PHYSIOLOGY IN PERSPECTIVE
Gary C. Sieck, Editor-in-Chief
Mayo Clinic, Rochester, Minnesota

PHYSIOLOGY 35: 286–287, 2020.
Published August 12, 2020; doi:10.1152/physiol.00025.2020

Physiology in Perspective: A Key Role of Physiology in Understanding COVID-19

Homeostasis is a central tenet of physiology reflecting the ability of our body to self-regulate and maintain stability against internal and external environments that are sub-optimal for survival. If homeostasis is successful, we survive and life continues; if unsuccessful, our fragile balance is disturbed and disease and possibly death can occur. Homeostasis requires a coordinated response of our physiological systems to correct any perturbation that disturbs our normal condition. SARS-CoV-2 infection represents a major challenge to our homeostatic response. The renin-angiotensin-aldosterone system (RAAS) is a key homeostatic system within our bodies that involves the brain, lungs, kidneys, and liver to regulate electrolyte balance, blood pressure, and fluid volume. Recent evidence implicates a dysregulatory interaction between SARS-CoV-2 infection and the RAAS homeostatic response, specifically via an interaction with the angiotensin-converting enzyme 2 (ACE2), a key component of RAAS. It now appears that the ACE2 receptor, which is ubiquitous throughout our bodies, facilitates entry of SARS-CoV-2 into host cells and disrupts the normal homeostatic response. This disruption is then amplified by inflammation and the effects of pro-inflammatory cytokines, resulting in a vicious cycle—a cytokine storm. The complexity of COVID-19 pathophysiology is evident by those who are at higher risk for poor outcome. It seems counterintuitive that, in obese and diabetic individuals, who are at higher risk for COVID-19, inhibition of the RAAS system protects against kidney and heart disease, and also reduces the incidence of diabetes. Inhibition of RAAS is also a major therapeutic strategy in treating hypertension and cardiovascular and renal diseases. In the elderly, another high-risk group for COVID-19, aging affects the responsiveness of the RAAS system, predisposing the elderly to imbalances that increase the incidence of disease. A better understanding of our complex physiology and the delicate balance of homeostatic control is essential to meet the challenge of finding an effective therapeutic intervention for COVID-19.

Emerging reports of COVID-19 pathophysiology suggests a wide spectrum of clinical severity, ranging from asymptomatic to fatal. Understanding the pathophysiological progression underlying the transition from mild to severe disease in SARS-CoV-2 infection is imperative to inform clinical decision-making and for development of effective treatments in this pandemic. An appropriate physiological immune response is a key feature of mild COVID-19. In their review, Bohn and colleagues (1) discuss the potential mechanisms by which patients mount a sufficient immune response, ultimately leading to viral clearance and resolution of the infection. They also detail how this response can become dysregulated and pathogenic, leading to multisystem organ failure and death. Ultimately, this review delineates and highlights the delicate balance between physiological and pathogenic immune response in SARS-CoV-2 infection. COVID-19 has caused a global pandemic wherein the lives of the world's citizens are affected on a daily basis. In lieu of vaccine deployment, our collective response relies on patient diagnosis, management, and monitoring. Understanding the pathophysiological features of this novel disease is key in developing therapeutic and monitoring strategies to resolve infections and improve patient outcomes.

Many individuals who are at higher risk for COVID-19 have impaired mitochondrial function. Mitochondrial homeostasis is mediated by members of the mitochondrial carrier family (SLC25), which transports inorganic ions, nucleotides, amino acids, carboxylic acids, fatty acids, and vitamins across the inner membrane of mitochondria. These transport steps provide building blocks for maintaining the cell, and linking the biochemical pathways of the mitochondrial matrix and the cytosol. These mitochondrial carriers are crucial for many important physiological processes, such as the synthesis of ATP from the oxidation of fats and sugars, amino acid metabolism, lipid and steroid synthesis, ion homeostasis, heme synthesis, iron-sulfur cluster synthesis, signaling, macromolecular synthesis, heat production, development, cellular differentiation, and cell death. An ever-increasing number of pathologies has been associated with dysfunction of mitochondrial carriers due to mutations. These diseases affect various organs in diverse ways at different stages of life, and they are much more common than originally thought. In their review (3), Kunji and colleagues examine the molecular basis of the diseases caused by missense mutations, based on our current understanding of the transport mechanism of mitochondrial carriers. These mutations are expected to affect the structure and function of mitochondrial carriers but may also interfere with their expression, targeting, insertion, and folding. This analysis will aid the identification of novel disease variants of mitochondrial carriers and associated mitochondrial diseases.

