Translational Research Approaches to Sugar-Induced Metabolic Disease

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CAPGM Forum
February 7, 2019
Our Patient:

- 29 yo man with uncontrolled T2D, HTN, Hyperlipidemia, schizoaffective disorder who was admitted on 9/6 with paranoia, depression and suicidal ideation.

- Last few HBA1c 7.5 - 8.7
- FSBGs in the 100-300s at home
- No hypoglycemia at home

- Consulted for uncontrolled diabetes with intermittent hypoglycemia during his hospitalization
Home regimen and glycemic control prior to admission:

- Glipizide 10 QD
- Metformin 500 BID
- Dulaglutide 0.75 mg
- Lantus 40 daily, 10 Aspart TID
  ➔ A total of 70 units insulin daily

- Upon admission, home regimen continued except for dulaglutide (not on formulary)
Dietary History:

• drinking “lots” of soda and fruit drinks
• 4-5 meals/day
Hospital Course:

- Recurrent hypoglycemic episodes on home regimen
- Pt reports feeling shaky when BG low
**Intervention:**

- Glipizide discontinued
- Insulin titrated down over several days
- Final Regimen: metformin + 1-2 units of correctional Humalog only

→ Improvement in diet ("No Concentrated Sweets" Diet) during hospital stay resulted in profound reduction in insulin requirement
Proportion of All Cause Mortality Attributable to Sugar-Sweetened Beverages (SSBs)
SSB Consumption Increases Risk for Death Related to T2D, CVD, and Cancer

- Worldwide, ~184,000 excess annual deaths are attributable to SSB consumption
  
  ~178,000 from Type 2 Diabetes and Cardiovascular Disease
  
  ~6,450 from Cancers

* These may be underestimates as risks attributable to obesity per se were regressed out of this analysis.
SSBs Increase Risk of Metabolic Syndrome
Comparing Extreme Quantiles of Consumption

N = 5,803 cases
SSBs Increase Risk of T2D
Comparing Extreme Quantiles of Consumption

N = 15,043 cases

Diabetes Care (2010), 33(11):2477-83
SSBs Dose-Dependently Associate with Increased Fasting Insulin

Figure 2. Forest plot of main association between sugar-sweetened beverage intake and fasting insulin.

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<thead>
<tr>
<th>Discovery Cohorts</th>
<th>Beta [95% CI]</th>
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<tr>
<td>CHS</td>
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<td>YRS</td>
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<td>Discovery Meta-Analysis</td>
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<th>All Cohorts Meta-Analysis</th>
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Multiplicative difference in fasting insulin (mmol/l) per each additional serving/d of SSB intake

N = 34,748 adults

~ 0.5 mIU/L insulin per daily SSB

Diabetologia. 2018 Feb;61(2):317-330
SSBs Dose-Dependently Associate with Increased Triglyceride and Lower HDL-Cholesterol Levels

N = 6,382

preliminary data, Danielle Haslam / Nicola McKeown
Pertinent Epidemiological Caveats

• SSB consumption consistently associates with cardiometabolic traits
  – Other measures of dietary sugar exposure **DO NOT**
  – Fruit consumption, the major source of “natural” sugar is healthful

• SSBs often correlate with other potentially adverse dietary or lifestyle choices

• Specific mechanisms by which SSBs might cause metabolic disease remain uncertain and/or controversial
Fructose-Induced Insulin Resistance and Hypertension in Rats

I-Shun Hwang, Helen Ho, Brian B. Hoffman, and Gerald M. Reaven

Hypertension, 1987, 10(5), 512-516.
Fructose-Sweetened Beverages, but not Glucose-Sweetened Beverages Promote Metabolic Syndrome in Overweight / Obese Humans

- **Fructose**, but not **Glucose**. Overfeeding Increased Serum Triglycerides

- **Fructose**, but not **Gluco**se. Overfeeding Increased Visceral Adiposity

- **Fructose**, but not **Gluco**se. Overfeeding Decreased Insulin Sensitivity

Stanhope KL, JCI, 2009
Queries:

1. Can detailed knowledge of the biology of fructose metabolism help us understand the pathogenesis of insulin resistance, T2DM, and cardiometabolic disease?

