Activating astrocytes in the basal forebrain keeps mice awake without any signs of sleepiness

August 26 2023, by Ingrid Fadelli

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Sleep is known to support the proper functioning of body, including the brain, allowing it to rest, recover, and recharge. While countless

neuroscientists and medical researchers have been trying to better understand this vital biological process, much of its neural underpinnings are still unknown.

Researchers at Washington State University (WSU) have been conducting studies investigating the role of astrocytes, a subtype of glial cells known to regulate different brain and bodily functions, in sleep and wakefulness. Their most recent paper, published in the *Journal of Neuroscience*, shows that the activation of astrocytes in the basal forebrain (i.e., a brain region that supports the regulation of sleep, waking-up and body temperature) caused mice to remain awake indefinitely, without showing any signs of sleepiness.

"Our study was part of a larger investigation into the brain cells and circuits that make us sleepy," Marcos Frank, one of the researchers who carried out the study, told Medical Xpress. "Scientists refer to this as 'sleep drive,' and we really don't have a complete explanation of sleep drive. Back in 2009, we published the first evidence that a class of non-neuronal cells called glial astrocytes influenced sleep drive in vivo. Since then, we have been trying to understand the precise role of astrocytes in sleep and wakefulness."

The key objective of the recent work by Frank and his colleagues was to better understand how astrocytes in the basal forebrain influence sleep, wakefulness, and overall sleep drive. To do this the researchers used a series of advanced genetic and chemical techniques to reversibly alter the activation of astrocytes in the mouse basal forebrain.

"We used a 'chemo-genetic' technique to express a receptor to a small molecule not normally expressed in the mammalian brain," Frank explained. "When activated by a special drug, this receptor activates astrocytes. We combined this with standard measures of brain activity and motor activity, which together tell us if the animal is awake or

asleep."

To ensure that the effects they observed were specifically linked with the chemo-genetic activation of astrocytes, the team also carried out several control experiments, where the same mice were observed in similar circumstances but without their astrocytes being activated. Ultimately, the researchers observed that the activation of basal forebrain astrocytes resulted in the mice being awake for hours on end, without exhibiting any typical signs of sleepiness.

"It seemed that the mice were awake without any 'cost,' or in other words no increased sleep drive," Frank said. "This was unexpected to us and has several important implications. First, our results challenge the notion that our need for sleep is generated by wakefulness per se. Instead, it may require a specific set of interactions between subtypes of brain cells."

Overall, the recent findings gathered by this team of researchers highlight the key role of some neuronal-glial circuits in modulating sleep drive and wakefulness. In the future, they could pave the way to exciting new discoveries about the neural underpinnings of sleep, potentially also enabling the creation of drugs that allow people to remain awake and lucid for prolonged periods of time.

"Imagine a world where (if this is translated to humans) shift-workers don't get sleepy, and for extended periods, astronauts, pilots, soldiers, health-care providers, first-responders can dispense with sleep," Frank added.

"We are very early in this process, but if this were to happen, it would forever change the limits of human performance. Our next works will focus on understanding what happens next in the chain of events when we activate basal forebrain astrocytes. Does this lead to changes in

surrounding neurons and how does that explain our results? What normally controls this process in the healthy brain, and is this astrocyte -activated waking the same as normal waking? These are all questions we hope to answer in our future studies."

More information: Ashley M. Ingiosi et al, Activation of Basal Forebrain Astrocytes Induces Wakefulness without Compensatory Changes in Sleep Drive, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.0163-23.2023.