Subtle chemical changes in brain can alter sleep-wake cycle

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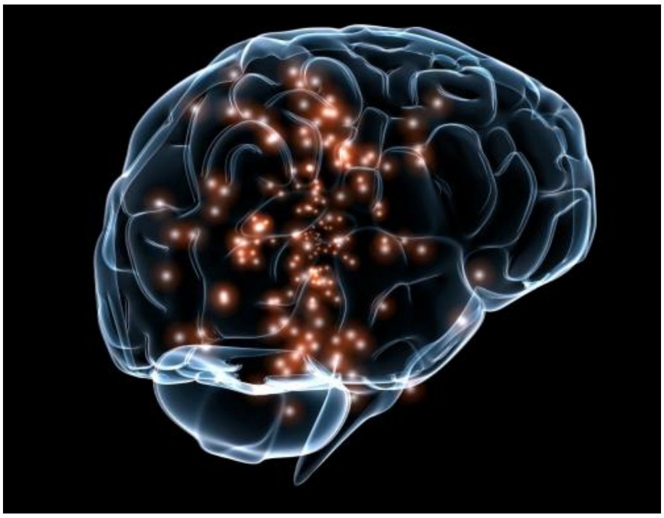

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A study out today in the journal *Science* sheds new light on the biological mechanisms that control the sleep-wake cycle. Specifically, it shows that a simple shift in the balance of chemicals found in the fluid that bathes and surrounds brain cells can alter the state of consciousness of animals.

The study, which focuses on a collection of ions that reside in the cerebral spinal fluid (CSF), found that not only do these changes play a key role in stimulating or dampening the activity of nerve cells, but they also appear to alter cell volume causing brain cells to shrink while we sleep, a process that facilitates the removal of waste.

"Understanding what drives arousal is essential to deciphering consciousness and the lack thereof during sleep," said Maiken Nedergaard, M.D., D.M.Sc., co-director of the University of Rochester Center for Translational Neuromedicine and lead author of the study. "We found that the transition from wakefulness to sleep is accompanied by a marked and sustained change in the concentration of key extracellular ions and the volume of the extracellular space."

The current scientific consensus is that the brain is "woken up" by a set of neurotransmitters - which include compounds such as acetylcholine, hypocretin, histamine, serotonin, noradrenaline, and dopamine - that originate from structures deep within the brain and the brain stem. This cocktail of chemical messengers serve to activate - or arouse - a set of neurons in the cerebral cortex and other parts of the brain responsible for memory, thinking, and learning, placing the brain in a state of wakefulness.

However, this model does not fully explain how the brain quickly activates the billions of nerve cells necessary to be become alert and begin processing information from the outside world, or how it winds down this activity when it is time to sleep. Nor does it explain how the brain maintains a state of wakefulness or sleep over time.

The new study reveals that our sleep-wake state appears to be dependent upon the concentration and balance of ions in the CSF. In fact, by altering the concentrations of potassium, calcium, magnesium, and proton ions found in the fluid, the researchers observed that they could manipulate the sleep-wake state of mice in the absence of neurotransmitters. Potassium in particular appears to play a key role as the levels of the ion fluctuate rapidly during sleep-wake transitions.

While these shifts in ion concentration outside of brain cells had been known to occur, these changes had always been regarded as a consequence rather than one of the causes of the sleep-wake cycle, as the new study suggests.

"The fact that a simple alteration of extracellular ion composition can wake a sleeping animal up and put a wake animal to sleep is direct evidence for that this mechanism plays a key role in regulating consciousness," said Nedergaard.

Because the ions are positively charged, as they move back and forth between CSF and brain cells, they can change the electrical activity of cells, causing them to either polarize or depolarize. When depolarization occurs in neurons, the cells become excitable, alert, and awake.

The findings may reveal how the brain is able to accomplish the task of activating billions of nerve cells quickly, simultaneously, and on a global scale when we transition from sleep to awake. It may also show how the brain is able to maintain a state of sleep or wakefulness over an extended period of time by altering the electrical potential of nerve cells.

The researchers also observed that the chemical changes impacted the volume of brain cells. Specifically, they found that nerve and support cells in the brain shrink while we sleep, creating more space for cerebral spinal fluid to flush away waste, a process that Nedergaard and her colleagues first described back in 2013.

By identifying this new control mechanism, the findings could point to new ways to regulate the sleep-wake cycle, leading to new sleep medications, and help scientists better understand prolonged losses of consciousness, such as during a coma. It is also speculated that changes in ion composition play a role in fatigue and impaired memory experienced during prolonged periods of wakefulness in sleep deprived individuals.

More information: "Changes in the composition of brain interstitial ions control the sleep-wake cycle," *Science* , DOI: 10.1126/science.aad4821

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