Epithelial cells of the lungs and gut are a prime target of SARS-CoV-2 infection and COVID-19 symptoms. Accordingly, it is important to understand the normal homeostasis of the gut epithelium. The natural polyamines (spermidine and spermine, and their precursor putrescine) are ubiquitous organic cations of low molecular weight in eukaryotic cells. Control of cellular polyamine levels has long been recognized as the central convergence point for multiple signaling pathways driving different cellular processes. Polyamines are involved in many aspects of biological functions by interacting with cellular anions such as DNA, RNA, proteins, and phospholipids. Disruption of the gut epithelium homeostasis and bar-

rier function occurs commonly in various human diseases, leading to the translocation of luminal toxic substances and bacteria to the blood stream, and, in some instances, resulting in multiple organ dysfunction syndrome and death. In their review (5), Rao et al. discuss the roles played by cellular polyamines in maintaining the integrity of the gut epithelium, focusing on the emerging evidence of polyamines in the regulation of gut epithelial renewal and barrier function. The molecular processes controlling the gut mucosal tissue levels of polyamines in response to stressful environments remain largely unknown. Polyamine metabolism holds promise for developing therapeutic targets to protect gut epithelium integrity and barrier function in patients with critical illnesses.

We know that regular exercise prevents the onset of disease, whereas lack of physical activity hastens its development. There are also pharmaceutical treatments such as metformin and statins that are prescribed to prevent the onset of disease (diabetes and cardiovascular disease, respectively). People interested in a healthy lifestyle often use multiple strategies such as exercise, nutrition, supplements, cognitive exercises, and sleep. In their review (4), Miller and Thyfault discuss exercise and drug interactions in people free of chronic disease. It is estimated that 150 million people worldwide take metformin, and statins are one of the most prescribed drugs in the world. Studies now suggest that these drugs can inhibit some positive effects of regular exercise training in human subjects. Most of these effects appear to be related to the mitochondria. A greater understanding of the mechanisms behind these detriments may reveal how to circumvent them to maximize potential benefits to human health.

The nervous system has the ability to reorganize itself by changing its structure, function, and connections in response to intrinsic and extrinsic stimuli. Permanent changes can result when the stimulus is persistent or severe. This neuroplasticity has been relatively well studied in the central nervous system (CNS), and our current understanding of underlying mechanisms is based on either patient biopsies or animal models. Although patient biopsies have broadened our understanding of the mechanisms that regulate the final stages of neuroplasticity, they do nothing to enlighten us about the development of neuroplasticity over time. Animal models are required for mechanistic studies, since they consider physiological complexity introduced by the integration of the nervous system within the body. However, physiological mechanisms of neuroplasticity in animal models may not translate to the human situation. The lack of human in vitro models for neuroplasticity in the peripheral nervous system (PNS) has impeded progress toward a better understanding of injury repair and regeneration in this important part of the nervous system. The emergence of human pluripotent stem cells (hPSCs) holds promise to resolve this deficit. In their review (2), Goldsteen et al. discuss the development of human in vitro models for the investigation of neuro-effector communication and neuroplasticity. Understanding the mechanisms that regulate the effect of chronic inflammation on PNS neuroplasticity could generate targets to diagnose and treat many diseases that affect almost all organs of the body. ■

No conflicts of interest, financial or otherwise, are declared by the author(s).

References

1. Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. *Physiology (Bethesda)* 35: 288–301, 2020. doi:10.1152/physiol.00019.2020.

2. Goldsteen PA, Dolga AM, Gosens R. Advanced modeling of peripheral neuro-effector communication and -plasticity. *Physiology (Bethesda)* 35: 348–357, 2020. doi:10.1152/physiol.00010.2020.

3. Kunji ERS, King MS, Ruprecht JJ, Thangaratnarajah C. The SLC25 carrier family: important transport proteins in mitochondrial physiology and pathology. *Physiology (Bethesda)* 35: 302–327, 2020. doi:10.1152/physiol.00009.2020.

4. Miller BF, Thyfault JP. Exercise-pharmacology interactions: metformin, statins, and healthspan. *Physiology (Bethesda)* 35: 338–347, 2020. doi:10.1152/physiol.00013.2020.

5. Rao JN, Xiao L, Wang J-Y. Polyamines in gut epithelial renewal and barrier function. *Physiology (Bethesda)* 35: 328–337, 2020. doi:10.1152/physiol.00011.2020.