深圳大学总医院
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The “Sodium-glucose co-transporter 1 （SGLT1） Bridge” As An Indication For “Surgical Diabetes”

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2023

Background

- **Bottleneck constraints：Indications to diabetic surgery**
- **The therapeutic mechanisms on diabetes after Metabolic & Bariatric Surgery(MBS) are not fully understood**

✓ The entero-insular axis (EIA) theory is questioned (including our previous studies)

✓ The theory of gut - brain - liver axis (GLBA) remains controversial.

✓ ***SGLT1 plays an important role in the therapeutic mechanisms on diabetes after MBS***

- Glucose absorption mainly depends on SGLT-1, and SGLT-1 is highly expressed in diabetic patients
- The effect of glucagon-like peptode-1(GLP-1) on glucose metabolism cannot well played in the absence of SGLT1
- MBS regulates the gluconeogenesis pathway that might be mediated by SGLT1

Bottleneck Constraints: Indications to diabetic surgery

- More than 16 prediction models, up to 2021.
- DiaRem and ABCD: the two most widely validated models to predict diabetes remission following bariatric surgery.

- The most externally validated models were ABCD and DiaRem. Although the ABCD and DiaRem models were primarily developed for predicting diabetes remission at 1-year follow-up, they have been validated in studies **predicting long-term** diabetes remission.

Table 1—Model development studies with their predictors

Prediction model	Predictors included	Discrimination (AUC) in model development studies	Discrimination (AUC) in external validation studies
ABCD; Lee et al. (16), 2013	Age, BMI, C-peptide, and diabetes duration	0.792 (0.728–0.856)*	Fig. 2*A*, *C*, and *E*
DiaRem; Still et al. (17), 2014	Age, HbA_{1c}, diabetes medication other than metformin, and insulin use	0.840 (0.795–0.886)*	Fig. 2*B*, *D*, and *F*
Robert et al. (31), 2013	BMI, diabetes duration, HbA_{1c}, fasting glucose, and diabetes medication	0.950 (0.838–0.992)	Shen et al.: 0.681 ± 0.056
DRS; Ugale et al. (33), 2014	Age, baseline BMI, diabetes duration, microvascular complications, macrovascular complication, insulin use, and stimulated C-peptides	NA	Ahuja et al.: 0.732 (0.633–0.83)*
Ad-DiaRem; Aron-Wisnewsky et al. (34), 2017	Age, HbA_{1c}, insulin use, diabetes medication other than metformin, number of glucose-lowering agents, and diabetes duration	0.911	Shen et al. 0.849 ± 0.039, Dicker et al. 0.85 (0.76–0.93), Kam et al. at 1 year 0.752 (0.688–0.808), Kam et al. at 3 years 0.794 (0.715–0.860), Sy-DR 84%
DiaBetter; Pucci et al. (35), 2017	HbA_{1c}, diabetes duration, and kind of diabetes medication	0.867 (0.817–0.916)	Shen et al. 0.826 ± 0.041, Kam et al. at 1 year 0.760 (0.697–0.815), Kam et al. at 3 years 0.804 (0.726–0.868),
IMS; Aminian et al. (18), 2017	Number of diabetes medication, insulin use, diabetes duration, and HbA_{1c}	NA	Shen et al. 0.849 ± 0.040, Park et al. 0.76 (0.685–0.836),* Chen et al. 0.766 (0.716–0.817)* in GB, Chen et al. 0.599 (0.501–0.697)* in SG, Umemura et al. 0.516 (0.330–0.702)*
DiaRem2; Still et al. (36), 2018	Age, HbA_{1c}, diabetes medication other than metformin and insulin use, diabetes duration	0.876	NA
Sy-DR (37), 2018	Preoperative factors: diabetes duration, no. of medications, HbA_{1c} Postoperative factors: no. of medications, fasting CBG, weight loss, 1-year remission	90%	NA
MDR (38), 2020	Age, HOMA2-B, diabetes duration, and HbA_{1c}	0.79 (0.71–0.88)	NA
Umemura et al. (39), 2020	Insulin, diabetes duration	0.865 (0.775–0.954)*	NA
Hayes et al. (40), 2011	Insulin use and HbA_{1c}	NA	0.632 ± 0.059
Dixon et al. (13), 2013	BMI, diabetes duration, C-peptide	0.90 (0.84–0.95)	0.800 ± 0.047
Ramos-Levi et al. (41), 2014	Model 1, age, sex, FG, diabetes duration, insulin Model 2: age, sex, FG, diabetes duration, insulin, C-peptide Model 3: age, sex, FG, diabetes duration, insulin, % wt loss Model 4: age, sex, FG, diabetes duration, insulin, % wt loss, C-peptide	0.838 (0.725–0.951) 0.923 (0.852–0.996) 0.923 (0.851–0.996) 0.981 (0.951–1.000)	0.811 ± 0.047
Cotillard et al. (42), 2015	Age, sex, BMI, fasting glycemia, HbA_{1c}, hypertension, diabetes duration, insulin therapy, number of antidiabetes drugs, C-peptide	NA	NA
Stallard et al. (43), 2016	Diabetes duration, FPG, use of noninsulin antidiabetes medications, and use of insulin	0.860 (0.763–0.957)	NA

CBG, capillary blood glucose; FG, fasting glucose; FPG, fasting plasma glucose; GB, gastric bypass; HOMA2-B, HOMA2 of β-cell function; NA, not available; SG, sleeve gastrectomy; wt, weight. *Calculated by authors of this systematic review.

Diabetes Care. 2021 44(11):2626-41.

Prediction models in diabetic surgery

Table 2—Study characteristics of model development studies

Publication reference	Source of data	Participant characteristics: Groups and numbers	Age (years)	BMI (kg/m²)	Diabetes duration (years)	HbA_{1c} (%)	Outcomes	Types of surgery	Presentation	Validation: V Dev	Ext V
ABCD; Lee et al. (16), 2013	Retrospective, Taiwan, multicenter, 2005–2010	*N* = 63; 17 M, 56 F					*n* = 48 (76%), FU = 1 year	RYGB	Scoring system	Y	Y
		R	36.5 ± 10.7	40.9 ± 8.9	2.1 ± 3.7	8.2 ± 1.8					
		NR	44.5 ± 7.7	33.3 ± 7.4	4.1 ± 4.5	8.5 ± 1.8					
DiaRem; Still et al. (17), 2014	Retrospective, U.S., multicenter, 1 January 2004–February 2011	*N* = 690; 184 M, 506 F					*n* = 463 (67%), FU = 14 months	RYGB	Scoring system	Y	Y
		NI (*n* = 438)	48.8 ± 10.3	49.5 ± 8.0	6.8 ± 1.2	NA					
		I (*n* = 252)	53.6 ± 8.9	49.2 ± 8.8	8.2 ± 1.7	NA					
Robert et al. (31), 2013	Retrospective, observation, France, 2007–2010	*N* = 46; M:F = 1:3	45.3 ± 1.6	49.5 ± 1.22	3 (IQR 2.0–6.42)	7.44 ± 0.24	DR = 62.8% at 1 year of FU	RYGB (26), GB (11), SG (9)	Scoring system	N	Y
DRS; Ugale et al. (33), 2014	Retrospective, India, single, 1 February 2008–March 2010	*N* = 75; 49 M, 26 F					*n* = 42 (56%), FU = 1–2.5 years	SG	Scoring system	N	Y
		IISG	51.7 ± 13.3	23.4 ± 4.5	9.9 ± 4.8	8.1 ± 0.59					
		IIDSG	57.6 ± 11.5	25.6 ± 4.5	10.1 ± 5	9 ± 0.78					
Ad-DiaRem; Aron-Wisnewsky et al. (34), 2017	Retrospective, France, 1999–2014	*N* = 213; M 30%					*n* = 97 (45.5%), FU = 1 year	RYGB	Scoring system	Y	Y
		R	46 ± 10	48.1 ± 7.4	3.5 ± 3.8	7.0 ± 1.1					
		NR	53 ± 9	45.4 ± 7	11.1 ± 7.6	8.4 ± 1.6					
DiaBetter; Pucci et al. (35), 2017	Retrospective, U.K., single, 1 January 2008–December 2015	*N* = 210					*n* = 144 (68.6%), FU = 2 years	RYGB, SG	Scoring system	Y	Y
		RYGB (107)	51.6 ± 8	43.1 ± 6.3	5.6 ± 5.1	4.7 ± 5.4					
		SG (103)	49.7 ± 8.8	48.2 ± 7.8	7.8 ± 1.5	7.3 ± 1.4					
IMS; Aminian et al. (18), 2017	Retrospective, U.S., single, 2004–2011	*N* = 659; F = 451 (68%)	51 ± 10	46.4 ± 9.0	6 (3–11)	7.4 (6.4–8.6)	*n* = 291 (44.2%), FU = 5 years	RYGB, SG	Scoring system	N	Y
DiaRem2; Still et al. (36), 2018	Retrospective, U.S., single, 2009–2015	*N* = 307; F = 69%	51.2 ± 10.1	49.2 ± 10.3	6	NA	*n* = 135 (44.0%), FU = 1 year	RYGB	Scoring system	N	N

