INSULIN AND ORAL ANTIDIABETICS

Dr. Zeliha BAYRAM

- The endocrine pancreas in the adult human consists of approximately 1 million islets of Langerhans
- Within the islets, at least five hormone-producing cells are present

- **Insulin→** the storage and anabolic hormone of the body

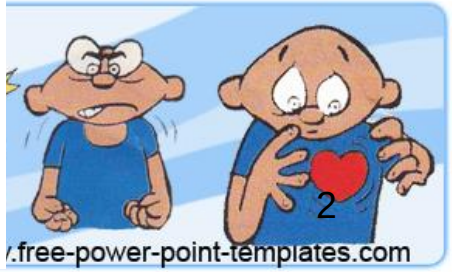
- **Islet amyloid polypeptide (IAPP,** or **amylin) →** modulates appetite, gastric emptying, and glucagon and insulin secretion

- **Glucagon →** the hyperglycemic factor that mobilizes glycogen stores

- **Pancreatic peptide →**a small protein that facilitates digestive processes by a mechanism not yet clarified

- **Ghrelin→** a peptide known to increase pituitary growth hormone release.

Cell Types	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3–5	Somatostatin
G cell	1	Gastrin
F cell (PP cell)[1]	1	Pancreatic polypeptide (PP)



DIABETES MELLITUS (DM)

- A chronic metabolic disorder is characterised by a high blood glucose concentration (**hyperglycemia)**

- caused by
  - **insulin deficiency** → absent or inadequate pancreatic insülin secretion
  - **insulin resistance** → a decrease in the response of peripheral tissues to insulin

Characteristics of DM

- hyperglycemia
- disturbance in metabolism of lipids, carbohydrates and proteins

Symptoms of diabetes

- Polyuria (urinating frequently)
- Polydipsia (very thirsty)
- Continuous hunger
- Weight loss

Other diabetes symptoms

- Fatigue
- Dry skin
- Frequent infections
- Feet ulceration
- Loss of sensibility in inferior extremities (legs)

Classification of DM

- Type 1 (Insulin-dependent diabetes mellitus, IDDM)
  - Immune Mediated
  - Idiopathic

- Type 2 (non-insulin-dependent diabetes mellitus, NIDDM)

→ Maturity onset

- Other specific types

→ refers to multiple *other* specific causes of an elevated blood glucose: pancreatectomy, pancreatitis, nonpancreatic diseases, drug therapy, etc

- Gestational Diabetes mellitus

→ defined as any abnormality in glucose levels noted for the first time during pregnancy.

→ During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester.

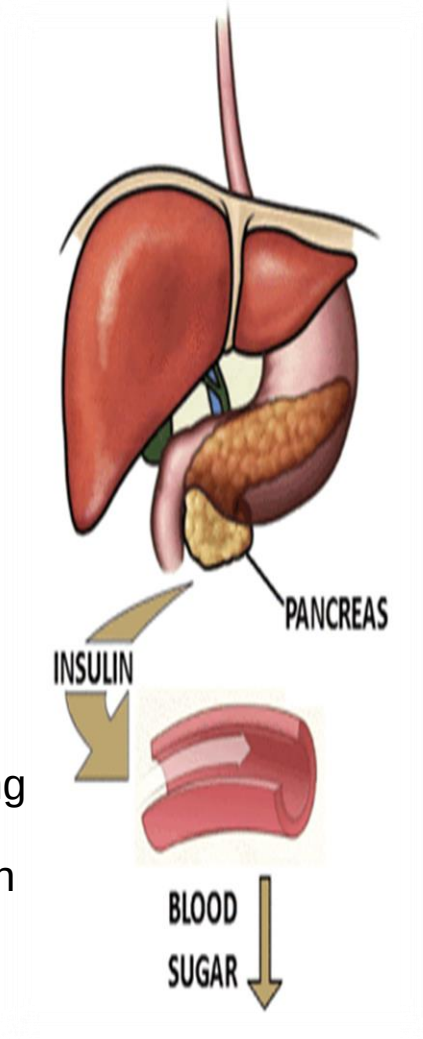


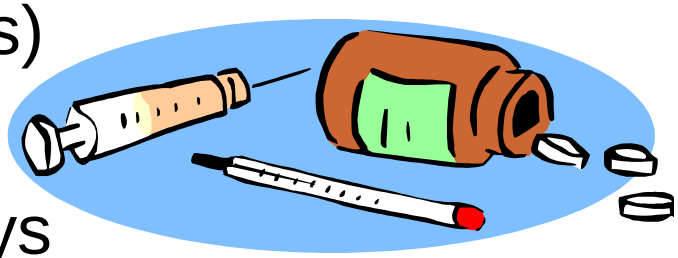
TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

	TYPE 1	TYPE 2
Etiology	Autoimmune destruction of pancreatic β-cells	Insulin resistance, with inadequate β-cell function to compensate
Insulin levels	Absent or negligible	Typically higher than normal
Insulin action	Absent or negligible	Decreased
Insulin resistance	Not part of syndrome but may be present (e.g., in obese patients)	Yes
Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis Wasting	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as type 1
Pharmacologic interventions	Insulin	A number of drug classes are available, including insulin if other therapies fail

Type 1 and type 2 diabetes mellitus are both associated with increased blood glucose levels, but the two diseases result from distinct pathophysiologic pathways. In type 1 diabetes mellitus, there is an absolute lack of insulin secondary to autoimmune destruction of pancreatic β-cells. The etiology of type 2 diabetes is less well understood but seems to involve impaired insulin sensitivity and an inadequate level of compensatory insulin production by pancreatic β-cells. Although type 1 and type 2 diabetes have different acute complications (*see text*), they share similar chronic complications. Insulin is the primary pharmacologic intervention for type 1 diabetes, while type 2 diabetes can be treated with a number of different agents.

