Pancreatic Hormones

- Insulin (β-cells); Glucagon (α-cells)
- Diabetes Mellitus

- A disease characterized by high blood sugar level?

- A disease characterized by insulin deficiency?

- A metabolic disorder manifested by abnormalities in CHO, lipid and protein metabolism

- Diabetes is a major cause of heart disease and stroke
- Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States
- Diabetes is the seventh leading cause of death in the United States

- Types of DM (2 types):
- Type I; juvenile-onset; IDDM

- 10-20% of diabetics

- Most commonly occurs in childhood or adolescence but may occur at any age

- Mainly affects children at an age 10-14 (not reported in kids less than 6 months)

- Type I DM pts have little or no pancreatic function
- Often pts present with ketoacidosis
- Characterized by downhill course-severe type of DM (mortality is high)
- Easy to diagnose (pts usually present C/O wt. loss; easy fatigability; polyuria; polydipsia; polyphagia…)

- **Type II; maturity or adult-onset; IIDM**

- Represents 80-90% of diabetics

- Usually discovered accidentally after an age of 30-40 yrs

- Most pts are obese and it is more common in females as compared to males

- Pts have strong family Hx (genetic background)

- Most cases of type II have mild polyuria and fatigue
- Ketoacidosis is rare in pts with type II DM unless in certain circumstances of unusual stress
- Insulin blood levels could be low, normal or high
- Insulin resistance is common (pre-receptor; receptor; post-receptor mechanisms)

- **Symptomatology:**

- Early

- Late

- **Early manifestations:**

Polyuria

Polydipsia

Polyphagia

Ketoacidosis (type I)

- Late manifestations or complications:

Atherosclerosis & IHD

Retinopathy

Nephropathy

Neuropathy

** Normalization of blood glucose level corrects immediately early manifestations… late complications???

- **Diagnosis:**

- Clinical manifestations

- Lab. Tests:

  Random blood sugar (RBS)

  Fasting blood sugar

  Glycosylated hemoglobin (HbA1c)

  Glucose tolerance test

- **Management:**

- Type I:

Diet

+ Insulin therapy

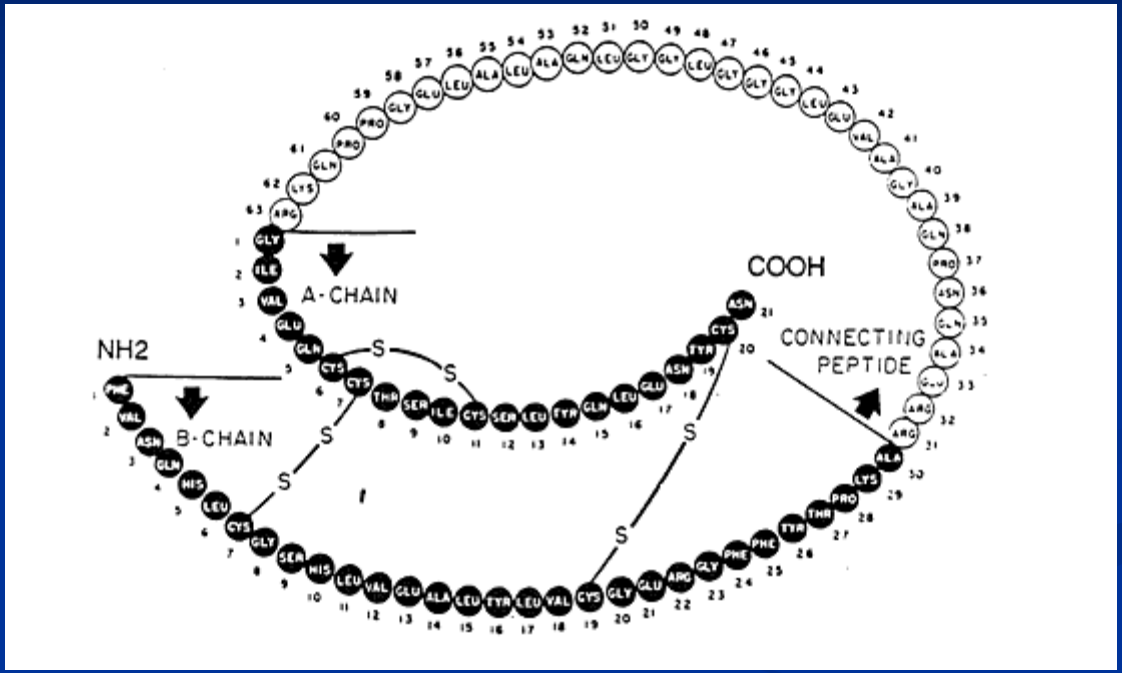
- Type II:

Diet + exercise

± Oral hypoglycemic agents

± Insulin

Insulin



Insulin

Protein; A (21 aa) & B (30 aa) chains; disulfied bonds

- **Biosynthesis of insulin:**

Proinsulin has slight insulin-like activity (1/10 the potency of insulin)

C-peptide is devoid of any insulin-like activity

- **Secretion of insulin:**

Ca^{++} dependent

[blood glucose] is the major regulator

- **Factors/drugs ↑ release:**

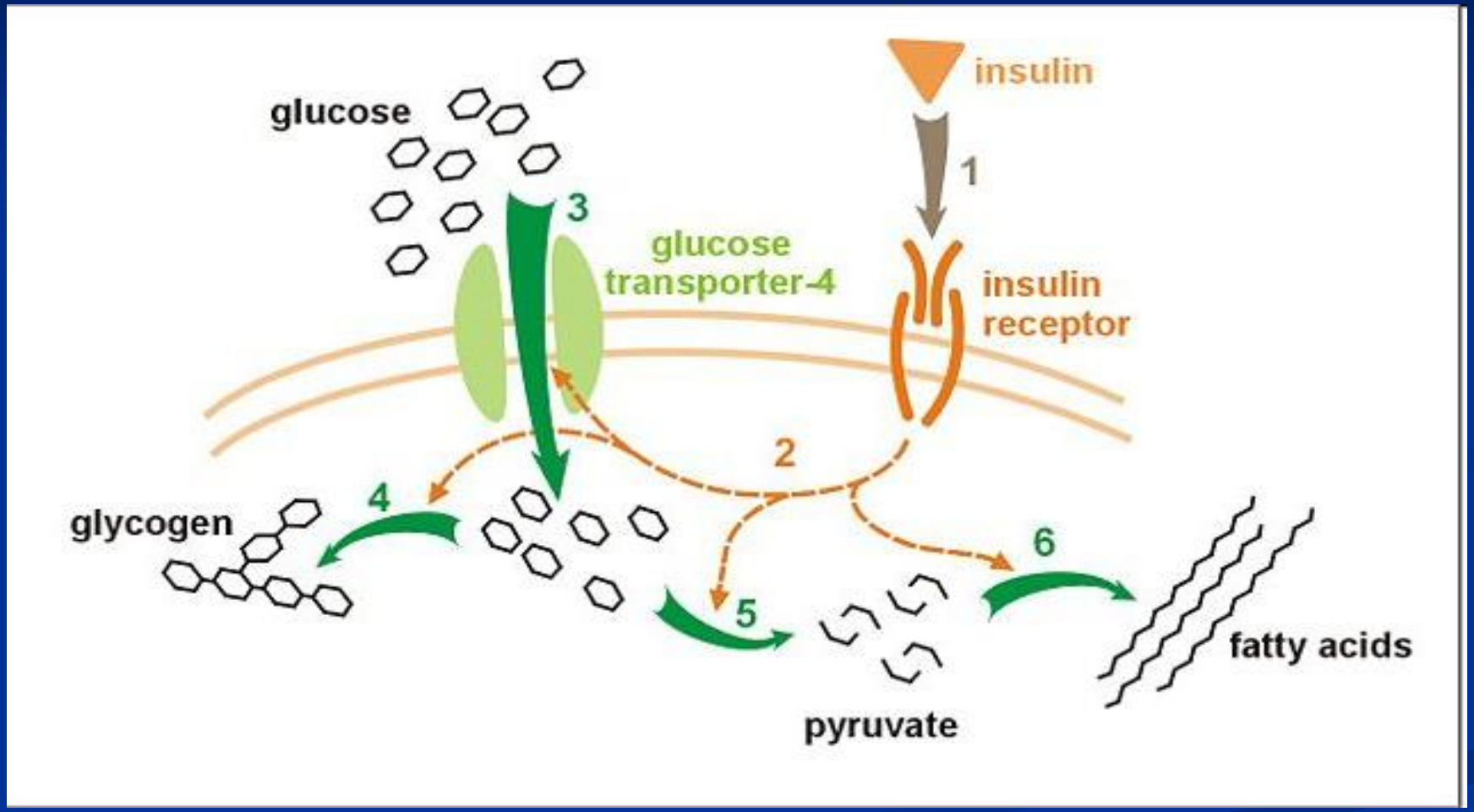
Glucose; a.a's; F.A's; GH; glucagon; ACTH; sulfonylureas; β-adrenergics, cholinergic drugs…