Continued on p. 2631

Table 2—Continued

Publication reference	Source of data	Participant characteristics: Groups and numbers	Age (years)	BMI (kg/m²)	Diabetes duration (years)	HbA_{1c} (%)	Outcomes	Types of surgery	Presentation	Validation: V Dev	Ext V
5y-DR (37), 2018	Retrospective, France	*N* = 175; F = 136 (77.71%)	48.3 ± 10.3	47.37 ± 7.43	6.75 ± 6.53	7.5 ± 1.6	66 (37.7) at 1 year, 94 (53.7) at 5 years, FU = 5.1 ± 0.7 years	RYGB	Scoring system	Y	N
MDR; Moh et al. (38), 2020	Retrospective, Singapore, 2007–2018	*N* = 114	46 ± 9	40.1 ± 6.6	6 (2–10)	8.8 ± 1.9	54 (47.4%), FU = 1 year	RYGB, SG	Scoring system	N	N
Umemura et al. (39), 2020	Retrospective, Japan, single, 2008–2018	*N* = 49; F = 22 (44.9%)	46.2 ± 12.6	42.5 ± 6.4	5.6 ± 5.7	8.0 ± 1.9	*n* = 38 (77.6%), FU = 1 year	SG	Scoring system	N	N
Hayes et al. (40), 2011	New Zealand, single, 1 November 1997–May 2007	*N* = 127; 45 M, 82 F	48.5 ± 10.1	46.8 ± 9.4	4.5 ± 5	7.7 ± 1.7	*n* = 107 (84.3%), FU = 1 year	RYGB	Logistic regression	Y	Y
Dixon et al. (13), 2013	Retrospective, Taiwan, single	*N* = 154; 49 M	39.5 ± 10.7	37.2 ± 8.8	2 (0.5–5.0)	9.1 ± 1.7	*n* = 107 (69.5%), FU = 1 year	RYGB	Logistic regression	N	Y
Ramos-Levi et al. (41), 2014	Retrospective, Spain, single, 2006–2011	*N* = 141; 30 M, 81 F	53	43.7 ± 5.6	5 (2.0–10.0)	7.3 (6.5–8.4)	*n* = 74 (52.5%), FU = 1 year	RYGB, SG, DS	Logistic regression	N	Y
Cotillard et al. (42), 2015	France, single	*N* = 84; 15 M, 45 F					*n* = 50 (59.5%), FU = 1 year	RYGB	Logistic regression	N	N
		DR (*n* = 50)	46.96 ± 9.14	46.93 ± 5.82	3.86 ± 4.64	7.01 ± 1.03					
		DNR (*n* = 34)	54.47 ± 11.02	46.1 ± 6.62	14.21 ± 7.63	8.21 ± 1.32					
Stallard et al. (43), 2016	Retrospective, Canada, single, 1 January 2011–June 2014	*N* = 98; 22 M, 76 F	49.7 ± 8.5	49.7 (48.1–51.1)	6.7 ± 6.6	7.6 (7.3–7.9)	*n* = 52 of 77 (67.5%), FU = 1 year	RYGB, SG	Logistic regression	N	N

Data are mean ± SD or median (interquartile range) unless otherwise indicated. *N* = total number of participants. *n* = number of participants achieving diabetes remission. DS, duodenal switch; Ext V, external validation; F, female; FU, follow-up; GB, gastric band; I, insulin; IIDSG, ileal interposition with diverted sleeve gastrectomy; M, male; NI, noninsulin; NR, nonremitters; R, remitters; single, single center; V Dev, validated in internal/external cohort in model development stage; Y, yes.

Diabetes Care. 2021 44(11):2626-41.

Prediction models: DiaRem & ABCD

- **DiaRem (Diabetes Remission Clinical Score):**
- Age,
- HbA1c,
- diabetes medication other than metformin,
- and insulin use.

- **“ABCD” score system:**
- Age（A），
- BMI(B)，
- C-peptide（C），
- Duration of diabetes（D）.

Prediction of remission

Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score

Variable	0	1	2	3
Age	>40	<40		
BMI	<27	27-34.9	35-41.9	>42
C-peptide (mmol/L)	<2	2-2.9	3-4.9	>5
Duration of DM (years)	>8	4-8	1-3.9	<1

Different procedure has different strength

ABCD score	HbA1c<6% (complete) (%)	HbA1c<6.5%(partial) (%)
0	5.9	5.9
1	5.0	20.0
2	26.3	38.6
3	31.9	42.0
4	52.5	67.8
5	55.4	75.0
6	61.7	78.3
7	77.0	92.3
8	85.2	96.3
9	87.1	87.1
10	93.3	93.3
Overall	52.2	64.7

J Biomed Res. 2015 Apr;29 (2):98-104

- **Lee WJ，Taiwan：Prediction of remission**
- **“ABCD” score system：**
- The higher the score, the more diabetic remissions.

Exceptional cases:
- extremely low scores combined with diabetic CRs.
- extremely high scores with no antidiabetic effects.

Obes Surg. 2016 26(10):2418-24.

Obes Surg, 2015, 25(10): 1772-1778.

“Surgical Diabetes” need to be redefined

Indication to diabetic surgery:

Besides the clinic indexes that in “ABCD” & DiaRem system

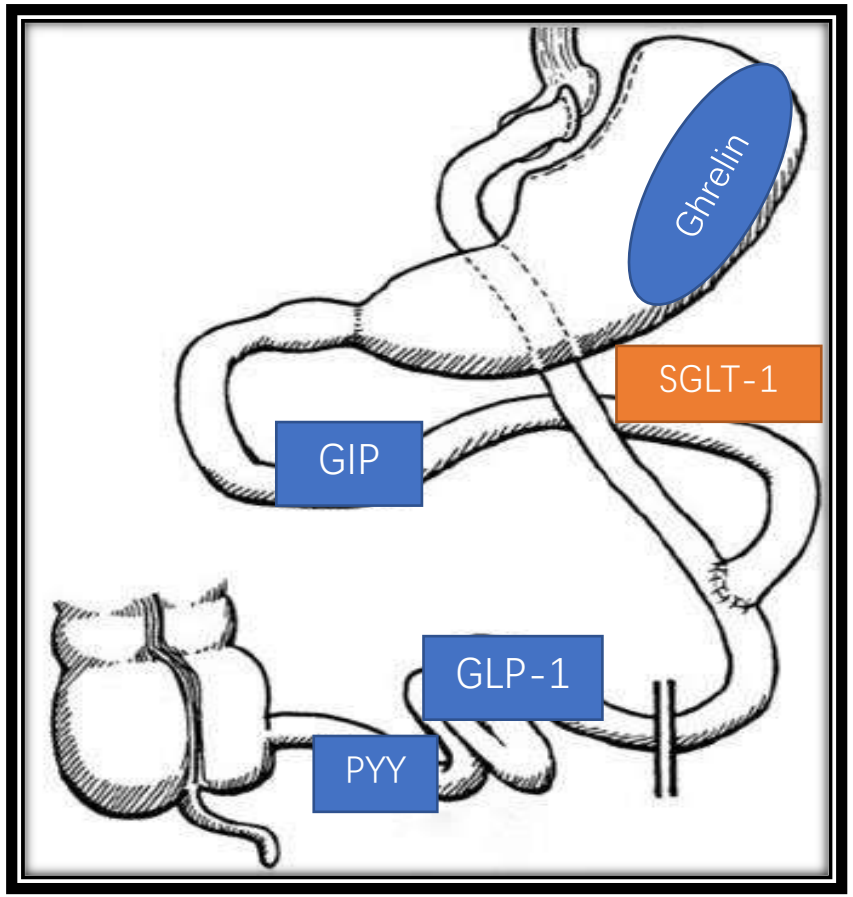
——There shoule be other variables that could influence diabetic remission rate.

“Surgical Diabetes” needs to be redefined.

"Surgical Diabetes" lacks ideal screening indicators,

which is likely due to the inconclusive therapeutic mechanism of diabetic surgery.

Therapeutic Mechanism for Diabetes after RYGB



Volume Restriction & Malabsorption

Foregut , Midgut, Hindgut, Gastric Hypothesis

The entero-insular axis (EIA) theory

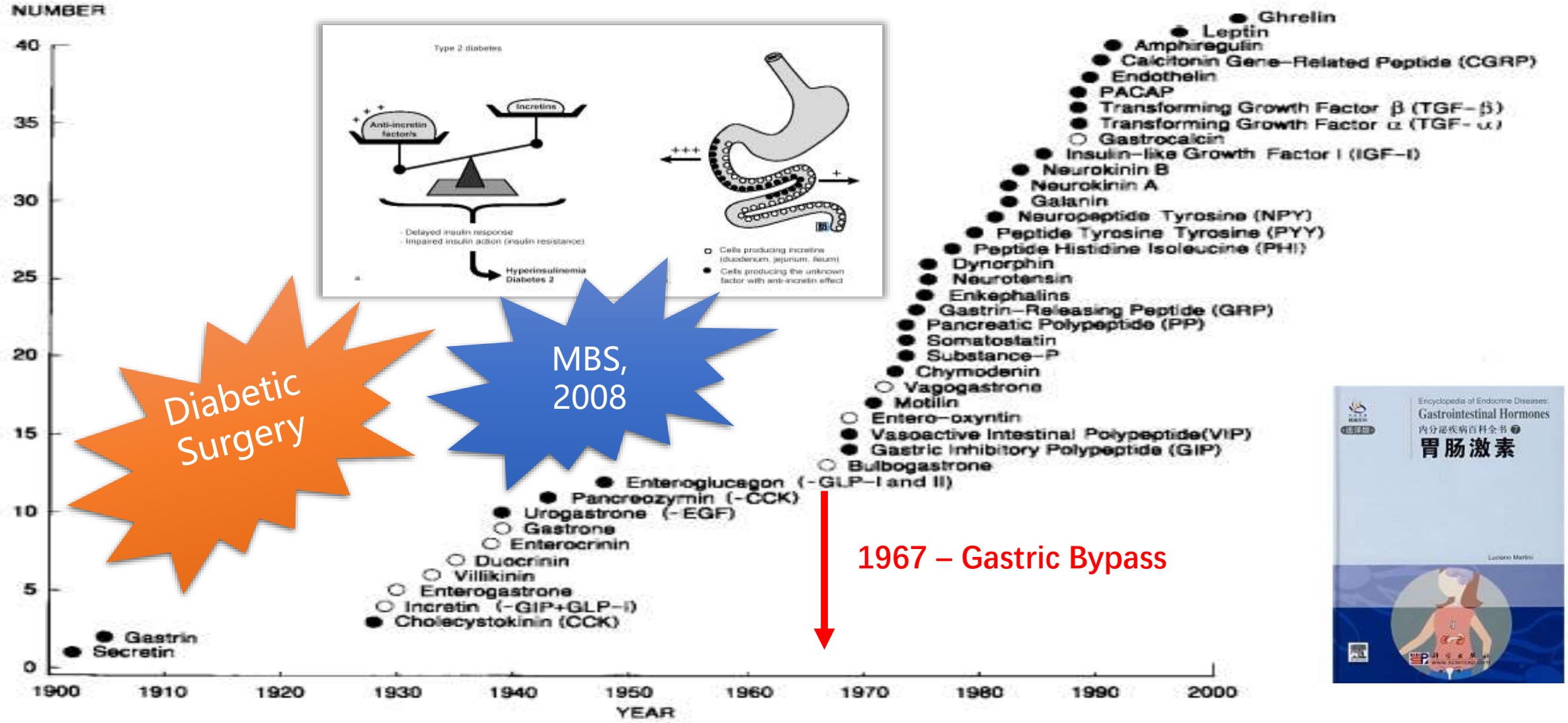
"incretin": Ghrelin, GIP, SGLT-1, GLP-1, PYY, et al.

The gut - brain - liver axis (GBLA) theory

Intestinal gluconeogenesis (GNG)-brain- liver GNG

Diabetes Care, 2008. 31 Suppl 2: p. S290-6.

The entero-insular axis (EIA) Theory: GI Hormones



Rubino F., Diabetes Care, 2008. 31 Suppl 2: p. S290-6.

Our cognition：incretin to SGLT1

2011

DPP-4 抑制剂及其与 2 型糖尿病的内外科治疗

手术治疗都存在无效病例。因此可大胆从 T2DM 的发病机制设想，是否存在一种 T2DM 的亚型，该亚型以肠促胰岛素分泌或活性障碍为发病机制；属此亚型者可用 DPP-4 抑制剂控制或手术治疗，而不属此亚型者，不适用 DPP-4 抑制剂或手术治疗。此外，对糖尿病外科手术治疗的适应证至今还没

2012

2 型糖尿病外科治疗临床路径

2.1.1.1 纳入标准：①年龄 18～65 岁，确诊为 T2DM，最好有近期口服糖耐量试验（OGTT）结果支持。②糖尿病病程10年以内为佳，最好是5年以内；必须将这点告知病史超过10年的患者。③空腹C肽大于 1 ng/mL（333 pmol/L），最好大于 2 ng/mL（666 pmol/L）。④有较明确的肠促胰岛素异常，最好有资料显示患者近期（2～4周）使用二肽基肽酶 4（dipeptidyl-peptidase 4，DPP-4）抑制剂或胰高血糖素样肽（glucagon like peptide 1，GLP-1）类似物或GLP-1受体激动剂明显有效。⑤伴有明

2016

·青年专家论坛·

胃肠道钠－葡萄糖共转运体 1 可能介导代谢减重手术改善血糖

SGLT1 Bridge Hypothesis

2018

Gastroenterol Rep . 2018. 6(4): 291-7.