Treatment and control

- Medications
  - (insulin vs. hypoglycaemic agents)
- Increase physical activity
  - at least walk for 30 min. most days
- Appropriate diet
  - vegetables
  - fruit
  - low in fat and carbohydrates
- Lifestyle changes



Classification of drugs

1. Insulin

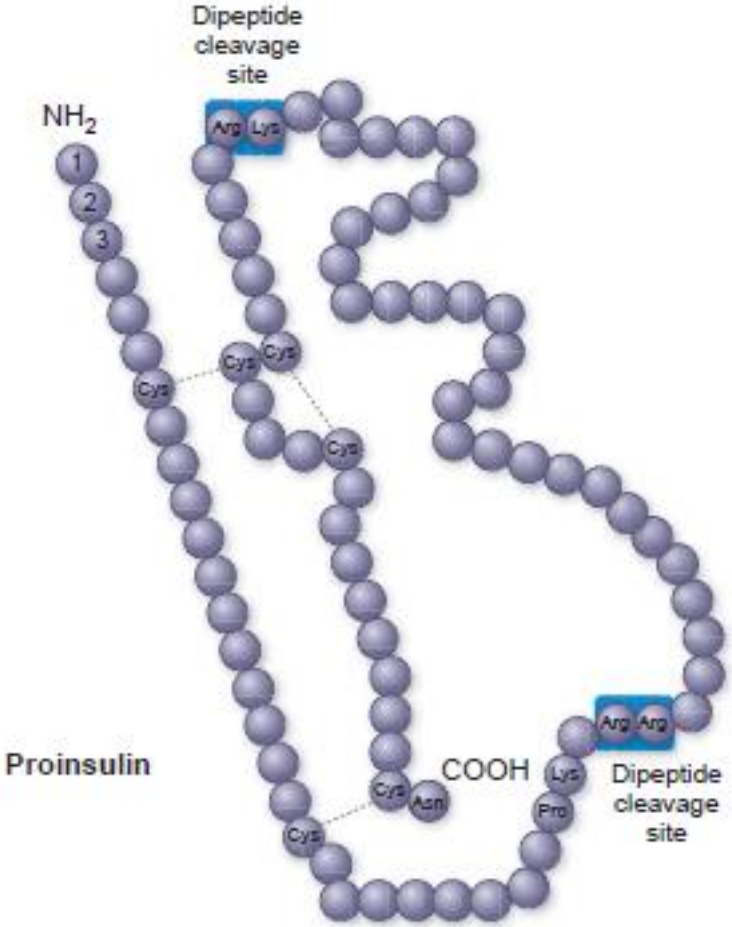
2. Oral Antidiabetics

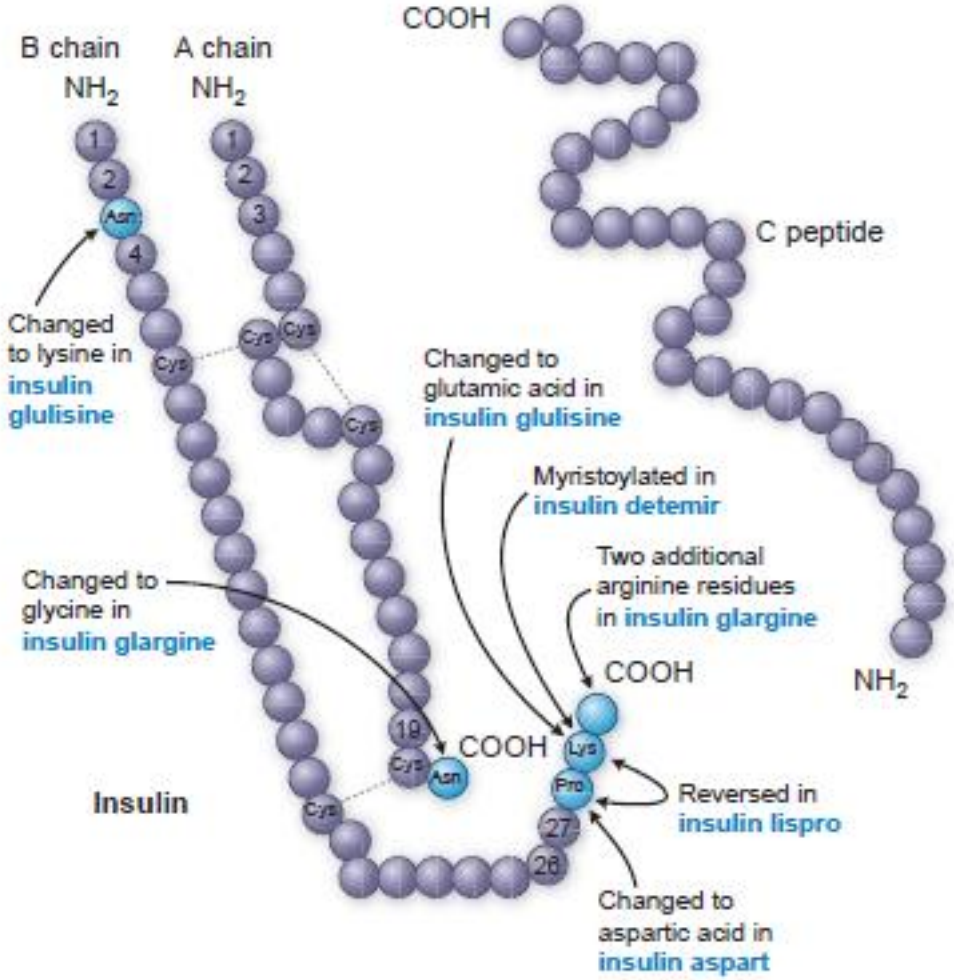
INSULIN

- A polypeptide hormone with two peptide chains that are connected by disulfide bonds (51 aa).
- Synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form insulin and C peptide, both of which are secreted by the ß cells of the pancreas triggered by high blood glucose..
- Insulin and glucagon regulate blood glucose levels.

