Living a Healthier Lifestyle

The roles of diet, activity, and exercise have long been recognized as essential to a healthy lifestyle. As Plato stated, “Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.” In his Physiology is Medicine editorial, Levine points out that humans were not meant to be sedentary, nor were they meant to eat the high-fat diets common to many of us. As a result, there is an epidemic of obesity and associated Type 2 diabetes facing the world, with long-term impact on health and the incidence of disease. In this issue of Physiology, we continue to explore the physiological impact of our sedentary, unhealthy life styles (cf., the March issue of Physiology that explored obesity).

The prevalence of obesity and associated metabolic abnormalities such as Type 2 diabetes is increasing rapidly. A reduction in physical activity and changes in dietary habits (e.g., increased consumption of fat-enriched, low-fiber diet) are the main driving forces of this epidemic. Although acute physiological adaptations may serve to cope with acute dietary changes, persistent intake of a fat-enriched, low-fiber diet may trigger profound alterations in the gut, in the interrelated mesenteric/visceral fat, and in the liver. In their review (4), Konrad and Wueest discuss the potential impact of obesity-related changes in gut and visceral adipose tissue biology. In particular, altered gut microbiota composition and impaired gut barrier function, together with interrelated mesenteric adipose tissue inflammation, result in an increased release of bacteria-derived factors such as endotoxins, proinflammatory cytokines, as well as lipids into the portal circulation. As a consequence, the liver is increasingly exposed to factors promoting the development of (hepatic) insulin resistance, hepatic steatosis, as well as the metabolic syndrome. Therefore, a better and comprehensive understanding of the apparent causal link between obesity-related changes in the gut as well as visceral adipose tissue biology and the development of insulin resistance may provide novel therapeutic targets for the prevention and/or treatment of obesity-associated metabolic diseases.

Hypoglycemia is currently the primary undesirable consequence of pursuing glycemic control in insulin-dependent diabetic patients (IDDM patients). The problem has actually grown worse as clinicians increasingly seek to aggressively lower blood glucose levels in diabetic patients in an attempt to potentially alleviate many long-term diabetic complications. Insulin replacement is imperfect, leading to an increased incidence of hypoglycemia, which itself causes further impairment of the counterregulatory responses needed to correct hypoglycemia. Known as hypoglycemia-associated autonomic failure, impaired counterregulatory responses are believed to derive from impaired glucose sensing, resulting in a renewed interest in the mechanisms underlying hypoglycemic detection. An extended network of glucose sensors serve to mediate physiological responses that restore euglycemia, i.e., counterregulatory responses. It is known that glucose-sensing neurons are widely distributed within the central nervous system as well as the periphery. In their review (1), Donovan and Watts focus on glucosensing in the periphery, particularly the portal-mesenteric vein glucose sensors, and how that information is transmitted to and integrated with brain glucose sensors. Although the relative importance of the various gluco-sensing loci remains an area of some debate, Donovan and Watts have shown that portal-mesenteric glucose sensors are particularly important for the detection of slow-onset hypoglycemia and the appropriate counterregulatory responses. Slow-onset hypoglycemia is a prevalent clinical manifestation among human diabetic patients.

Melatonin is an endogenously produced and highly beneficial molecule that is useful to all cells in both the plant and the animal kingdoms. Melatonin protects organisms from the toxicity of free radicals; it exhibits anti-cancer actions, promotes a healthy immune system, enhances successful sleep, and stabilizes circadian rhythms. Via these multiple actions, melatonin has the capacity to resist the development of a number of diseases processes. Melatonin levels in humans wane during aging, and its loss may be related to a number of diseases associated with growing old. In their review (7), Reiter and Galano discuss the beneficial therapeutic effects of melatonin. Melatonin is being tested in a variety of human diseases, and in most of these situations it has proven beneficial. Examples of melatonin’s utility in humans include as an agent to improve sleep, depress blood pressure, resist bone loss, inhibit cancer, prevent dysregulation of circadian rhythms, limit tissue destruction due to ionizing radiation, and protect against free-radical damage resulting from drug toxicity, ischemia-reperfusion injury, heavy metal exposure, and excessive alcohol consumption. Preventing the loss of melatonin during aging may help in maintaining better health in the elderly. Reducing or deferring frailty and ill-health is particularly important in current societies where people are living longer than ever before.

