device that analyzes the amount of melatonin in the sample. The data then is sent to a computer, which records the internal rise and fall of melatonin.

Since animals produce melatonin only at night, knowing when the master clock turns on melatonin production gives Borjigin a precise time for the beginning of the SCN's circadian night in that animal. When melatonin production is turned off, she knows exactly when the SCN starts its circadian day.

Borjigin is the only scientist using chemical changes inside the pineal gland as a biomarker to track the activity of the circadian clock. Other scientists measure changes in body temperature over a 24-hour period, or the timing of an animal's activity, like running on an exercise wheel. Neither of these is as precisely timed on a day-to-day basis as melatonin release.

"Melatonin is the most precise marker of the circadian clock," Borjigin says. "The pineal gland's production of melatonin is controlled by signals from the circadian clock, but melatonin also goes back to the clock in a feedback mechanism and affects its activity directly."

Daniel B. Forger, Ph.D., an assistant professor of mathematics in the U-M College of Literature, Science, and the Arts (LSA) and one of Borjigin's research collaborators, creates mathematical models of the master clock.

The SCN has a difficult job, according to Forger, because it receives multiple competing signals from the environment. The primary thing the SCN entrains to is light. But if it's cloudy, the SCN gets a different signal than if it's a sunny day. The SCN has to figure out how to interpret all this data into something useful that the body needs to know: Is it time to wake up or time to go to sleep?

"That's why Jimo's work is so important," Forger says. "The technique she developed to measure melatonin in a living animal is the most accurate, direct measurement we have of what's happening inside the pineal gland and the SCN."

Scientists agree that melatonin binds to a receptor molecule in the SCN and that it is important to the normal functioning of the master clock. But no one knows exactly how it works.

In humans, it's been established that melatonin lowers body temperature and affects sleep, Borjigin says. Normally, melatonin secretion increases first and then, within an hour or two, people get sleepy. But it doesn't work the same way for everyone. There are clear variations between individuals.

Complicating the mystery is the fact that, in all species, the pineal gland secretes melatonin only at night. So nocturnal mammals like rats have high levels of melatonin during the most active part of their 24-hour cycle. In diurnal mammals like people, the hormone is at its highest level while they are sleeping.

SHEDDING LIGHT ON OTHER FACTORS

Obviously, something else, in addition to light and melatonin, must be affecting the rhythms of the circadian master clock.

"Ten to 15 years ago, we thought of the clock as this thing that paid attention to light and only to light. Now we know that's not true," says Theresa Lee, Ph.D., a professor of psychology in LSA. "I think what the clock pays attention to, in addition to light, may be species-specific. Birds pay attention to bird song. Rodents pay attention to smells. Humans are highly social and we pay attention to social cues from other humans."

Like most scientists who study circadian rhythms, Lee works with laboratory rats. But she also studies small hamster-like rodents from Chile called degus (pronounced day-goos), because they have many similarities to people.

Unlike most rodents, degus are diurnal, meaning they are active during the day and sleep at night. They live together in colonies, take a long time to reach sexual maturity, and have circadian cycles that are similar to those of human beings. This makes them a valuable model for Lee's research on how other factors, especially sex hormones, influence the timing of the circadian clock.

Recently, Daniel Hummer, a U-M graduate student working with Lee, discovered another similarity between the circadian rhythms of degus and people — one that is familiar to parents of teenagers everywhere: When adolescent ➤

Theresa Lee with a Chilean degu. Because of their similarities to humans, degus are a valuable model for Lee's research on factors influencing the circadian clock.

degus go through puberty, they start sleeping later in the morning.

Other students working in Lee's lab have shown that a female degu responds to the smell of another female in a different cage by shifting her circadian clock, so both animals are on the same sleep/wake cycle.

Lee's research confirms that rats and degus have definite differences in circadian-related activity. And she sees individual differences in how animals from the same species respond to light exposure.

"There are differences in the sense of morning- or evening-type animals versus the majority that are somewhere in the middle," Lee explains. "We find that evening-type animals don't respond to light in the morning in the same way as our morning-type animals do."

MOVING THE CLOCK'S HANDS

One way to find out how intimately the body's circadian rhythms are tied to the light/dark cycle is to get on an airplane and fly across time zones. The fuzzy, disoriented, irritable feeling we call jet lag is what happens when circadian rhythms are out of sync with the environment and with each other.

Jet lag's symptoms are caused by the fact that the body's rhythmic cycles all readjust at different rates, according to Borjigin. The sleep/wake rhythm may adapt within three to four days, but the body temperature cycle may take six days, while urinary potassium output may not return to normal for 10 days. Until all these rhythms are resynchronized to the new time zone, your body won't feel right.

Borjigin doesn't have the research budget to send her laboratory rats on trans-Atlantic flights, but she can change their exposure to light and dark over a 24-hour period to mimic the effects of jet lag and then track melatonin production to see how each animal's body clock adjusts to the new circadian cycle.

In recent experiments, Borjigin changed the light/dark cycle to simulate traveling west for three hours, six hours and 12 hours. She found that rats took at least six days to adjust completely from a three-hour shift in the normal light/dark cycle and even longer for six- and 12-hour shifts.

