ENDOCRINE
PHARMACOLOGY

06

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ORAL HYPOGLYCEMIC AGENTS

widely used in the management particularly of type 2 DM patients, they are classified according to their chemical structure and their mechanism of action into: biguanides, sulfonylureas…

You'll learn many of them during this lecture inshallah, so focus and enjoy.

• Biguanides

For ex. Metformin, Buformin.

Possible mechanism of action:

↑ peripheral utilization of glucose

↑ response to insulin

↓ CHO absorption

↓ hepatic gluconeogenesis; ↑ glycolysis

↓ glucagon release

***Side effects of biguanides:**

- Nausea and vomiting, metallic taste.

- Abdominal pain and diarrhea

- Hypoglycemia (rare)

- Lactic acidosis

- ↓ vitamin B12 absorption

***Metformin is only effective in type II DM because it requires insulin for mediating its effects.**

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

• Sulfonylureas

** 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	±

Classified into first and second generations based on their potency and a little extent of their metabolic fate, the second generation has more potency than the first one.

(+): active metabolite.
(-): inactive metabolite.

***Sulfonylureas:**

↑ insulin release (major MOA) (Receptor-mediated effect)

↑ no. of β-cells, ↑ no. of insulin receptors *(upregulation of insulin receptors for ex.)*

↑ peripheral cells sensitivity to insulin effect

↑ insulin binding to its receptors

↑ insulin affinity to its receptors

↓ hepatic gluconeogenesis

↓ glucagon release, ↑ somatostatin release…

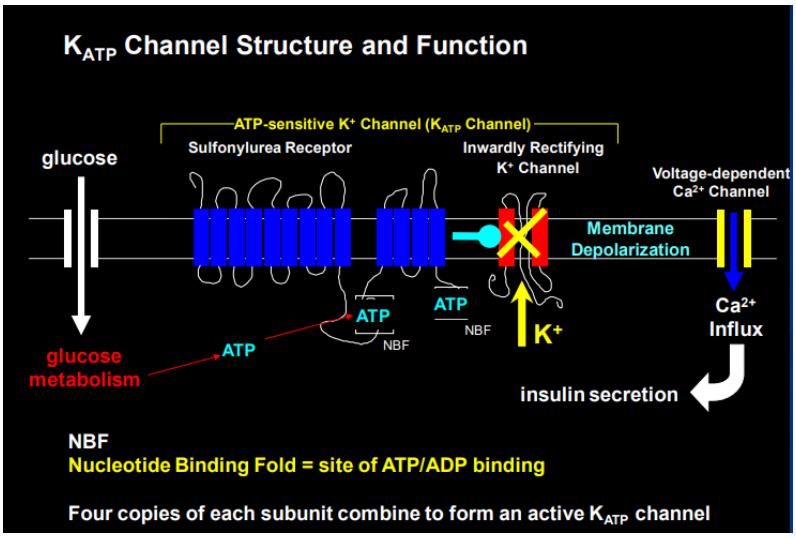
***Mechanism of action of sulfonylureas:**

- 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.



This short video will help you to understand.

(7) SULFONYLUREAS MECHANISM OF ACTION EXPLAINED *ANIMATED* - YouTube

- **Sulfonylureas differ in potency, bioavailability, duration of action, tolerance, extent of protein binding and metabolic fate.**
- **Drug-drug interactions (many): Propranolol, sulfa drugs, oral anticoagulants, aspirin...etc which ↑ effects of sulfonylureas**

- **Clinical uses to sulfonylureas:**

- DM ***(particularly type 2, since such drugs act through insulin and type one patients are characterized by complete deficiency in their insulin)***

- Nocturnal enuresis (Glyburide → ↑ ADH release)

- **Side effects to sulfonylureas:**

- Hypoglycemia

- N & V, dizziness

- Allergy

- Agranulocytosis

- Hepatic dysfunction

Nocturnal enuresis, also informally called bedwetting, is involuntary urination while asleep after the age at which bladder control usually begins. Glyburide can help in this situation through increasing ADH release.

- **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.**
- **It's been found that these inhibitors reduce incidence or risk of atherosclerosis in diabetics** ***(most of oral hypoglycemic agents will lead to this effect because they normalize or reduce high blood glucose levels with respect to atherosclerosis and blood pressure).***
- **Taken before or with meals.**
- **Could be given with insulin and sulfonylureas.**
- **Side effects: Abdominal pain and diarrhea.**

• Prandial glucose regulators:

Repaglinide; Nateglinide (has faster OOA), Mitiglinide…

- **↑ insulin release (have similar MOA to sulfonylureas).**

- **Taken before meals (every meal).**
- **Could be taken with metformin or insulin**
- **Hypoglycemia is infrequent.**

• Thiazolidinediones (TZD's):

Pioglitazone

- **Mainly used in NIDDM *(non-insulin dependent diabetes mellitus*) who have insulin resistance.**
- **MOA: Peroxisome Proliferator-Activated Receptors = PPAR (γ isoform) agonist. *(This drug is agonist for these receptors)***
- **PPAR's are members of the superfamily of ligand-activated transcription factors located in adipose tissue, skeletal muscle and large intestine.**

- **TZD' s effects in these tissues:**

  ↑ sensitivity of peripheral tissues to insulin effect.

  ↓ glucose exit or output from the liver.

  ↓insulin resistance.

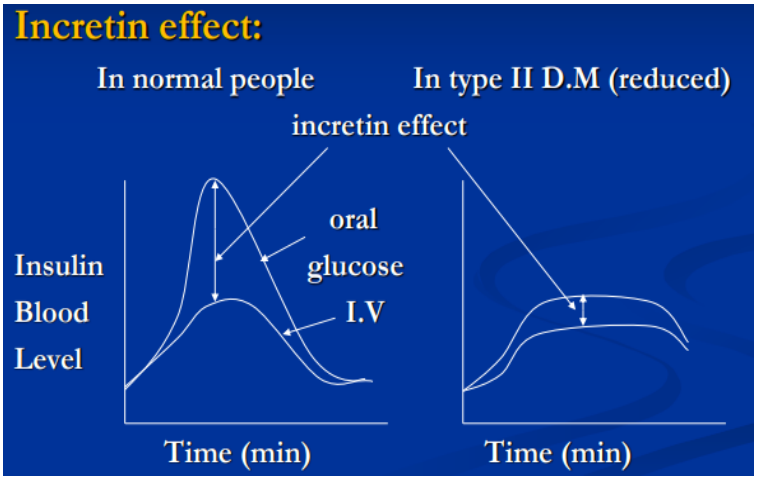
- **Good for patients with high insulin levels which are believed to be responsible for high B.P, increased lipids and atherosclerosis in patients with insulin resistance.**

• INCRETIN EFFECT

- ***The incretin effect simply compares insulin release from the pancreas in response to oral vs IV glucose administration.***

- ***In normal individuals it's been found when you give glucose orally, it results in an increase in the amount of insulin released from the pancreas, and it has been noticed that when glucose is giving IV, again it's going to increase insulin release but to a lesser extent as compared to orally administrated glucose. So, there's something in the intestine that***

increase the amount of insulin released from pancreas when glucose is administrated orally → *Incretin hormones/protein.*



- *In diabetic patients it has been reported that incretin effect decreases, in certain patients the amount of insulin released after oral glucose administration is nearly the same as that amount which is released after IV.*

- **Incretin hormones are 2 polypeptides that increase glucose absorption by gut:**

  1. Glucagon-like peptide-1 (GLP-1); Produced by the L cells in ileum and colon, it

  ↑ insulin release.

  ↓ 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. ***(Note that there's no effect on glucagon release like the first hormone).***

- **Both GLP & GIP are metabolized by the enzyme dipeptidyl peptidase-4 (DPP-4) which is present in gut, liver, kidneys, lymphocytes and endothelial cell** ***= peripheral targets of the insulin).***

- **Since diabetic patients have lower levels or no such protein, what's your management??**

  Either you give such proteins from outside or inhibit their breakdown enzyme (DPP-4).

- # INCRETIN MIMETIC DRUGS

1. **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.

