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The Adipocyte: Storage Depot or Node on the Energy Information Superhighway?

Minireview

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In a world where food availability is intermittent, survival requires the capacity to store ingested calories in excess of immediate requirements so that energy may be released at a later point upon demand. To orchestrate these processes of energy storage and release, highly integrated systems have evolved, and these operate on several physiological levels. As for many complex physiologic systems, the brain provides an essential coordinating role. Most important are the hypothalamic centers (see Figure 1) that coordinate energy homeostasis through regulation of food intake (hunger and satiety), energy expenditure (thermogenesis), and the secretion of hormones (especially insulin) that regulate substrate interconversion, storage, and mobilization. But where does the energy storage take place? Enter the adipocyte, and along with it obesity, a remarkably prevalent disorder that is defined as a state of pathologically increased adipose cell mass. Is the adipocyte an innocent bystander, or does it play an active role in the regulation of energy homeostasis and body composition? Although adipose cell enlargement and eventual hypertrophy are the defining features of obesity, the adipocyte has been viewed as a largely passive participant in the disease process, accumulating or losing lipid stores in response to alterations in substrates and regulatory signals produced at distant sites. As a cell type, therefore, the adipocyte has received a great deal of attention only recently, and obesity, the dominant disease affecting adipocyte function, has lacked major breakthroughs in the realm of molecular pathogenesis. Indeed, much of the important research in obesity has taken place in departments of psychology and psychiatry. Recent advances in the area of adipocyte development and evidence that the adipocyte can function as an endocrine cell have promised to change this situation radically and permanently, and these are the subject of this minireview.

The Black Box of Energy Balance

Viewed broadly, obesity is a disorder of energy balance, occurring when energy intake chronically exceeds energy expenditure. It is now clear that in normal physiology, these two components of the energy balance equation (i.e., energy intake and expenditure) are linked, not independent, variables. When food intake increases, so does energy expenditure, and vice versa. Teleologically, this could be viewed as a mechanism to conserve calories when food deprived and to prevent obesity when excess food is ingested. Much has been learned about the mechanism by which chronic overfeeding increases energy expenditure beyond the energetic costs of digestion, absorption, metabolic interconversions, and carrying around the extra weight. This adaptive thermogenesis involves the activation of the sympathetic nervous system, and, at least in rodents, subsequent stimulation of heat production in brown adipose tissue (BAT) (Himms-Hagen, 1989). BAT is the physiologic opposite of white adipose tissue, being designed to burn, not store, energy, and to release the energy as heat. BAT accomplishes this through a unique mitochondrial protein (thermogenin, or uncoupling protein) that uncouples fuel oxidation from ATP generation by collapsing the hydrogen ion gradient across the inner mitochondrial membrane (Nicholls and Locke, 1984). The recent demonstration that animals made deficient in BAT through a transgenic toxigene (Lowell et al., 1993) developed not only efficient metabolism and obesity but hyperphagia as well, strongly suggested that food intake and energy expenditure are linked through BAT, via an as-yet-unknown signaling mechanism. The existence of such a physiologic link between energy intake and expenditure has also been suggested by several of the genetic models of spontaneous obesity in rodents that have been studied for the past 30 years (Bray and York, 1979; Friedman and Leibel, 1992). In these single-gene autosomal recessive disorders (*ob/ob*, *db/db*), severe obesity is always accompanied by both hyperphagia and diminished energy expenditure, the latter associated with BAT dysfunction due to inadequate stimulation by the sympathetic nervous system. The molecular link between excessive food intake and decreased energy expenditure, although fundamental, has remained obscure. Since closely apposed hypo-

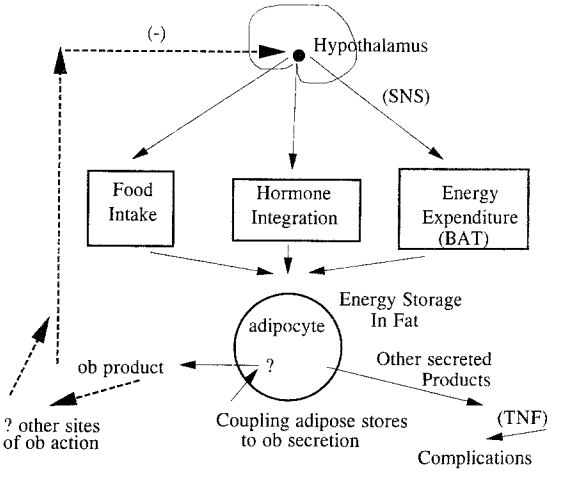

Figure 1. Major Components of the Body Weight Regulatory System

The brain, working primarily through hypothalamic centers, influences body weight through effects on hunger and satiety, integration of secretion of key hormones such as insulin, and energy expenditure, including actions to regulate BAT via sympathetic nervous system (SNS) innervation. These combine to determine the the state of energy storage in adipose cells. The adipocyte plays an active role through the regulated secretion of a number of secreted products. These include the product of the *ob* gene, which is predicted to regulate hypothalamic function through feedback that may be direct or indirect. The mechanism coupling expression of the *ob* product to fat cell stores is unknown. Other secreted products, such as TNFα, may contribute to the morbid complications of obesity through overexpression in enlarged adipocytes.

thalamic centers can regulate these two processes, it had been surmised that primary defects in the hypothalamus may underlie these obesities. It is now apparent, however, that the adipocyte itself may be a central player in the signaling loop. This concept fits well with the gathering evidence that the adipocyte is not quite as passive as it once appeared.

