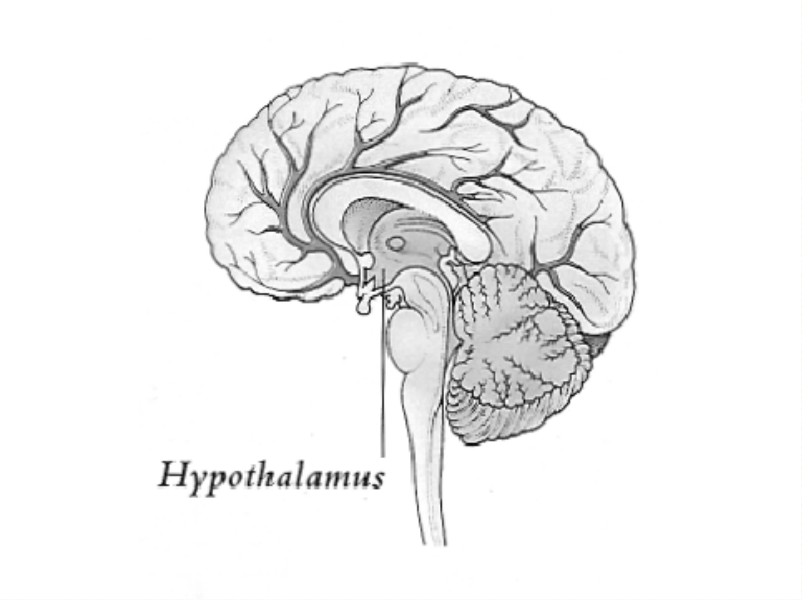
Appetite, Metabolism and Obesity

Acrobat PDF file can be downloaded by clicking here.

Central Control of Appetite.

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. Our current energy requirements are little more than that required for basal metabolism and are very easily exceeded. For a simplified discussion of this, click here.

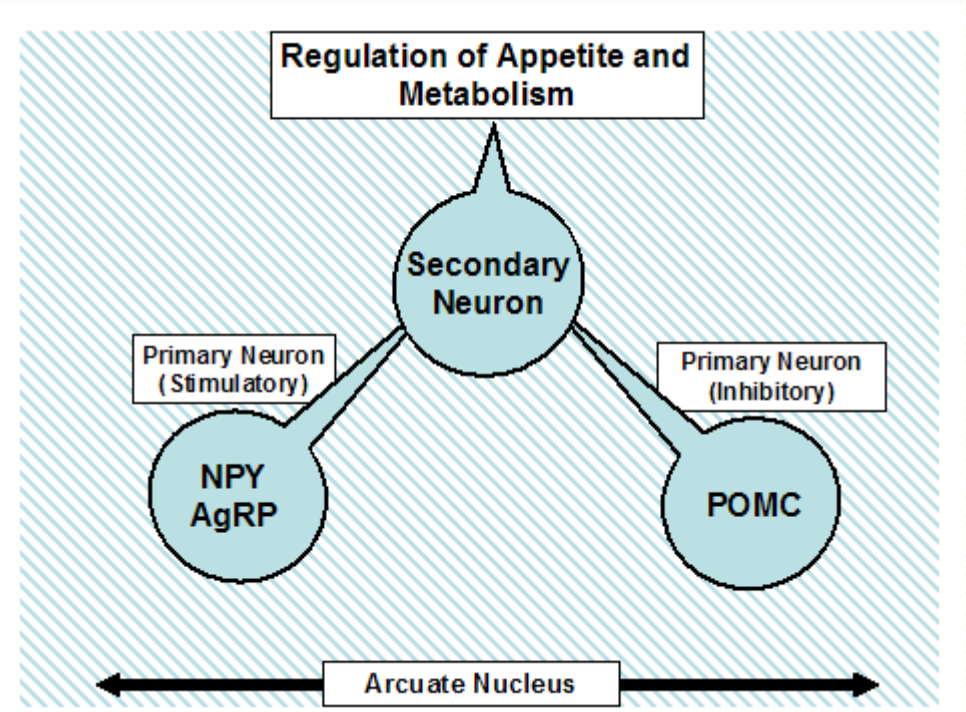


Appetite control is a function of the brain, more specifically, the hypothalamus. This is a small area lying between the thalamus and pituitary, controlling the anterior segment of the pituitary and the many of the body's organs through vagus nerve stimulation. The hypothalamus contains several clusters 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:

