“Sweet Taste Receptors Modulate Glucose Absorption”

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Taste Receptors are nutrient chemosensors beyond the tongue.
Nutrient sensing

Uptake and Metabolism

Receptor-mediated signaling
Sweet Taste Receptor sensing:
Same machinery, different context

mouth cavity

intestinal lumen

blood

STRs regulate plasma glucose homeostasis in response to “oral” glucose delivery

** intra-gastric glucose tolerance test (IG.GTT) **

Glucose (1.0g/kg)

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Smith et al, Mol Metab. 2018
Peripheral glucose disposal

Glucose malabsorption

Glucose transit

Gut microflora

Gut metabolites

Kyriazis GA et al. Endocrinology 2014
T1R2 intestines have reduced rate of 3-OMG flux

3-OMG (10 or 30mM)  

14C 3-O-methylglucose

mucosa → serosa

human intestinal explants

Smith et al, Mol Metab. 2018
The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans

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1Phase I Research Unit, Department of Biomedicine, and 2Division of Gastroenterology, University Hospital Basel, Basel, Switzerland
Submitted 17 February 2011; accepted in final form 1 May 2011

Inhibition of sweet chemosensory receptors alters insulin responses during glucose ingestion in healthy adults: a randomized crossover interventional study1,2

Eliaz Karimian Azar,5,6 Kathleen R Smith,5,6 Fanhuo Yi,5 Timothy F Osborne,5 Roberto Rizzotto,5 Andrea Marti,5 Richard E Pratley,5,6 and George A Kyrlikis5,6
5Center for Metabolic Origins of Disease, Sanford Burnham Prebys Medical Discovery Institute, Orlando, FL; 6Translational Research Institute for Metabolism and Diabes, Florida Hospital, Orlando, FL; and 5Institute of Neuroscience, National Research Council, Padova, Italy
Glucose transport in the small intestine

(G. Kellett, E. Brot-Laroche, Diabetes, 2005)
T1R2 mice have reduced rate of GLUT2 translocation in response to an ig glucose load

**Pearson's Correlation Coefficient**

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>T1R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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Smith et al, Mol Metab. 2018
Intestinal perfusion with sucralose potentiates GLUT2 translocation in rats.
Potential mechanisms for the reduced rate of GLUT2 translocation in T1R2 intestines

GLP1
Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1

GLP2
Rapid insertion of GLUT2 into the rat jejunal brush-border membrane promoted by glucagon-like peptide 2
Anita Ali, Alina GUPTA, Paul SCHEMBRI and Chris. J. CHEESEMAN
Membrane Protein Research Group, Department of Physiology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, T6G 2H7, Canada


GLUT2
Enteroendocrine

SGLT1

Lumen

Enterocyte

GLUT2

Blood vessels

insulin

Insulin Internalizes GLUT2 in the Enteroocytes of Healthy but Not Insulin-Resistant Mice
Vanessa Toubin,1,5,6,7 Marie Le Gall,5,6,7,8 Lester Florencio,1 Jérôme Stohrer1,3,5,6,7 Emmanuela Sebrenzke,1,3,5,6,7 Alba G. Bitarre,1,2,3 Christophe Klein,31,2,3 Magali Prigent,3 Patricia Serrada,1,3,6,7 Marie-Béatrice Cuff,3 Christophe Magnan,3 Arielle Leturque1,3,6,7,8 and Edith Broitman1,3,6,7,8

DIABETES, VOL. 57, MARCH 2008

insulin glucocorticoids

Stress and glucocorticoid inhibit apical GLUT2-trafficking and intestinal glucose absorption in rat small intestine
Emma J. Shepherd, Philip A. Hellwell, Oliver J. Mace, Emma L. Morgan, Nick Patel and George L. Kellett
Department of Biology (Arne), University of York, YO10 5YW, UK

Mechanism for the reduced rate of GLUT2 translocation in T1R2 intestine

**Insulin (µg/L)**
- WT
- T1R2

**Plasma GLP-1 (pM)**
- WT
- T1R2

**Corticostrone (ng/mL)**
- WT
- T1R2

**Acetaminophen (µg/mL)**
- WT
- T1R2

**Ex vivo Glucose flux**
- WT
- T1R2

**HPV plasma GLP-2 (pg/mL)**
- Vehicle
- Glucose

Smith et al, Mol Metab. 2018 unpublished
The GLP2 analogue, teduglutide, restores plasma glucose response during an igGTT in T1R2 mice

**IG.GTT**

![IG.GTT Diagram](image)

**3-OMG (+/- Ted)**

![3-OMG Diagram](image)

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Smith et al, Mol Metab. 2018
Current working model

Pathways:
- GLP-1
- GLP-2
- Insulin

Low glucose → T1R2 → SGLT1 → GLUT2 → Blood → GLP-1 → insuline
High glucose → T1R3 → SGLT1 → GLUT2 → Blood → GLP-1 → insuline

Smith et al, Mol Metab. 2018
Is T1R2-mediated nutrient chemosensing relevant to the development of metabolic disease?
Functional adaptations of intestinal STRs in response to dietary sugars

Kyriazis GA et al, Endocrinology 2014
Overnight high sucrose diet (HSD) downregulates intestinal STR expression

High Sucrose Diet (60%)→16-hours→mRNA→STRs→Intestine

Ad lib glucose (7d HSD)

ig.GTT ($^{13}$C glucose)

GLP-1

Ad lib glucose (mg/dL)
GLUT2 Accumulation in Enterocyte Apical and Intracellular Membranes
A Study in Morbidly Obese Human Subjects and ob/ob and High Fat–Fed Mice

Amal Ait-Omar,1 Milena Monteiro-Sepulveda,1 Christine Poitou,2,3 Maude Le Gall,1
Aurélie Cotillard,2 Jules Gilet,1 Kevin Garbin,1 Anne Houllier,1 Danièle Château,1 Amélie Lacombe,4
Nicolas Veyrie,2,5 Danielle Hugol,6 Joan Tordjman,2 Christophe Magnan,4 Patricia Serradas,1
Karine Clément,2,3 Armelle Leturque,1 and Edith Brot-Laroche1

unpublished
Deletion of T1R2 decreases glucose excursions during an IG.GTT in Ob/Ob mice

[Graphs showing glucose levels and flux with annotations and significance levels indicated.]
Unanswered questions

Which type of cell(s) express STR? 
Where are they located?  
What are their characteristics? 
How they regulate gut biology?
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