ORIGINAL ARTICLE

Ileal transposition rapidly improves glucose tolerance and gradually improves insulin resistance in non-obese type 2 diabetic rats

Hengliang Zhu[1,2], Huaiming Wang[3], Zhihai Zheng[4], Bailiang Ye[4], Xiaojiao Ruan[4], Xiaofeng Zheng[4] and Guoxin Li[1,*]

[1]Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, [2]Department of Gastrointestinal Surgery, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China, [3]Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China and [4]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

2020

·青年专家论坛·

胆汁酸途径可能介导胃旁路术改善糖代谢

Journal of Chinese obesity and metabolic disease，2020

2022

Original Article

Sodium-glucose co-transporter 1 (SGLT1) differentially regulates gluconeogenesis and GLP-1 receptor (GLP-1R) expression in different diabetic rats: a preliminary validation of the hypothesis of "SGLT1 bridge" as an indication for "surgical diabetes"

Hengliang Zhu[1,2^], Huajie Cai[3], Xiaokun Wang[4], Tao Chen[1], Chaohui Zhen[2], Zhenzhan Zhang[1], Xiaojiao Ruan[3], Guoxin Li[1]

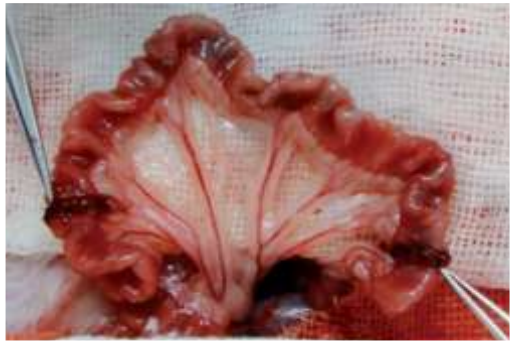
Ann Transl Med, 2022;10(8):481.

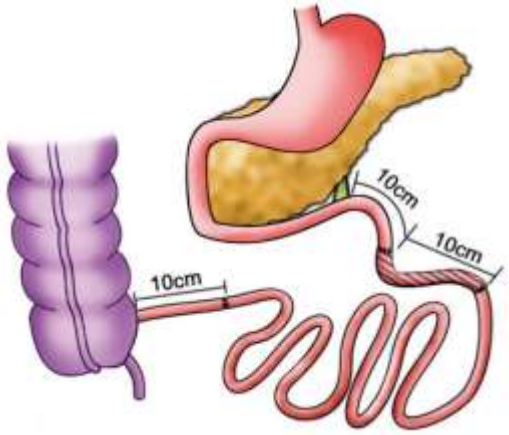
Preliminary validation of "SGLT1 Bridge" Hypothesis;
Initiatively raise up: "Surgical Diabetes".

Background: Sodium-glucose co-transporter 1 (SGLT1) may play a synergistic role in gluconeogenesis

The EIA theory has been questioned

- GLP-1 secretion is not in proportion to diabetes remission.
- GLP-1(R) agonists are far less effective than RYGB.
- Our previous studies: GLP-1 may only be the intermediate link in the therapeutic mechanisms involved in diabetes after MBS.





Ileal transposition (IT), GK rats

Gastroenterol Rep . 2018. 6(4): 291-7.

doi: 10.1093/gastro/goy027
Advance Access Publication Date: 24 July 2018
Original article

2018

ORIGINAL ARTICLE

Ileal transposition rapidly improves glucose tolerance and gradually improves insulin resistance in non-obese type 2 diabetic rats

Hengliang Zhu[1,2], Huaiming Wang[3], Zhihai Zheng[4], Bailiang Ye[4], Xiaojiao Ruan[4], Xiaofeng Zheng[4] and Guoxin Li[1,*]

[1]Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, [2]Department of Gastrointestinal Surgery, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China, [3]Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China and [4]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

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Abstract

GLP-1 is merely an intermediate link? !

The theory of gut - brain - liver axis (GLBA) remains controversial

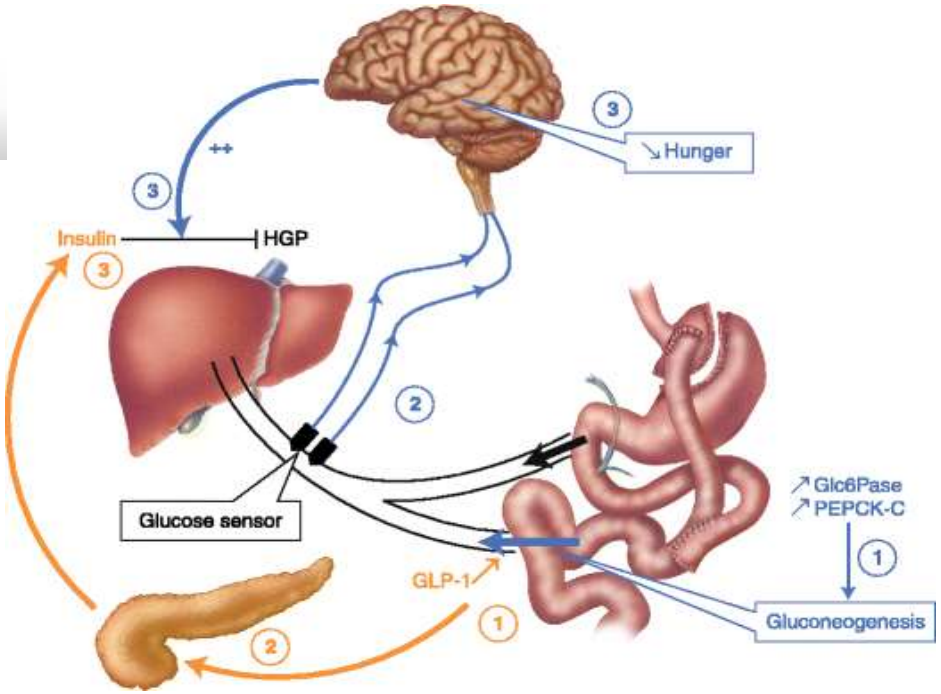
•The main physiological significance of gluconeogenesis(GNG) is to ensure a relatively constant blood glucose level in the presence of starvation.

•Belongs to endogenous glucose production (EGP), usually refers to liver gluconeogenesis (HGNG);

• Intestinal gluconeogenesis (IGNG) significantly enhanced in starvation state, accounting for more than 20% of the effective response of GNG.

GBLA： starts with IGNG and ends with HGNG

It is controversial due to the lack of differences in glucose metabolism between RYGB groups with or without vagus nerve preservation, which makes the gut-brain-liver axis (GBLA) theory questionable to explain the surgical treatment mechanism.

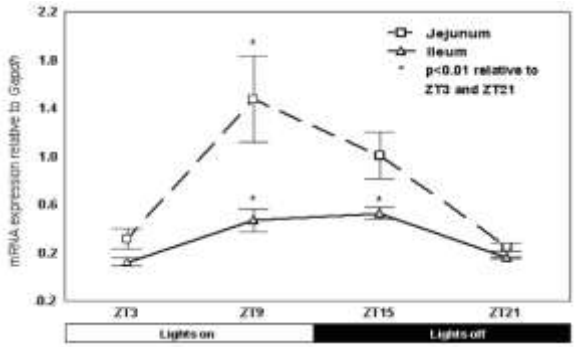


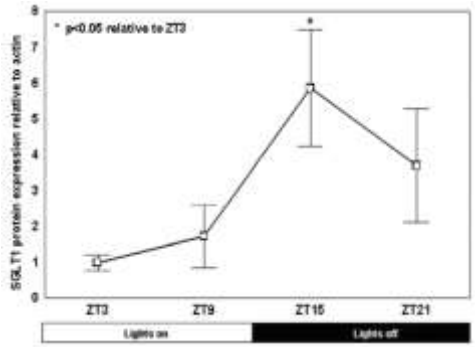
Intestinal Glu-Portal glucose signal（PGS）-Vagus N -Hypothalamus-Liver (EGP)

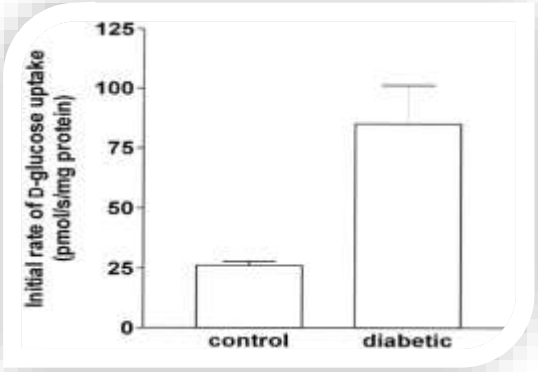
Nutr Hosp. 2013; 28(Supl. 2):109-114.

