PHARMACOLOGY

Drugs for Diabetes

Non-insulin

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What was one of your highlights from summer break?

0

Nobody has responded yet.

Hang tight! Responses are coming in.

DISCLOSURE

None

OBJECTIVES

1. Identify appropriate drugs and drug classes for managing diabetes.
2. Explain the mechanism of action of drug classes (sulfonylureas, glucagon-like peptide [GLP-1] receptor agonists, dipeptidyl peptidase inhibitors [DPP-4] inhibitors, biguanides, thiazolidinediones, and sodium-glucose co-transporter 2 [SGLT2] inhibitors) for managing diabetes and how this relates to the underlying pathophysiology of their clinical use.
3. State adverse effects and contraindications to sulfonylureas, glucagon-like peptide (GLP-1) receptor agonists, dipeptidyl peptidase inhibitors (DPP-4) inhibitors, biguanides, thiazolidinediones, and sodium-glucose co-transporter 2 (SGLT2) inhibitors.
4. Describe the clinically important drug interactions of sulfonylureas, glucagon-like peptide (GLP-1) receptor agonists, dipeptidyl peptidase inhibitors (DPP-4) inhibitors, biguanides, thiazolidinediones, and sodium-glucose co-transporter 2 (SGLT2) inhibitors.
5. Identify drugs for managing diabetes that may also be used for the management of obesity.

Insulin, integral to the management of diabetes, will be covered elsewhere in the curriculum.

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PRE-ASSESSMENT

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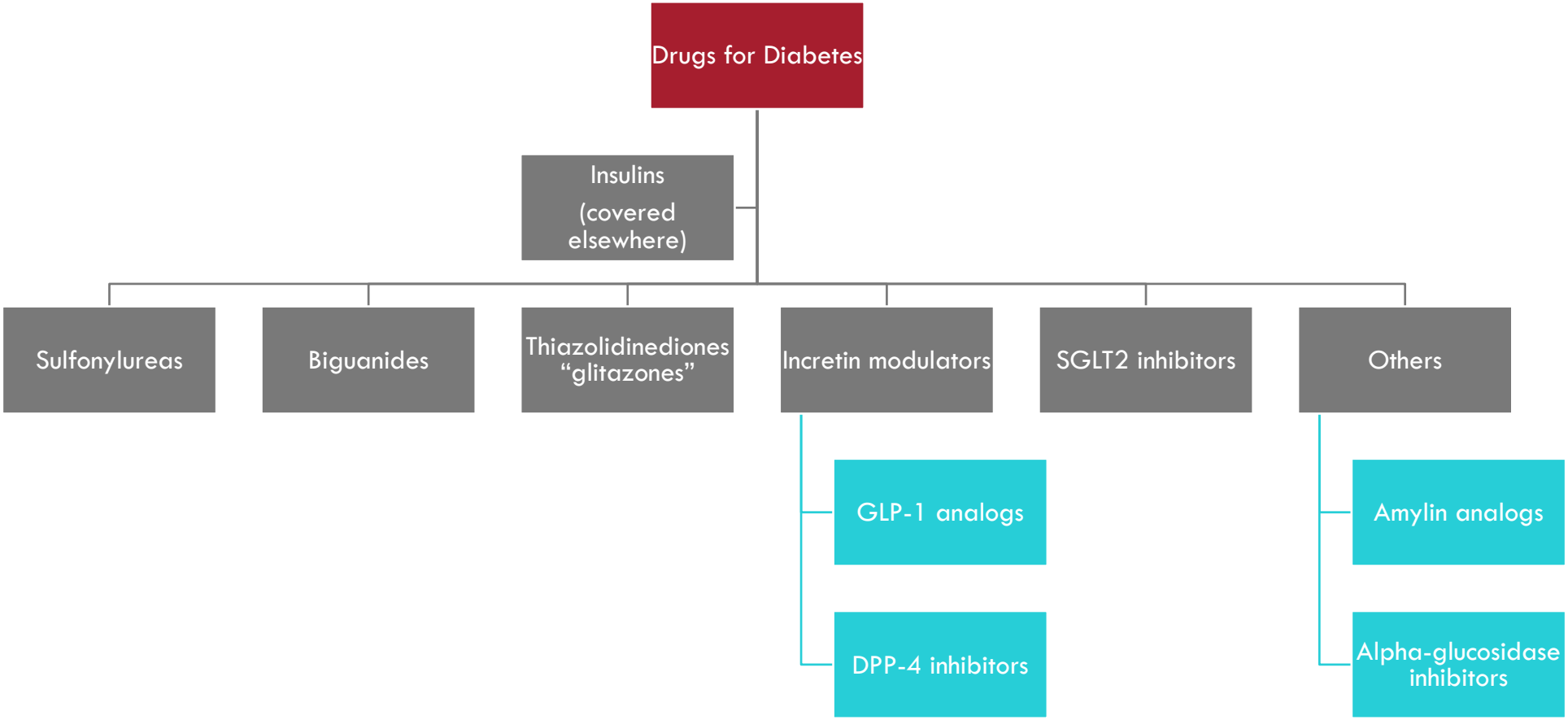
INTRODUCTION


Drugs for Diabetes
Insulins (covered elsewhere)
Sulfonylureas
Biguanides
Thiazolidinediones "glitazones"
Incretin modulators
SGLT2 inhibitors
Others
GLP-1 analogs
DPP-4 inhibitors
Amylin analogs
Alpha-glucosidase inhibitors

