Oral hypoglycemic agents

** **Biguanides:**

Metformin, Buformin

Possible MOA:

- ↓ CHO absorption
- ↓ hepatic gluconeogenesis; ↑ glycolysis
- ↓ glucagon release
- ↑ peripheral utilization of glucose
- ↑ response to insulin

Metformin is only effective in type II DM (effects require insulin)

?? Other uses: Obesity (↓ fat deposition) and polycystic ovarian syndrome (↓ androgen production by ovaries and adrenals)

<u>Side effects:</u>

- N & V, metallic taste
- Abdominal pain and diarrhea
- Hypoglycemia (rare)
- Lactic acidosis
- ↓ vitamin B_{12} absorption

** Sulfonylureas

- Classification

* First generation	$t_{1/2}$	DOA	Metabolic fate
Tolbutamide	7	6-12	-
Chlorpropamide	34	24-72	+
Tolazamide	7	12-16	+
Acetohexamide	5	12-18	+

* Second generation	$t_{1/2}$	DOA	Metabolic fate
Glyburide (Glibenclamide)	4	20-24	±
Glipizide	3	14-16	–
Gliclazide	8	10-15	–
Glimeperide	5	18-22	±

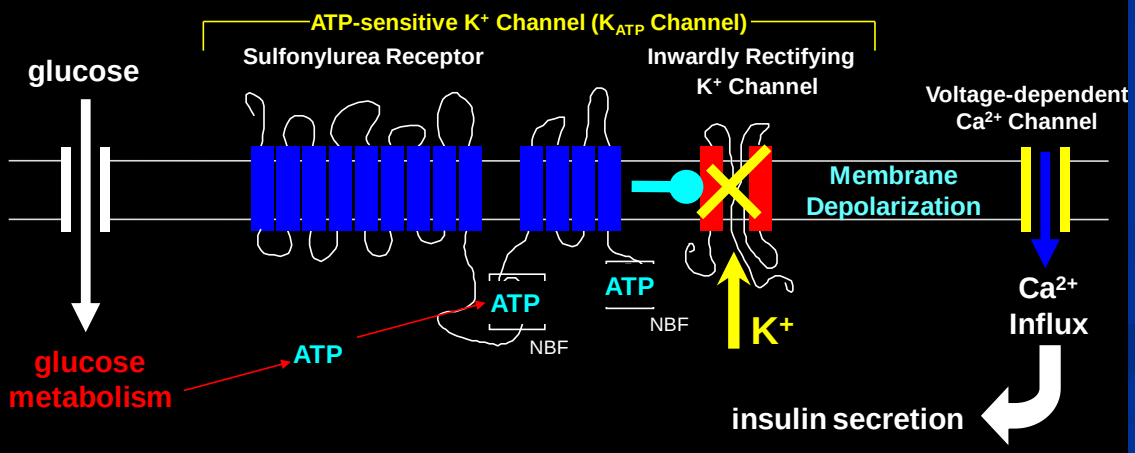
- **Sulfonylureas:**

- ↑ insulin release (major MOA) (Receptor-mediated effect)
- ↑ no. of β-cells, ↑ no. of insulin receptors
- ↑ peripheral cells sensitivity to insulin effect
- ↑ insulin binding to its receptors
- ↑ insulin affinity to its receptors
- ↓ hepatic gluconeogenesis
- ↓ glucagon release, ↑ somatostatin release…

- **Mechanism of action of sulfonylureas:**

- High affinity sulfonylurea receptors found on beta cells linked to ATP-ase sensitive K^{+} ion channel
- Following binding, voltage dependent Ca^{++} channels open in response to depolarization and allow influx of Ca^{++}
- Ca^{++} binds to calmodulin which activates kinases that cause exocytosis of insulin containing secretory granules
- Beta cells sense glucose more efficiently, producing more insulin