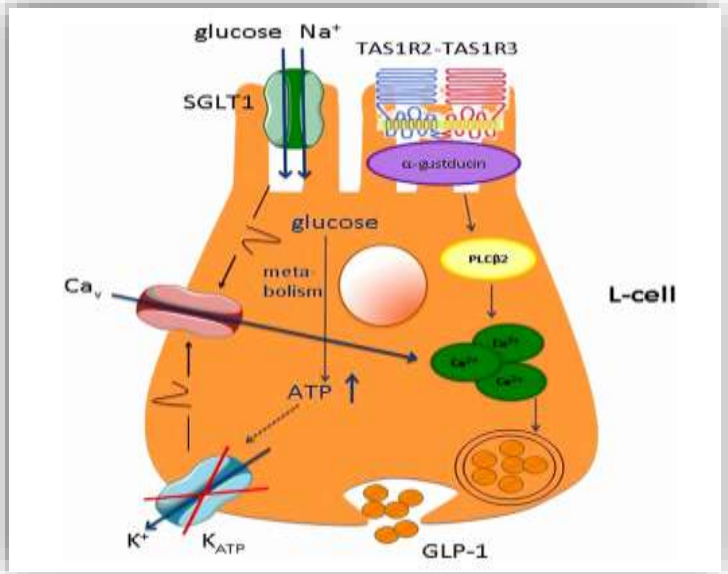
Sodium-glucose co-transporter 1 (SGLT1)

- SGLT1: the main factor of intestinal glucose absorption, with obvious circadian rhythm.
- SGLT1 mainly located in duodenum; lesser distributed in the distal bowel
- SGLT1 is highly expressed (2-3 times) in the diabetic patients's GI tract.
- Regulation of GLP-1 expression by SGLT1 has been demonstrated (at the cellular level) .







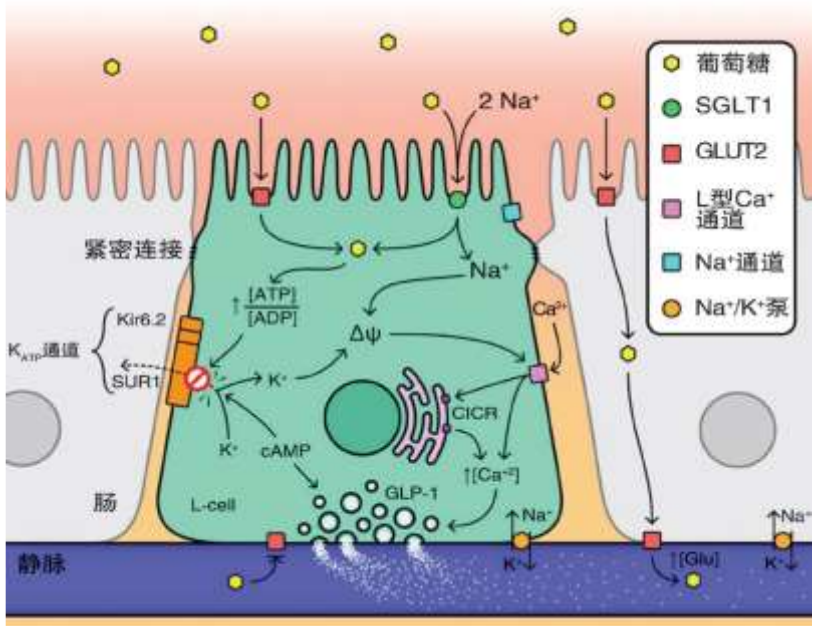


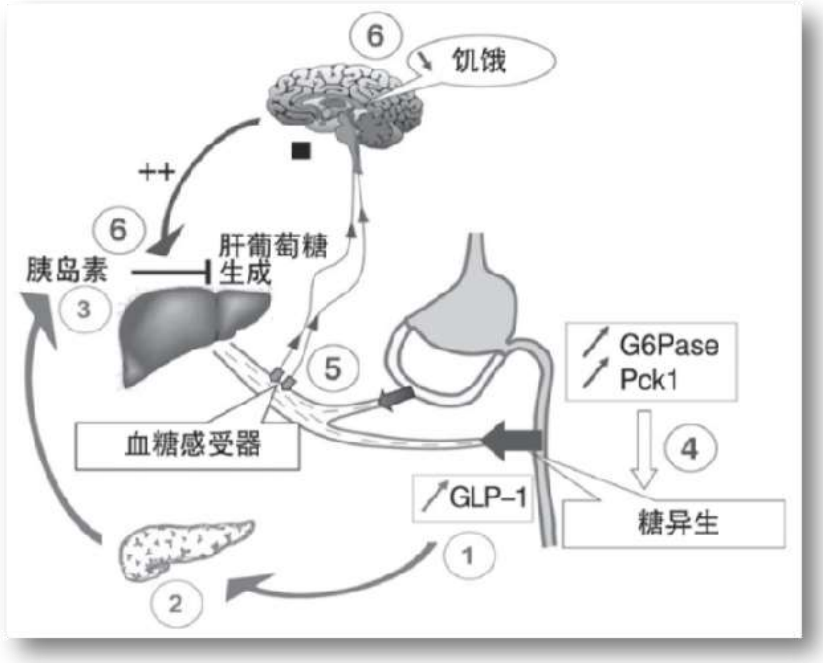
Diabetologia,2012,55:2445-55.

Surgery. 2008; 143(6):813-8.

SGLT1 as a Mediator of the Effect of GLP-1/GNG on Glucose Metabolism

- SGLT1 can regulate intestinal glucose-dependent GLP-1 expression remotely.
- SGLT1 may induce MBS to exert regulatory effects on gluconeogenesis(GNG) pathway.





Diabetes. 2015; 64(2): 370-382. Nutr Hosp. 2013; 28(Supl. 2):109-114. Curr Diab Rep. 2012; 12(2): 167-71. 中华肥胖与代谢病杂志. 2016; 2(2)：80-84.

Proposed: “SGLT1 Bridge” Hypothesis

The traditional theories of "enteric-insular islet axis (EIA)" and "gut-brain-liver axis (GBLA)" cannot perfectly explain the mechanism of gastrointestinal surgery in the treatment of diabetes. ——intermediate link? SGLT1, upstream of EIA and GBLA?

SGLT1 Bridge

SGLT1 may be the "bridge" between the "GBLA" and the "EIA", which is initiated by MBS, i.e. gastric bypass.

