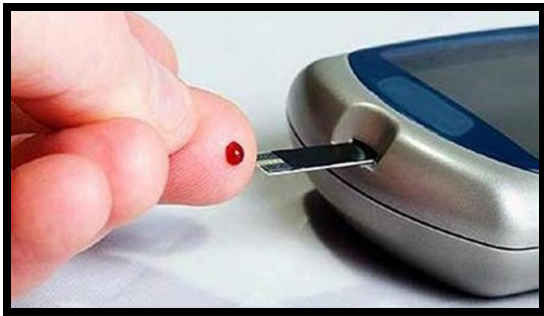
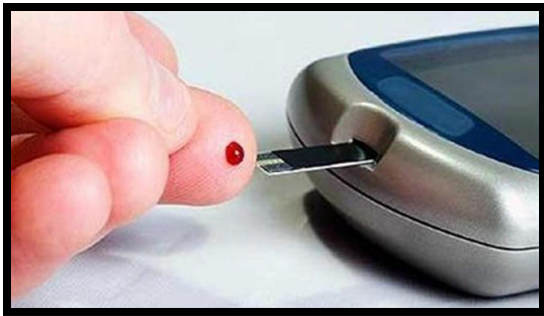


"Targeting SGLT2 Inhibitors for the Treatment of Type 2 Diabetes"

Ernest Wright
UCLA



"Targeting SGLT2 Inhibitors for the Treatment of Type 2 Diabetes"

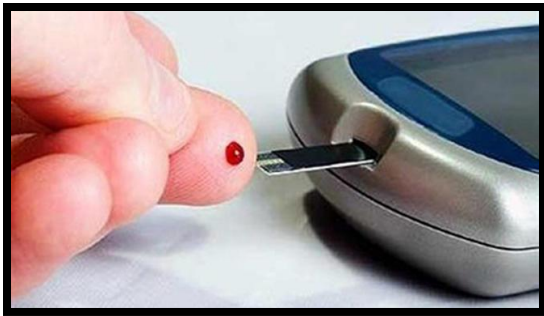


Diabetes mellitus - high blood glucose, large volumes of sweet urine

ASCPT 2016

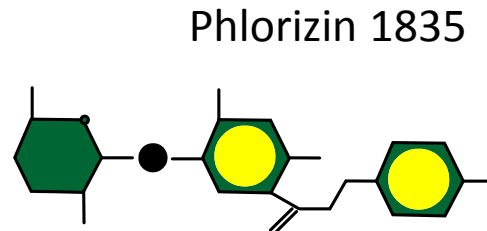
26 million patients in USA

"Targeting SGLT2 Inhibitors for the Treatment of Type 2 Diabetes"



Diabetes mellitus

ASCPT 2016



1886 Produces glucosuria



SGLT2 -1992

- SLC5A2 in SLC5 (Wright Lab) GENE Family

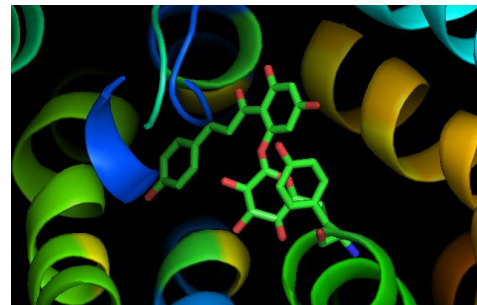
SLC5 12 genes

SLC 52 gene families

coding for 395 transporters

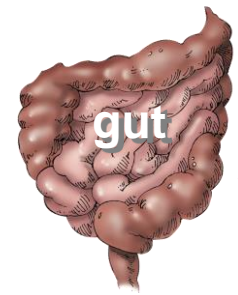
SGLT2 protein expression limited to kidney

Model of phlorizin binding site
in SGLT2

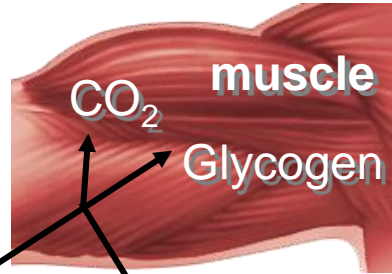


Glucose homeostasis

Dietary glucose
~ 180 g/day

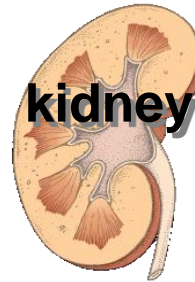
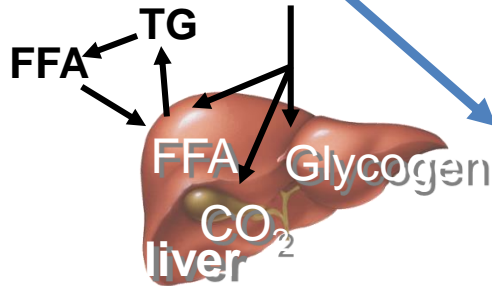
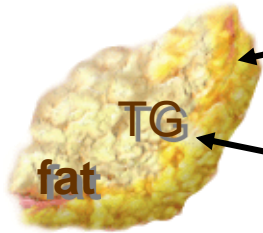


