nature neuroscience gateway

NEUROTECHNIQUES

Awakenings

Neuroscience Gateway (October 2007) | doi:10.1038/aba1790

Photostimulation of lateral hypothalamic neurons expressing a light-activated cation channel induces awakening from sleep.

Can you import sunlight if you live in a cave? Researchers have used light to stimulate neurons on or near the dorsal surface of the brain that express light-activated cation channels. What about neurons that lie beneath the brain surface? Adamantidis *et al*. report optogenetic control of neurons in the hypothalamus involved in sleep in a recent article in *Nature*.

The hypothalamus is a ventral brain structure. Hypocretin, which regulates energy expenditure, localizes to the lateral hypothalamus. Loss-of-function mutations in hypocretin are associated with narcolepsy, a disease that makes people fall asleep at inappropriate times.

Channelrhodopsin-2 (ChR2) is a cation channel from algae that depolarizes neurons in the presence of blue light. The authors drove ChR2 expression with the hypocretin promoter in a lentiviral expression vector (*Hcrt::ChR2*). They cannulated mice and stereotactically injected *Hcrt::ChR2* or a control lentivirus into the lateral hypothalamus. Hypocretin neurons infected with *Hcrt::ChR2* stably expressed ChR2 for at least 2 months. Blue light induced inward current in hypocretin neurons expressing ChR2, as shown by voltage-clamp recordings in lateral hypothalamic slices. Pulses of blue light or continuous blue illumination induced repetitive action potentials in neurons expressing *Hcrt::ChR2*.

To stimulate and record from behaving mice, the authors permanently implanted mice with electroencephalography (EEG) and electromyography (EMG) electrodes and inserted an optical fiber into the same cannula used for lentiviral injections. Blue illumination increased the expression of the immediate early gene product c-Fos in lateral hypothalamic neurons expressing *Hcrt::ChR2*, suggesting that light stimulation from the implanted optical fiber activated lateral hypothalamic neurons, allowing the researchers to study the effects of this activation on sleep.

Mammalian sleep occurs in phases. Slow-wave sleep (SWS) is deep sleep that is characterized in EEG by slow (0.5–4 Hz) delta waves. Rapid eye movement (REM) sleep is a lighter sleep phase than SWS and is characterized by EEG recordings that are similar to the awake state. EMG recordings are nearly silent for mice in REM and SWS sleep but are active in awake mice. After blue light stimulation, *Hcrt::ChR2* mice awoke faster from both SWS and REM sleep than did mice treated with control lentiviruses. Durations of sleep and wake periods were similar in control and *Hcrt::ChR2* mice. However, photostimulation increased the probability of transitioning to the awake state from both SWS and REM sleep in *Hcrt::ChR2* mice.

Does hypocretin secretion regulate wakefulness in the lateral hypothalamus? A hypocretin receptor 1 antagonist blocked the light-induced decrease in sleep-to-wake latency in *Hcrt::ChR2* mice, and hypocretin knockout *Hcrt::ChR2* mice showed increased latency to wake relative to wild-type *Hcrt::ChR2* mice.

Together, these data indicate that the activation of hypocretin neurons induces hypocretin secretion and drives arousal. Therefore, optogenetic tools can be used to selectively activate defined neural populations throughout the brain to determine their roles in complex behaviors.

Debra Speert

1. 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* 10.1038/nature06310 (2007). | Article |