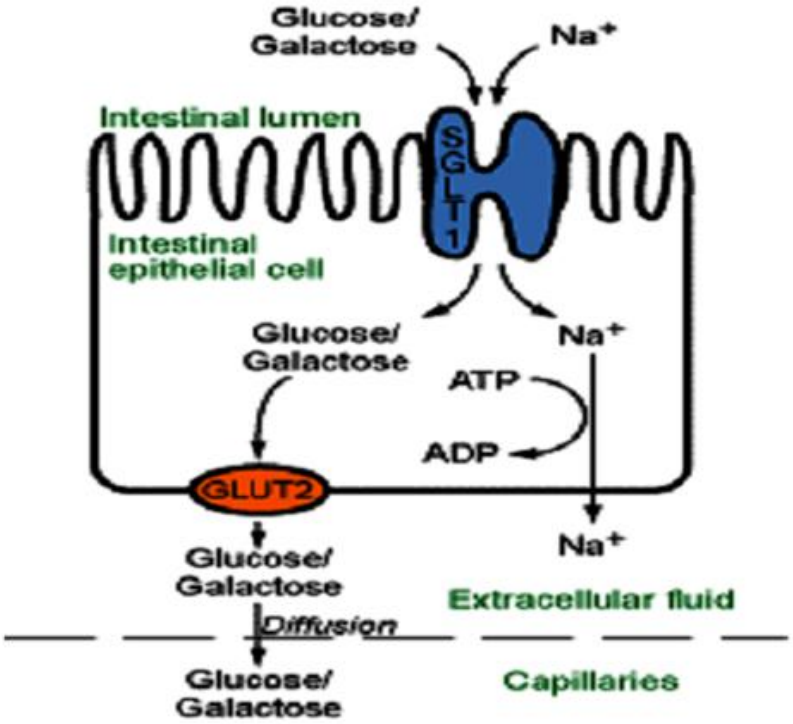
读书报告

郑文佳

2016年10月29日



Sglt1-Glut2 介导的葡萄糖/半乳糖转运示意图

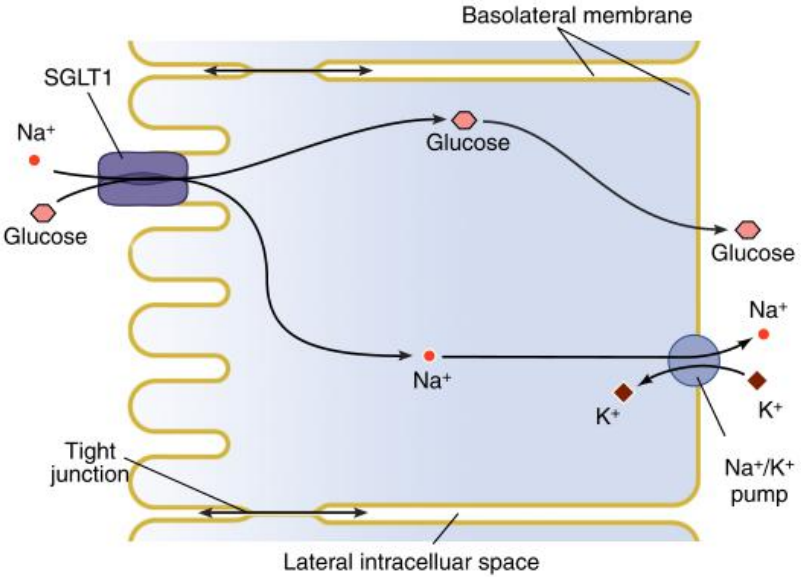
1958年，Riklis研究发现猪肠道葡萄糖吸收依赖于钠离子，Crane据此提出了经典的**葡萄糖跨膜假说**。

American Physiological Society
Physiological Reviews®

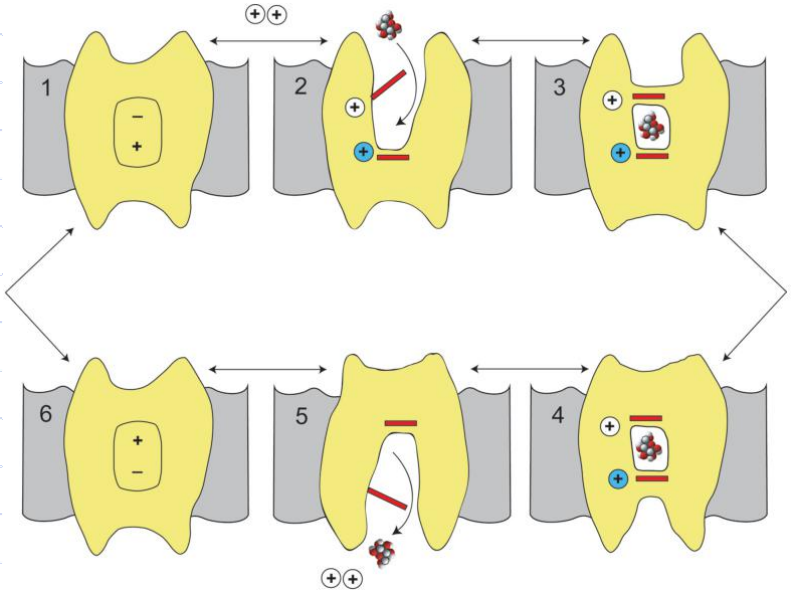
Biology of Human Sodium Glucose Transporters

Ernest M. Wright, Donald D. F. Loo, Bruce A. Hirayama

Physiological Reviews Published 1 April 2011 Vol. 91 no. 2, 733-794 DOI: 10.1152/physrev.00055.2009

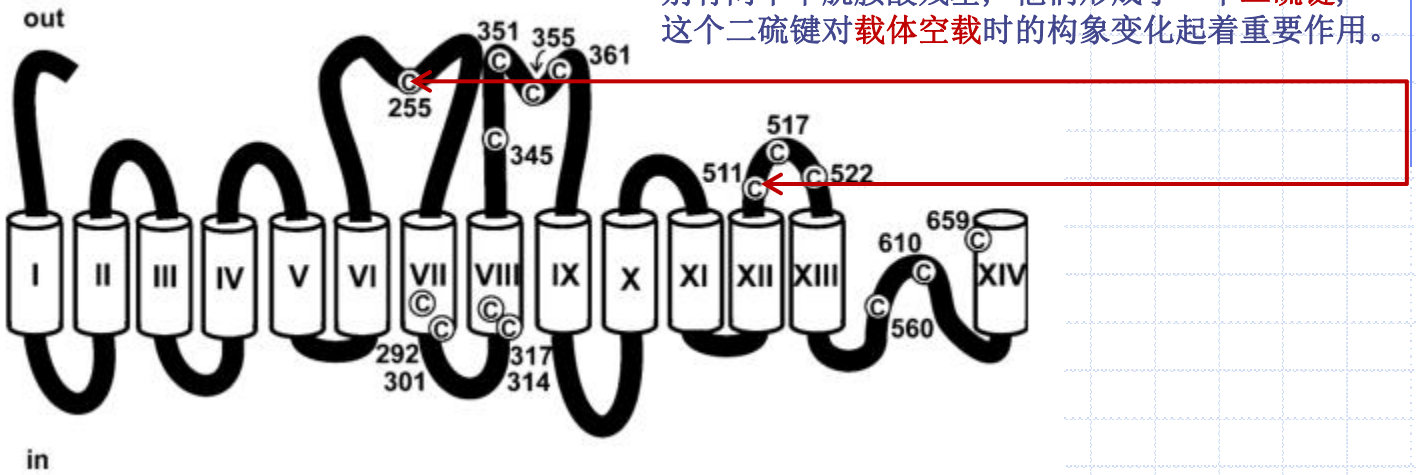


肠道葡萄糖转运模型



Sglt1与配体结合的动态模型

在TMS4(Cys255)和TMS7(Cys511)间的外部环中分别有两个半胱胺酸残基，他们形成了一个二硫键，这个二硫键对载体空载时的构象变化起着重要作用。



SGLT1 是分子量约为75 kDa的膜蛋白，其二级结构由14个跨膜的α螺旋（transmembrane segments, TMS1-TMS14）组成．N末端位于TMS1的细胞外，C末端位于TMS14的胞质边缘，靠近C末端有5个连续的跨膜　螺旋，是葡萄糖结合与转运的结构域（称为C5结构域）．

- 饲料成分
- 转录因子
- 生理节律
- 个体发育

SGLT1

表达

活性

附表　葡萄糖转运蛋白在体内的分布

Table 1 *SLC5* genes responsible for Na/glucose cotransport

Transporter	Substrate	$K_{0.5}$ mM	Distribution
SGLT1 (SLC5A1)	Glucose, galactose	0.5	Intestine, trachea, kidney, heart, brain, testis and prostate
SGLT2 (SLC5A2)	Glucose	2	Kidney, brain, liver, thyroid, muscle and heart
	Galactose	Not transported	
SGLT4 (SLC5A9)	Glucose and mannose	2.4	Intestine, kidney liver, brain, lung, trachea, uterus and pancreas
SGLT5 (SLC5A10)	Not known	Not known	Kidney
SGLT6 (SMIT2,SLC5A11)	Myo-Inositol, glucose	0.12	Brain, kidney, intestine
		35	
SMIT1 (SLC5A3)	Myo-inositol, glucose	0.055	Brain, heart, kidney and lung
		>30	

Substrate specificity, affinity ($K_{0.5}$ for αMDG) and RNA expression of *SGLT* (SLC5) genes. Substrate specificity and αMDG transport were measured by using heterologous expression systems [29, 53–55 and M. Coady pers. comm.]. RNA distribution is based on RNase protection assays (M. Bing, M.G. Martin and E.M. Wright, unpubl. data) and Northern blots (SMIT1 and SMIT2) [2].

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组织　　运输

SCIENTIFIC REPORTS

OPEN

SGLT1 activity in lung alveolar cells of diabetic rats modulates airway surface liquid glucose concentration and bacterial proliferation

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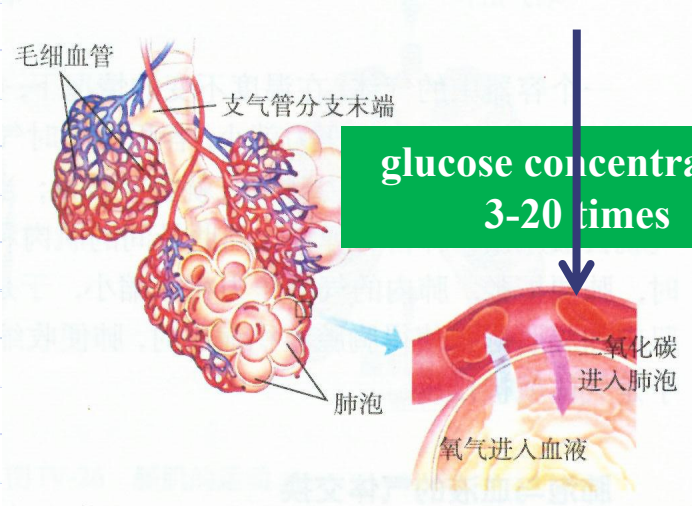
Tales Lyra Oliveira[1,2], Návylla Candeia-Medeiros[1], Polliane M. Cavalcante-Araújo[1], Igor Santana Melo[1], Elaine Fávaro-Pípi[3], Luciana Alves Fátima[4], Antônio Augusto Rocha[2], Luiz Ricardo Goulart[5,6], Ubiratan Fabres Machado[4], Ruy R. Campos[2] & Robinson Sabino-Silva[7]

interstitium

细胞旁路途径

ASL
glucose uptake



glucose concentration
3-20 times

GLUT2

proximal airways

SGLT1

distal lung

肾脏

JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Molecular Analysis of the *SGLT2* Gene in Patients with Renal Glucosuria

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American Diabetes Association. diabetes

Diabetes. 2013 Oct; 62(10): 3324–3328.
Published online 2013 Sep 17. doi: 10.2337/db13-0604
PMCID: PMC3781482

Novel Hypothesis to Explain Why SGLT2 Inhibitors Inhibit Only 30–50% of Filtered Glucose Load in Humans