- **Factors/drugs ↓ release:**

α-adrenergics; anticholinergics; phenytoin; alloxan; streptozotocin (streptozocin)

- **Insulin mechanism of action**

Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor leading to phosphorylation of insulin-receptor complex (1) which in turn starts many protein kinases activation cascades (2). These include: translocation of Glu transporter-4 to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).


glucose
insulin
1
3
glucose
transporter-4
insulin
receptor
2
4
glycogen
6
5
fatty acids
pyruvate

- **Insulin effects:**

- ↑ glucose uptake or transport → muscles & adipocytes
- ↑ glucose oxidation by muscles
- ↓ hepatic gluconeogenesis
- ↑ hepatic glycogen synthesis and storage; ↓ glycogenolysis
- ↑ a.a uptake and protein synthesis by muscles and liver
- ↓ lipolysis
- ↓ ketogenesis

- **Insulin preparations:**

- Natural

Insulins of animal source are no more used and natural human insulin extracted from the pancreas is characterized by having low bioavailability and short $t_{1/2}$ due to problems with its stability

- Synthetic

rHI to all preparations are available

Insulins are classified according to duration of action (DOA)

** Ultra-rapid onset; very short acting:

	O (hr)	P (hr)	DOA (hr)
- Insulin Lispro	0.25-0.5	0.5-1	3-4
- Insulin Aspart	10-20 min		
- Insulin Glulisine			

** Rapid onset & short acting:

- Crystalline zinc (regular; soluble; insulin injection)	0.3-0.7	2-4	5-8
- Insulin zinc prompt (Semilente)	0.5-1	2-8	12-16

** Intermediate onset & action:

- Insulin zinc suspension (Lente)	1-2	6-12	18-24
- Isophane insulin suspension (NPH; Humulin)	1-2	6-12	20-28

** Slow onset & action:

- Protamine zinc suspension	4-6	14-20	24-36
- Extended insulin zinc suspension (Ultralente)	4-6	16-18	24-36

Insulin Glargine	1-2	-	24-36
(peakless insulins)			
Insulin Detemir	1-2	-	24-36
** Mixed insulins:			
Int. + short	0.5-1	3-8	20-24
Int. + long	2-4	4-16	22-24