2. Exenatide, Liraglutide, Tirzepatide...

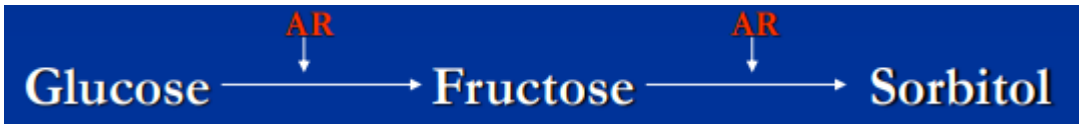
- Synthetic analogs to GLP-1

  ↑ insulin

  ↓ 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.
- Recently approved by FDA in the management of obesity 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

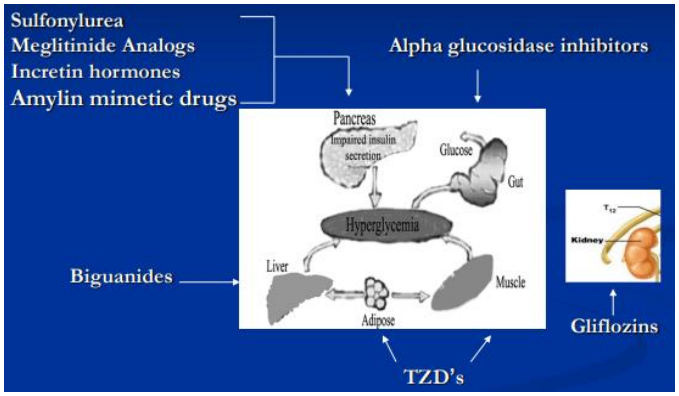
- Amylin is released from pancreatic beta cells along with insulin in response to meals.

- 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 the FDA in March 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

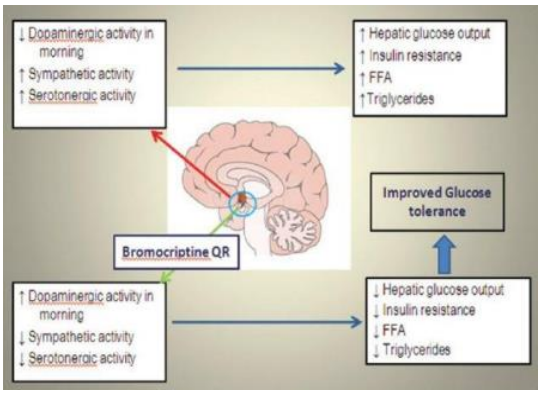
- Canagliflozin; Dapagliflozin…
- SGLT2 is responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine.
- Found to decrease incidence of heart attacks and strokes in patients with type II DM.
- Effective orally along with metformin ± sulfonylurea in the management of type II DM.
- Still under extensive post marketing screening for side effects in patients with type II DM.

This slide demonstrates the different sites where different oral hypoglycemic agents act.
Like sulfonylurea acts on the pancreas increasing insulin secretion.
Alpha-glucosidase inhibitors act on the intestine.
Biguanides have also have effects on the intestine as well as the liver but mainly the liver.
And so on…



- # BROMOCRIPTINE

- **A sympatholytic D2-dopamine agonist recently approved for the management of type 2 diabetes.**
- **Its administration within 2 h of awakening increases hypothalamic dopamine levels and inhibit excessive sympathetic tone within CNS, resulting in a reduction in post meal plasma glucose levels by suppressing hepatic glucose production.**
- **It reduces plasma glucose, triglycerides, Free Fatty Acid (FFA) levels, and possibly cardiovascular events in type 2 diabetics.**
- **Side effects; mild most common nausea**



- # SOMATOSTATIN

- **In low doses → decrease glucagon release.**
- **Under evaluation.** ***(The synthetic analogues of somatostatin to be used in diabetes is under evaluation, or clinical evaluation so far).***

Role of ACEI's ***(angiotensin-converted enzyme inhibitors)*****; ARB's** ***(angiotensin receptor blockers)*****; Statins**

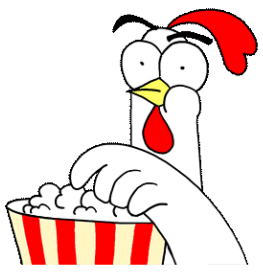
these drugs are widely used in the management of hyperlipidemia and diabetics even though they have normal blood level of cholesterol for example, or they don't have hypertension or whatever, as a prophylactic agent since such patients have high risk of developing hypertension, hyperlipidemia, atherosclerosis, etc. In compared to other people and this proved clinically.

