INSULIN, ORAL HYPOGLYCAEMIC AGNETS AND GLUCAGON

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INSULIN, ORAL HYPOGLYCAEMIC AGENTS AND GLUCAGON

- Insulin is an endocrine hormone produced by the beta cells of islets of Langerhans in the pancreas.
- Regulates blood glucose levels, glycogenesis and lipid synthesis.
- Discovered by Frederick banting and Charles best.
- MW → 6000 Daltons
- Consists of two amino acid chain A and B connected by two disulphide bridges.
- Chain A – 21 AA Chain B – 30 AA
- Disulphide bridges are responsible for its biological activity.

BIOSYNTHESIS

Pre- proinsulin.
↓1
Proinsulin
↓2
Insulin

The three portions of proinsulin are

1. Chain A – Carboxy terminal (21 AA)
2. Chain B – Amino terminal (30 AA)
3. Connecting peptide -- (35 AA)

1. The signal peptides of pre-proinsulin is cleaved, forming proinsulin.
2. Proinsulin is folded in the ER, then transported to the Golgi apparatus where the c-peptide is cleaved using type I and type II endoproteases to form free C peptide and mature insulin.

FACTORS STIMULATING INSULIN RELEASE

-- Hyperglycemia
-- Glucocorticoids
-- Thyroxine
-- Gastrointestinal hormones
-- Estrogens
-- Ach

FACTORS INHIBITING INSULIN RELEASE

-- Catecholamine's
-- Hypoxia
-- Serotonin
-- Sympathetic stimulation
-- Starvation

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

PHARMACOKINETICS

- Administered Subcutaneously.
- Oral – Instant degradation.
- IM -- Rapid absorption.
- IV -- Only in emergencies.
- T ½ life –> 5-10 min.
- Metabolism by kidneys and liver.
- Insulin tightly bound to tissue receptors. So even through rapid clearance.
- Daily secretion of insulin is 40 units.
- Insulin response to glucose is greater for oral ingestion than for IV infusion.
- Most of the endogenous insulin i.e. about 60 % is degraded by the enzyme insulinase is the liver.

PHARMACOLOGICAL EFFECTS

1. **ON CARBOHYDRATE METABOLISM**
   a. Liver -- Facilitates glucose uptake and increases glycogenesis.
      -- Inhibits glycogenolysis and gluconeogenesis.
   b. Muscles -- Facilitates glucose uptake through GLUT-4.
      -- Increases glycolysis and glycogenesis
   c. