Diabetes Mellitus

Oral Hypoglycemic Agents

Non-Insulin Hypoglycemic Agents

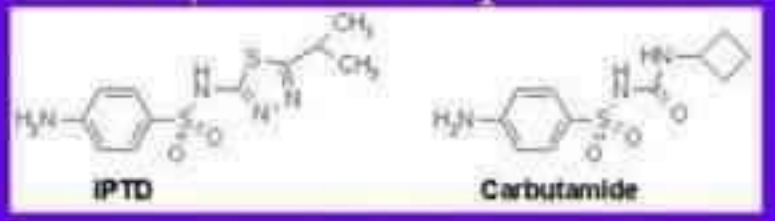
Oral

- Biguanides
- Sulfonylureas
- Meglitinides
- Thiazolidinediones
- Alpha Glucosidase inhibitors
- Incretin Enhancers (DPP-IV inhibitors)
- Resin binder

Parenteral

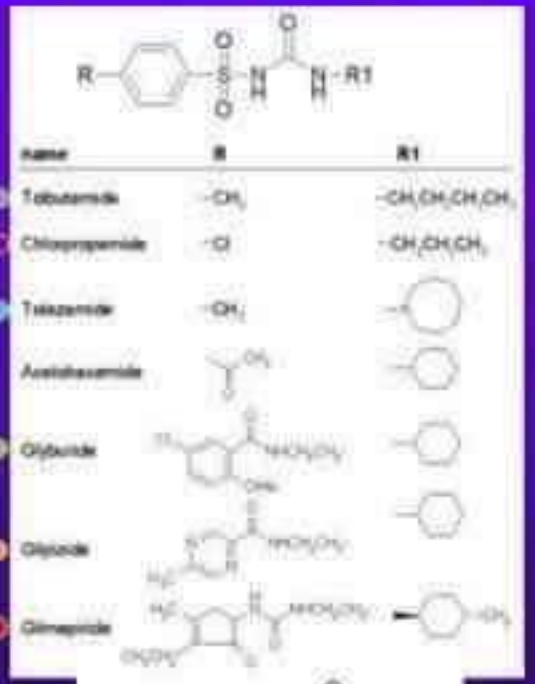
- Amylin analogs
- Incretin mimetics

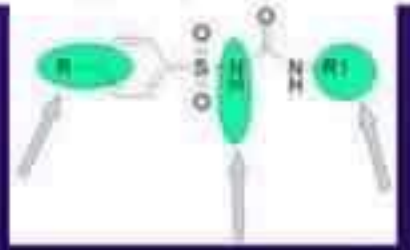
Sulfonylureas : stimulate β cells to produce more insulin



2-(p-aminobenzenesulfonamido)-5-isopropyl-thiadiazole (IPTD)
=> as used as treatment of typhoid fever in 1940's => hypoglycemia

Currently > 12,000





Rel Potency

- 1st generation
  - (1) Orinase (tolbutamide)
  - (3) Tolinase (tolazamide)
  - (6) Diabinese (chlorpropamide)

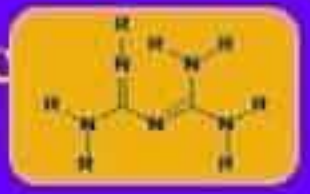
  may become inactivated → delayed activity
- 2nd generation
  - (75) Glucotrol (glipizide)
  - (150) Glucotrol XL (ex. rel. glipizide)
  - (150) Micronase, Diabeta (glyburide)
  - (250) Glynase (micronized glyburide)
- 3rd generation
  - (350) Amaryl (glimepiride)

*Hydroxylation of the aromatic ring appears to be the most favored metabolic pathway
*Hydroxylated derivatives have much lower hypoglycemic activity

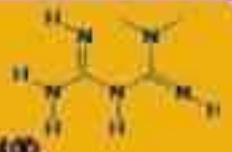
Pharmacology - Sulfonylureas

Compound	• Glibenclamide/Glyburide • Glipizide • Gliclazide • Glimepiride
Mechanism	Closes K_{ATP} channels on β-cell plasma membranes
Action(s)	↑ Insulin secretion
Advantages	• Generally well tolerated • Reduction in cardiovascular events and mortality (UKPDS f/u)
Disadvantages	• Relatively glucose-independent stimulation of insulin secretion: Hypoglycemia, including episodes necessitating hospital admission and causing death • Weight gain • Primary and secondary failure

