Central Control of Appetite and Body Weight

Coordination of energy use and food intake is necessary for regulation of body weight. Today’s world-wide obesity epidemic reflects a mismatch in these factors. Appetite control is a function of the brain, more specifically, the hypothalamus. This is a small area lying between the thalamus and pituitary, controlling the anterior segment of the pituitary and the many of the body’s organs through vagus nerve stimulation. The hypothalamus contains several clusters of neurons, commonly designated as nuclei. Current research indicates that one of these, the arcuate nucleus, houses the appetite center. Here we find sensors that monitor lipid and sugar levels in the circulation and others which respond to specific hormones. Not only does the arcuate nucleus measure metabolites and hormone levels, it also coordinates metabolism through adjustment of the activities of the liver, kidneys, intestine and adipose tissue. The hypothalamus controls appetite and coordinates this with energy utilization. It is, therefore, responsible for maintenance of body weight, carefully adjusting food intake to physical activity. Loss of sensitivity to hormones and metabolites in the arcuate nucleus can lead to unbalanced energy intake and use, resulting in overweight and obesity.

The Appetite Center.

The appetite center in the arcuate nucleus appears to be composed of at least two classes of neurons: primary neurons that sense metabolite levels and regulating hormones, and secondary neurons that synchronize information from primary neurons and which coordinate bodily functions through vagal signaling.
The primary neurons can be divided into two groups:

1. Those which stimulate appetite through secretion of neuropeptide Y (NPY) and the agouti-related peptide (AgRP).

2. Neurons which depress appetite through secretion of proopiomelanocortin (POMC).

Thus, a feeling of hunger can be induced through several competitive mechanisms. Activation of the NPY/AgRP releasing neurons will increase appetite as will inhibition of the POMC-releasing neurons. Inhibition of the first group (NPY/AgRP secreting cells) will dampen appetite as will activation of the POMC-producing neurons.
Hormones that Control Eating.

Several hormones are instrumental in control of the appetite center. Some increase hunger, others reduce the urge to eat. These have both short-term and long-term actions and are essential for control of body weight. Key regulators were presented by Schwartz and Morton in a "NEWS" article published in Nature. Several hormones were discussed:

1. **Ghrelin.** This is a peptide hormone which is released by the stomach and activates NPY/AgRP releasing neurons, thereby stimulating appetite. Ghrelin is released from the empty stomach. Its secretion abruptly stops following food intake.

2. **PYY₃₋₃₆** is a small peptide released from intestinal endocrine cells. It inhibits "appetite-stimulating" NPY/AgRP producing neurons, thereby signaling food intake and damping hunger.

![Regulation of Appetite and Metabolism](image)

Thus, hormones released directly from the digestive system steer appetite in tact with food consumption.

3. **Insulin and leptin.** Insulin release from pancreatic islets cells follows intake of both carbohydrates and proteins. We usually assume that the brain is not dependent upon insulin for uptake and metabolism of substrates for energy metabolism. After all, the brain has a large and relatively constant requirement for glucose as its primary energy source. Uptake of glucose from the circulation to the CNS must not vary according to insulin levels. However, the arcuate nucleus appears to have many properties that are in contrast to those of the rest of the brain. Among these are receptors for protein hormones involved in the control of metabolism. The
arcuate nucleus responds to both insulin and leptin. Insulin dampens appetite by inhibiting NPY/AgRP-secreting neurons and by activating POMC-releasing neurons. Insulin appears to have both short-term and long-term actions and is essential in regulation of body weight. Resistance to insulin is very often associated with obesity and the loss of insulin's regulation of metabolism as seen in diabetes type 2.

Leptin levels follow body fat levels; circulating leptin levels are increased in obesity. As is the case with insulin, leptin dampens appetite by inhibiting stimulatory neurons and stimulating inhibitory fibers. Leptin release from adipose tissue is enhanced by insulin. Leptin is, therefore, one of the hormones that are coupled to food consumption. It appears that the arcuate nucleus can become leptin-resistant. Obese persons are found with high circulating leptin levels but without response to leptin in the arcuate nucleus. Abnormalities in leptin signaling appear to be correlated to overeating and obesity.

Click on the following to go to the original paper: Obesity: Keeping hunger at bay, M. W. Schwartz and G. J. Morton, Nature 418, 595-597 (2002).

**Amylin.**

Amylin is a small peptide (32 amino acid residues) that is secreted together with insulin from the β-cells of the Islets of Langerhans. It was first identified as late as 1987 and information about its physiological functions is incomplete. Never the less, amylin has been shown to work together with insulin to suppress postprandial glucagon secretion and slow gastric emptying. Amylin reduces hunger and appears to be involved in control of body weight. It has been proposed that the major area of action of amylin is central, perhaps at the area postrema in the brain stem. Diabetic patients with an inadequate insulin secretion (type 1 and late type 2) also show a reduced secretion of amylin. This may contribute to inadequate appetite regulation and obesity in these patients. For more information click on: Glucose metabolism and regulation: beyond insulin and glucagon, S. L. Aronoff et. al., Diabetes Spectrum 17, 183-190 (2004).
Circulating Metabolites also Control Appetite.

