The Underlying Basis for Obesity: Relationship to Cancer

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ABSTRACT An increase in the risk of cancer is one of the consequences of obesity. The predominant cancers associated with obesity have a hormonal base and include breast, prostate, endometrium, colon and gallbladder cancers. As the basis for understanding the problem of obesity has advanced, a number of new ideas have emerged about the relationship of obesity to cancer. The conversion of androstenedione secreted by the adrenal gland into estrone by aromatase in adipose tissue stroma provides an important source of estrogen for the postmenopausal woman. This estrogen may play an important role in the development of endometrial and breast cancer. Of interest is that experimental animals lacking aromatase or the estrogen receptor α are obese. Leptin is one of the many products produced by fat cells and has given rise to the ideas that the fat cell is an endocrine cell and that adipose tissue is an endocrine organ. The increased release of cytokines from this tissue may play a role in the inflammatory state that is associated with obesity. The gut also plays an important role in signaling satiety in response to food intake. Colon cancer is an important human disease, and experimental mice lacking gastrin are obese and have an increased risk of developing colon cancer in response to carcinogenic drugs. Efforts to control obesity through preventive strategies and treatment can be expected to have a benefit in reducing the risk of cancer.


KEY WORDS: aromatase, fat cells, leptin, gastrin, obesity, cancer

The risk of cancer increases as body weight rises. This has been demonstrated for both men and women. The most widely used index of weight for these estimates is the body mass index (BMI), calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m²). With this system, normal weight is a BMI of 18.5 to <25, overweight is a BMI of 25 to <30 and obesity is a BMI ≥ 30. Table I shows the prevalence of cancers for overweight individuals with a BMI > 25 and for those who are labeled as obese with a BMI > 30.

The incidence of cancer of the endometrium, breast, colon and gallbladder is increased in women, and the incidence of cancer of the colon and prostate is increased in men. One explanation for these cancers is the increased production of estrogenic compounds by aromatase conversion of androstenedione, produced in the adrenal gland, into estrone. Because this rate of production is related to the size of the adipose depots, it can be a significant source of estrogenic compounds, particularly in postmenopausal women.

To make an attack on obesity and thus an assault on cancer that is related to obesity requires some understanding of the nature of obesity. The next section provides an overview of the newer ideas that are directing the current efforts to develop strategies to control obesity and its related cancers.

Newer understanding of obesity

Research over the past two decades has provided an unprecedented expansion of our knowledge about the physiological and molecular mechanisms regulating body fat. Perhaps the greatest impact has resulted from the cloning of genes corresponding to the five mouse monogenic obesity syndromes and the subsequent characterization of the pathways identified by these genetic entry points. Extensive molecular and reverse genetic studies (mouse knockouts) have helped establish other critical players in energy balance as well as validated or refuted the importance for previously identified pathways.

As a framework for this discussion, I will use a feedback model. In such a system, afferent signals tell the central controls in the brain about the state of the external and internal environment related to food. In turn, this central controller transduces these messages into efferent control signals governing the search for and acquisition of food as well as modulating its subsequent disposal inside the body. Finally, a control system ingests, digests, absorbs, transports, stores metabolizes

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The abbreviations used: BMI, body mass index; c/EBP-β, CCAAT/enhancer binding protein; GLP-1, glucagon-like peptide-1; α-MSH, α-melanocyte-stimulating hormone; PPAR-γ, peroxisome proliferator-activated receptor; PTP-1B, protein tyrosine phosphatase-1B; UCP, uncoupling protein.

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and excretes the waste from the ingested foodstuffs. We will begin with the controlled system (1) (Fig. 1).

**Energy balance and the controlled system**

The first law of thermodynamics tells us that obesity results from an imbalance between energy expenditure and energy intake. Energy expenditure can be divided into three major components. The largest of these is the resting energy expenditure, followed quantitatively by physical activity and thermic effect of food. Energy expenditure is most strongly associated with fat-free body mass. A low rate of basal energy expenditure predicts future weight gain in some studies (2).