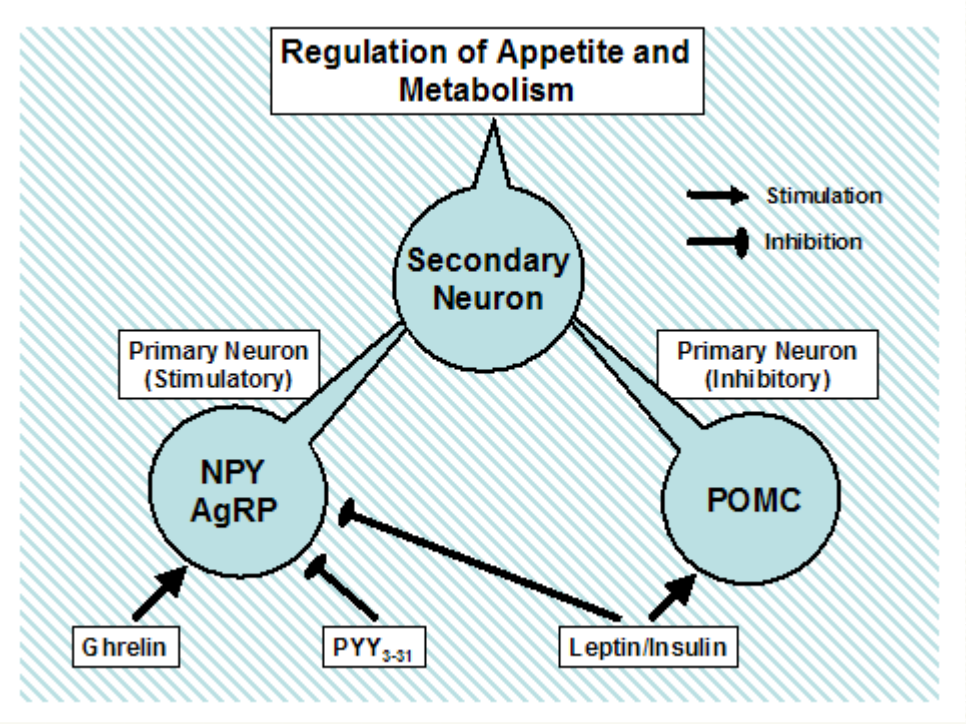
1. **Those which stimulate appetite through secretion of neuropeptide Y (NPY) and the agouti-related peptide (AgRP).**

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. PYY_{3-36} is a small peptide released from intestinal endocrine cells. It inhibits "appetite-stimulating" NPY/AgRP producing neurons, thus signaling food intake and damping hunger.

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 ß-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).

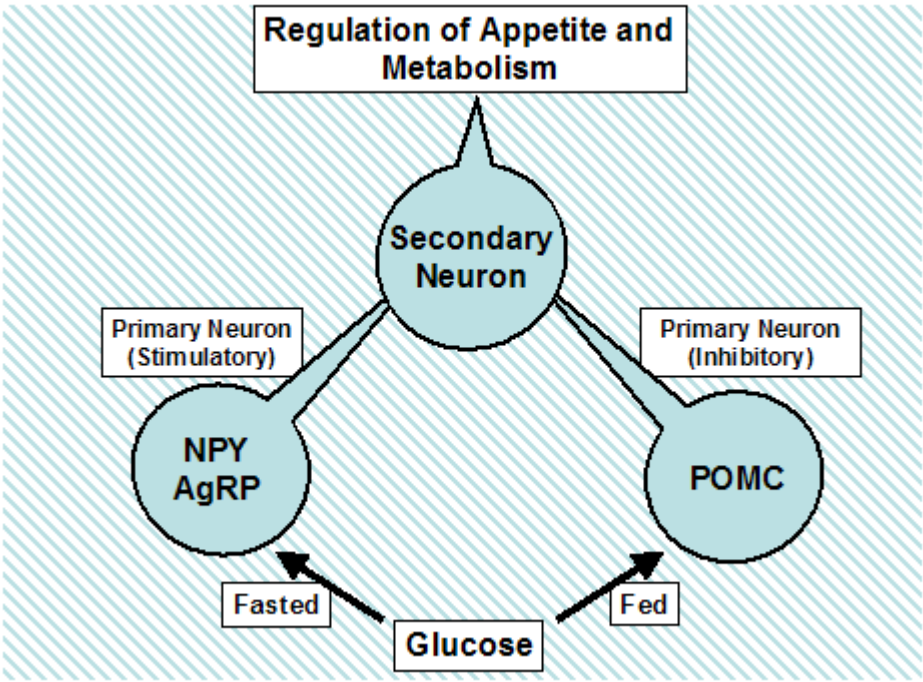
Pramlintide:

Amylin is difficult to work with clinically as it tends to aggregate and form insoluble particles. Exchange of three acids (two serines and an alanine) with proline get around this problem. This modified amylin, known as Pramlintide, is now being investigated as a hypoglycemic agent in early type two diabetes. It potently reduces glucagon secretion and, therefore, postprandial hyperglycemia. For more information go to The Diabetes-Obesity Continuum: The Growing Body of Evidence for a Multi-hormonal Approach to Treatment, (CME, Medscape, December 2007).

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 ac counts for 20% of the total glucose phosphorylation activity in this



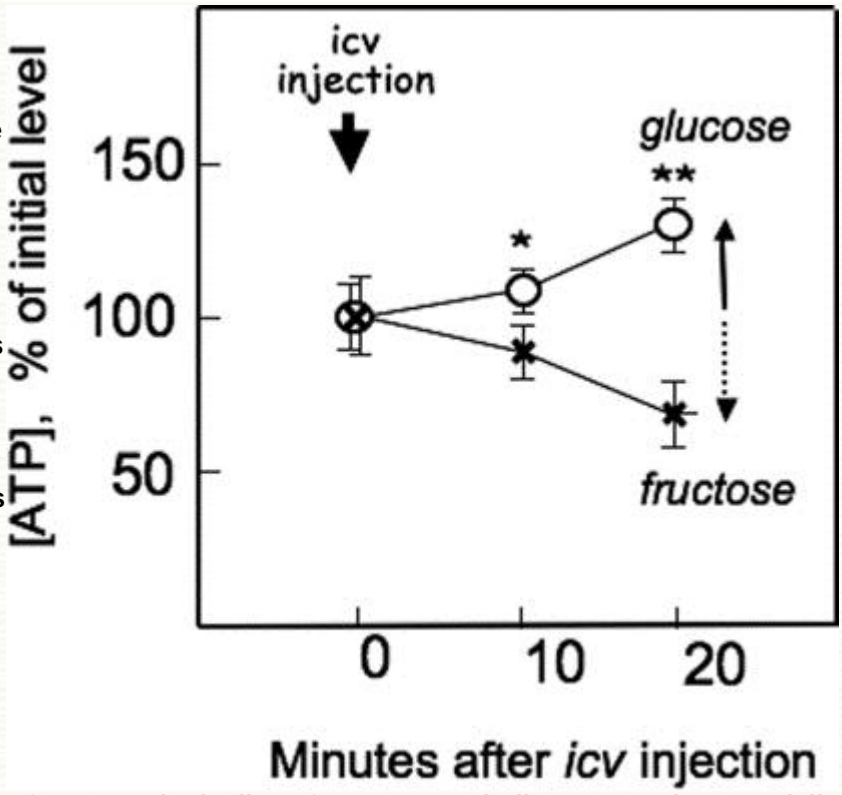
organ. Because of its high K_m, glucokinase activity swings in tact with normal variations in blood sugar levels. As in pancreatic ß-cells, the GLUT2-GK system measures sugar levels and reports these as increases or decreases in ATP production. While the mechanism for coupling of GLUT2-GK to appetite 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).