- ☐ **Intestinal glucose absorption is directly reduced**
- ☐ **“SGLT1-IGNG-GBLA-HGNG”： FPG declined**
- ☐ **“SGLT1-GLP-1-insulin”： postprandial glucose improved**

·青年专家论坛·

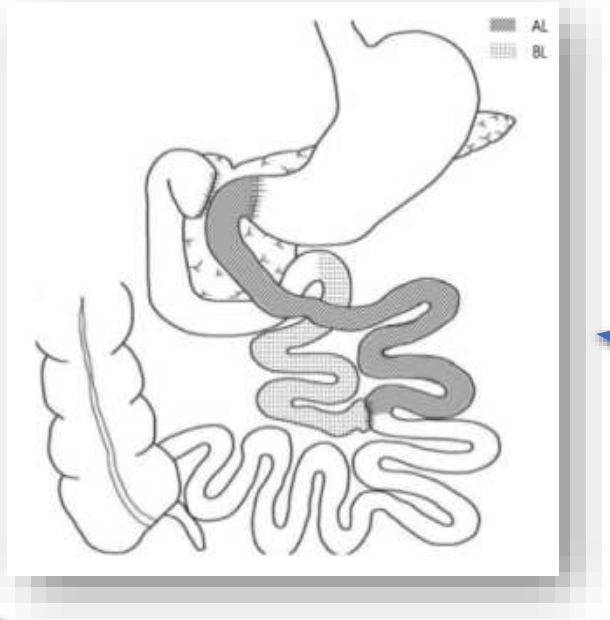
胃肠道钠－葡萄糖共转运体 1 可能介导代谢减重手术改善血糖

2016

中华肥胖与代谢病杂志. 2016; 2(2)：80-84.

Roles of SGLT1 in MBS

Once SGLT1 in the "bypassed" duodenum and the upper part of jejunum down-regulated after RYGB and DJB surgery, what will be happened to the EIA and GBLA?



Type 2 diabetes: dustbin of diagnosis

Controversial

Scattered reports:

Author	Rats	Diabetes type	SGLT1	GLP-1(R)	GNG	Surgery
Jurowich CF	STZ induced Lewis	type 1	√			√
Kim M.	SD	None	√		√	√
Sun D.	GK	type 2, advanced		√	√	√
Zhu H.	ZDF &GK	type 2, early & advanced	√	√	√	

Ann Surg, 2013, 258(1):89-97 Obes Surg, 2015, 25(4): 635-41. Obes Surg. 2013; 23(11): 1734-1742. Ann Transl Med. 2022;10(8):481 Surg Obes Relat Dis. 2014; 10(4):641-646.

Our Study Validated & Defined

A hypothesis: the "SGLT1 Bridge" Hypothesis

A concept: "Surgical Diabetes"

› Ann Transl Med. 2022 Apr;10(8):481. doi: 10.21037/atm-22-1769.

Sodium-glucose co-transporter 1 (SGLT1) differentially regulates gluconeogenesis and GLP-1 receptor (GLP-1R) expression in different diabetic rats: a preliminary validation of the hypothesis of "SGLT1 bridge" as an indication for "surgical diabetes"

Hengliang Zhu [1,2], Huajie Cai [3], Xiaokun Wang [4], Tao Chen [1], Chaohui Zhen [2], Zhenzhan Zhang [1], Xiaojiao Ruan [3], Guoxin Li [1]

Affiliations + expand

PMID: 35571394 PMCID: PMC9096370 DOI: 10.21037/atm-22-1769

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Methods: simulations

- **Diabetic Rats： male, 10w**
  - ✓ ZDF rats （obese）
  - ✓ GK rats (non-obese)

- **Gavage solution：**
  - ✓ -Glu group： glucose solution
  - ✓ -P group： Glu+SGLT1 inhibitor (Phlorizin)

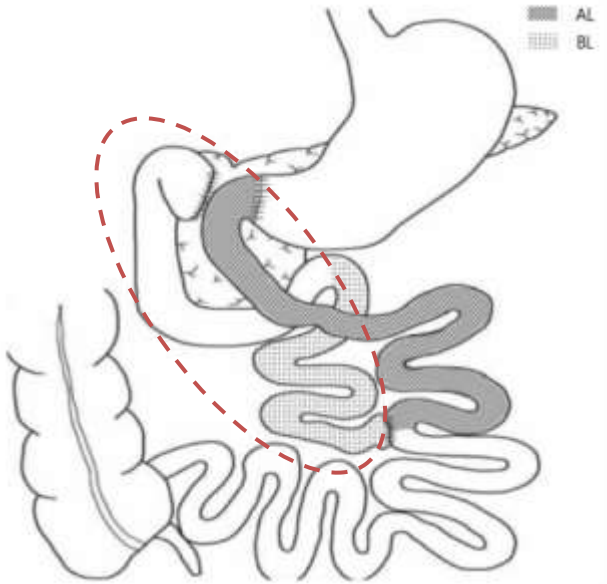
Simulation 1:

ZDF rat ⟶ IR, early stage DM

GK rats ⟶ IGT, advanced stage DM

- **Types**
- WHO: type 1 vs type 2
- Groups:
  - Autoimmune DM
  - Insulin-deficient DM
  - Insulin-resistant DM
  - Obesity-related DM
  - Age-related DM

Simulation 2: SGLT1 inhibitor ⟶ DJB



Duodenojejunal bypass (DJB)

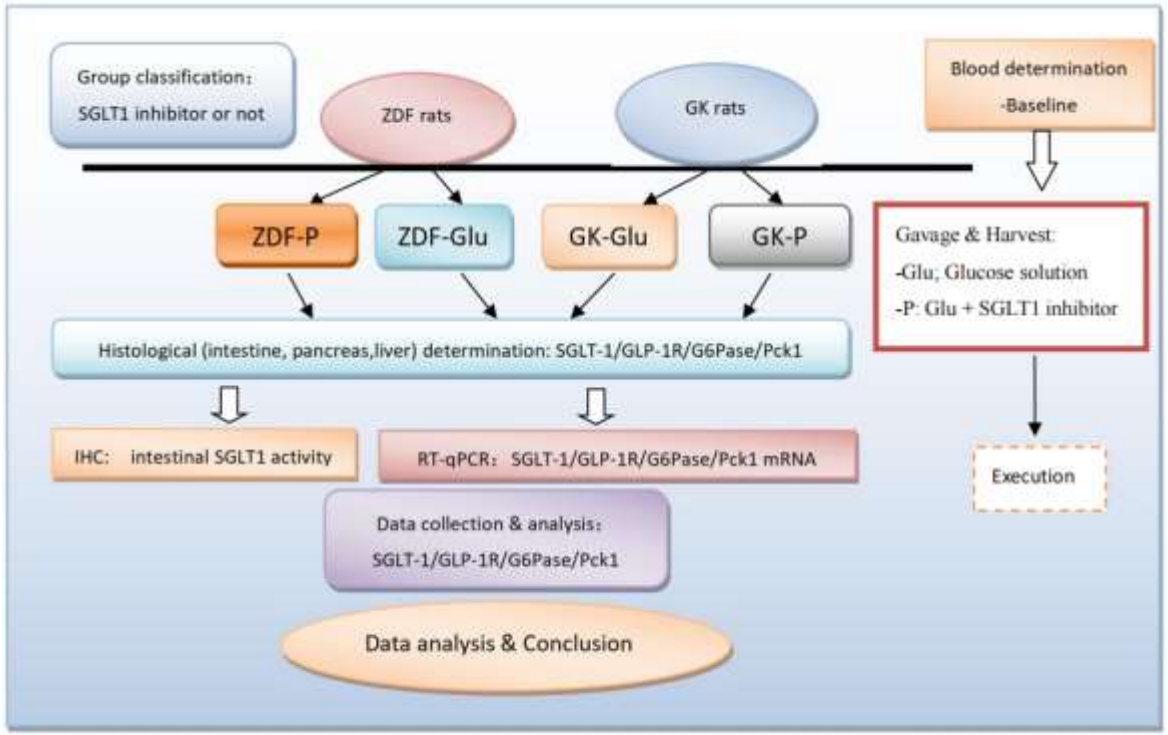
Setting: Comparative Study

- **SGLT1 expression:**
  - ✓ ZDF-Glu vs GK-Glu
- **Regulatory effects of SGLT1 inhibition:**
  - ✓ ZDF-Glu vs ZDF-P
  - ✓ GK-Glu vs GK-P

	Duodenum	Jejunum	Ileum	Pancreas	Liver
SGLT1	√ √	√ √	√ √	√	√
GLP-1R		√	√	√	
G6Pase	√	√	√		√
Pck1	√	√	√		√

