UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

Natural brain substance blocks weight gain in mice, UT Southwestern researchers discover

DALLAS – Jan. 28, 2009 – Mice with increased levels of a natural brain chemical don't gain weight when fed a high-fat diet, researchers at UT Southwestern Medical Center have found.

The chemical, orexin, works by increasing the body's sensitivity to the "weight-loss hormone," leptin, the researchers report.

Finding a way to boost the orexin system may prove useful as a therapy against obesity, said Dr. Masashi Yanagisawa, professor of molecular genetics at UT Southwestern and senior author of the study, which appears in the January issue of *Cell Metabolism.*

"Obese people are not deficient in leptin," Dr. Yanagisawa said. "They have tons of leptin floating around. The problem is that their brain isn't very sensitive to it."

Orexin, which Dr. Yanagisawa discovered about a decade ago, is involved in controlling appetite and sleep. He found that reduced levels of orexin lead to the sleep disorder narcolepsy in both rodents and humans.

Orexin can boost the appetite in the short term, but, paradoxically, a lack of orexin leads to obesity in the long run. "It's been confusing," said Dr. Yanagisawa, an investigator with the Howard Hughes Medical Institute at UT Southwestern.

Part of the confusion comes about because orexin acts on two different molecules in the brain, OX1R and OX2R. In the current study, the researchers aimed to distinguish which action was involved in weight control.

The researchers increased the levels of orexin in mice, either through genetic engineering or by administering the hormone into the brain.

When these mice were fed a healthy diet, the increased levels of orexin made little difference in their weights compared to normal mice; however, when the mice were fed a high-fat diet, the high-orexin mice remained lean while the normal animals became obese. This difference was due to an increase in the rate of metabolism – high-orexin mice burned fuel up to 20 percent faster than normal mice.

The high-orexin mice had lower blood levels of leptin, implying that the leptin was more effective in controlling weight in these mice. In addition, when the researchers administered leptin to the

(MORE)

high-orexin mice, the animals responded with a much greater loss of appetite and weight compared to normal mice given leptin.

The researchers also administered a substance that activates only OX2R to separate out orexin's possible double action. The mice given this substance showed the same beneficial response to high-fat diets and leptin, confirming that OX2R controls the interaction.

These results clarify the action of orexin and point to OX2R as a potential route to help treat obesity, but any practical use is still far off, Dr. Yanagisawa said.

A primary hurdle to orexin-based drug development is a defense system in the body called the blood-brain barrier, which prevents many substances in the blood from penetrating into the brain. Because of this, orexin cannot reach the brain when it is given orally or as an intravenous or subcutaneous injection.

"Fortunately, however, high-orexin mice show no sleep/wake disturbance or other serious side effects," Dr. Yanagisawa said.

"This study suggests that if we can develop a compound that mimics the action of orexin on its receptor, we might be able to treat narcolepsy and other sleep disorders, as well as obesity," Dr. Yanagisawa said. "We have already screened out some such 'orexin mimics.' The next step is to do serious medicinal chemistry to make variations of these compounds to get them more potent and specific. If we could advance to early clinical trials in five years, I'd say we'd be lucky.

"I hope that in the long run a suitable orexin mimic might help people be more mentally productive during the day, as well as be able to lose weight more easily."

Other UT Southwestern researchers involved in the study were co-lead authors Dr. Hiromasa Funato, a former postdoctoral fellow now at the University of Yamaguchi in Japan, and graduate student Allen Tsai; Dr. Jon Willie, a former student in the Medical Scientist Training Program now at Washington University; Dr. Yasushi Kisanuki, a former postdoctoral fellow now at the University of Michigan, Ann Arbor; and Clay Williams, former research specialist with the HHMI. Dr. Takeshi Sakurai of the Japan Science and Technology Agency also participated.

The study was funded by the HHMI and the Perot Foundation.

###