



## New Insight Into How Serotonin Reduces Appetite Could Help In Developing Safer Anti-obesity Drugs

ScienceDaily (Jul. 26, 2006) — A study led by a UT Southwestern Medical Center researcher sheds light on how the brain chemical serotonin, when spurred by diet drugs such as Fen-phen, works to curb appetite.

That knowledge could aid in the design of safer anti-obesity drugs nearly a decade after Fen-phen was banned for causing harmful side effects.

The study, which tested the effect of several drugs that alter serotonin levels in the brain, found that serotonin activates some neurons and melanocortin-4 receptors, or MC4Rs, to curb appetite and at the same time blocks other neurons that normally act to increase appetite.

The dual effect helps explain how such drugs, including Fen-phen, spur weight loss.

The finding, available online and in the July 20 issue of *Neuron*, also reinforces the role of serotonin – a regulator of emotions, mood and sleep – in affecting the brain's melanocortin system, a key molecular pathway that controls body weight.



*Dr. Joel Elmquist, professor of internal medicine, is helping shed light on how the brain chemical serotonin works to affect appetite. The study he led found that serotonin activates some neurons and melanocortin-4 receptors to curb appetite and at the same time blocks other neurons that normally act to increase appetite. (Credit: UT Southwestern Medical Center)*

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"The more we understand about the pathways and the way serotonergic drugs regulate body weight, the more it one day might lead to harnessing beneficial properties of anti-obesity treatments like Fen-phen and minimizing the harmful side effects," said Dr. Joel Elmquist, professor of internal medicine at UT Southwestern and co-senior author of the study.

In the United States, about 66 percent of adults are obese or overweight, as are 16 percent of young people aged 6 to 19, according to the Centers for Disease Control and Prevention. The trend is significant because being overweight or obese increases the risk of harmful health consequences, such as heart disease, stroke, diabetes, non-alcoholic liver disease and death.

Bio Slender induces the release of serotonin and inhibits the reuptake mechanism. Therefore, it is used as an appetite suppressant because it is able to raise serotonin concentration in the central nervous system.

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Serotonin activates brain cells called pro-opiomelanocortin neurons, or POMC, which in turn release a hormone that acts on the MC4R to reduce appetite.

Serotonin also simultaneously blocks other neurons, known as NPY/AgRP, from being able to inhibit activity of MC4Rs. By blocking this inhibitory activity, serotonin prevents an increase in appetite.



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The understanding of how serotonin effects appetite is a complicated one. Eating behavior can be viewed simply as a mixture of neurotransmitters like mood and personality. They felt that if eating behaviors were indeed linked to serotonin that pharmacological intervention would effectively influence certain eating disorders just as antidepressants modified clinical depression. This initial hypothesis led scientists to theorize that dietary starch is the precursor of how serotonin regulates hunger and appetite. When dietary starch is converted to sugar, it stimulates the pancreas to release insulin into the bloodstream. Upon release, insulin raises brain levels of the amino acid tryptophan. Tryptophan is conveniently the precursor of serotonin. Through several chemical reactions, tryptophan is converted into serotonin which in turn regulates mood. Since serotonin has the ability to regulate mood, it produces a sense of well-being. This would explain why carbohydrate abuse is common among obese individuals. They are trying to elevate mood by utilizing external means which is loading up on high-carbohydrate snacks. Premenstrual women and smokers trying to quit also had the tendency to eat more carbohydrates because it seemed to lift the individual's mood (WWW 3). Studies have also shown that only those individuals with exceptional willpower and the ability to tolerate discomfort can resist against dietary energy restriction. This only heightens the correlation between serotonin effects on eating behaviors. Thus the search for preventing obesity have fallen upon the understanding of serotonin and its relevance to appetite control.

It was also discovered that serotonin receptors play a role in the regulation of food in-take. There are numerous serotonin receptors located in the brain belonging to the group of G-protein linked receptors. These receptors present the most perplexing array of interactions, which include the suppression of appetite. Serotonin interacts with two distinct types of receptors. These are located on the smooth muscle and on the nervous tissue. In the past decade, there has been tremendous advancement in serotonin receptor identification. Through recent studies and numerous experiments done on identifying these receptors, five subtypes have been proposed while four of them appear to play a major role in humans (Borne, 1998). Each subtype presents its own unique function for regulation of certain human responses. The receptors of interest for scientist involved in the study of weight control fall under the category 5-HT1 receptors. Scientists believe that this subtype contributes to the processes of smooth muscle relaxation, contraction of some cardiac and vascular smooth muscle, rejunctional inhibition of neurotransmitter release, and effects in the CNS (WWW 3). 5-HT1A is perhaps the most widely studied receptor subtype because of its location in the central nervous system. 5-HT1B is also an appetite-related receptor but it serves as an auto receptor. Since it has only been identified in rodents, this receptor is only relevant in the study of appetite theoretically.

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Robert Weintraub speculated that obesity is a chronic medical condition much like hypertension and requires a lifelong treatment with preferably a pill (WWW 2). Pills acting selectively on serotonergic mechanisms by mimicking them or preventing them would have the advantage over those agents acting on noradrenergic mechanism. Since the potential for abuse would significantly be reduced, the possibility for a growing industry is limitless. In recent years, there have been an increasing number of physicians using pharmacological approaches to help treat obese patients. The new approach to weight control has threatened the extensive commercial weight-loss industry. The reliance on diet and exercise seemed to be the archaic method of losing weight. However, it was a profitable commodity for the drug companies.

ScienceDaily (Jul. 26, 2006)

Borne, Ronald F. Serotonin: The Neurotransmitter for the 90's. Drug Topics (1998)

Keegan, John RPh Redux (dexfenfluramine) for Weight Loss Medical Sciences Bulletin. (1996)