The metabolic mixture oxidized by the body is related to the types of foods eaten, adaptive capacity of the body and rate of energy expenditure. The maintenance of energy balance requires that the mix of fuels eaten be oxidized. The capacity for storage of carbohydrate as glycogen is very limited, and the capacity to store protein is also restricted. Only the fat stores can readily expand to accommodate increasing levels of energy intake above those required for daily energy needs. Several studies now show that a high rate of carbohydrate oxidation predicts future weight gain (3). One explanation for this is that when carbohydrate oxidation is higher than intake of carbohydrate, the body needs carbohydrate to replace the limited stores because it cannot convert fatty acids to carbohydrate and the conversion of amino acids to carbohydrate mobilizes protein stores. Obese individuals who have lost weight are less effective in increasing fat oxidation in the presence of a high-fat diet than are normal-weight individuals (4).

The energy expended in physical activity is directly related to body weight. Physical activity gradually declines with age, and maintaining a regular exercise program is difficult for many people, particularly as they get older. Adaptation to a change from a low- to a higher-fat diet takes time and can be accelerated by exercise (5).

The thermic effect of food is the third component of energy expenditure. After food is ingested, there is a rise in energy expenditure, which accounts for ~10% of the day’s energy expenditure. The sympathetic nervous system controls part of this process. The control of sympathetic activity and its noradrenergic output offers a possible strategy for treating obesity by raising energy expenditure. The thermic effect of food is blunted when insulin resistance is high and may account for the impaired thermic effect of food in obesity (6).

The original brown fat uncoupling protein (UCP1) has a well-established role in temperature and body weight regulation in rats and mice (7). Increased expression or activation of this protein uncouples oxidative phosphorylation, resulting in the conversion of energy to heat (thermogenesis). The impor-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Relative risk (overweight vs normal weight)</th>
<th>Relative risk (obese vs normal weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (postmenopausal)</td>
<td>1.12</td>
<td>1.25</td>
</tr>
<tr>
<td>Colon</td>
<td>1.15</td>
<td>1.33</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1.59</td>
<td>2.52</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.06</td>
<td>1.12</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.36</td>
<td>1.84</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.34</td>
<td>1.78</td>
</tr>
</tbody>
</table>


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**FIGURE 1** A feedback model of food intake. The bottom of the figure represents the gastrointestinal (GI) tract and the entry of food through the mouth. Vagal fibers carry information about taste and the size and activity of the gut to the brain. In addition, a variety of GI peptides act as signals about the size and content of the GI tract. Other metabolic signals are provided by nutrients. The adipose organ produces leptin, which is a major signal for modulating food intake. The brain represented at the top consists of a receiver for external signals, a transducer, a comparator and effector signal generators that affect food intake and metabolism. 5-HT, serotonin (hydroxytryptamine); ACTH, adrenocorticotrophic hormone; AGRP, agouti-related peptide; ARC, arcuate nucleus; BAT, brown adipose tissue; CART, cocaine-amphetamine-regulated transcript; DA, dopamine; DMV, dorsomotor nucleus of the vagus; GABA, y-aminobutyric acid; GLU, glutamate; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; MPG, motor pattern generator; MSH, melanocyte-stimulating hormone; NE, norepinephrine; NPY, neuropeptide Y; NTS, nucleus of the tractus solitarius; ORX, orexin (hypocretin); PAG, periaqueductal gray; PBN, parabrachial nucleus; SNS, sympathetic nervous system. (Copyright 1999 George A. Bray.)
for obesity is that these mice do not become obese when eating a high-fat diet. The reason for the protection from diet-induced obesity is unknown.

Enzymes involved in fat metabolism are important in obesity. A notable example is the recently identified acyl coenzyme A:diacylglycerol transferase, the enzyme responsible for the final step in the glycerol phosphate pathway of triglyceride synthesis. Mice that cannot express this enzyme have increased thermogenesis, and like mice with PTP-1B deficiency, they do not become obese when consuming a high-fat diet.

**Afferent signals**

The controlled system and the external environment both provide signals that play a role in the control of feeding. The information to the brain coming from sight, sound and smell are all distance signals for identifying food or for avoiding it.

The oral and nasal cavities are the first lines of exposure to foodstuffs. Taste and smell can produce important positive and negative feedback signals. The recent discovery of taste and smell receptors for polyunsaturated fatty acids on the taste bud that involves a potassium rectifier channel (K+ 1.5) offers an opening into modifying taste inputs to the food intake system (9).

