Overview on Sodium-Glucose Cotransporter 2(SGLT2) Inhibitors in Glucose Homeostasis

2013/11/8

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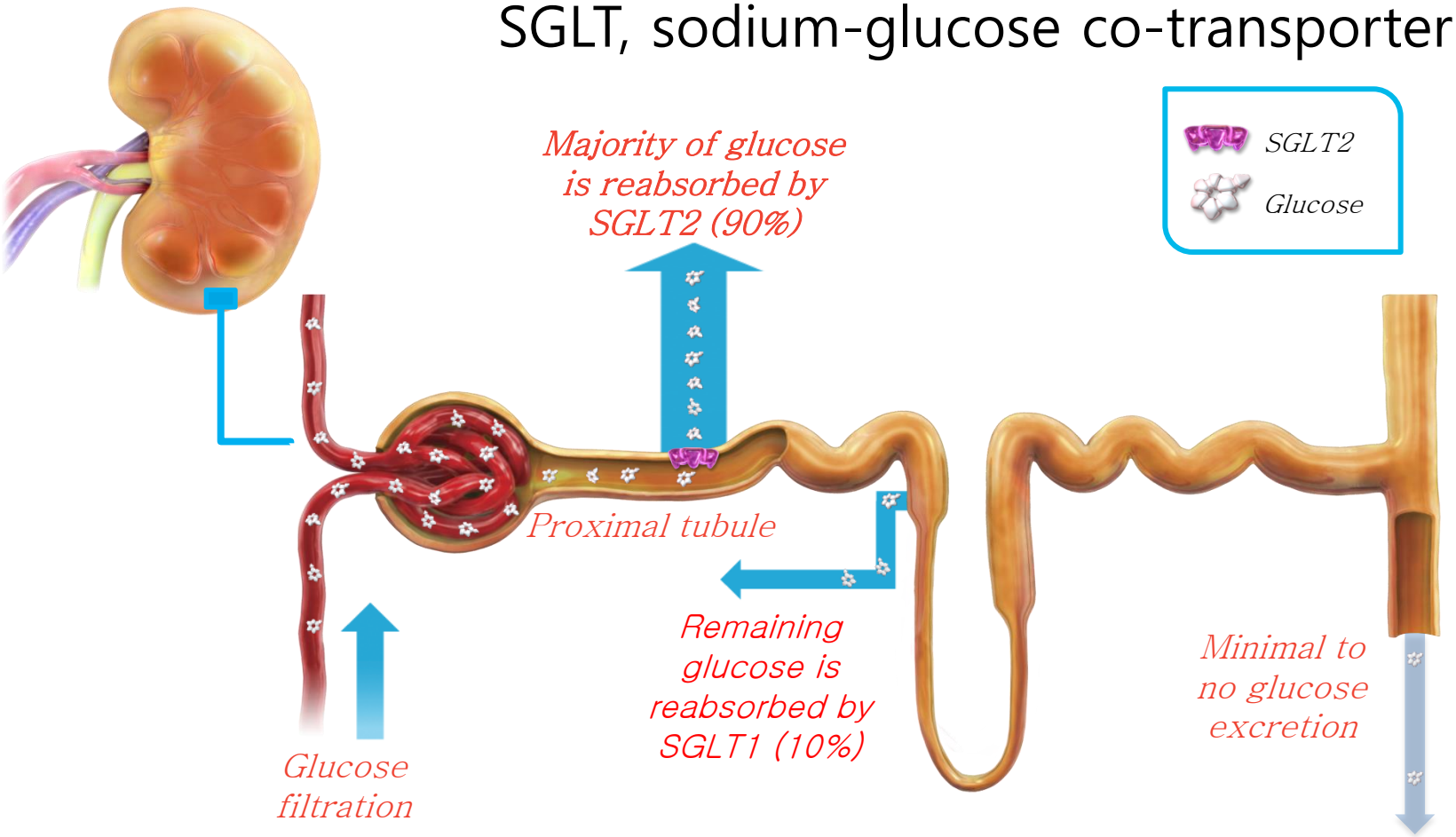
Normal renal glucose handling

SGLT, sodium-glucose co-transporter

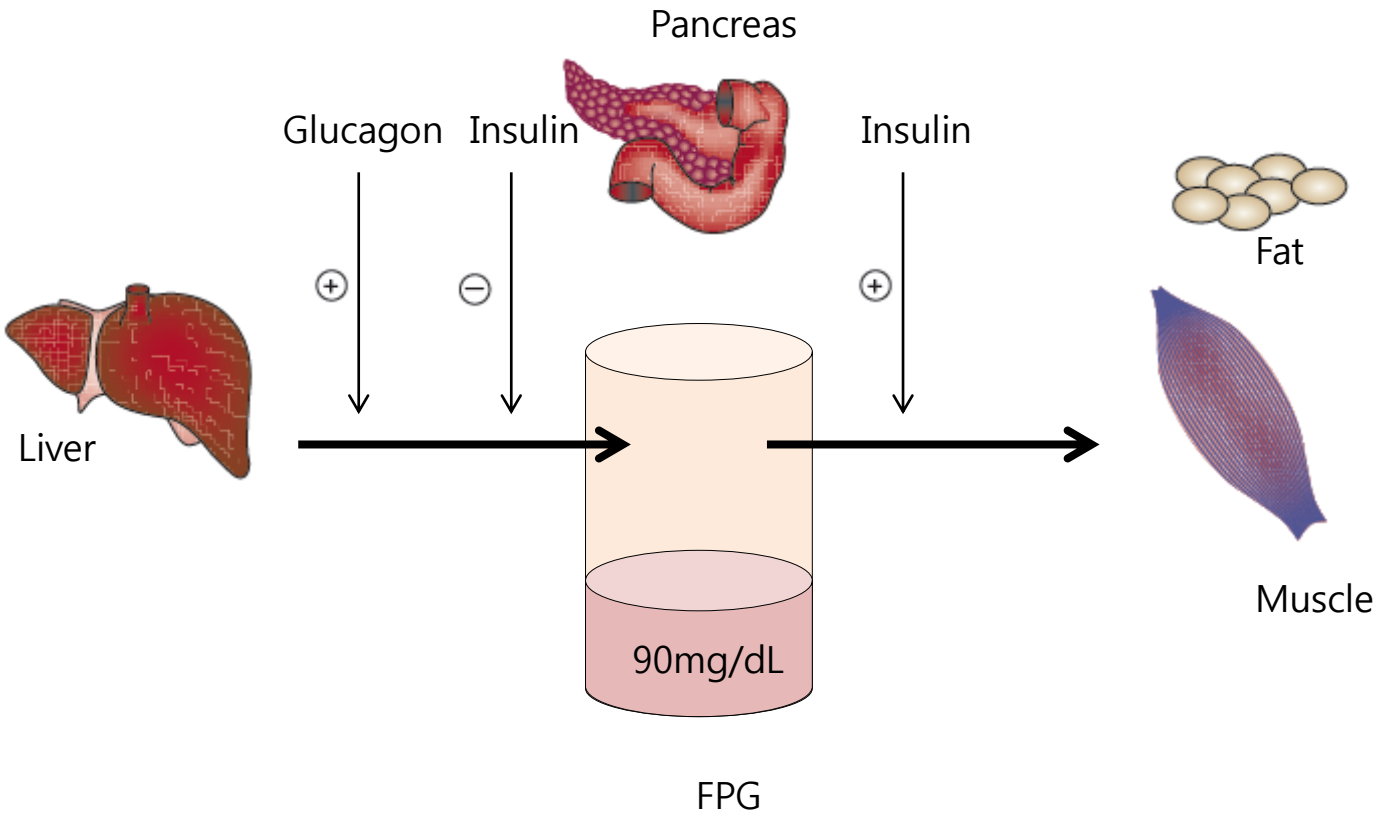


Forxiga web site. http://www.forxiga.eu/useful-links-and-resources, Accessed Sep 21,2013

OUTLINE

I. **Glucose homeostasis**
II. Renal handling of glucose
III. Metabolic effects of SGLT2 inhibition
IV. Genetic model of SGLT2 inhibition
V. Conclusions