K_{ATP} Channel Structure and Function



NBF
Nucleotide Binding Fold = site of ATP/ADP binding

Four copies of each subunit combine to form an active K_{ATP} channel

- Sulfonylureas differ in potency, bioavailability, DOA, tolerance, extent of protein binding and metabolic fate
- Drug-drug interactions (many):

Propranolol, sulfa drugs, oral anticoagulants, aspirin...etc ↑ effects of sulfonylureas

- Clinical uses to sulfonylureas:

- DM

- Nocturnal enuresis (Glyburide → ↑ ADH release)

- **Side effects to sulfonylureas:**

- Hypoglycemia
- N & V, dizziness
- Allergy
- Agranulocytosis
- Hepatic dysfunction

- **Other orally effective drugs in DM:**

- α-glucosidase inhibitors

Acarbose; Miglitol (more potent)

Effective in type II DM

↓ CHO absorption

Inhibits α-glucosidase , an enzyme in the brush border of intestine responsible for breakdown of CHO, and hence ↑ glucose absorption

Such inhibitors ↓ fasting and postprandial hyperglycemia

α-glucosidase inhibitors also ↓ insulin secretion following administration sparing β-cells

Its been found that these inhibitors reduce incidence or risk of atherosclerosis in diabetics

Taken before or with meals

Could be given with insulin and sulfonylureas

<u>Side effects:</u>

Abdominal pain and diarrhea

- **Prandial glucose regulators:**

Repaglinide; Nateglinide (has faster OOA),
Mitiglinide…

↑ insulin release (have similar MOA to sulfonylureas)

Hypoglycemia is infrequent

Taken before meals (every meal)

Could be taken with metformin or insulin

Hypoglycemia is infrequent

- **Thiazolidinediones (TZD's):**

Pioglitazone (has shorter $t_{1/2}$), Troglitazone…

Mainly used in NIDDM who have insulin resistance

MOA:

Peroxisome Proliferator-Activated Receptors=PPAR (γ isoform) agonist

PPAR's are members of the superfamily of ligand-activated transcription factors located in adipose tissue, skeletal muscle and large intestine

