Metabolic Hormone FGF21: From Physiology to Pharmacology

Mangelsdorf/Kliwer Lab
University of Texas Southwestern Medical Center
**FGF21 Introduction**

- Functions as a hormone
- Crosses the blood-brain barrier
- Acts on cell surface receptor complex
- Induced in liver by fasting to regulate starvation response:
  - induces hepatic fatty acid oxidation and ketogenesis
  - inhibits growth
  - inhibits female reproduction
FGF21’s Pharmacologic Actions

- Pharmacologic administration of FGF21 to obese rodents, monkeys and humans
  - causes weight loss
  - improves insulin sensitivity
  - lowers triglyceride levels

Where is FGF21 acting?
**FGF21 Receptor**

- FGF21 acts through FGFRs 1, 2 or 3 in complex with βKlotho
- FGFRs 1-3 and βKlotho are co-expressed in adipose tissue and brain

*Where is FGF21 acting?*
The Case for Adipose Tissue

- FGF21 stimulates glucose uptake and thermogenesis in BAT (Hondares et al. *Cell Metab* 2010; Ding et al. *Cell Metab* 2012)
- FGF21 promotes browning of WAT (Fisher et al. *Genes Dev* 2012)
- FGF21 induces secretion of adiponectin from WAT, and the metabolic effects of FGF21 are blunted in adiponectin-KO mice (Holland et al. *Cell Metab* 2013; Lin et al. *Cell Metab* 2013)

Does FGF21 act through adipose tissue?
Adipose-Specific βKlotho-KO Mice

Xunshan Ding
Tian Lan

Klb
LoxP
LoxP
Adipoq-Cre

Klb(Adipoq)-KO
adipocyte-specific

Acute effects on glucose uptake?

Klb mRNA

<table>
<thead>
<tr>
<th>Tissue</th>
<th>fl/fl</th>
<th>Klb(Adipoq)-KO</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>eWAT</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>scWAT</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Liver</td>
<td>1.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Statistical significance

Xunshan Ding
Tian Lan

Klb
Exon 1
Adipoq-Cre

Klb(Adipoq)-KO
adipocyte-specific

Acute effects on glucose uptake?
FGF21 Acts Directly on Adipose Tissue

Euglycemic-hyperinsulinemic clamp, 1.5 hrs FGF21 DIO mice

Increased glucose uptake into BAT

Longer term effects?
**FGF21 Effects Are Adipose Independent**

DIO, 2 wk FGF21 via minipump

**Body weight**

<table>
<thead>
<tr>
<th></th>
<th>veh</th>
<th>F21</th>
<th>veh</th>
<th>F21</th>
</tr>
</thead>
<tbody>
<tr>
<td>fl/fl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klb(Adipoq) KO</td>
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**Insulin**

<table>
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<tr>
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**Hepatic Trigs**

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<td>*</td>
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</table>

Where is FGF21 acting?
βKlotho Selectively Expressed in Brain

In situ hybridization

Hypothalamus

Hindbrain

These regions regulate metabolism

FGFR1 expressed in SCN, AP and NTS

Does FGF21 act through CNS?
CNS-Specific βKlotho-KO Mice

Klb

Exon 1

Camk2a-Cre

Klb(Camk2a)-KO
CNS-specific

Klb mRNA

Relative levels

fl/fl
Klb(Camk2a)

Hypothalamus
Hindbrain

0
0.5
1.0
1.5

*
FGF21 Causes Weight Loss Via CNS

DIO mice
2 wk FGF21 via minipump

Bryn Owen
FGF21 Lowers Insulin Via CNS

**Insulin**

- veh fl/fl: 4 ng/ml
- F21 fl/fl: 6 ng/ml
- veh Klb(Camk2a) KO: 4 ng/ml
- F21 Klb(Camk2a) KO: 5 ng/ml

**Glucose**

- veh fl/fl: 100 mg/dl
- F21 fl/fl: 120 mg/dl
- veh Klb(Camk2a) KO: 100 mg/dl
- F21 Klb(Camk2a) KO: 120 mg/dl

