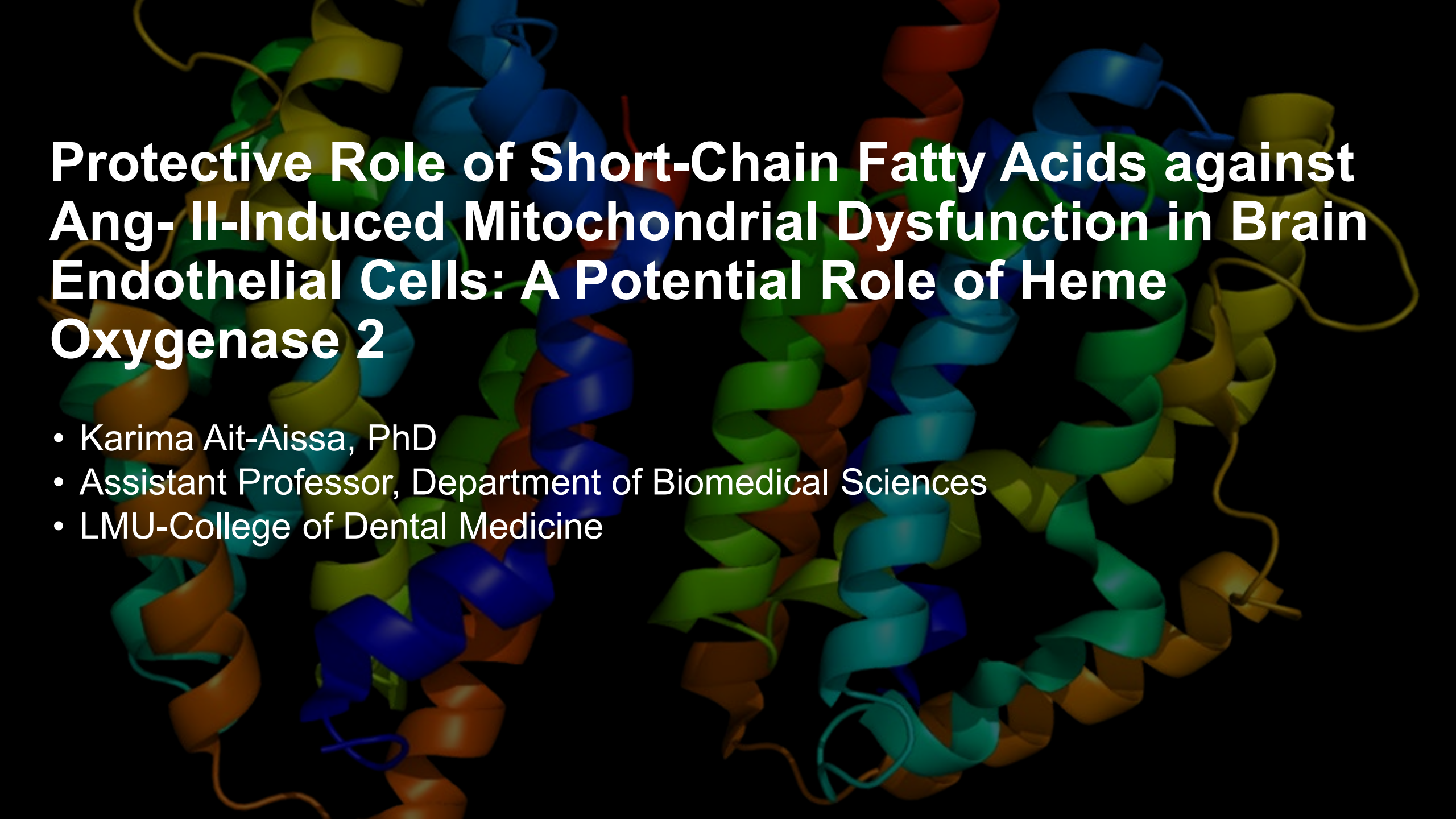
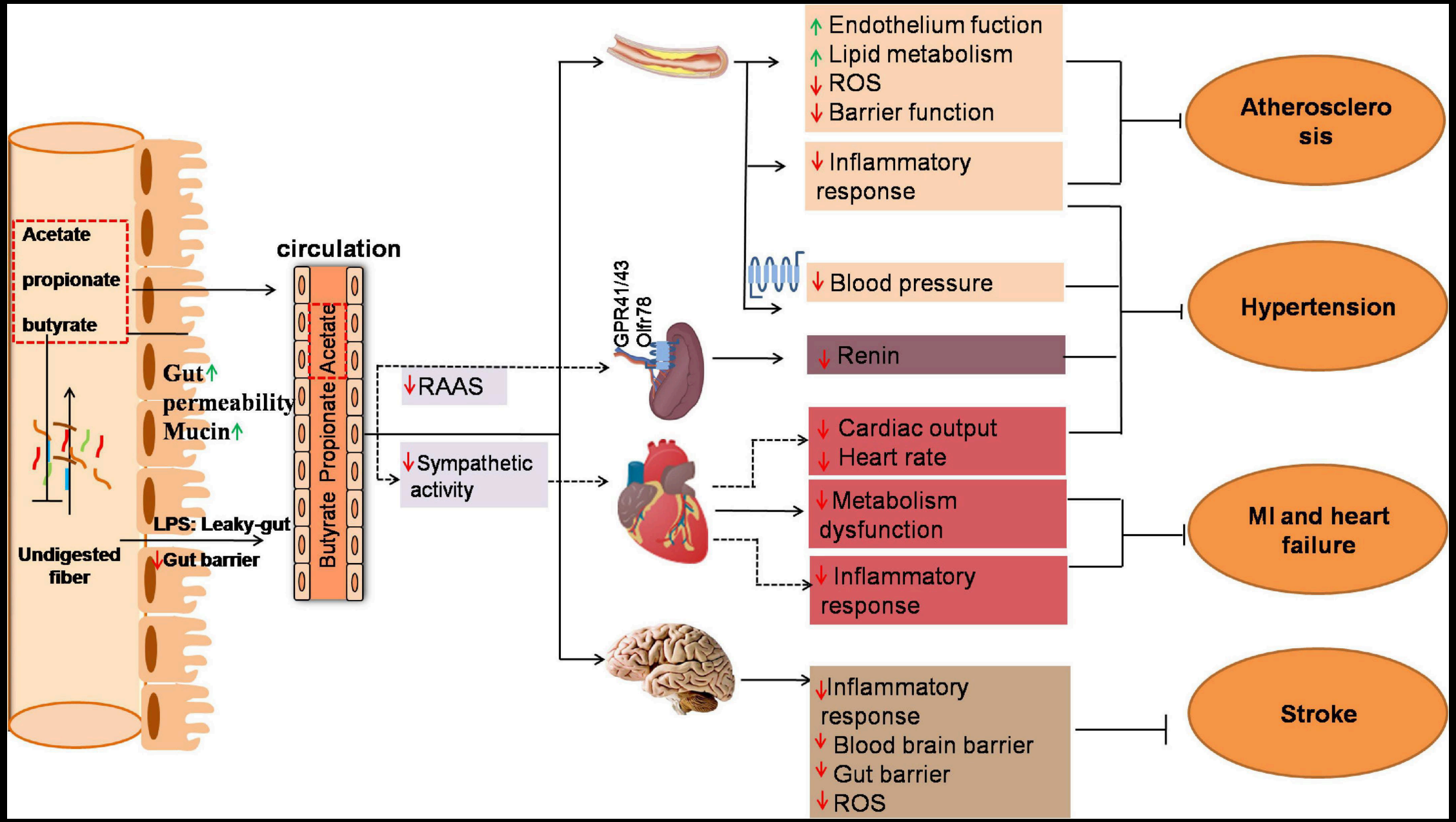


