Physiology in Perspective: The Burden of Obesity

Obesity has been described as the biggest health threat facing the Western world, and this statement will probably need to be revised shortly to encompass the entire world. The social and economic impact of this pandemic is enormous. Currently, a third of all Americans are obese, and this may reach 50% by 2050. Worldwide, there are more than 600 million obese people at the present time. Obesity is clearly a major human problem, dramatically increasing the risk for serious life-threatening diseases, including Type 2 diabetes mellitus, heart disease, and cancer. Yet, how much of obesity’s underlying physiology do we really understand? In this issue of Physiology, we explore novel theories on the evolutionary roots of obesity and weight management. We also examine recent findings concerning the cellular mechanisms for energy sensing, abnormalities of which may underlie obesity. In addition, we delve into the underlying pathophysiology and major complications of obesity, one of which—cardiovascular disease—is the leading cause of death in both men and women. Over the years, physiological research has provided considerable insight into the mechanisms of cardiovascular disease and its link to obesity, improving prevention, diagnosis, and treatment. As pointed out in the January issue of Physiology, sex differences in the incidence of cardiovascular disease are well known, yet few studies are focusing on sex differences in the risk for hypertension and cardiovascular disease, including obesity. The origins of increased risk for hypertension and cardiovascular disease may relate to events that occur during early life. One review in this issue of Physiology highlights the potential mechanisms involved in sex differences in the developmental origins of cardiovascular disease. Another review in this issue examines neurally controlled autonomic mechanisms that provide protection from cardiovascular disease. Cellular signaling mechanisms provide therapeutic targets for treating cardiovascular disease, including phosphodiesterases (PDEs), which are the subject of another review in this issue highlighting their role in modulating cyclic nucleotide signaling.

Why does obesity develop in humans? A well-established genetic component to obesity suggests that its roots lie in our evolutionary history. However, understanding the evolutionary background is complex. There is also a paradox. At the level of an individual, body weight is regulated quite closely, revealing a disconnect with the phenomenon of obesity at the population level, where there is a growing epidemic. Understanding how this paradoxical situation arises will help discover new ways to treat the problem of obesity. In humans, energy balance is regulated on different time scales: from minutes to hours, energy balance depends on glucose and glycogen storage, but from days to weeks, it relates to fat storage. These temporal differences suggest that, evolutionarily, energy balance, and thus body fatness, is regulated by two systems. At the lower margin, the risk of starvation prevents energy stores from being too low, but at the upper margin, the risk of predation prevents stores from being too large. Consistent with this view, most of the genetic polymorphisms linked to obesity have not been located in the system that regulates the lower margin. In his review (6), Speakman suggests broadening the understanding of the physiology of obesity by studying the genetic drift that occurred due to the reduction in predation risk over the last 2 million years. Six-hundred million obese people in the world underscore the importance of gaining knowledge that may lead to new ways to prevent obesity.

Adenosine monophosphate (AMP)-activated protein kinase (AMPK) appears to have evolved in single-celled eukaryotes as a cell-autonomous energy sensor. However, during evolution of more complex multicellular organisms, the role of AMPK has adapted so that it also responds to hormones regulating whole-body energy balance. AMPK principally serves as an energy sensor monitoring the cellular ratios of AMP to ATP and/or ADP to ATP. Once switched on, AMPK activates catabolic pathways that generate ATP and suppresses nonessential ATP-requiring processes, thus acting to restore energy homeostasis. In their review (3), Hardie and Ashford discuss the two distinct levels at which the AMPK system operates. These include the ability of the starvation hormone ghrelin to activate AMPK by the Ca^{2+}–CaMKK pathway and the ability of insulin, and perhaps leptin, to inhibit AMPK activation by promoting phosphorylation. This review illustrates the important role of AMPK in the regulation of energy homeostasis, an important element in addressing the obesity epidemic.

Obesity-associated Type 2 diabetes accounts for 90–95% of all diagnosed cases of diabetes. Several new drug classes exploit recent developments in our understanding of Type 2 diabetes. Glucagon-like peptide-1 (GLP-1) is an incretin, a group of gastrointestinal hormones that increase the release of insulin, thereby decreasing blood glucose levels. Dipeptidyl peptidase-4 (DPP4) also plays a major role in glucose regulation by degrading incretins such as GLP-1. Accordingly, GLP-1 receptor agonists and DPP4 inhibitors (DPP4i) are now widely used clinically for the treatment of Type 2 diabetes, although their mode of action is not yet fully established. In their review (1), Burcelin and colleagues discuss studies using DPP4i that uncovered the paracrine role of GLP-1 on the enteric nervous system, which may explain the pleiotropic action of this hormone. Further studies with GLP-1 receptor agonists uncovered the role of GLP-1 on numerous other physiological systems, including the heart and the brain. Outcomes on cardiovascular and neurodegenerative diseases are expected from appropriate clinical trials of these pharmacological drugs.

Events occurring early in life may contribute to the risk for cardiovascular disease. Sex differences in the incidence of cardiovascular disease may reflect differences in the early origins of cardiovascular disease, which are poorly understood. In their review (4), Intapad and colleagues discuss novel experimental models that indicate testosterone serves as a...
pro-hypertensive agent by the developmental programming of increased blood pressure and cardiovascular risk. Conversely, developmental exposure to estrogen exerts anti-hypertensive influences against programmed increases in blood pressure and sensitivity to vasoactive factors. Additional studies are necessary to elucidate the contribution of sex and age to the mechanisms underlying the early origins of cardiovascular disease. Such studies have a high likelihood of improving preventive, diagnostic, and treatment strategies in cardiovascular disease.

Alterations in the neural mechanisms that control autonomic (sympathetic and parasympathetic) outflow to the heart appear to play an important role in cardiovascular diseases. Despite successful reperfusion of acutely ischemic myocardium, many patients develop large infarcts and are likely to develop congestive heart failure. Recent data suggest that activation of autonomic reflex pathways contributes to powerful innate mechanisms of cardioprotection underlying the remote (pre)conditioning phenomena. In their review (2), Gourine and Gourine highlight the importance of neural mechanisms in protecting the heart against lethal myocardial ischemia/reperfusion injury. Understanding nervous mechanisms of cardioprotection may prove important for the development of novel treatment strategies in patients with acute myocardial infarction and congestive heart failure.

Compartmentalization, the structural and functional restriction of signaling domains, allows distinct pools of cyclic nucleotide to interact with particular effectors. Novel technological advances have improved our understanding of how cyclic nucleotides are able to convey signals faithfully between cellular compartments. Phosphodiesterases (PDEs) are key modulators of cyclic nucleotide signaling. However, due to their ubiquity within signaling cascades, even with the current generation of more specific PDE inhibitors, pathology can result when applied without respect to functional localization. In their review (5), Lomas and Zaccolo discuss the use of competing peptides or small molecules to displace a specific PDE isoform from a particular complex as a means by which to test whether selective manipulation of pools of cyclic nucleotides, at specific locations, may avoid global off-target affects in other compartments. The concept of compartmentalization represents opportunities to improve the efficacy of PDEs as therapeutic agents for cardiovascular, respiratory, neurodegenerative, and inflammatory diseases.

References
6. Speakman J. If body fatness is under physiological regulation, then how come we have an obesity epidemic? Physiology 29: 88–98, 2014.