ENDOCRINE SYSTEM

Pharmacology

Lec. 8

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ما ينطق به الدكتور من شرح سيكون باللون الاحمر
وما يكون مهما في شرح الدكتور يكون باللون البنفسجي
ما يكون مهما في السلايدات يكون بخطين أو بخط

Pancreatic Hormones

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

- α-glucosidase inhibitors (α-glucosidase is an enzyme involved in carbohydrate absorption from the intestine, so if you inhibit it you inhibit glucose absorption.)

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

Side effects:

Abdominal pain and diarrhea

- Prandial glucose regulators: diabetics حبوهم كثير ال

Repaglinide; Nateglinide (has faster OOA (onset of action)), 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): they act as agonists to some nuclear receptors known as peroxisome proliferator-activated receptors.

Pioglitazone

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

Many of them were withdrawn because of severe side effects

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 (hypertension),↑ lipids (hyperlipidemia) and atherosclerosis in patients with insulin resistance

Such nuclear receptors alter specific genes in the nucleus, genes which are involved in carbohydrate and lipid metabolism.

Now, if we gave any individual 50 grams of glucose orally, then we gave 50 grams of glucose intravenously, which glucose administration (given in the same amount) results in more insulin release from the pancreas?

We said that the major regulator of insulin release by the pancreatic beta cells is glucose blood level.

They have found that more insulin release resulted from oral administration… This is known as the 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 الشبع

2. Glucose-dependent insulinotropic polypeptide (GIP)

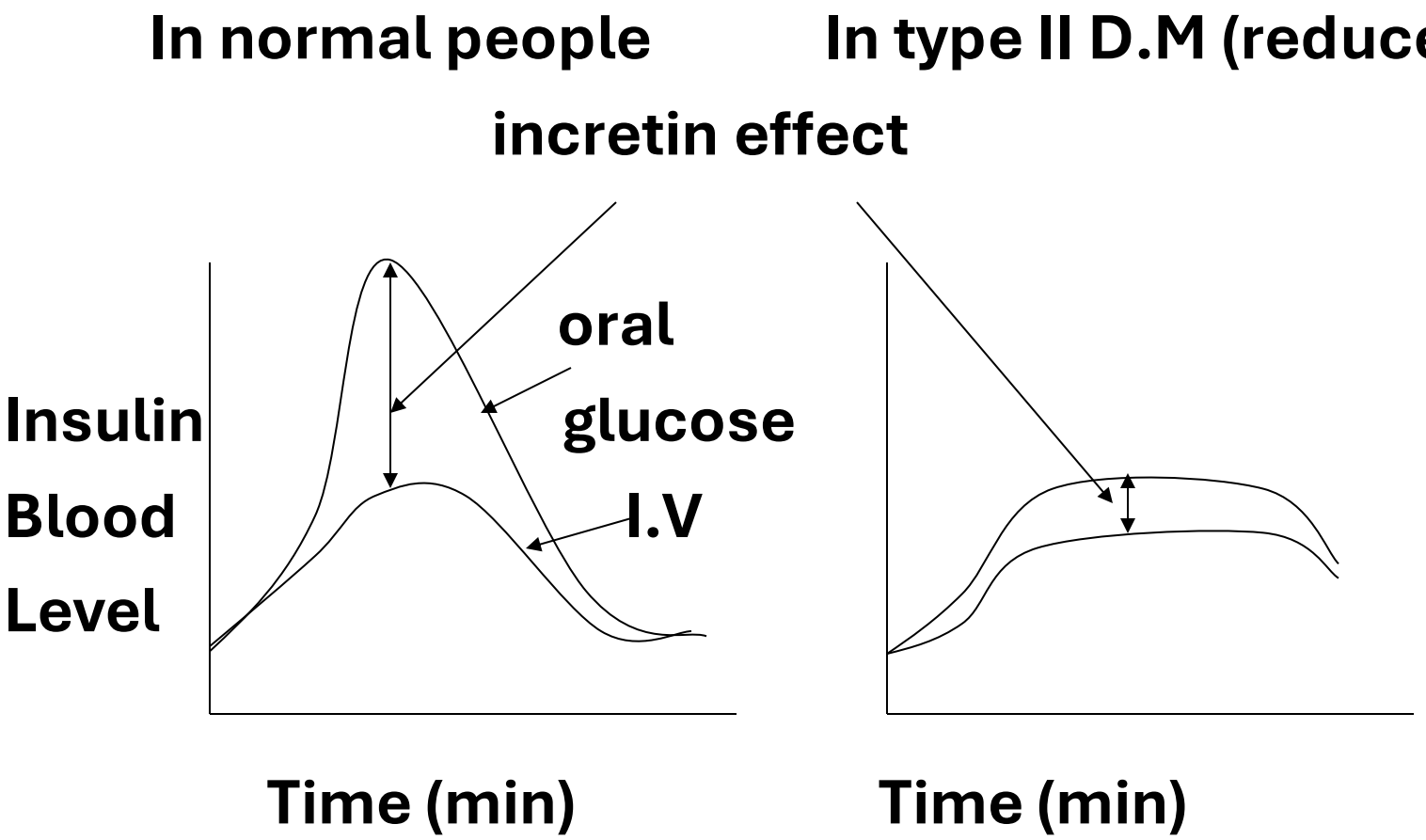
Produced by the K cells in the proximal gut (duodenum & proximal jejunum)