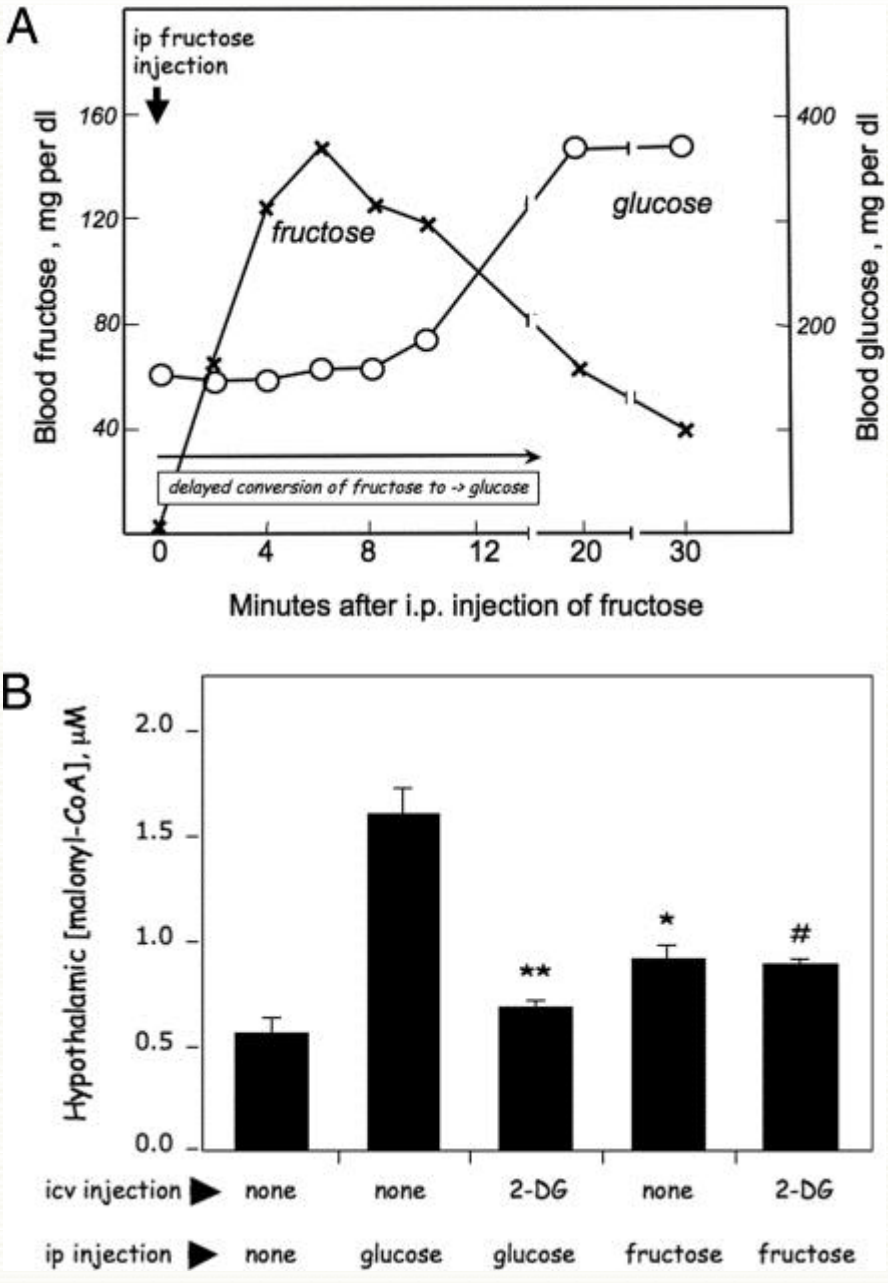
Fructose



As stated above, the hypothalamus resembles the liver in its ability to take up several circulating substrates and metabolize them. Among these is fructose. Both the essential membrane transporters and enzymes required to process fructose are found in the hypothalamus. Furthermore, while centrally administrated glucose reduces appetite and food intake, fructose has been shown to increase appetite and food intake when injected centrally. These two sugars are isocaloric, however their metabolism differs. Processing of glucose is carefully regulated and coupled to production of energy, that is, of ATP. As in the liver, fructose metabolism proceeds essentially without control. The result in the hypothalamus is a decrease in ATP levels following fructose oxidation, a situation that resembles hepatic fructose intolerance. This is a real decrease in the energy state of the hypothalamus and appears to initiate increased appetite.

The figure and the two which follow are reproduced with permission from "Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake, S. Cha et al, PNAS 105, 16871-16875. Click here to call up the publication.