Protective Role of Short-Chain Fatty Acids against Ang- II-Induced Mitochondrial Dysfunction in Brain Endothelial Cells: A Potential Role of Heme Oxygenase 2

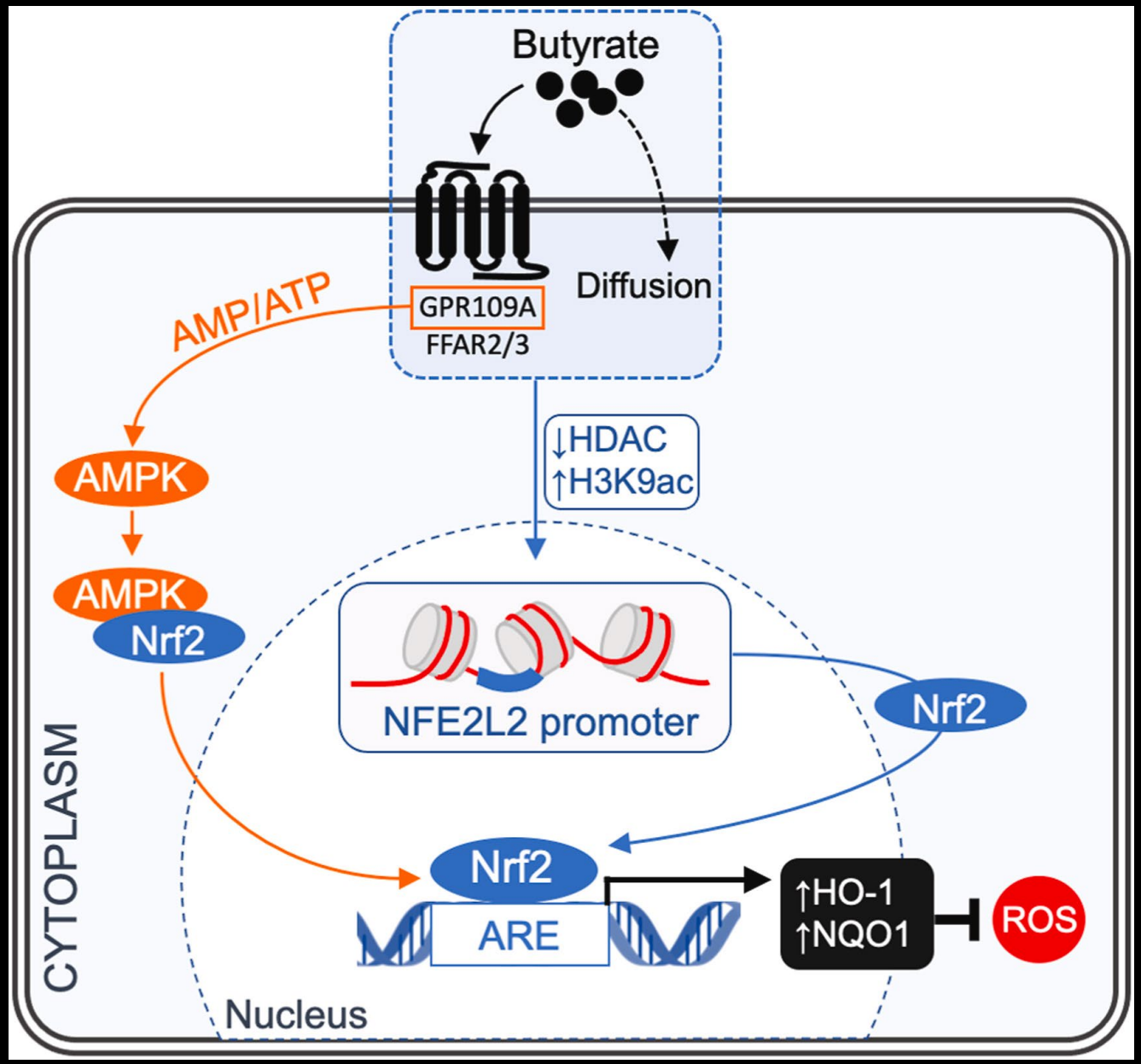
- Karima Ait-Aissa, PhD
- Assistant Professor, Department of Biomedical Sciences
- LMU-College of Dental Medicine

SCFAs in several key tissues under cardiovascular disease (CVD)



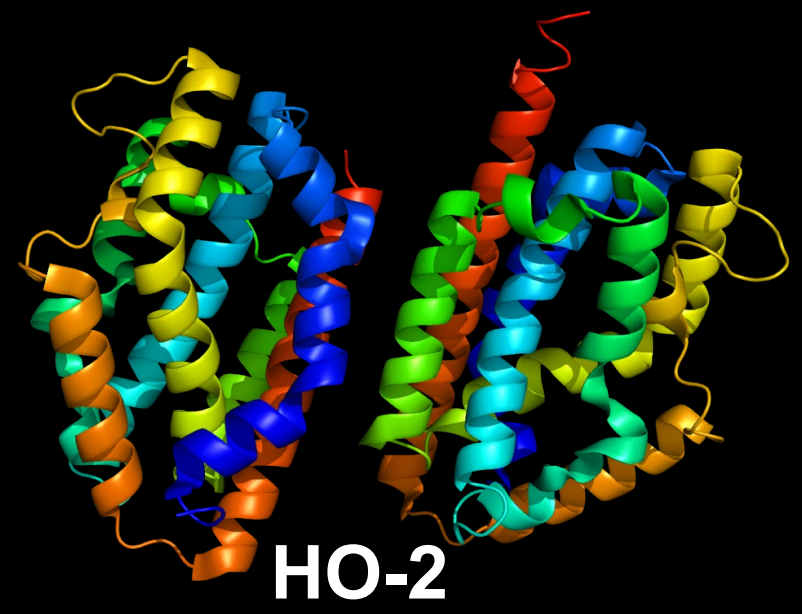
Yingdong Lu et al., Frontiers in Cardiovascular Medicine 2022