INSULIN EFFECTS

INCREASE SECRETION OF INSULIN

ACTION TYPE

DIRECT

- Sulfonylureas
- Meglitinides

INDIRECT

Glucose-Induced

- GLP-1 Receptor Agonists
- Dipeptidyl Peptidase Inhibitors (DPP-4 inhibitors)

"SECRETAGOGUES"

INSULIN EFFECTS

ACTION TYPE	INCREASE SECRETION OF INSULIN	INCREASE SENSITIVITY TO INSULIN
DIRECT	• Sulfonylureas • Meglitinides	• Biguanides (also decrease intestinal absorption) • Thiazolidinediones (TZDs)
INDIRECT	**Glucose-Induced** • GLP-1 Receptor Agonists • Dipeptidyl Peptidase Inhibitors (DPP-4 inhibitors)	• Amylin analogs
	"SECRETAGOGUES"	"SENSITIZERS"

INSULIN EFFECTS

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	"SECRETAGOGUES"	"SENSITIZERS"

NUTRIENT LOAD EFFECTS

ACTION TYPE	REDUCERS
ABSORPTION INHIBITORS	• Alpha-glucosidase inhibitors • Biguanides (also increase insulin sensitivity)
EXCRETION ENHANCERS	• Sodium-glucose co-transporter 2 (SGLT2) inhibitors

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INTRODUCTION

PATHOPHYSIOLOGY

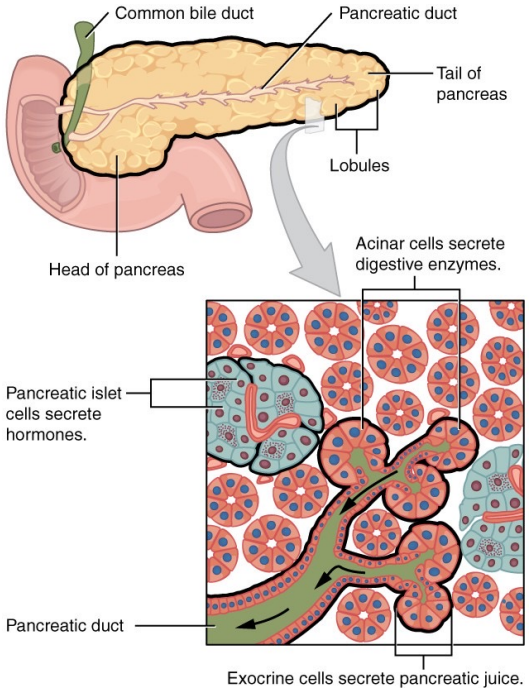
Inadequate control of plasma glucose

Various classifications (Type 1, Type 2, gestational, steroid-induced, etc.)

Pancreatic islets of Langerhans secrete:

- Insulin (beta-cells)
- Glucagon (alpha-cells)
- Others (amylin, ghrelin, somatostatin, pancreatic peptide)

Insulin is absent or has impaired actions → hyperglycemia



INSULIN SECRETION

Naturally at a basal rate

Stimuli

- Glucose and other sugars
- Amino acids such as leucine, arginine
- Hormones such as
  - Glucagon-like polypeptide 1 (GLP-1)
  - Glucose-dependent insulinotropic polypeptide (GIP)
  - Glucagon
  - Cholecystokinin
- High concentrations of fatty acids
- Beta-adrenergic sympathetic activity

ACTIVE LEARNING

Based on what you know about the pathophysiology of diabetes and contributors to insulin secretion, what are potential drug therapy targets? Please annotate the screen with your answers.

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SULFONYLUREAS

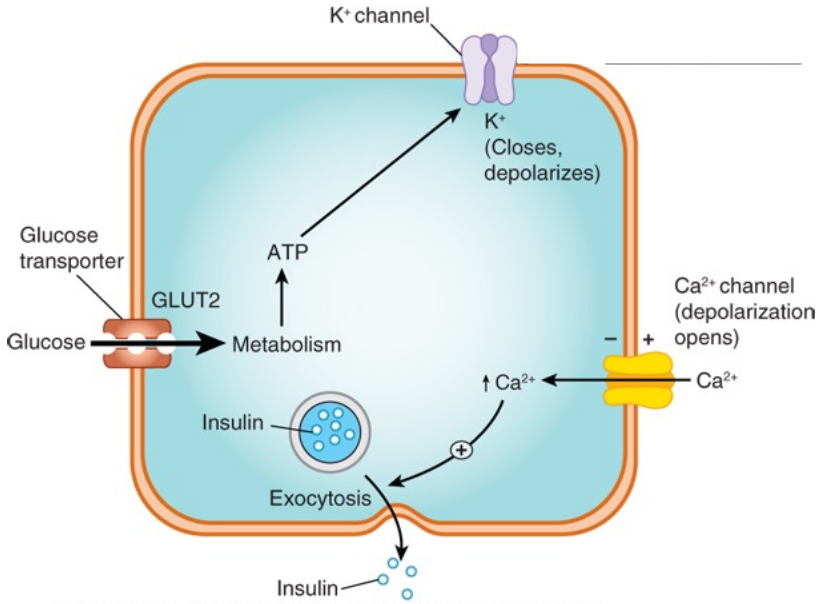
GLUCOSE-DEPENDENT INSULIN RELEASE

Pancreatic beta-cells

↑ extracellular glucose concentrations → glucose entering cells via GLUT2 glucose transporter