Is fructose an important regulator of appetite?

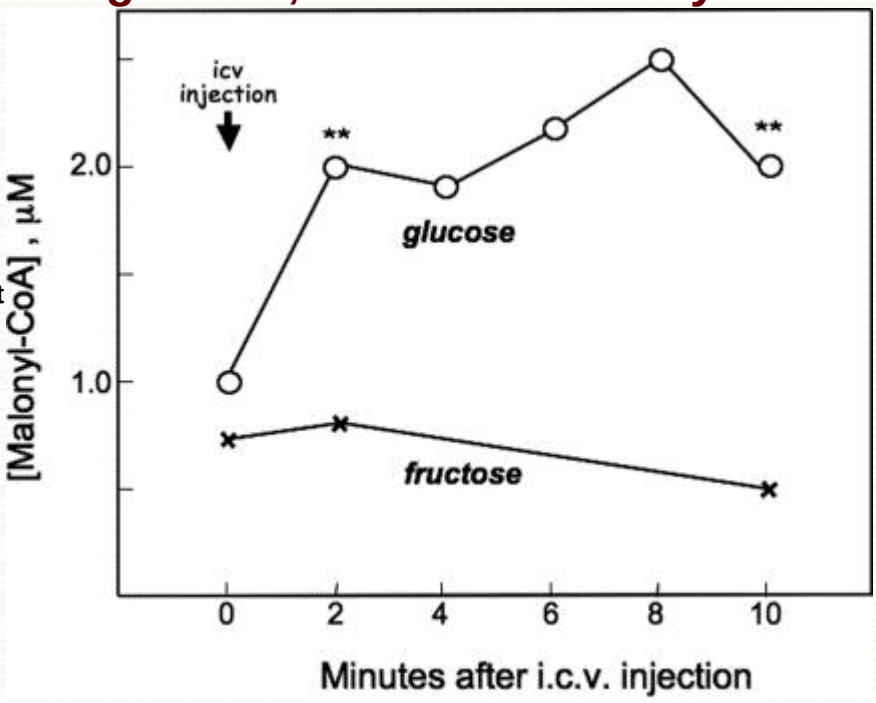


The question of the role of fructose in appetite regulation has been prompted by the acknowledgement that sweetening agents are strongly involved in the global obesity epidemic. There is little question of the caloric burden that sugar (sucrose) and HFCS (high fructose corn syrup) impose on weight regulation. However, it is important to recognize that these agents are metabolically quite similar. Both contain approximately 50% fructose. Sucrose is a 1-to-1 dimer of glucose and fructose. HFCS usually is 45% or 55% fructose, the rest being glucose. It is very likely that their physiological effects of sucrose and HFCS do not differ significantly.

Intake of fructose results in a very rapid hepatic conversion to glucose. Therefore and in contrast to glucose, circulating fructose levels are minimal shortly after ingestion (see figure A). This means that the hypothalamus is almost always exposed to far greater levels of glucose than the fructose originating from ingested food. A caution is perhaps relevant here. The hypothalamus uses glucokinase to phosphorylate glucose. This enzyme has a relative high Km and is activated by glucose levels in excess of fasting levels. Fructokinase (or ketohexokinase) is activated by low levels of fructose. The differing affinities for substrates could influence the appetite regulation effects of these sugars. However, as shown below, intraperitoneal injection of fructose slightly raised hypothalamic malonyl-CoA levels.

Panel B in the figure shows hypothalamic malonyl-CoA levels after intraperitoneal fructose or glucose administration. Malonyl-CoA levels increase slightly after fructose administration, quite in contrast to centrally administered fructose. This is most likely due to the glucose arising from hepatic conversion of fructose to glucose. Thus, while fructose can influence appetite, it would appear doubtful that this is an important regulatory element when ingested as a part of the diet.

The mechanism of glucose, fructose and fatty acid regulation of appetite?



