

mation required to automatically transcribe speech to written text is simply insufficient for the larger task of creating a machine conversationalist that “understands.” For example, if someone says something that contradicts his or her earlier statement, we would expect a plausible machine conversationalist to spot it. Without some structure and memory, however, it is hard to see how a system could check statements for consistency. One could never expect to learn to do that simply from data: We just do not see or hear enough sentences to have previously encountered all the inconsistencies that we could spot immediately.

At the moment, people encounter machine conversationalists only in recreational chatbots on the Web, or in simple phone transactions such as ordering travel tickets. But research systems are already much better than that, and the range of projects expected to deliver usable prototypes has expanded in recent years. These efforts range from the Defense Advanced Research Projects Agency’s Cognitive Assistant that Learns and Organizes project (8) to the European Commission’s new Companions project (9) to create a long-term conversational partner (see the figure). Such a Companion would learn its person’s likes and

dislikes, carry out Web-related tasks accordingly, and prompt reminiscences about the person’s photo collection so as to build up his or her life story through conversation (10).

Researchers generally agree that although these large goals need more research, speech recognition technology is still not accurate enough to build a reliable machine partner capable of understanding what we say, unless it has a considerable amount of stored knowledge to enable it to understand; mere reactive chatbots will be no more help than ELIZA was. The current paradigm split in research is about how it will be possible to capture and store knowledge and language experience in large enough detail and volume to build such assistants, outside of very small domains such as recording a complicated pizza order. A long-term assistant to an astronaut on a voyage to another planet, or one to help elderly people recover their past through conversation and organize it in text and images, is a much larger goal, and one that will require better machine learning techniques than have been deployed so far.

The crux of the current research issue is this: Will a successful technology end up recreating by means of automated learning

much of the linguistic and logical content that was abandoned in the 1990s? That might be closer to what our own cognitive structures seem to be. In any case, language data will remain central, and the World Wide Web has, as an unexpected benefit through chat rooms, provided researchers with potentially infinite resources of data on human conversations.

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## PHYSIOLOGY

# An Integrative View of Obesity

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The World Health Organization estimates that at least 1 in 10 adults worldwide are obese, and in some western countries, a far greater percentage (25% or more) is affected (1). Obesity is a serious concern because it increases the risk of cardiovascular disease, type 2 diabetes, and some cancers, among other health problems. The evolution of public health policies and treatment options depends upon an improved understanding of how genetic and environmental factors interact to favor weight gain, and how excessive weight disrupts metabolism. But getting at the causes of obesity and related metabolic disorders is a formidable challenge, in part because so many body systems are affected. Because disturbances in one organ or tissue can compromise the function of several others, separating cause and effect is often difficult. Yet common themes are emerging that

may offer a new viewpoint. Among these is the notion that metabolic dysfunction arises from exposure of the body’s cells to an excess of nutrients (2). A possible extension of this view is that although the cellular consequences of nutrient excess are similar across diverse cell types, the shared nature of the underlying cellular responses can be obscured by the complexity of the events they initiate. In this light, successful identification of shared cellular responses that underlie disease requires a broad and integrative approach that may ultimately reveal more effective obesity treatment strategies.

Fundamental to understanding obesity is the fact that, like body temperature, body fat stores are ordinarily maintained within a narrow range through a process called “energy homeostasis.” This process involves brain areas that control appetite and energy metabolism, as well as signals that circulate throughout the body, conveying information about the status of body fuel stores. Among the latter are nutrients themselves, such as glucose and free

Comparisons of responses of various cell types to excess nutrients are yielding patterns that may provide insight into the causes and consequences of obesity.

fatty acids, and hormones, such as insulin and leptin (3). Specialized neurons in the hypothalamus and other brain areas sense these factors and control both metabolic rate and the desire to eat. When circulating concentrations of these signals decrease due to weight loss, the drive to eat increases and energy expenditure declines, favoring the recovery of depleted fuel stores. Conversely, when food is consumed in amounts that exceed energy requirements, the circulating concentrations of these signals increase. In this way, homeostatic response mechanisms in the brain are poised to protect the body against changes in fat stores or swings in nutrient availability. Thus, obesity does not simply arise from the passive accumulation of excess weight; rather, it involves the active defense of an elevated level of body fat, and deciphering the causes of obesity should take this into account. Certainly, individual genetic makeup may contribute to variations in the capacity to mount these responses, and may explain why some people are protected against weight gain

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while others are not, despite living in the same environment and eating the same food.

When energy intake exceeds energy expenditure, the resulting state of nutrient excess can trigger responses in many cell types—endothelial cells (vascular) (4), hepatocytes (liver) (2), myocytes (muscle) (5), adipocytes (fat) (2), and monocytes or macrophages (immune cells)—that could give rise to metabolic dysfunction. Among several adverse cellular responses to nutrient excess is the production of reactive oxygen species. These molecules are generated during fuel (e.g., glucose or free fatty acids) oxidation by mitochondria and from metabolic processes elsewhere in the cell. Excessive production of these molecules creates “oxidative stress,” which can damage cellular structures and trigger an inflammatory response (2). In some cells, nutrient excess also impairs functioning of the endoplasmic reticulum (which processes newly synthesized proteins into their mature forms), giving rise to the “unfolded protein response” in this organelle. Like reactive oxygen species, this response can induce inflammation. A third cellular response to nutrient excess is the accumulation of long-chain fatty acyl coenzyme A molecules, fatty acid derivatives that are ordinarily oxidized by mitochondria to generate adenosine 5′-triphosphate (which powers many cellular processes). Making matters worse is a decrease of mitochondrial activity in response to nutrient excess. This creates a vicious cycle by further raising the concentration of these fatty acid derivatives (5).