Leads to ↑ intracellular ATP production → closure of ATP-dependent K+ channels

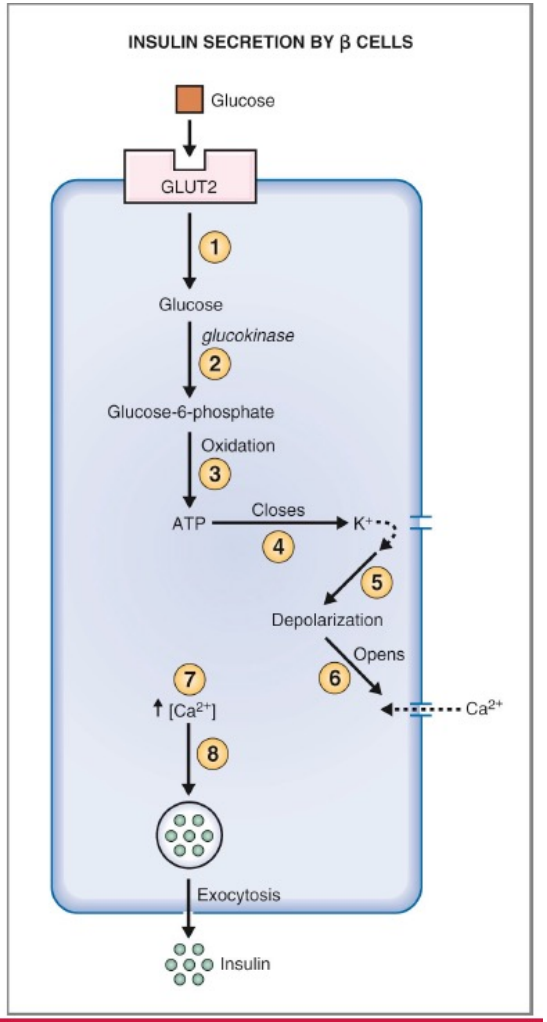
Leads to membrane depolarization → opening of voltage-gated Ca2+ channels → ↑ intracellular Ca2+ → **insulin secretion**



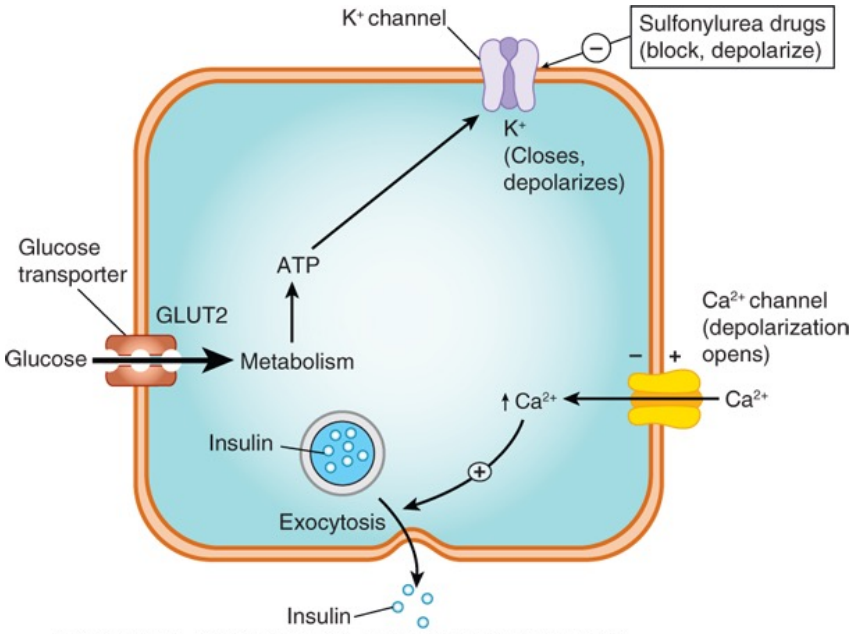
B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

Insulin Secretion

1. Transport of glucose into the β cell.
2. Phosphorylated to glucose-6-phosphate by glucokinase.
3. Glucose-6-phosphate is subsequently oxidized, producing ATP.
4. ATP closes ATP-sensitive K^+ channels.
5. Depolarizes the β cell membrane.
6. Depolarization caused by ATP opens these Ca^{2+} channels.
7. Intracellular Ca^{2+} concentration increases.
8. Increased intracellular Ca^{2+} causes insulin secretion.



SULFONYLUREA MOA: PANCREATIC



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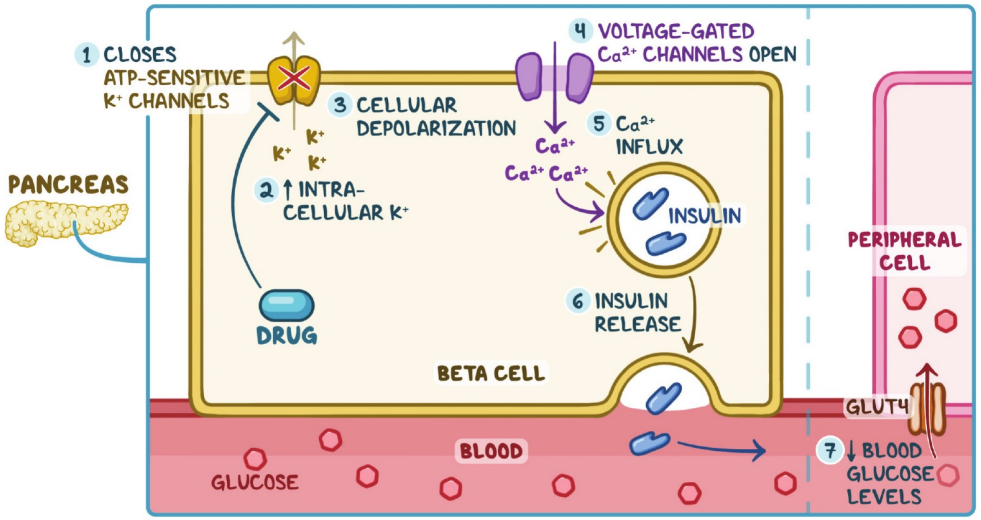
SULFONYLUREA MOA: PANCREATIC