Biguanides : improves insulin's ability to move glucose into cells (esp. musc



- Metformin
  - Glucophage®, Fortamet®, Riomet®

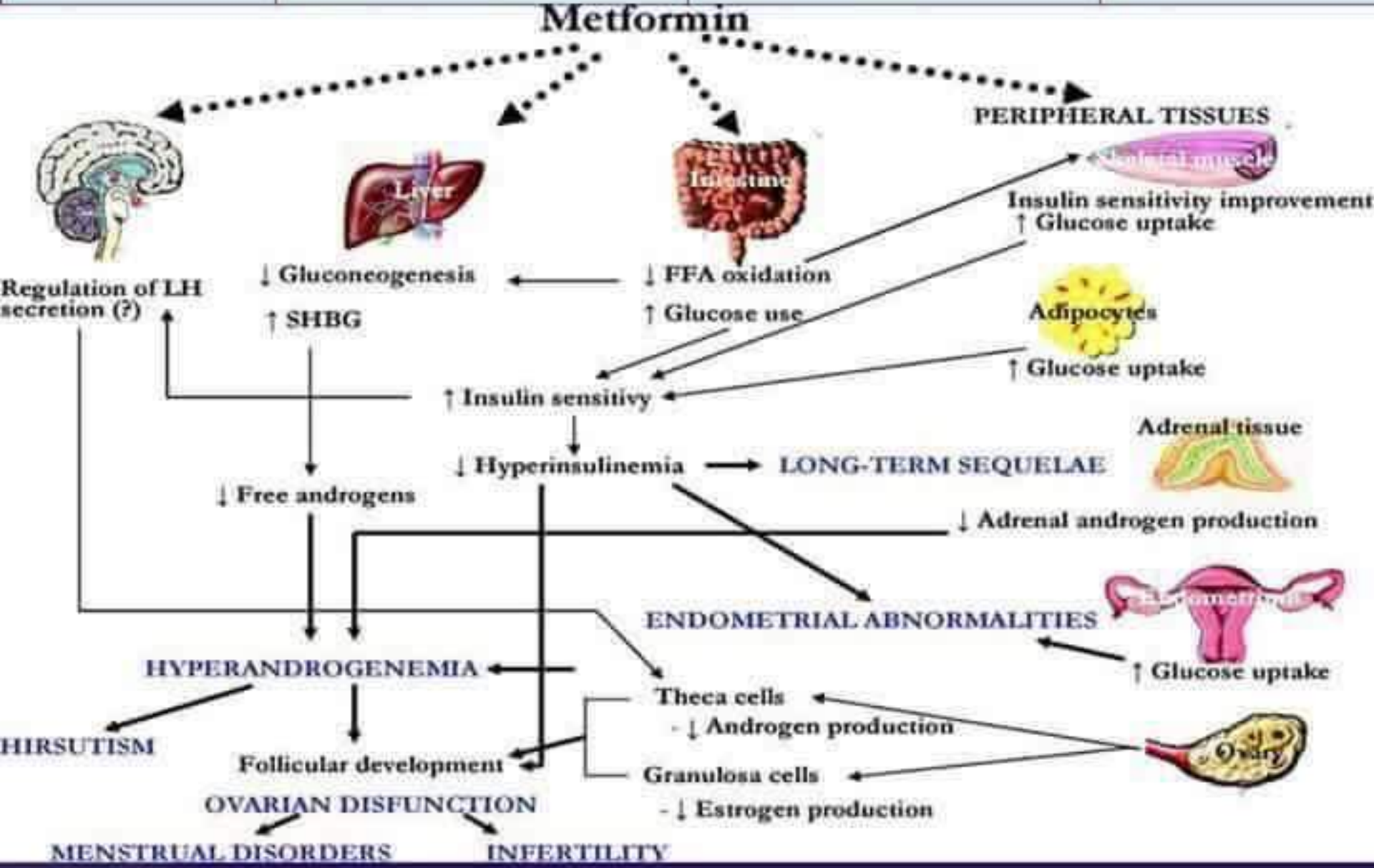


- mechanism improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
- Zhou *et al* (2001) showed that metformin stimulates the hepatic enzyme AMP-activated protein kinase
- Metformin was first described in the scientific literature in 1957 (Unger *et al*).
- It was first marketed in France in 1979 but did not receive FDA approval for Type 2 diabetes until 1994.