In a recent review article M. J. Wolfgang and M. D. Lane (FEBS Journal 278 (2011) 552-558) suggest that malonyl-CoA, the first metabolite in fatty acid synthesis, is responsible for central control of appetite by glucose. Malonyl-CoA levels in the arcuate nucleus follow glucose uptake and metabolism here. The enzyme responsible for formation of malonyl-CoA is ACC or acetyl-CoA carboxylase. This enzyme is the link between carbohydrate and lipid metabolism. Its activity is regulated by AMPK (5´ AMP activated protein kinase) and thus closely coupled to the cellular energy state. Decreases in ATP levels result in increases in AMP, stimulation of AMPK and inhibition of malonyl-CoA synthesis.

Thus, central administration of fructose, in contrast to glucose administration, lowers levels of malonyl-CoA due to reduction of hypothalamic ATP levels and increased AMP. However, as I have reasoned above, ingested fructose probably plays little or no role in appetite regulation.

Click here for more information about malonyl-CoA metabolism. Wolfgang and Lane's discussion presents possibilities for pharmacological modification of appetite, metabolic activity and control of obesity. You can download the article here.

An excellent lecture (audio and slides) by Professor Schwartz concerning CNS control of weight and appetite can be downloaded here.

Central control of insulin sensitivity (insulin resistance).

Type 2 diabetes is characterized of two processes, a slowly developing resistance to insulin signaling and a compensatory increase in beta cell release of the hormone. With time, the beta cells no longer produce enough insulin to maintain control of metabolism and type 2 diabetes results. While the underlying cause of insulin resistance is unknown, there is a striking correlation between obesity, increased plasma lipids and resistance. Today's treatment of type 2 diabetes aims at reducing body weight and blood lipids through dieting, increasing hepatic insulin sensitivity with metformin and increasing beta cell insulin release through various medications. For many patients, this results in a slowing of the progress from prediabetes to diabetes, but the end result is often that patients must go over to use of insulin.

This section of MedBio has shown data indicating that several central neural pathways are involved in control of metabolism. Recently (November 2007) an international group has clearly shown that central receptors for serotonin play a major role in glucose homeostasis. Thus far, their work has been limited to experiments in obese mice. They have demonstrated that small doses of a known classical serotonin agonist, metachlorophenylpiperazine (mCPP), markedly lowed plasma insulin levels and increased insulin sensitivity without affecting food intake, body weight or fat mass. The downstream target of the involved serotonin receptor appeared to be melanocortin-4 receptors, found in the same brain area described above (the arcuate nucleus of the hypothalamus). The serotonin effects on insulin resistance were coupled to sympathetic nervous stimulation as are the CNS actions of the insulin, leptin, ghrelin and PYY $_{3-31}$.

This report opens new and exciting therapeutic approaches for treatment of type 2 diabetes. It remains to be seen whether or not these findings can be reproduced in humans at acceptable doses of mCPP.

See "Serotonin 2C Receptor Agonists Improve Type 2 Diabetes via Melanocortin-4 Receptor Signaling Pathways, Cell Metabolism 6, 398-405 2007. Click here if you are connected to a library.

A review can be found in Nature Signaling Gateway by clicking here.

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 flavor 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 centers and how they respond to fats, carbohydrates and proteins..., but how those centers are driven by the brain mechanisms underlying the flavors of those foods and the desire to consume them". Click on the highlighted text to come further.