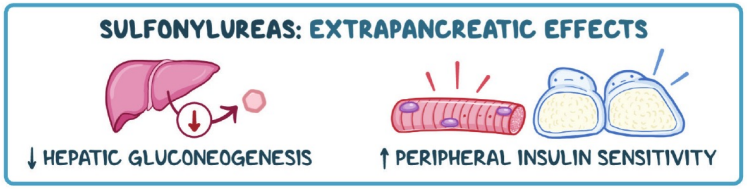
1. Bind to high-affinity sulfonylurea receptor associated with beta-cell inward rectifier ATP-sensitive potassium channel
    1. Close ATP-sensitive potassium channels (K-ATP channels)
2. ↑ intracellular K+
3. Cell depolarization
4. Opening of voltage-gated Ca2+ channels
5. Calcium influx (↑ intracellular calcium)
6. Preformed insulin release
7. ↓ glucose levels



SULFONYLUREA MOA: EXTRAPANCREATIC

↓ hepatic gluconeogenesis
- Less glucose production

↑ peripheral insulin sensitivity
- Enhanced response to insulin



ACTIVE LEARNING

Considering the mechanism of action of sulfonylureas, what adverse effects might be associated with their use? Please annotate the screen with your answers.

SULFONYLUREAS (-IDE)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Second Gen Glipizide Glyburide Glimepiride	Type 1 DM DKA Sulfonamide allergy*	Hypoglycemia Weight gain GI Upset SJS (rare) Disulfiram-like reactions with first gen	May potentiate effects of other hypoglycemics Highly protein-bound sulfonylureas may compete for binding sites
First Gen Chlorpropamide Tolbutamide Tolazamide			

*Scientific basis has been challenged

ACTIVE LEARNING

Glyburide has a plasma half-life ($t_{1/2}$) of 1-2 hours and is hepatically metabolized to products with hypoglycemic activity.

Glipizide ($t_{1/2}$ = 2 – 4 hours) and glimepiride ($t_{1/2}$ = 5 - 9 hours) are metabolized to products with weak or no activity.

Which sulfonylurea would have the shortest biologic effect? Longest?

Which sulfonylurea might be best for use in an older adult?

CLINICAL USE & ADME

Type 2 DM

Glyburide hepatically metabolized to products with hypoglycemic activity

Glipizide and glimepiride metabolized to products with weak or no activity

ACTIVE LEARNING

An oral glucose load provokes a higher insulin response compared with an equivalent dose of glucose given intravenously.

Which hormones are thought to be responsible for this phenomenon?

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INCRETIN MODULATORS

INCRETINS

Hormones secreted from enteroendocrine cells w/in minutes of eating

- Insulin secretory response of incretins (incretin effects) accounts for ≥50% of total insulin secreted after oral glucose ingestion

Regulate the amount of insulin that is secreted

Incretins

- Glucagon-like peptide-1 (GLP-1)
- Glucose-dependent insulinotropic peptide (GIP)

Rapidly deactivated by dipeptidyl peptidase 4 (DPP-4)

INCRETIN MODULATORS FOR DIABETES

GLP-1 Receptor Agonists

Dual-acting GLP-1 and GIP Receptor Agonists

DPP-4 Inhibitors

GLP-1 RECEPTOR

Glucagon family of GPCRs

Found on various tissues

- Pancreatic beta cells, pancreatic ducts, gastric mucosa, kidney, lung, heart, skin, immune cells

Increases cAMP and free intracellular concentration of calcium

GLP-1 RECEPTOR AGONIST MOA

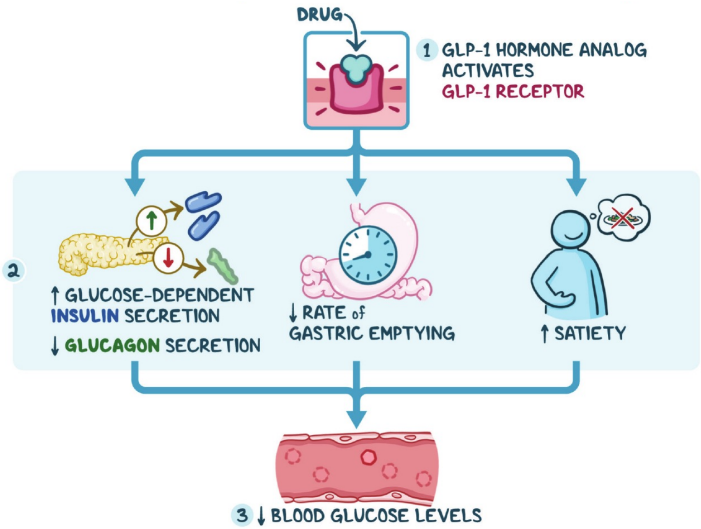
Activate GLP-1 receptors (analogs)

