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SLEEP CONTROL

Regular as clockwork

If you didn't need your alarm clock this morning, your natural circadian rhythm probably woke you up. In mammals, many biological functions maintain a daily rhythm, which is directed by a central clock in the brain in response to light. New research in *Nature* sheds light on how the neurons involved in this process send time-dependent messages around the whole body.

Wakefulness is controlled by a small group of neurons in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The molecular clockwork consists of positive and negative feedback loops. The positive elements include the transcription factors Clock and Bmal1, which form heterodimers and drive the transcription of the *Period* and *Cryptochrome* genes. The Per and Cry proteins then act as negative components of the feedback loop. The genes are turned on and off periodically and continually, and mutations that affect the stability of the loop are known to cause sleep disorders. Cells in the dorsal hypothalamus also have an effect on wakefulness, and secrete hypocretin/orexin peptides that have a powerful excitatory effect in sustaining this state. An outstanding question has been the missing molecular connection between the SCN cycle and the neural machinery that directly causes sleep.

Cheng *et al.* have identified a small protein — prokinectin 2 (PK2) —

that might fulfil this communication role. PK2 consists of 81 amino acids, and has previously been shown to act as a regulator of gastrointestinal smooth-muscle contractions. The protein fulfils several criteria that are expected of the predicted missing link. In mice, Pk2 shows rhythmic expression in the SCN, and its regulatory sequence contains target domains for Clock, Bmal1, Per and Cry. Expression of *Pk2* is downregulated in Clock-deficient or Cry-deficient mice, which both lack circadian cycles. Conversely, expression of *Pk2* is activated by illumination of the retina. By changing the timing of the light, the *Pk2* expression pattern shifts, as does the activity–rest cycle of the mice. The authors also showed that the receptors for Pk2 are located in the SCN, as well as the dorsal hypothalamus. There is the possibility that Pk2 amplifies its own production by modifying metabolism in the SCN.

Levels of Pk2 are high in mice during the daytime, and as both mice and humans share the same expression pattern of clock components, it is

likely that PK2 will also be high in humans at the same time. However, the circadian clocks have opposite effects in nocturnal animals and humans, so it is likely that, although Pk2 promotes rest in mice, it will probably promote activity in humans. PK2 could prove to be important in regulating gastrointestinal function, which is a chronic problem with shift workers, as well as a problem seen in jet-lagged travellers. PK2 and its receptor could also offer the opportunity to intervene in sleep disorders.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Cheng, M. Y. *et al.* Prokinectin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. *Nature* **417**, 405–410 (2002)

FURTHER READING Hastings, M. H. Circadian clockwork: two loops are better than one. *Nature Rev. Neurosci.* **1**, 143–146 (2000) | Akhtar, R. A. *et al.* Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr. Biol.* **12**, 540–550 (2002) | Allada, R. *et al.* Stopping time: the genetics of fly and mouse circadian clocks. *Ann. Rev. Neurosci.* **24**, 1091–1119 (2001)

WEB SITES

Encyclopedia of Life Sciences:
<http://www.els.net>
circadian rhythms