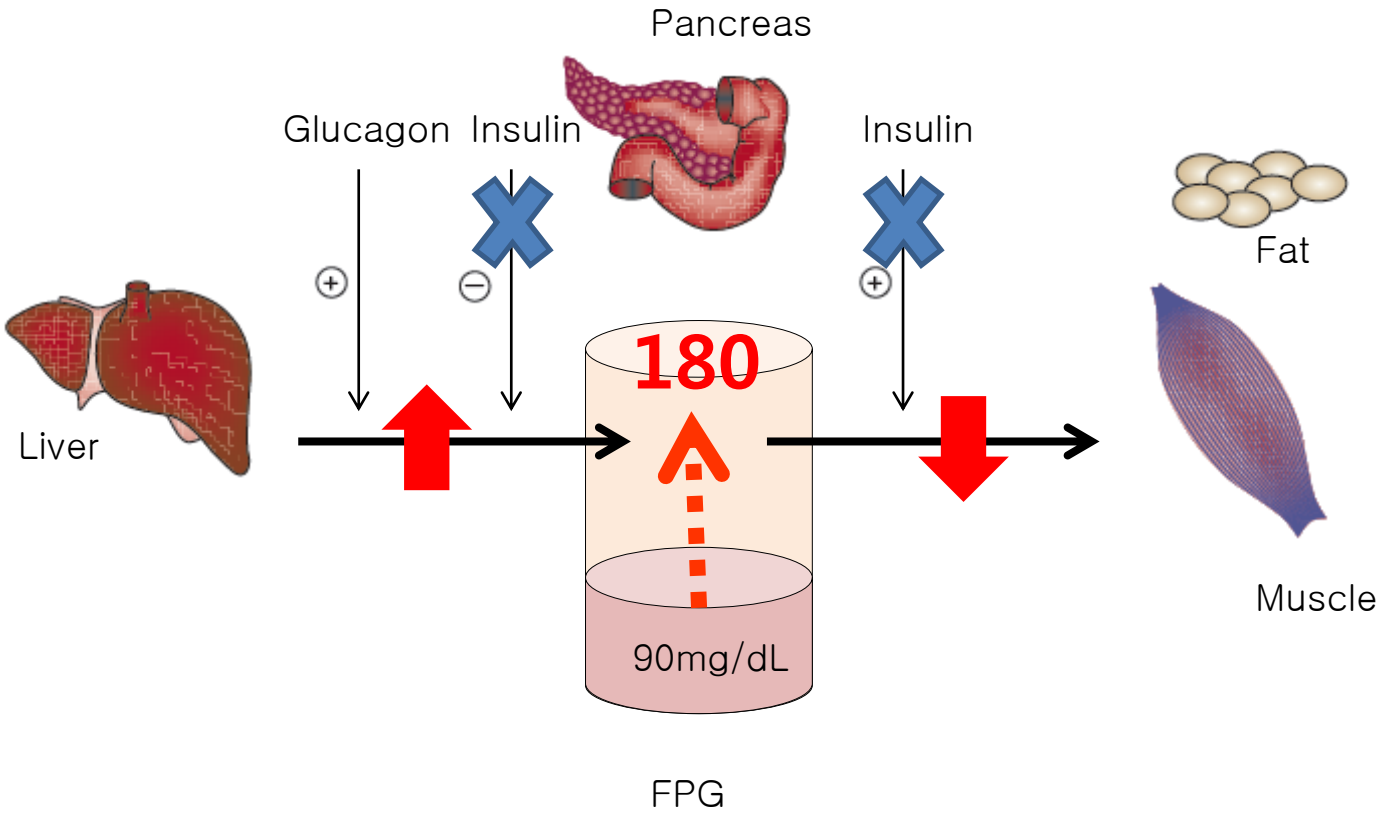
Normal glucose homeostasis



FPG; Fasting plasma glucose

Chao EC, Nat Rev Drug Discov. 2010 Jul;9(7):551-9

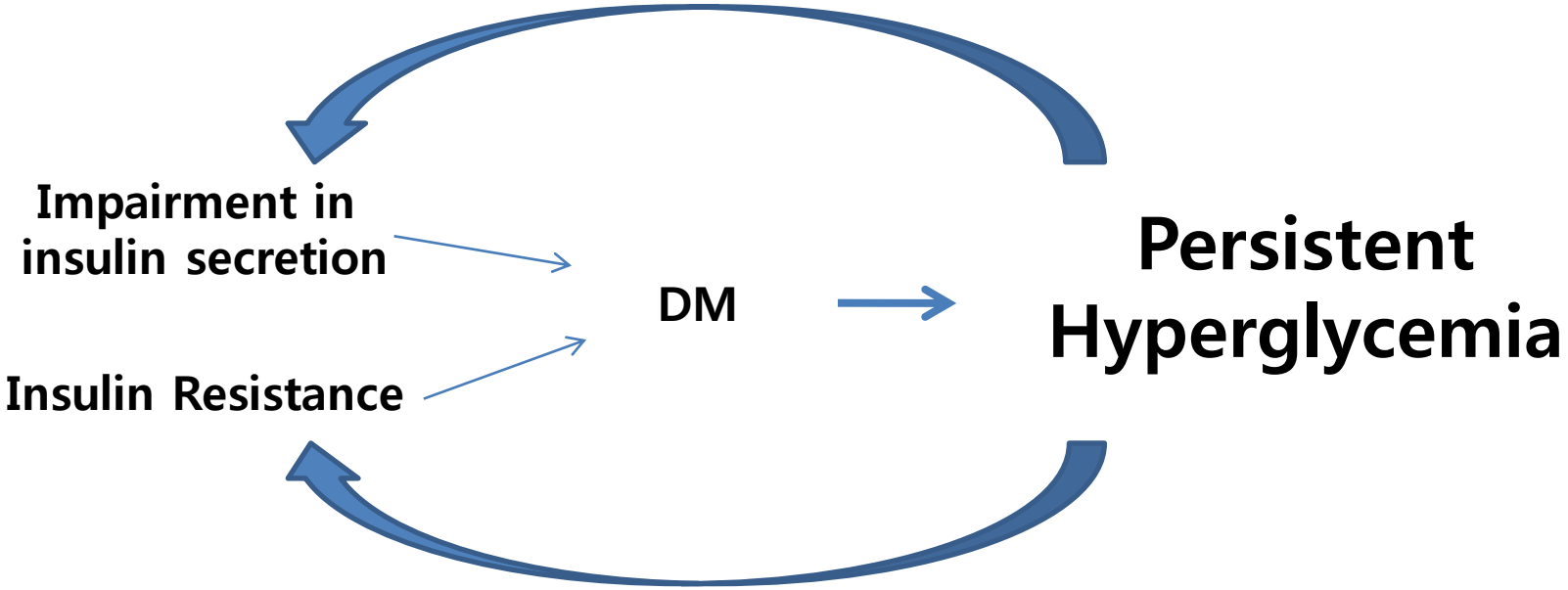
Pathophysiology of T2DM



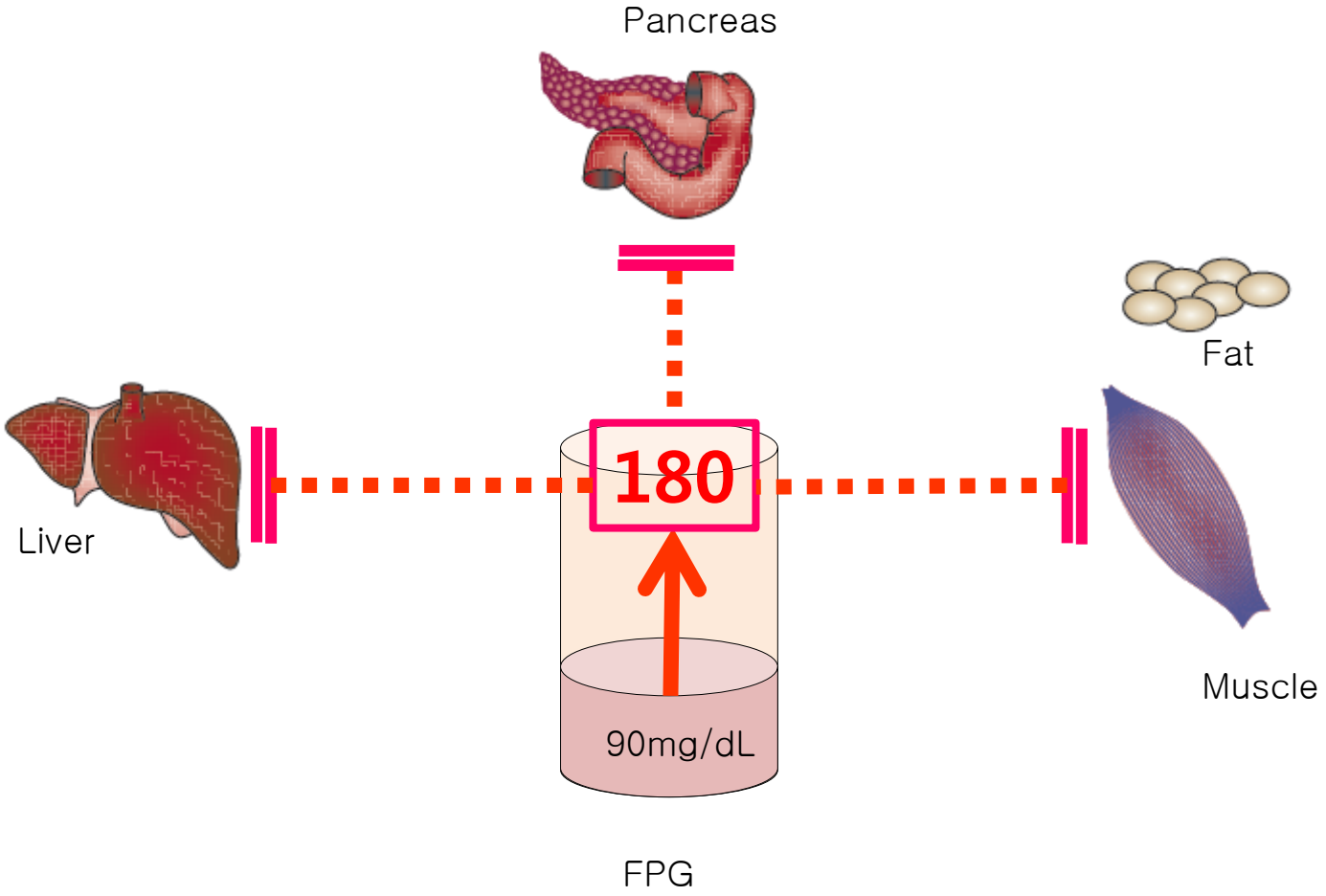
FPG; Fasting plasma glucose

Hyperglycemia

- =cause of diabetes
- "glucotoxicity" contributes to insulin resistance and impaired insulin secretion



Role of glucotoxicity in the pathophysiology of T2DM



FPG; Fasting plasma glucose

The Kidneys Play an Important Role in the Handling of Glucose

	Non-DM
• Total glucose stored in body	~450 g/day
• Glucose utilization	~250 g/day
• Brain	~125 g/day
• Rest of body	~125 g/day
• Glucose in (Western) diet	~180 g/day
• Glucose production (gluconeogenesis + glycogenolysis)	~70 g/day
• **Renal glucose filtration and reabsorption**	**~180 g/day (720kcal)**
• Plasma glucose concentration	~90 mg/dL
• Approximate total blood glucose	4 to 5 g

Wright EM, J Intern Med. 2007.