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.

Such proteins are in someway deficient in certain diabetic patients. The solution is to provide them with synthetic analogs to such proteins, or inhibit their metabolism.

Incretin effect:



As you see, oral glucose resulted in more release of insulin, and the difference in the released amount of insulin following oral vs. IV administration of the same amount of glucose is known as the incretin effect. This incretin effect is reduced in diabetics. This tells you that there's something in the intestine that increases glucose absorption and hence insulin release, and some proteins in the intestine that inhibit glucagon release as well.

Incretin mimetic drugs

- **Sitagliptin, Gemigliptin, Linagliptin…**

Orally effective selective DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors)

↑ blood levels of GLP-1, GIP (both metabolized by the same enzyme) and increase 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, Semaglutide, Tirzepatide…**

Incretin mimetics, Synthetic analogs to GLP-1 (Glucagon-Like Polypeptide-1)

Exenatide, Liraglutide and Semaglutide are GLP-1 agonists

Tirzepatide (Mounjaro®) is a dual GIP and GLP-1 receptor agonist

↑ insulin and ↓ glucagon blood levels

Considered as an adjunct (helper) 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 (controversial! However, it results in great loss of weight in a short period of time.)

Given S.C

Hypoglycemia is infrequent

- Aldose reductase (AR) inhibitors (another class belonging to hypoglycemic agents)

Epalrestat; Ranirestat; Fidarestat

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

AR inhibitors proved to improve diabetic

Orally effective

These drugs inhibit the enzyme that converts glucose to fructose and fructose to sorbitol; Aldose Reductase enzyme.
Sorbitol is believed to deposit in neurons and kidneys.
***Neuropathy is mostly numbness (خدران في اليد)**

- **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 ((the protein)) 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 ± sulfonylyrea in the management of type II DM

- Still under extinsive postmarketing screening for side effects in patients with type II DM