SCFAs activate pathways leading to upregulation of Heme Oxygenase 1



Gonzalez-Bosch et al., Redox biology, 2021

Heme oxygenase (HO) enzymes



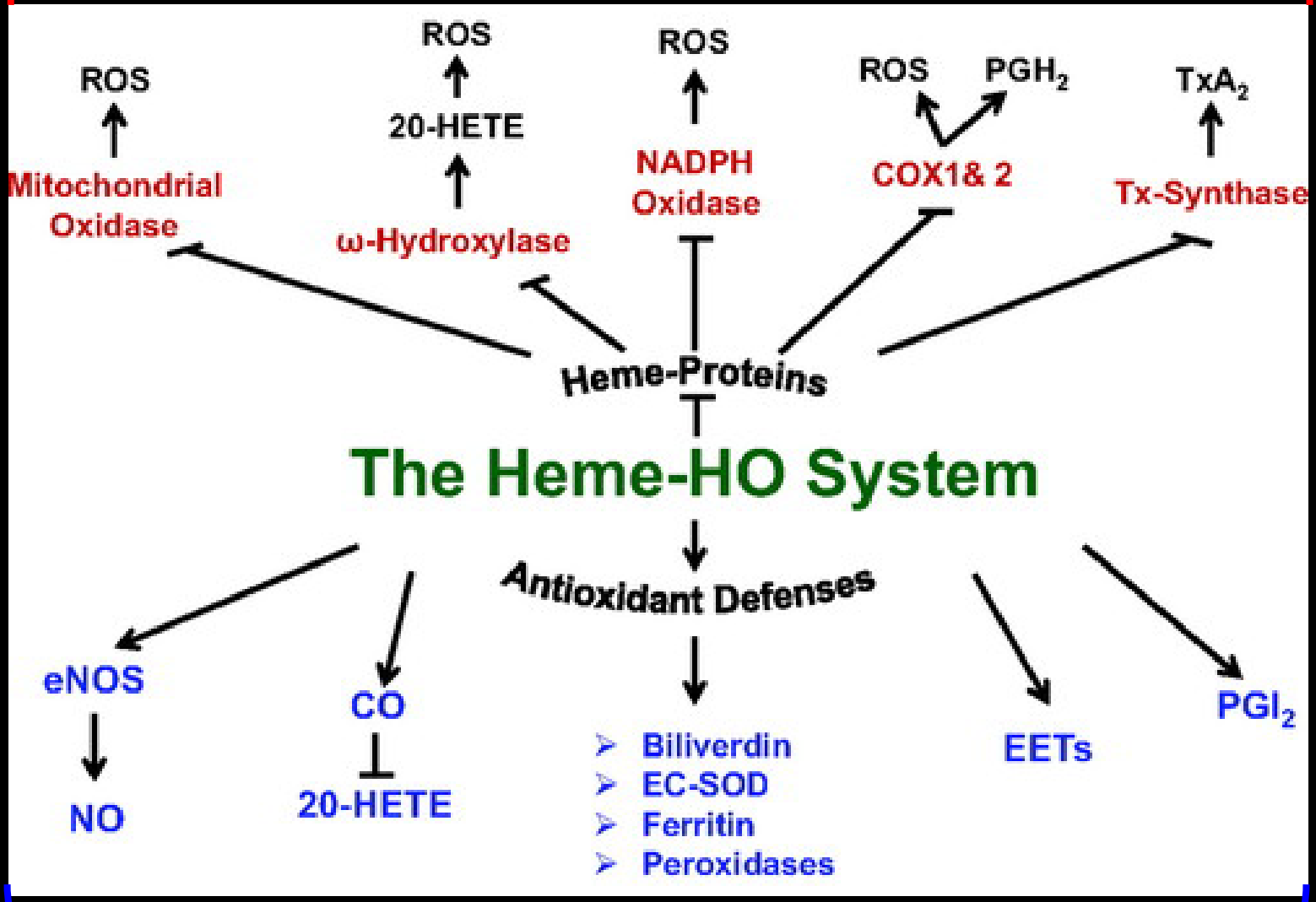
Rate-limiting enzymes in the breakdown of heme
Critical for maintaining cellular homeostasis

Two isoforms have been reported to date: HO-1 and HO-2

<u>The isoform HO-1:</u>
Translocates to the mitochondria and acts through calcium channels (such as the Mitochondrial Calcium Uniporter channel) and peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha to regulate mitochondrial biogenesis, oxygen consumption, adenosine triphosphate (ATP) production, and electron transport chain activity to produce cytoprotective effects.

<u>The isoform HO-2:</u>
Abundant in endothelial cells, particularly in the brain →potential relevance of HO-2 involvement in brain vascular function

Pro-oxidant and vasoconstrictor Pathways



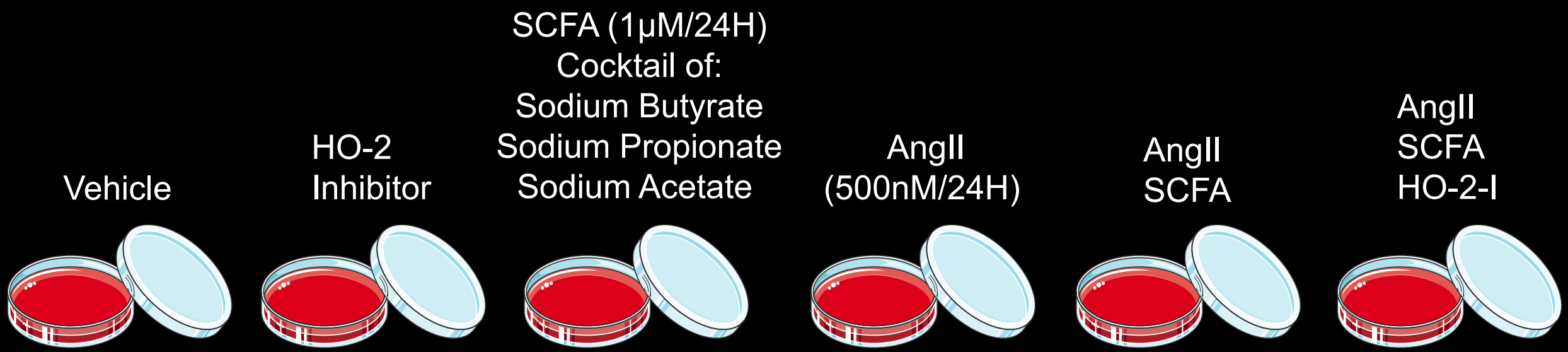
Anti-oxidant and Vasodilator Pathways

Objective

Hypothesis: SCFA act on HO-2 to induce an anti-oxidant and anti-inflammatory effect in brain endothelial cells leading to a protective effect during cerebrovascular diseases

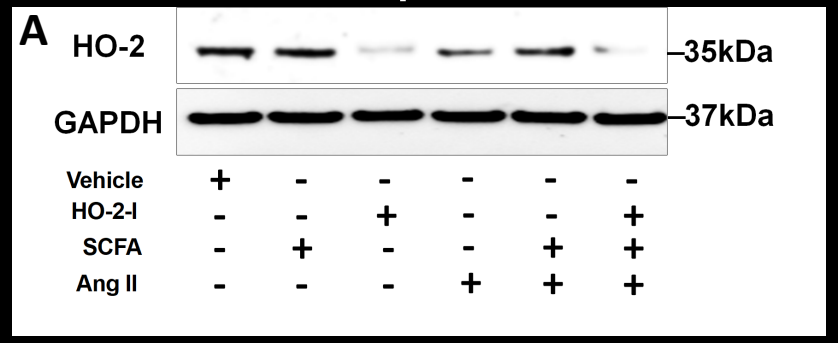
- Determine the effect of SCFA treatment on endothelial and mitochondrial integrity following oxidative stress.
- Demonstrate whether SCFAs act on Heme Oxygenase 2 to prevent/counteract oxidative stress-induced endothelial impairment, inflammation, and mitochondrial dysfunction