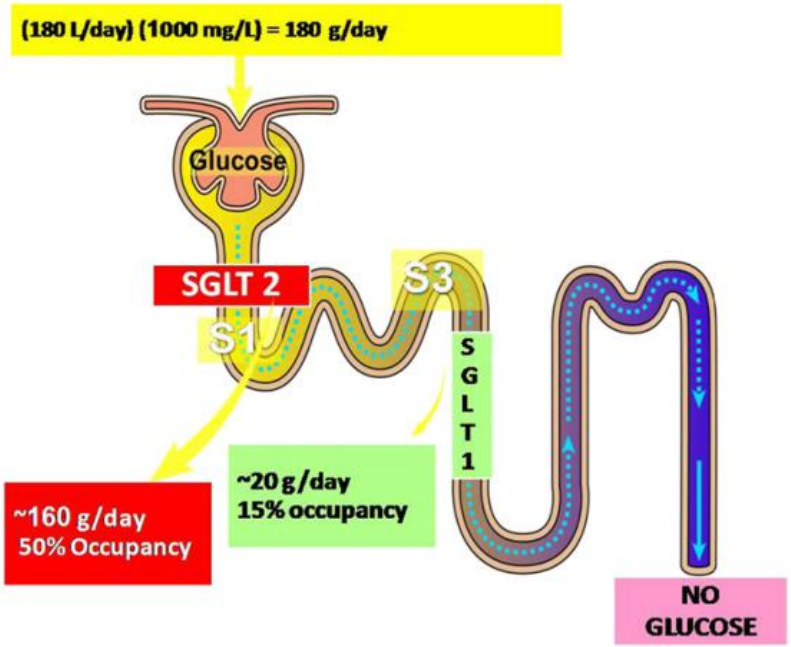


FIG. 1. Renal glucose reabsorption in the proximal tubule in NGT individuals under physiologic conditions.

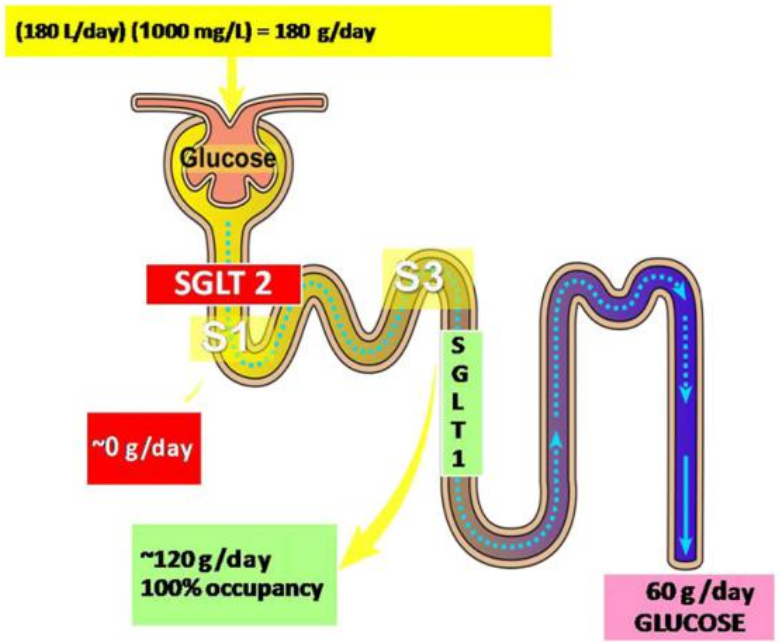


FIG. 3. Renal glucose reabsorption in the proximal tubule in NGT individuals under complete SGLT2 inhibition.

肠促胰素

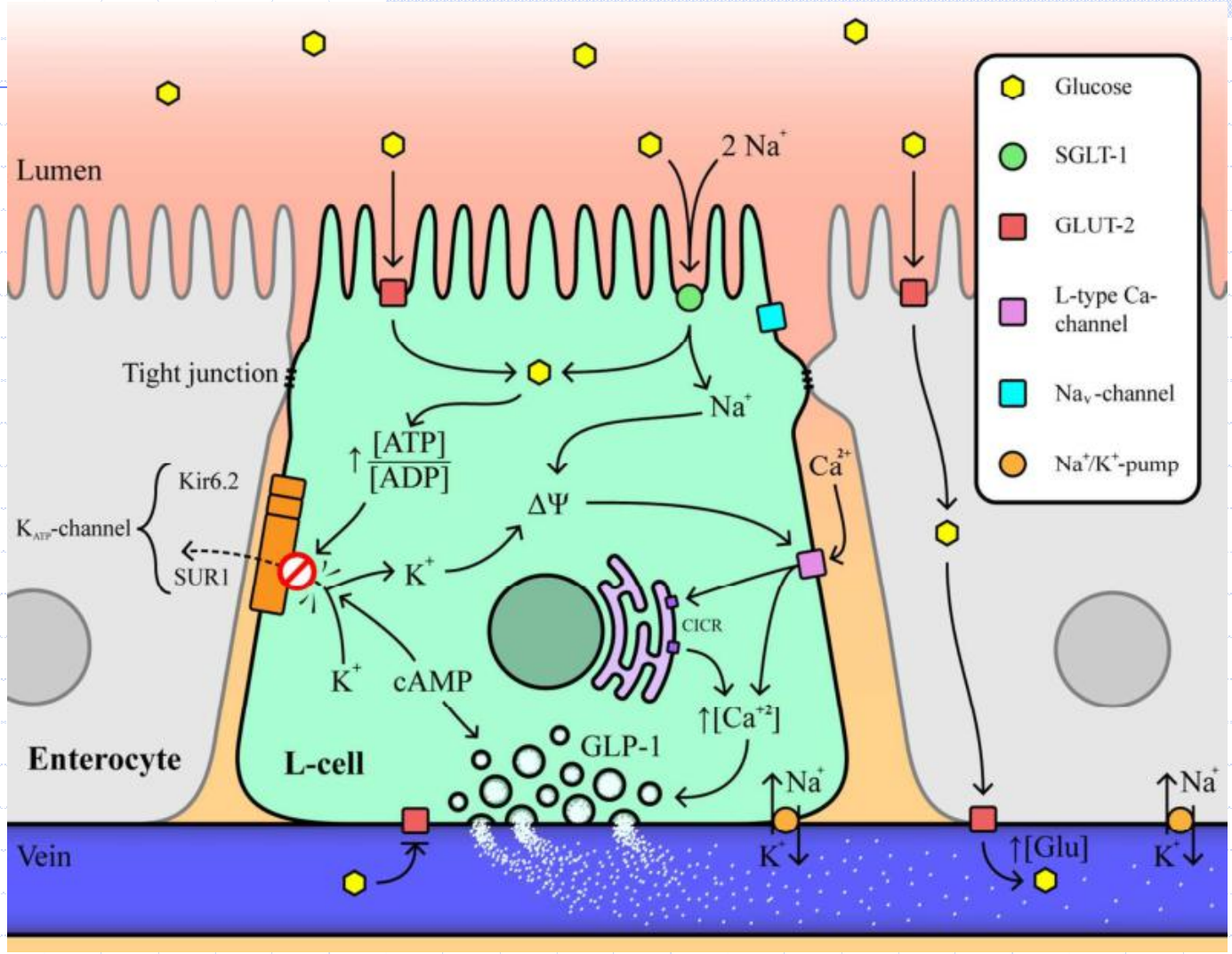
胰高血糖素样肽-1（glucagon-like peptide 1，GLP-1）是由肠道内分泌L细胞合成、分泌的一种肠促胰岛素，以葡萄糖依赖性方式促进胰岛β细胞分泌胰岛素，并减少胰岛α细胞分泌胰高血糖素。

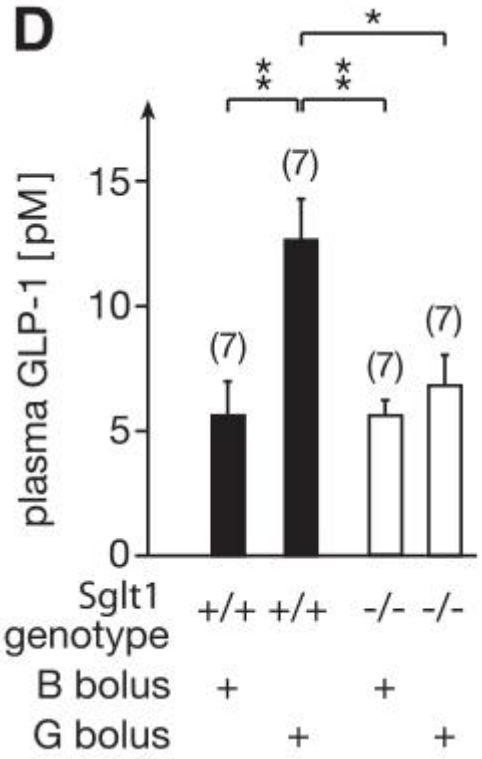
葡萄糖是促进GLP-1分泌的重要因素之一，目前认为由葡萄糖介导的GLP-1分泌主要有3条途径：