"We found that morning-type animals recover from jet lag much sooner than evening-type animals," Borjigin says. "It is not yet known whether the same is true for humans."

Borjigin also found wide variation in how individual rats readjust their circadian clocks to time zone differences, even the one-hour difference we experience twice each year when most of the country switches on or off daylight-saving time.

In addition to sleep and concentration, jet lag can affect that most intimate of daily activities — having a bowel movement. Sandra Hoogerwerf, M.D. — an assistant professor of gastroenterology, who recently joined the Medical School — conducts research with mice to learn how clock genes regulate the activity of muscles and neurons that control movement of the stomach and colon.

"Within the GI tract, there are lots of things that happen every 24 hours," she says. "For example, stomach emptying slows down at night and bowel movements usually happen in the morning."

Hoogerwerf says it often takes several days for bowel habits to return to normal after long-distance travel or changes in feeding times, because clock genes in the GI tract may need time to reset themselves to the new cycle.

Eventually, Hoogerwerf hopes to apply what she learns from mice to people with abnormal gastrointestinal motility — including diabetes patients whose irregular patterns of stomach and bowel motility cause severe constipation and diarrhea. Hoogerwerf believes this could be related to lost circadian expression of clock genes in people with diabetes.

In addition to her studies of jet lag, Borjigin recently found that the mammalian circadian clock may be far more sensitive to light at night than was previously believed. When she exposed laboratory rats to a single 10-minute pulse of light at night, their circadian melatonin rhythms were disrupted immediately. It took the animals more than two weeks to recover completely from the light pulse.

"These studies suggest that the negative consequences of interrupted or shortened sleep on the circadian timing system may last much longer than we think," she says.

TAKING TIME TO SET THE CLOCK

Although many questions remain unanswered, researchers at the U-M and other institutions are well on their way to solving the mysteries of the body's circadian clock. Based on their research, scientists one day may be able to develop safe and effective therapeutic drugs or behavioral interventions to help people reset their clocks to a healthier rhythm.

What will be more difficult is changing society's attitude toward sleep and how important maintaining a healthy circadian rhythm is to our health and well-being.

Think how much more productive our working lives could be if employers rewarded employees for getting a full eight or nine hours of sleep, or encouraged time off to adjust to jet lag after overseas travel. What if schools and businesses provided flexible start times for students and employees? What if daily exposure to sunlight in hospitals and nursing homes was considered as important to a patient's recovery as drugs and surgery?

How different our lives could be, if we lived the way we were born to live — in synchrony with the rhythms of the rising and setting sun. m

THE LINK TO DEPRESSION

Just like Jimo Borjigin's rats, some people have more trouble adjusting to time changes than others, according to Roseanne Armitage, Ph.D., a U-M professor of psychiatry who directs the Sleep and Chronophysiology Laboratory at the U-M Depression Center. Armitage studies the connection between sleep and circadian rhythm disturbances and psychiatric illness.

Her research indicates that people with depression or bipolar disorder have circadian rhythm disturbances similar to those seen in people suffering from jet lag or lack of sleep. Depressed patients also are more vulnerable to jet lag and sleep deprivation, because it's much more difficult for them to reset their circadian clock. So for people at risk for depression, maintaining a regular sleep cycle is especially important.

Armitage's research suggests that disturbances in sleep and circadian rhythms can be a precursor to, not just a result of, depression. So treating depression alone without addressing the underlying sleep problem is not enough, because the depression is likely to return.

"It doesn't mean that everybody who has circadian rhythm abnormalities or sleep disturbances will go on to develop depression or substance abuse, but the risk is significantly higher," Armitage explains.

Armitage's research shows that the link between abnormal circadian rhythms and depression can show up at an alarmingly early age. One of her studies involves 7- and 8-year-old girls who have been diagnosed with depression. Using actigraphs — watches that measure motion and record light levels every 60 seconds — Armitage tracked each girl's pattern of activity for 21 days.

"If you look at how your day is organized, you switch tasks or take a rest about every 90 minutes," Armitage explains. "This 90-minute rhythm persists throughout the sleep period in the REM/non-REM sleep cycle. One of the things we noticed in these young depressed girls is that the strength or amplitude of their rhythm was half what it is in healthy girls," she says.

In another study, Armitage is testing a behavioral intervention approach to strengthen circadian rhythms and see if this can improve or prevent depression. Her research subjects are children who have been diagnosed with depression or have a high risk of developing the disease, because they have a parent with depression.

Roseanne Armitage

Children in the program follow a strict schedule with regular periods of activity and light exposure at appropriate times during the day. They wake up, eat, exercise and go to bed at the same time every day, even on weekends. After just eight weeks on the program, the children showed tremendous improvement in the strength of their circadian rhythms, according to Armitage.

"One of the things we want families to recognize is that if you have kids at high-risk for depression, the last thing you want to do is keep an erratic sleep/wake schedule," she says. "No staying up late and sleeping until noon on the weekend, and then getting up at 6 a.m. on Monday."

That advice about maintaining a regular sleep cycle goes for adults, too, Armitage adds. "If you are at risk for depression, cheating a little sleep-wise packs a bigger wallop then it does for a healthy individual."

—Sally Pobojewski