Researchers discover compound with potent effects on the biological clock

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Using automated screening techniques developed by pharmaceutical companies to find new drugs, researchers from UC San Diego and three other research institutions have discovered a molecule with the most potent effects ever seen on the biological clock.

Dubbed "longdaysin," for its ability to dramatically slow down the biological clock, the new compound could pave the way for a host of new drugs to treat severe sleep disorders or quickly reset the biological clocks of jet-lagged travelers who regularly travel across multiple time zones. The researchers demonstrated the dramatic effects of longdaysin by lengthening the biological clocks of larval zebra fish by more than 10 hours. The article will be published in next week's issue of the online, open access journal PLoS Biology.

"Theoretically, longdaysin or a compound like it could be used to correct sleep disorders such as the genetic disorder Familial Advanced Sleep syndrome, which is characterized by a clock that's running too fast," said Steve Kay, dean of UCSD's Division of Biological Sciences, who headed the research team. "A compound that makes the clock slow down or speed up can also be used to phase-shift the clock—in other words, to bump or reset the hands of the clock. This would help your body catch up when it is jet lagged or reset it to a normal day-night cycle when it has been thrown out of phase by shift work."

Biologists in Kay's laboratory and the nearby Genomics Institute of the Novartis Research Foundation, led by Tsuyoshi Hirota, the first author

of the paper, discovered longdaysin by screening thousands of compounds with a robot that tested the reaction of each compound with a line of human bone cancer cells that the researchers genetically modified so they could see visually the changes in the cells' circadian rhythms. This was done in the cells by attaching a clock gene to a luciferase gene used by fireflies to glow at night, so that the cells glowed when the biological clock was activated.

The robot screened more than 120,000 potential compounds from a chemical library into individual micro-titer wells—a system used by drug companies called high-throughput screening—and automatically singled out those molecules found to have the biggest effects on the biological clock. Once Kay's group had isolated longdaysin, they turned to biological chemists in Peter Schultz's laboratory at The Scripps Research Institute to characterize the molecule and figure out how it lengthened the biological clock. That analysis showed that three separate protein kinases were responsible for the dramatic effect of longdaysin, one of which, CK1alpha, had previously been ignored by chronobiology researchers.

The researchers then showed that longdaysin had the same effect of lengthening the biological clock in mouse tissue samples and in zebrafish larvae that carried luciferase genes attached to their clock genes. Kay's research team plans to test longdaysin on mice in the near future, but their goal isn't to develop longdaysin into a drug. "Longdaysin is not as potent as we would like," he adds. "This will be a tool for research."

More information: Hirota T, Lee JW, Lewis WG, Zhang EE, Breton G, et al. (2010) High-Throughput Chemical Screen Identifies a Novel Potent Modulator of Cellular Circadian Rhythms and Reveals CKIa as a Clock Regulatory Kinase. PLoS Biol 8(12): e1000559. doi:10.1371/journal.pbio.1000559