Altered Renal Glucose Control in Diabetes

- **Gluconeogenesis is increased in postprandial and postabsorptive states in patients with Type 2 DM**
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without diabetes
- **Glucose reabsorption**
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with diabetes vs. normoglycemic individuals

Marsenic O. Am J Kidney Dis. 2009;
Bakris GL, et al. Kidney Int. 2009;
Rahmoune H, 3t al. Diabetes.2005.

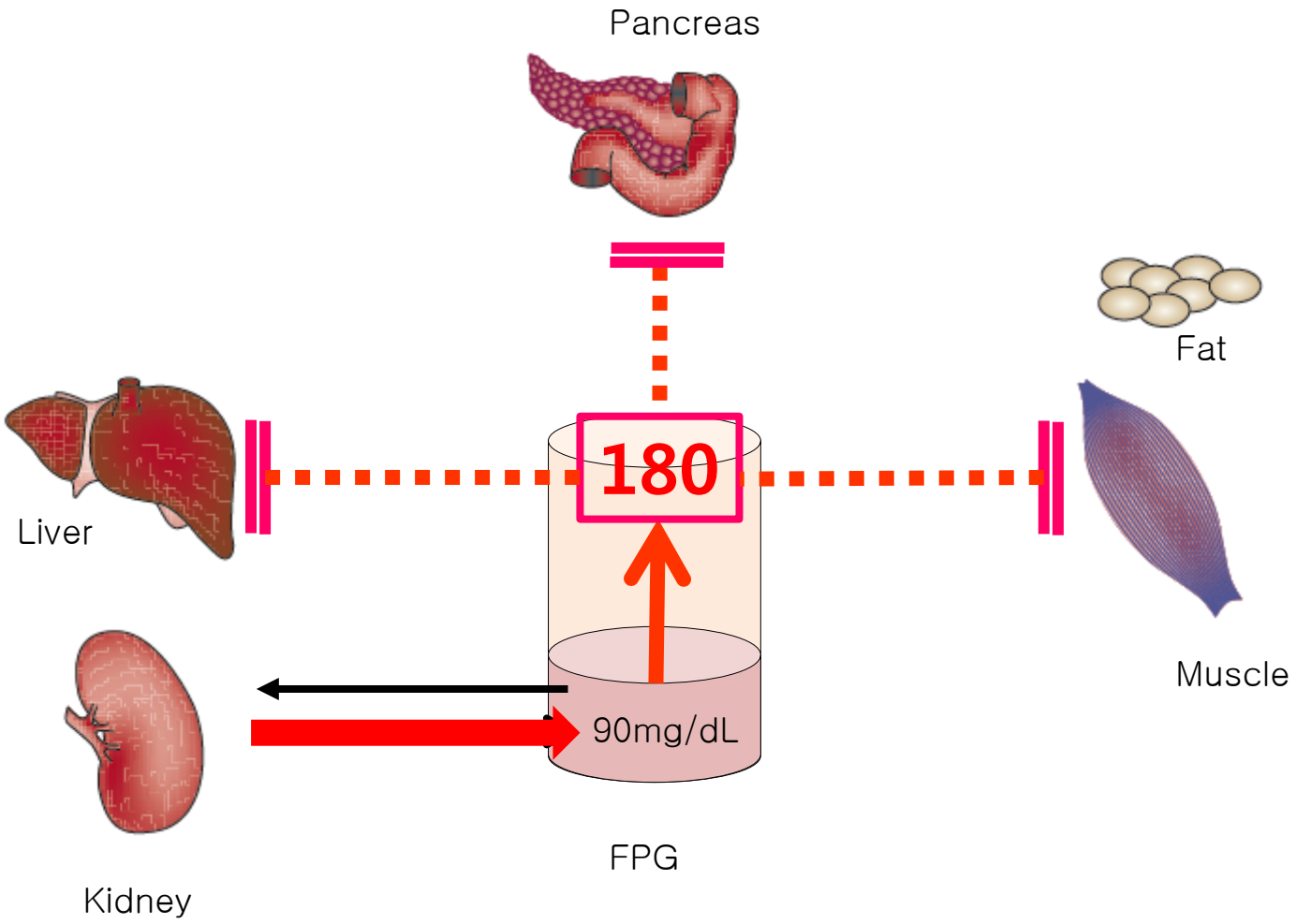
Rationale for SGLT2 inhibitor therapy

- Normalization of the plasma glucose concentration – independent of the mechanism – is a cornerstone of diabetes management

SGLT2 inhibitors- Mechanism of Action

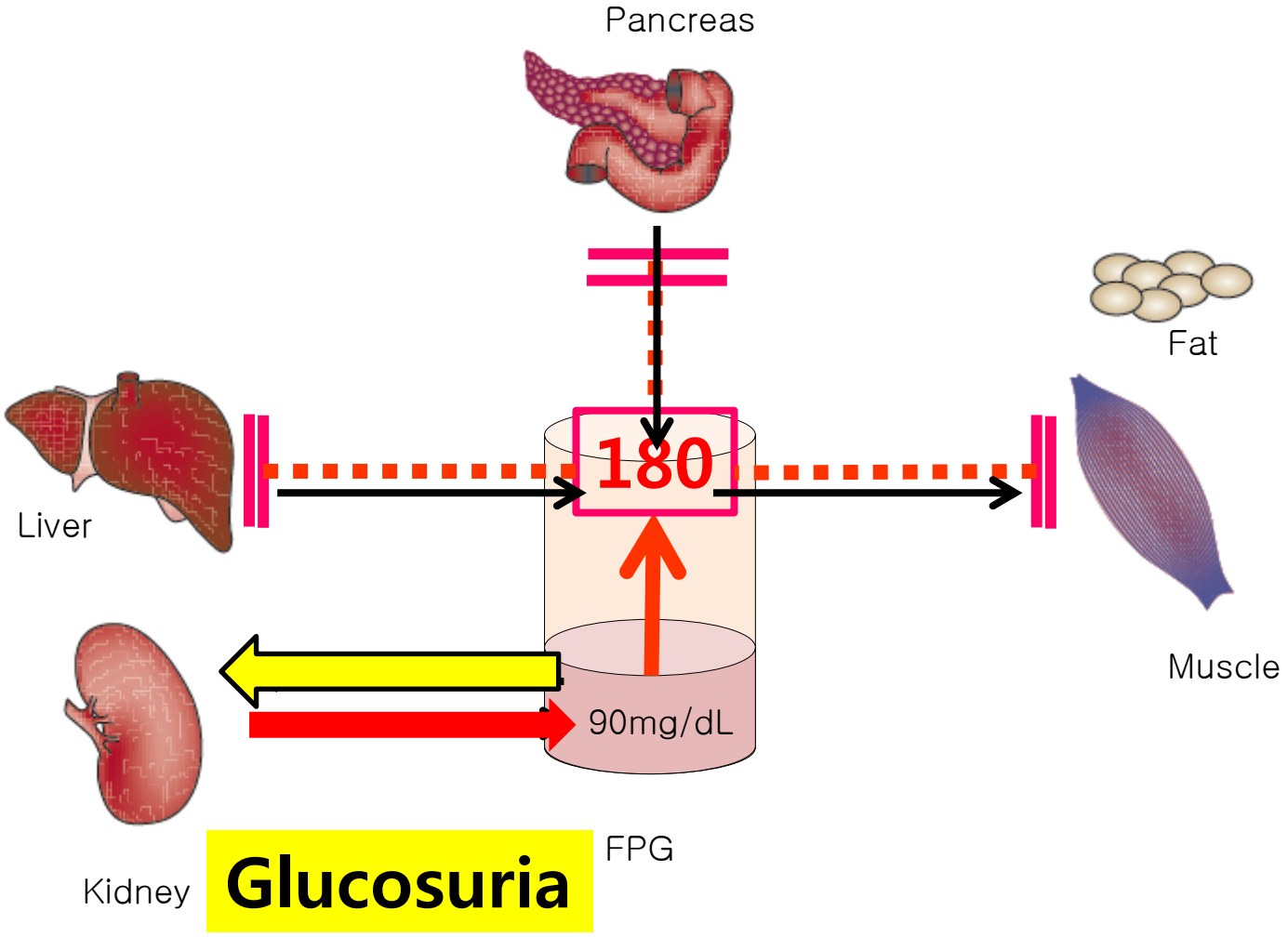
- Inhibit glucose reabsorption in the renal proximal tubule
- The resultant glucosuria leads to a decline in plasma glucose and reversal of "glucotoxicity"
- Simple, nonspecific