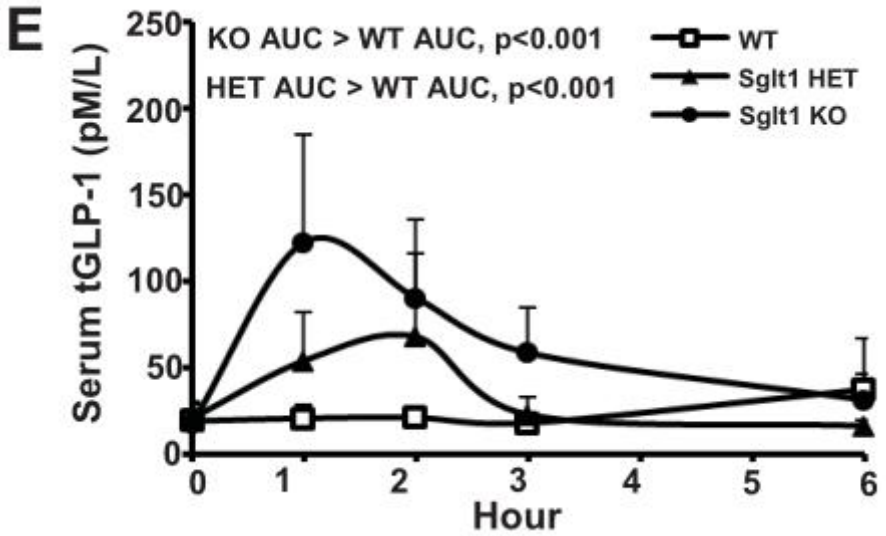
（1）胰岛中β细胞的葡萄糖应答与ATP敏感型K离子（K_{ATP}）通道关闭有关；

（2）味觉受体通路，实验发现分泌GLP-1的肠道内细胞同样表达甜味受体；

（3）由SGLT1介导来实现。


Lumen
2 Na+
Glucose
SGLT-1
GLUT-2
L-type Ca-channel
Nav-channel
Na+/K+-pump
Tight junction
Na+
[ATP]/[ADP]
Ca2+
ΔΨ
Kir6.2
KATP-channel
SUR1
K+
CICR
K+
cAMP
↑[Ca+2]
GLP-1
Enterocyte
L-cell
Na+
Na+
Vein
K+
↑[Glu]
K+





Gorboulev V *et al.*, *Diabetes*; 2012

aps American Physiological Society
AMERICAN JOURNAL of PHYSIOLOGY
Endocrinology and Metabolism

Improved glycemic control in mice lacking Sglt1 and Sglt2

David R. Powell, Christopher M. DaCosta, Jason Gay, Zhi-Ming Ding, Melinda Smith, Jennifer Greer, Deon Doree

葡萄糖介导GLP-1分泌有早晚两时相性：

5-10 min：SGLT1-KO 小鼠GLP-1分泌水平是下降的，这一短时间的分泌过程需要通过SGLT1介导；

几小时：SGLT1-KO 小鼠GLP-1分泌水平升高，其分泌不依赖于SGLT1对葡萄糖的转运，而由其他传导信号通路的激活来介导.

AMERICAN JOURNAL of PHYSIOLOGY
Gastrointestinal and Liver Physiology
American Physiological Society

Search

对于T2DM患者，GLP-1作用未受影响，主要是分泌受损，外源性输入 GLP-1能显著增加胰岛素分泌、降低血糖.

糖尿病患者和糖尿病鼠的肠道上皮细胞中SGLT1表达增多，但是SGLT1上调后糖尿病患者GLP-1分泌却没有增加.