2. Can it help us resolve outstanding questions and controversies related to the public health effects of sugar consumption?

3. Can it move us towards a science of personalized nutrition with respect to sugar consumption?
Fructose (12 g)

Fructose ~ 1 mM

KHK

Fructose ~ 0.1 mM

Lactate, Glucose, Lipid, CO2, ...

Loss of KHK Results in Benign Essential Frucotsuria (in humans and mice)

Ishimoto T, et al. PNAS. 2012
Fructose

Ketohexokinase

Glut2/5/8

ATP

ADP

AMP

Adenosine Deaminase

Fructose-1-p

Hexose/Triose-P

G6P

Malonyl-CoA

Uric Acid / Energetic Stress

1

Substrate Utilization

2

Glucose Production

Lipogenesis / Steatosis

3

Activation of Signaling Systems
ChREBP (aka Mlxipl)  
**Carbohydrate Responsive-Element Binding Protein**

- Carbohydrate sensing function conserved throughout eukaryotes
- Expressed in liver, kidney, small intestine, and adipose tissue.
- **Common Variants** in the ChREBP locus associate with hypertriglyceridemia and low HDL cholesterol in human populations.
Global ChREBP Knockout (ChKO) Mice Are Fructose Intolerant

the \( ChREBP^{-/-} \) mice (Fig. 3). \( ChREBP^{-/-} \) mice fed a high-fructose diet became moribund in a few days.

Glucose-activated ChREBP-α transactivates expression of the potent ChREBP-β isoform
De novo lipogenesis in human fat and liver is linked to ChREBP-β and metabolic health

Leah Eissing1,*, Thomas Scherer2,*,†, Klaus Tödter1, Uwe Knippschild3, Jan Willem Greve4, Wim A. Buurman5, Hans O. Pinnschmidt6, Sander S. Rensen5, Anna M. Wolf3, Alexander Bartelt1, Joerg Heeren1, Christoph Buettner2 & Ludger Scheja1
Fructose, but not Glucose Gavage Acutely Increases Expression of Hepatic ChREBP-β and its Targets

* Wild-type mice gavaged with water vs glucose vs fructose (4 g/kg BW) and euthanized 100 minutes later

ChREBP is Necessary for Hepatic Fructose-Induced Gene Expression
ChREBP is Necessary for Hepatic Fructose-Induced Gene Expression

The “Pathogenic Paradox” of Hepatic Insulin Resistance

Healthy Liver

Insulin

AKT

Srebplc

Fatty Acid Synthase

Acetyl-CoA Carboxylase

Lipogenesis

Foxo1

PEPCK Glucose-6-Phosphatase

Glucose Production

Glucose-6-Phosphatase
The “Pathogenic Paradox” of Hepatic Insulin Resistance

“Insulin Resistance”

Insulin

AKT

Srebp1c

Acetyl-CoA Carboxylase
Fatty Acid Synthase

Lipogenesis

Foxo1

PEPCK
Glucose-6-Phosphatase

Glucose Production

?
ChREBP Mediates Hepatic G6P Homeostasis

- Glucose
- G6Pase
- G-6-P
- Glycogen
- Pyruvate Kinase
- Pyruvate
- ACC, FAS
- Fatty Acid Synthesis
- Lactate
- Fructose
- KHK

ChREBP

ChREBP Upregulates G6Pc Independently of Hepatic Insulin Signaling

![Graphs showing mRNA levels for different conditions](image)

The “Pathogenic Paradox” of Hepatic Insulin Resistance

“Insulin Resistance”

- Insulin
  - AKT
    - Srebplc
      - Lipogenesis
        - Fructose
      - Acetyl-CoA Carboxylase
        - Fatty Acid Synthase
    - ChREBP
        - Glucose-6-Phosphatase
        - Glucose Production
Conclusions 1

• Fructose consumption activates hepatic ChREBP which regulates hepatic metabolic gene expression programs.