Glucose.

Once again, the arcuate nucleus has some surprises for us. We are accustomed to think that the brain has a very active glucose-uptake mechanism with a low $K_m$. This is required for normal brain function at all physiological levels of blood glucose. However, the arcuate nucleus responds to swinging blood sugar levels, appetite being stimulated when blood glucose levels fall and inhibited with the high blood sugar levels encountered after a meal. The secret to this is the presence of glucokinase (GK) in the arcuate nucleus. In contrast to the rest of the CNS, glucokinase accounts for 20% of the total glucose phosphorylation activity in this organ. Because of its high $K_m$, glucokinase activity swings in tact with normal variations in blood sugar levels. As in pancreatic β-cells, the GLUT2-GK system measures sugar levels and reports these as increases or decreases in ATP production. While the mechanism for coupling of GLUT2-GK to appetite control is not yet clear, increased glucose concentrations sensed and "reported" by GLUT2-GK appear to stimulate NPY/AGRP producing neurons in the fasted state and the POMC-secreting neurons in the fed state. That is, glucose stimulates hunger between meals and inhibits hunger after meals. For an excellent review of the latest in this area, click here: Isabelle Bady et al, Diabetes 55, 988-995 (2006) if you have library connections.
**Fatty acids.**

Another "metabolic surprise" is that fatty acids are taken up and metabolized in the arcuate nucleus. Again, we "know" that normal brain tissue will not take up fatty acids and that a rapid fall in blood glucose quickly leads to an energy crisis and loss of consciousness. Fatty acids must be converted to ketone bodies before they can be taken up and metabolized by the brain.

The arcuate nucleus presents another picture. Here, fatty acids are taken up and are converted to long-chain -fatty acyl-CoA intermediates (LCFACoA). These are formed from both circulating fatty acids and from fatty acids produced in the arcuate nucleus. The mechanisms for control of appetite by LCFACoA are not yet known. However, the circulating levels of fatty acids are an excellent signal of the total metabolic situation, and the LCFACoA formed in the arcuate nucleus dampen appetite and reduce food intake. Click on the following link for more information: M. W. Schwartz and D. Porte jr., *Diabetes, Obesity and the Brain*, Science 307, 375-379 (2005).

**Self-control of appetite?**

The signals and control elements involved in management of appetite and body weight have evolved over many 100,000 years. They are based on the amount of physical work needed to survive under “primitive” conditions. That is, we have evolved in a time without machines and energy-saving appliances. It is estimated that a normal total energy expenditure for both sexes was about 3000 kcal/day until about 100 years ago. Our basal metabolism requires approximately 1500-1600 kcal daily. Food intake amounting to circa 1500 kcal was necessary to balance energy intake and output. Today’s daily physical effort requires about 500-1000 kcalories giving a total energy need of between 1800-2500 kcalories. That is, the difference between basal metabolism and today’s total energy use is much smaller than that which was common 100 years ago. Maintaining an appropriate balance between energy requirements and food intake becomes difficult as more and more precise control elements are required to measure small differences in “input and output”. And, evolution of control takes time! Our life style has changed faster that evolution can adjust our bodies to “fast food” and “energy-saving appliances”. We can determine to eat a little more of that “good food” even though our “appetite center” says “stop”. We can choose to reduce physical work by using self-powered machines. And we can choose to just sit and watch TV or a PC screen. Is this the basis for the global obesity epidemic we now face? Are demands on our “appetite control center” too extensive? One factor that complicates this is that the brain seems to defend our maximal weight. That is, appetite seems to be partially driven by an urge to maintain maximal weight. Appetite increases when we try to reduce food intake. At the same time, central elements reduce the basal metabolic rate in an effort to maintain balance between “input and output”. It is difficult to lose weight and maintain this reduction over time!
NB: I became aware of the following publication just after I mounted this section. The article is found in the November 2006 issue of Nature: *Smell images and the flavour system in the human brain, S. G. Shepherd, Nature 444, 316-321 (2006).* This is a extremely fascinating review article, giving insight into the mechanisms of taste and smell and their coupling to appetite control. To quote the author "The key point is that understanding overeating and obesity involves not only understanding the hypothalamic feeding centres and how they respond to fats, carbohydrates and proteins..., but how those centres are driven by the brain mechanisms underlying the flavours of those foods and the desire to consume them". Click on the highlighted text to come further.

**References:**

For those who wish to come further I can strongly suggest the following 2 references (click to retrieve them):


2.  *[The brain as a molecular target for diabetic therapy, E. Prodi and S. Obici, Endocrinology 147, 2664-2669 (2006).*](#)