SOUTHWESTERN NEWS

Contact: Susan A. Steeves
(214) 648-3404
or E-mail: susan.steeves@email.swmed.edu

UT SOUTHWESTERN RESEARCHERS CREATE MICE WITH NARCOLEPSY

DALLAS – August 6, 1999 – Using an infrared, nighttime video camera to study genetically engineered mice lacking a molecule known to affect appetite, UT Southwestern Medical Center at Dallas researchers unexpectedly discovered they had created a rodent with the sleep disorder narcolepsy.

This finding is significant because there is no cure or long-term treatment for the illness, which affects 200,000 Americans and can alter social, personal and professional activities because those suffering from it frequently fall asleep at inappropriate times. Knowing what causes narcolepsy could lead to treatments.

The research will be published in the Aug. 20 issue of *Cell,* but the journal lifted the embargo two weeks early because the Aug. 6 issue contains a related report.

The UT Southwestern scientists created the disorder in the mice when they removed the neuropeptide orexin to examine how removal of this protein, found in nerve cells of the brain's lateral hypothalamus, changed the animals' habits. They found that the mice unexpectedly fell asleep in the middle of high activity, said Dr. Masashi Yanagisawa, professor of molecular genetics and senior author of the study.

He and his colleagues last year discovered orexin-A and orexin-B, the ligands or keys, and OX_1 and OX_2, the receptors or locks, that fit together to begin an intercellular communication process that stimulates food consumption. The work that led to the narcoleptic mice was a continuation of the orexin research.

"During the course of our work, we decided that it was best to study the mice at night, which is when they are most active," said Yanagisawa, also a Howard Hughes Medical Institute (HHMI) investigator and holder of the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science.

In observing the rodents, Dr. Richard Chemelli, the lead author and a pediatric research

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fellow, noticed that the animals sometimes fell over on their sides, staying that way for one or two minutes, with about 15 attacks during a four-hour period. The researchers first thought the mice might be experiencing epileptic seizures.

They discussed the problem with Dr. Christopher Sinton, an assistant professor of psychiatry who specializes in sleep disorders and also works with rodents. He and Chemelli fashioned tiny electrodes hooked to tethers so the mice could move around normally in their cages while the scientists monitored their brain waves, muscle activity and behavior. The animals' readings matched those of humans with narcolepsy, Yanagisawa said. The mice manifested the same abnormalities of sleep patterns, including rapid eye movement (REM) sleep at the beginning of a sleep period instead of after a normal period of non-rapid eye movement sleep (NREM).

People and animals not affected by narcolepsy usually have about an hour and a half of NREM before entering the REM stage, which is a deep sleep and is when dreams occur.

All of the mice lacking the orexin ligand had narcolepsy while none of the normal mice experienced the chronic sleep disorder.

In the related study published Aug. 6, Stanford University researchers reported mutations of the OX_2 receptor gene in narcoleptic dogs.

The other researchers involved in the UT Southwestern-led study were: graduate students Jon Willie and Yumei Xiong; Dr. James Richardson, associate professor of pathology; HHMI research technician Clay Williams; psychiatry senior research associate Thomas Fitch; Dr. Robert Hammer, professor of biochemistry and HHMI senior associate; and researchers at Beth Israel-Deaconess Medical Center in Boston and Miyazaki Medical College in Miyazaki, Japan. Chemelli is also a National Institutes of Health (NIH) fellow of the Pediatric Scientist Development Program.

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