Role of Stearoyl-CoA Desaturase Enzyme-1 in Nutritional Programming of Adult Obesity

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Disclosures

• Speaker: Jennifer K. Yee
• Dr. Yee has no disclosures.
Background

- Obesity is increasing in prevalence worldwide. Associated health problems include DM2, cardiovascular disease, and metabolic syndrome.

- Prenatal (intrauterine) nutritional restriction often leads to adult disease such as obesity and related problems.
  - Dutch famine studies
  - Intrauterine growth retardation rat models

- Such effects are known as nutritional programming.
Background

• Nutritional programming is believed to act through changes in metabolic adaptation, including fatty acid metabolism.
• Among fatty acid metabolic pathways, the stearoyl-CoA desaturase enzyme-1 (SCD1) pathways have generated much interest.
Background

- SCD1 is found in the liver and adipose tissue and is responsible for the synthesis of monounsaturated fatty acids.

  - **C16:0 palmitate** → **C16:1 palmitoleate**
  - **C18:0 stearate** → **C18:1 oleate**

  - **SCD1** DESATURATION

  - **Triglycerides, wax esters, phospholipids, cholesteryl esters**

  - Important for membrane fluidity and lipoprotein metabolism!

- SCD1 has been found to be upregulated in the skeletal muscle of obese humans. Hulver, Cell Metab, 2005

- The SCD1 KO mouse is resistant to diet-induced obesity Ntambi, PNAS, 2002.
Hypothesis

Nutritional programming of adult obesity and metabolic syndrome is mediated by an increase in SCD1 activity resulting in a change in the desaturation index.

Objective

To establish preliminary data on the desaturation indices of plasma fatty acids in the IUGR rat model at different ages.
Materials and Methods: The Rat Model

A well-described rat model of programmed obesity was studied.

FR mom → FR pup cross-fed to Adlib mom = FR/Adlib adult
Ad lib mom → Adlib pup fed by Adlib mom = Adlib/Adlib adult

FR/Adlib pups compared to Adlib/Adlib controls:
• FR/Adlib are smaller at birth, but obese as adults
• Hyperphagic
• Have increased total body fat
• Have increased leptin levels
FR/Adlib rats have abnormal triglyceride levels

FR/Adlib rats have abnormal metabolic profiles

* p < 0.01 compared to AdLib/AdLib

Materials and Methods: Fatty acid analysis

- Study utilized left over rat plasma samples to obtain preliminary data.
- Frozen plasma was collected and analyzed from rats at 1 day (pooled), 3 weeks, and 9 months of age from FR/Adlib offspring and from control offspring.
- Plasma was saponified, fatty acids extracted, and GC/MS analysis was performed.
SCD1 Activity: The Desaturation Index

• SCD1 activity was estimated from the desaturation index of plasma fatty acids.

• Desaturation indices were calculated as the ratio of monounsaturated fatty acid to the corresponding saturated fatty acid, determined by the calculated intensities of the gas chromatogram peaks.

\[
\text{Desaturation index} = \frac{\text{Monounsaturated fatty acid}}{\text{Saturated fatty acid}}
\]

- less SCD conversion
- more SCD conversion
Results - Gas Chromatogram

Time (minutes)

Palmitate C16:0

6.18

Palmitoleate C16:1

6.72

Oleate C18:1

9.46

Stearate C18:0

8.88

9.79

Abundance

TIC: 0203004.D
The 18:1/18:0 desaturation index is not different in 1 day old rats born to food restricted mothers

p = 0.36
The desaturation index is not different in 3 week old rats born to food restricted mothers.

\[ p = 0.50 \]
The desaturation index trended toward an increase in 9 month old rats born to food restricted mothers, $p = 0.059$. 
The desaturation index trended towards a decrease from 1 day to 9 months of age in the Adlib control group, but not in the FR group.

\[ p = 0.09 \]

\[ p = 0.31 \]
Discussions/Conclusions

• The desaturation index reflects both absorption of dietary fat and de novo fatty acid synthesis of the liver.

• In the 1 day old pups and in 3 week weaning pups, the desaturation indices of the FR/Adlib and control groups were not significantly different probably due to the effect of high fat content of the mother’s milk.

• The trend towards higher desaturation indices at 9 months of age in FR/Adlib rats is consistent with the development of obesity and increased liver SCD1 activity for de novo fatty acid synthesis.
Discussions/Conclusions

• Observations were limited by small number of animals and lack of information regarding desaturation indices of fatty acids in adipose tissue.