Red √: 120min after gavage; black √: 90min after gavage.
（ √: mRNA， √√: IHC+mRNA）

G6Pase and Pck1: key enzymes of gluconeogenesis



Procedure of rats experiment

Regulatory effects of SGLT1 inhibitor (Phlorizin) on different diabetic rats

- Regulatory effects of SGLT1 inhibitor on SGLT1 expression（-P vs -Glu）
- Regulatory effects of SGLT1 inhibitor on GLP-1R expression（-P vs -Glu）
- Regulatory effects of SGLT1 inhibitor on the expression of key enzymes of gluconeogenesis（-P vs -Glu）

Inhibition of SGLT1 Expression by Phlorizin in Diabetic Rats

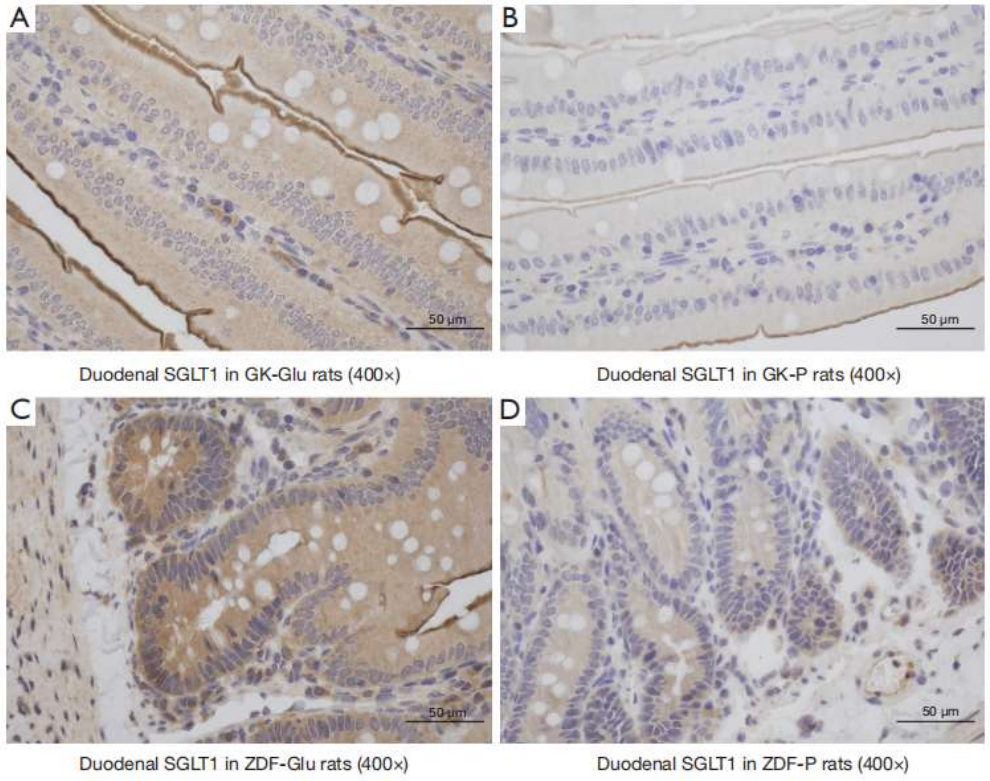


Fig. SGLT1 activity expression in the duodenum

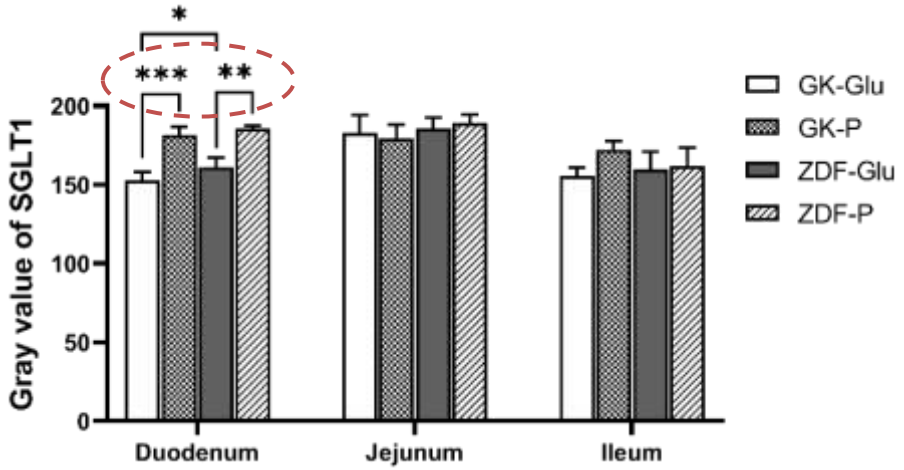


Fig. The activity of SGLT1 expression in the intestine

Data were analyzed using ANOVA with post hoc analysis with LSD's comparison test. *P<0.05, **P<0.01, ***P<0.001.

Plorizin inhibited duodenal SGLT1 activity in both GK rats ($p<0.001$) and ZDF rats ($p<0.001$).

Prerequisite obtained: SGLT1 inhibitors significantly inhibited intestinal SGLT1 expression.

Regulatory effects of Plorizin on GLP-1R expression (-P vs -Glu)

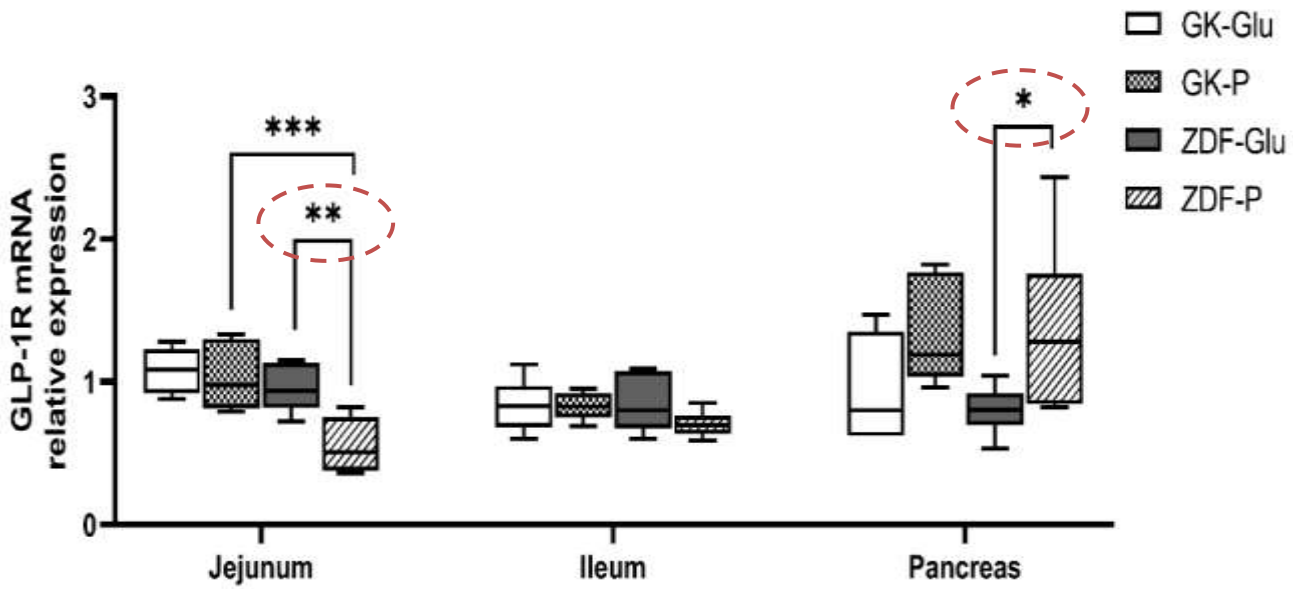


Fig. GLP-1R mRNA expression in the intestine and the pancreas

Data were analyzed using ANOVA with post hoc analysis with LSD's comparison test. *P<0.05, **P<0.01, ***P<0.001.

