DRUGS THAT BOOST OUR CIRCADIAN RHYTHMS COULD SAVE OUR LIVES

Before there was electricity or the internet or screens illuminated by thousands of liquid crystals rotating polarized pulses of photons, humans mostly lived by the daily comings and goings of the yellow burning ball of gas in the sky. Like every other organism that walks, flies, swims, scurries, sways, or photosynthesizes on Earth, people evolved circadian rhythms tuned to this solar circuit.

Yours, like that of most other organisms, is controlled by waves of proteins encoded in just a handful of master clock genes. Every day, as if tracing the rise and fall of the sun through the firmament, concentrations of special timekeeping protein complexes surge and ebb inside nearly every cell in your body, in a sinusoidal curve that repeats itself every 24 hours. These proteins predictably bind and release your DNA, flipping thousands of genes on and off in synchronized choreography. They dictate more than just your sleep patterns. Fluctuations in most of your critical body functions, including blood pressure, body temperature, metabolism, and even your moods and behaviors all run on a meticulous 24-hour schedule.

But lots of things can throw your clock out of whack—consuming calories at all hours of the day, binge-watching Netflix on a blue-tinged screen at 3 am, even just getting older. And when your internal timekeeper starts ticking off-beat, lots of other things start to go wrong, from depression and other mood disorders to metabolic malfunctions and heart disease. Which is why one of the newest ideas in the emerging field of circadian medicine is to create drugs that actually amplify the cadence of our internal timers. The scientists leading this charge think such “clock-enhancing molecules” could help astronauts in the future stay on Earth-time even as they’re up in orbit or en route to Mars. Closer to home, these drugs could one day be used to combat the obesity epidemic, stave off incurable diseases like Alzheimer’s, and even slow aging itself.

Up until the mid-2000s, circadian rhythm science had been mostly viewed as a kind of cute, niche little corner of biology. But advances in gene sequencing technologies post-Human Genome Project led scientists to realize that the clock controlled more than 10,000 genes in nearly every cell in the human body. Even more recently, they discovered that clock was malleable. “Almost all the important functions in your body have a temporal component that we can tweak through the power of circadian manipulation,” says Jake Chen, a biochemist at the University of Texas Health Science Center in Houston. He’s spent the last ten years hunting for compounds with circadian-boosting properties and testing the hypothesis that they can make people live happier, healthier, longer lives. If he’s right, curing or preventing some of

society's most common and costly diseases might come down to chemically resetting our clocks. "The time has come for the biomedical research community to recognize that biological timing is a bonafide therapeutic target."

Chen's interest in circadian-modifying molecules began back in 2008, when he was a postdoc in the lab of a biochemist named Steven McKnight. At that time, most of the genes that control our molecular clocks had already been mapped out by a few dedicated chronobiologists, including a trio of American scientists who would go on to win the 2017 Nobel Prize in medicine for their contributions. But no one was quite sure how to use that knowledge to help people live healthier lives. Chen thought if he could find compounds that nudged the hands of that clock by activating or deactivating the genes that control it—speeding it up, slowing it down, making it disappear altogether— he could help identify what happens inside the bodies of people whose clock genes turn on willy-nilly or not at all. What he found instead, after screening more than a quarter-million chemicals, was a class of molecules that supercharged cells' clock functions. If you imagine the clock as an oscillating sine wave that represents the rate of timekeeping protein production, like a sound wave coming out of your Bluetooth speaker, these compounds make the peaks higher and the troughs lower, the molecular equivalent of turning the volume knob way up. And the louder the clock keeps time, the more the body's tissues stick to their respective schedules.

The effects can be drastic. Take a chemical called nobiletin, which is found in the oily peel of some orange and kumquat species and has proven itself one of Chen's most promising candidates. The small molecule binds to one of the core clock proteins responsible for stabilizing the 24-hour cycle. When his team administered nobiletin to mice that were fed a high-calorie diet (Chen describes it as an "all-McDonald's every day" diet), they stayed slim, even as control mice packed on nearly twice their body weight in just 10 weeks. Nobiletin also improved other markers of healthy metabolism, like fasting glucose and cholesterol levels.

Chen's team published those results in 2016, and more recently, they've tested nobiletin's potential to reverse some of the common ailments associated with aging. As we get older our metabolism slows down, which impacts everything from exercise endurance and heat production to the ability to sleep for long stretches of time. Evidence suggests this metabolic tail-off is tied to mitochondrial burnout. Our cells' energy factories just aren't outputting as much as they used to. And why is that? Because mitochondrial function is closely regulated by our circadian clocks, which also get weaker as we age—they tick more quietly. In work that is currently under

review, Chen's group used nobiletin to restore the circadian clocks in muscle cells of aged mice. As a result, the mice were stronger, slept better, and lived longer than their untreated counterparts. "Chronologically they were 28 months, but they behaved much younger," Chen says.

Encouraged by these results, he is now expanding into an even more ambitious project —testing whether or not circadian-enhancing drugs could be used to treat Alzheimer's disease, the debilitating neurodegenerative condition that will affect about 10 percent of the US population before the middle of the century. Spurred by these projections, the National Institutes of Health and Congress have begun to aggressively fund Alzheimer's research in the last few years, and Chen is a recipient of this spending bonanza. Last year he received a five-year, $3.6 million NIH grant to test his most promising molecules in mouse models of Alzheimer's. It's part of a larger project that will also look at genetic interventions that amp up the circadian clock by operating on the DNA that controls it directly. "We know that in Alzheimer's disease patients, the circadian rhythm is dampened," Chen says. "So we're hoping that by rejuvenating the circadian rhythm it's going to improve brain function, sleep cycles, and possibly even alleviate the behavioral deficits that are a hallmark of the disease."

That work is just getting going. But it has other researchers in the field excited about the long-term prospects of circadian medicine. "Having drugs that reinforce and reset our clocks would be useful for combating the negative health effects of shift work, jet lag, and getting off the Earth," says Carrie Partch, a structural biologist at the University of California Santa Cruz's Center for Circadian Biology. On the International Space Station, astronauts have a 90-minute day, an unnatural environment that NASA's recent Twin Study showed can alter both circadian rhythms and your DNA.

Back on Earth, scientists still don't know whether the clock weakens because we get older, or if aging is itself a symptom of a diminishing circadian rhythm. And if it's the latter, then invigorating our clocks could theoretically put more sand in the hourglass. "If a molecule can make that clock stronger so that our bodies can fight off all those changes, then 70 really would be the new 50," Partch says. "That's the promise of enhancing circadian rhythms." Modern technology may have liberated the human species from millennia of obligate diurnality, but our bodies evolved to respond to the sun, not to screens.

So until science delivers some magic clock-boosting pill, maybe just, you know, go outside more often.