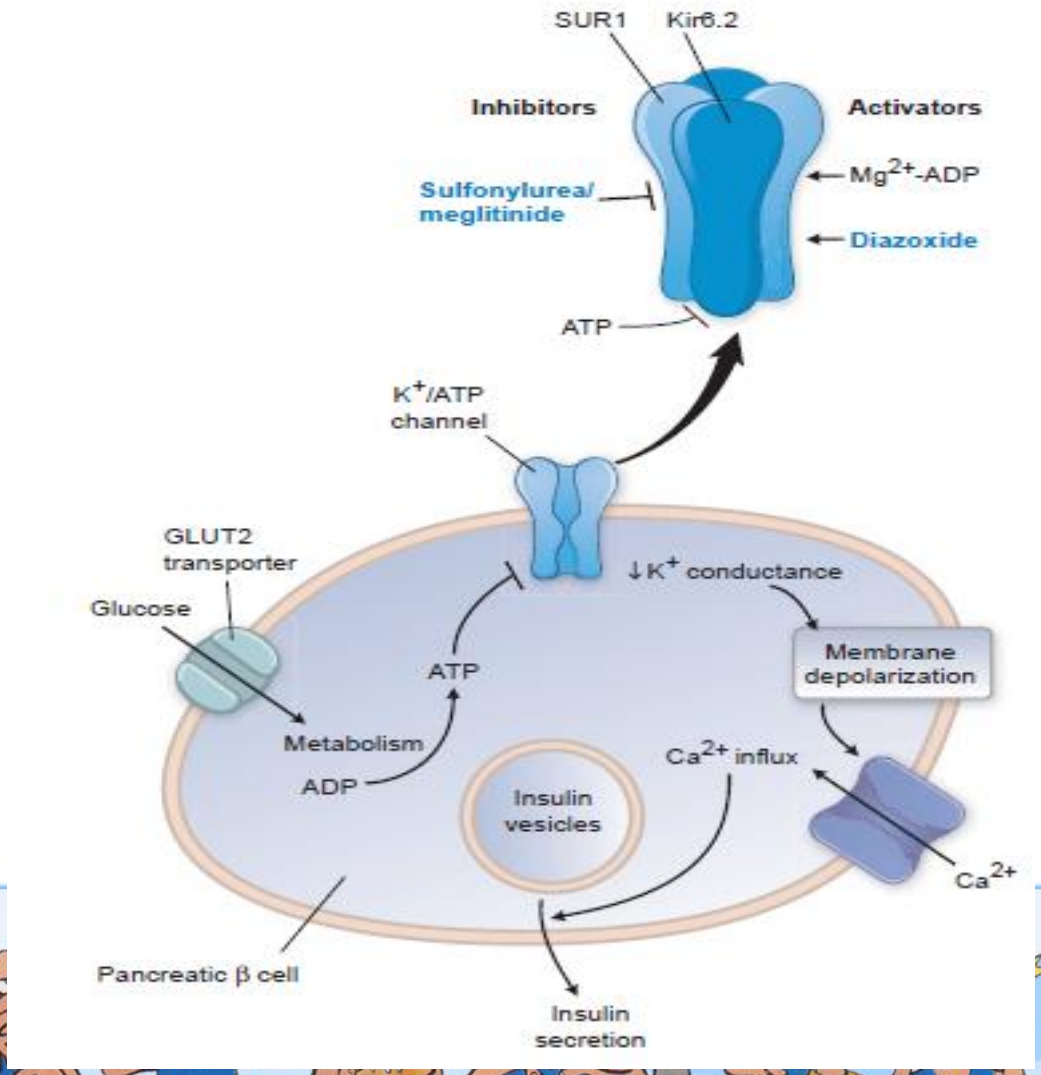
ACTIONS :

- Controls intermediary metabolism, having actions on liver, muscle and fat.
- Conserves fuel by facilitating the uptake and storage of glucose, amino acids and fats after a meal





Mechanism of Insulin release



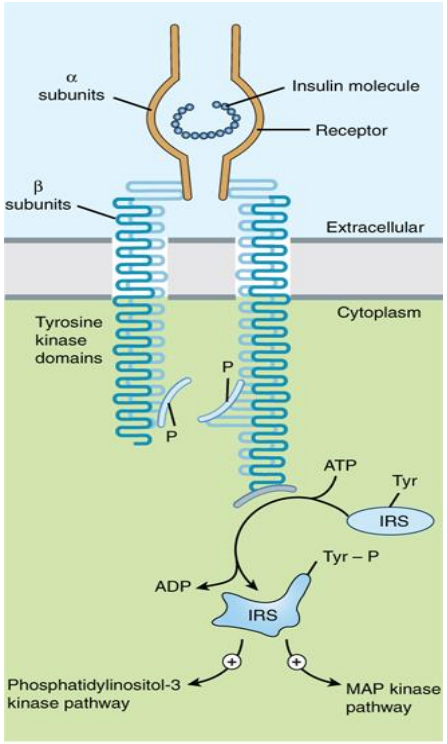
- ## Sources of insulin :