**Mechanism?**

No changes in food intake or activity
FGF21 Increases Energy Expenditure

- FGF21 activates BAT (Hondares et al. *Cell Metab* 2010)
- FGF21 causes browning of WAT (Fisher et al. *Genes Dev* 2012)

Requires $\beta$Klotho in CNS?
FGF21 Induces UCP1 Via CNS

**Ucp1 in BAT**

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<tbody>
<tr>
<td>veh</td>
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<td></td>
</tr>
<tr>
<td>F21</td>
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</table>

C_t~17

**Ucp1 in scWAT**

<table>
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<tr>
<th></th>
<th>fl/fl</th>
<th>Klb(Camk2a) KO</th>
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<tbody>
<tr>
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<tr>
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* C_t~24

Similar data for Dio2 and Elovl3
FGF21 Acts Centrally to Increase Energy Expenditure

Sympathetic nervous system?
Sympathetic Nerve Recording
Kamal Rahmouni, U Iowa

Filtering and Amplification

Quantification
FGF21 Induces Sympathetic Activity

Nerve activity in iBAT

Percent change in SNA

Time (h)

Vehicle
FGF21 (iv)
FGF21 (iv) + PD173074 (icv)
FGF21 Induces Sympathetic Activity

Nerve activity in iBAT

Mechanism for increased sympathetic activity?

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Percent change in SNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

- fl/fl + FGF21 (iv)
- Klb(Camk2a)-KO + FGF21 (iv)
FGF21 Induces Corticotropin-Releasing Factor

FGF21

↑CRF

HPA axis

SNA to BAT

CORT release from adrenals

thermogenesis and weight loss

Arase/Stock, Am. J. Physiol., 1987; LeFeuvre/Bray, Neuropharmacology, 1988
FGF21 Activates HPA Axis

Is CRF required for FGF21’s effects on BAT?
FGF21 Acts Via CRF

Nerve activity in iBAT
FGF21 (i.v.) ± CRFR antagonist (i.c.v.)
FGF21 Regulates the Fuel and Fire

- FGF21
- CNS
  - ↑CRF
- BAT
  - ↑glucose uptake
  - ↑SNA
- thermogenesis
- weight loss
  - insulin sensitivity
FGF21 Linked to Nutrient Preference in Humans

Novel locus including **FGF21** is associated with dietary macronutrient intake

Audrey Y. Chu¹, Tsegasellassie Workalemahu²,⁶, Nina P. Paynter¹, Lynda M. Rose¹, Franco Giulianini¹, Toshiko Tanaka⁷ and Julius S. Ngwa⁸ on behalf of the CHARGE Nutrition Working Group, Qibin Qi²,⁶, Gary C. Curhan², Eric B. Rimm²,⁶, David J. Hunter²,⁶, Louis R. Pasquale³,⁹, Paul M. Ridker¹,⁴, Frank B. Hu²,⁶, Daniel I. Chasman¹,⁵,† and Lu Qi²,⁶,*,† on behalf of the DietGen Consortium

- **Synonymous SNP in the first exon of the FGF21 gene**
- **Associated with increased carbohydrate intake, decreased fat and protein intake**

Does FGF21 affect nutrient preference in mice?
FGF21 Reduces Sweet Preference

Bryn Owen
Yuan Zhang

How?
**FGF21 Suppresses Neurotransmitters**

Nucleus accumbens = reward center

![Brain diagram with an arrow pointing to the nucleus accumbens]

Does FGF21 affect other reward behaviors?

**Dopamine**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>ng/mg protein</td>
<td>*</td>
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**Serotonin**

<table>
<thead>
<tr>
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Genaro Hernandez
Parkyong Song
FGF21 Reduces Alcohol Consumption

Will this translate to humans?
Can FGF21 be used to treat addiction?
Pharmaceutical Opportunities?

FGF21

- Weight loss
- Insulin sensitivity
- Lipids

OBESITY

TYPE 2 DIABETES

Alcohol/sweet preference

ADDICTION
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