Physiology in Perspective: The Life We Take for Granted

The simple things in life we often take for granted: that our sex matters in how we respond to our environment; that regular exercise protects us from cardiovascular disease; that we depend on the oxygen levels in the air that we breathe; and that we live in a 24-h cycle of light and dark. As physiologists, we are wonderfully curious, and our discoveries reveal the fascinating complexities that are the reality of these apparently simple things in life. This issue of Physiology explores various aspects of sex differences in cardiovascular physiology, the benefits of exercise, our responses to hypoxia, and the synchronization of our internal clocks to the daily cycle of light and dark.

Sex and age have important influences on sympathetic neural control of blood pressure in humans. In their review (3), Hart and Charkoudian discuss how sympathetic neural mechanisms controlling blood pressure are different between men and women, and how these mechanisms change as people age. Sympathetic nerve activity and the risk of hypertension are lower in younger people and increase as people age. Young women appear to be relatively “protected” from hypertension compared with young men, in part because of a β-adrenergic vasodilator mechanism in this group. This mechanism appears to be lost at menopause, contributing to the increased risk for hypertension in older women. Research in this area has the potential to improve daily life by providing the foundation for development of medical and surgical treatments for blood pressure problems in men and women across the lifespan. In fact, several successful treatments for hypertension and other cardiovascular diseases have been developed in recent years based on research regarding sympathetic neural mechanisms in the cardiovascular system. Important future steps for clinical application will be to use our increasing understanding of blood pressure mechanisms specific to women (as described in this article) to help develop treatments specifically tailored for women before and after menopause.

Disturbed regulation of Na⁺ balance by the kidney is well recognized as a primary cause of high blood pressure as seen in a number of inherited forms of hypertension, such as Pseudohypoaldosteronism Type II (PHAII) and Liddle syndrome. In these disorders, mutations in genes encoding key renal proteins (channels, transporters, and regulators) result in disturbed Na⁺ handling and hypertension. In their review (7), Ronzaud and Staub discuss the crucial role of ubiquitylation, an important intracellular signaling mechanism, in the control of renal Na⁺ balance and blood pressure. Such mutations either affect the function of the proteins of the ubiquitin system (e.g., in PHAII) directly, or they impair either key renal protein interaction sites or ubiquitin system proteins (e.g., in PHAII and Liddle syndrome), thus leading to the overstimulation of Na⁺ reabsorption. Hypertension affects over one billion people worldwide and is one of the principal causes of cardiovascular death. Manipulation of these specific ubiquitylation pathways poses an attractive alternative for the development of new antihypertensive therapeutics.

Myocardial ischemia-reperfusion (I-R) injury (heart attack) is the major contributor to the morbidity and mortality associated with coronary artery disease. Endurance and resistance exercise has been shown to provide profound cardioprotection against I-R injury. Evidence indicates that both short-term (days) and long-term (weeks) endurance exercise training significantly reduces I-R-induced myocardial injury. After the cessation of exercise training, this exercise-induced cardioprotection is rapidly lost. In their review (4), Powers and colleagues discuss the mechanisms proposed as responsible for exercise-induced cardioprotection. Current evidence suggests that an important role is played by a rise in cardiac antioxidants and alterations in key mitochondrial proteins. Determining the specific molecules responsible for exercise-induced cardioprotection could lead to the identification of a biological target as a countermeasure to protect the heart against I-R injury.

Carotid bodies detect hypoxia in arterial blood, translating this stimulus into physiological responses via the central nervous system. It has long been established that ion channels are critical to this process. More recent evidence indicates that gasotransmitters (nitric oxide, carbon monoxide, and hydrogen sulphide) exert powerful influences on O₂ sensing by the carotid body. In their review (5), Prabhakar and Peers discuss the current understanding of hypoxia-dependent production of gasotransmitters, how they regulate ion channels in the carotid body, and how this impacts carotid body function. Heightened carotid body sensitivity to hypoxia has been implicated in autonomic dysfunction associated with the most prevalent cardiorespiratory diseases, such as sleep apnea, congestive heart failure, and hypertension. Aside from satisfying academic curiosity, further research is necessary to determine how gasotransmitters and their interactions with ion channels in the carotid body are altered in disease states.

Although prolonged intermittent hypoxia, as experienced with sleep apnea, causes multiple pathologies, repetitive brief exposures to low oxygen augment aerobic athletic performance and have beneficial effects in the nervous system, upregulating proteins in the spinal cord that promote neuron survival and enhancing motor functions such as breathing and walking. In their review (1), Dale and colleagues discuss recent studies where low-dose, intermittent hypoxia has restored respiratory and nonrespiratory motor functions in animal models of cervical spinal injury and motoneuron disease. In humans with chronic spinal injury, intermittent hypoxia has been found to restore lost respiratory and nonrespiratory motor function. Available evidence suggests that low-dose, intermittent hypoxia may represent a safe and effective treatment to restore lost motor function in diverse clinical disorders that impair motor function, such as chronic spinal cord injury, stroke, cerebral palsy, Parkinson’s disease, and multiple sclerosis.
This research suggests a fundamental physiological response that protects highly vulnerable motoneurons from intermittent hypoxia. For example, in aquatic species living in hypoxic aqueous environments, many species utilize air as a supplemental oxygen source, linking swimming, breathing, and intermittent hypoxia. The ability to protect motoneurons and motor behaviors may represent a key evolutionary adaptation as vertebrates first invaded land. Other intriguing possibilities for further exploration include the use of intermittent hypoxia to enhance neuromotor function and athletic performance in normal humans, and perhaps even to improve cognitive function.

The neural control of rhythmic breathing is fundamental to life and has been the focus of intense physiological investigation. The combined medullary and pontine networks controlling breathing are complex and thus suitable models for studying modern systems physiology as they produce a clear output activity in cranial nerves. This allows identification of fundamental principles of network performance and adjustment to various behavioral conditions. In their review (6), Richter and Smith discuss cellular biophysics and cell-specific connectivity verified by analysis of defined postsynaptic activities that control rhythm and pattern generation in the in vivo network. This basic research should increase our understanding of human physiology and form a valid basis for future application in the treatment of patients with life-threatening respiratory disturbances, such as after brain tumor surgery, brain stem atrophy, and brain stem infarction.

Disruption of circadian rhythms, by shift work or transmeridian travel, for example, can lead to adverse effects in several organ systems and pregnancy. Ten percent of the human transcriptome and many physiological processes, including heart rate, metabolism, and hormone release, display circadian rhythmicity, yet, in most preclinical and clinical studies, timing is not taken into account. In their review (2), Du Pré et al. focus on the origination of circadian rhythms as they discuss in utero and in vitro development of circadian rhythms at the molecular and functional level both in the central clock in the brain and in peripheral tissues. A better understanding of the physiological interaction between maternal rhythms and embryonic development may prevent unwanted effects of disrupted day-night cycles on unborn children during pregnancy. In addition, since fully differentiated stem cells are needed to test feasibility and toxicity of drugs, and in regenerative medicine to create tissues in the laboratory, the influence of circadian rhythms on development may be used to optimize differentiation of stem cells.

References