Pathophysiology of T2DM



 FPG; Fasting plasma glucose

SGLT2 inhibition in T2DM: Physiologic consequences



FPG; Fasting plasma glucose

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II. Renal handling of glucose
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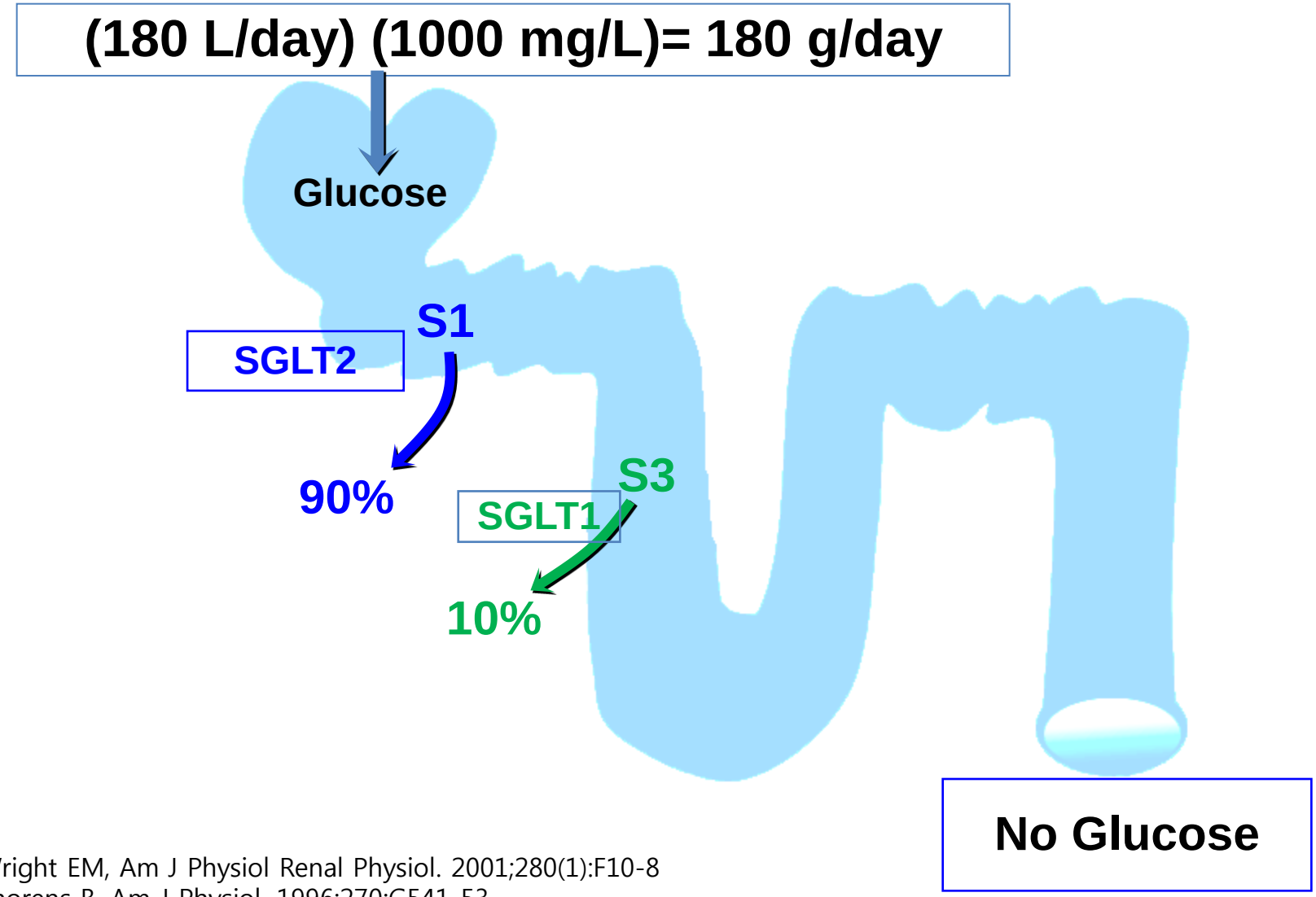
Normal Renal Glucose Handling



Wright EM, Am J Physiol Renal Physiol. 2001;280(1):F10-8
Thorens B, Am J Physiol. 1996;270:G541-53

Glucose Transporters

- 2 families of glucose transporters[1]
- Responsible for[2]:
  - Absorption of glucose from small intestine
  - Reabsorption from glomerular filtrate
  - Brain uptake across blood-brain barrier
  - Uptake and release of glucose in all cells

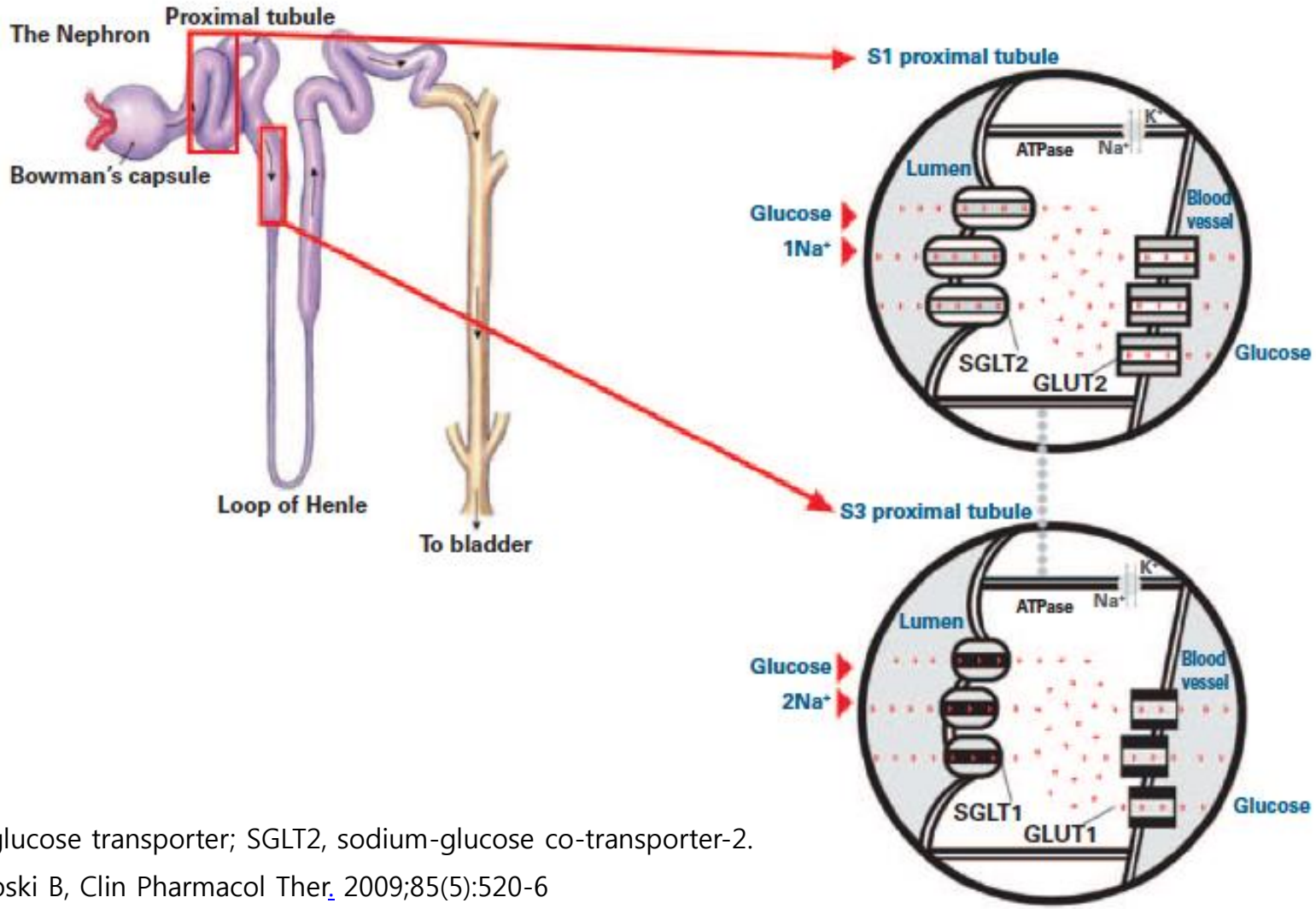
1. Wright EM, J Intern Med. 2007;261:32-43.
2. Jabbour SA, Int J Clin Pract. 2008;62(8):1279-84

Two Families of Glucose Transporters

GLUT Family	SGLT Family
Facilitated glucose transporters	Sodium coupled glucose cotransporter
Passive, downhill transport	Active transport of glucose
• GLUT1 (widespread including the kidneys) • GLUT2 (kidneys, pancreas, liver) • GLUT4 (muscle & adipose tissue)	• SGLT 1 (brush border of small intestine) • SGLT 2 (proximal tubule)

 Longo N, Adv Pediatr. 1998;45:293-313

SGLT2 Mediates Glucose Reabsorption In The Kidney



GLUT, glucose transporter; SGLT2, sodium-glucose co-transporter-2.

