

Molecular biology of sleep apnea could lead to new treatments

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Researchers at the University of Pennsylvania School of Medicine have provided, for the first time, a detailed look at the molecular pathways underlying sleep apnea, which affects more than twelve million Americans, according to the National Institutes of Health. Sleep apnea is a condition characterized by temporary breathing interruptions during sleep, in which disruptions can occur dozens or even hundreds of times a night.

The team found that in an animal model of sleep apnea poorly folded proteins accumulate in one compartment of a muscle nerve cell, which, under certain conditions, tells a cell to heal itself or destroy itself. The findings appear in a recent issue of the *Journal of Neuroscience*.

"Muscles relax as a normal part of sleep, causing the airway to close," explains senior author Sigrid C. Veasey, MD, Associate Professor of Medicine, at the Penn Center for Sleep. "But in patients with sleep apnea, oxygen levels in cells drop too low, sending an arousal signal to wake by gasping for air. This happens all night long, so patients experience bad quality sleep. In addition to problems with sleepiness, subtle peripheral neural injury occurs."

In a mouse model of sleep apnea, the researchers found that motor neurons of the jaw and face had swollen endoplasmic reticula, the part of the cell where proteins get folded properly. They surmised that misfolded proteins accumulated as the endoplasmic reticula of mice were exposed to decreased oxygen and oxygen fluctuations during sleep



over eight weeks. The involvement of the endoplasmic reticula has never been shown before in explaining the physiology of sleep apnea on a cellular level, says Veasey.

But how does this work? Sensor proteins sitting on the surface of the endoplasmic reticula get activated by poorly folded proteins within. The Penn group worked with one of those proteins, called PERK. When PERK gets activated, two things can happen: The cell can take a pathway to fix itself or one that leads to self destruction. The cell makes that decision based on its initial health.

"If a patient has sleep apnea with healthy cells, the cells will take the fixit path. Then good things happen; the cell activates another molecule called eIF-2alpha, which turns on helpful molecules like anti-oxidants that degrade the misfolded proteins," explains Veasey.

However if cells are unhealthy to begin with, the PERK pathway can also turn on molecules that cause the cell to turn on itself and activate apoptosis or cell death. "In this event, we predict that patients with sleep apnea may lose motor neurons," notes Veasey. "Eventually sleep apnea could continue to worsen since the few remaining neurons are already stressed when gasping for air during sleep."

A drug called salubrinal does keep the eIF-2alpha path active, thereby preventing vulnerable cells from going down the cell-death path. But salubrinal is a double-edged sword: Just the right amount keeps the cell happy, but too much can shut down all protein synthesis, a highly toxic outcome.

The research team is now working on how to ramp up the eIF-2alpha path with changes in the mouse diet. "This paper shows which pathways are important for treating sleep apnea, but we'll need to come up with therapies other than salubrinal," says Veasey. "Ultimately if we can do



healthy things that protect the endoplasmic reticula of cells, then sleep apnea won't be such an insult, not only to motor neurons, but neurons involved in cognition and alertness."

Source: University of Pennsylvania

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