The Adipocyte Acquires New Roles

The established role for the adipocyte is to serve as the site of triglyceride storage or free fatty acid release in response to changing energy needs. However, the notion that the adipocyte might also function as a more active component of energy homeostasis has been around for many years. It was proposed that the adipocyte might be capable of sensing excessive energy stores and, in response, provide a signal (the "adipostat") that would limit food intake, thereby facilitating maintenance of a desired "set point" of body fat (Kennedy, 1953; Mrosovsky, 1986). As the discovery of a candidate effector for signaling from the adipocyte failed to materialize, the interest in this hypothesis waned.

In recent years, the hypothesis has been reawakened, alongside observations that the adipocyte was capable of producing and secreting molecules with regulatory potential. Adipsin is a serine protease secreted by adipocytes that was discovered as a differentiation-dependent mRNA in a cultured adipocyte cell line (Cook et al., 1985). The observation that expression of this molecule was massively reduced in many models of rodent obesity and that its circulating levels were similarly reduced raised a hope that this could be the long-sought adipostatic signal (Flier et al., 1987). Further studies revealed that adipsin was a member of the alternative complement pathway (complement factor D) (Rosen et al., 1989) and that its repletion failed to alter the physiology of obesity. Obese humans, unlike rodents, are not adipsin/D deficient. Although the consequences of regulated expression of this molecule in adipocytes remain unclear, recent evidence that adipsin/D might have actions to generate complement peptides with the ability to stimulate triglyceride acylation may be a clue (Baldo et al., 1993). Subsequently, the adipocyte became known as a site for dysregulated expression and secretion of an increasing number of interesting molecules, including peptides such as angiotensinogen (Frederich et al., 1992) that are produced in other sites as part of regulatory systems unrelated to fuel homeostasis.

A provocative example of such a molecule is tumor necrosis factor α (TNFα). TNFα is a cytokine that is expressed in macrophages and a number of other cells; its expression is induced by bacterial lipopolysaccharide. The discovery that this molecule is also expressed by adipocytes was an outgrowth of studies on the regulation of complement proteins in adipocytes and was made all the more remarkable by the surprising observation that adipocytes of obese animals and humans have markedly increased TNFα expression (Hotamisligil et al., 1993, 1994). Recent studies reveal that the consequences of TNFα dysregulation are clearer than underexpression of adipsin has so far proved to be. Thus, it is strongly linked to one of the most deleterious consequences of the obese state: insulin resistance. Considerable attention is now being focused on the mechanism by which TNFα induces resistance in the cascade of insulin signal transduction, the mechanism for tissue-specific overexpression in the obese adipocyte, and the possibility that interference with this pathway could be a new therapeutic approach to abrogating insulin resistance and thereby obesity-linked diabetes. Whether TNFα expression in obesity participates in a physiologic loop, perhaps related to limitation of obesity at the expense of insulin resistance, may require metabolic studies of mice with genetic alterations in the TNFα system.

The ob *Gene*

The autosomal recessive mutation causing the syndrome of obesity in mice, known as *ob/ob*, was discovered in the mouse colony of The Jackson Laboratory in 1950 and was mapped to chromosome 6. These mice develop severe obesity from a very early age and display both marked hyperphagia and diminished energy expenditure. The latter is made evident by the development of obesity in *ob/ob* mice fed identical calories with lean littermates and by their poor tolerance for exposure to environmental cold, which requires regulated increases in energy expenditure. Through a positional cloning approach, the identification of the *ob* gene was very recently reported (Zhang et al., 1994), and the preliminary indication is that this gene provides a major new insight into the regulatory role of the fat cell in energy balance.

The *ob* gene encodes a 4.5 kb mRNA that is apparently expressed solely in adipose tissue (presumably adipocytes). The predicted protein product is a 167 amino acid protein with no homology to proteins in the data bases. The presence of a signal sequence suggests that it is a secreted protein. Of two coisogenic strains of *ob* mice, one (the original) has a nonsense mutation, and the other has no mRNA and a presumed deletion affecting the promoter region. This genetic evidence is powerful and will hopefully be rapidly followed by a demonstration that the ob protein exists in plasma and is absent in the *ob/ob* mice and that repletion of the active protein will reverse the disease. If so, what will be the major questions to be answered?