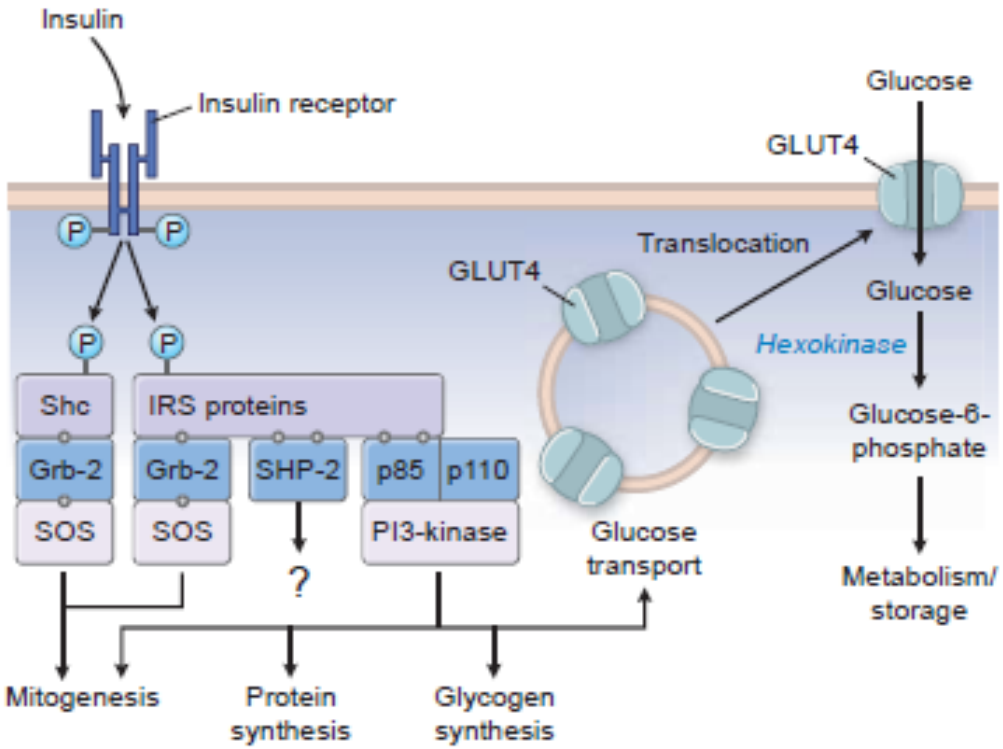
Human insulin is produced by recombinant DNA technology using special strains of Escherichia coli or yeast that have been genetically altered to contain the gene for human insulin.

- ## Mechanism of Action (MOA):

Acts on insulin receptors on liver cells ,fat cells and stimulates glucose transport across membrane by ATP dependent transporters like GLUT 4 &GLUT 1

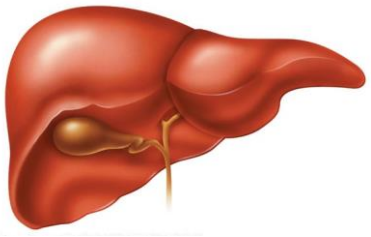
Downstream Effects of Insulin Receptor Activation





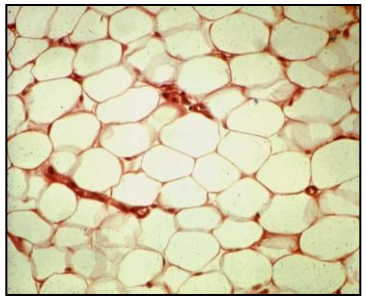
Effects of Insulin

Liver



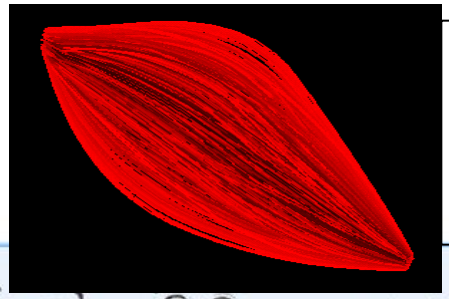
Inhibits glycogenolysis
Inhibits gluconeogenesis
(conversion of amino acids to glucose)
Promotes glycogen synthesis

Fat



+ glucose uptake
+ storage of TG
Inhibits lipolysis

Muscle



+ protein synthesis
+ glycogen synthesis
- Protein breakdown

TYPES OF INSULIN PREPARATIONS

1. Rapid-acting insulin preparations :

insulin lispro, insulin aspart and insulin glulisine

- these insulin preparations reach peak plasma concentration in 30-90 mins.
- with very fast onset and short duration

- **Insulin lispro** is an insulin analogue in which a lysine and a proline residue are 'switched'

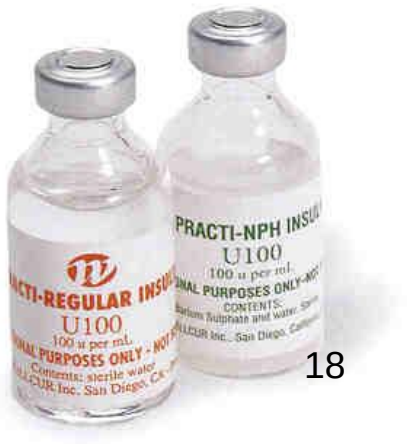
TYPES OF INSULIN PREPARATIONS

2. Short-acting insulin preparation :

Regular insulin

- Its effect appears within 30 minutes, peaks between 2 and 3 hours after subcutaneous injection, and generally lasts 5–8 hours.