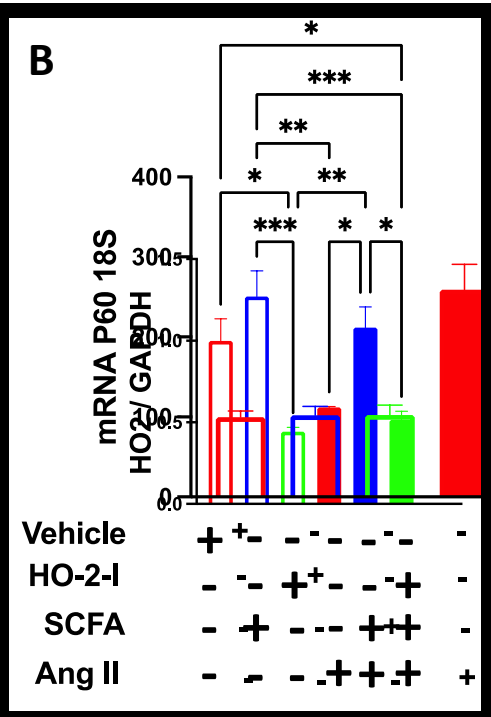
Experimental design



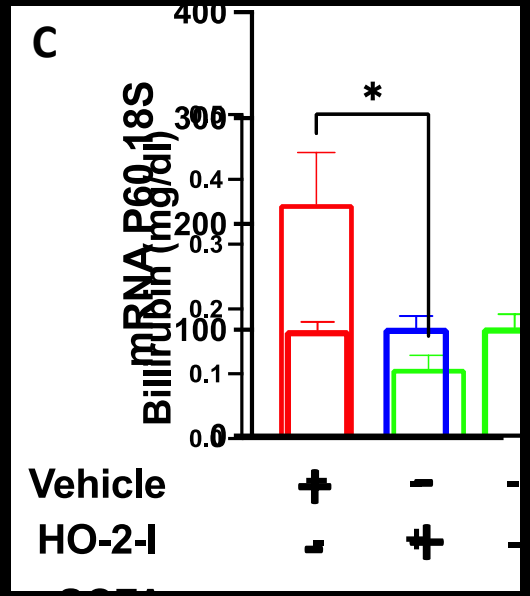
SCFAs Reverse Ang-II-Induced Downregulation of HO-2

