SOUTHWESTERN NEWS

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HORMONES FOUND IN THE BRAIN MAY DETERMINE HOW MUCH YOU EAT AND AFFECT OBESITY AND DIABETES

DALLAS – February 20, 1998 – Scientists at UT Southwestern Medical Center at Dallas believe newly discovered hormones produced in the brain may influence development of obesity and diabetes.

The researchers, who discovered the hormones, said in today's issue of *Cell* that further research into these neuropeptides — proteins found in nerve cells — and receptors may reveal ways to inhibit eating. The hormones were found to stimulate the appetite of laboratory rats. The neuropeptides, or ligands, which are called orexin-A and orexin-B, and the receptors, OX_1R and OX_2R, allude to the Greek word *orexis*, for appetite.

"These receptors and ligands regulate feeding behavior, which is a very important area of medical research," said Dr. Masashi Yanagisawa, professor of molecular genetics and Howard Hughes Medical Institute (HHMI) investigator. "This is an excellent area for further drug research to determine whether orexins and their G protein-coupled cell-surface receptors can be targeted to suppress eating habits."

In the first part of their investigation, the scientists found the receptors, which are closely related proteins. When bound to ligands, the receptors trigger a G protein, which in turn sets off a series of messages to turn on or turn off genes. Next, they found the two ligands, members of a previously unidentified family of neuropeptides, which bind with OX_1R and OX_2R to begin the signaling cascade. These proteins are located in a portion of the brain called the lateral hypothalamus, the region that controls appetite.

After determining that they had the locks (receptors) and keys (ligands) that fit together to begin the intercellular communication process, the investigators tested it on rats. They used catheters to administer some of the neuropeptides to the animals' brains and found that the proteins stimulated food consumption.

"When we limited the food intake of the animal, even more of the neuropeptide was

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produced, which is what we expected of a hormone that physiologically regulates appetite," Yanagisawa said. "The neuron tells the animal it is hungry by producing more orexin peptides. Increased peptides increased the animal's appetite. In other words, it is part of a feedback loop in the biochemical process."

He said an important part of upcoming research will be to produce rodents missing three genes — one ligand and the two receptor genes — to see if the rats' appetites can be decreased by inhibiting any of them.

"These neuropeptides are a very plausible molecular basis for some classical experiments on eating habits," Yanagisawa said. "The question is what happens in the brain to control the highly complex feeding behavior, as well as body weight."

The brain translates information it receives from different organs into metabolic-rate changes, which affect how much food people consume and how fast their bodies burn it off.

"The brain is doing a lot of things like a black box in dealing with all this information," Yanagisawa said. Part of this biochemical process involves maintaining equilibrium between food consumption and energy expenditure. This helps determine whether someone becomes obese and/or develops adult-onset diabetes mellitus.

"Now is the time when we start to understand the neural network and the molecular players that form the very complex regulation of this entire biochemical process of appetite," he said. "We believe that neuropeptides, including orexins, are very important components."

Other authors of the study were: Drs. Hirokazu Tanaka and Richard Chemelli, postdoctoral fellows in molecular genetics and HHMI associates; Dr. James Richardson, associate professor of pathology; Dr. Gerald Koslowski, associate professor of physiology; S. Clay Williams, HHMI research technician; Makoto Ishii, a UT Southwestern summer undergraduate fellow; Drs. Takeshi Sakurai, Akira Amemiya and Ichiyo Matsuzaki, former UT Southwestern postdoctoral fellows and HHMI associates, now continuing their studies in Japan; and researchers at SmithKline Beecham Pharmaceuticals.

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