TZD's

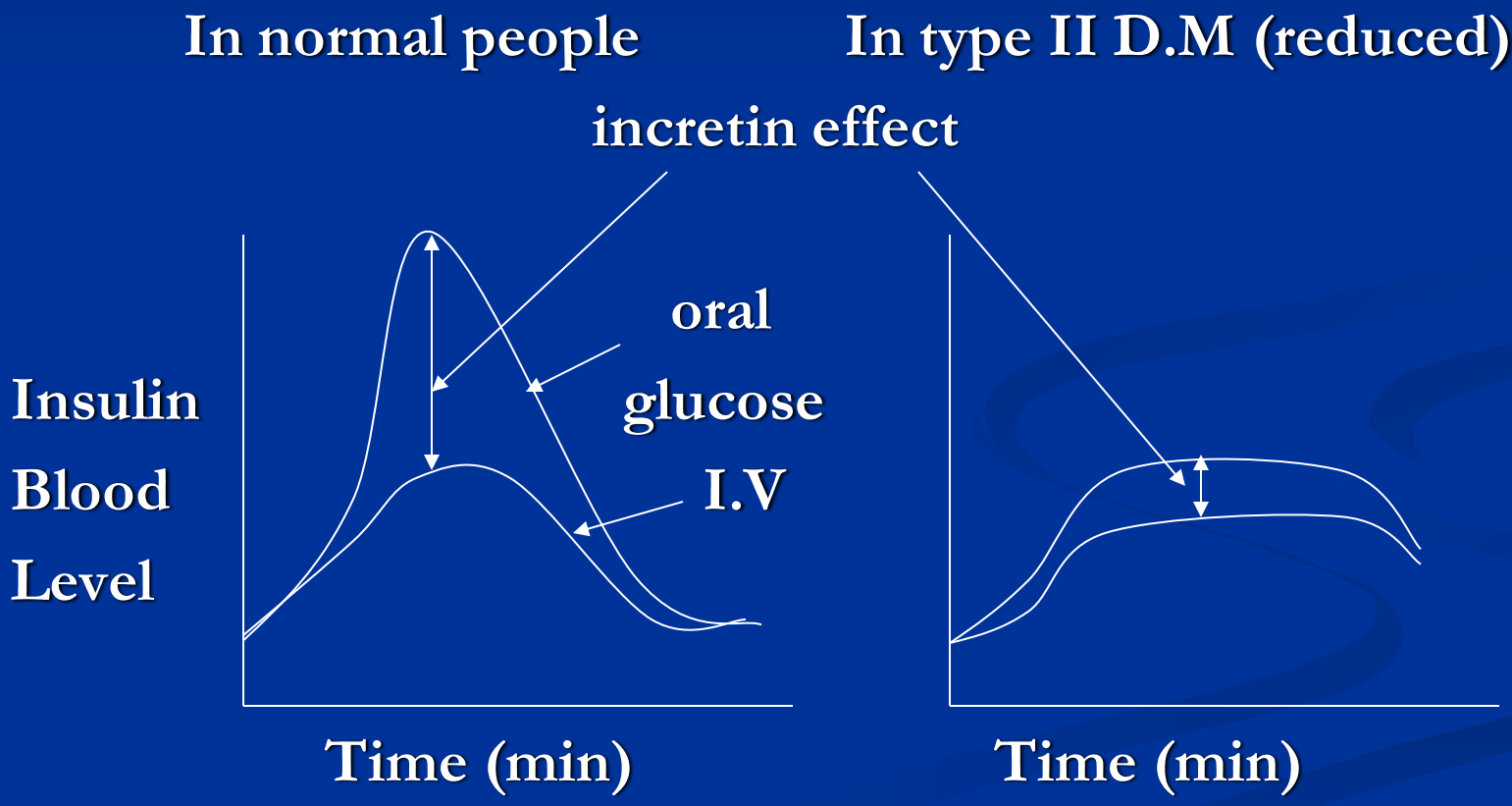
↑ sensitivity of peripheral tissues to insulin effect

↓ glucose exit or output from the liver

↓insulin resistance

Good to patients with ↑ insulin levels which are believed to be responsible for ↑ B.P,↑ lipids and atherosclerosis in patients with insulin resistance

Incretin effect:



- Incretin hormones

2 polypeptides ↑ glucose absorption by gut

1. Glucagon-like peptide-1 (GLP-1)

Produced by the L cells in ileum and colon

It ↑ insulin release and ↓ glucagon release following meals

+ ↓ gastric emptying & leads to induction of satiety

2. Glucose-dependent insulinotropic polypeptide (GIP)

Produced by the K cells in the proximal gut (duodenum & proximal jejunum)

It stimulates glucose-dependent insulin release from β-cells

Both GLP & GIP are metabolized by the enzyme dipeptidyl peptidase-4 (DPP-4) which is present in gut, liver, kidneys, lymphocytes and endothelial cells

- **Sitagliptin, Gemigliptin, Linagliptin…**

Orally effective selective DPP-4 inhibitors

↑ blood levels of GLP-1, GIP insulin and C-peptide and ↓ glucagon blood levels

An oral dose daily reduces high blood glucose and HbA1c levels

Could be taken with metformin or sulfonylureas

Hypoglycemia is infrequent

- **Exenatide, Liraglutide...**

Synthetic analogs to GLP-1

↑ insulin and ↓ glucagon blood levels

Considered as an adjunct therapy to metformin or sulfonylureas in patients with type 2 D.M who still have suboptimal glycemic control

Given S.C 60 min before meal

Hypoglycemia is infrequent

- Aldose reductase (AR) inhibitors

Epalrestat ; Ranirestat; Fidarestat

Sorbitol has been implicated in the pathogenesis of retinopathy, neuropathy and nephropathy