Brain Glucose Consumption
125 g/day



glucose

lactate

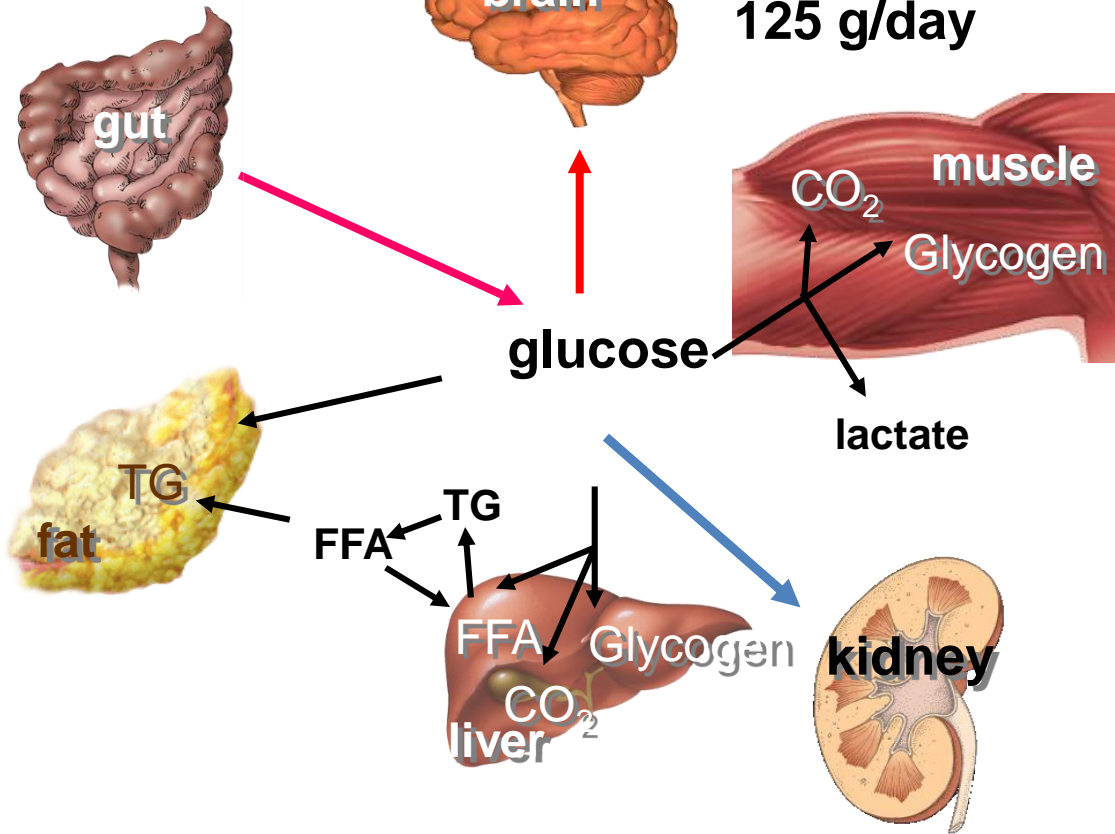


Glucose Renal excretion (< 0.5 grams/day)

Reabsorption 180 grams/day

Glucose homeostasis

Dietary glucose
~ 180 g/day



Brain Glucose Consumption
125 g/day

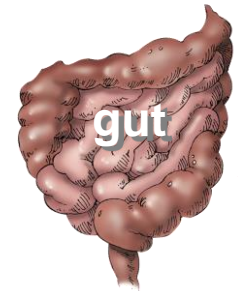
DIABETES

Blood Glucose up
- Low Insulin or
Insulin resistance

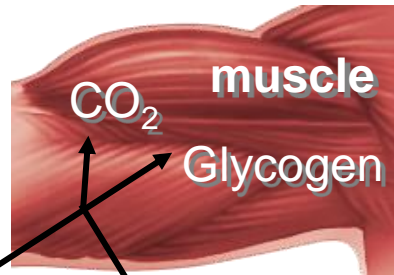
Glucose Renal excretion (> 0.5 grams/day)

Glucose homeostasis

Dietary glucose
~ 180 g/day

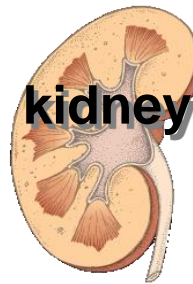
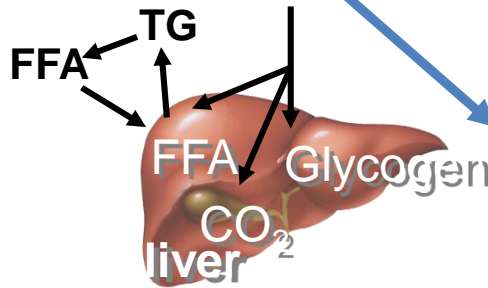
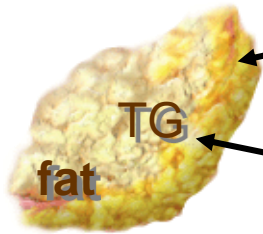


Brain Glucose Consumption
125 g/day



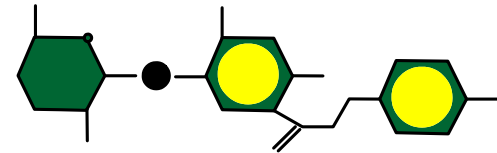
glucose

lactate



PHLORIZIN

Renal excretion
> 125 grams/day



Glucose transporters: two gene families

GLUTs (SLC2)

- Sodium independent
- Facilitated transporters
e.g. GLUT4

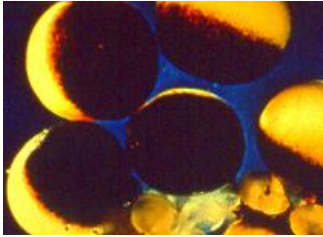


SGLTs (SLC5)

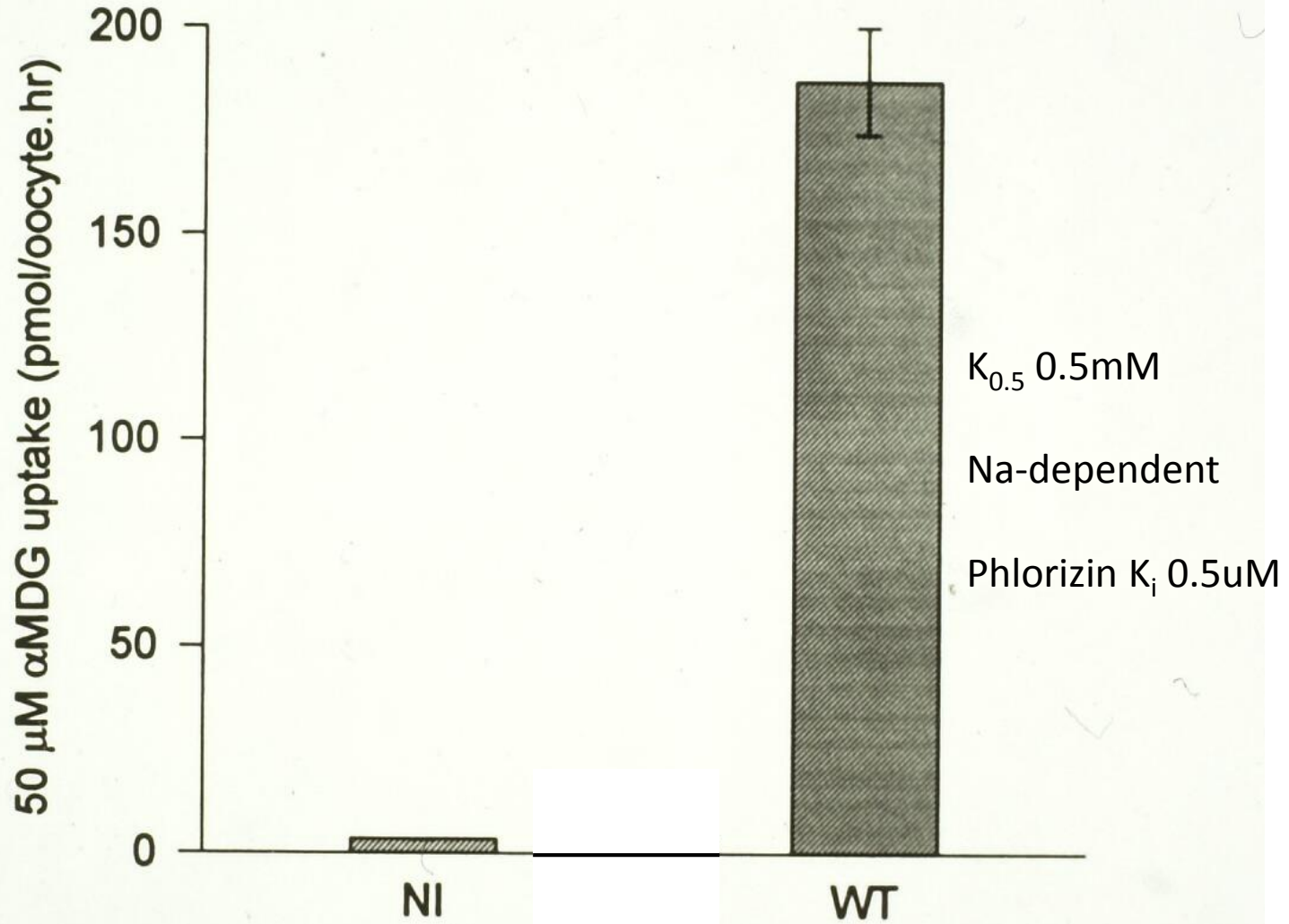
- Sodium/sugar cotransporters
- Symporters
e.g. SGLT2