Binding
- Activates cAMP-PKA pathway and several GEFs
- Initiates signaling via PKC and PI3K
- Alters activity of several ion channels

Results in pancreas
- ↑ glucose dependent insulin secretin
- ↓ glucagon secretion

Results in CNS
- ↓ rate of gastric emptying
- ↑ satiety

Ultimately
- ↓ blood glucose levels



INCRETIN MODULATORS: GLP-1 RAs (-GLUTIDE/-TIDE)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
GLP-1 RAs Dulaglutide 💉 (Trulicity) Liraglutide 💉 (Saxenda, Victoza) Semaglutide 💉💊 (Ozempic, Rybelsus, Wegovy) Exenatide 💉 (Byetta)	History of pancreatitis, medullary thyroid cancer T1DM <u>Cautions:</u> Gastroparesis Renal impairment	GI (nausea, vomiting) Pancreatitis Increase satiety Weight loss Injection site reactions	Increased risk of hypoglycemia May delay absorption of other medications

Boxed Warnings: Risk of thyroid C-cell tumors

GLP-1 RECEPTOR AGONISTS & OBESITY

FDA approved semaglutide in 2021 for weight loss

Semaglutide
- Sold as Wegovy

Liraglutide

DUAL-ACTING GLP-1/GIP RAs MOA

Dual GLP-1 and GIP receptor agonist

Dual agonism ability leads to more significant reduction of hyperglycemia than GLP-1 agonist agents alone

Stimulates insulin release from the pancreas

↑ levels of adiponectin

Lowers appetite

INCRETIN MODULATORS: DUAL-ACTING GLP-1/GIP RAs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Dual GLP-1 and GIP receptor agonist Tirzepatide 💉 (Mounjaro)	History of medullary thyroid cancer T1DM	**GI symptoms (pain, constipation, decreased appetite, dyspepsia, nausea, vomiting)** AKI Diabetic retinopathy Gallbladder disease	Increased risk of hypoglycemia May delay absorption of other medications
Boxed Warnings: Risk of thyroid C-cell tumors			

DPP-4 INHIBITOR ("GLIPTIN") MOA

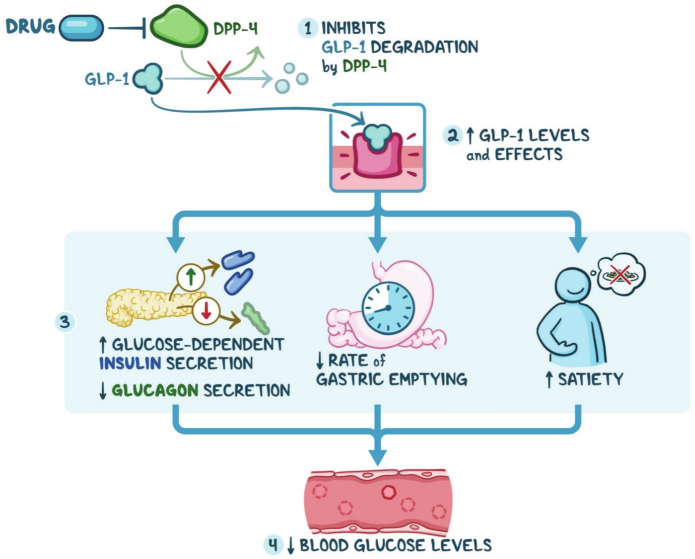
Inhibit GLP-1 degradation by DPP-4

- DPP-4 is serine protease that deactivates GLP-1 and GIP

↑ GLP-1 and GIP levels/effects

- ↑ glucose-dependent insulin secretion
- ↓ glucagon secretion
- May ↓ rate of gastric emptying, ↑ satiety

↓ blood glucose



INCRETIN MODULATORS: DPP-4 INHIBITORS (-GLIPTIN)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
DPP-4 Inhibitors Linagliptin (Tradjenta) Saxagliptin (Onglyza) Sitagliptin (Januvia)	Concurrent GLP-1 RA use	Respiratory and urinary infections Weight neutral Increased satiety GI upset Nasopharyngitis **Pancreatitis** **Heart failure** Joint pain disease	Increased risk of hypoglycemia May delay absorption of other medications