J Clin Invest. 1994 Feb; 93(2): 578–585.
doi: 10.1172/JCI117010
PMCID: PMC293881

Small intestine hexose transport in experimental diabetes. Increased transporter mRNA and protein expression in enterocytes.

味觉受体

目前已经确定的哺乳动物的味觉受体基因家族有两个：

1.味觉受体第一家族（taste receptorfamily 1 members，T1Rs）

T1R1　　T1R2　　T1R3

甜味受体

（以异源二聚体的形式发挥作用）

2.味觉受体第二家族taste receptor family 2 members，T2Rs）

研究表明，动物肠道的粘膜上存在着表达味觉受体和味觉相关因子的细胞，调控着肠道激素如GLP-1和GIP的分泌以及糖转运体SGLT1和GLUT2的表达。

甜味剂 → 激素分泌
载体表达 → 葡萄糖
吸收和利用

肠道味觉的研究有助于揭示肠道消化吸收功能的调控机理， 同时为糖尿病、肥胖、代谢失调及其它饮食相关疾病的治疗提供新的切入点。

British Journal of Nutrition

THE NUTRITION SOCIETY
Advancing Nutritional Science

Article

葡萄糖和人工甜味剂等可以增加SGLT1表达水平和肠道葡萄糖吸收，提示甜味受体的激活可以上调SGLT1。

Access Cit

British Journal of Nutrition, Volume 104, Issue 5
September 2010, pp. 647-655

Expression of Na^+/glucose co-transporter 1 (SGLT1) in the intestine of piglets weaned to different concentrations of dietary carbohydrate

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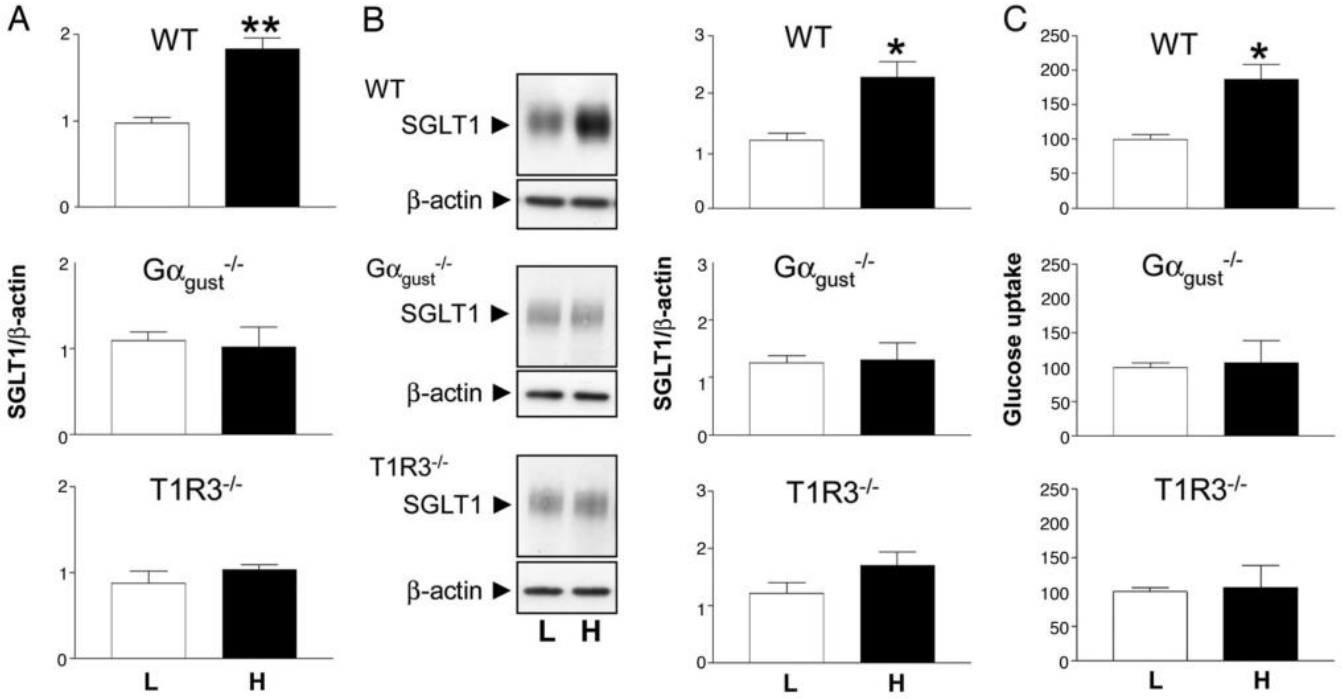
PNAS
Proceedings of the National Academy of Sciences of the United States of America