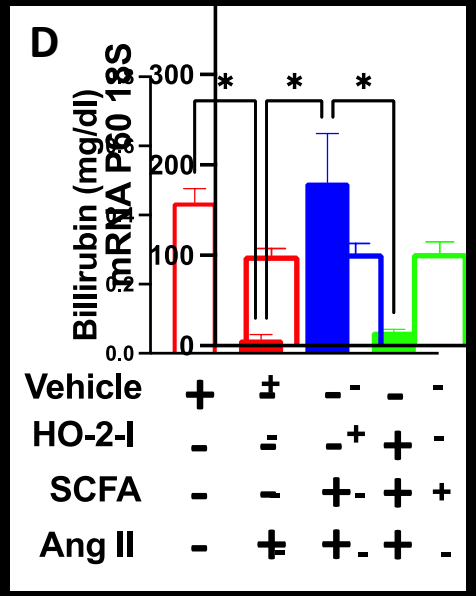
HO-2 expression





HO-2 function





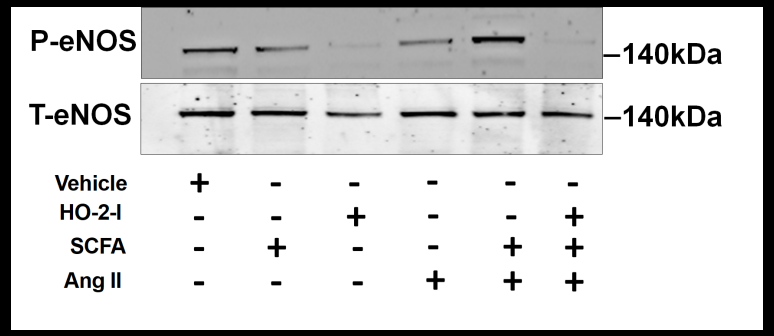
Ang-II → ↓HO-2 levels/function

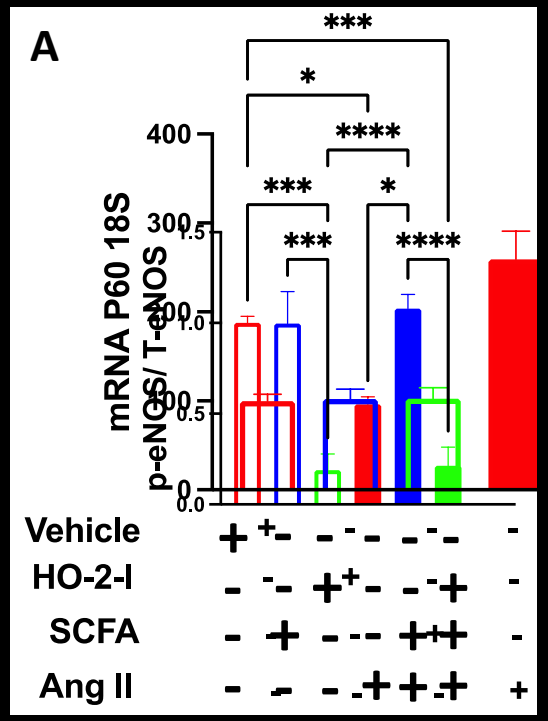
⊤

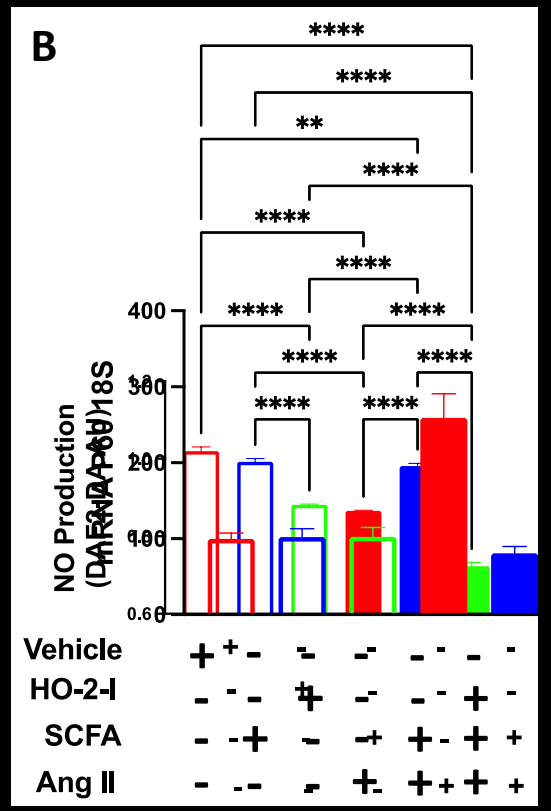
SCFAs

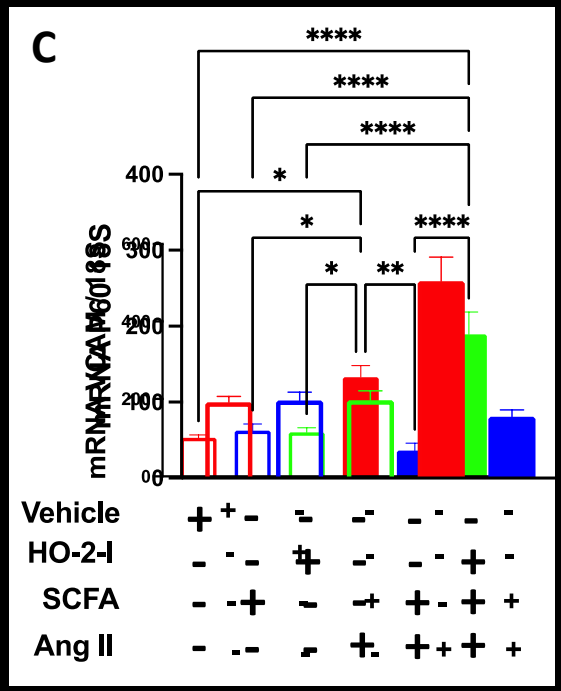
Kassan et al, Antioxidants, 2023

SCFAs Improve Ang-II-Induced Endothelial Dysfunction by Regulating HO-2









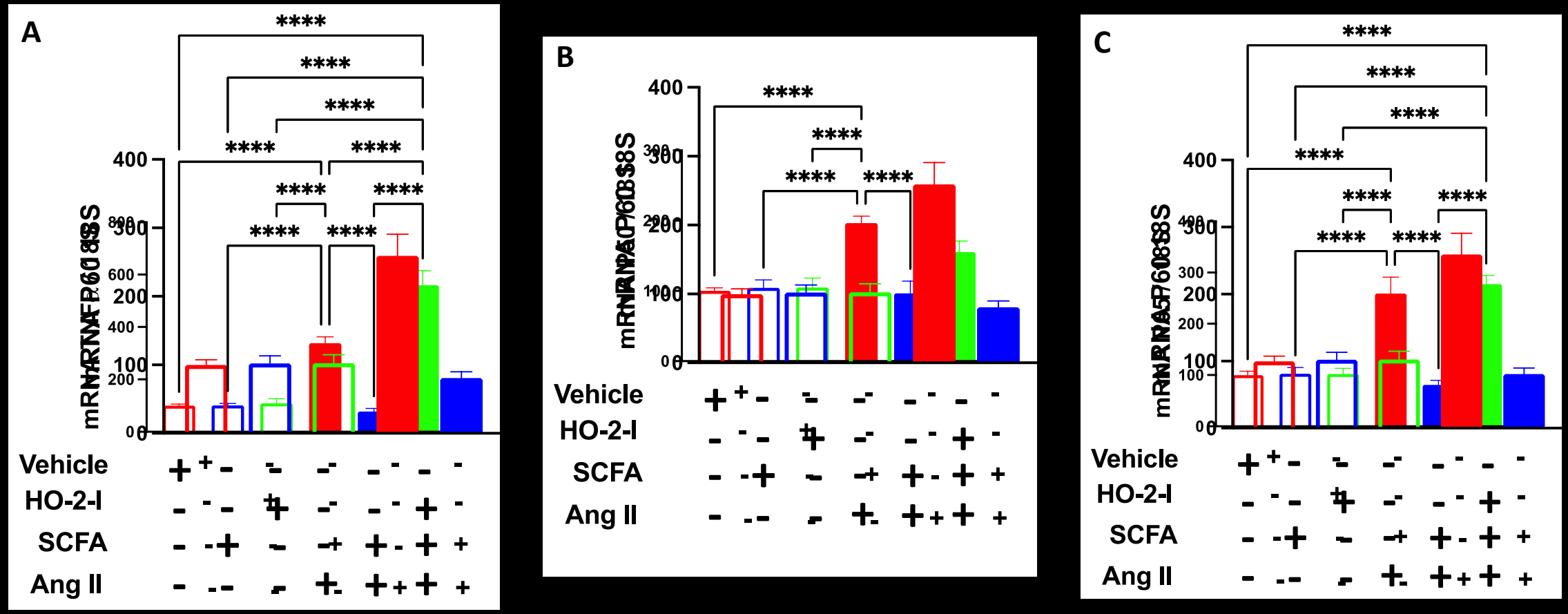
