Resetting the metabolic clock

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Circadian rhythms are affected by things like travel over time zones, diet and light exposure. Credit: Peter Allen illustration

We've all heard about circadian rhythm, the roughly 24-hour oscillations of biological processes that occur in many living organisms. Yet for all its influence in many aspects of our lives—from sleep to immunity and, particularly, metabolism—relatively little is understood about the mammalian circadian rhythm and the interlocking processes that comprise this complex biological clock.

Through intensive analysis and computer modeling, researchers at UC Santa Barbara have gained insight into factors that affect these oscillations, with results that could lend themselves to circadian regulation and pharmacological control. Their work appears in the early edition of the *Proceedings of the National Academy of Sciences*.

"Our group has been fascinated with circadian rhythms for over 10 years now, as they represent a marvelous example of robust control at the molecular scale in nature," said Frank Doyle, chair of UCSB's Department of Chemical Engineering and the principal investigator for the UCSB team. "We are constantly amazed by the mechanisms that nature uses to control these clocks, and we seek to unravel their principles for engineering applications as well as shed light on the underlying cellular mechanisms for medical purposes."

"Focus is often given to metabolism, cell division and other generic cell processes, but circadian oscillations are just as central to how life is organized," said Peter St. John, a researcher in the Department of Chemical Engineering and lead author of the study.

Blood pressure, he noted, varies with time of day, as do visual acuity, smell and taste. Certain hormones are released at certain times to do their tasks. We get sleepy or become more alert at different hours. All these various highs and lows, rises and falls are the result of our circadian rhythm.

"There are genes and proteins that are expressed in a cell and their activity, or expression level, changes with time of day," explained St. John. "These oscillations are caused by genetic circuits. So you'll have a gene that's produced, and when it's in its finished form, it will turn itself off." The proteins and genes get cleared away, after which production starts all over again, in a cycle that takes roughly 24 hours to complete.

While genetics plays a role in these rhythms—for instance if your parents were night owls, it's likely you will be one too—environment, habits and lifestyles also affect the clock.

"It's not just this free-running oscillator," said St. John. "It gets these inputs from light. For instance if you get light early in the morning, it'll speed up something so your phase is adjusted to the time of day." Other influences include food (not so much what you eat but when), drugs, shift work and frequent travel across time zones.

The healthiest circadian rhythms are the ones that are considered to be "high-amplitude"—where different and complementary processes occur in the body during distinct and regular daytime and nighttime phases.

"We're very different animals during the night and the day," said St. John. "If you're fasting at night and you're asleep, the demands on your cells will be very different than if you're awake and running around. There's this temporal separation between the genes that you need during the day and those you need at night."

Problems occur when the amplitude gets repressed, often because of modern-day schedules and lifestyles. Too much light at night, insufficient or irregular sleep hours, and eating or exercising too late in the evening are all habits that don't allow for the necessary nighttime-phase cellular activity. This in turn can lead to disorders such as diabetes, heart disease and obesity. In very preliminary studies, Alzheimer's

disease and certain liver conditions are also associated with low-amplitude rhythms.

Establishing high-amplitude circadian rhythms could be as simple as modifying our schedules, but for some people—those with sleep disorders, for example, or those whose work requires long and irregular hours—it can be difficult, if not impossible.

By studying the regulation of the clock proteins called Period (PER) and Cryptochrome (CRY)—proteins that are thought to be involved with metabolism—St. John and Doyle were able to model the mechanisms of two small-molecule drugs—Longdaysin and KL0001—that regulate the expression of the clock proteins. The insight they gained could lead to therapies that can help those with repressed circadian rhythms.

"Everybody thought that these were very similar proteins," said St. John. "They bind to each other. They enter the nucleus together." The assumption was that perturbations to those proteins would produce similar results. "But when we analyzed the data," St. John continued, "it turned out that when you stabilize PER you get these higher-amplitude rhythms, but when you stabilize CRY you get these lower-amplitude rhythms."

These results—obtained by studying cultured human cells that glow depending on their circadian phase, as well as through computer modeling—shed light on the mechanisms behind the metabolic aspect of circadian rhythms and pave the way for drug therapies that could decrease the risk of disease for those with disrupted rhythms. The UCSB researchers worked in collaboration with experimental scientists Tsuyoshi Hirota and Steve Kay from UC San Diego and USC, respectively.

"These collaborative partnerships with life scientists are crucial to the

success of a project like this," said Doyle, "and this kind of collaborative research team can implement the paradigm of systems biology with combined mathematical modeling and high-throughput experimental biology."

Future modeling studies will try to determine if there is an optimal phase for taking one drug or the other to improve the amplitude of circadian rhythms. Experimental work will focus on improving specificity and bioavailability—the amount of drug that actually reaches the target tissues before being discharged by the body.

More information: Spatiotemporal separation of PER and CRY posttranslational regulation in the mammalian circadian clock, Peter C. St. John, DOI: 10.1073/pnas.1323618111

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