• ChREBP stimulates Glucose-6-phosphatase expression to drive glucose production and this is dominant over insulin’s ability to suppress it.
GWAS Provides Insight into the Genetic Architecture of T2D and Metabolic Traits

• 76+ T2D genetic loci increasing risk
• T2D is ~ 30-40% heritable, but aggregated loci only account for 5-10% of heritability

Diabetes Genetics Replication and Meta-analyses Consortium (DIAGRAM), Nat Genetics 2014
Lessons from GWAS about the Architecture of Complex Disease

• ~ 90% of Common Genetic Variants Associated with Complex Disease Reside in Non-coding, Regulatory Elements.

• The Causal Gene(s) Regulated by the Majority of Trait- and Disease-Associated SNPs are Uncertain

• Missing Heritability
  – Many distinct uncommon variants of large effect?
  – Epigenetic heritability?
  – Is heritability overestimated?
  – Gene x Environment (Diet) interactions?
Can Interactions Between Diet and Genes Account for Missing Heritability?
Rationale and Clinical Relevance

1. No Clear Consensus Among Physicians or Public Health Advocates as to the “Best” Diet for Obesity, Diabetes, or other Metabolic Conditions

2. Precision Medicine Initiative scope:

- Individual variability in genetic, biomarkers, phenotypic and lifestyle characteristics
Different People Have Distinct Glycemic Responses to Different Foods
Towards a Science of Personalized Nutrition?
Elements Important for a Science of Personalized Nutrition

• Accurate means to assess diet / nutrient intake.

• Good measures of meta-phenotypes relating short-term affects of nutrients to disease progression.
  – Surrogate markers indicative of biological response to specific nutrients.
  – Simple means to test dynamic responses to specific nutrients.

• Detailed knowledge of biological pathways likely to mediate interactions between diet and genes on phenotype
Query:

Can knowledge of a fructose-ChREBP axis be used to interrogate the biological response to fructose consumption in people?
ChREBP-Mlx Is the Principal Mediator of Glucose-induced Gene Expression in the Liver

Received for publication, February 17, 2006, and in revised form, July 3, 2006. Published, JBC Papers in Press, August 2, 2006. DOI 10.1074/jbc.M601576200

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From the Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, Minnesota 55455

![Cellular diagram showing induced and repressed genes by glucose and dnMlx](image)

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Increased Fibroblast Growth Factor 21 in Obesity and Nonalcoholic Fatty Liver Disease

JODY DUSHAY,* PATRICIA C. CHUI,* GOSALA S. GOPALAKRISHNAN,* MARTA VARELA-REY,† MEGHAN CRAWLEY,* FFOLLIOTT M. FISHER,* MICHAEL K. BADMAN,* MARIA L. MARTINEZ-CHANTAR,‡ and ELEFThERIA MARATOS-FLIER*

*Beth Israel Deaconess Medical Center, Boston, Massachusetts; and †CIC bioGUNE, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberedh), Technology Park of Bizkaia, Bizkaia, Spain


Serum FGF21 Levels Are Increased in Obesity and Are Independently Associated With the Metabolic Syndrome in Humans

Xinmei Zhang,1,2 Dennis C.Y. Yeung,1,2 Michal Karpisek,3 David Stejskal,4 Zhi-Guang Zhou,8 Feng Liu,5,6 Rachel L.C. Wong,1,2 Wing-Sun Chow,1,2 Annette W.K. Tso,1,2 Karen S.L. Lam,1,2 and Aimin Xu1,2,7

Study Population

• Healthy volunteers, male and female
• No diabetes, no thyroid disease
• BMI 21-27.9
• Age 24-47

