

Neuropharmacology of Obesity: My Receptors Made Me Eat It

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Issue: *Specific neurotransmitter and hormone receptors regulate appetite, eating behavior, and weight gain.*

Body weight is regulated by complex interrelationships between central and peripheral factors. Satiety, appetite, and craving are CNS drives, whereas metabolism and energy utilization are peripheral endocrine actions. Recent discoveries are lending important insights into how these central and peripheral components of weight control are mediated by receptors for several key neurotransmitters and hormones. Since obesity results from an imbalance between caloric intake and energy expenditure, these new findings suggest that treatment of obesity can be based both on central mechanisms that decrease the urge to eat and on peripheral mechanisms that increase the mobilization of energy.

5-HT_{2C} Receptors

For many years, pharmacologists have known that increasing the availability of serotonin (5-HT) in the synaptic cleft or direct activation of some 5-HT receptors reduces food consumption, while decreasing 5-HT receptor activation brings about the opposite effect.¹ Recent research more specifi-

cally implicates the 5-HT_{2C} receptor subtype as playing the key role in regulating appetite.^{1,2} For example, mutant mice that lack the 5-HT_{2C} receptor are obese. Activating 5-HT_{2C} receptors decreases eating behavior in rats.

A 5-HT_{2C} mechanism may also underlie weight reduction in humans taking appetite suppressants. Specifically, fenfluramine (now withdrawn from marketing) releases serotonin to act at all 5-HT receptors, but it may be the action of serotonin specifically at the 5-HT_{2C} subtype that is important, since fenfluramine and its metabolite norfenfluramine may also be agonists at the 5-HT_{2C} receptor.¹

Serotonin reuptake inhibitors, including both selective serotonin reuptake inhibitors (SSRIs) and dual 5-HT plus norepinephrine reuptake inhibitors (SNRIs), can also reduce appetite, at least acutely.^{3,4} Fluoxetine, arguably the most anorexigenic of the SSRIs, and with a specific indication for bulimia, is also the only SSRI with direct 5-HT_{2C} agonist activity in addition to its 5-HT reuptake blocking properties.⁵ The most recently marketed appetite suppressant is sibutramine (Meridia); its mechanism works by both 5-HT and norepinephrine reuptake blockade,⁴ much like higher doses of venlafaxine. The dual proserotonergic and pronoradrenergic actions of sibutramine may have a net pharmacologic effect similar to fenfluramine, namely, 5-HT release by fenflur-

amine and norepinephrine/dopamine release by phentermine.⁴ Proadrenergic actions thus seem to synergize with proserotonergic actions at 5-HT_{2C} receptors. This may be either by a central mechanism that reduces food intake or by a peripheral mechanism that increases thermogenesis via stimulation of β_3 -adrenergic receptors in adipose tissue.⁴

β_3 -Adrenergic Receptors

The 3 distinct subtypes of β receptors⁶ are the β_1 receptor, which is predominantly a cardiac receptor and the target for β blockers; β_2 receptor, which is in the lungs (the target of bronchodilating β agonists) and also found in uterus and skeletal muscle; and β_3 receptor, expressed primarily in adipose tissue, where it regulates energy metabolism and thermogenesis (turning fat into heat and energy), especially in response to norepinephrine.^{6,7}

Evidence that the β_3 -adrenergic receptors play an active role in weight control in humans comes from the finding that a genetic variant of this receptor constitutes a susceptibility factor for the onset of morbid obesity as well as non-insulin-dependent diabetes.⁷ Specifically, this variant of the β_3 receptor is associated with hereditary obesity in Pima Indians from Arizona and demonstrated an increased incidence in obese patients in Japan. It also exists in nonobese individuals, including a fourth of African Americans and

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about 10% of the general population in Europe and the United States.⁷

These various findings suggest a strategy for treating obesity by stimulating metabolism and peripheral burning of fat, rather than by acting on central satiety. The pro-adrenergic agent sibutramine increases norepinephrine peripherally at the β_3 -adrenergic receptors in adipose tissue,⁴ thus stimulating thermogenesis and increasing oxygen consumption, leading to weight loss.

Histamine-1 Receptors

The exact neurotransmitter role of histamine in the CNS still remains an enigma. However, regulation of arousal and appetite by histamine has long been suggested by observations that H_1 antagonists are not only sedating but also increase appetite and weight in experimental animals and humans.⁸ Binding studies of antidepressants and antipsychotics suggest that sedation and weight gain in humans are proportional to their ability to block these H_1 receptors.⁸

Neuropeptide Receptors and the Leptin Story

At least 3 peptides are implicated in the regulation of food intake, energy expenditure, and whole body energy balance in both rodents and humans, and are found both peripherally as hormones and centrally. These are galanin, neuropeptide Y, and leptin.⁹⁻¹² The physiologic roles of these peptides in regulating body weight via their CNS receptors remain somewhat obscure, although the effects of leptin on food intake and energy expenditure are thought to be mediated centrally via neuropeptide Y.⁹⁻¹²

Take-Home Points

- ◆ Central nervous system neurotransmitter receptors for serotonin and histamine regulate both appetite and feeding behavior
- ◆ Receptors outside the brain are also implicated in the regulation of food intake and energy expenditure
- ◆ Both genetic predisposition as well as unhealthy lifestyles leading to obesity may be mediated in part by leptin, neuropeptide Y, and β_3 -adrenergic receptors

The role of peripheral leptin has been more extensively investigated.⁸⁻¹¹ Leptin, a member of the interleukin 6 cytokine family, is a peptide found in multiple tissues and secreted by white adipose cells, where it is highly correlated with body fat mass and size of fat cells. The peripheral effects of leptin include regulation of insulin secretion, and energy metabolism in fat cells and skeletal muscle, where it seems to play a role in ensuring the maintenance of adequate energy stores and thereby protects against starvation. It also acts as a metabolic signal that regulates how nutritional status affects reproductive function. Cortisol and insulin are potent stimulators of leptin, whereas β -adrenergic agonists reduce leptin expression.

Administration of leptin to genetically obese mice reduces their food intake and makes them lose weight.⁹⁻¹² Congenital leptin deficiency in humans is associated with severe early-onset obesity. Somewhat paradoxically, however, plasma leptin levels are increased in obese women and decreased in women with anorexia nervosa.¹³ Plasma neuropeptide Y and galanin levels are also increased in obese women. Since leptin levels are chronically increased in obese humans, this suggests that obesity may be associated with malfunctioning leptin receptors, a condition called *leptin resistance*, since leptin is unable to generate an adequate response when its receptor is occupied. Improving responsiveness to leptin in

obese patients may be one key to weight loss.

Understanding the neuropharmacology of weight gain will hopefully lead to better management of obesity. ◆

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