Na/Glucose Cotransport in SGLT1 expressing cells



Oocytes/cell lines



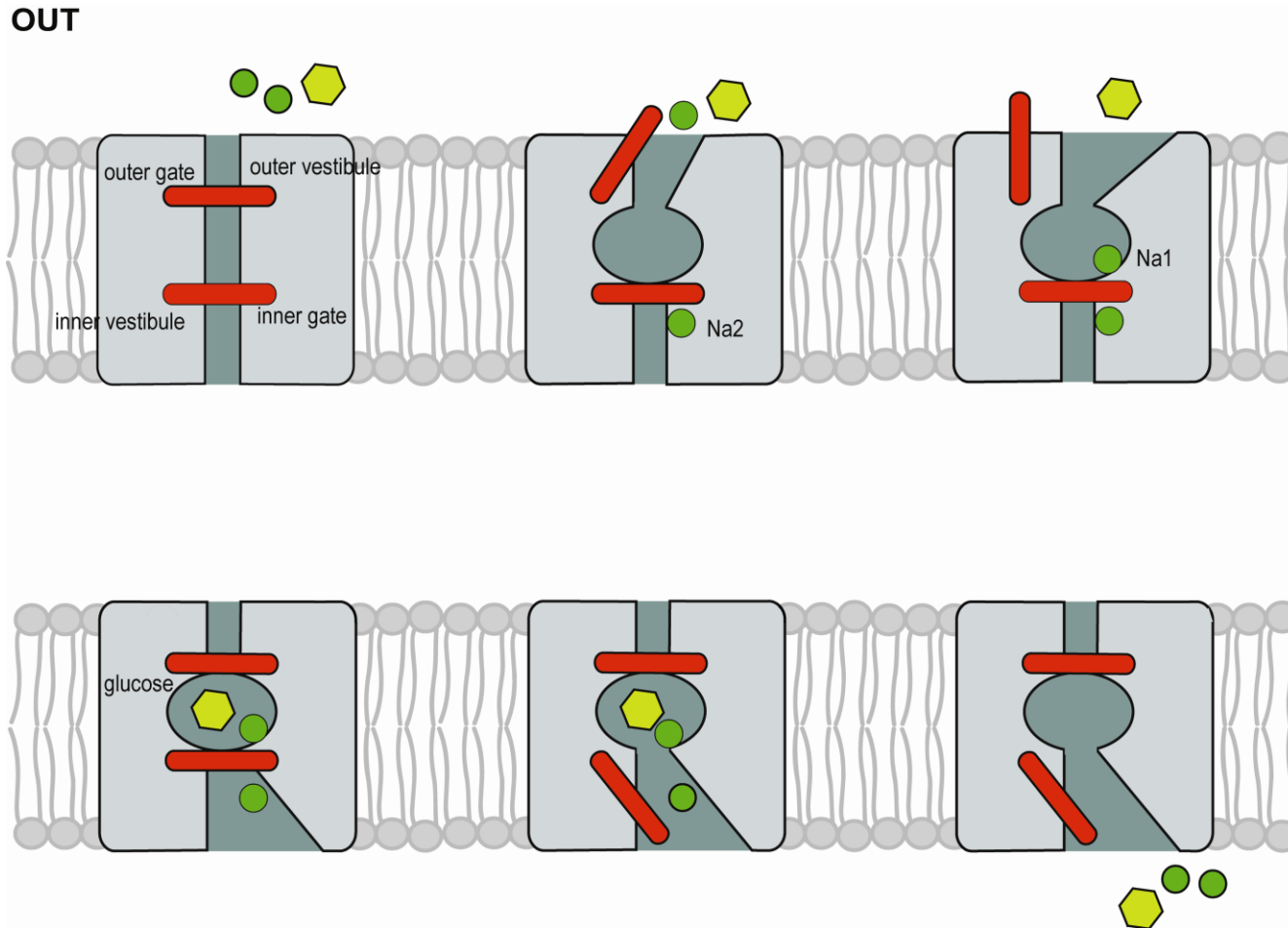
Natural substrates of the human SGLTs

Protein (<i>gene</i>)	Natural substrate
SGLT1 (<i>SLC5A1</i>)	Glucose, galactose
SGLT2 (<i>SLC5A2</i>)	Glucose
SGLT3 (<i>SLC5A4</i>)	Glucose sensor
SGLT4 (<i>SLC5A9</i>)	Mannose, Glucose
SGLT5 (<i>SLC5A10</i>)	Fructose, Mannose, Glucose, Galactose
SGLT6/SMIT2 (<i>SLC5A11</i>)	Chiro-inositol

Kinetic properties of hSGLT2 and hSGLT1

	hSGLT2	hSGLT1
Glucose Km (mM)	4.9 ± 0.6	1.8 ± 0.2
Na⁺:glucose coupling (<i>n</i>)	1:1	2:1
Phlorizin Ki (nM)	11 ± 0.9	140 ± 15

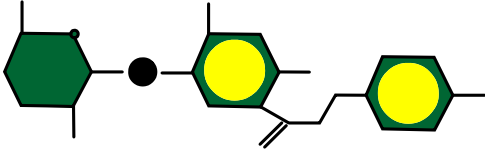
Model for SGLT Na-coupled sugar transport