T1R3 and gustducin in gut sense sugars to regulate expression of Na^+-glucose cotransporter 1



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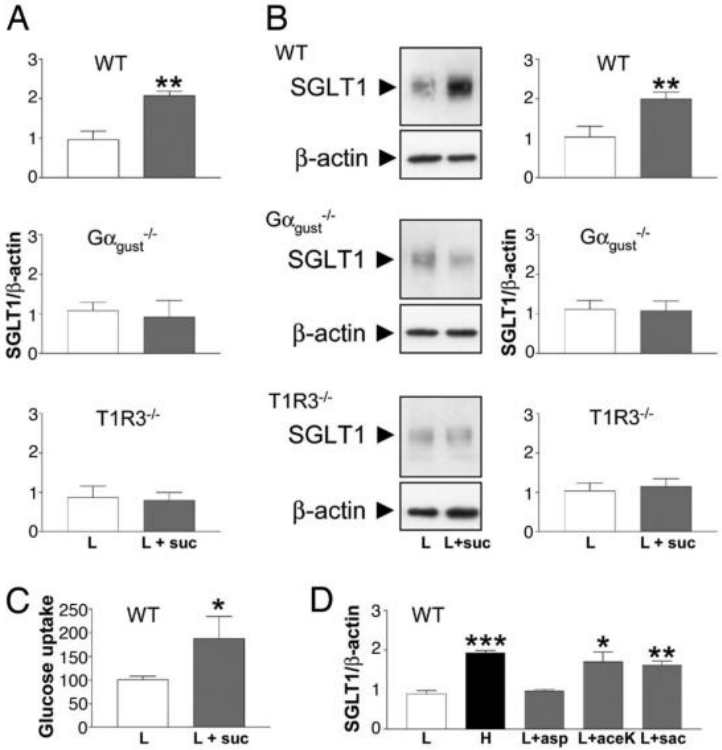
PNAS
Proceedings of the National Academy of Sciences of the United States of America

T1R3 and gustducin in gut sense sugars to regulate expression of Na^+-glucose cotransporter 1



α -gustducin或者TIR3基因缺失的小鼠甜味受体信号转导障碍，观察不到高糖饮食导致的SGLT1表达水平提高。

实验同时观察到不管高糖还是低糖饮食, 基因敲除的小鼠的SGLT1表达水平和低糖饮食的野生型小鼠相同。

表明体内基础水平SGLT1的表达不依赖于葡萄糖激活肠道中甜味受体或者α-gustducin, 甜味受体的激活后上调SGLT1的表达需要依赖肠道中的甜味受体转导通路.

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AMERICAN JOURNAL of PHYSIOLOGY
Regulatory, Integrative and Comparative Physiology

Expression of sweet receptor components in equine small intestine: relevance to intestinal glucose transport

The Journal of Physiology
A Publication of The Physiological Society

Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2

用甜味剂刺激肠道甜味受体细胞：

引起$[Ca^{2+}]_i$的增加；
增加GLP-1、GIP、SGLT1、GLUT2及其它肠道激素的释放。

进而影响胰岛素的分泌来调节血糖浓度、营养素的吸收及其它肠道功能。

用甜味剂刺激野生型小鼠肠道内分泌细胞：

介导糖类物质吸收的SGLT1和GLUT2的表达量都随着的甜味剂含量增加而显著提高。

高糖膳食下，$G_{\alpha\text{-gust}}$ 和T1R3 遗传缺失型小鼠的SGLT1 表达水平与低糖膳食无异，都与低糖膳食下野生型小鼠SGLT1的表达水平相当。$G_{\alpha\text{-gust}}$ 缺失型小鼠GLP-1和胰岛素的分泌量明显减少，影响机体血糖浓度

感悟

组织

影响因素

THANKS