



## How Obesity Causes Diabetes: Not a Tall Tale

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earnest. To paraphrase Winston Churchill, in the area of common disease genetics we are certainly not at the end, nor are we even at the beginning of the end, but we may, perhaps, be at the end of the beginning.

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#### VIEWPOINT

# How Obesity Causes Diabetes: Not a Tall Tale

Mitchell A. Lazar

The epidemic of obesity-associated diabetes is a major crisis in modern societies, in which food is plentiful and exercise is optional. The biological basis of this problem has been explored from evolutionary and mechanistic perspectives. Evolutionary theories, focusing on the potential survival advantages of "thrifty" genes that are now maladaptive, are of great interest but are inherently speculative and difficult to prove. Mechanistic studies have revealed numerous fat-derived molecules and a link to inflammation that, together, are hypothesized to underlie the obesity-diabetes connection and thereby represent prospective targets for therapeutic intervention.

Type 2 diabetes stems from the failure of the body to respond normally to insulin, called "insulin resistance," coupled with the inability to produce enough insulin to overcome this resistant state. This common form of diabetes is often associated with obesity, and the current epidemics of these two conditions are seemingly related (1). This is glaringly evident in children, who are increasingly plagued by obesity and in whom the prevalence of type 2 diabetes (formerly termed "adult onset") is approaching that of type 1 diabetes (formerly termed "juvenile onset") (2). The epidemic of diabetes has a huge associated cost in terms of healthcare dollars as well as human morbidity and mortality (3). Recent studies predict that one in three Americans born in the year 2000 will develop diabetes in their lifetime (4), and a similarly ominous future confronts nearly all developed nations. Here, I discuss the relationship between obesity and diabetes, first in terms of the evolutionary forces that might explain their increased incidence in the modern world and then in terms of the pathogenic pathways that link the two

conditions and inform rational strategies for prevention and therapy.

#### Why We Have Epidemics of Obesity and Diabetes: An Evolutionary Perspective

The evolutionary perspective has successfully guided much of modern biology, yet it is not always definitive. Take, for example, the giraffe's long neck, which would seem to provide a competitive advantage for obtaining food, thus favoring survival and reproduction of the species. However, in his essay "The Tallest Tale," Gould argued that the weight of scientific evidence favors alternative selective pressures as having led to the giraffe's long neck, including combat advantages, sighting of predators, and efficient heat loss (5).

There are no known survival advantages of morbid obesity, and increased body fat is associated with increased mortality (6). Hence, natural selection is unlikely to have favored obesity per se. On the other hand, during periods of prolonged famine that plagued early human hunter-gatherers, a survival advantage would have been conferred by genes that favor the economical use and storage of energy: so-called "thrifty" genes (7). The existence of thrifty genes was initially proposed by Neel, who focused on the efficient use of glucose as a biological

fuel; he suggested that evolutionary pressure to preserve glucose for use by the brain during starvation led to a genetic propensity toward insulin resistance in peripheral tissues (8). Biological systems store energy most efficiently as fat and, hence, another function of thrifty genes is to promote an increase in adipose tissue. In the modern setting of sedentary lifestyles and unrestricted access to high-calorie foods, thrifty genes have been suggested to underlie the twin epidemics of obesity and diabetes (7).

Human obesity has a clear genetic component but is rarely monogenic (9). Thus, there are likely to be multiple thrifty genes, and the inheritance of several polymorphisms leading to small differences in expression can make populations more or less susceptible to obesity and diabetes (10). Several candidate thrifty genes have been proposed and are reviewed elsewhere (11). In principle, there could be separate sets of thrifty genes that promote body fat deposition or insulin resistance. Indeed, this concept is supported by a paradox: Insulin actually increases the production and storage of fatty acids in adipose tissue, thereby exacerbating obesity, whereas tissues such as muscle are insensitive to insulin (12). Nevertheless, Occam's Razor (the principle that plurality of causes should not be postulated unless absolutely necessary) argues for thrifty genes that both increase energy storage and cause insulin resistance.

Perhaps the best thrifty gene candidate is the gene that encodes leptin, a hormone produced by adipose tissue and the absence of which leads to obesity and insulin resistance in rodents and humans (13). Leptin functions physiologically as a signal of energy stores, inhibiting food intake and accelerating energy

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metabolism (13). During starvation, it is the fall in circulating leptin levels that triggers increased appetite and decreased metabolic rate. Consistent with this, rodents and humans with only one functional copy of the leptin gene have increased body fat (14), and leptin deficiency due to lipodystrophy causes insulin resistance (15, 16). Because a reduction in leptin levels appears to be the physiological signal for a thrifty metabolic response, leptin itself must have been evolutionarily selected for another function. Indeed, leptin replacement reverses amenorrhea in leptin-deficient females with low body weight (17), providing the mechanistic explanation for the link between body fat and reproductive capacity that was first proposed three decades ago by Frisch on the basis of epidemiological studies of indigenous and modern populations (18). This physiological function of leptin thus favors survival of the species by conferring a reproductive advantage to individuals who are nutritionally fit.

