Researchers find clue to safer obesity drugs

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(PhysOrg.com) -- Once hailed as a miracle weight-loss drug, Fen-phen was removed from the market more than a decade ago for inducing life-threatening side effects, including heart valve lesions. Scientists at UT Southwestern Medical Center are trying to understand how Fen-phen behaves in the brain in order to develop safer anti-obesity drugs with fewer side effects.

In a study appearing in the Nov. 25 issue of *Neuron*, the researchers define a circuit in the brain that explains the ways fenfluramine, a component of Fen-phen, suppresses appetite.

"Our findings provide evidence that the neural circuit we've proposed is sufficient for the neurotransmitter serotonin to regulate food intake and body weight, " said Dr. Joel Elmquist, professor of internal medicine and pharmacology at UT Southwestern and senior author of the study. "Fen-phen works directly on this pathway. Unfortunately, that drug also adversely affects peripheral tissue such as the heart."

For the current study, the researchers engineered mice in which the expression of a serotonin receptor called 5-hydroxytryptamine 2C was blocked throughout the entire body. This was previously known to produce obese mice resistant to the anorexic actions of fenfluramine. When activated by serotonin, however, this receptor is also known to suppress appetite. Using this mouse model, the authors engineered another set of mice in which the same serotonin receptor was blocked everywhere in the body except within a group of brain cells called pro-opiomelanocortin, or POMC, neurons. The POMC neurons, which are

found in the hypothalamus, are also known to play an important role in suppressing appetite and inducing weight loss.

The researchers found that the animals with no serotonin 2c receptors expectedly developed obesity as well as other metabolism disorders such as increased food intake, hyperactivity and leptin insensitivity. They also were prone to spontaneous seizures, said Dr. Elmquist.

In contrast, the mice in which the serotonin receptor was re-expressed and functioning only in the POMC neurons stayed slim and responded to fenfluramine.

"The POMC-specific reactivation of the receptor only in POMC neurons normalizes the abnormal metabolism in these mice," Dr. Elmquist said. "The animals don't eat excessively. Their hyperactivity is also gone."

Previous work from the UT Southwestern group led to the hypothesis that Fen-phen worked by activating the serotonin 2c receptor in the POMC neurons in the hypothalamus. The current work provides genetic proof supporting this model.

"Conventional wisdom is that fenfluramine increases serotonin release that then activates serotonin receptors in the brain to regulate food intake and body weight, but unfortunately, this drug also causes lesions in heart valves," he said. "If you could develop a drug that would travel to both the brain and the peripheral tissues, and then give a blocker to protect the heart, it's possible that you could prevent the harmful side effects and still aid weight loss. Admittedly, that's a bit farfetched, but this mouse model could be used to test that theory."

The team's next step is to determine whether they've identified the sole circuit required to suppress appetite and induce weight loss.