PHLORIZIN BINDS FROM OUTSIDE TO GLUCOSE BINDING SITE

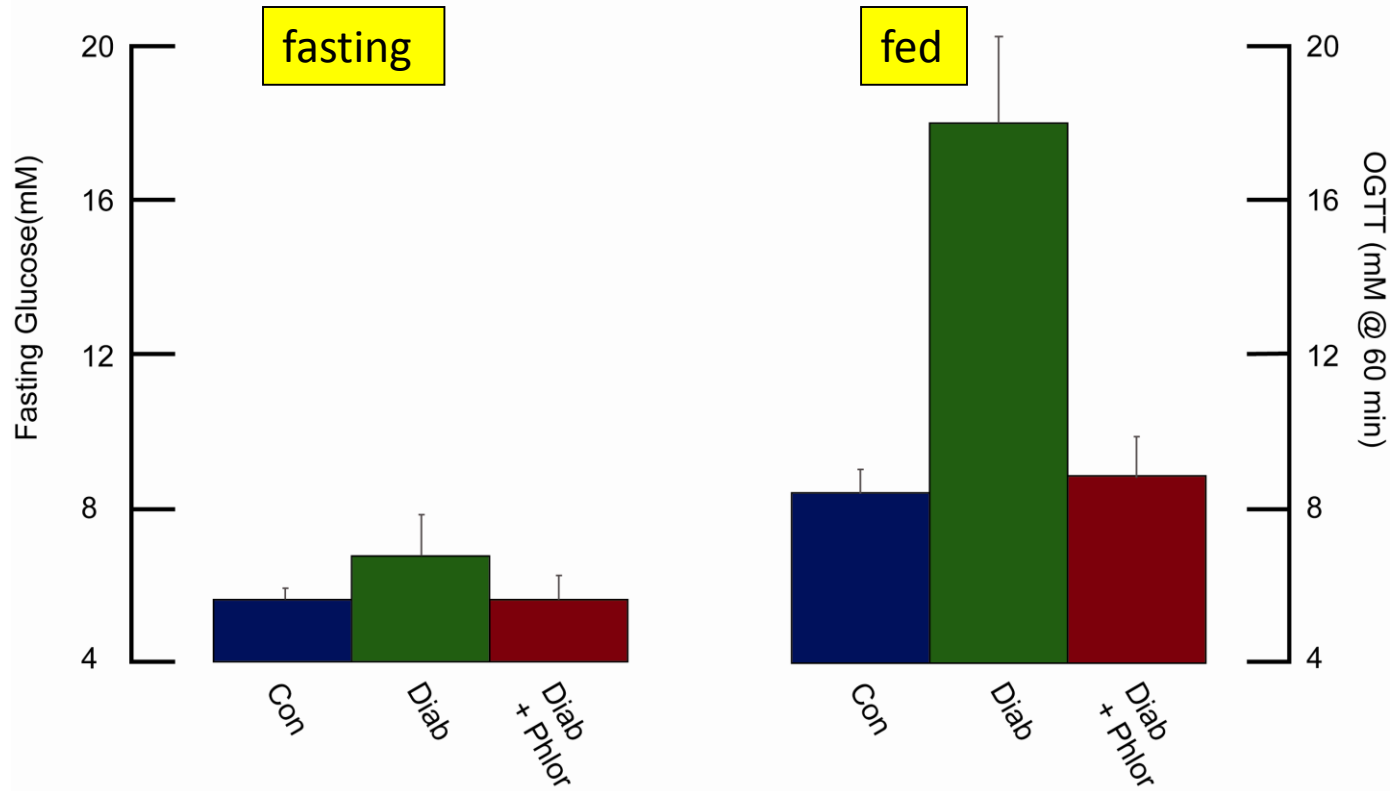
DIABETES

Ralph DeFronzo 1987



PHLORIZIN CORRECTS PLASMA GLUCOSE LEVELS IN DIABETES RATS

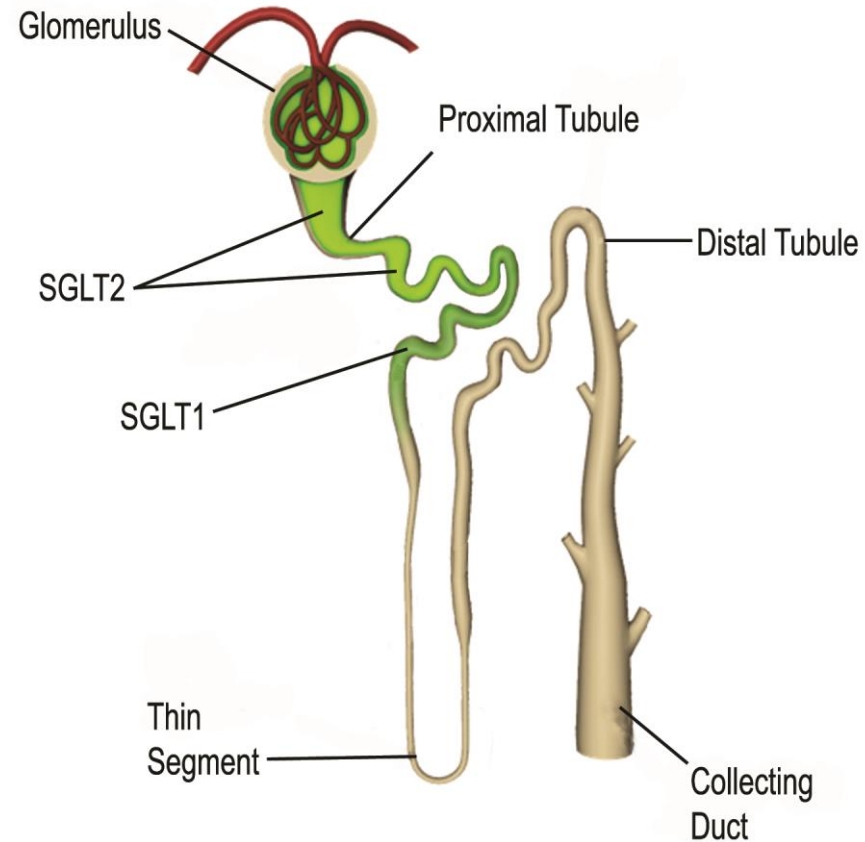
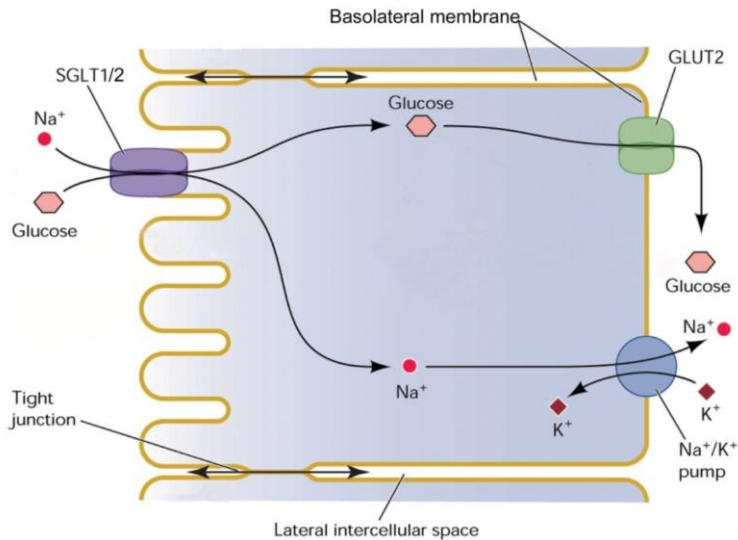
Rossetti, JCI 79:1510-15, 1987



