Scientists find first evidence of 'local' clock in the brain

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Researchers have gained fresh insights into how 'local' body clocks control waking and sleeping.

All animals, from ants to humans, have internal 'circadian' clocks that respond to changes in light and tell the body to rest and go to sleep, or wake up and become active.

A master clock found in part of the brain called the suprachiasmatic nucleus (SCN) is thought to synchronise lots of 'local' clocks that regulate many aspects of our metabolism, for example in the liver. But until now scientists have not had sufficient evidence to demonstrate the existence of these local clocks in the brain or how they operate.

In a new study looking at mice, researchers including Professors Bill Wisden and Nick Franks at Imperial College London and Dr Mick Hastings' group at the MRC Laboratory of Molecular Biology in Cambridge have investigated a local clock found in another part of the brain, outside the SCN, known as the tuberomamillary nucleus (TMN). This is made up of histaminergic neurons, which are inactive during sleep, but release a compound called histamine during waking hours, which awakens the body.

The researchers deleted a well-known 'clock' gene, Bmal1, from the histaminergic neurons and found that the mice produced higher levels of the enzyme that makes histamine and were awake for much longer periods than usual. The mice also experienced a more fragmented sleep, a shallower depth of sleep, and much slower recovery after a period of sleeplessness.

This finding indicates that there is an active clock-like mechanism in histaminergic neurons, providing evidence for the first time that local clocks work alongside the master SCN clock. The results are reported in the journal *Current Biology*.

Senior researcher Professor Bill Wisden from the Department of Life Sciences at Imperial College London said: "Getting enough good quality sleep is crucial – it helps keep us mentally and physically healthy, as well as being a key factor in having a good quality of life. A lot of people would love to have more a concentrated and restful night's sleep, but at the moment we still don't know enough about exactly why we fall and

stay asleep. Our work with mice suggests that local body clocks play a key role in ensuring their sleeping and waking processes work properly. When a local clock was disrupted, their whole sleep and wake system malfunctioned. Ultimately, understanding local clocks better might enable us to target them to help people have a better night's sleep."

Lead author Dr Xiao Yu also from the Department of Life Sciences at Imperial College London said: "It is really exciting to find significant evidence of a local body clock. Now we know that the master clock is not working alone, but relies on lots other of helpers to wake up our whole body."

In the study, the researchers used EEG (electroencephalography) analysis to compare brain activity and sleep-wake cycles of mice bred without the Bmal1 gene in the TMN with that of mice that had the gene.

Results showed that deleting Bmal1 destabilised the histamine system, with the mice making more of the histamine-producing enzyme histidine decarboxylase (HDC) than normal, at the wrong time of day. Mice are normally nocturnal, but this pattern was disrupted.

Due to the higher levels of HDC, the mice without Bmal1 were much more excited and significantly more active than typical mice. This meant the mice had a more fragmented sleep.

The researchers also tested how well the mice were able to recover from periods without sleep. The mice were placed in a cage with lots of plastic tubes and pieces of paper to play with, which discouraged them from sleeping. After five hours of playing, the mice without Bmal1 had a recovery sleep that was six hours shorter than that of the control mice, as their HDC levels remained high and kept them in a more wakeful state.

Results showed that lack of sleep also affects memory, as

Bmal1-deficient mice had poorer performance in an object recognition test. In the test mice are shown a series of new objects, which they sniff and explore to uncover what they are. Mice will only explore an object if it is entirely new to them. Bmal1-deficient mice were unable to decipher between new and old objects and were excited by all objects equally, showing that they had forgotten what they had already seen.

The scientists are now looking to investigate whether there is direct communication between the master SCN and local clocks, to find out how the SCN gives and receives sleep-wake messages.

More information: X. Yu et al. 'Circadian factor Bmal1 in histaminergic neurons regulates sleep architecture'. *Current Biology*, December 2014. DOI: dx.doi.org/10.1016/j.cub.2014.10.019

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