CLINICAL USE

T2DM

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BIGUANIDES

Sensitizer
Nutrient Load Reducer

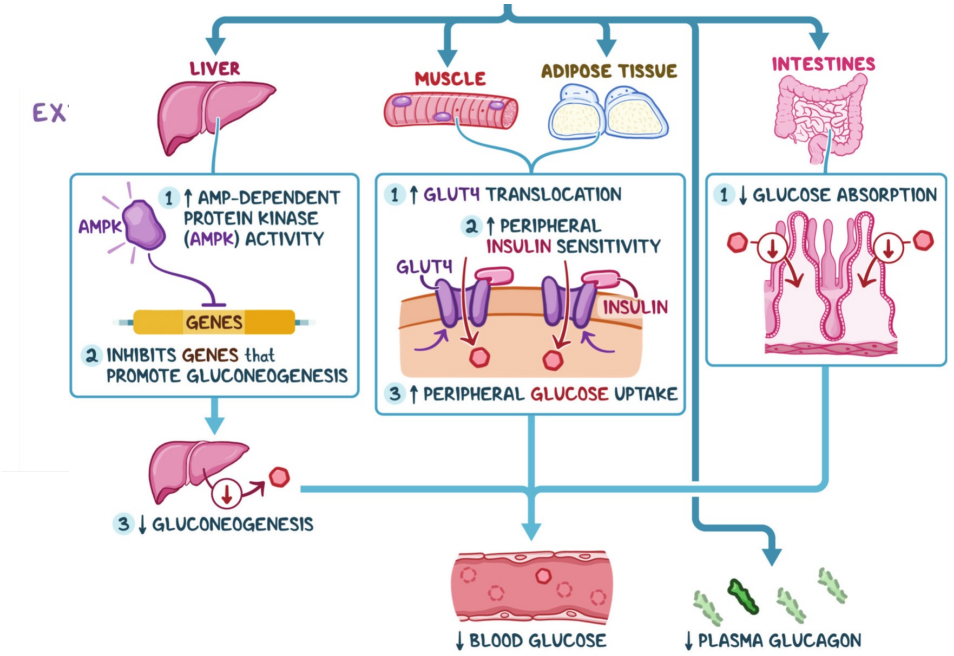
BIGUANIDES (METFORMIN) MOA

↑ hepatic AMP-dependent protein kinase activity ⟶ ↓ genes that promote gluconeogenesis ⟶ inhibit gluconeogenesis ⟶ ↓ blood glucose

↑ adipose/muscle GLUT4 translocation ⟶ ↑ peripheral insulin sensitivity ⟶ ↑ peripheral glucose uptaee ⟶ ↓ blood glucose

↓ intestinal glucose absorption ⟶ ↓ blood glucose

↓ plasma glucagon



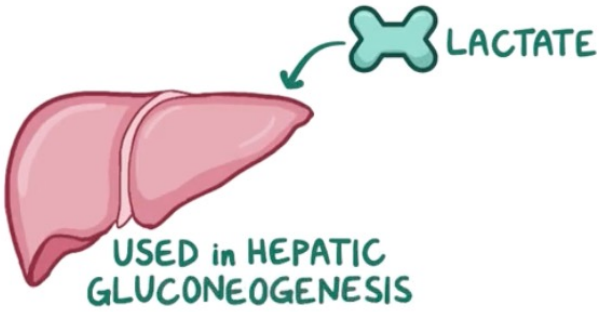
BIGUANIDES (METFORMIN)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Metformin	CI: eGFR < 30 mL/min/1.73m2; acute or chronic metabolic acidosis Note: May be used in pregnancy	**GI effects** **Lactic acidosis** (caution w/ renal dysfunction) **Vitamin B12 deficiency**	Increased risk of lactic acidosis with carbonic anhydrase inhibitors, contrast agents

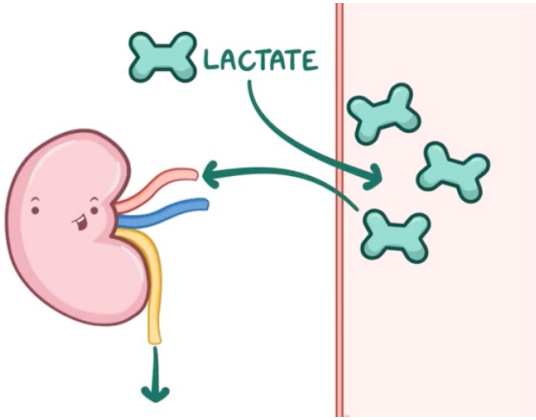
Boxed Warnings: Risk of lactic acidosis that may result in death, hypothermia, hypotension, and resistant bradyarrhythmia.

LACTIC ACIDOSIS & METFORMIN

Lactate is taken up by liver during process of hepatic gluconeogenesis

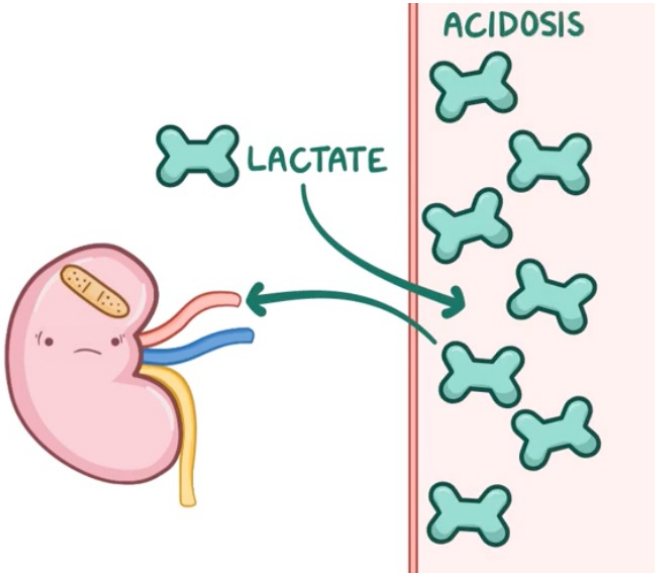


Metformin inhibits gluconeogenesis → plasma lactate build up.
In healthy individuals, excess lactate usually fine because kidneys able to excrete it in the urine.