Renal glucose handling

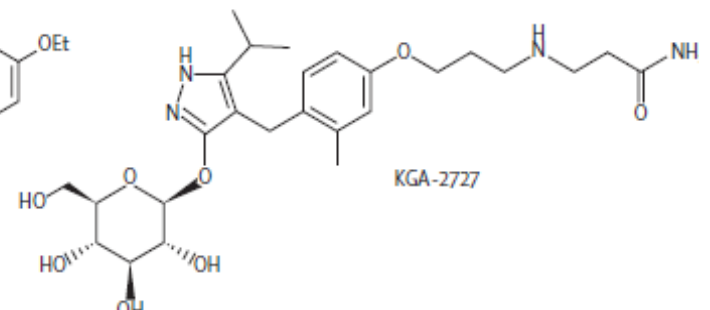
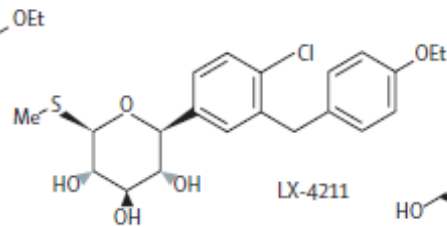
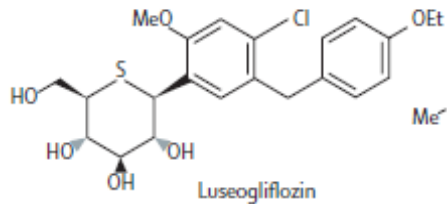
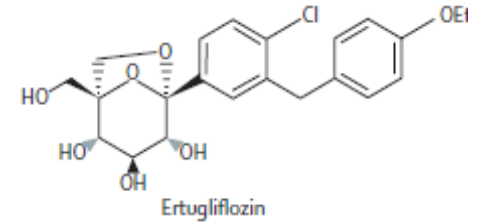
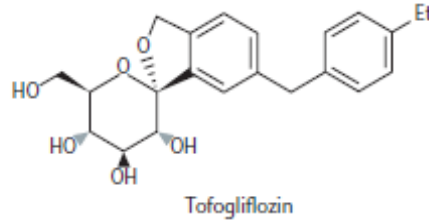
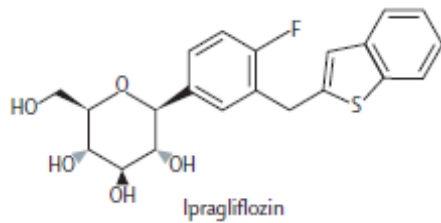
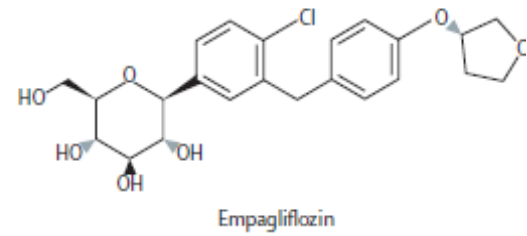
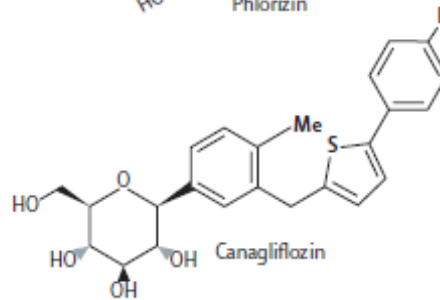
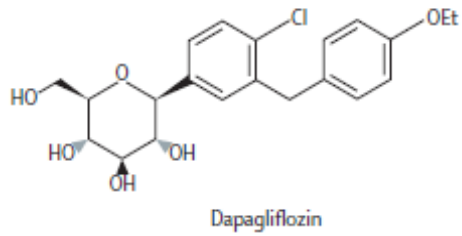
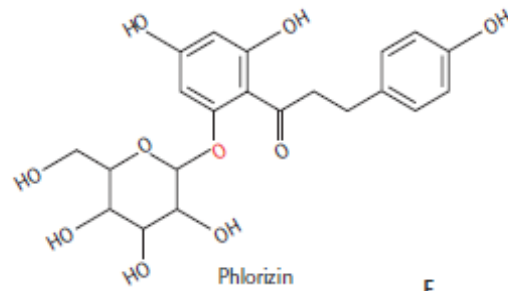
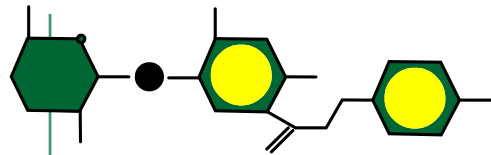
Proximal

Lumen



SGLT - Sodium Glucose transporter

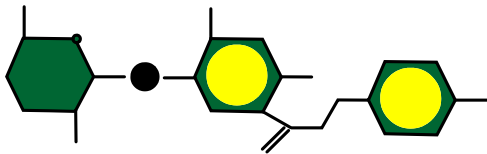
GLUT - Glucose Transporter



Inhibitors of SGLT2 and SGLT1

The inhibitors are variants of phlorizin.