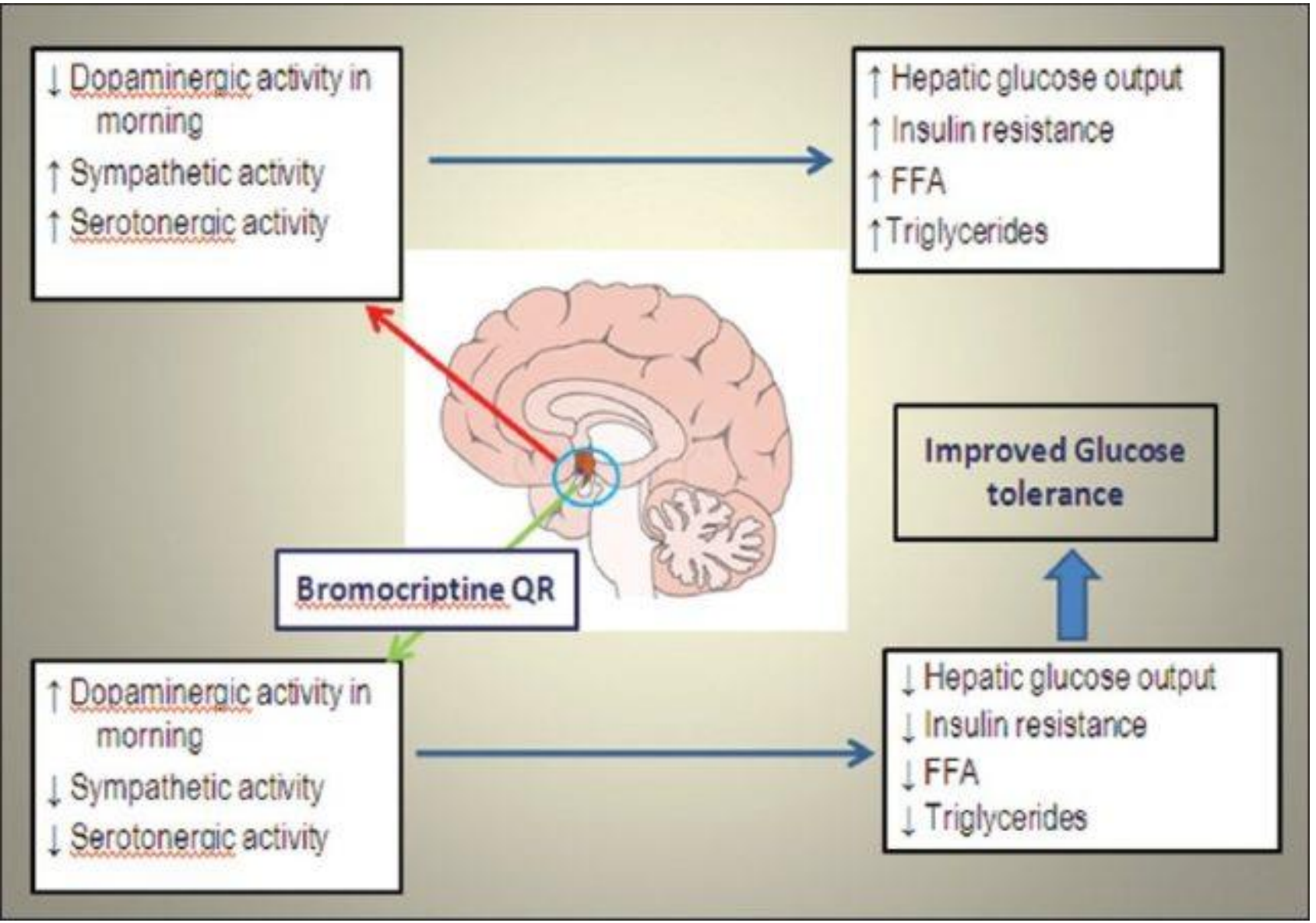
- **Bromocriptine** **(we said that in addition of inhibiting prolactin synthesis (being the no. 1 drug in the management of hyperprolactinemia in both males and females irrespective of the cause), it inhibits growth hormone, …)**

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 (that is why it's known as a sympatholytic), resulting in a reduction in postmeal 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



Certain diabetic patients experience drop in dopaminergic activity when they wake up in the morning, increased sympathetic activity and serotonergic activity. This could lead to an increase in hepatic glucose production, insulin resistance, FFA and triglycerides synthesis. So decreased dopamine should be replaced by agonists to enhance its effect in the CNS, which leads to decreased sympathetic and serotonergic activities, decreased hepatic glucose production, insulin resistance, FFA and triglycerides synthesis. The net result is an improved glucose tolerance.