* Collaboration with E. Maratos-Flier and Jody Dushay
**Protocol**

- 16h overnight fast

- 75g oral glucose (oGTT) and a 75g oral fructose tolerance test (oFTT) in each individual

- Blood collected for glucose, insulin, TG, and FGF21 levels
Fructose Ingestion Acutely and Robustly Increases Circulating FGF21 in Lean, Healthy Humans
FGF21 Response to Oral Fructose in Healthy vs MetSynd Subjects

![Graph showing FGF21 response to oral fructose in healthy vs MetSynd subjects.](image)

* * *
Conclusions 2

- FGF21 is a ChREBP transcriptional target and is upregulated by fructose consumption.

- Circulating FGF21 is acutely and robustly regulated in human subjects by fructose or a combination of glucose and fructose ingestion.

- Fructose-stimulated FGF21 is enhanced in subjects with the metabolic syndrome.

- Fructose-stimulated FGF21 is the only known biomarker for an individual’s acute metabolic response to fructose ingestion.
Query:

Does FGF21 participate in the biological response to fructose / sugar ingestion?
SNPs in the FGF21 Locus Associate with Carbohydrate vs Fat Preferences in Human Populations
FGF21 Regulates Sugar Preferences in Genetic Mouse Models

Query:

Do genetic variants in ChREBP or its targets interact with sugar-sweetened beverage consumption to impact cardiometabolic risk factors in human populations?

Collaboration with:
• Danielle Haslam (USDA Jean Mayer Center for Nutrition and Aging)
• Nicola McKeown PhD (USDA Jean Mayer Center for Nutrition and Aging)
• Joseé Dupuis, PhD (Boston University)
• The Charge Consortium
*Adjusted for age, sex, energy intake, cohort, smoking, education, physical activity, BMI, alcohol intake, % energy from saturated fat, and servings of food groups (fruit, vegetables, whole grains, fish, nuts/seeds).

~ 11 mg/dl

Preliminary data
Mean difference in ln(TG) when T allele is replaced with G allele at rs35797675 stratified by category of sugar-sweetened beverage intake (SSB)

\[ \text{Mean Difference ln(TG)} \]

\[ \begin{array}{cc}
<1 \text{ serving} & >5 \text{ servings} \\
\text{SSB/mo} & \text{SSB/wk} \\
\end{array} \]

\[ p=0.0001 \quad p=0.002 \]

\[ p_{\text{interaction}} = 0.88 \]

\[ \sim 12 \text{ mg/dl} \]
Increase in In-transformed fasting triglycerides when C allele is replaced with a T allele at rs113727690 stratified by category of sugar-sweetened beverage intake (SSB).

~ 19 mg/dl

p=0.003  p=0.74
p_{interaction} = 0.04

preliminary data
Conclusions 3

• SSBs dose-dependently associate with increased triglyceride levels

• Multiple independent variants in the ChREBP locus associate with hypertriglyceridermia

• The variants in the ChREBP locus that associate with hypertriglyceridermia in the population as a whole appear to be distinct from the variants that may interact with SSBs in this locus to effect hypertriglyceridermia
Acknowledgements

Herman Lab
Inna Astapova
Misung Kim
Sarah Krawczyk
Ludivine Doridot
Sarah Hannou
Ashot Sargsyan
Alan Fowler
Greg McElroy
John Riley

DMPI Proteomics/Metabolomics
Tabitha George
Guo-Fang Zhang
Olga Ilkayeva
Paul Grimsrud

Newgard Lab
Phillip White
Rob McGarrah
Jie An
Jonathan Haldeman
Amanda Lapworth
Michelle Arlotto

UTSW
Guosheng Liang
Jay Horton
David Chuang
Max Wynn

BIDMC
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Jason Kim
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Josee Dupuis
Gina Peloso
Hassan Dashti
Caren Smith

Charge Consortium

American Heart Association®
life is why™

NIH NIDDK

Duquesne University School of Medicine
American Diabetes Association®