Gastrointestinal peptides have long been studied as potential regulators of satiety. Cholecystokinin was one of the first peptides shown to reduce food intake. It occurs in both animals and human beings (10). Ghrelin, a recently discovered peptide produced in the stomach, is believed to be the natural regulators of satiety. Cholecystokinin was one of the opening into modifying taste inputs to the food intake system (9).

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**Adipose tissue signals**

The fat cell is a true endocrine cell that secretes a variety of factors (Fig. 2) (15), including metabolites such as lactate, fatty acids, prostaglandin derivatives and a variety of peptides, including cytokines (leptin, tumor necrosis factor α, interleukin-1 and -6, adiponectin), angiotensinogen, complement D (adipsin), plasminogen activator inhibitor-1 and undoubtedly many others.

Leptin is the best known of the afferent fat signals and the best candidate for the primary signal communicating body fat information to the central controller. Identification of this peptide through positional cloning in 1994 provided important new insights into the regulation of food intake, energy expenditure and body fat (16). It is now clear that this cytokine, derived primarily from fat cells but also from the placenta and possibly the stomach, reduces food intake and increases the activity of thermogenic components of the sympathetic nervous system. Modulation of neurons in the arcuate nucleus by leptin results in reduced secretion of neuropeptide Y and agouti-related protein and increased secretion of the precursor of α-melanocyte-stimulating hormone (α-MSH), which reduces food intake and the peptide product of cocaine-amphetamine-regulated transcript (17). Because of these coordinated effects of leptin, this adipocyte-derived cytokine has been used in a clinical trial where there was a dose-related weight loss but significant discomfort occurred at the injection site (18). It has also been shown to be clinically effective in those rare individuals who lack leptin and to almost completely eliminate body fat in a transgenic mouse that overexpresses leptin (19).

The brain serves at least three functions with respect to food intake. It acts as a transducer of information from sensory...
organisms and the internal milieu, an integrator of this information and an activator of the motor system, the endocrine system and the autonomic nervous system. Some of these relationships are shown in Figure 1.

In recent years the most intensively explored areas of food intake regulation have been the analyses of central monoamines and neuropeptide pathways. The hydroxtryptamine (serotonin) system has been the most heavily studied of the monoamines pathways because serotonin receptors modulate both the quantity of food and macronutrient selection. Stimulation of the serotonin receptors in the paraventricular nucleus reduces fat intake with little or no effect on the intake of protein or carbohydrate (21). The reduction in fat intake by fenfluramine probably occurs through 5-hydroxytryptamine2C receptors because its effect is attenuated in 5-hydroxytryptamine2C knockout mice (22). Serotonin receptors may be effective sites for modulation of both total intake and fat intake. However, the unfortunate development of valvulopathy with fenfluramine and dexfenfluramine will surely dampen further efforts at new drug development using serotonin receptors (23).

The stimulation of α2-noradrenergic receptors reduces food intake (24). Phenylpropanolamine is an α2-agonist that has a modest effect on food intake, but this drug has been removed from the market for safety reasons (24). Some of the antagonists to the α2-receptors that are used to treat benign prostatic hypertrophy produce weight gain, indicating that this receptor is clinically important. Stimulation of α2-receptors will increase food intake in experimental animals, and a polymorphism in the α2-β-adrenoceptor has been associated with reduced metabolic rate in humans. On the other hand, the β2-receptors in the brain reduce food intake. These receptors can be activated by agonist drugs, the release of norepinephrine in the vicinity of these receptors or the blocking of norepinephrine reuptake.

The number of neuropeptides shown to affect food intake has grown rapidly (25). However, the degree of biological validation and likely relative importance varies considerably. Neuropeptide Y is among the most potent stimulators of food intake (26,27). A natural agonist, α-MSH, reduces food intake, and humans and a mouse lacking the precursor of α-MSH that reduces food intake are obese. The biological importance of this receptor system became clear when it was shown that MC4 receptor knockout mice became massively obese. The melanocortin receptor system is the one on which the genetic defect in the agouti locus of the yellow mouse plays out its role.

Melanin concentrating hormone is produced by neurons in the lateral hypothalamus and microinjection of this peptide increases food intake (28). Melanin concentrating hormone knockout mice are lean, suggesting that the peptide has a physiological role in the control of food intake and body fat stores.