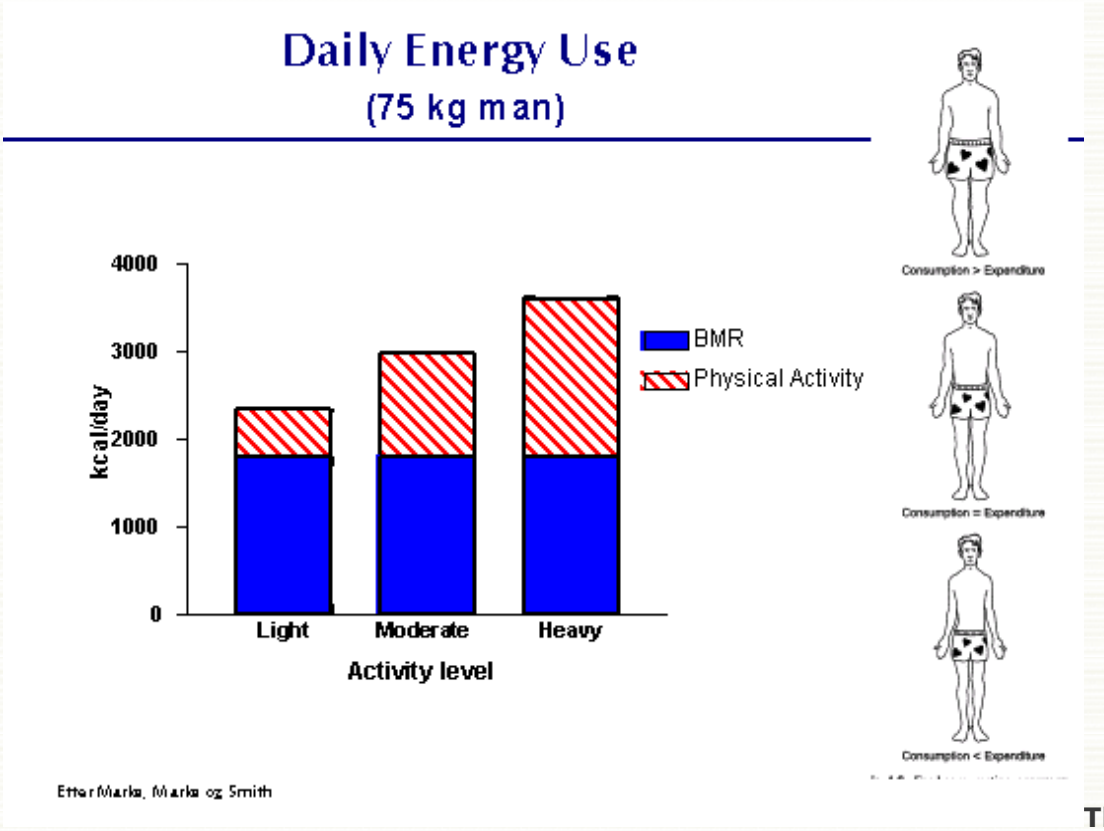
Regulation of "hedonic" or "pleasure-related" eating (October 2012).

Most of us must acknowledge that we often continue to eat after becoming satiated. We have room for dessert in spite of having consumed a large main course. This "over-eating" is an important factor in the obesity epidemic now found almost globally. The mechanisms activated by this "hedonic" or pleasure related eating appear to be based on increased dopamine release in various areas of the brain. A recent publication by D. M. Mebel, J. C. Y. Wong, Y. J. Dong and S. L. Borgland in the European Journal of Neuroscience Vol. 36, 2336-2346, 2012 present a detailed investigation of CNS dopamine release and control of the levels of this neural signal substance by insulin. They identify the phosphoinositol 3-kinase - mTor signal pathway as a major controller of dopamine uptake in brain neurons, thus pin-pointing the mechanism of insulin's effects on dopamine levels in determined areas of the brain. Thus, regulation of "pleasure-related" eating is found in the balance between insulin and hormones and signals arising from observation of attractive and "delicious reward-giving" foods. This is perhaps the basis for the "self-control of appetite" discussed in the previous section. This investigation may give an important clue in the search for methods to curb the obesity epidemic. Click here for an introduction and comments. Click here to call up the article.

Overweight/Obesity.

A Simplistic Approach to Weight Regulation

There are very many factors involved in normal weight regulation. However, the end result is the consequence of the balance between the amount of energy in the ingested food and the amount of energy used. Hormone levels, altered hormone receptors, mutated metabolic enzymes; all of these do influence appetite and energy use. However, the bottom line is, you are what you eat (and do not burn). Look at the next figure (modified after Marks, Marks and Smith, Basic Medical Biochemistry).



The activity levels shown here correspond to those that are normal in a modern society. A young male student uses most of the energy in his food to support normal body functions (basal metabolism or BMR). Only about 20% of the consumed energy go to support physical activity.

If one leads a more active life (cycling to work, using stairs instead of the elevator, some sports after studying), the total daily energy use increases to about that level that the average person used for 100-150 years ago. It is estimated that, at that time, both men and women used about 3000 kcal/day for the usual daily chores. Note that at this activity level physical activity still accounts for not more than 25-30% of the total energy used daily.

A heavy activity level, as judged by our modern standards, will increase energy use to around 3500 kcalories/ day. By the way, lumberjacks using axes and hand saws are said to have used about 5000 kcalories per day!