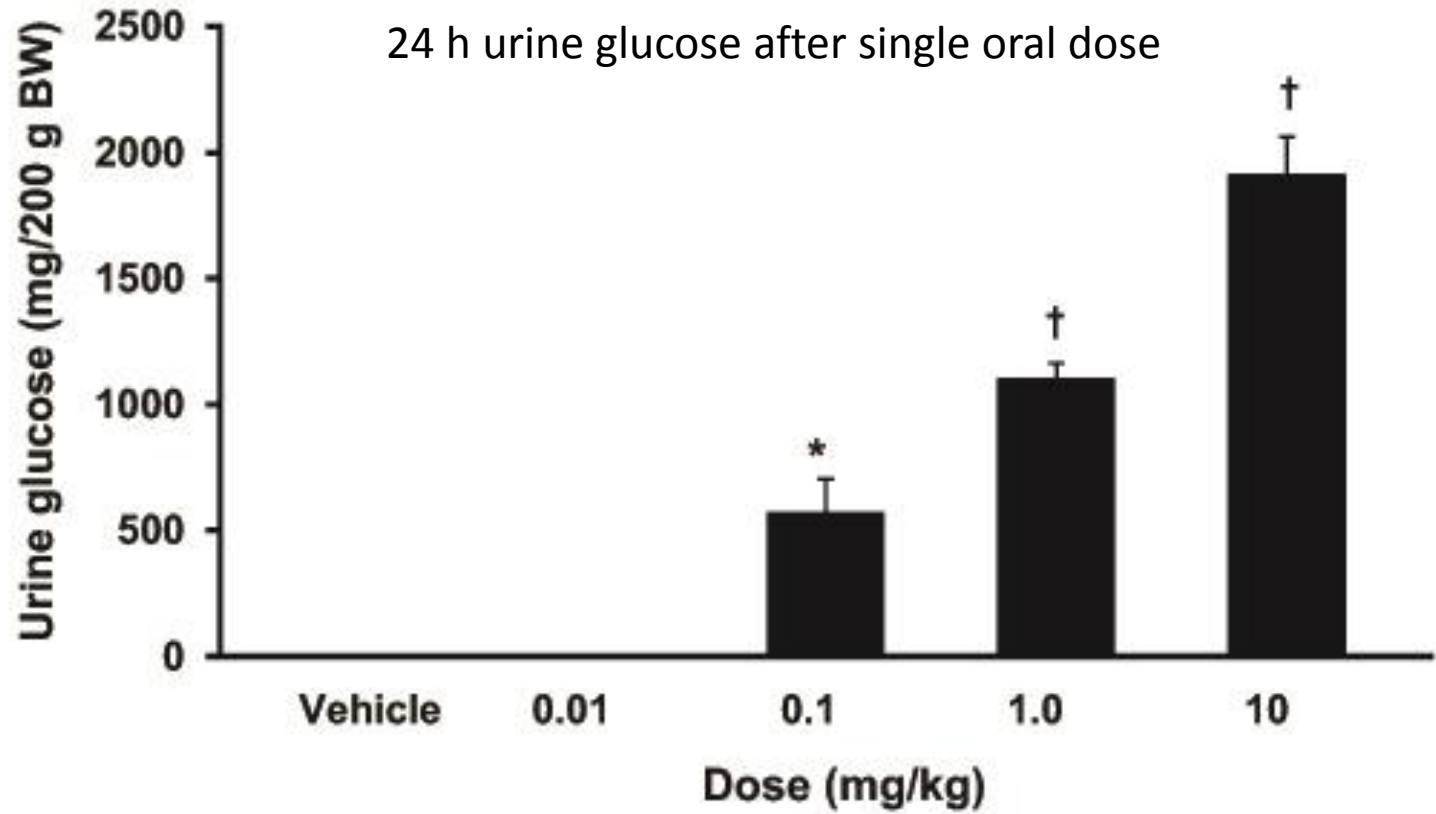
Inhibitors of human SGLT2 and SGLT1



EC₅₀ values in
Nanomolar in cells

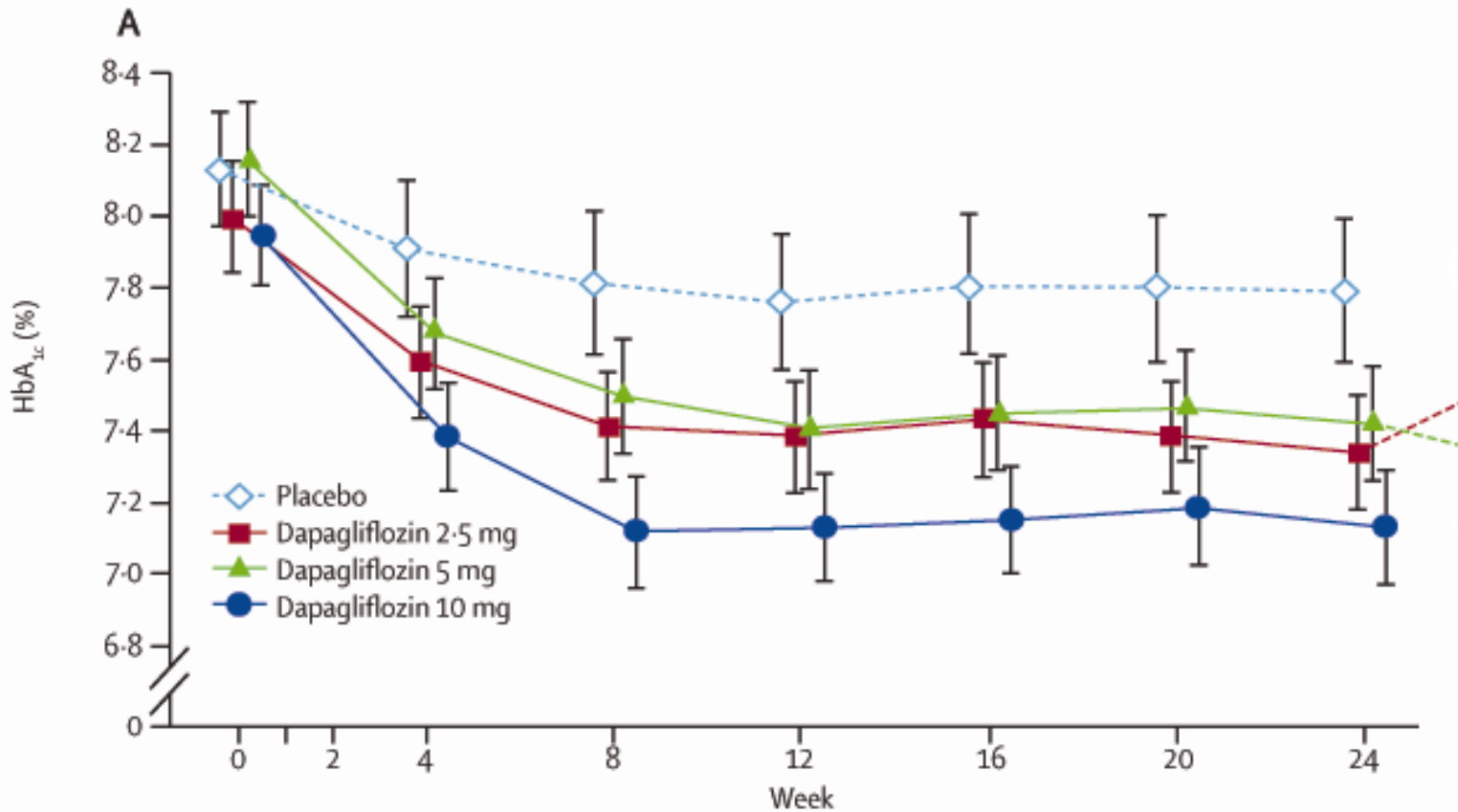
	SGLT2	SGLT1
Dapagliflozin	1	1,400
Canagliflozin	3	710
Empagliflozin	3	8,300
Ipragliflozin	5	3,000
Tofogliflozin	6	12,000