LACTIC ACIDOSIS & METFORMIN

In patients with renal dysfunction, kidneys unable to clear excess lactate → acidosis



CLINICAL USE & ADME

T2DM

Off-label use:

- Antipsychotic-induced weight gain
- Prevention of T2DM
- Gestational diabetes
- PCOS

Excreted by kidneys as active drug

- Use safely with eGFR between 60 and 45 mL/min/1.73 m2
- Use cautiously with stable eGFR between 45 and 30 mL/min/1.73 m2
- Contraindicated if eGFR is less than 30 mL/min/1.73 m2

Titrate dose

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ALTERNATE APPLICATIONS: METFORMIN & AGING

Cell Metabolism

CellPress

Perspective

Benefits of Metformin in Attenuating the Hallmarks of Aging

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https://doi.org/10.1016/j.cmet.2020.04.001

Biological aging involves an interplay of conserved and targetable molecular mechanisms, summarized as the hallmarks of aging. Metformin, a biguanide that combats age-related disorders and improves health span, is the first drug to be tested for its age-targeting effects in the large clinical trial—TAME (targeting aging by metformin). This review focuses on metformin's mechanisms in attenuating hallmarks of aging and their interconnectivity, by improving nutrient sensing, enhancing autophagy and intercellular communication, protecting against macromolecular damage, delaying stem cell aging, modulating mitochondrial function, regulating transcription, and lowering telomere attrition and senescence. These characteristics make metformin an attractive gerotherapeutic to translate to human trials.

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THIAZOLIDINEDIONES (TZDs OR GLITAZONES)

Sensitizer

PPAR GAMMA

Peroxisome proliferator-activated receptor-gamma (PPAR-gamma)

Member of the steroid and thyroid superfamily of nuclear receptors

- Family of ligand-activated transcription factors of nuclear hormone receptors
- Regulate energy homeostasis

Genes activated by PPAR-gamma present in fat, muscle, and liver

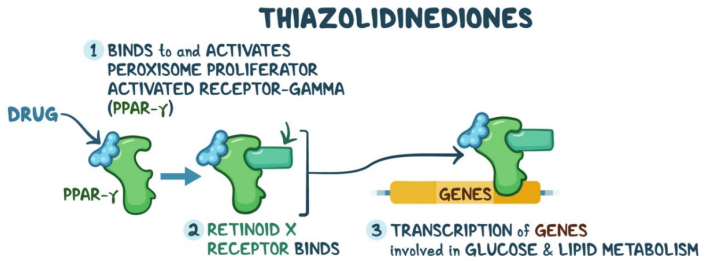
- Regulate glucose metabolism, fatty acid storage, adipocyte differentiation
- Adipocytes have highest concentration of PPAR-gamma receptors in body

ACTIVE LEARNING

Recall pharmacology from your MS1 year. Which of the following also work on PPAR?

A. Calcium channel blockers
B. Fibrates
C. Progesterone
D. Thiazide diuretics

TZD MOA



TZDs are ligands of PPAR-gamma

- PPAR found in muscle, liver, and fat

Bind to Retinoid X receptor and activate PPAR-gamma → modulation of gene expression involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation

- ↑ GLUT1 and GLUT4 expression
  - ↑ glucose uptake in adipocytes & skeletal muscle in response to insulin (↑ insulin sensitivity)
- ↓ hepatic glucose production and ↑ hepatic glucose uptake
- ↓ free fatty levels
- ↑ adiponectin

TZDs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Pioglitazone Rosiglitazone	NYHA Class III/IV HF <u>Cautions:</u> Monitor liver enzymes	**Weight gain** **Fluid retention; heart failure (HF)** Increased risk of fractures Hepatitis; liver failure Pioglitazone: bladder cancer Rosiglitazone: increased LDL, MI, CV death	Vasodilators increase ischemic effects of rosiglitazone Pioglitazone induces CYP3A4
TZD Boxed Warnings: Heart failure **Rosiglitazone-specific: myocardial infarction**			

CLINICAL USE & ADME

T2DM

Off-label

- Pioglitazone: nonalcoholic steatohepatitis

Metabolized in liver

- CYP2C9
- CYP3A4

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SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

Nutrient Load Reducer

SGLT2 INHIBITORS MOA

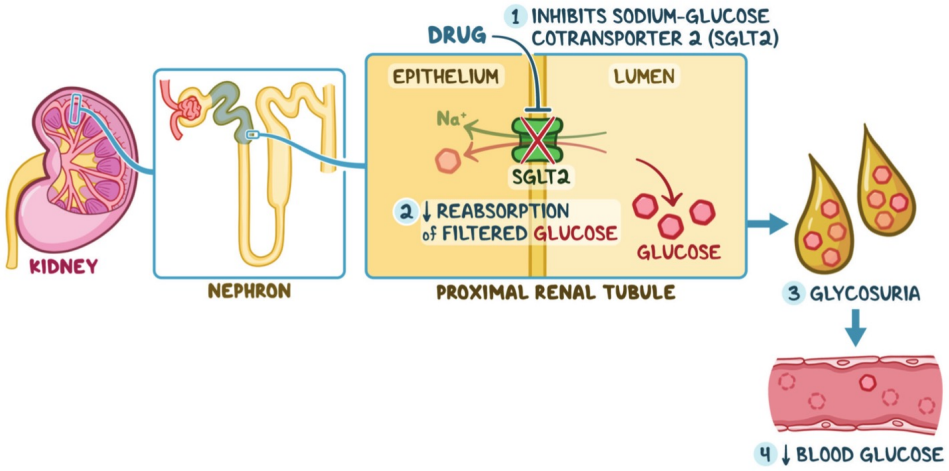
Inhibit SGLT2 in proximal renal tubules

- Accounts for 90% of all renal glucose reabsorption

↓ reabsorption of filtered glucose

Causes glucosuria

↓ blood glucose



SGLT2 INHIBITORS (-GLIFLOZIN)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)	Dialysis Cautions: Check renal function Canagliflozin: Increased risk of LL amputations w/ CVD	**Genitourinary infections (eg, vaginal candidiasis)** Volume depletion Ketoacidosis **AKI** Weight loss Increased LDL Risk of Fournier gangrene	Increases digoxin concentrations Increased hypotensive effects of loop diuretics 3A4 inducers decrease levels