Metformin is a widely used monotherapy, and also used in combination with the sulfonylureas in treatment of type 2 diabetes

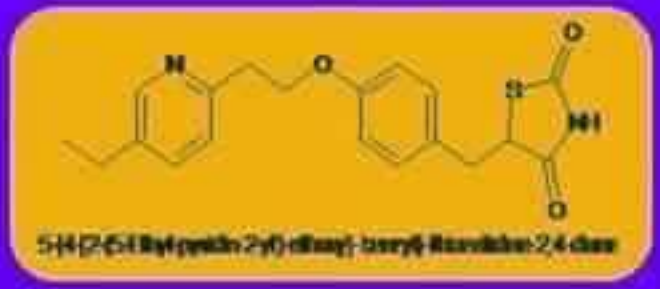
*only anti-diabetic drug that has been proven to reduce the complications of diabetes, as evidenced in a large study of overweight patients with diabetes (UKPDS 1998).

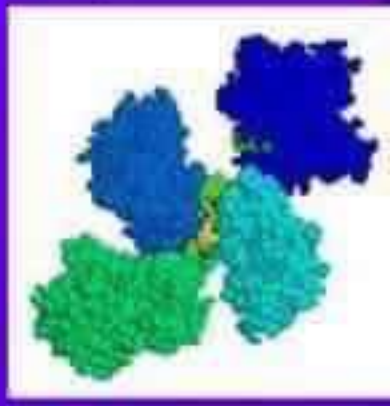
Metformin	Glucophage	500, 850, 1000 mg	tablets
	(Glucophage XR)	500, 750 mg XR	tablets



Thiazolidinediones (TZD's) : make cells more sensitive to insulin (esp. fatty cells)

