Dr. Herbert and Nicole Wertheim Leadership in Healthcare and Medicine Lectureship

Presents

Mitochondrial Mechanisms in the Cerebral Vasculature in Health and Disease

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Venue: AHC2 160

Biography

Dr. Busija received his Ph.D. from the University of Kansas and completed his post-doctoral training at the Cardiovascular Center at the University of Iowa under the direction of Dr. Donald D. Heistad. Following faculty positions at Johns Hopkins Medical School, the University of Tennessee Medical School in Memphis, and Wake Forest University Health Sciences, Dr. Busija became Regents Professor and Chairman of the Department of Pharmacology at Tulane University Medical Center on January 1, 2011. Dr. Busija was awarded the prestigious Doctorem Medicinae Honoris Causa by the University of Szeged Medical School (formerly Albert Szent-Györgyi Faculty of Medicine), Hungary, one of the prominent medical schools of Europe. The honorary degree, presented during a ceremony at the university in November, 2009 attended by the president of Hungary, was awarded for sustained contributions to research and academic development in the Department of Physiology at the University of Szeged over the past 15 years, including the training of numerous visiting faculty, students and post-doctoral fellows. The continuing collaboration has resulted in more than 55 joint publications. He also has long-standing professional relationships with Semmelweis Medical School in Budapest, Hungary, and Keio Medical School in Tokyo, Japan. His laboratory, which is supported by four grants from the National Institutes of Health, has published over 270 original articles, reviews, and book chapters on various aspects of vascular and brain physiology and pathology. He also has a record of success in training a diverse array of students, fellows, and younger faculty in his laboratory to be independent scientists. His scientific areas of interest focus on the control of the brain vasculature during normal and disease conditions such as insulin resistance and stroke, cellular protective mechanisms in neurons and astroglia, and the biology of mitochondria.

Abstract

Mitochondrial initiated events protect the neurovascular unit, composed of vascular cells, neurons, and astroglia, against lethal stresses via a process called preconditioning and also acutely promotes changes in cerebrovascular tone through shared signaling pathways. Activation of the adenosine triphosphate (ATP)-dependent potassium channels on the inner mitochondrial membrane (mitoKATP channels), with pharmacological agents such as BMS-191095 and diazoxide, is a specific and reproducible way to induce protection of neurons, astroglia, and cerebral vascular endothelium. Through the opening of mitoKATP channels, mitochondrial depolarization leads to activation of protein kinases and transient increases in cytosolic calcium levels that activate terminal mechanisms such as nitric oxide production and increased catalase levels that protect the neurovascular unit against lethal stress. Release of reactive oxygen species from mitochondria has similar protective effects. Signaling elements of the preconditioning pathways also are involved in the regulation of vascular tone but with an unusual twist. Activation of mitoKATP channels in cerebral arteries causes vasodilation, with cell-specific contributions from endothelium (nitric oxide), vascular smooth muscle (calcium sparks), and nerves (nitric oxide). Pre-existing chronic conditions, such as insulin resistance or diabetes, prevent preconditioning and impair relaxation to mitochondrial centered responses in cerebral arteries. Furthermore, mitochondrial mechanisms in the cerebral vasculature are sex dependent. Surprisingly, mitochondrial mechanisms following transient ischemic stress protect cerebral vascular endothelium and promote the restoration of blood flow. Therefore, mitochondria may represent the elusive link between blood flow and metabolism under normal conditions as well as providing an important, but underutilized target in attenuating vascular dysfunction and brain injury in stroke patients.

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