As early as the 2nd century BCE, experiments showed that a component of air was necessary for combustion. Later, it was shown that this same component of air was also necessary for life in vertebrate organisms. In the mid 1770s, oxygen was discovered independently by two scientists: the Swedish scientist Carl Wilhelm Scheele in 1772 (results not published until 1777), who called it “fire air” because it supported combustion, and the British scientist Joseph Priestley in 1774 (results published in 1775), who called it “dephlogisticated air” since it lacked the element phlogiston that remained after combustion (based on the phlogiston theory that prevailed at that time). It appears that following communication with both Scheele and Priestley, the French scientist Antoine-Laurent Lavoisier also discovered oxygen in 1775, recognizing it as a distinct element and giving it the name oxygen based on the Greek roots meaning “acid-producer,” because he incorrectly thought that it was essential in the formation of acids. Key in these discoveries was the essential nature of O2 for life in vertebrate animals. The air we breathe in earth’s atmosphere contains ~21% O2, but PO2 levels in our cells and tissue can vary depending on the environment (e.g., high altitude) and with changes in cardiopulmonary O2 delivery. Humans and other living organisms require molecular O2 for survival, so it is not surprising that physiologists have focused considerable attention on the respiratory and cardiovascular systems involved in O2 delivery to cells and tissues, and the consequences of O2 deprivation.

In the first review of this issue of Physiology, Prabhakar and Semenza (4), address two essential questions related to the physiology of altered O2 availability. 1) How do organisms sense hypoxia? And 2) how do they maintain homeostasis under conditions of O2 deprivation? Nearly 90 years ago, Jean-Francois Heymans and his son Corneille Heymans discovered the role of the carotid bodies as O2-sensing organs and the chemosensory reflex as a critical regulator of circulatory and respiratory systems, ensuring that each cell in the body receives adequate O2. It is now widely recognized that O2 sensing is mediated by a complex interplay between carbon monoxide and hydrogen sulfide generated by the carotid body. O2 sensing is not uniform but exhibits remarkable inter-individual variations in humans, which has serious physiological consequences. Hypersensitivity to hypoxia often develop mountain sickness when exposed to high altitude and are limited in their exercise capacity. In 1992, hypoxia-inducible factor 1 (HIF-1) was discovered as the master regulator of the transcriptional program needed for maintenance of homeostasis under conditions of chronic hypoxia. HIF-mediated O2 homeostasis is critical for red blood cell production in cancer biology, as well as in myocardial infarctions and in peripheral artery disease, to name a few. O2 deprivation resulting from cardiovascular disease and stroke is the leading cause of death worldwide in humans. On the other hand, a high incidence of cardiovascular disease and stroke-related mortality is exceedingly rare among mammals in the wild. In their review (5), Williams and et al. examine the highly active lifestyles of wild mammals on land and in the seas as models for a healthy heart. Since heart function is remarkably similar for humans and other mammal species ranging from 0.002-kg shrews to 43,000-kg whales, neither body size nor longevity seems to play a major role in vulnerability to cardiovascular disease. A major difference, however, is the daily challenge of exercise. The majority of humans of all ages underutilize the heart through a lifelong habit of sedentary living, whereas large, wild mammals accomplish the American Heart Association’s recommended weekly exercise levels in one daily hunting trip. By examining the limits of heart function in elite wild animals and extreme athletes, this study demonstrates resiliency of the mammalian heart to high levels of activity and suggests that humans adopt a wilder daily exercise plan.

The ischemia and hypoxia/anoxia resulting from stroke can lead to neuronal death. After a stroke, the surviving neurons undergo dramatic and widespread reorganization. Although the extensive axonal sprouting, dendritic remodeling, and synapse formation happen in both hemispheres of the brain, behavioral function is not necessarily improved. In their review (1), Jones and Adkins discuss current knowledge on post-stroke motor system reorganization, much of which is based on coincidental correlations between brain and behavioral change. It is likely that the non-paralyzed limb becomes the dominant force in driving post-stroke brain reorganization as it is called upon to learn new compensatory skills. For this reason, early onset rehabilitative treatments may be more effective, both because of more effective neural remodeling to benefit the paralyzed limb and also because it may prevent the unaffected limb from developing maladaptive reorganization. While cortical stimulation shows much potential, its efficacy can vary with post-stroke timing, injury locus, and injury severity. A deeper understanding of post-stroke motor system reorganization has the potential to improve functional outcomes as new methods of manipulating behavior and neural activity are developed.

Glial cells and astrocytes greatly outnumber neurons in the brain but are often overlooked when the computational capacity of the brain is considered. In their review (2), Kadala et al. highlight the role of astrocytes in the homeostasis of extracellular ions, which have a direct impact on firing patterns of neurons and their ability to discharge rhythmically. Rhythmic neuronal pattern generation is the basic substrate for several important motor functions like respiration, mastication, and locomotion. Conversely, rhythmic neuronal oscillations...
are also observed in pathological conditions like epilepsy and Parkinson’s disease. It is noteworthy that astrocyte physiology is altered or impaired in these diseases. Thus astrocytes play a role in both the normal and the unhealthy brain. A better understanding of the role of astrocytes will potentially offer new therapeutic targets for treatment of several illnesses that affect neuronal rhythmicity.

The neural circuitry of the brain’s fear system is not well understood, but recent research suggests that the central amygdala (CeA) has a significant role. It is becoming increasingly clear that the CeA is a site of plasticity and memory formation and is subject to tight regulation since it influences the acquisition, expression, and even consolidation of conditioned fear. In their review (3), Keifer and colleagues examine the evidence for the three CeA roles in fear processing. Understanding the physiological responses to fear will advance our understanding of common psychiatric disorders and improve diagnosis, treatment, and prevention of disorders such as posttraumatic stress disorder, panic attacks, and phobias.

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References