- a short-acting soluble crystalline zinc insülin with rapid onset of action



TYPES OF INSULIN PREPARATIONS

3. Intermediate-acting insulin preparations:

a. Insulin zinc suspension (lente)

b. Neutral Protamine Hagedorn (NPH)

- Neutral protamine Hagedorn (NPH) insulin is a suspension of crystalline zinc insulin combined at neutral pH with a positively charged polypeptide, protamine
- Delayed absorption of the insulin because of its conjugation with protamine, forming a less-soluble complex

TYPES OF INSULIN PREPARATIONS

4. Long-acting insulin preparations :

a. Insulin glargine

b. Insulin detemir

The length of time to onset is 3 to 4 hours and the maximum duration is 20 to 24 hours.

TABLE 41–4 Some insulin preparations available in the USA.[1]

Preparation	Species Source	Concentration
Rapid-acting insulins		
Insulin lispro, Humalog (Lilly)	Human analog	U100
Insulin aspart, Novolog (Novo Nordisk)	Human analog	U100
Insulin glulisine, Apidra (Aventis)	Human analog	U100
Short-acting insulins		
Regular Novolin R (Novo Nordisk)	Human	U100
Regular Humulin R (Lilly)	Human	U100, U500
Intermediate-acting insulins		
NPH Humulin N (Lilly)	Human	U100
NPH Novolin N (Novo Nordisk)	Human	U100
Premixed insulins		
Novolin 70 NPH/30 regular (Novo Nordisk)	Human	U100
Humulin 70 NPH/30 regular (Lilly)	Human	U100
75/25 NPL, Lispro (Lilly)	Human analog	U100
70/30 NPA, Aspart (Novo Nordisk)	Human analog	U100
Long-acting insulins		
Insulin detemir, Levemir (Novo Nordisk)	Human analog	U100
Insulin glargine, Lantus (Aventis/Hoechst Marion Roussel)	Human analog	U100

[1]These agents (except insulin lispro, insulin aspart, insulin detemir, insulin glargine, insulin glulisine, and U500 regular Humulin) are available without a prescription. All insulins should be refrigerated and brought to room temperature just before injection.

NPL, neutral protamine lispro; NPA, neutral protamine aspart.

Insulin administration

Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. It therefore is generally administered by subcutaneous injection

All insulin preparations are administered subcutaneously

Regular insulin can be administered i.v & i.m also

Pharmacokinetics of Insulin

- Destroyed in the gastrointestinal tract, and must be given parenterally-usually subcutaneously, but intravenously or occasionally intramuscularly in emergencies

- Insulin should be administered 15-20 mins prior to meal

Adverse effects of insulin

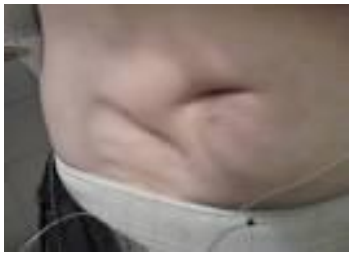
1. Hypoglycemia (most serious and common)

Treatment- oral glucose

50ml of 50% dextrose i.v

2. Local reactions

lipodystrophy, swelling, erythema



3. Allergy and resistance

Oral Antidiabetics

- Agents that are given orally to reduce the blood glucose levels in diabetic patients
- Six types of oral antidiabetic drugs are currently in use:

1. agents that bind to the sulfonylurea receptor and stimulate insulin secretion (sulfonylureas, meglitinides)

2. agents that lower glucose levels by their actions on liver, muscle, and adipose tissue (biguanides, thiazolidinediones)

3. agents that principally slow the intestinal absorption of glucose(α-glucosidase inhibitors)

Oral Antidiabetics

4. agents that mimic incretin effect or prolong incretin action (glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors)

5. agents that inhibit the reabsorption of glucose in the kidney (sodium-glucose co-transporter inhibitors [SGLTs]),

6. agents that act by other or illdefined mechanisms (pramlintide, bromocriptine, colesevelam).

Oral Antidiabetics

- The oral antidiabetic drugs are of value only in the treatment of patients with type 2 (NIDDM) diabetes mellitus whose condition cannot be controlled by diet alone.

- These drugs may also be used with insulin in the management of some patients with diabetes mellitus, Use of an oral antidiabetic drug with insulin may decrease the insulin dosage in some individuals.

1. DRUGS THAT PRIMARILY STIMULATE INSULIN RELEASE BY BINDING TO THE SULFONYLUREA RECEPTOR

Sulfonylureas

- **1st generation** : Tolbutamide, Chlorpropamide, Tolazamide

- **2nd generation :** Glibenclamide, Glipizide, Glimperide

MOA : Acts on B cells increase insulin release

- Inhibits SUR-1 receptors present on ATP sensitive K^+ channels → depolarization followed by Ca^+ entry → insulin release
- Glucagon levels are suppressed

Sulphonylureas

First Generation

Tolbutamide

- Half-life : 6-12 hrs
- Pharmacokinetics : Orally administered, Some converted in liver to weakly active hydroxytolbutamide; some carboxylated to inactive compound. Renal excretion
- It is weaker, short acting, less likely to cause hypoglycemia

Chlorpropamide

- Half-life: 32 hrs
- It is more potent, long lasting,
- risk of prolonged hypoglycemia
- Potentiates ADH action

Tolazamide

- Half-life: 7 hrs
- comparable to chlorpropamide in potency
- has a shorter duration of action

Sulphonylureas (contd)

Second Generation

Glibenclamide (glyburide)

- Duration of action: lasts for 10-24 Hrs
- It is more potent than tolbutamide, risk of severe hypoglycemia .