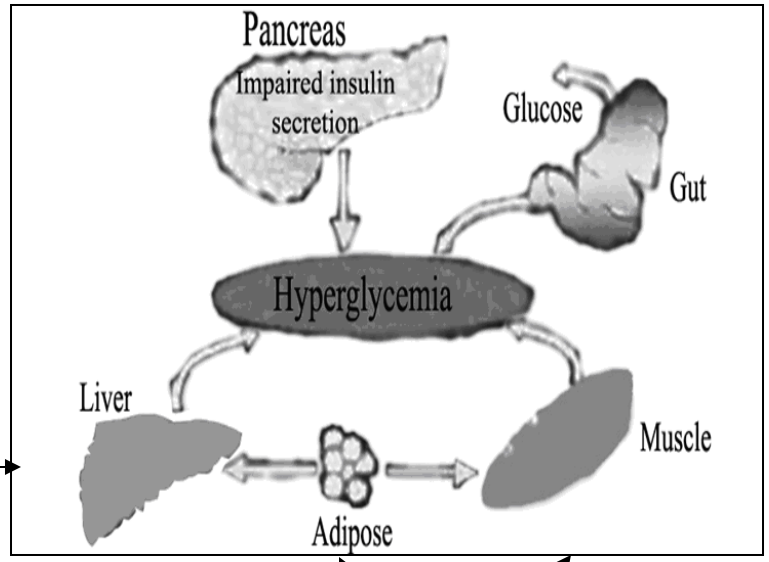
Sulfonylurea

Meglitinide Analogs

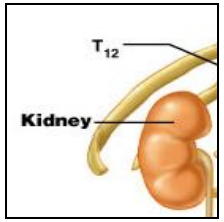
Incretin hormones

Amylin mimetic drugs

Alpha glucosidase inhibitors



Biguanides



TZD's

Gliflozins

This shows the different oral hypoglycemic agents other than insulin involved in the management of DM.
*Gliflozins act on the kidney.
*Biguanides on the liver.
*Thiazolidinediones on its target tissues.
*Sulfonylurea, Meglitinide Analogs, Incretin hormones, Amylin mimetic drugs usually work on the pancreas increasing insulin and some others decrease glucagon, etc...

- Somatostatin

In low doses → ↓ glucagon release

Under evaluation (to be used to manage DM since it has an effect on the glucagon released by pancreas)

- Role of ACEI's; ARB's; Statins (there are trends of using such drugs as prophylactic agents in diabetic patients, the doctor disagrees with this because not all diabetics may develop hypertension or hyperlipidemias or dyslipidemias, if it occurs we intervene or think of using)

** Role of Glucagon in diabetics?!!! (Hypoglycemia is manifested as overactivity of the sympathetic nervous system (anxiety, dizziness, tachycardia) and is managed by oral administration of glucose (eating sugar), but if the patient faints, IV glucose should be given. If you had a patient with hypoglycemic coma and you couldn't find a vein for IV (glucose cannot be given SC or IM),the patient will die! In this case you can use glucagon (recombinant human glucagon) SC or IM. Extreme case.

** Pancreatic transplantation and gene therapy (in transplantation, rejection is a problem, but it is performed. Gene therapy involves gene injection, transdermal injection of gene that codes for insulin is under study. Beta cells implantation rather than the whole pancreas can be performed.)

** Drugs ↓ blood glucose levels:

β-blockers, salicylates, indomethacin, naproxin (NSAID), 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

Sulfonamides were introduced to the market before sulfonylureas. Some sulfonamides when were used as chemotherapeutic agents showed hypoglycemic effects, they then modified its structure to remove this feature and synthesized sulfonylureas that are devoid of any chemotherapeutic activity).

Notes:

β-blockers decrease blood glucose levels under counter effects of catecholamines which usually elevate blood sugar level, so when this activity is blocked we end up with decreased blood glucose level.

Direct effects of β-blockers on insulin released from pancreas cause increased blood glucose level.

β-blockers are not preferred antihypertensive agents for diabetics with hypertension. They are NOT contraindicated, pay attention, one has to be careful in prescribing β-blockers to diabetics, especially patients with insulin and other hypoglycemic agents. This is called compelling indication, meaning that the patient has 2 problems. Thiazides, for example, are not considered the 1st line therapy in the management of hypertension in diabetics because they elevate blood sugar level.

The major reason why β-blockers are not advised is that they mask manifestations of hypoglycemia by blocking sympathetic system action. The patient has hypoglycemia but he can't feel it!

Goals of DM treatment!!=Control

- **Ensure good Pt-clinic relationship (most important)**
- **Control symptoms**
- **Prevent acute metabolic crisis of KA (ketoacidosis) & hypoglycemia**
- **Maintain normal growth & BW (body weight)**
- **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…