UT SOUTHWESTERN MEDICAL CENTER NEWS

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Hormone links sleep, hunger and metabolism, researchers find

DALLAS – Nov. 14, 2007 – While investigating how the hormone orexin might control sleep and hunger, researchers at UT Southwestern Medical Center have discovered, to their surprise, that it activates a protein, HIF-1, long known to stimulate cancerous tumor growth.

The study, appearing today in the online version of the journal *Genes and Development,* is among the first to show how HIF-1 operates in healthy tissues rather than in tumors, said Dr. Thomas Kodadek, chief of translational research at UT Southwestern and senior author of the study.

"HIF-1 is very big in the cancer community," Dr. Kodadek said. "So we were intrigued to find this important and very basic mechanism that is unrelated to cancer."

Orexin was already known for its role in sleep and hunger. Researchers, including Dr. Masashi Yanagisawa, professor of molecular genetics at UT Southwestern, had found that lack of orexin causes the sleep disorder narcolepsy.

"It's really the most straightforward system relevant to the biology of sleep you can look at," Dr. Kodadek said. "You lack orexin? You've got narcolepsy. End of story."

Dr. Kodadek's project is part of an initiative funded by the National Heart, Lung and Blood Institute to develop technologies to understand and treat sleep disorders.

In the current study, the researchers used a massive gene-screening technique to identify genes that orexin either turned on or inhibited.

Surprisingly, the activity of a component of *HIF* called *HIF1-alpha* was among the most highly activated of any gene in the study. And when orexin stimulated *HIF1-alpha*, it in turn increased the expression of a variety of genes dedicated to burning sugar to provide energy for the body. Studies in brain slices of mice with and without orexin receptors support their results.

The findings help explain orexin's link to the metabolic system, the researchers said. The body is known to step up its production of orexin when blood sugar gets low. The researchers hypothesized that when a body has low blood sugar and gets hungry, the increase in orexin activates

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HIF-1 production, revving up metabolism so the body gets the most energy out of the sugar on hand.

This action of HIF-1 when stimulated by orexin is different than how it acts in tumors, Dr. Kodadek said. In tumors, HIF-1 changes cells' metabolism so they can burn sugar for energy without oxygen. This method is inefficient, but allows cells to stay alive.

Orexin, on the other hand, forces HIF-1 to switch cells to burn sugar *using* oxygen, which burns sugar faster but more efficiently. This strategy makes sense, they said, in terms of evolution.

"You need to be active and energetic, especially when you're hungry, so you can search for a meal," said Dr. Devanjan Sikder, instructor of internal medicine and lead author of the study.

"This orexin pathway we found is basically an overdrive function. Even though blood sugar levels are low, you're not only awake, but you're also energetic because of the action of HIF-1," said Dr. Kodadek. "In retrospect, our findings make a lot of sense, but they were surprising at the time."

Not only was this orexin-HIF link unexpected, but it showed an entirely new way HIF-1 operates, Dr. Kodadek said. There have been a few recent studies on its function in healthy tissues, but none involving mechanisms related to sleep, he said.

The study also illustrates a potential complication of anti-cancer therapies that target HIF-1, Dr. Kodadek said. These results reveal that anti-HIF-1 chemotherapy could interfere with this essential function.

"If anything, our findings may be a cautionary tale about whether HIF-related mechanisms are going to be appropriate targets for chemotherapy," Dr. Kodadek said.

The researchers next plan to genetically engineer mice that lack HIF-1 in the brain in order to determine the effects on wakefulness and activity levels of the animals. They also plan to further study how orexin and oxygen levels interact to control energy metabolism in cells.

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