Glipizide

- Duration of action: lasts for 10-24 Hrs
- Less potent than glibenclamide but more potent than tolbutamide
- Risk of prolonged hypoglycemia

Gliclazide

- Duration of action :same as glipizide
- More potent than tolbutamide
- Has an antioxidant and antiplatelet action
- Less weight gain

Glimepiride

- Same as glipizide

Sulphonylureas

Pharmacokinetics

- well absorbed
- PPB is high
- Metabolized in liver or kidney and excreted in urine

Adverse effects

- Hypoglycemia
- Weight gain
- Cross placental barrier and enter breast milk– contraindicated in pregnancy and in breast feeding

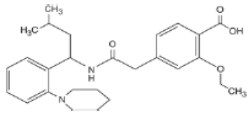
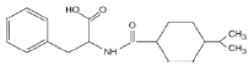
Drug interactions

NSAIDs, MAO inhibitors, anti bacterials, and anti fungals

Meglitinide Analogs

- These act, like the sulfonylureas, but they don't have sulfonylurea moiety.
- These include **repaglinide** and **nateglinide**
- MOA : Same as sulfonylureas .
- Short duration of action and a low risk of hypoglycaemia.
- Given orally, rapidly metabolized by liver enzymes

TABLE 41–7 Other insulin secretagogues.

Drug	Chemical Structure	Oral Dose	t1/2	Duration of Action (hours)
Repaglinide (Prandin)		0.25–4 mg before meals	1 hour	4–7
Nateglinide (Starlix)		60–120 mg before meals	1 hour	4

2. DRUGS THAT PRIMARILY LOWER GLUCOSE LEVELS BY THEIR ACTIONS ON THE LIVER, MUSCLE, & ADIPOSE TISSUE

BIGUANIDES

Phenformin: Its use has been discontinued because of lacticacidosis

Metformin : is the only drug of this class presently available in market

- It does not cause hypoglycaemia
- **MOA :** It increases glucose uptake and utilisation in skeletal muscle (thereby reducing insulin resistance) and reduces hepatic glucose production (gluconeogenesis).
- Pharmacokinetic aspects : Metformin has a half-life of about 3 hours and is excreted unchanged in the urine.
- Causes anorexia, no weight gain
- The primary drug of choice for diabetes by ADA guidelines.
- Dose: 500mg twice a day after meals

Biguanides Contd

Advantages

- Perpetuates weight loss
- Can be combined with insulin to reduce insülin requirements
- Decreases risk of macro & microvascular disease

Disadvantages

- Nausea, Vomiting and diarhorrea (5%),
- Vitamin B12 Deficiency (0.5%)

Adverse effect

- Nausea, metallic taste, anorexia, flatulence & diarrhoea

Thiazolidinediones (Glitazones)

- **Rosiglitazone (**withdrawn from the market in Oct. 2010 risk of Heart failure and MI) and **Pioglitazone**

- **MOA :** Stimulates (nuclear receptor) i.e. **P**eroxisome **P**roliferator **A**ctivated **R**eceptor-gamma (PPAR-Ɣ) → promotes transcription of insulin responsive genes which control glucose & lipid metabolism → **↑ insulin sensitivity** & ↓ insulin resistance
- Promotes uptake and utilization of glucose by increasing the GLUT-4 transporters
- Decrease glucose output by inhibiting gluconeogenesis

Thiazolidinediones (Glitazones)

- P'kinetics : Absorbtion→Orally, highly plasma protein bound, peak plasma concentration-within 2 hrs

  Metabolism→ liver enzymes.

  Elimination→ Rosiglitazone metabolites in urine, Pioglitazone metabolites in bile

- Adverse effets : Weight gain, fluid retention, headache, fatigue and gastrointestinal disturbances.

- Contraindicated in Hepatic failure, pregnancy, lactating mother, children and heart failure

3. DRUGS THAT AFFECT ABSORPTION OF GLUCOSE

α-Glucosidase inhibitors

- Acarbose, Miglitol, Voglibose
- MOA : It delays carbohydrate absorption, reducing the postprandial digestion and absorption of carbohydrates by inhibiting α – glucosidase enzyme

Advantages:

- Selective for postprandial hyperglycaemia
- No hypoglycaemic symptoms

Disadvantages:

- Abdominal distension and flatus
- Only effective in mild hyperglycaemia

4.DRUGS THAT MIMIC INCRETIN EFFECT OR PROLONG INCRETIN ACTION

- **Glucagon Like Peptide-1 (GLP-1) Receptor Agonists**

- **Dipeptidyl peptidase-4 (DPP-4) Enzyme Inhibitors**

What are Incretins?

