Body clock drugs could ease psychiatric disorders and jet lag

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UK researchers have successfully used a drug to reset and restart the natural 24 hour body clock of mice in the lab. The ability to do this in a mammal opens up the possibility of dealing with a range of human difficulties including some psychiatric disorders, jet lag and the health impacts of shift work.

This work is led by Professor Andrew Loudon from the University of Manchester and Dr Mick Hastings of the MRC Laboratory of Molecular Biology in Cambridge, working with a multi-disciplinary team of scientists from Pfizer led by Dr Travis Wager, and is published today in *PNAS*.

Professor Loudon said "It can be really devastating to our brains and bodies when something happens to disrupt the natural rhythm of our body clocks. This can be as a result of disease or as a consequence of jet lag or frequent changing between day and night shifts at work.

"We've discovered that we can control one of the key molecules involved in setting the speed at which the clock ticks and in doing so we can actually kick it into a new rhythm."

Most living creatures and plants have an internal body timing system - called the circadian clock. This is a complex system of molecules in every cell that drives the rhythmicity of everything from sleep in mammals to flowering in plants. Light and the day and night cycle are very important for resetting the clock and the fine adjustments are made through the action of several enzymes, including one called casein kinase 1, which has been the centre of this project.

Professor Loudon continued "The circadian clock is linked to the 24 hour day-night cycle and the major part of the clock mechanism 'ticks' once per day. If you imagine each 'tick' as represented by the rise and fall of a wave over a 24 hour period, as you go up there is an increase in the amount of proteins in the cell that are part of the clock mechanism, and as you go down, these substances are degraded and reduce again. What casein kinase 1 does is to facilitate the degradation part.

"So you can imagine that the faster casein kinase 1 works, the steeper the downward part of the wave and the faster the clock ticks - any change in casein kinase 1 activity, faster or slower, would adjust the 'ticking' from 24 hours to some other time period. Consider that if your body suddenly starts working on a 23 hour or 25 hour clock, many of your natural processes, such as sleeping and waking could soon become out of step with day and night."

The team found a drug that slows casein kinase 1 down and used it in mice where the circadian rhythm has ceased i.e. the clock has stopped ticking all together. In live mice and also in cells and tissue samples from mice, they were able to re-establish the ticking of the clock by using the drug to inhibit the activity of casein kinase 1.

Professor Loudon concluded "We've shown that it's possible to use drugs to synchronise the body clock of a mouse and so it may also be possible to use similar drugs to treat a whole range of health problems associated with disruptions of circadian rhythms. This might include some psychiatric diseases and certain circadian sleep disorders. It could also help people cope with jet lag and the impact of shift work."

Professor Janet Allen, BBSRC Director of Research said "The most effective way to develop drugs to treat a health problem is to understand the basic biology that underpins what is going on in our bodies. In this case, by understanding the basic biology of the enzyme controlling biological clocks the research team have been able to identify potential drug-based solutions to a range of issues that affect many people's health and quality of life."

Dr Michel Goedert, Head of the Neurobiology Division at Medical Research Council Laboratory of Molecular Biology said "We're all familiar with jet-lag and that sense of being disoriented in time. What is probably less widely understood is how this effect can impact on those with certain mental illnesses. It is crucial to find out what can go wrong at the molecular and cellular level in the brain if we are to determine what treatments will work for patients. If further studies in humans confirm what this study has shown in mice, this could eventually lead to an entirely new approach to treating mental illnesses such as bipolar disorder."

Dr. Wager, Associate Research Fellow, Pfizer said "It is amazing what can be accomplished when first-rate academic groups and pharmaceutical discovery units team up. Leveraging each other's talents we now have a deeper understanding of the role casein kinase plays within biological systems. Having the ability to entrain or re-entrain an arrhythmic system opens the door to new treatment option for circadian rhythm disorders. Targeting the inhibition of casein kinase with small molecules may lead to the discovery of novel drugs for the treatment of bipolar depression and other circadian rhythm disorders. The burden of these disorders is enormous and new treatment options are needed."

More information: Meng et al. 2010, "Entrainment of disrupted circadian behavior through inhibition of casein kinase 1 (CK1) enzymes", *PNAS* 107(34) p15240

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