Dapagliflozin* increases renal glucose excretion in rats



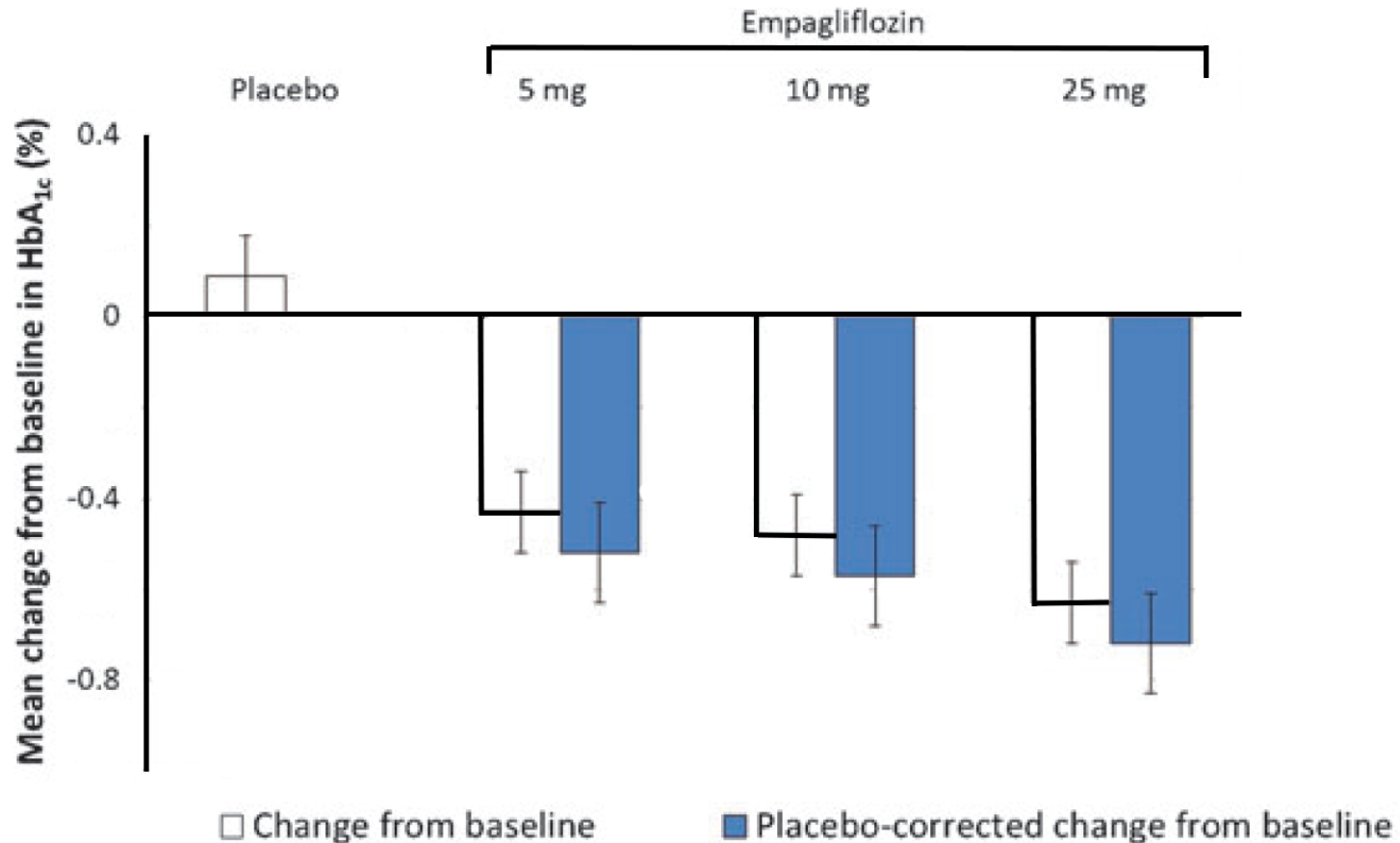
*BMS

TIME COURSE OF CHANGE IN HbA_{1c} IN DAPAGLIFLOZIN*-TREATED DIABETIC SUBJECTS



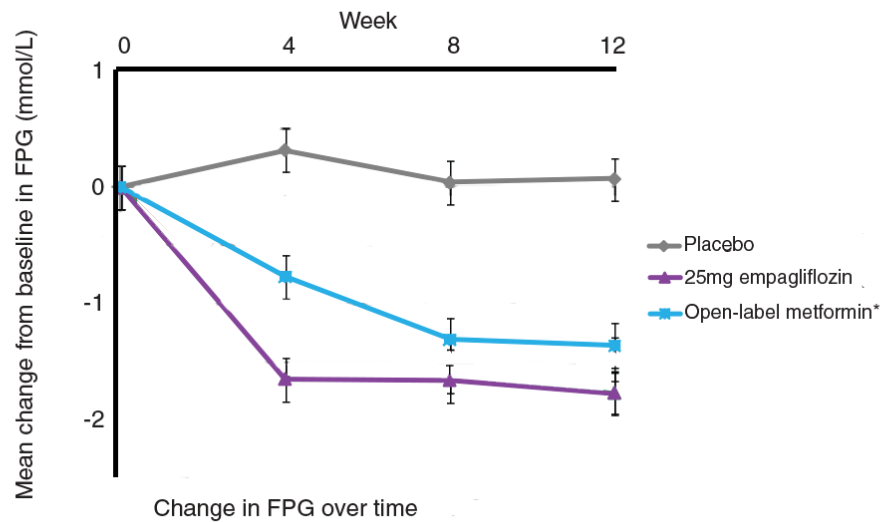
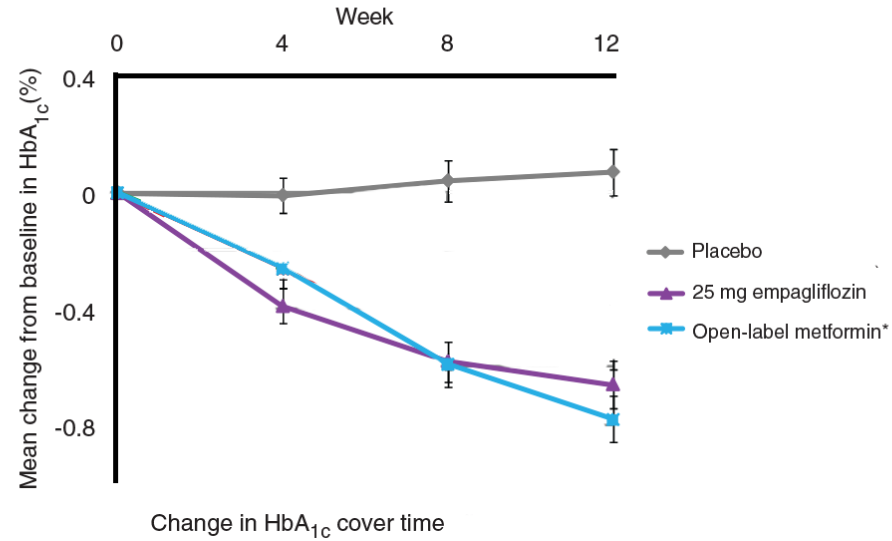
* BMS