➢ a group of hormones (GLP & GIP) – released after meals and augment glucose-dependent insulin secretion

GLP-1 (glucagon-like peptide 1) **(*More Imp)**

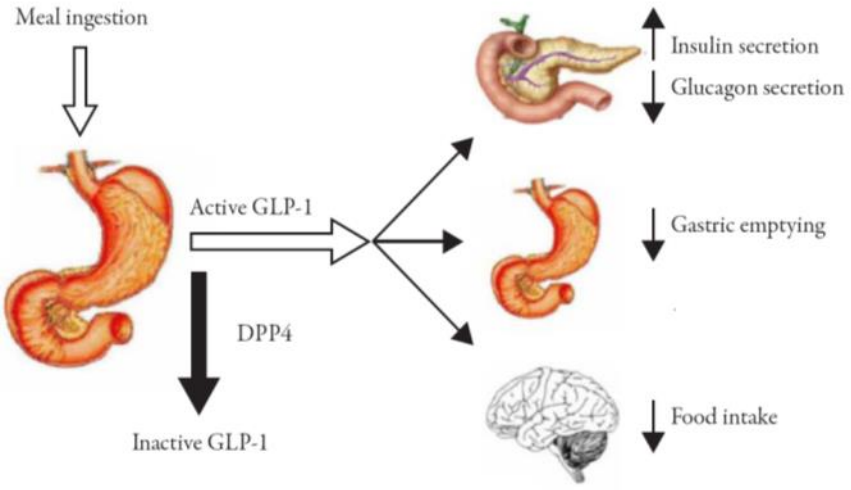
- is a prominent insulinotrophic incretin.
- half life- 1-2 min.
- metabolized quickly by dipeptidyl peptidase-4 (DPP-4).

GIP: Glucose-dependent insulinotrophic polypeptide

Small effect in Type 2 diabetes.

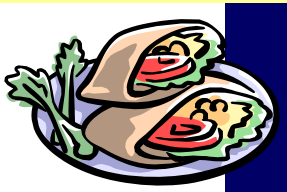
Glucagon Like Peptide-1 (GLP-1) Receptor Agonists

- **G**lucagon **L**ike **P**eptide – 1 (**GLP-1**) → released after meals from the upper & lower bowel → augment glucose dependent insulin secretion, during the phase of nutrition absorption from GIT
- t ½ GLP-1 – 1 to 2 min
- Metabolized quickly by **DPP-IV enzyme**



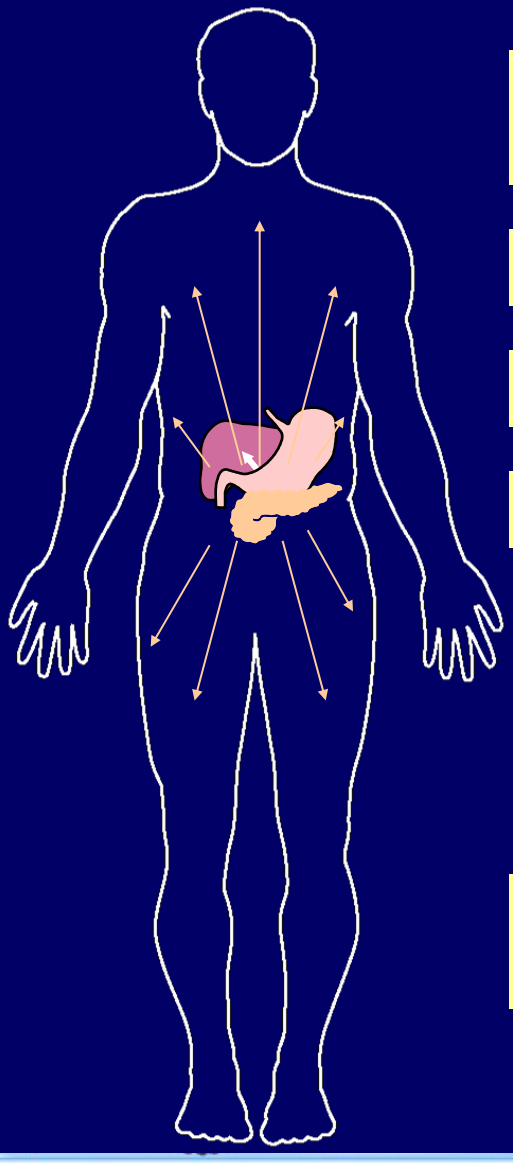
GLP-1 Modes of Action in Humans

Upon ingestion of food…



GLP-1 is secreted from the L-cells in the intestine

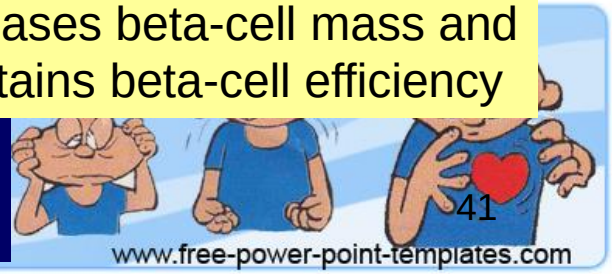
This in turn…



- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Reduces food intake

Long term effects demonstrated in animals…

- Increases beta-cell mass and maintains beta-cell efficiency



Exenatide [first GLP-1 agonist]

- Obtained from salivary gland venom of Gila monster
- Resistant to DPP-IV degradation
- Potent agonist of GLP-1 receptor, Orally inactive
- **Given SC** (5-10µg) twice daily, 30-60 min before meals
- It reduces only post meal glucose rise
- Exenatide is approved as an injectable, adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control

MOA

- Stimulates insulin secretion from β- cells
- Decreases glucagon release

Advers Effects

- Diarrhea, nausea, anorexia

Other GLP-1 Agonists

- **Liraglutide** → i a soluble fatty acid-acylated GLP-1 analog.
- **Albiglutide** →a human GLP-1 dimer fused to human albumin
- **Dulaglutide** →consists of two GLP-1 analog molecules covalently linked to an Fc fragment of human IgG4

Advers-effects:

-decreased gastric motility

-nausea, vomiting, diarrhea, weight loss

-All of the GLP-1 receptor agonists may increase the risk of pancreatitis

DPP-IV Inhibitors

Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin

- Orally active
- Selective inhibitors of DPP-IV enzyme that deactivates GLP-1

MOA

- Increase insulin secretion
- Decrease glucagon release
- Delay gastric emptying
- Suppress appetite

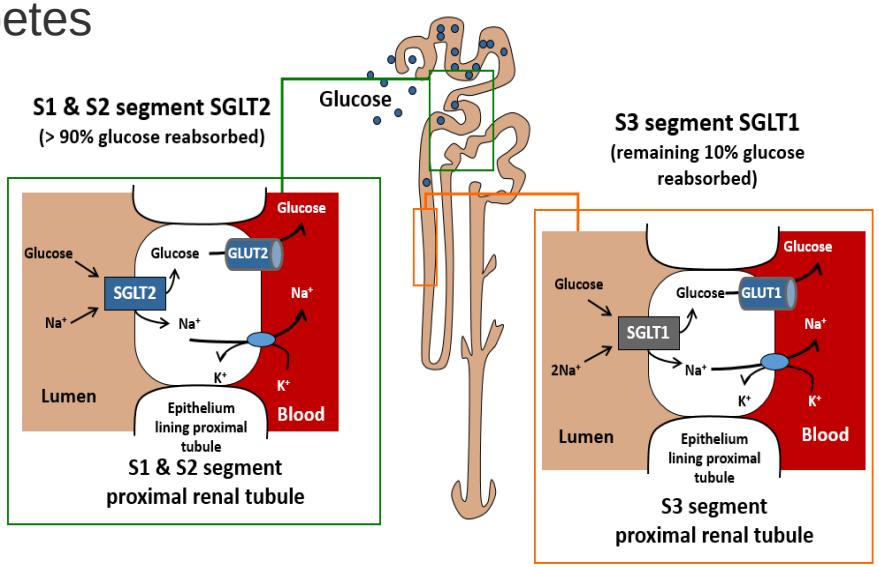
Advers Effects

- Nasopharyngitis because substance P is also a substrate for DPP-IV, whose levels get elevated, GIT distress and diarrhea

5. Agents that inhibit the reabsorption of glucose in the kidney (sodium-glucose co-transporter inhibitors [SGLTs])

SGLT-2 INHIBITORS

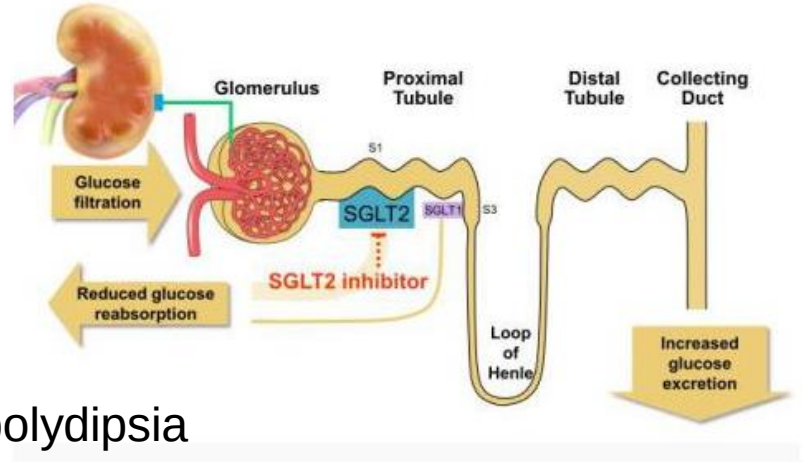
- Newer antidiabetic drugs
- Glucose is freely filtered by the renal glomeruli and is reabsorbed in the proximal tubules by the action of sodiumglucose transporters (SGLTs).
- Sodium-glucose transporter 2 (SGLT2) accounts for 90% of glucose reabsorption
- Inhibition of SGLT – 2 decreases glucose re-absorption, lowers glucose levels in patients with type 2 diabetes



Adapted from Bailey CJ, Day C. *Br J Diabetes Vasc Dis.* 2010;10:193-199.

SGLT-2 Inhibitors

Canagliflozin, Dapaglifozin, Empagliflozin



Advantages

- Weight loss
- No hypoglycemia

Disadvantages

- Because of polyuria there will be more polydipsia
- Increased risk of urinary infection in presence of glycosuria
- Risk of Na^{2+}loss

6. OTHER HYPOGLYCEMIC DRUGS

Amylin →A hormone co-secreted with insulin from β- cells

- Inhibit glucagon secretion
- Delay gastric emptying
- Suppress appetite

Pramlintide → an islet amyloid polypeptide (IAPP, amylin) analog

- SC before meals
- No hypoglycemia

Advers Effects

- Nausea, diarrhea, headache

Colesevelam hydrochloride →the bile acid sequestrant and cholesterol-lowering drug

→is approved as an antihyperglycemic therapy for persons with type 2 diabetes who are taking other medications or have not achieved adequate control with diet and exercise

→the exact mechanism of action is unknown

Adverse Effects

- Gastrointestinal complaints (constipation, indigestion, flatulence).

Bromocriptine →the dopamine agonist

→The mechanism by which it lowers glucose levels is not known.

Adverse Effects:

- nausea, fatigue, dizziness, vomiting, and headache.

**Colesevelam and bromocriptine have very modest efficacy in lowering glucose levels and their use for this purpose is questionable.

Sites of action of Antidiabetics