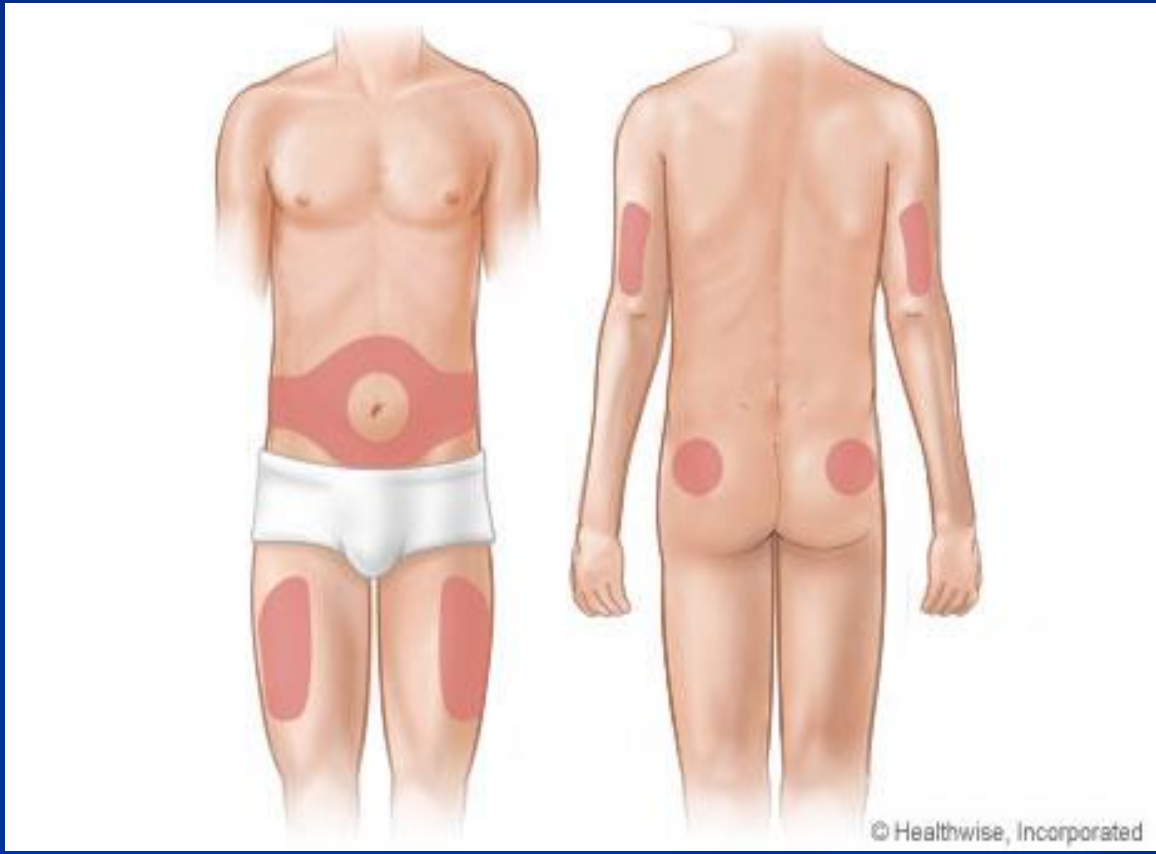
All insulin preparations are mainly given S.C except regular insulin, insulin Glulisine & insulin Aspart (SC & I.V)… Instructions to pt

- Advantages of peakless insulins over intermediate-acting insulins:

- Constant circulating insulin over 24hr with no pronounced peak

- More safe than NPH & Lente insulins due to reduced risk of hypoglycemia (esp. nocturnal hypoglycemia)

- Clear solution that does not require resuspension before administration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- **Factors affecting insulin absorption:**

- Site of injection:

abdomen > arm > buttocks > thigh

- Exercise = blood flow at site
- Depth of injection
- Concentration and dose of insulin
- Addition of protamine or isophane to insulin preparations to form a complex delaying absorption and hence alter DOA

- Insulin is metabolized in tissues (liver, muscles and kidneys) and metabolites are excreted renally

- **Dose of insulin:**

Insulin is given in units and its need varies tremendously

- **Side effects to Insulin therapy:**

- Hypoglycemia; ↑ sympathetic activity (instructions to pts)
- Lipodystrophy
- Allergy
- Induration