A fundamental question is the precise mechanism by which the putative ob hormone acts to influence appetite, energy expenditure, and other systems (such as reproduction and growth) that are known to be abnormal in mutant *ob/ob* mice. The most likely may be an action of this peripherally produced protein/hormone to influence hypothalamic function. One problem confronting such a hypothesis is the presence of the blood–brain barrier. However, a number of peripheral peptides, including angiotensin II, can rapidly affect the hypothalamus through nerve cells in the region of the circumventricular organs that lie outside the blood–brain barrier (Tanaka and Nomura, 1993). Alternatively, as seems to be the case for the gut peptide CCK, signals could be brought to the hypothalamus via stimulation of vagal afferent axons. Either ob itself or a molecule in the periphery whose levels are influenced by ob could bring this signal to the brain. It will be interesting

to determine how ob relates to other peptides in the peripheral circulation already viewed as having the capacity to regulate appetite, such as CCK and insulin itself.

In any case, a major focus of investigation will turn to the hypothalamus and to attempts to identify a molecular and anatomical target(s) for the action of the ob protein (or its downstream mediator) in the brain. It is interesting to note that, based on parabiosis studies performed at The Jackson Laboratory in the 1950s, the *ob* gene was hypothesized to encode a satiety molecule and the *db* gene to encode a required component of the response to this satiety molecule (Coleman, 1973). Whether this hypothesis will be validated and whether such validation will first result from positional cloning of the *db* gene or from studies of the ob protein remain to be determined. In any event, both for basic biology and for the anticipated development of new anti-obesity drugs, the focus on the presumed hypothalamic targets will be intense. One clue might be derived from recent observations with the yellow agouti mouse. These mice have an autosomal dominant syndrome of obesity due to a genetic lesion that causes widespread ectopic expression of the agouti protein, a protein normally restricted to the skin (Bultman et al., 1992). The observation that agouti can antagonize the melanocyte-stimulating hormone α-MSH (Lu et al., 1994) is interesting, since receptors for this neuropeptide are expressed in the hypothalamus.

A second issue involves the nature of regulated *ob* expression in the adipose cell and the role that the protein normally plays in short- or long-term regulation of body fat content. By what mechanism might the level of *ob* reflect the state of adipose stores? Is the level of *ob* expression regulated by a critical intracellular metabolite, by one or more hormones (e.g., insulin) that parallel the state of adipose storage of triglyceride, or by a combination of these and other factors?

Finally, a substantially conserved human homolog of *ob* mRNA has been identified in human fat, and assessing the role of the encoded protein in human obesity and in obesity-linked diabetes will require additional study. Perhaps some rare cases of severe early-onset obesity in humans will be due to mutations in the *ob* gene. It will also be critical to determine whether more common varieties of human obesity will be associated with altered regulation of the ob protein or resistance to its action.

Whither the Adipocyte?

With the realization that the adipocyte is a "smart cell," possessing (quite likely) the capacity to communicate directly or indirectly with the brain, interest in the origin and fate of this cell type is certain to be piqued. Fortunately, another breakthrough in this area greets us. Spiegelman et al. have reported what appears to be the holy grail itself: identification of a gene whose protein product may regulate the determination of the adipocyte lineage, as seen after forced expression to physiologic levels in fibroblasts (Tontonoz et al., 1994a). The gene is expressed exclusively in adipocytes and encodes a member of the peroxisome proliferator-activated receptor subfamily of nuclear hormone receptor transcription factors, designated PPARγ2 (Tontonoz et al., 1994b). Two aspects of the regulatory potential of this factor are worthy of emphasis. First, PPARγ2 may operate in concert (and synergistically) with a basic–leucine zipper transcription factor, C/EBPα, which, although not adipocyte specific, is induced (somewhat later) with differentiation and can influence the expression of several fat-specific genes and differentiation itself (Samuelson et al., 1991; Umek et al., 1991). Second, and potentially of even greater importance, is the fact that PPARγ2 is a lipid-activated transcription factor. As such, this suggests a mechanism whereby lipid metabolism or flux might directly regulate the number of adipose cells in tissue, perhaps analagous to the ability of cardiac stretch to induce hypertrophy of that tissue. Whether the activating ligand is any free fatty acid or a specific metabolite is a key question now amenable to an answer, and this should provide a tool that could enable discovery of potent new drugs, capable of regulating adipose cell number in vivo.

Would such a drug be valuable if developed? In a sense, this brings us back to our initial question regarding the role of the adipocyte in the genesis of obesity. If the adipocyte was merely a repository for stored calories, interference with the process of adipogenesis in the face of excess food intake might limit obesity (since the maximal size of an adipocyte is finite), but produce adverse consequences through uncontrolled exposure to lipid at other tissue sites. On the other hand, given the fact that the adipocyte plays a key role in the regulation of food intake and energy expenditure, restricted expansion of adipose cell number might have favorable consequences. This was suggested many years ago by investigators who argued that "hyperplastic" obesity was more refractory to diet therapy than was "hypertrophic" obesity, in which adipose cells enlarge, but their number is unchanged.

Conclusion

It is clear that adipocytes, both brown and white, will receive far more attention from the scientific community than they once did. These cells are at the center of a key regulatory system for maintenance of energy stores, and henceforth obesity must be viewed as a disorder both of and by the adipocyte. From both the basic and applied perspectives, the next few years will likely be the "fat years" of obesity research.

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