AR inhibitors proved to improve diabetic polyneuropathy

Orally effective

- **Amylin mimetic drugs**

Pramlintide

- Amylin is released from pancreatic beta cells along with insulin in response to meals
- Deficient amylin secretion is a well-recognized phenomenon in type I diabetes and in a later-stage in type II, in whom pancreatic insulin production is markedly reduced
- Amylin physiological effects mimic in part those of GLP-1 decreasing glucagon secretion from pancreatic alpha cells, thereby attenuating hepatic glucose production
- It also delays gastric emptying and likely possesses a central effect to enhance satiety

- Pramlintide is a synthetic hormone for parenteral (subcutaneous) administration, resembling human amylin effects
- It reduces the production of glucose by the liver by inhibiting the action of glucagon and diminishes postprandial glucose fluctuations
- Pramlintide was approved by FDA in 2005. While it seems to be a satisfactory adjuvant medication in insulin-dependent diabetes, it is unlikely to play a major future role in the management of type II DM

- **Inhibitors of subtype 2 sodium-glucose transport protein (SGLT2), in kidney**

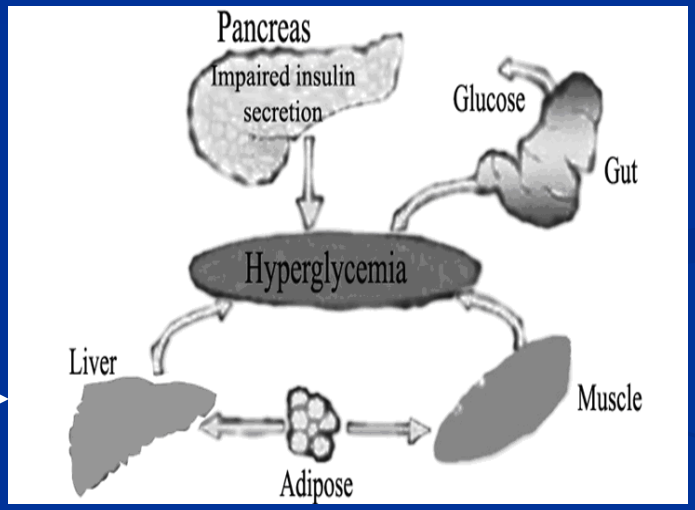
Canagliflozin; Dapagliflozin…

- SGLT2 is responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine

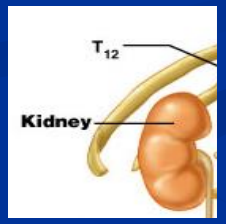
- Effective along with metformin ± sulfonylyrea in the management of type II DM

Sulfonylurea
Meglitinide Analogs
Incretin hormones
Amylin mimetic drugs

Alpha glucosidase inhibitors



Biguanides



Gliflozins

TZD's
Glitazars

- Somatostatin

In low doses → ↓ glucagon release

Under evaluation

- Role of ACEI's; ARB's; Statins

** Role of Glucagon in diabetics?!!!

** Pancreatic transplantation and gene therapy

** Drugs ↓ blood glucose levels:

β-blockers, salicylates, indomethacin, naproxin, alcohol, sulfonamides, clofibrate, anabolic steroids, lithium, Ca^{++}, ampicillin, bromocriptine…

** Drugs ↑ blood glucose levels:

β-blockers, thiazides and loop diuretics

Glucocorticoids

Oral contraceptive drugs

Ca^{++} channel blockers

Phenytoin, morphine, heparin

Nicotine, clonidine, diazoxide

H_2-receptor blockers

Goals of DM treatment!!=Control

- Ensure good Pt.-clinic relationship
- Control symptoms
- Prevent acute metabolic crisis of KA & hypoglycemia
- Maintain normal growth & BW
- Encourage self-reliance & self-care
- Eliminate risk factors

Smoking, ↑ BP, ↑ lipids…

Cont. goals:

- Prevent psychological complications

- Accept restrictions on life

- Diet control

- Monitoring blood glucose & insulin adjustment

- Know manifestations of hypoglycemia & how avoiding them

- Early treatment of complications

Photocoagulation, foot care advices...