An alternative to thrifty genes is the "thrifty phenotype" hypothesis, first proposed by Hales and Barker on the basis of clinical observations that poor fetal and/or postnatal nutrition is associated with obesity and type 2 diabetes later in life (19). This hypothesis posits that fetal malnutrition alters metabolic pathways that result in tissue adaptations favoring the thrifty use of nutrients in utero and in postnatal life, thereby leading to obesity and diabetes in the setting of subsequent adequate nutrition. The focus on an inadequate maternal-fetal nutritional environment differs from the focus on thrifty genes. Indeed, the thrifty phenotype hypothesis postulates epigenetic memory of the fetal/neonatal environment. Epigenetic regulation of gene expression involves chemical modification of chromatin by enzymes such as sirtuins, whose activities are linked to cellular energy stores and, in lower organisms, interface with insulin signaling pathways (20, 21).

If fetal adaptations to malnutrition are preserved later in life, as proposed by the thrifty phenotype hypothesis, gene sets that facilitate these epigenetic changes would favor survival and reproduction in adulthood. Thus, in the thrifty phenotype model, there would be ample selective pressure for genes that protect from early malnutrition but promote obesity and diabetes under modern conditions.

### How Obesity Causes Diabetes: A Biological Perspective

Although once considered a passive fuel depot, adipose tissue is now recognized to be an endocrine organ that communicates with the brain and peripheral tissues by secreting hormones regulating appetite and metabolism (22). These functions appear to be modulated by the location of the adipose tissue (visceral versus subcutaneous) (23), by the size of the average adipocyte in the tissue (24), and by adipocyte metabolism of glucose (25) and corticosteroids (26).

Except in rare cases where the leptin gene is defective, leptin levels are elevated in obesity (13). This is due to resistance to the actions of leptin at the cellular level, which may be mechanistically related to insulin resistance, as discussed below. Several other adipocyte-derived factors have been shown to contribute to systemic insulin resistance. One such factor is the increased levels of adipocyte-derived free fatty acids that have been shown to contribute to insulin resistance in liver and muscle in obesity (27, 28). Adipose tissue also secretes a large number of proteins in addition to leptin that modulate glucose metabolism and insulin action (22, 29) (Table 1). The causal role of several of these proteins in insulin resistance and diabetes has been established through studies of mouse genetic models. Studies of humans generally suggest that circulating levels of these proteins are elevated in in-

dividuals with type 2 diabetes. One exception is adiponectin, which enhances insulin action yet circulates at reduced levels in obesity (30). Each of these proteins constitutes a potential target for therapies aimed at uncoupling insulin resistance from obesity.

A subset of these adipose-derived proteins are adipocyte-specific, whereas others are not. Intriguingly, many proteins that are adipose-derived but not adipocyte-specific play a role in innate immunity, a relatively primitive defense mechanism against infection (31). Cytokines such as tumor necrosis factor  $\alpha$  and interleukin-6 are produced by macrophages as well as by adipocytes; they act directly on inflammatory cells and also contribute indirectly to inflammation by acting on the liver to produce acute phase proteins. These cytokines also induce suppressor of cytokine signaling-3 (SOCS-3), an intracellular signaling molecule that impairs the signaling of both leptin and insulin. SOCS-3 levels are elevated in obesity and thus may represent a final common pathway of obesity-associated resistance to the actions of both leptin and insulin (32).

The similarity between macrophages and adipocytes extends beyond cytokine production. Both cell types express peroxisome proliferator-activated receptor  $\gamma$ , a transcription factor that is the target of insulin-sensitizing therapies (33) and that has been dubbed "the ultimate thrifty gene" because of its role in lipid accumulation (34). It has also become evident that macrophage infiltration of adipose tissue is characteristic of obesity (35, 36), although the pathophysiological consequences are unknown. The anatomic blurring of the line between adipocytes and macrophages is paralleled by the tissue expression of the polypeptide hormone resistin, whose levels are increased in insulin-resistant mice and humans (37, 38). Resistin is expressed exclusively in adipocytes in mice (39) but predominantly in macrophages in humans (40). The evolutionary and functional implications of this remain to be determined. Perhaps the commonalities of adipocyte and macrophage function are remnants of an ancestral evolutionary adaptation; indeed, invertebrates concentrate endocrine and immune functions in a single cell type resembling the macrophage (41, 42).