Phase IIb study of the SGLT2 inhibitor Empagliflozin* in patients with type 2 diabetes



* BI

Phase IIb study of the SGLT2 Empagliflozin* in DMT2 patients



*BI

SGLT2 Inhibitors

Lowers fasting and postprandial plasma glucose
30 – 60 mg% (without hypoglycemia)

Lose 2-3% body weight

Reduction of blood pressure 5 mm Hg

Adverse side effects

Genital infections (5% female 2% male)

Contraindications

Severe renal impairment (<30 mL/min/1.73 m²)

SGLT2 INHIBITORS TO TREAT T2DM

InvokanaTM
canagliflozin tablets



Jardiance[®]
(empagliflozin) tablets
10 mg/25 mg

SUCCESS* WITH SGLT2 INHIBITORS TO TREAT T2DM - A CHRONIC DISEASE IN 8% OF POPULATION

RECOGNITION THAT INHIBITING KIDNEY GLUCOSE REABSORPTION MIGHT REGULATE PLASMA GLUCOSE

SGLT2 PROTEIN EXPRESSION LIMITED TO KIDNEY CORTEX

NATURAL COMPOUND PHLORIZIN IS VERY SPECIFIC FOR SGLTS

GREAT CHEMISTRY

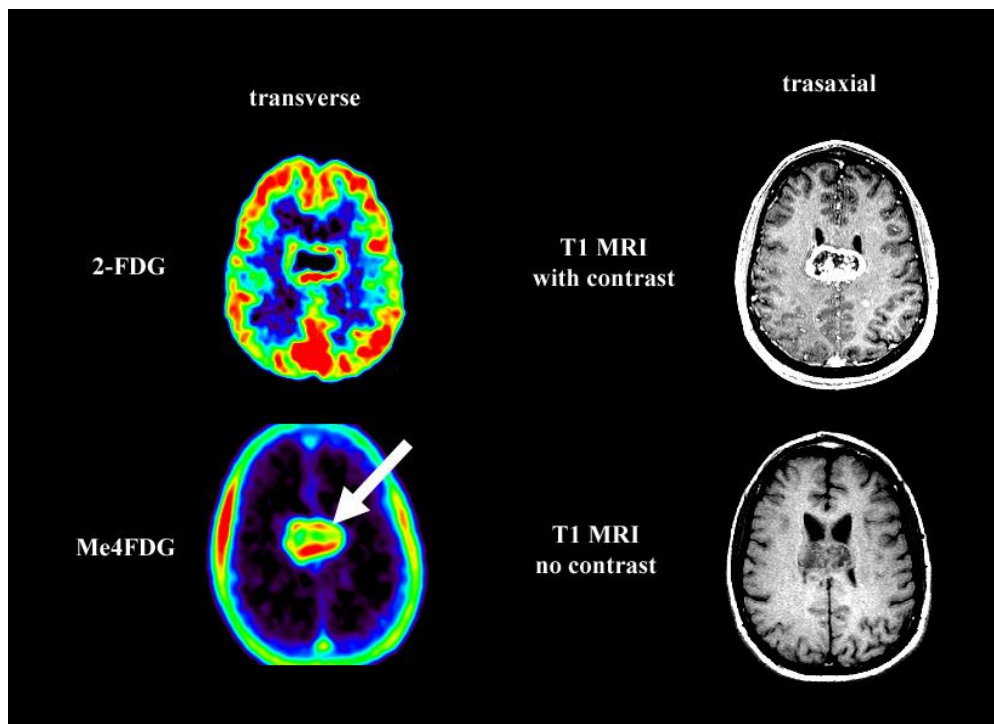
DRUGS WITH LONG PLASMA LIFE TIME

METABOLITES INACTIVE AND EXCRETED BY KIDNEY AND LIVER

ISSUES?

* > \$1 Billion/yr in sales

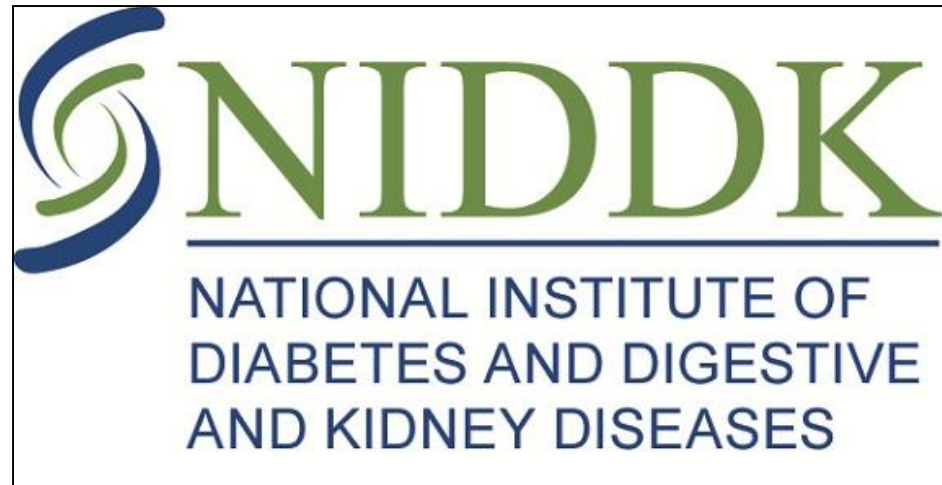
TUMORS, INCLUDING GLIOBLASTOMAS, DETECTED USING Me4FDG PET



SGLT2 INHIBITORS TO TREAT T2DM



EMW Supported by Grants from



DK19567-01-034



Familial Renal Glucosuria (FRG) SGLT2 mutations

PATIENTS WITH ISOLATED GLUCOSURIA 1-202 g/1.73 m² /d

Rare Autosomal Recessive

60% with homozygous and 40% with compound heterozygous mutations

Missense (17), Nonsense (3), Frame shift (3), Splice site (1), Deletions (4)

A Patient with premature stop codons, e.g. 347X, has a severe glucosuria (126-162 g/1.73 m² /d), whereas one with another, W440X, has only 69 g/1.73 m² /d

Van den Heuvel (2002)

Caldo (2004)

Santer (2004)

Geller (2004)

Magen(2005)