** Diabetic → to E.R with coma; management?!!!!

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	±

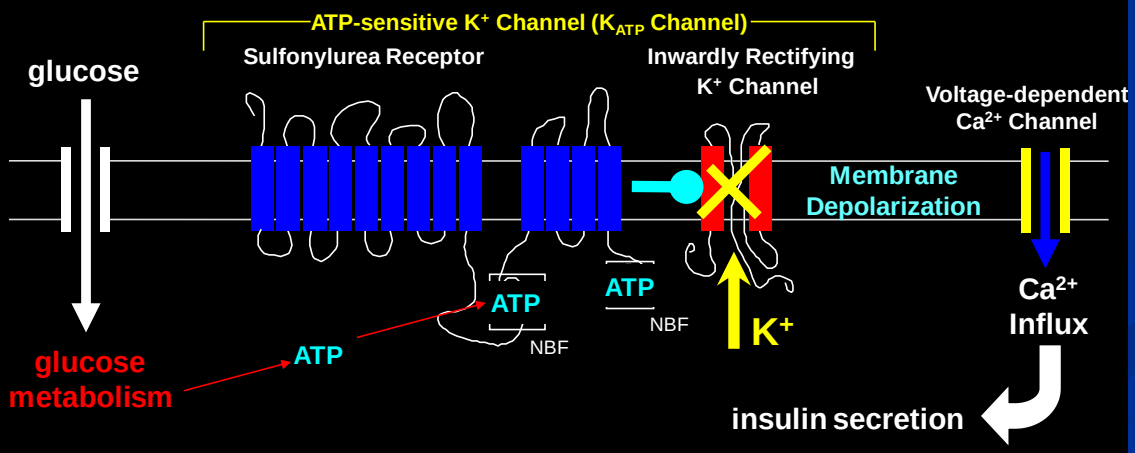
- **Sulfonylureas:**

- ↑ 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)

Taken before meals (every meal)

Could be taken with metformin or insulin

Hypoglycemia is infrequent

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

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

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 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

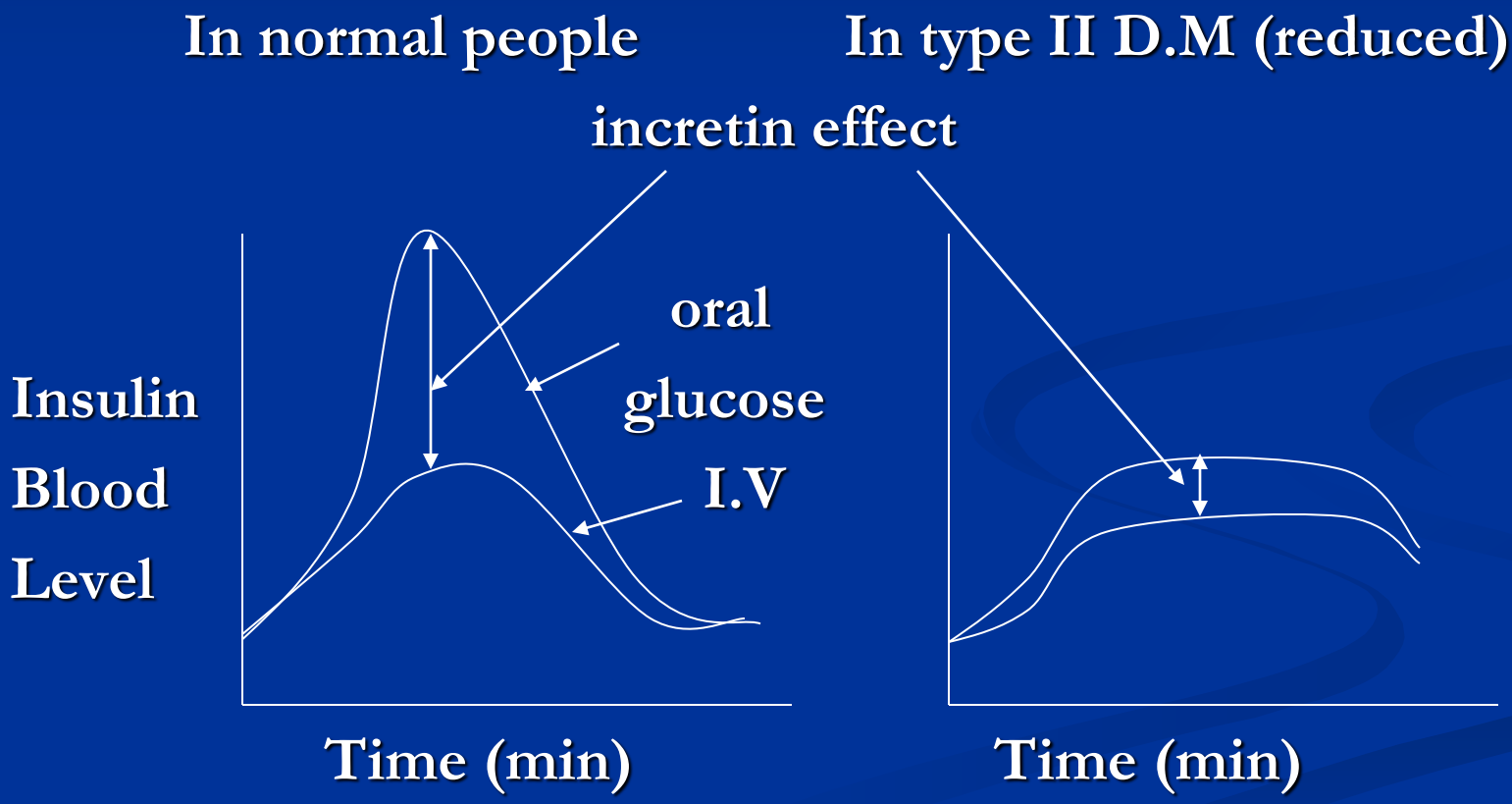
2. Glucose-dependent insulinotropic polypeptide (GIP)