The drawings on the right show the result of balancing (or not balancing) food intake with energy expenditure. Clearly, eating more than one uses is "expansive", a balanced food and energy use results in a stable body mass while under nutrition leads to weight loss. An important point to keep in mind is that the caloric requirement to maintain a relatively sedate life is only 400-600 kcal over the basal requirement. In other words, it is very easy to exceed the food intake required to maintain a normal weight (BMI from 20-25) with today's physical activity. Remember, those good chocolate cupcakes packed temptingly in cellophane contain around 500 kcalories! Maintaining an even weight while doing only light work is a real challenge!

"The Easy way and the hard way..."

Most experts believe that a sedentary or passive life style is the best explanation for the trend to overweight. That is, weight gain is more closely related to energy use than energy intake. What has changed in the past decade?

A recent editorial in Mayo Clinical Proceedings

The easy way and the hard way...

Table 1. Examples of Sedentary and Active Energy Expenditures for Common Activities*

Sedentary	kcal	Active	kcal
Using remote control device to change television channel	<1	Getting up and changing channel	3
Reclining for 30 min of phone calls	4	Standing for 3 10-min phone calls	20
Using garage door opener	<1	Raising garage door 2×/d	2-3
Hiring someone to clean and iron	0	Ironing and vacuuming each for 30 min	152
Waiting 30 min for pizza delivery	15	Cooking for 30 min	25
Buying presliced vegetables	0	Washing, slicing, chopping vegetables for 15 min	10-13
Using a leaf blower for 30 min	100	Raking leaves for 30 min	150
Using a lawn service	0	Gardening and mowing each for 30 min/wk	360
Using car wash 1×/mo	18	Washing and waxing car, 1 h/mo	300
Letting dog out the back door	2	Walking dog for 30 min	125
Driving 40 min, walking 5 min (parking)	22	Walking 15 min to bus stop 2×/d	60
Sending e-mail to colleague, 4 min	2-3	Walking 1 min, talking (standing) 3 min	6
Taking elevator up 3 flights	0.3	Walking up 3 flights	15
Parking as close as possible, 10-s walk	0.3	Parking in 1st spot, walking 2 min, 5×/wk	8
Letting cashier unload shopping cart	2	Unloading full shopping cart	6
Riding escalator 3×	2	Climbing 1 flight of stairs, 3×/wk in mall	15
Shopping online 1 h	30	Shopping at mall, walking 1 h	145-240
Sitting in car at drive-in window, 30 min	15	Parking and walking inside, 3×/wk, total of 30 min	70
Paying at the pump	0.6	Walking into station to pay, 1×/wk	5
Sitting and listening to lecture, 60 min	30	Giving lecture	70

*Data for this table were adapted from Beil.[15]

listed some examples of sedentary and active ways of doing things. Many of the recent advances (read labour-saving) in our daily environment reduce energy utilization. If you make some assumptions you can calculate the approximate difference in total energy use between the "easy and hard" ways of doing common tasks. This lies somewhere around 10,000-15,000 kcal every month or two. That is just about the equivalent of 1-1,5 kilograms of body fat. Few of us take this into account when we plan our meals! Doing things the active way, a partial switch to a plant-based diet with no more than 30-35 calorie-% fat and moderate daily motion for between 30-60 minutes should help keep the fat away for many people.

We all have heard that "our western way of life" leads to the physical downfall that we have experienced during the past 10-20 years. The fact is that obesity is a global phenomena linked more to physical activity than race and culture.

WHO has stated "At the other end of the malnutrition scale, obesity is one of today's most blatantly visible – yet most neglected – public health problems. Paradoxically coexisting with malnutrition, an escalating global epidemic of overweight and obesity – "globesity" – is taking over many parts of the world. If immediate action is not taken, millions will suffer from an array of serious health disorders".

References:

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

1. Central nervous system control of food intake, M. W. Schwartz, S. C. Woods, D. Porta Jr., Randy J. Seeley and D. G. Baskin, Nature 404, 661-671 (2000).

2. The brain as a molecular target for diabetic therapy, E. Prodi and S. Obici, Endocrinology 147, 2664 (2006).