Ang-II → ↓eNOS activation/NO production

⊤

SCFAs

Kassan et al, Antioxidants, 2023

SCFAs Reduce Ang-II-Induced Endothelial Inflammation by Regulating HO-2



Ang-II → ↑Inflammatory markers

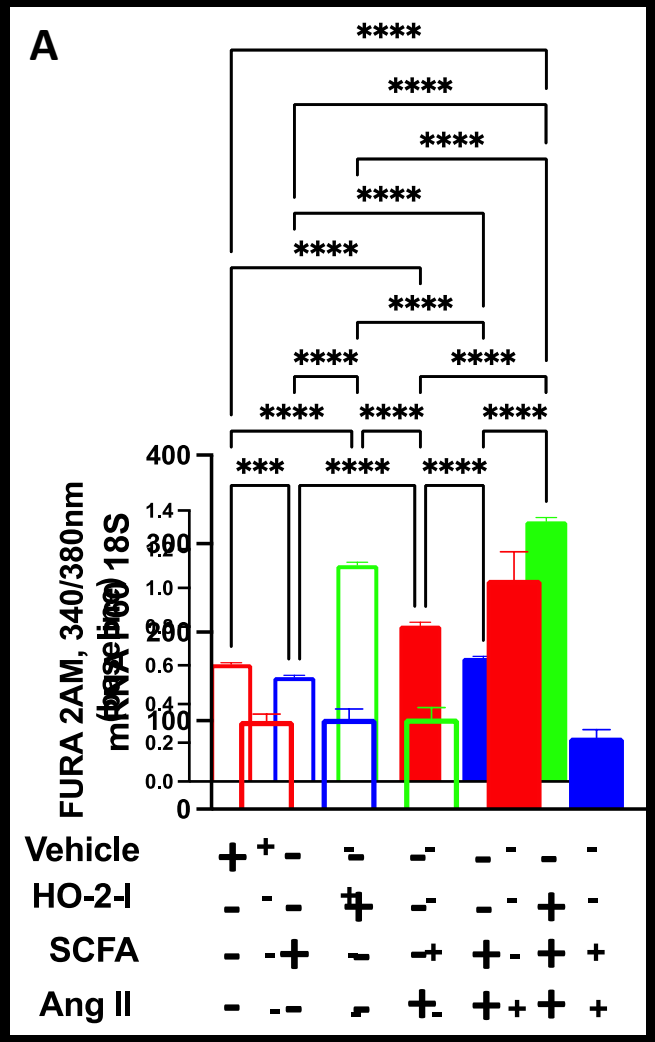
⊤

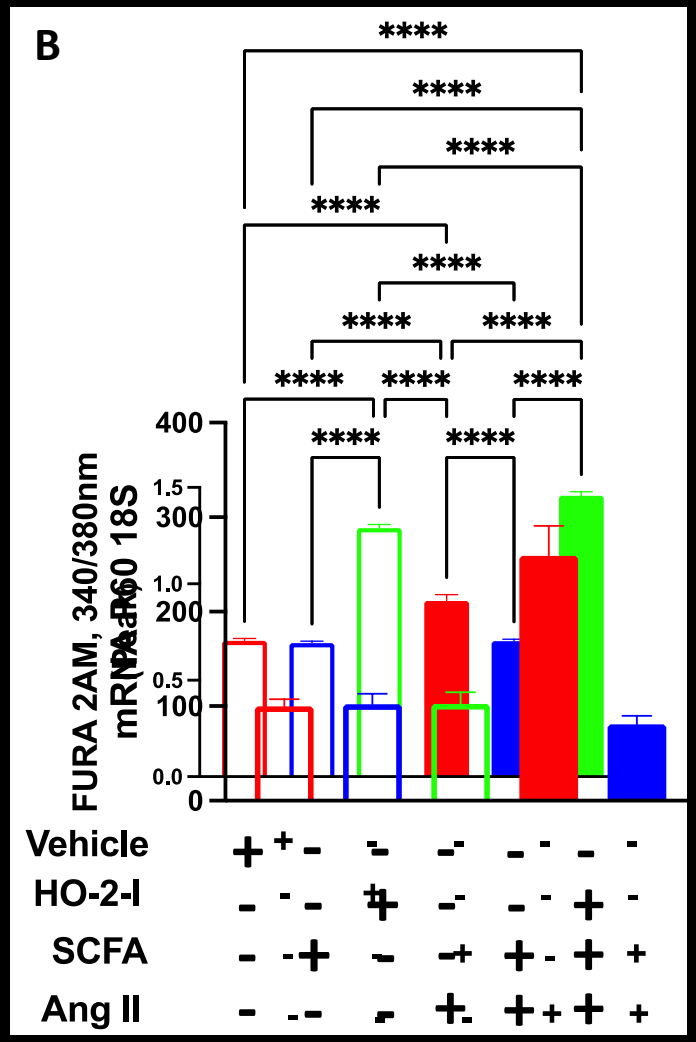
SCFAs

Kassan et al, Antioxidants, 2023

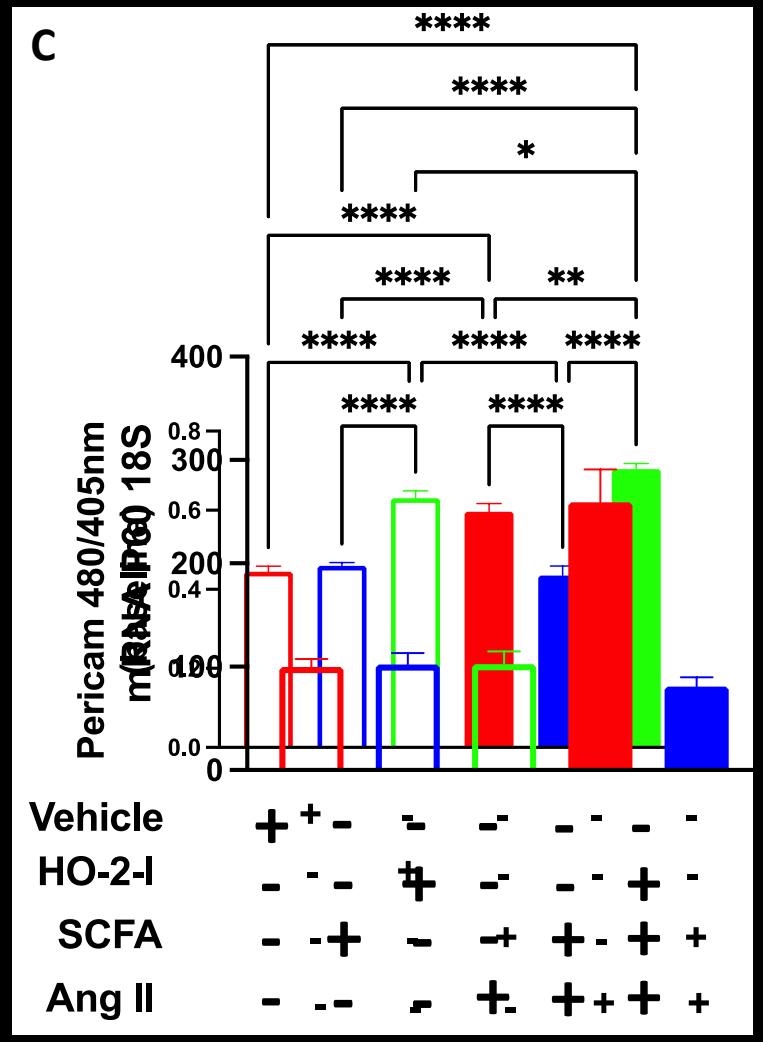
The SCFAs/HO-2 Axis Regulates Calcium Homeostasis in Mitochondria from Cerebral ECs

