Literature Review – Vascular and Metabolic Function

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Research Questions

- Does increased NADPH oxidase (Nox)-derived reactive-oxygen species production in people with obesity hinder blood glucose profiles by reducing insulin-mediated suppression of lipolysis?
- What is the mechanism by which Nox increases lipolysis?
- Does the increase of Nox contribute to insulin resistance and endothelial dysfunction in patients with obesity? How does this compare to a person with a healthy body weight?

Abstract

Endothelial function is the description how endothelial cells, lining the inside of vessels and arteries, function to create dilation or contraction with blood flow. A study to test this will specifically try and find relation between endothelial function due to exercise performance. Using ultrasounds to perform experiments, as well as other laboratory equipment are the main ways to collect data from the sounds waves and thus analyze it in terms of endothelial and vascular function. This could ultimately allow furthering into conclusions about why exercise can aid the human body's overall health. Overall, in this poster, we will be highlighting different literary sources in order to further explain the testing and research done on these topics.

Specific Aim

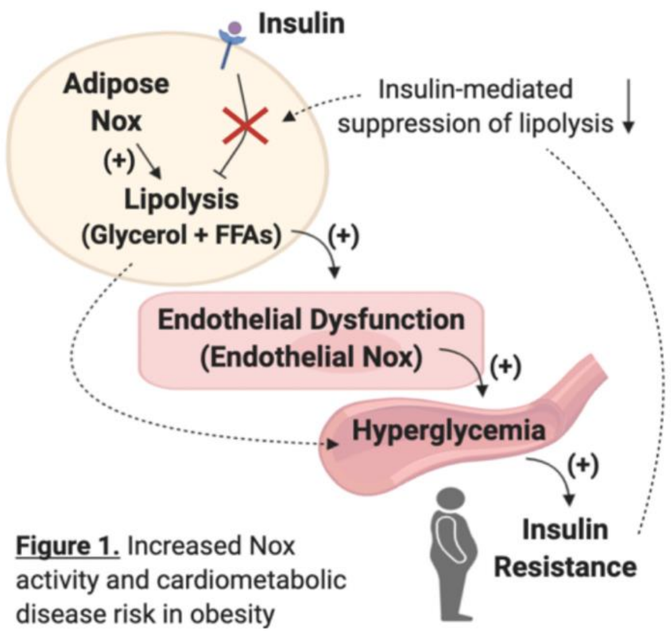


Figure 1. Increased Nox activity and cardiometabolic disease risk in obesity

Background

Cardiovascular disease has posed a serious health concern within the United States, as one third of the population has been diagnosed with having obesity. Identifying other cardiovascular risk factors, such as hypertension, is essential in preventing the onset of cardiovascular disease and type 2 diabetes and/or reducing the negative effects if it has already developed. Oxidative stress plays an important role in evaluating insulin resistance and endothelial dysfunction. Insulin employs metabolic effects on the liver, adipose tissue, and skeletal muscle (Cerosimo and Defonzo 2006). When an individual becomes obese or develops type 2 diabetes, insulin resistance can occur, which limits fatty acid oxidation causing an increase in intracellular fatty acyl-CoA, which will ultimately inhibit the carnitine palmitoyl-transport system (Cerosimo and Defonzo 2006). Vasodilation and vasoconstriction also function improperly when insulin becomes restricted, resulting in an inability to activate nitric oxide synthase (NOS), which is responsible for NO synthesis (Cerosimo and Defonzo 2006). Nitric oxide is essential in vascular smooth muscle cells because it can cause inappropriate vasoconstriction if it were lacking (Cerosimo and Defonzo 2006). Endothelium is essential in the regulation of blood flow, blood pressure, delivery of nutrients, and disposal of waste built up from the metabolic processes (Cerosimo and Defonzo 2006). When these processes are inhibited, atherosclerosis can develop due to improper vasodilation in the arteries (Cerosimo and Defonzo 2006). Reactive oxygen species (ROS) are also to be taken into consideration, as it can cause apoptosis and increased cellular permeability (La Favor et al 2016).

Methods

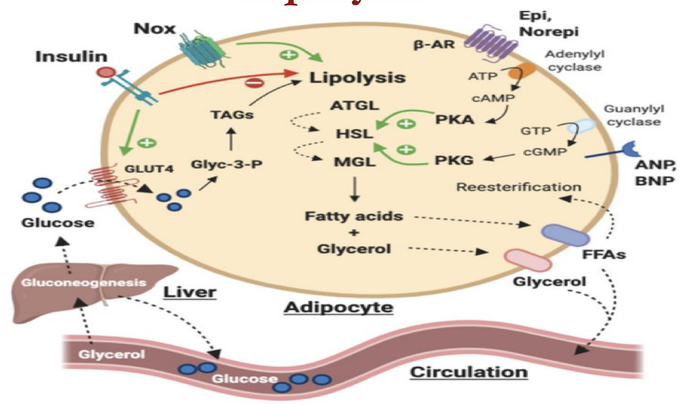
Participants:

- Sample size n = 30; 15 – normal weight, 15 – obese
  - Aim 1: Fasting conditions
  - Aim 2: Fasting & Non-fasting conditions
- Aim 1: Participants were subject to a microdialysis test, where apocynin (lipolysis inhibitor) will be infused into fat tissue via micro-dialysis probes, after infused with either isoproterenol or ANP, which stimulates lipolysis.
- Aim 2: Participants were also subject to a microdialysis test, yet will be infused with a "glucose stable isotope tracer" along with "a normal glucose solution". Participants will then be perfused with "acetylcholine into microdialysis probes" into the fat tissue.

Study Protocol (Example Timeline for One Participant)

Day -10	Day -7	Day –3 to -1	Test Day
Recruited, screened, enrolled and tested: body composition analysis	Resting Metabolic Rate, VO2 Peak	3- Day Food Log	Microdialysis, hyperinsulinemic euglycemic clamp, biopsies

Lipolysis



Clinical Implications

This research can also play an important role in the mitigation of obesity and other vascular health diseases by pinpointing areas of focus for treatments, which can decrease the burden associated with treating obesity. Further, the implications of this area of research can be used to prevent the early progression of cardiovascular diseases as well as reduce later adverse events in patients.

Discussion

Aim 1:

- This is testing to see if the Nox (protein) increases the breakdown of fat storage in the body (lipolysis).
- The "interstitial glycerol" will thus be measured to see the differences in relationships between glycerol present, Nox expression, and "lipolysis signaling molecules" of the 2 sample groups present.

Aim 2:

- This aim looks at individuals "before and after hyperinsulinemia" to see if "Nox-mediated increases in lipolysis".
- We will collect "adipose tissue biopsies" to see whether Nox increases are "associated with reduced expression of insulin signaling molecules" in the process of "glucose uptake and nitric oxide production".

- We hypothesize that overproduction of Nox-derived ROS in people with obesity impairs blood glucose profiles by reducing insulin-mediated suppression of lipolysis.

References

Cersosimo, Eugenio, and Ralph A. DeFronzo. "Insulin Resistance and Endothelial Dysfunction: The Road Map to Cardiovascular Diseases." Diabetes/Metabolism Research and Reviews, vol. 22, no. 6, 2006, pp. 423–436.

La Favor, Justin D., et al. "Microvascular Endothelial Dysfunction in Sedentary, Obese Humans Is Mediated by NADPH Oxidase." Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 36, no. 12, 2016, pp.2412-2420

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