UT SOUTHWESTERN MEDICAL CENTER NEWS

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# UT Southwestern researchers identify molecule that helps the sleep-deprived to mentally rebound

DALLAS – Feb. 24, 2009 – Sleep experts know that the mental clarity lost because of a few sleepless nights can often be restored with a good night's rest. Now, UT Southwestern Medical Center researchers have identified a key molecular mechanism that regulates the brain's ability to mentally compensate for sleep deprivation.

Working with mice, they found that a molecule called an adenosine receptor is necessary for sleep-restricted animals to attain adequate levels of slow-wave activity in the brain once normal sleep resumes. It is this increase in slow-wave activity, or SWA, during rebound sleep that helps restore normal working memory and attention skills to the sleep-deprived, the scientists report in the Feb. 4 issue of the *Journal of Neuroscience*.

"Normal society pushes people to burn candles at both ends – going to bed late, getting up early, and somehow performing mentally with lack of adequate sleep," said senior author Dr. Robert Greene, professor of psychiatry at UT Southwestern. "We need to have our adenosine receptors intact to do that."

Adenosine receptors on nerve cells, including brain cells, are akin to docking points for the molecule adenosine. Adenosine levels increase in the brain with each hour of waking activity, and "docking" of the molecule with its receptor is shown in this study to help promote the slow-wave activity of sleep. Scientists have known that recovery from sleep deprivation involves not only an increase in sleep time, or rebound sleep, but also an elevation in this slow-wave activity.

To investigate how adenosine receptors and SWA might be linked, Dr. Greene and his team engineered mice that lacked a receptor to pair up with adenosine.

Sleep-restricted mice were kept awake by being placed on a moving treadmill. Researchers then electronically monitored sleep and waking activity of both normal and genetically engineered mice, including monitoring electronically the brain waves of the animals. The mice also traveled a maze with eight paths, each with a piece of chocolate at the end of it.

Electronic measurements showed that, unlike normal mice, the mice lacking the adenosine receptor could not increase the intensity of their slow-wave activity in response to the sleep

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deprivation. Under normal sleep conditions both the normal and mutant mice were almost error-free on the maze test. However, when sleep-deprived, the engineered mice made significantly more errors on the maze test than their normal counterparts. This type of skills test represents the human equivalent of the attention and working memory needed to multitask or build on tasks already done, such as being given a phone number, reaching for a pen to write it down and recalling the number, said Dr. Greene.

Linking the lack of functioning adenosine receptors to depressed normal SWA rebound response might aid in developing treatments for people with sleep-related cognitive deficits, he said.

The research also further explains the effects of caffeine, which also "docks" to adenosine receptors, preventing the docking of adenosine and keeping the caffeine-drinker awake. Dr. Greene compared the study mice's behavior response on the maze test to how a person drinking a "permanent cup of coffee" might behave.

"They probably won't get the regular amount of slow-wave activity or deep sleep as they normally would," Dr. Greene said. "This is not to say that coffee is bad, but drinking it all the time or in the evening could affect your mental performance the next day."

The researchers next will investigate the relationship between sleep, adenosine and energy metabolism, a biological process in which adenosine plays a key role.

Other researchers from UT Southwestern involved in the study were lead author Dr. Theresa Bjorness, postdoctoral research fellow in psychiatry, and Virginia Poffenberger, research technician in psychiatry.

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