The Effects of NADPH Oxidase on Reactive Oxygen Species and Adipose Tissue Lipolysis

Ely J. Nieves, Karelia Paz, Cesar A. Meza, Dr. Robert C. Hickner
Department of Nutrition & Integrative Physiology , Florida State University, Tallahassee, FL

Background

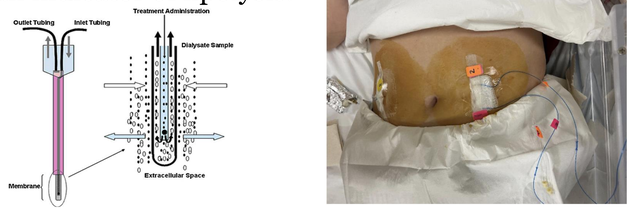
- Rapidly increasing rates of cardio-metabolic diseases have become a major health concern in recent years due to high mortality rates and physiological complications (CDC, 2022).
- Nicotinamide adenine dinucleotide phosphate oxidase (Nox) is an enzyme present in adipose cells that has been previously correlated with the development of insulin resistance in mouse models of obesity (Ding et al. 2019).
- It is possible that the effects of Nox on metabolism occur through increased reactive oxygen species (ROS) production and lipolysis, which is the breakdown and release of triglyceride stores in adipose cells (Krawczyk et al. 2012).
- Dysregulated lipolysis has been linked to several cardio-metabolic complications (Figure 2). However, it remains poorly understood how Nox influences lipolysis and cardio-metabolic health outcomes in human participants.

Purpose

• To determine the signaling pathway(s) by which Nox stimulates lipolysis under fasted and hyperinsulinemic conditions.

Methods

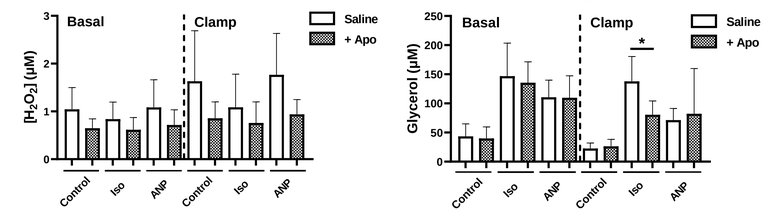
- N = 8 males and females; Age = 22.3 ± 5.0 years; Body mass index: 25.0 ± 9.5 kg/m²
- Three microdialysis probes were inserted in subcutaneous abdominal adipose tissue. Microdialysis procedures commenced with the participant in a fasted state and repeated under a "fed" state.
- A Nox Inhibitor (Apocynin) was perfused into the adipose tissue microdialysis probes either with isoproterenol or atrial natriuretic peptide (ANP), which stimulate lipolysis via different signaling pathways (Figure 1).
- A hyperinsulinemic-euglycemic clamp mimics a meal through the infusion of glucose at a variable rate together with insulin infusion at a fixed rate (12 mU/m²/min).
- Dialysate samples were analyzed using a fluorometer to determine ROS levels (the combination of hydrogen peroxide H_2O_2 and superoxide O_2 concentrations). Glycerol was used as an indicator of lipolysis.



Representation of microdialysis probe and technique

Results and Conclusions

3A. **Reactive Oxygen Species ($H_2O_2 + O_2\cdot$)** 3B. **Lipolysis**

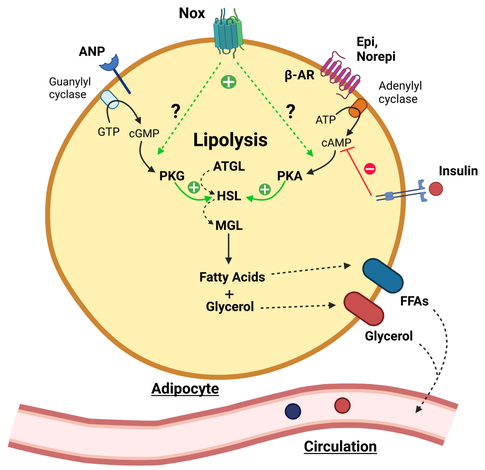


Apo- Apocynin (Nox inhibitor) **Iso-** Isoproterenol **ANP-** Atrial Natriuretic Peptide

- ROS levels decreased when the local Nox-inhibitor, apocynin, was introduced, providing evidence for the first time in human participants that Nox stimulates increased adipose tissue ROS production *in vivo* (Figure 3A).
- Nox-derived ROS levels were enhanced during hyperinsulemic conditions compared to fasted conditions (Figure 3A).
- Local Nox inhibition significantly reduced glycerol levels in the Isoproterenol probe during hyperinsulinemic conditions (Figure 3B).
- Nox contributed to increased lipolysis through the β-adrenergic signaling pathway, which is an effect that was augmented during the clamp compared to fasted conditions.
- Further experimentation will investigate if elevated Nox levels in obese individuals diminish insulin's anti-lipolytic effect and change microvascular function.

General Schematic of Lipolysis

Figure 1. Lipolysis Pathways in Adipocyte



Elevated Nox Progression

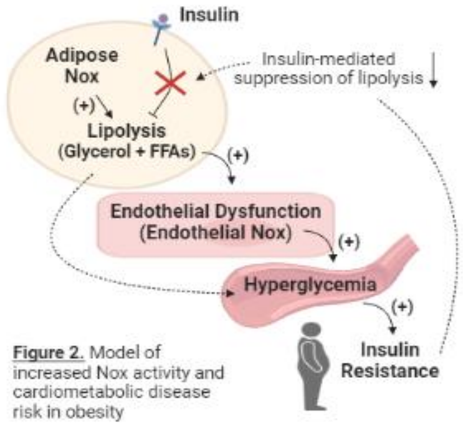


Figure 2. Model of increased Nox activity and cardiometabolic disease risk in obesity

Acknowledgments

Thank you to our mentor Cesar A. Meza and other members of the Hickner Lab, the Undergraduate Research Opportunity Program, and all those who have supported us furthering our research experience through feedback and learning opportunities.

References

Ding, Lei, et al. "Adipose Afferent Reflex Is Enhanced by TNFα in Paraventricular Nucleus through NADPH Oxidase-Dependent ROS Generation in Obesity-Related Hypertensive Rats." Journal of Translational Medicine, vol. 17, no. 1, 2019, pp. 256–256, https://doi.org/10.1186/s12967-019-2006-0.

Krawczyk et al. (2012). Reactive oxygen species facilitate translocation of hormone sensitive lipase to the lipid droplet during lipolysis in human differentiated adipocytes. *PLoS One, 7*(4), e34904.