Komoroski B, Clin Pharmacol Ther. 2009;85(5):520-6

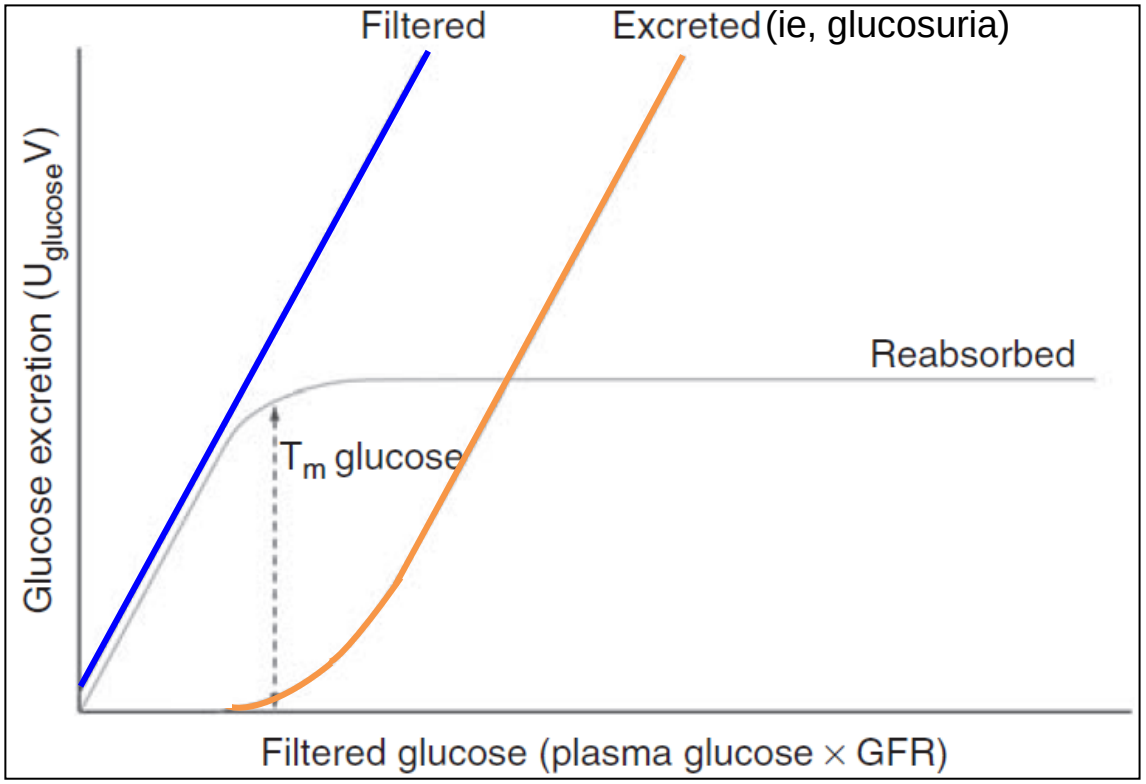
SGLT (Sodium-Glucose Cotransporters)

	SGLT1	SGLT2
Distribution	Mostly intestine, with some kidney	Exclusively kidney
Sugar specificity	Glucose or galactose	Glucose
Glucose affinity	High K_m=0.4 mM	Low K_m=2 mM
Glucose transport capacity	Low	High
Role	• Dietary absorption of glucose and galactose (inhibition : osmotic diarrhea) • Renal glucose reabsorption	• Renal glucose reabsorption

 Lee YJ, Kidney Int Suppl.2007:106:S27

Glucosuria reflects the resorptive capacity of renal proximal tubule

The threshold $Tm_{Glucose}$ represents the maximal resorptive capacity of the proximal tubule

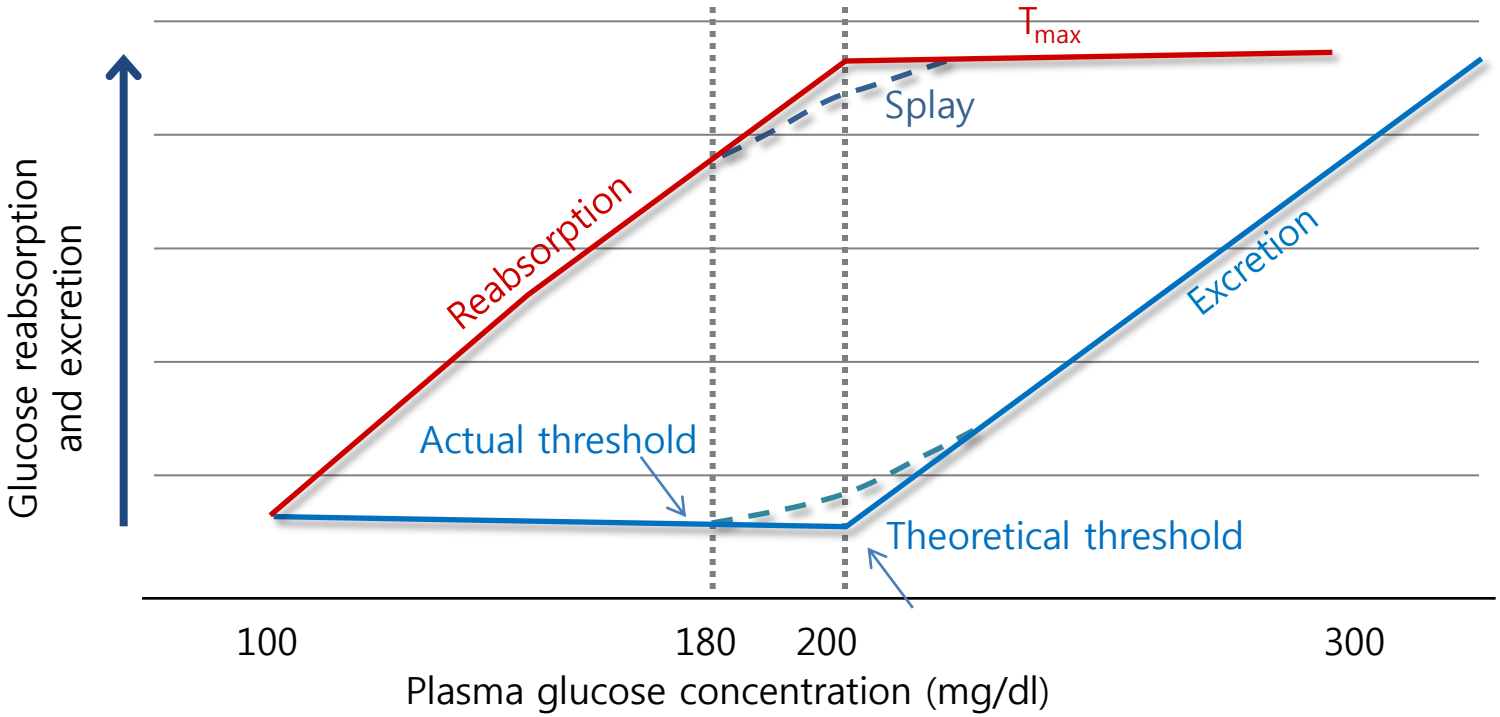


Tm glucose ; maximal glucose reabsorptive capacity

GFR; glomerular filtration rate

Adapted from Brenner and Rector's The Kidney, 8th ed. Philadelphia,PA:Saumders;2007.

Kinetics of renal glucose handling

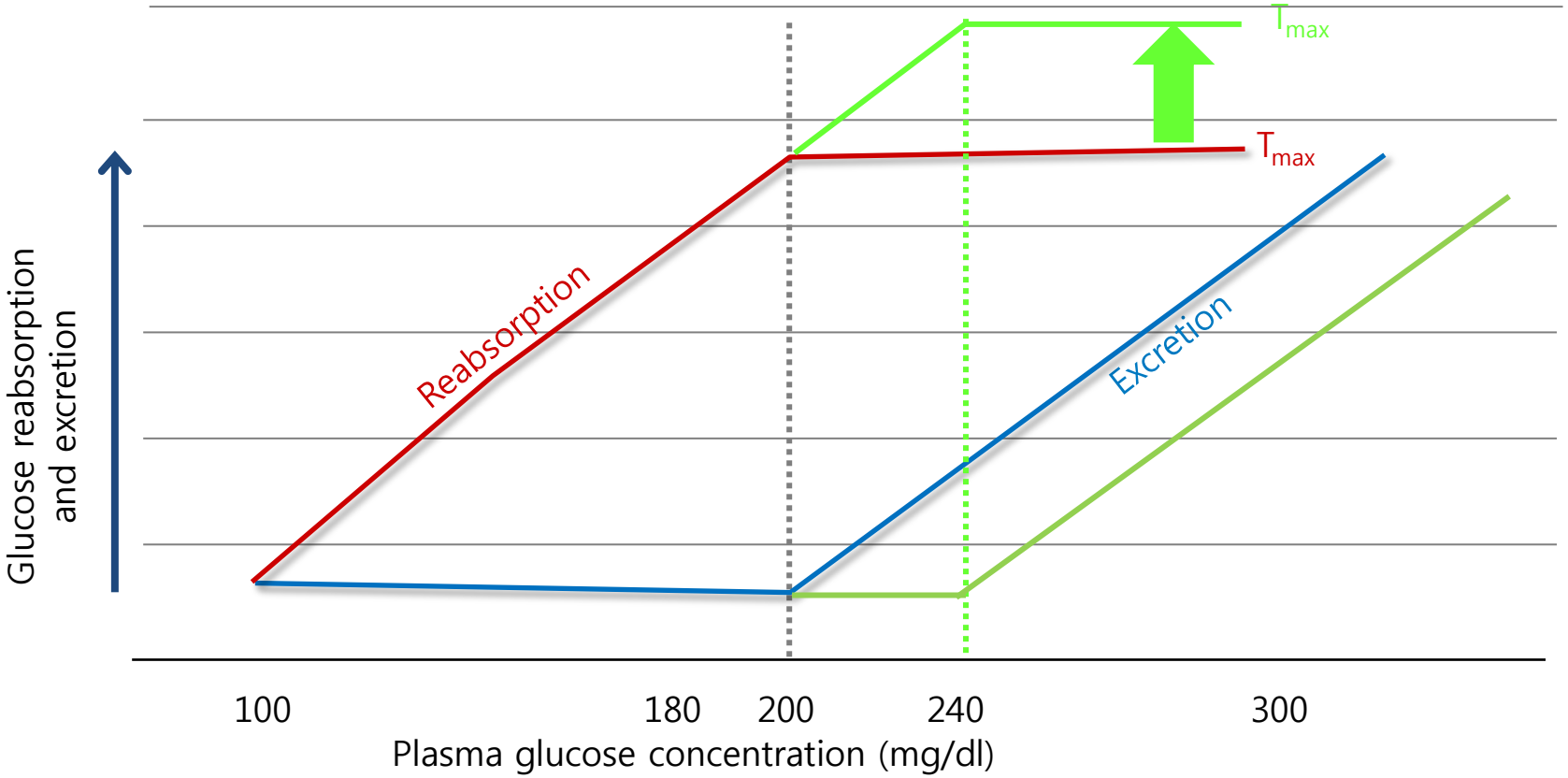


SGLT2, sodium-glucose co-transporter-2; T_{max}, maximal glucose reabsorptive capacity.

