Stephenson School of Biomedical Engineering
Seminar Series Presents

ADJUSTMENT OF CEREBRAL BLOOD FLOW VIA NEUROVASCULAR COUPLING

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Friday, March 6, 2020 | 1:30 p.m. | DEH 270

ABSTRACT

Moment-to-moment adjustment of Cerebral Blood Flow via neurovascular coupling has a critical role in maintenance of healthy cognitive function. In advanced age increased oxidative stress and cerebromicrovascular endothelial dysfunction impair neurovascular coupling, likely contributing to age-related decline of higher cortical functions. There is increasing evidence showing that mitochondrial oxidative stress plays a critical role in a range of age-related cellular impairments, but its role in neurovascular uncoupling remains unexplored. In several recent studies we tested the hypothesis that attenuation of mitochondrial oxidative stress may exert beneficial effects on neurovascular coupling in aging. In one of our studies we treated 24 months old C57BL/6 mice with a cell permeable, mitochondria-targeted antioxidant peptide (SS-31) for 2 weeks. We found that neurovascular coupling responses and ATP-induced endothelium-dependent CBF responses were significantly impaired in aged mice, however treatment with SS-31 significantly improved neurovascular coupling responses, at least in part, by increasing NO-mediated cerebromicrovascular dilation. These findings are paralleled by the protective effects of SS-31 on mitochondrial production of reactive oxygen species in cultured cerebromicrovascular endothelial cells derived from aged animals. Similar results were obtained by treating aged animals with nicotinamide mononucleotide (NMN), a key NAD+ intermediate. NMN supplementation rescued NVC responses by increasing endothelial NO-mediated vasodilation, which was associated with significantly improved spatial working memory and gait coordination. These findings were paralleled by the sirtuin-dependent protective effects of NMN on mitochondrial production of reactive oxygen species and mitochondrial bioenergetics in cultured cerebromicrovascular endothelial cells derived from aged animals. On the basis of these findings, we propose that novel therapeutic interventions should be developed to target vascular mitochondrial health and rescue functional hyperemia in elderly patients to prevent/delay cognitive impairment.

BIO

Anna Csiszar is Professor and Donald W. Reynolds Endowed Chair at the Reynolds Oklahoma Center on Aging, Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center. Csiszar's research centers on age-related vascular alterations leading to cognitive impairment. She received her MD degree in 1998 from the Semmelweis University of Medicine in Budapest, Hungary. In 2002 she earned a PhD in Physiology from the same institution. After 3 years of post-doctoral fellowship she joined the faculty of New York Medical College, NY in 2004. Her mentor was Gabor Kaley, one of the leading scientists of the field of microvascular pathophysiology. In 2009 she was recruited by the University of Oklahoma. Her work focuses on the cardiovascular complications of aging. She elucidated molecular mechanisms responsible for oxidative stress and low-grade vascular inflammation in aging, by introducing novel approaches to aging research, such as tools of comparative biology. Her current research focuses on age related cerebrovascular alterations leading to mild cognitive impairment. In addition to numerous scientific articles, she is the author of several book chapters and she serves as a reviewer for scientific journals as well as for NIH, AHA and AFAR. She has over 170 peer-reviewed publications in this field and she is the recipient of multiple grants (currently 2 R01s from NIH, AHA, OCAST, PHF). Currently she serves as a Core Leader of the Animal Model Development and Behavioral Assessment Core of the Geroscience COBRE Program as well.

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