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Study Title:	Investigation of the Effect of Branched Chain Amino Acids on Fat-Induced Insulin Resistance in Healthy Adults

Purpose:
This double-blind, randomized, crossover study aims to determine the effect of excess BCAAs in combination with excess free fatty acids on insulin sensitivity. Do excess branch chain amino acids (BCAAs) worsen free fatty acid-induced insulin resistance? Elevations in BCAAs are strongly associated with insulin resistance (IR) and type 2 diabetes, but mechanisms for this relationship are unclear.

Type 2 diabetes is preceded by insulin resistance (IR) in adipose tissue, liver, and muscle. The slow progression of IR can take many years before frank diabetes develops, so research focused on understanding the pathogenesis of IR holds great potential for developing treatments that prevent diabetes.

Following a small scale dose-confirmation study, (IR) in response to low-dose lipid infusion will be compared across simultaneous infusions of BCAAs, leucine, valine, or saline to better understand the mechanistic contribution of each BCAA to the development of (IR) in humans

Brief Description
We are now enrolling into an initial cohort of 12 completers in order to confirm intralipid rate (high-dose / low-dose). This first part of the study is expected to last 1 year and subject participation will include 4 visits in 3 months. 3 participants have completed this initial study.

We will then continue into the second part of the study where we are aiming for 30 completers. This second part of the study is expected to last 5 years and subject participation will include 5 visits in 4 months.

Participants will undergo metabolic testing (hyperinsulinemic euglycemic clamps) occurring over four separate days under 4 conditions so we may compare insulin sensitivity response to lipid infusion and so we may better understand the mechanistic contribution of each type of BCAA to the development of insulin resistance in humans:
1. leucine alone
2. valine alone
3. isoleucine, leucine and valine combination
4. control (placebo)

Participants will be instructed to follow a weight maintaining diet and avoid strenuous physical activity for 3 days prior to each clamp visit. Patients will spend the night on the inpatient research unit (CHPS) in HUP on 1 Dulles, fed a standardized meal at ~6:30 PM, and receive nothing more by mouth (except water) after 8:00 PM. Each subject will undergo the clamps a minimum of one week apart, and complete all four clamps within 4 months.

Eligibility

MAIN INCLUSION CRITERIA:
- Male or female subjects age 18 to 39 years.
- Body weight stable for past 4 months.
- Subjects who are able to provide written informed consent and to comply with the procedures of the study protocol.

MAIN EXCLUSION CRITERIA:
- History of diabetes.
- History of diabetes in parents or siblings
- Body mass index (BMI) 19 or 27kg/m2
- HbA1c >5.7%
- Blood Pressure: systolic 150 mmHg or diastolic 95 mmHg
- Estimated glomerular filtration rate 60 ml/min/1.73 m2
- Presence of soy or egg allergies (due to possible reactions with fat infusate).
- Use of tobacco within the previous year
- Baseline hemoglobin concentration 11 g/dl in women and 12 g/dl in men.
- Cardiac disease, characterized by any one of these conditions:
a.) history of myocardial infarction
b.) history of cardiac ischemia
c.) history of left ventricular ejection fraction 30%.
- Elevation of liver function tests 1.5 times normal upper limits.
- Hyperlipidemia (fasting LDL cholesterol 130 mg/dl, treated or untreated; and/or fasting triglycerides 200 mg/dl).
- Receiving treatment for a medical condition requiring chronic use of systemic steroids.
- Presence of a seizure disorder

Compensation (if applicable)
Participants will receive $50 as compensation for the screening visit and $200 as compensation for each of the overnight CHPS visits for the clamp studies. In addition, parking tickets will be validated at each visit if needed and participants will receive $100 after completion of all visits. Participants will receive a visa gift card which the study team will load in an ongoing manner after each visit has been completed.

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