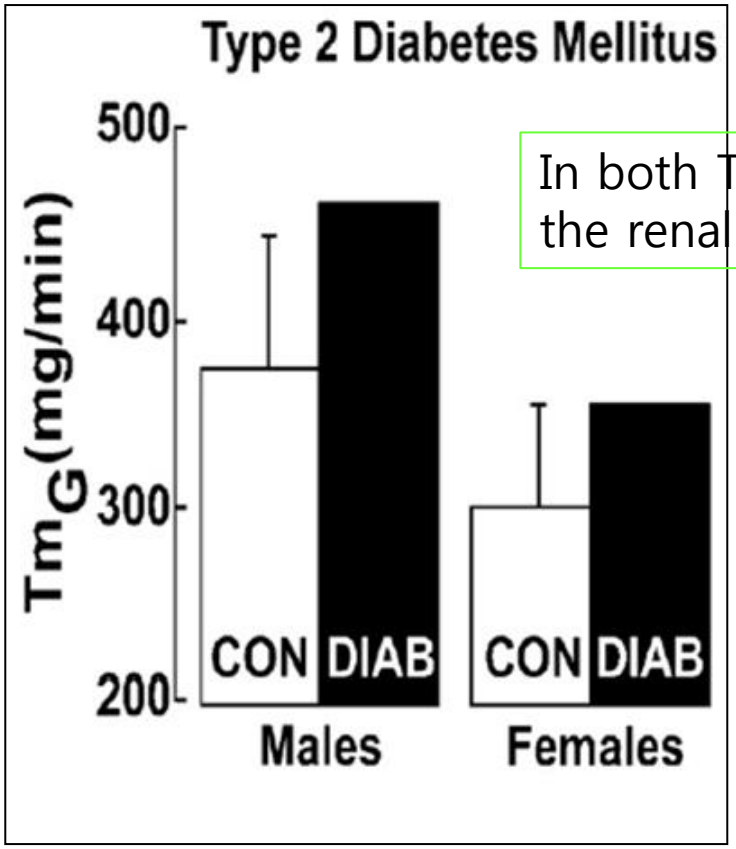
Adapted from: Abdul-Ghani MA, et al. Endocr Pract 2008;14:782–90; Gerich JE. Diabet Med 2010;**27**:136–42.