Cytosolic Calcium



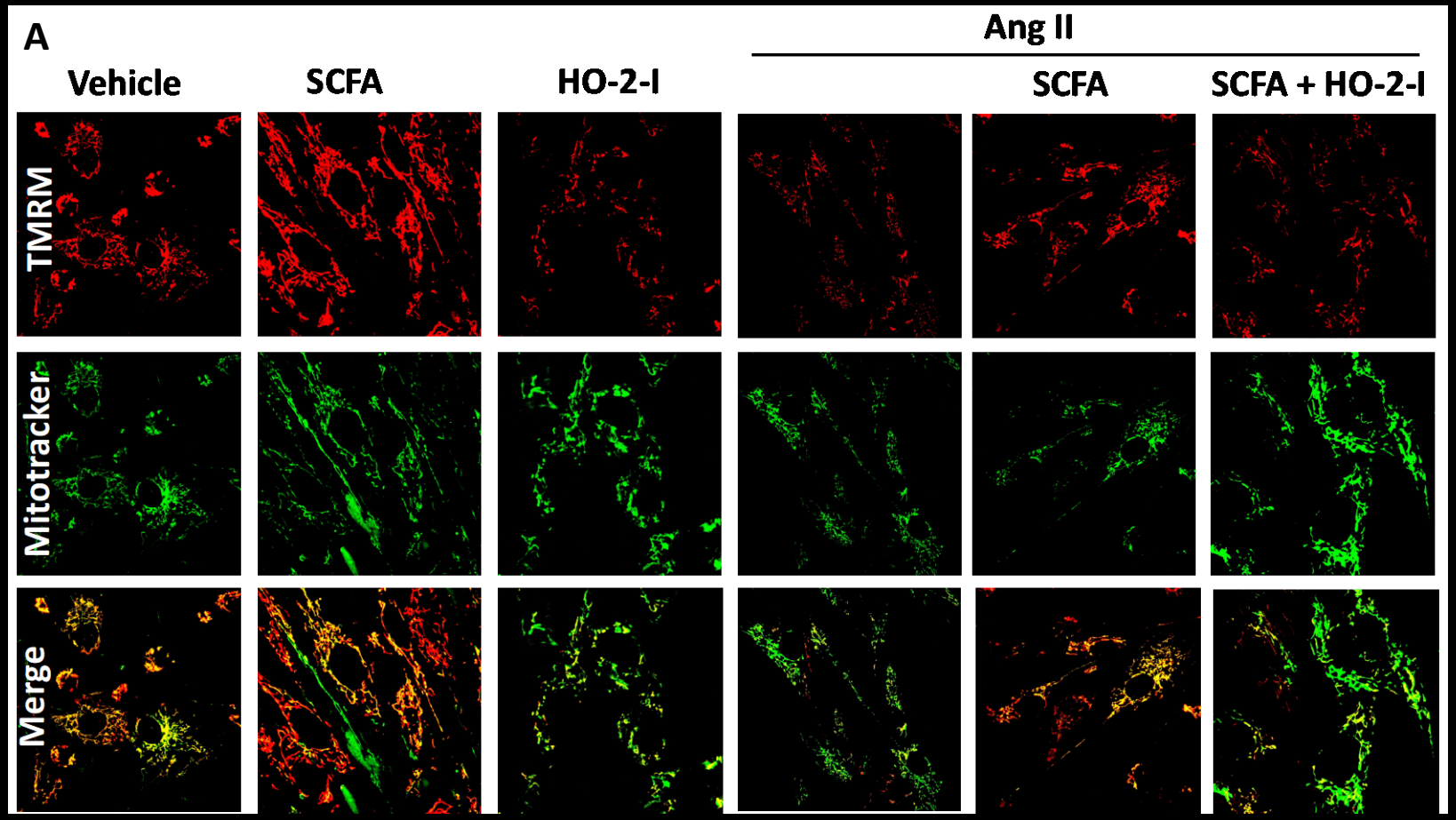


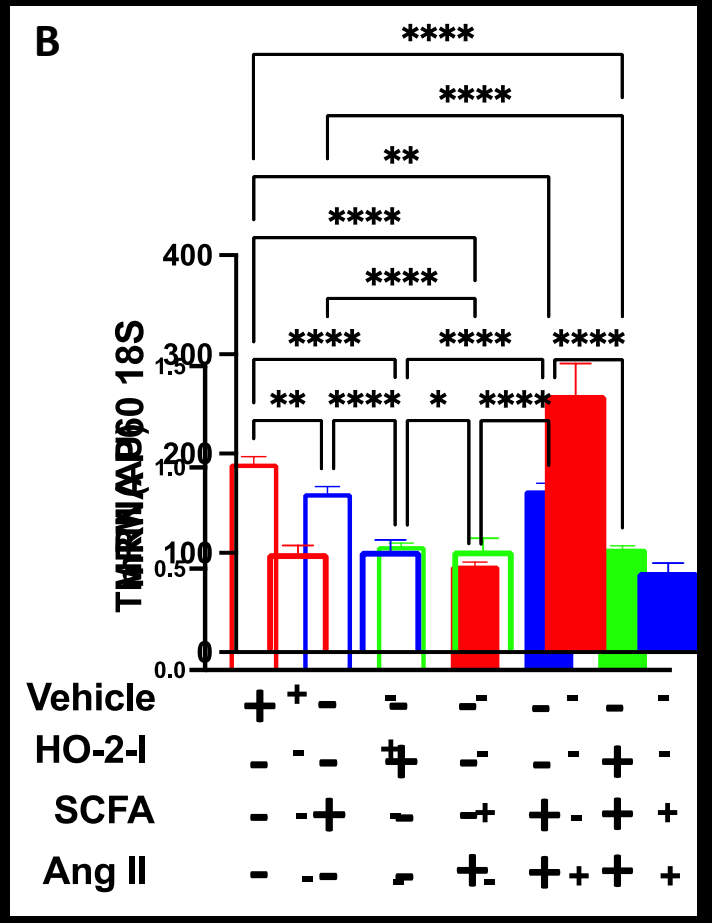
Mitochondrial Calcium



Kassan et al, Antioxidants, 2023

SCFAs Normalized Mitochondrial Membrane Potential by Mediating HO-2 following Ang-II Treatment

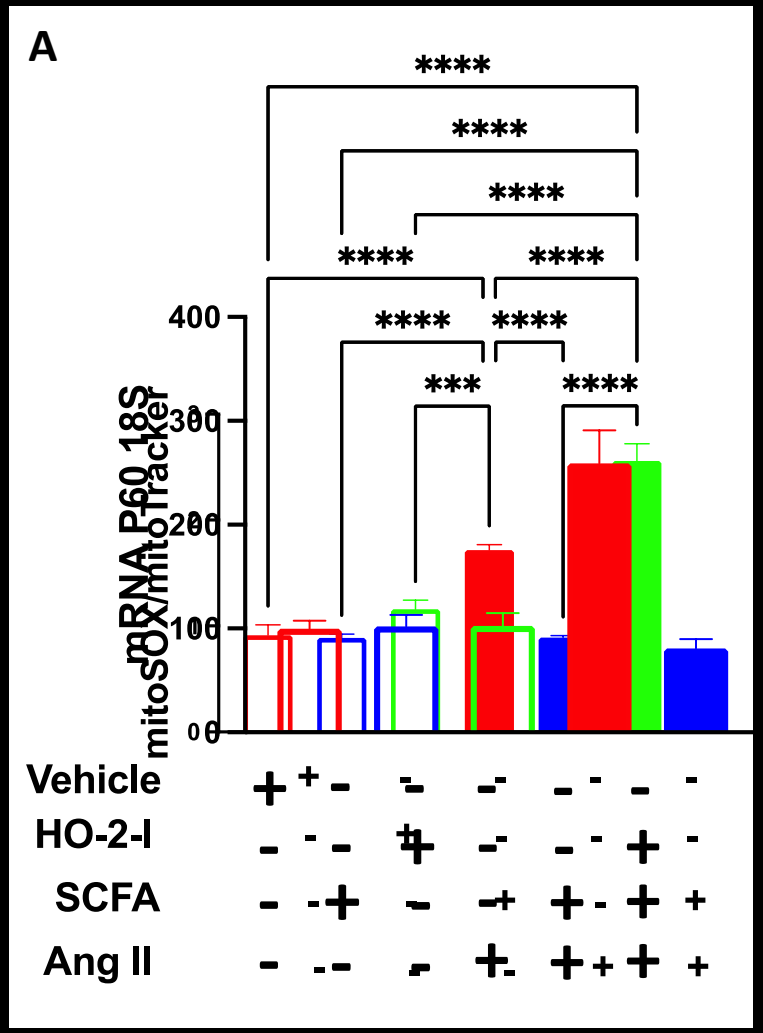




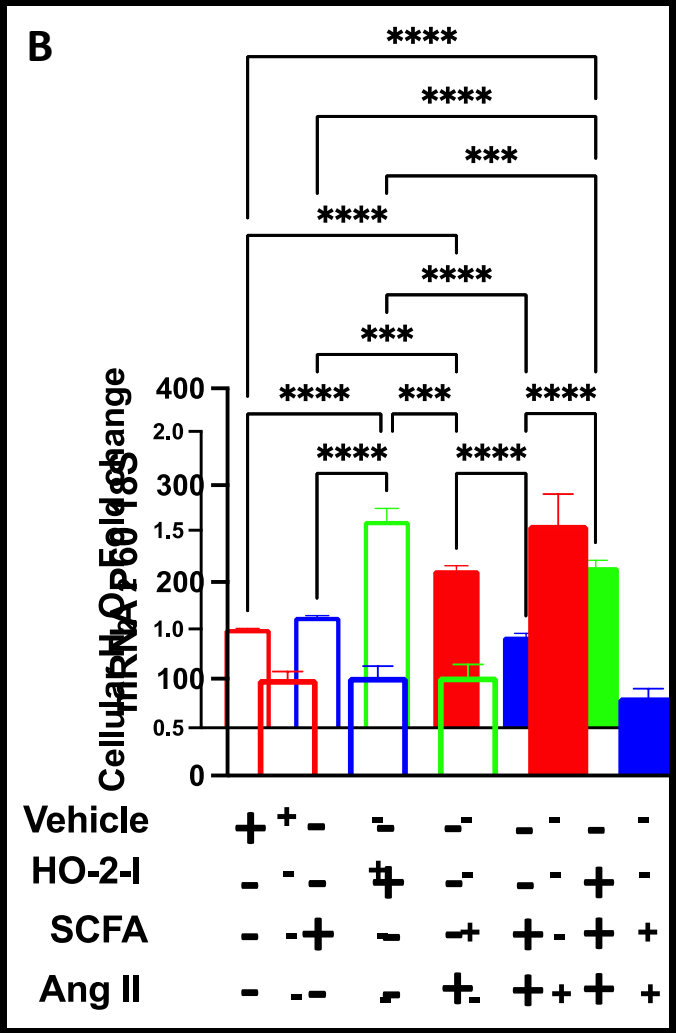
Kassan et al, Antioxidants, 2023

The SCFAs/HO-2 Axis Regulates Mitochondrial ROS, H_2O_2 and Mitochondrial Function