The close relationship between inflammation and diabetes is supported by the observation that stimulation of the innate immune response [by bacterial endotoxin during sepsis, for example (43)] results in insulin resistance that contributes to the high mortality of critical illness (44). The interaction between inflammation and insulin signaling is also suggested by the ability of aspirin to improve insulin resistance, in part by preventing the antagonistic effects of fatty acids and cytokines (45).

**Table 1.** Proteins secreted by adipose tissue that are also thought to play a role in obesity-associated insulin resistance and diabetes (22, 29, 51). ASP, acylation stimulatory protein; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IL-6, interleukin 6; MCP-1, macrophage and monocyte chemoattractant protein 1; PBEF, pre-B cell colony enhancing factor; PAI-1, plasminogen activator inhibitor 1.

Adipose-derived protein	Effect on insulin sensitivity	Other tissue sources
Leptin	Improvement	None
Adiponectin	Improvement	None
Adipsin/ASP	Decline	None
Resistin	Decline	None (rodent) Macrophage (human)
TNF- $\alpha$	Decline	Macrophage
IL-6	Decline	Macrophage
MCP-1	Decline	Macrophage
Visfatin (PBEF)	Improvement	Liver, lymphocytes
PAI-1	Decline	Liver
Angiotensinogen	Decline	Liver
Serum amyloid A	Not known	Liver
$\alpha$ 1-acid glycoprotein	Not known	Liver

Why is obesity an inflammatory state and why does inflammation cause diabetes? The search for answers to these questions takes us again to evolutionary considerations. Perhaps the response to infection is more effective when glucose is shunted from muscle to the inflammatory cells involved in the immune response and tissue repair (46). A potentially unifying view is that the body's ability to survive major stress, including infection and starvation, is enhanced by peripheral insulin resistance that preserves the brain's glucose supply (47). This hypothesis might explain why cortisol, the major stress hormone, causes insulin resistance and stimulates the innate immune response (31), even though chronic cortisol exposure is anti-inflammatory because of down-modulation of the acquired immune response. The stress connection may extend to individual cells, as it has recently been shown that intracellular stress induces insulin resistance in a manner that is exacerbated by obesity, potentially through adipocyte-secreted factors (48). Moreover, chronic metabolic stress impairs the ability of pancreatic beta cells to secrete sufficient insulin to overcome insulin resistance, which is a hallmark of type 2 diabetes (49).

### Not a Tall Tale: How Will it End?

Humanity has been curious about the giraffe's long neck since time immemorial. Although it is very likely that this unusual phenotype contributed to the survival of that species, there is as yet no molecular or genetic explanation for it. We are now curious about the explanation for the dramatic rise in human obesity and diabetes. It is interesting to speculate about the origin of genes that make us particularly susceptible to these metabolic diseases in the setting of

modern lifestyles. The theories that emerge may provide clues to the underlying mechanisms, especially if they can be supported by studies in model organisms (50). Of course, natural selection itself has the potential to solve these health crises, but only when they threaten the survival of our species. A more optimistic view is that we can turn the tide of these epidemics by focusing on mechanistic questions such as how obesity causes diabetes. It is hoped that harnessing this knowledge will allow us to successfully intervene before natural selection takes over.

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### VIEWPOINT

# Diabetes, Obesity, and the Brain

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Recent evidence suggests a key role for the brain in the control of both body fat content and glucose metabolism. Neuronal systems that regulate energy intake, energy expenditure, and endogenous glucose production sense and respond to input from hormonal and nutrient-related signals that convey information regarding both body energy stores and current energy availability. In response to this input, adaptive changes occur that promote energy homeostasis and the maintenance of blood glucose levels in the normal range. Defects in this control system are implicated in the link between obesity and type 2 diabetes.

More than a century ago, the renowned physiologist Claude Bernard observed that diabetes could be induced in animals by puncture of the floor of the fourth cerebral ventricle ("pique diabetique") (1). Although this striking finding suggested a key role for

the brain in glucose homeostasis, its importance was largely neglected after the discovery of insulin in 1923. However, new findings have revived interest in the role played by the brain in both glucose homeostasis and the mechanism linking obesity to type

2 diabetes. As Bernard might have predicted, this new information suggests that a full understanding of the pathogenesis of these disorders must incorporate a role for the brain in metabolic regulation.

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