- **Pioglitazone**
  - Actos®, Avandia®



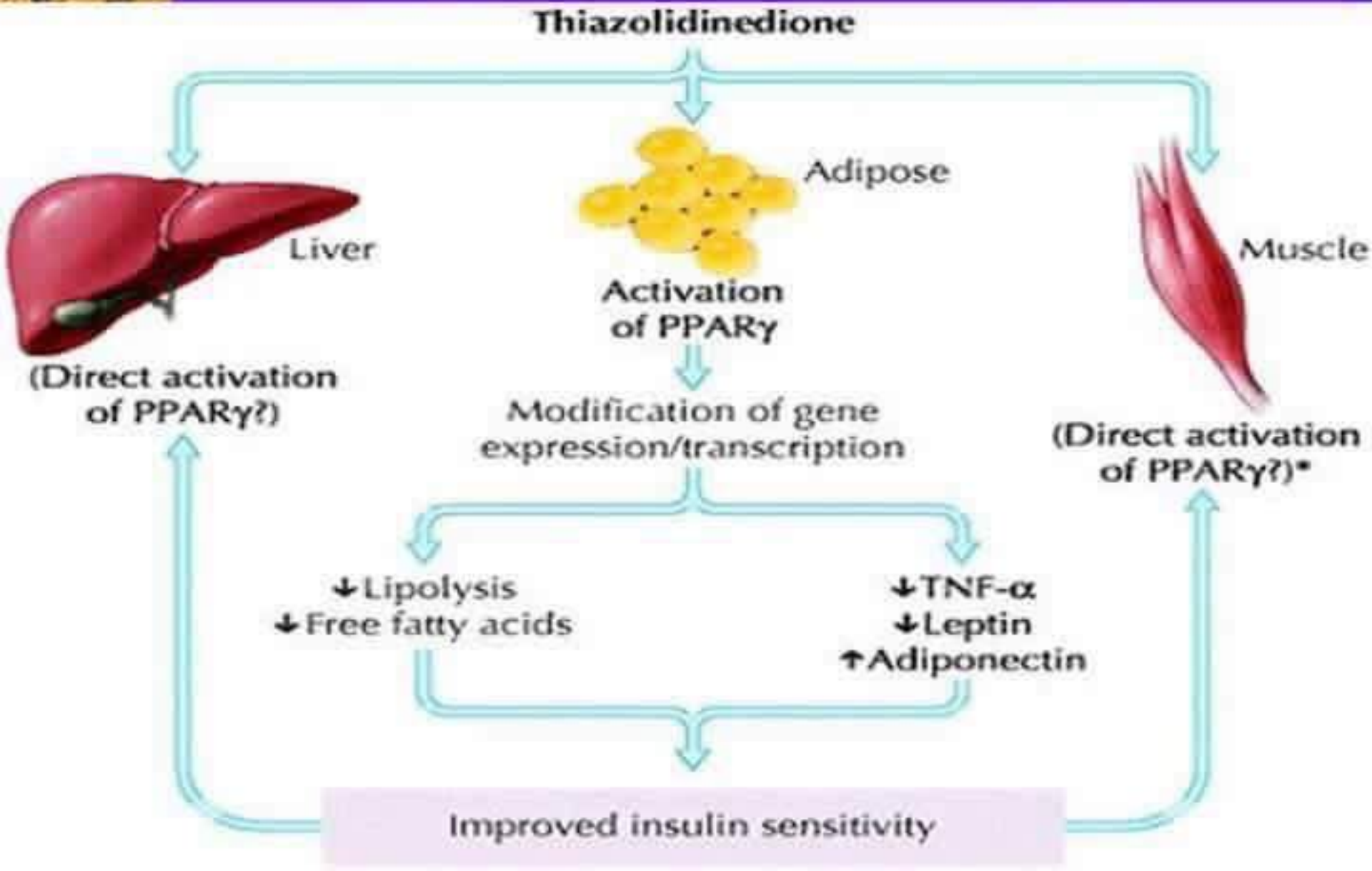


- binds to and activates (PPARγ).
- PPARγ is a member of the steroid hormone nuclear receptor superfamily, and is found in adipose tissue, cardiac and skeletal muscle, liver and placenta

- upon activation of this nuclear receptor by a ligand such as a TZD, PPARγ–ligand complex binds to a specific region of DNA and thereby regulates the transcription of many genes involved in glucose and fatty acid metabolism.

PPAR - γ

Pioglitazone	(Actos)	15, 30, 45 mg	tablets
Rosiglitazone	(Avandia)	2, 4, 8 mg	tablets



Pharmacology – Thiazolidinediones (TZD)

Compound	Rosiglitazone (Avandia®)
Mechanism	Activates the nuclear transcription factor PPAR-γ
Action(s)	Peripheral insulin sensitivity ↑
Advantages	No hypoglycemia
Disadvantages	• LDL cholesterol ↑ • Weight gain • Edema • Heart failure (CI with stages III and IV) • Bone fractures • Increased cardiovascular events (mixed evidence) • FDA warnings on cardiovascular safety

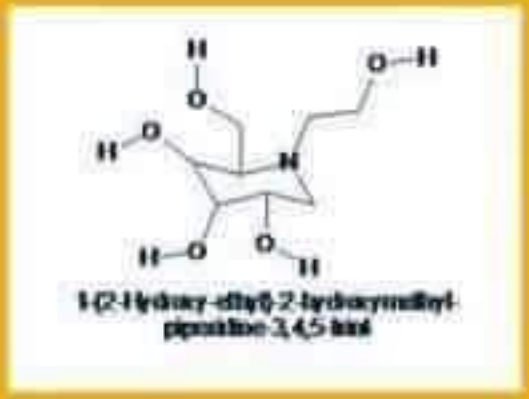
Alpha – glycosidase inhibitors :

