Acute effects of urolithin A on mitochondrial respiration in vascular smooth muscle cells of ApoE-/- mice

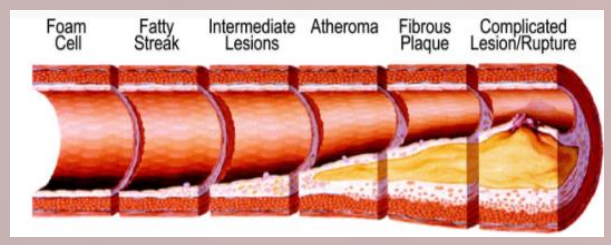
Jesse Corbin[1], Francis Parenteau[1], David H. St-Pierre[2], Andreas Bergdahl[1]

1. Department of Health, Kinesiology & Applied Physiology, Concordia University, Montreal, Canada

2. Département des Sciences de l'Activité Physique, Université du Québec à Montréal, Montréal

Introduction

- Cardiovascular disease is responsible for 45% of all noncommunicable disease deaths worldwide and is the second leading cause of death in Canada
- Vascular smooth muscle cells (VSMCs) undergo dedifferentiation and migration to promote atherosclerotic plaque formation
- When contributing to plaque formation, VSMCs exhibit altered bioenergetic demands, increasing mitochondrial respiration rates
- Gut-microbiota derived metabolite urolithin A (UA) obtained from pomegranates has been shown to improve cardiovascular function
- There is a lack of research exploring the acute effects UA has on VSMC mitochondrial respiration



Koenig & Khuseyinova (2006)

Objectives

- Examine the effect acute UA may have on mitochondrial respiration in VSMCs
- Determine the mechanism of action of UA on the electron transport chain

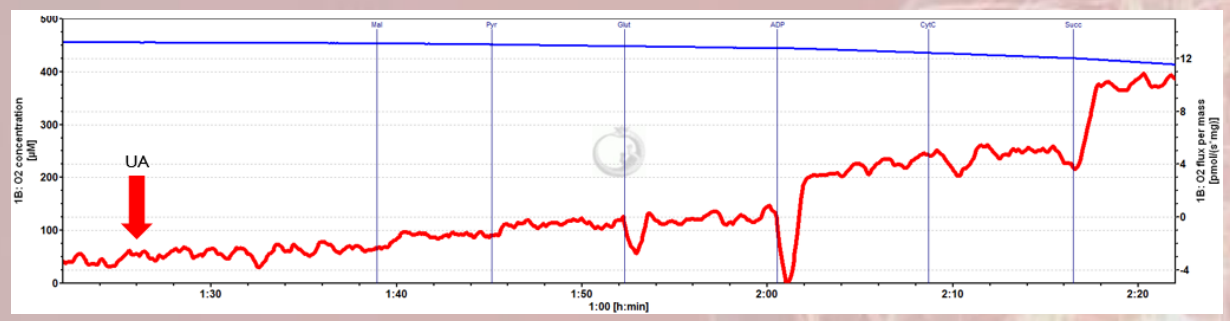
Materials and methods

Animals

- Male apolipoprotein E (ApoE) -/- mice aged 3-4 months

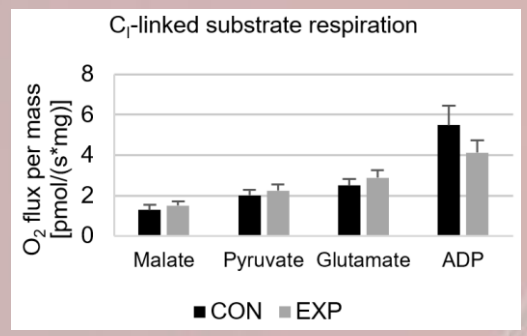
Tissue analysis

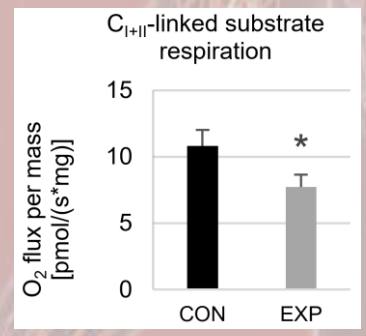
- Aortic tissue was collected and underwent plasma membrane permeabilization
- The Oroboros oxygraph was used to examine substrate-linked respiration rates
- Prior to the addition of substrates, the experimental group (EXP) received 0.04 mg of UA per mg of tissue while the control group (CON) received the vehicle dimethyl sulfoxide (DMSO)
- Below is a representative oxygraph of an EXP sample with the horizontal blue line indicating the O_2 concentration within the chamber and the red line indicating O_2 flux per unit mass

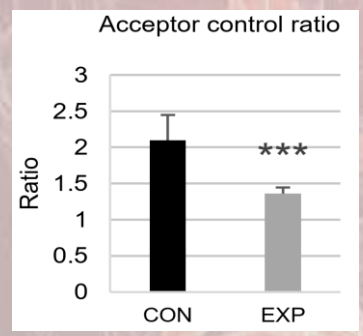


Results

- Complex I-linked substrate respiration, with and without complex V (ADP) activation, was not significantly affected by the presence of UA
- UA exposure reduced complex I+II-linked substrate respiration ($P = 0.05$) in the EXP group
- Addition of UA in the EXP group significantly reduced the oxidation:phosphorylation coupling efficiency ($P < 0.01$), which is represented as the acceptor control ratio (ACR)







Conclusions

- Acute UA exposure reduced complex I+II-linked maximal respiration compared to the CON group, suggesting UA may lower ATP production capability
- Acute UA exposure significantly reduced the ACR compared to the CON group indicating a lower production of ATP per O_2 flux
- It is still unclear whether UA has an effect on ATP synthase
- By reducing mitochondrial ATP production, UA may inhibit atherogenic processes mediated by VSMCs such as migration, proliferation, and secretion of extracellular matrix proteins and cytokines

Future research

- Investigate the acute effects of varying UA concentrations in VMSC mitochondrial respiration
- Examine the long-term effects of UA exposure regarding plaque formation and VSMC dedifferentiation
- Determine the impact UA may have on reactive oxygen species production
- Explore the effect UA may have on mitochondrial density and subunit expression using western blot

For further information

More information on this and related projects can be obtained from Jesse Corbin at Concordia University, 7141 Sherbrooke St W, Montreal, QC, H4B 1R6

Email: Corbinjesse95@gmail.com

www.bergdahllab.com