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

Incretin effect:



Incretin mimetic drugs

- **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, Tirzepatide…**

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

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 ± sulfonylyrea in the management of type II DM
- Still under extinsive postmarketing screening for side effects in patients with type II DM

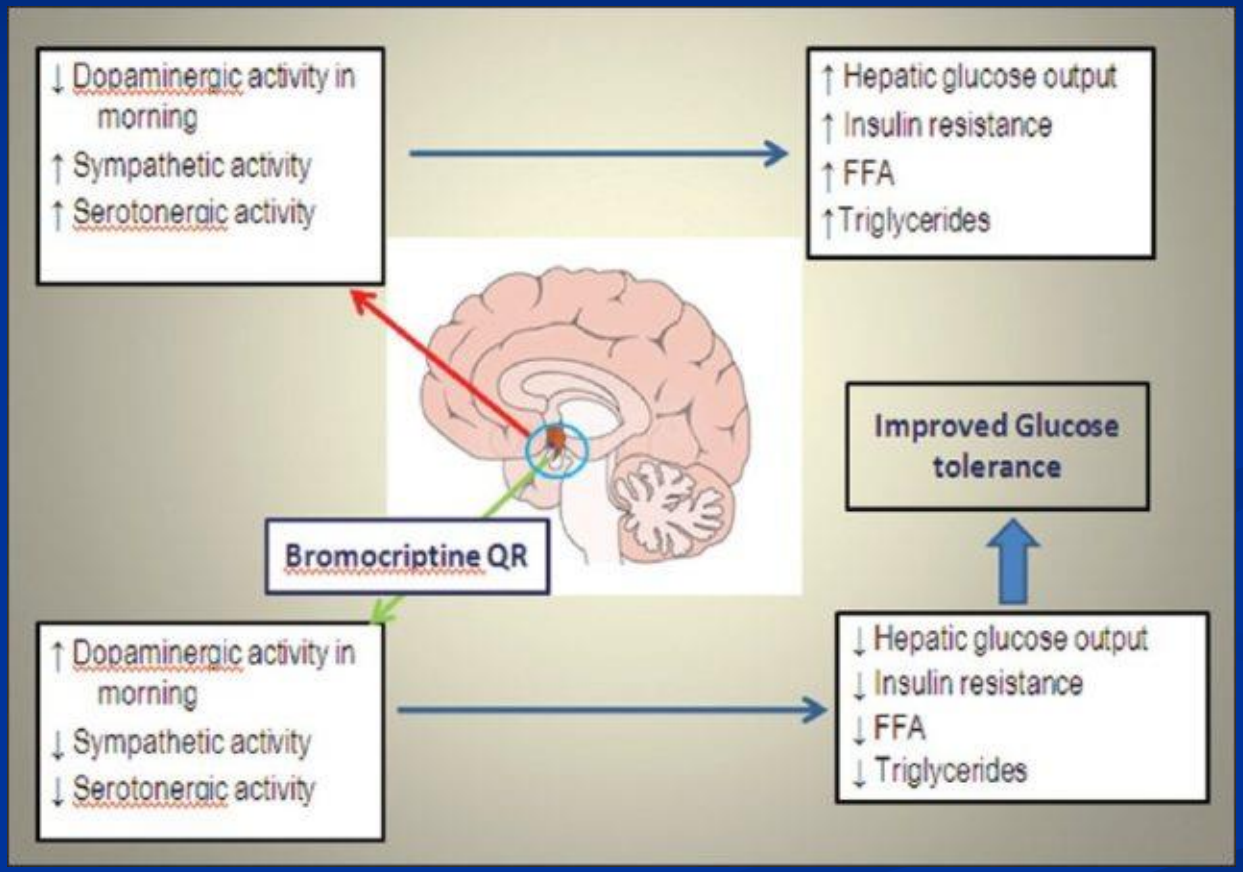
- **Bromocriptine**

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 postmeal plasma glucose levels by suppressing hepatic glucose production

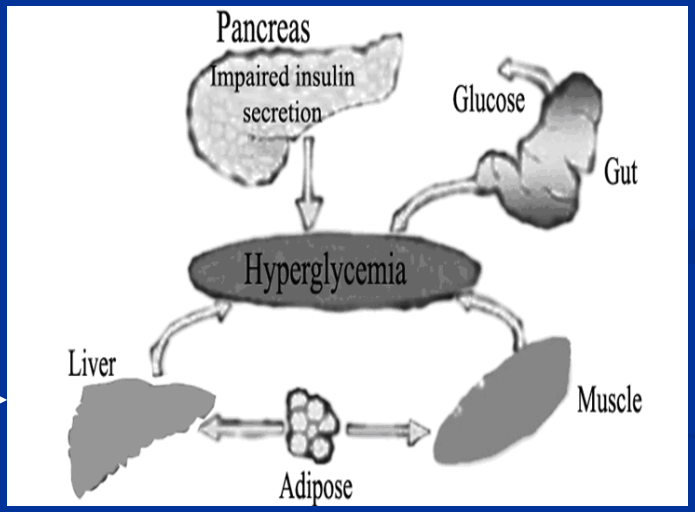
It reduces plasma glucose, triglycerides, Free Fatty Acid (FFA) levels, and possibly cardiovascular events in type 2 diabetics

Side effects mild most common nausea

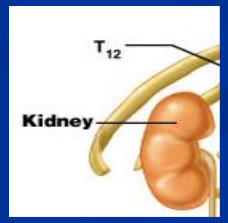

↓ Dopaminergic activity in morning
↑ Sympathetic activity
↑ Serotonergic activity
↑ Hepatic glucose output
↑ Insulin resistance
↑ FFA
↑ Triglycerides
Improved Glucose tolerance
Bromocriptine QR
↑ Dopaminergic activity in morning
↓ Sympathetic activity
↓ Serotonergic activity
↓ Hepatic glucose output
↓ Insulin resistance
↓ FFA
↓ Triglycerides

Sulfonylurea
Meglitinide Analogs
Incretin hormones
Amylin mimetic drugs

Alpha glucosidase inhibitors



Biguanides



Gliflozins

TZD's

- 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...