The opioid receptors were the first group of peptide receptors shown to modulate feeding. They also modulate fat intake. Both the μ- and κ-receptors can affect feeding, but whether this strategy can be applied to development of new drugs because of the linguistic connotations of “opioid-like” is uncertain.

Several other peptides that stimulate food intake are of lesser interest to us because they have been associated with other significant biological events. Galanin is the first example. Mice lacking galanin are unable to maintain lactation, suggesting that modulation of milk-producing hormones may be the primary role for this peptide. Hypocretin (also called orexin A), which stimulates food intake, is deficient in dogs with narcolepsy. Thus orexin may serve an arousal function with feeding as one part of its action. Whether sleepiness is a good alternative to eating is debatable. Corticotropin-releasing hormone and the closely related urocortin have been shown to affect food intake and body weight.

Efferent signals

The motor system for acquisition of food and the endocrine and autonomic nervous systems are the major efferent control systems involved with acquiring food and regulating body fat stores. Among the endocrine controls are growth hormone, thyroid hormone, gonadal steroids (testosterone and estrogens), glucocorticoids and insulin.

During growth, growth hormone and thyroid hormone work together to increase growth of the body. At puberty, gonadal steroids enter the picture and lead to shifts in the relationship of fat to lean body mass in boys and girls. Testosterone increases lean mass relative to fat, and estrogen has the opposite effect. Testosterone levels fall when human males grow older, and there is a corresponding increase in visceral and total body fat and a decrease in lean body mass. This may be compounded by the decline in growth hormone that is also associated with an increase in fat relative to lean mass.

Glucocorticoids are critical for the development of obesity. In all forms of experimental obesity, glucocorticoids are necessary for the development and maintenance of obesity. Adrenalectomy in animals with a ventromedial hypothalamic lesion reverses the obesity. In the genetically obese animals, adrenalectomy stops the progression, but does not reverse the syndrome. In humans excess production of glucocorticoids produces modest obesity, and destruction of the adrenal glands is associated with loss of body fat. The enzyme 11β-hydroxysteroid dehydrogenase is involved in the conversion of cortisone, the active steroid, to cortisol, the inactive one. An increase in the level of this enzyme in visceral adipose tissue has been suggested as a basis for the development of visceral obesity; that is, central adiposity is a form of visceral Cushing’s disease (29). A transgenic model in which this enzyme is overexpressed has increased deposition of visceral fat, lending credence to this hypothesis (30).

Both androgens and estrogens are involved in obesity and fat distribution. At puberty the production of testosterone in males is associated with a reduction in the percentage of body fat. In females the increase in estrogens is involved in the remodeling that produces the female shape. When the ovaries are removed surgically in animals, obesity frequently develops and can be reversed by giving injections of estradiol. The importance of this mechanism has been highlighted by the study of animals with transgenic defects in the gonad hormone receptors. Animals without estrogen receptor α are obese, as are animals lacking aromatase.

Insulin is essential for the development of obesity (31). It plays a key role in lipogenesis and inhibition of lipolysis. Destruction of the beta cells in experimental forms of obesity...
sloths or arrests the development of obesity. Absence of insulin, seen in type 1 diabetics, is associated with nearly normal body weight. Treatment of diabetics with insulin or drugs that increase insulin secretion from the beta cell increase body fat relative to other forms of treatment for diabetes.

The autonomic nervous system is the other major regulator of internal metabolism. The effenter parasympathetic (vagal) system modulates gastric emptying, hepatic metabolism and insulin secretion, among other controls. The sympathetic nervous system, on the other hand, modulates thermogenesis, insulin secretion and vascular reactivity through regionally controlled effects. In a variety of experimental studies, a strong reciprocal relationship was shown between food intake and thermogenic component of the sympathetic nervous system (32). Clinical studies with a thermogenic drug combination of ephedrine and caffeine shows that more than half of the weight loss results from a decrease in food intake (33). This suggests that drugs that modulate thermogenesis may also have important effects on food intake.

From this brief review of the control of energy expenditure and some of its underlying mechanisms, it is easy to sense the complexity of the system that regulates food intake and the problems involved in tackling obesity as a cause of cancer.

LITERATURE CITED