Acute kidney injury (AKI) is a common medical condition with significant associated morbidity, mortality, and financial costs. Frequent causes include ischemia-reperfusion injury, septic shock, drug toxicity, and glomerulonephritis. Despite extensive previous research into AKI, the pathogenesis remains poorly understood, and treatment options for patients are limited. Furthermore, patients who survive acute insults are often left with long-term deficits in kidney function. There is, therefore, a pressing need for new research methodologies that will increase knowledge about underlying cellular pathways and mechanisms in AKI to generate new targets for therapeutic intervention. In their review (2), Hall and Molitoris discuss the use of multiphoton microscopy (MPM), a form of fluorescence imaging, to visualize various aspects of kidney function non-invasively in live, anesthetized rodents. MPM is ideally suited to visualize dynamic processes in intact functioning tissues, and it provides measurements at subcellular levels of optical resolution that are unmatched by...
other in vivo imaging techniques. MPM has been applied to study various different types of AKI in animal models and has yielded important and novel insights into cellular mechanisms. Moreover, it has been used to investigate the efficacy of putative therapeutic agents. In summary, MPM has an important and expanding role to play in translational research relevant to AKI.

It has been more than 100 years since Bayliss first discovered that small arteries exhibit the remarkable and seemingly paradoxical behavior of constricting in response to increases in pressure. It has also long been known that the shear stress associated with blood flow tends to have the opposite effect, causing vessels to dilate. Yet, despite this long history, and notwithstanding concerted research efforts, the underlying molecular mechanisms that mediate responses to these mechanical forces have remained elusive. In their review (3), Hill-Eubanks and colleagues explore the role of mechanosensitive transient receptor potential (TRP) channels in mediating vascular responses to flow and pressure. This research continues to peel back layers to reveal a richer complexity than was originally envisioned and will no doubt provide additional surprises along the way. A clearer understanding of mechanosensing circuits in the vasculature will bring with it the beginnings of an answer to basic physiology questions first posed over a century ago and the promise of new targets in the treatment of cardiovascular diseases.

Calcium (Ca\(^{2+}\)) controls a variety of cellular functions and is vital to survival. The multifunctional nature of Ca\(^{2+}\) is highly dependent on the cellular origin of the signal. The nucleus has recently been identified as a fundamental organelle for independent and localized Ca\(^{2+}\) signaling that can impact cell physiology and organism homeostasis. In their review (6), Oliveira and colleagues focus on nuclear Ca\(^{2+}\) signals and their role in regulating physiological and pathological processes. Nuclear Ca\(^{2+}\) signals are involved in the regulation of cellular proliferation and gene expression. Instability of Ca\(^{2+}\) signaling has been associated with several pathologies including tumor growth, cell sensitivity to radiotherapy, and cardiac hypertrophy. Understanding nuclear Ca\(^{2+}\) signaling pathways in different systems could target nuclear Ca\(^{2+}\) as a potential therapy in a variety of diseases.

Optical coherence tomography (OCT) is a high-resolution imaging technique that uses reflections of near infrared light waves to study the in vivo structure of lung tissue at a scale of tens of micrometers. In their review (5), McLaughlin and colleagues assess the current capability of OCT in examining the integrity of the layered structure of airway walls, quantifying airway size, and imaging individual alveoli. Strategies include hand-held external scanning, endoscopic imaging of airways, and highly miniaturized imaging probes encased in medical needles that are inserted deep below the surface of the tissue. Although studies conducted to date remain largely at the proof-of-principle level and await more extensive validation, they show great promise. Of most relevance are applications requiring near histology scale imaging but where removal of tissue is unacceptable, such as in vivo assessment of airway wall structure. OCT has the potential to become a powerful tool for physiologists and clinicians since it contributes to improved understanding of disease processes.

References