• Programming effects are manifested through growth and development.

• SCD1 is an inducible enzyme and its expression may be necessary for programming.
Effects of SCD1 inhibition in 3T3 cell culture

18:1/18:0 Desaturation Index

Differentiated control

Differentiated + inhibitor

p<0.001
Effects of SCD1 inhibition in 3T3 cell culture

Differentiated

Differentiated + inhibitor added

ORO staining

Cell counts

Diff control

Diff + inhibitor

Cells/mL x 10^6

p<0.001
Discussions/Conclusions

• Future studies are planned to investigate the developmental aspect of SCD1 in nutritional programming.

• SCD1 expression in liver and adipose tissues will be correlated with the desaturation indices in this IUGR rat model.
Future Plans: Translational Rat Study

• Experiment will be repeated with a larger n.
• The desaturation indices will be compared for males and females in each group, as well as for males and females together.
• Gene expression and enzyme activity of SCD1 will be determined.
• Determination of new synthesis of fatty acids as well as total fatty acids will be possible in the adult rats by giving them deuterium-enriched water.
• SCD1 inhibition on primary adipocyte cell cultures will be performed using stable isotope techniques to determine effects on the two SCD1 pathways.
• The effects on phenotype of SCD1 inhibition in early postnatal life will be compared to a known rat model of obesity prevention by maternal food restriction during the lactation period.
Future Plans: Clinical Study

Hypothesis
The plasma desaturation index will be predictive in development of adiposity from nutritional programming in young human subjects.

Objective
To compare the desaturation index in infants exposed to in utero overnutrition and undernutrition, versus normal controls, and to follow changes in the desaturation index of the cohort of children over three years of life and correlate these changes with body composition and biomarkers of metabolism.
Future Plans: Clinical Study

Human subjects:

- Study subjects will be enrolled after birth.
  - control group: normal infants (23)
  - infants born LGA or infant of GDM (23)
  - infants with asymmetric IUGR, SGA (23)
- Birth/family/medical histories, and feeding plan will be obtained.
- Anthropometrics and body composition will be measured.
- Cord blood will be studied for fatty acid levels, insulin, c-peptide, glucose, lipids, triglycerides, and adipokines (leptin, and adiponectin).
- Desaturation indices will be calculated.
Future Plans: Clinical Study

Subjects will return yearly for three years for the longitudinal study.

• Blood drawing for fatty acid levels, c-peptide, glucose, lipids, triglycerides, leptin and adiponectin will be drawn.
• Anthropometric and body composition measurements, including BIA.
• Medical history, updated family history, and social history will be obtained.
• Dietary history will be obtained including breastfeeding vs formula feeding, duration of breastfeeding, timing of introduction of solid foods, etc.
• Desaturation indices will be calculated and correlated to development of adiposity.
Power Analysis

20 subjects/group was determined based on available information on desaturation indices in the literature. 20 subjects per group are sufficient

- to detect 20% group mean differences in 18:1/18:0 ratios early in the study and
- to detect 23% differences at year three, if there is 25% loss-to-follow-up, with 15 subjects/group then.

We are adding 3 more patients in each group in order to maintain power in the event of loss to follow-up.
Statistical Analysis

- The primary outcome of desaturation indices will be measured in 3 groups at 0, 1, 2, and 3 years. (For rats, 2 groups at 3 time points.)
- Mean differences among groups will be compared at each time, and estimated linear changes per year will be compared among groups using repeated measures ANOVA, using log(ratios). Brown and Prescott, Wiley and Sons, 1999.
- Mixed model implementation of the ANOVAs to account for loss-to-follow-up for some human subjects
- Further secondary analyses: Comparison of demographic and behavioral and feeding measures among the three subject groups, and to add those found to be potential confounding factors to the primary ANOVAs.
Significance

- Metabolic programming is a lifelong process.
- This project is designed to investigate changes in the SCD1 pathways as a mechanism for development of obesity and metabolic disease in nutritional programming.
- Differentiation into an adipocyte phenotype may occur under specific environmental conditions.
- There exists the possibility that nutritional modulation may steer the path in a different direction.
- If at-risk individuals are identified after prenatal programming events, then perhaps, early postnatal nutritional manipulation can “counterprogram” the effects.
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