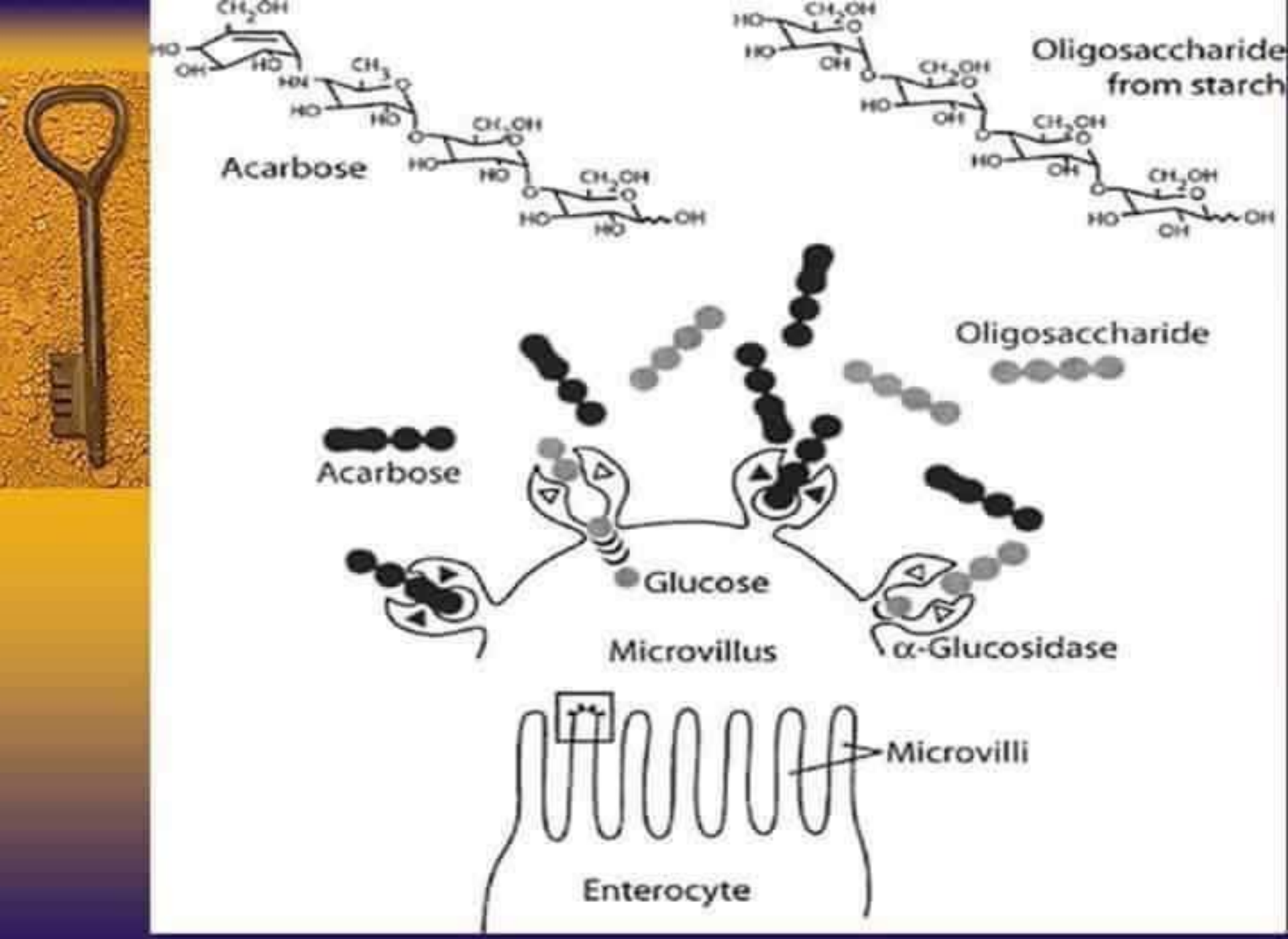
Block enzymes that help digest starches → slowing the rise in BS.

- AGI's

- Precose® (acarbose),

- Glyset® (miglitol)




Acarbose
Oligosaccharide from starch
Oligosaccharide
Acarbose
Glucose
Microvillus
α-Glucosidase
Microvilli
Enterocyte

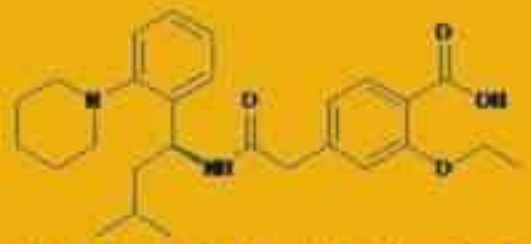
Pharmacology – Alpha-Glucosidase Inhibiters

Compound	• Acarbose • Miglitol
Mechanism	Inhibits intestinal α-glucosidase
Action(s)	Intestinal carbohydrate digestion and absorption slowed
Advantages	• Nonsystemic medication • Postprandial glucose ↓
Disadvantages	• Gastrointestinal side effects (gas, flatulence, diarrhea) • Dosing frequency

Meglitinides : Stimulate more insulin production ; dependant upon level of glucose present

- Meglitinides

- Prandin ® (repaglinide)



- Starlix ® (nateglinide)

Meglitinides

- Examples: repaglinide, nataglinide
- It is a benzoic acid derivative and a short-acting insulin releaser.
- It stimulates the release of insulin from the pancreatic beta cells by closing ATP-sensitive potassium channels.
- It has no significant effect on plasma lipid levels
- Rapid onset and short duration of action make multiple daily doses necessary (take it immediately before each meal!).

