SOUTHWESTERN NEWS

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# UT Southwestern research halts narcolepsy symptoms

DALLAS – March 15, 2004 – Researchers at UT Southwestern Medical Center at Dallas have discovered a potentially new avenue for treating human narcolepsy, and the work may also lead to more effective ways for insomniacs to boost their wakefulness during the daytime.

Artificially reintroducing a brain chemical called orexin into mice that lack the ability to produce the chemical on their own rids the mice of their narcolepsy symptoms, UT Southwestern researchers have discovered. Their work appears in an upcoming issue of the *Proceedings of the National Academy of Sciences* and is currently available online.

The genetically engineered mice used lacked a particular type of nerve cell in the brain that produces orexin. Most researchers believe that in humans, a lack of or deficiency in orexin causes narcolepsy, a rare disease in which people uncontrollably fall asleep, have excessive daytime sleepiness, and experience sudden muscle weakness called cataplexy.

"Assuming that narcoleptic humans are like these mice, which is a very plausible assumption, our experiments provide a strong proof of concept that introducing into the brain a molecule that mimics the effect of orexin will be the fundamental cure for human narcolepsy," said Dr. Masashi Yanagisawa, professor of molecular genetics and the paper's senior author.

Orexins are small chains of molecules made by nerve cells, or neurons, in the region of the brain called the hypothalamus. In 2001 Dr. Yanagisawa, an investigator in the Howard Hughes Medical Institute at UT Southwestern, and his research group were the first to genetically engineer knockout mice that lacked orexin-producing brain cells. Without these neurons, the mice did not wake up to feed as normal mice did, and they also experienced cataplectic arrests. "We believe these mice represent the closest model of human narcolepsy," Dr. Yanagisawa said.

In their latest research, Dr. Yanagisawa and his colleagues "rescued" the orexin knockout mice from their orexin deficiency – and relieved their narcoleptic symptoms – in two different ways. One method involved genetics, the other, injections.

In the genetic rescue, the researchers made transgenic, or genetically engineered, mice that not only lacked the orexin-producing neuron, but also continuously and diffusely expressed orexin

(MORE)

everywhere in their brains. The mice did not experience any sleep abnormalities or cataplectic arrests, and they were able to maintain wakefulness.

Dr. Yanagisawa noted, however, that the transgenic mice never really experienced the orexin deficiency state because, even though they had no orexin-producing neurons, they had orexin in their brains from birth. That prompted a second experiment, in which the brains of orexin neuron-ablated mice were injected with orexin peptides.

"No one had done this before," Dr. Yanagisawa said. "In order to strengthen our argument, and also looking toward possible future medical treatments, we tried to pharmacologically rescue the mice."

The researchers found that the orexin injections increased wakefulness and suppressed cataplectic arrests. Also, there was no "rebound sleep" after the orexin effect wore off.

"This is extremely important because it shows that these mice retain the ability to respond to orexin," Dr. Yanagisawa said. "The downstream pathways, including the orexin receptors, are normal even in the absence of orexin-producing neurons. Also, the mice wake up, but do not try to regain that lost sleep, which is important with respect to therapeutic applications."

Wild-type mice that received the injection also woke up, but the waking up effect was more pronounced in the orexin neuron-ablated mice.

Dr. Yanagisawa said any new drug therapies for narcolepsy would be based on developing molecules, called orexin receptor agonists, that mimic the effect of orexin and that are small enough to cross the blood-brain barrier. Such drugs might also be effective for insomniacs.

"Things like orexin receptor agonists might also be applied in the treatment of insomnia, boosting energy and wakefulness during the daytime," he said.

Other UT Southwestern researchers contributing to the orexin study were Dr. Christopher Sinton, assistant professor of internal medicine, and first authors Dr. Michihiro Mieda, a postdoctoral research fellow in molecular genetics, and M.D./Ph.D. student Jon Willie. Also contributing were researchers from the University of Tsukuba in Japan. The research was funded in part by the Perot Foundation and Exploratory Research for Advanced Technology/Japan Science and Technology Agency.

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