Hyperglycemia and Renal Glucose Reabsorption

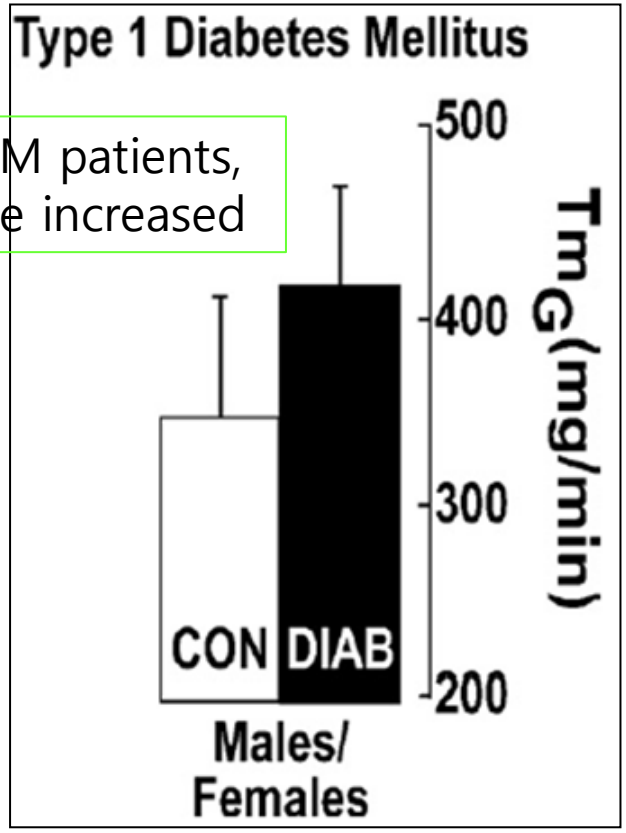
Renal glucose handling in diabetes



Effect of hyperglycemia on the renal Tm for glucose in T2DM and in T1DM



In both T2DM and T1DM patients, the renal Tm for glucose increased



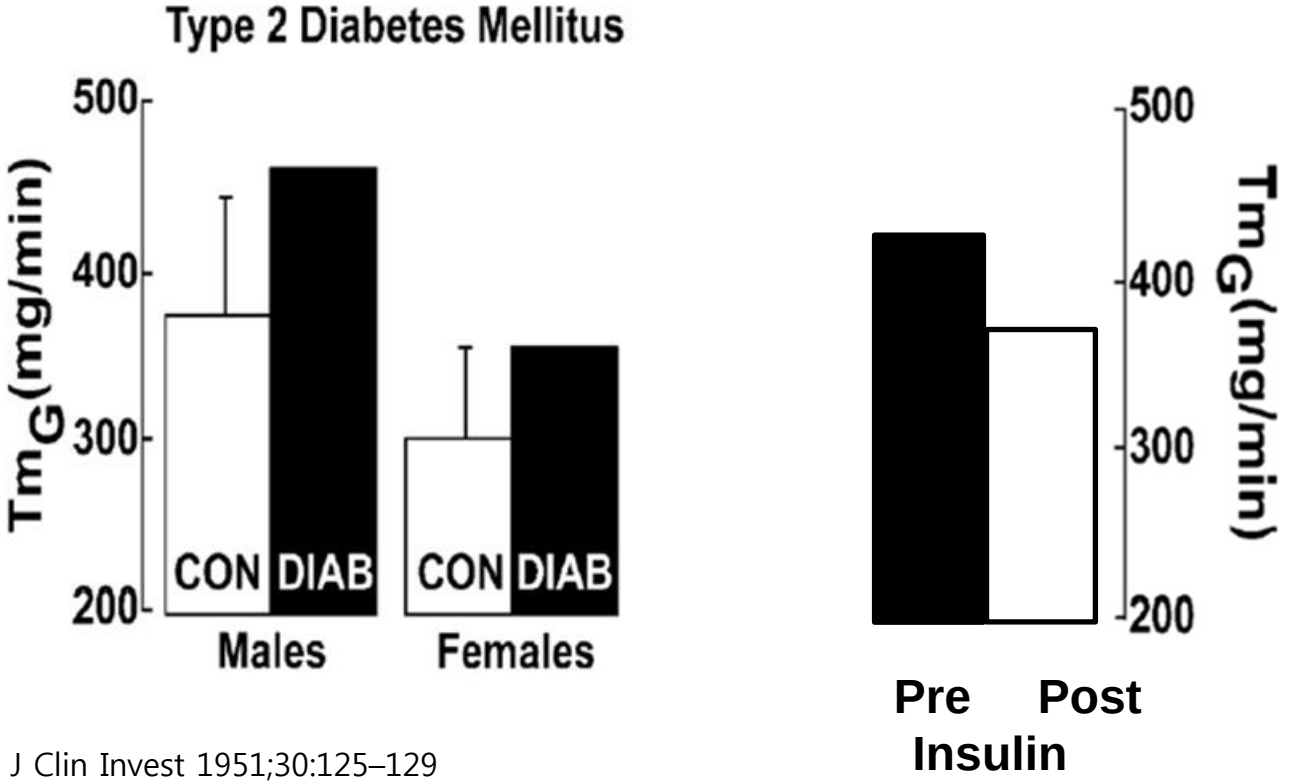
Faber SJ,
J Clin Invest 1951;30:125–129

Mogensen CE ,
Scand J Clin Lab Invest 1971;28:183–193

CON, Control; DIAB, Diabetes

Effect of T2DM and insulin on the renal Tm for glucose

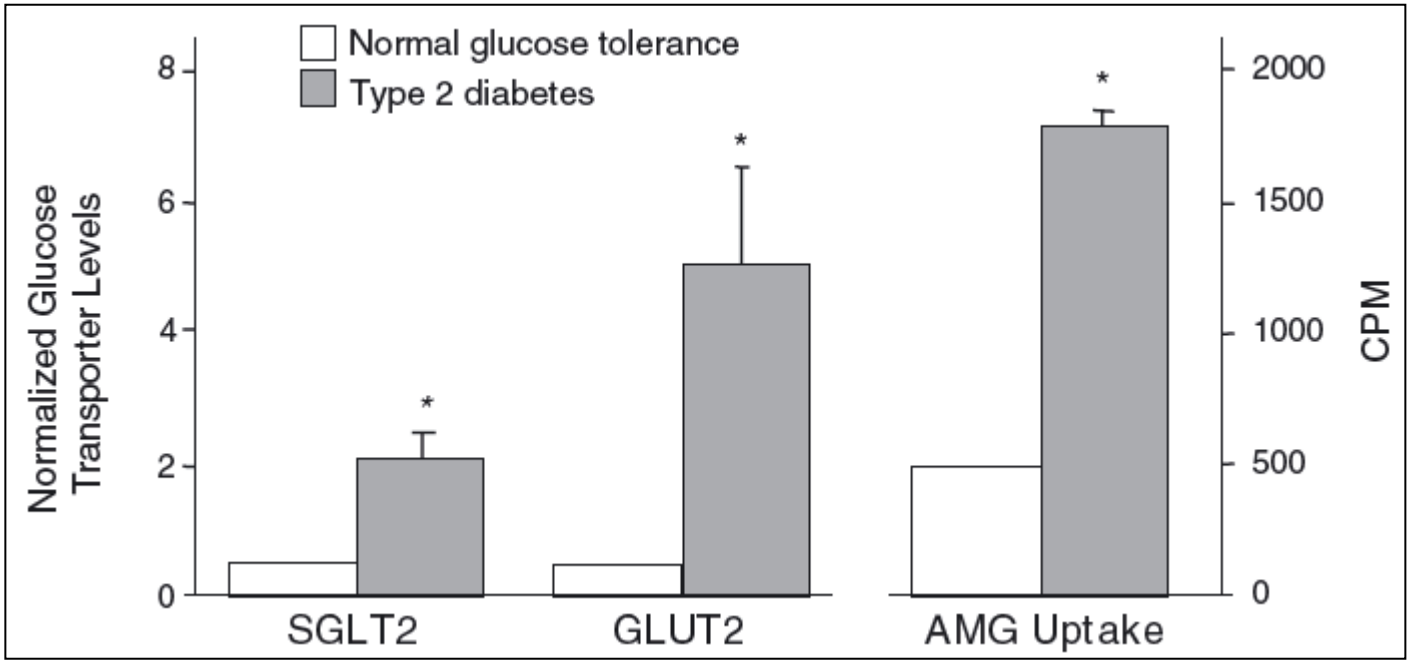
Correction of the hyperglycemia resulted in a decrease in Tm for glucose and the appearance of glucosuria



Farber SJ, J Clin Invest 1951;30:125–129

CON, Control; DIAB, T**2**DM.

Increased glucose transporter in human renal proximal tubular cells



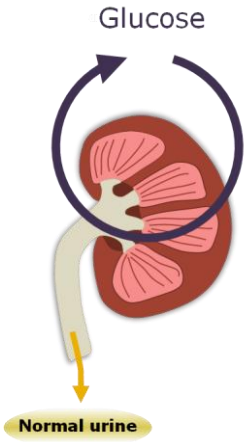
AMG, alpha-methyl-glucoside

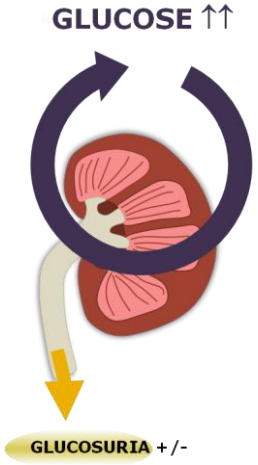
 Rahmoune H, Diabetes 2005;54: 3427–3434

Summary : Renal tubular glucose reabsorption in diabetes

- In human T1DM and T2DM, the maximum renal tubular reabsorptive capacity (Tm for glucose) is increased
- Cultured human proximal renal tubular cells demonstrate increased SGLT2/GLUT2 mRNA and protein levels and increased glucose transport(AMG).

Implications





- An adaptive response to conserve glucose (ie, for energy needs) becomes *maladaptive* in diabetes
  - In the presence of hyperglycemia, it would be desirable for the kidney to excrete the excess filtered glucose load to restore normoglycemia.
  - In contrast, the diabetic kidney has an increased Tm for glucose, thereby minimizing glucosuria and exacerbating the hyperglycemia.
  - Moreover, the ability of the diabetic kidney to conserve glucose may be augmented in absolute terms by an increase in the renal reabsorption of glucose

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SGLT2 inhibitor in development

- 1835 phlorizin isolated from the bark of apple trees → glucosuria
- 1980s ; phlorizin acting on SGLT
- 2000 ; analogs of phlorizin (**gliflozin)

	SGLT1	SGLT2	Selectivity for SGLT 2 *vs.* SGLT1
Phlorizin	35.6	330	10
T-1095	6.6	211	30
Sergliflozin	9.2	>8000	>90
Dapagliflozin	1.1	1390	1200

Effect of SGLT2 inhibitors on insulin resistance

- Targeting the renal glucose transporter

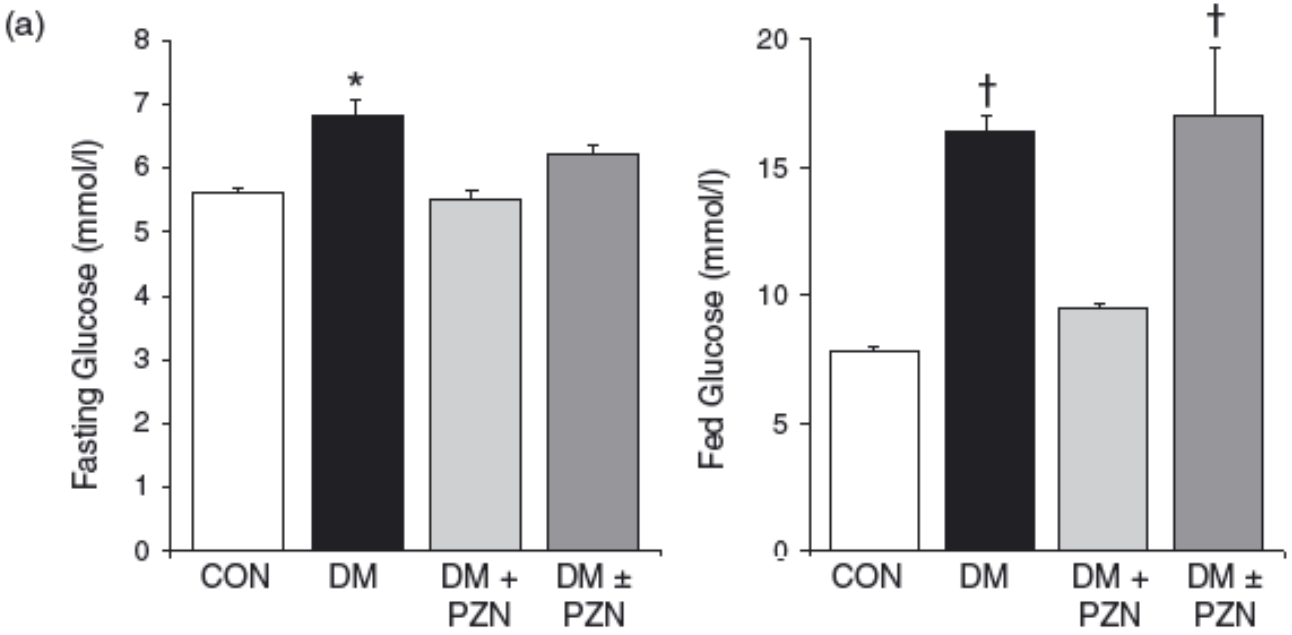
→improve glucose homeostasis

Experimental Protocol

- Sprague-Dawley rats ; treatment period=4 weeks
  - GROUP I– sham operated controls
  - GROUP II– partial(90%) pancreatectomy
  - GROUP III– 90% pancreatectomy + phlorizin sc
  - GROUP IV– {90% pancreatectomy + phlorizin sc} – phlorizin

 Rossetti L, J Clin Invest 1987; 79: 1510–1515

Effects of phlorizin treatment on fasting and fed plasma glucose



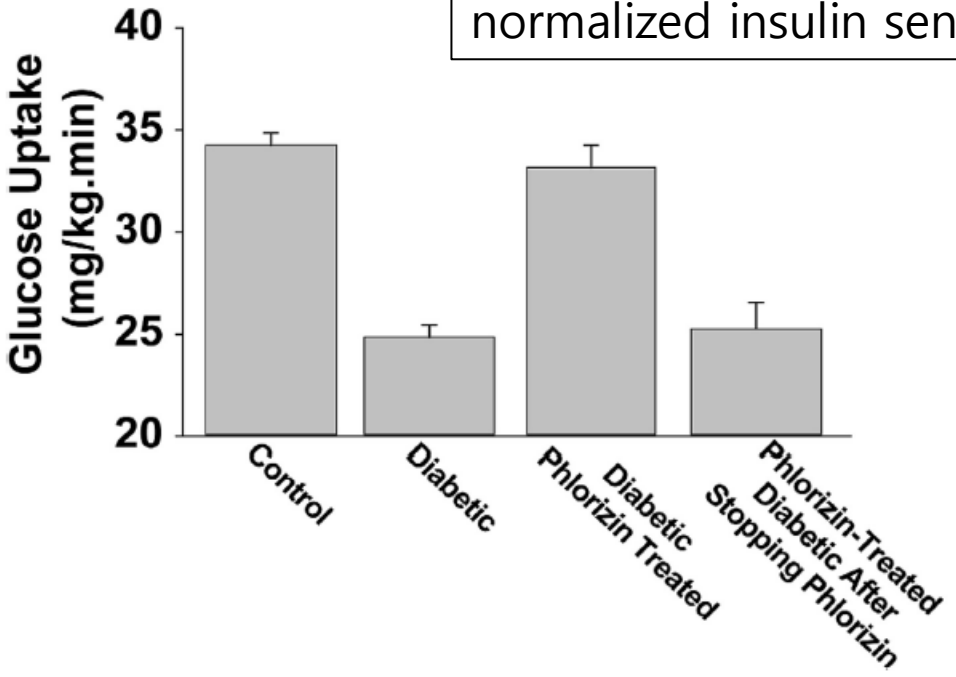
 Rossetti L, J Clin Invest 1987; 79: 1510–1515