** Role of Glucagon in diabetics?!!!

If you remember the management of coma in diabetic, we mentioned that diabetics could experience two types of comas: Hypoglycemic coma (that could be managed orally if the patient is conscious, if s/he is in coma → IV glucose), Hyperglycemic coma (managed by administration of regular or soluble insulin along with potassium). Now supposed that you have a case of diabetic patient with a hypoglycemic coma, and you can't give glucose orally or even IV cause the patient may have for example collapsed pains, we have a human recombinant glucagon available and could be given SC and intramuscular, in another words, glucagon could be given in irrespective because of the hypoglycemia because it elevates blood glucose level.

** Pancreatic transplantation and gene therapy.

So far what we have mentioned regarding insulin as well as the difference classes of oral hypoglycemic agents, we're controlling DM. Now the trends and the extensive researches are going on towards treating DM, we want to reach a complete cure (it's possible to do pancreas transplantation but it's very expensive operation, there's no money good enough) but with advanced technology especially what is known as gene therapy and stem cells therapy it's possible for example to reach a point of cure to diabetes by adopting advanced methods like taking stem cells from embryonic blastocyst and inject it in the body near the pancreas, and could differentiate into β-cells and produce insulin, yes, but still all such experiments are under clinical evaluation (we don't have therapy nowadays) even do not have the gene therapy which is a transdermal transplantation of gene coding for insulin, although it is so easy to put such gene in the pancreas, but again still under evaluation.. and not only that, but you can also take β-cells (the islets itself) from donor after death and then implant them. So, such techniques are under extensive research nowadays, this is an attempt to reach a point to cure DM since it's a common disease.



- **Drugs ↓ blood glucose levels: β-blockers *(common sense as they oppose effects of catecholamine which elevate blood glucose level, but also such β-blockers increase blood glucose level, how? Maybe it depends on the dose, because they have a direct inhibitory effect on insulin release, and this is proved in vitro, but more frequently it could lead to hypoglycemia)*, salicylates, indomethacin, naproxen, alcohol, sulfonamides, clofibrate, anabolic steroids, lithium, Ca++, ampicillin, bromocriptine…**

!! You must be careful when a diabetic patient who is in a large dose of insulin and you give a β-blockers for hypertension, what happens? Because they could mask the manifestations of overactivity of sympathetic system (sweating, tachycardia, dizziness.) so they can pass unnoticed, and the patient will go into severe hypoglycemia & then in bad consequences. (Notice that they are not contraindicated).

- **Drugs ↑ blood glucose levels: β-blockers, thiazides and loop diuretics, Glucocorticoids, Oral contraceptive drugs, Ca++ channel blockers Phenytoin, morphine, heparin Nicotine, clonidine, diazoxide H2 -receptor blockers.**

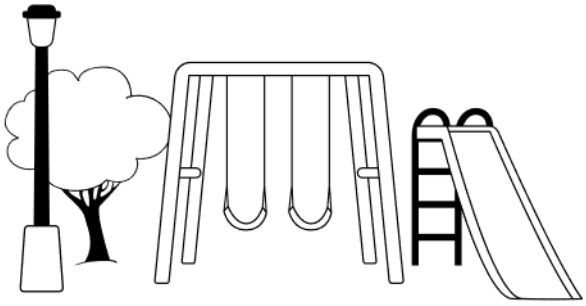
• GOALS OF DM TREATMENT!!=CONTROL

- **Ensure good patient clinic relationship. *(it's very important to advise diabetic patients to consult or to go to a diabetic clinic, through which many instructions could be given to such patient, for the benefit of the patient (good control will be associated with less complications).***
- **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 by:**

  Ask the patient to accept restrictions on life, Diet control, Monitoring blood glucose & insulin adjustment, know manifestations of hypoglycemia & how to avoid them.

- **Early treatment of complications:** ***for example, if the patient has some problem with the eye we have*** **Photocoagulation, foot care advice.**

TAKE A BREAK



V3

** Sulfonylureas

- Classification

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Tolbutamide	7	6-12	-
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* 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	±

These drugs are classified as a second generation of sulfonylureas.

*Aldose reductase inhibitors are not incretin mimetic drugs.

عدّلناها فوق