Regulatory effects of Plorizin on EIA were investigated in ZDF rats, not in GK rats.

- ✓ Down-regulated jejunal GLP-1R mRNA expression in ZDF rats(p=0.001)
- ✓ Up-regulated GlP-1R mRNA expression in pancreas of ZDF rats(p=0.021)。
- ➢ However, the regulatory effects of GLP-1R mRNA expressions in GK rats were not observed.

Regulatory effects of SGLT1 inhibitor on the expression of key enzymes of GNG （-P vs -Glu）

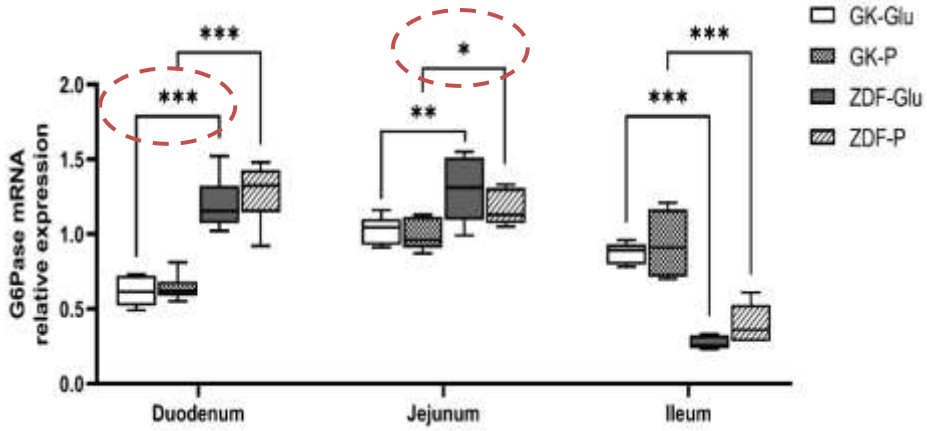


Fig. G6Pase mRNA expression in the intestine

Plorizin，*IGNG*↑

ZDF，SGLT1-IGNG；HGNG↓，SGLT1-GLBA pathway.

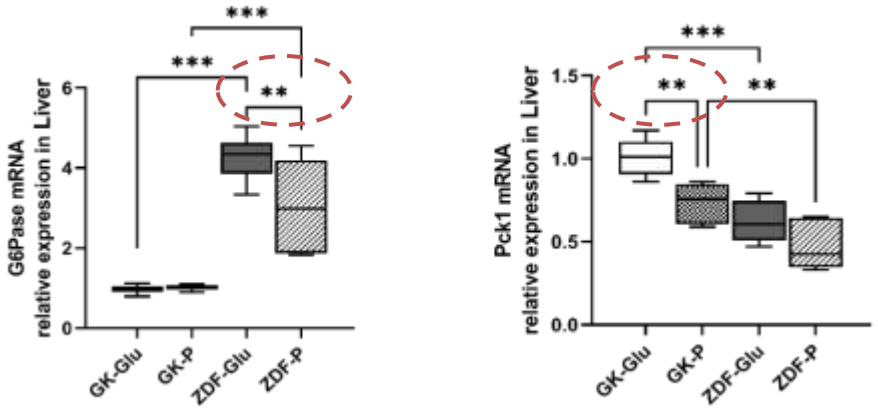


Fig. G6Pase & Pck1 mRNA expression in the liver

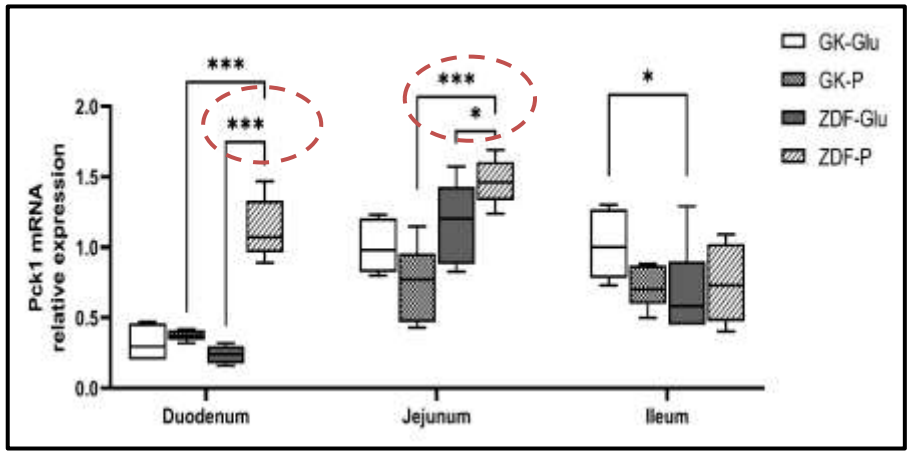
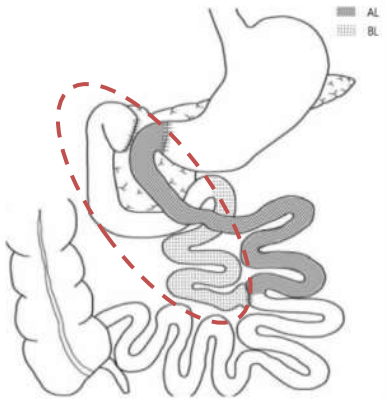


Fig. Pck1 mRNA expression in the intestine

✓<u>Up-regulated</u> the duodenal(p= 0.000) and jejunal(p=0.038) Pck1 mRNA expression in ZDF rats, but not in that of GK rats.

✓<u>Down-regulated</u> <u>hepatic</u> G6Pase mRNA expression in ZDF rats (p=0.005) and hepatic Pck1 mRNA expression in GK rats(p=0.001). *[No changes in hepatic SGLT1 expression: "remote effects" (GBLA)]*

Summary



SGLT1 inhibitor

SGLT1 ↓

GLP-1R

- GK-rats:
- SGLT1-GLP-1R✗
- ZDF-rats:
- SGLT1-GLP-1R√

GLP-1R (PA) ↑

EIA

PA: Insulin ↑

ZDF & GK rats (DU)

Glu ↓

HGNG ↓

GBLA

IGNG

- ZDF-rats:
- SGLT1-IGNG√
- GK-rats:
- SGLT1-IGNG✗

IGNG↑
PGS: Glu

GBLA

Brain

- ✓ SGLT1 showed synergistic regulatory effects on the entero-insular axis (EIA) and the gut-brain-liver axis (GBLA), preliminarily validating the "SGLT1 bridge"hypothesis.
- ✓ The distinct expression of SGLT1 and its differentially regulatory effects on diabetic rats with different pathophysiological conditions may provide probable potential indications involved in the "Surgical Diabetes" that is supposed as the inclusion for diabetic surgery.

Surgical Diabetes
—Multiple factors, pathways related to SGLT1

PV: portal vein; VN: vagus nerve; IGNG: intestinal GNG; HGNG: hepatic GNG.

Conclusion & Prospect

- **“Surgical Diabetes” has been proved that exists with a specific pathophysiological condition strongly related to the “SGLT1 Bridge”, which might be independent of the clinical manifestation.**

- **Clinical factors (i.e. BMI, duration of diabetes) can predict diabetes remission, but specific indicators for “Surgical Diabetes” must focus on the therapeutic mechanisms of diabetes remission after MBS. [Phenomenon & Essence]**

- **If the "SGLT1 Bridge" is validated as an indication for "Surgical Diabetes" in humans , it could solve the bottleneck that limit the indications for diabetic surgery.**

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Thank You !

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