SLEEP

# Light sleeper

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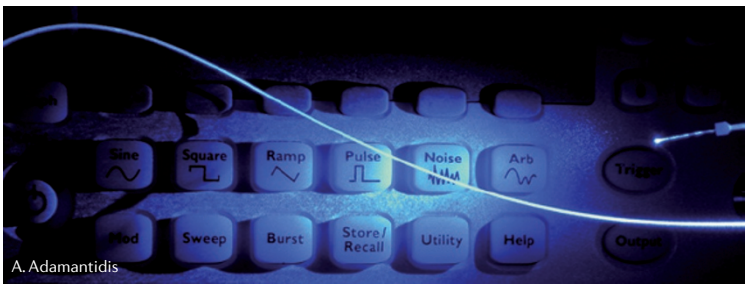

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During sleep certain brain areas work together to prevent the body waking up. Similarly, during wakefulness arousal-stabilizing brain centres are active. But what is the neural process that underlies the sleep-to-wake transition? Using optogenetic techniques, de Lecea, Deisseroth and colleagues have now shed light on this issue.

Hypocretin (HCRT)-producing neurons in the lateral hypothalamus have a role in arousal stability, but it was unknown whether changes in the activity of these neurons actually cause the transition from sleep to wakefulness. To investigate this question, the authors made use of the microbial cation channel channelrhodopsin 2, which depolarizes membranes upon exposure to blue light. They used a lentiviral vector to express channelrhodopsin 2 under the control of a promoter that is specific to HCRT-producing neurons and delivered this vector to the lateral hypothalamus of mice. By using an implanted fibre optic to illuminate this area of the brain, the authors were able to selectively manipulate HCRT-producing neurons in freely moving mice.

To examine the role of HCRT-producing neurons in the sleep-to-wake transition, the authors first determined the frequency and duration of optical stimulation that resulted in the highest increase in neuronal activation, and then observed the effects of this stimulation on the behaviour of the mice. They found that activating the HCRT-producing neurons resulted in significantly reduced latencies from both slow-wave sleep and rapid-eye-movement sleep to wakefulness, compared with controls. There was no effect on the duration of the wakeful periods, indicating that the role of the HCRT-producing neurons is specific to sleep-to-wake transitions.

To test whether this role is dependent on HCRT release, the authors investigated the effect of an HCRT receptor 1 antagonist, SB334867. They found that administration of this antagonist 45 minutes before photostimulation prevented the reduction in sleep-to-wake latencies in the transduced mice, in a dose-dependent manner. Furthermore, in mice that lacked the *Hcrt* gene, wake latencies were also less reduced by photostimulation; however, the reduction was not blocked completely, indicating that other neurotransmitters in these neurons might also have roles in the sleep-to-wake transition.

These findings show that HCRT-producing neurons have a role in initiating the transition from sleep to wakefulness. However, the sleep state as a whole is dependent on the cumulative effects of various systems, and through the selective control of HCRT-producing-neuron activity, it should be possible to investigate the interactions of these various brain centres with HCRT-producing neurons and elucidate their contribution to sleep and wakefulness.

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**ORIGINAL RESEARCH PAPER**
Adamantidis, A. R., Zhang, F., Aravanis, A. M., Deisseroth, K. & de Lecea, L. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature* 17 Oct 2007 (doi:10.1038/nature06310)