Pharmacology – Meglitinides

Compound	• Repaglinide (Prandin®) • Nateglinide (Starlix®)
Mechanism	Closes K_{ATP} channels on β-cell plasma membranes
Action(s)	Insulin secretion ↑
Advantages	Accentuated effects around meal ingestion
Disadvantages	• Hypoglycemia, weight gain • Dosing frequency

Diabetes – Oral Medications

Summary

5 Classes :

- Sulfonylureas stimulate β cells
- Biguanides improves insulin's ability to move glucose
- Thiazolidinediones cells more sensitive to insulin
- Alpha-glycosidase inhibitors Block enzymes that help digest starches
- Meglitinides *stimulate β cells (dependant upon glucose conc.)*

Pharmacology – Bile Acid Sequestrants

Compound	Colesevelam (Welchol®)
Mechanism	Binds bile acids/cholesterol
Action(s)	Bile acids stimulate receptor on liver to produce glucose
Results	• Lowers fasting and post prandial glucose
Advantages	• No hypoglycemia • LDL cholesterol ↓
Disadvantages	• Constipation • Triglycerides ↑ • May interfere with absorption of other medications

Drug Pearls

Medication	PRO	CON
Metformin	Low cost, A1c lowering, + CV effects, weight loss, PCOS	Renal or hepatic impairment
Sulfonylurea	Low cost, A1c lowering	Hypoglycemia, treatment failure
Meglitinides	Erratic meals, renal insufficiency	Hypoglycemia, treatment failure
Pioglitazone	Insulin resistance, decrease in adipose tissue, TG reduction	Edema, wt gain, CI with HF class III and IV
α-glucosidase inhibitors	Patients with constipation	Long duration of T2DM, patients with GI problems
DPP-4	Well tolerated	? long term safety

Monotherapy	Route of Administration	A1c (%) Reduction
Sulfonylurea	PO	1.5-2.0
Metformin	PO	1.5
Glitazones	PO	1.0-1.5
Meglitinides	PO	0.5-2.0
α-glucosidase inhibitors	PO	0.5-1.0
DPP-4	PO	0.5-0.7
Insulin	Injectable	Open to target

Mostly targets FASTING hyperglycemia	Mostly targets POSPRANDIAL hyperglycemia
Insulin (long and intermediate action)	Insulin (regular, rapid-action)
Colesevelam	α-glucosidase inhibitors
Metformin	Meglitinides
	Pramlinitide
	DPP-4 inhibitors
	GLP-1 agonist

PHARMACOLOGIC MANAGEMENT

- The stepwise approach described in the 1998 CDA Clinical Practice Guidelines implied that it was acceptable to wait for up to 8 to 16 months before implementing aggressive therapy to treat hyperglycemia.

- It is now recommended that the management regimens of patients with type 2 diabetes be tailored to the individual patient, aiming for glycemic targets as close to normal as possible and, in most people, as early as possible.

- Multiple therapies may be required to achieve optimal glycemic control in type 2 diabetes.
- The choice of antihyperglycemic agent(s) should be based on the individual patient.
- Target A1C should be attainable within 6 to 12 months.

Type 2 Diabetes Recommendations

- Metformin + lifestyle changes at diagnosis providing no contraindication
  - Medications are ALWAYS to be used in combination with healthy meal planning and regular physical activity (150 minutes per week)
- If marked elevation of A1c /blood glucose and/or symptomatic consider insulin (+ or – other agents) from the onset
- If noninsulin monotherapy at maximal tolerated dose does not achieve /maintain the A1c goal over 3–6 months, add a second oral agent, a GLP-1 receptor agonist, or insulin

ADA. V. Diabetes Care. *Diabetes Care* 2012;35(suppl 1):S21

THANK YOU.....