Effect of SGLT2 inhibitors on insulin resistance

Experimental Protocol

- a 2-step euglycemic insulin clamp

Correction of hyperglycemia with phlorizin normalized insulin sensitivity in diabetic rats

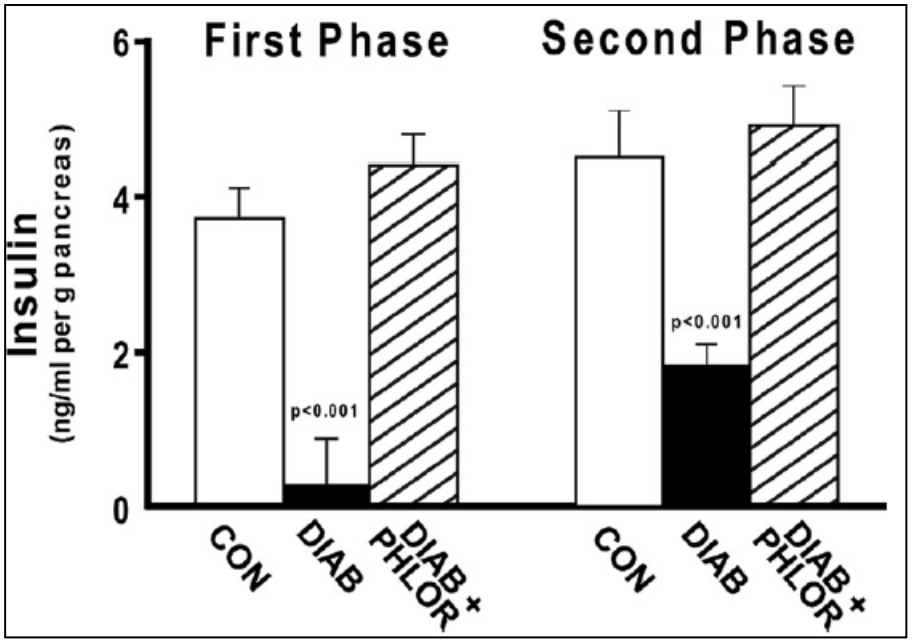


 Rossetti L, J Clin Invest 1987; 79: 1510–1515

SGLT2 inhibitors and β-cell function

Experimental Protocol

- Sprague Dawley rats; treatment period=3 weeks
  - Group I-sham operated
  - Group II- partial panx (90%)
  - Group III-partial panx + phlorizin
- Hyperglycemic clamp



Rossetti, J Clin Invest. 1987 ; 80(4): 1037–1044

Mechanism of Action of SGLT2 Inhibitors

Inhibition of renal SGLT2
⇒ reversal of hyperglycemia
⇒ reversal of "glucotoxicity"

⇑ **Insulin sensitivity in muscle**

⇑ **Insulin sensitivity in liver**

⇓ **Gluconeogenesis**

⇑ **Improved beta cell function**

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Rationale for SGLT2 Inhibition in Diabetes: Functional Disorders

- ❖Familial renal glucosuria
  - Due to SGLT2 gene mutations
- ❖Intestinal glucose-galactose malabsorption
  - Due to SGLT1 gene mutations
  - Severe diarrhea
    - Suggests major role for SGLT1 in intestinal reabsorption
    - Corrected by removing glucose, galactose, lactose from the diet
  - Mild glucosuria consistent with minor SGLT1 role in renal reabsorption

Wright EM. *J Intern Med*. 2007.

Familiar Renal Glucosuria

- Autosomal recessive
- Rare disorder of renal glucose transport
- Isolated defect of glucose reabsorption
- Mutations of SGLT2
- Characterized by persistent urinary glucose excretion, with normal plasma glucose concentration
- Urinary glucose excretion varies from a few grams to greater than 100g/day

Francis J, et al. Nephrol Dial Transplant. 2004;19:2893-2895

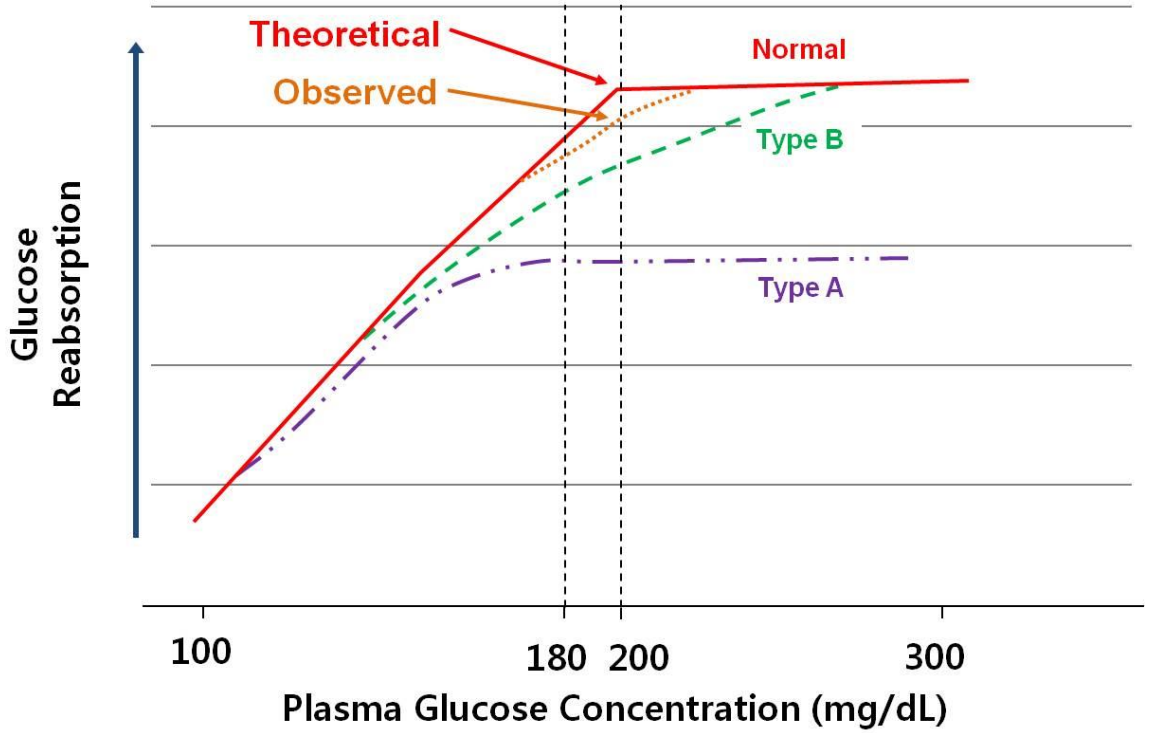
Familial Renal Glucosuria

Presentation	• Asymptomatic • No hypoglycemia or hypovolemia
Kidney / bladder	• No tubular dysfunction • Normal histology and function
Complications	• No increased incidence of – Chronic kidney disease – Diabetes – Urinary tract infection

Santer R, et al. *J Am Soc Nephrol.* 2003;14:2873-2882;
Wright EM, et al. *J Intern Med.* 2007;261:32-43.

2 Types of Familial Renal Glucosuria

Type A	Type B
•Decreased Tm for glucose	•Exaggerated splay
•Reduced amount of normal SGLT2 protein	•Reduced affinity of SGLT2 transporter for glucose



 Santer R, et al. *J Am Soc Nephrol.* 2003;14:2873-2882.

Analysis of SGLT2 Gene in Patients With Renal Glucosuria

- 23 families analyzed for mutations
- In 23 families, 21 different mutations were detected in SGLT2
- Cause of glucosuria in other 2 families remains unknown

Santer R, et al. *J Am Soc Nephrol.* 2003;14:2873-2882.

Analysis of SGLT2 gene in patients with renal glucosuria

- 14 of 21 individuals were homozygous or compound heterozygous with severe glucosuria = 15~200 grams/day
- Heterozygous family members had mild glucosuria (up to 4.4 grams/day) or no glucosuria
- Nonsense mutations, missense mutations, and small deletions were scattered over the SGLT2 coding sequence

Santer, J Am Soc Nephrol 14:2873-82, 2003

Renal Glucosuria: 20-Year Follow-up of the Original Patient

- On diagnosis at age 11:
  - 109-140g glucose excreted per day
  - Persistent nocturnal enuresis
  - Polyuria and polydipsia
  - Episodes of polyphagia
  - Marked delay of growth and puberty
- On reevaluation at age 31:
  - Reached a final height of 175cm and weight of 74kg; BP 125/85mmHg
  - No sign of hyperfiltration syndrome or microalbuminuria
  - Continued polyuria 3-5 L/day
  - Creatinine :0.6mg/dL; creatinine clearance;135mL/minute
  - No chronic nephrologic complications observed

Scholl-Bürgi,Nephrol Dial Transplant (2004) 19: 2394–2396

V. CONCLUSIONS

- SGLT2 inhibition represents a novel approach to the treatment of Type 2 DM
- Studies in experimental models of diabetes have demonstrated that induction of glucosuria restores normoglycemia and improves beta cell function and insulin sensitivity-reversal of glucotoxicity
- Genetic mutations leading to renal glucosuria have documented the long term safety of SGLT2 inhibition in man