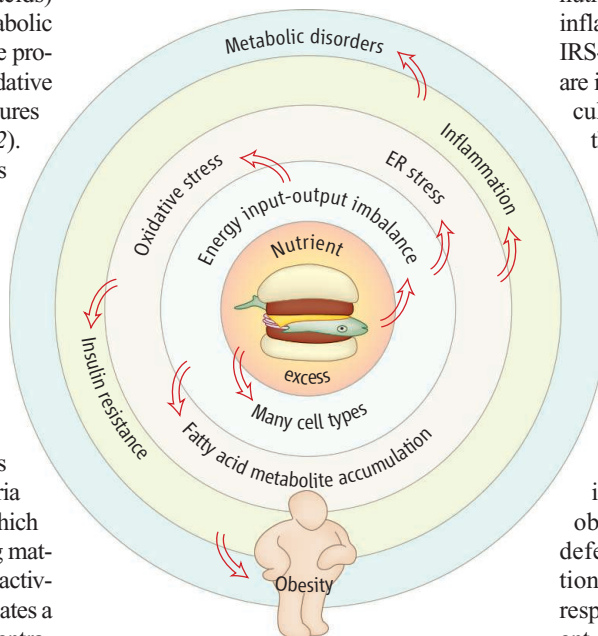
Each of these responses share the ability to activate signaling pathways (such as the c-Jun N-terminal kinase and the inhibitor of kappa B kinase beta–nuclear factor kappa B pathways) (2, 4–6) that promote inflammation. Thus, inflammation appears to be a common endpoint. In turn, inflammation can limit further exposure to nutrients by blocking the action of insulin (2, 5), the hormone that stimulates target cells to take up nutrients. The enzyme phosphatidylinositol 3-OH kinase (PI3K) is part of a cell signaling pathway [the insulin receptor substrate (IRS)-PI3K pathway] that mediates insulin action and is particularly sensitive to inactivation by molecules that promote inflammation. From the perspective of an individual cell, this protective response—insulin resistance—makes sense in that it limits further nutrient uptake. With continued nutrient excess, however, neighboring cells and distant tissues that remain insulin sensitive are placed at greater risk. As insulin resistance progresses and inflammation worsens, a vicious cycle can evolve as additional pro-inflammatory factors are recruited by these cells (2).

In addition to regulating nutrient utilization in peripheral tissues, IRS-PI3K signaling is also implicated in the neuronal actions of insulin and leptin (3). As in peripheral tissues, the integrity of neuronal IRS-PI3K signaling can be undermined by nutrient excess (7). Studies in rodent models indicate that even short-term exposure to a highly palatable, energy-dense diet impairs the brain’s response to insulin and leptin, and reduced IRS-PI3K signaling may be among several mechanisms responsible for neuronal resist-

insulin resistance. Thus, cellular consequences of nutrient excess similar to those that impair the function of other tissues could potentially contribute to the link between insulin resistance and  $\beta$  cell dysfunction in diabetes pathogenesis.

Nutrient excess also has deleterious effects on vascular tissue. A major function of endothelial cells that line blood vessels is to generate and release nitric oxide, a vasodilator. The IRS-PI3K signaling pathway is a key determinant of nitric oxide production and, as in other tissues, nutrient excess rapidly induces endothelial inflammation. In response, both endothelial IRS-PI3K signaling and nitric oxide generation are inhibited (4). Thus, the response of the vasculature to nutrient excess is reminiscent of that observed in other tissues, and offers a plausible link between nutrient excess and cardiovascular disease.

**Common threads.** Cellular responses to nutrient excess are shared across many different cell types, and may have common endpoints that are coupled to the development of obesity and its metabolic consequences. ER, endoplasmic reticulum.



ance to these hormones (7, 8). Having lost its ability to detect an ongoing increase in body fat stores, the brain seemingly does nothing to counter it; rather, it actively defends what it perceives to be a stable, unchanging amount of body fat (9). Thus, impaired IRS-PI3K signaling in the hypothalamus may be a factor that contributes to the defense of elevated body weight and hence to continued exposure to nutrient excess (3).

Might similar cellular responses to nutrient excess contribute to the link between obesity and type 2 diabetes? If inflammation and reduced IRS-PI3K signaling were also to occur in pancreatic  $\beta$  cells (which produce insulin), as has been suggested (6), impaired insulin secretion—which, when combined with insulin resistance, leads to type 2 diabetes—could result, because IRS-PI3K signaling is essential for the survival of these cells (6). This concept extends “the  $\beta$  cell exhaustion” hypothesis (10), which states that type 2 diabetes results when pancreatic  $\beta$  cells can no longer meet the heightened demand for insulin secretion imposed by

Clearly, impaired IRS-PI3K signaling is not the single key to understanding obesity and its consequences. Rather, this defect illustrates how complex manifestations of metabolic disease could arise from responses that are shared across many different cell types (see the figure). In addition to research that focuses on one organ or physiological system to the exclusion of others, more integrative approaches for studying metabolic disease may ultimately inform strategies aimed at preventing or reversing obesity and its sequelae.

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