CLINICAL USE

T2DM

BROMOCRIPTINE

Dopamine receptor agonist

Indicated for T2DM, treatment of Parkinson's disease, and hyperprolactinemia

Adverse effects

- Nausea, fatigue, dizziness, orthostatic hypotension, vomiting, headache

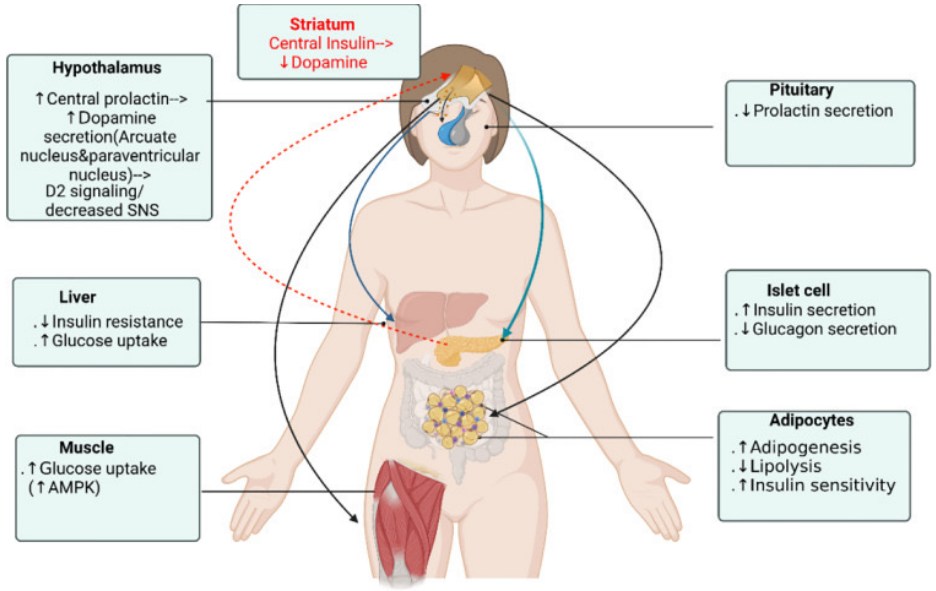


Image credit:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10012161/#:~:text=Dopamine%20agonists%20affect%20glucose%20homeostasis%20by%201)%20stimulating%20central%20prolactin,and%20on%20adipocyte%2C%20hepatocyte%2C%20skeletal

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CLINICAL CONSIDERATIONS

COMPARISON

Drugs	Ability to Lower Glucose	Risk of Hypoglycemia	Weight Change
2nd Generation SU	High	Yes	Increase
Metformin	High	No	Neutral- modest weight loss
TZDs	High	No	Increase
DPP-4 inhibitors	Intermediate	No	Neutral
SGLT2 inhibitors	Immediate	No	Decrease
GLP-1 receptor agonists	High	No	Decrease

COMPARISON

Drugs	Effect on ASCVD	Effect on HF	Effect on Renal Disease
2nd Generation SU	Neutral	Neutral	Neutral
Metformin	Potential Benefit	Neutral	Neutral
TZDs	Potential Benefit (Pioglitazone)	Increased	Neutral
DPP-4 inhibitors	Neutral	Potential Increase (saxagliptin and alogliptin)	Neutral
SGLT2 inhibitors	Potential Benefit	Benefit	Benefit- Reduced progression of renal failure
GLP-1 receptor agonists	Benefit	Neutral- Potential Benefit	Benefit- Decreased proteinuria

PREGNANCY

ACOG pharmacologic recommendations for gestational diabetes

- Insulin
- Metformin
- **AVOID:** glyburide (macrosomia and birth injury)

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REFERENCE LIST

Eggleton JS, Jialal I. Thiazolidinediones. [Updated 2023 Feb 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551656/#

Kulkarni AS, Gubbi S, Barzilai N. Benefits of Metformin in Attenuating the Hallmarks of Aging. Cell Metab. 2020;32(1):15-30. doi:10.1016/j.cmet.2020.04.001

Masharani U, Kroon L. Pancreatic Hormones & Glucose-Lowering Drugs. In: Katzung BG, Vanderah TW. eds. Basic & Clinical Pharmacology, 15e. McGraw Hill; 2021. Accessed July 20, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250601239

Pancreatic Hormones, Antidiabetic Drugs, & Glucagon. In: Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. eds. Katzung & Trevor's Pharmacology: Examination & Board Review, 13e. McGraw Hill; 2021. Accessed July 20, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255306810

Powers AC, D'Alessio . Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed July 20, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172482821

Sapra A, Bhandari P. Diabetes. [Updated 2023 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551501/1

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ANY QUESTIONS?