Mitochondrial Oxidative stress



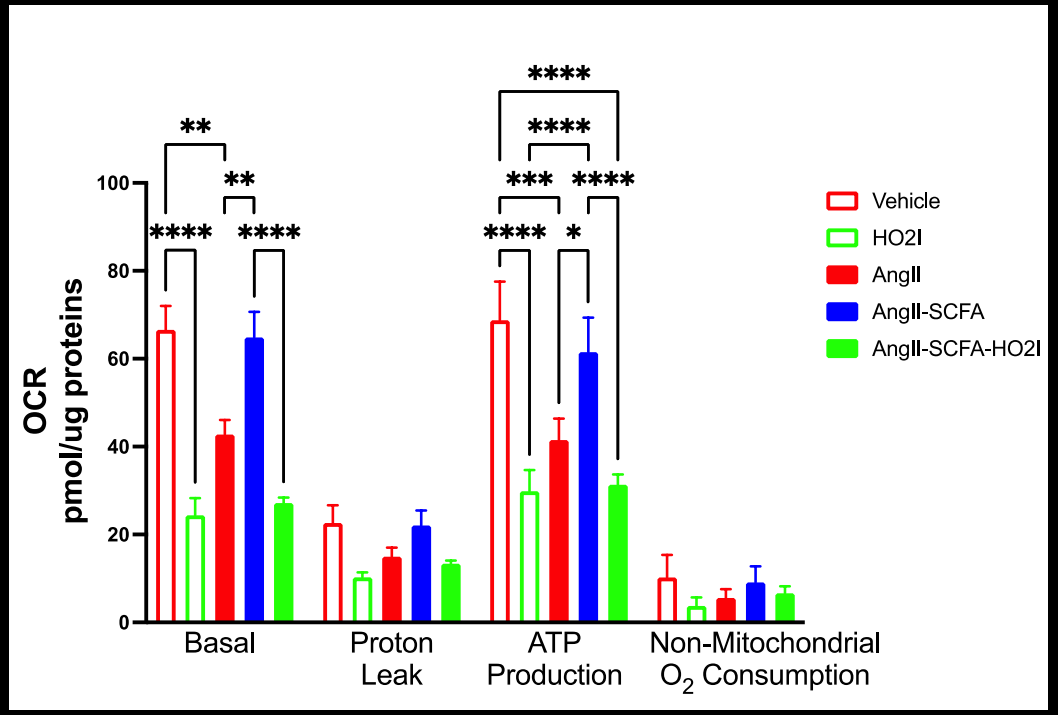
Cellular Oxidative stress



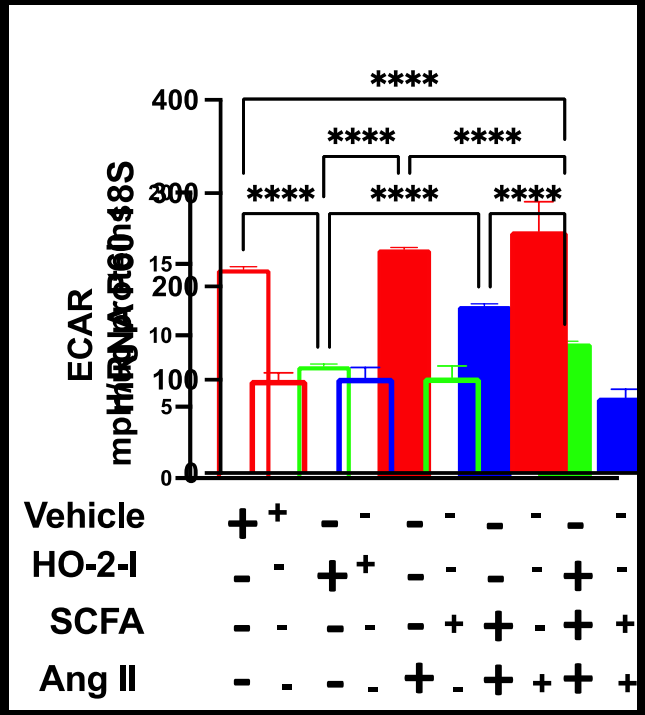
Kassan et al, Antioxidants, 2023

The SCFAs/HO-2 Axis Regulates Mitochondrial ROS, H_2O_2 and Mitochondrial Function

Oxygen consumption/Respiration



Extracellular acidification/Glycolysis



Ang-II → ↓mitochondrial function

⊤

SCFAs

Kassan et al, Antioxidants, 2023

Summary and conclusions

- HO-2 expression and activity are altered during cellular stress
- Reduction in HO-2 expression and activity in cerebrovascular endothelial cells causes mitochondrial and endothelial dysfunction.
- SCFAs were able to restore the level of HO-2 and therefore rescued the mitochondrial and endothelial function.

In our in vitro study, we elucidate a potential mechanism by which SCFA could influence cerebrovascular physiology.
Our results provide a framework for molecular studies to better characterize the molecular mechanisms of SCFAs

Extrapolating this data to an in vivo model of cerebrovascular disease is of great clinical significance since it could be a key step in developing novel therapeutic targets to treat central nervous diseases.

Future directions

- Dissect further the mechanism by which SCFAs activate/protect the expression and function of HO-2
- Extrapolate the in vitro findings into an in vivo model to define the physiological impact of SCFA/HO-2 axis activation during health and disease.
- Determine the effect of stimulating SCFA-producing bacteria on the development of chronic oxidative stress and inflammation associated diseases such as cerebrovascular and periodontal diseases.

Acknowledgment

Modar Kassan, PhD
LMU college of Dental Medicine

Ammaar Abidi, DDS
LMU college of Dental Medicine

Undral Munkhsaikhan, PhD
LMU college of Dental Medicine

Funding

National Institutes of Health:
7R01HL150360-02
The American Heart Association:
2021CDA853499
the Instituto de Salud Carlos III (ISCIII):
grant PI20/01004

Youngin Kwon, University of Tennessee Health Science Center, Memphis, TN
Amal M. Sahyoun, McGill University, Montreal, Canada
Tauheed Ishrat, University of Tennessee Health Science Center, Memphis, TN
María Galán, University Rey Juan Carlos, Madrid Spain
Alexis A. Gonzalez, Pontificia Universidad Católica de Valparaíso, Chile
Adam Kassan, West Coast University, Los Angeles, CA

American Heart Association.

NIH
National Institutes of Health

LMU Lincoln Memorial University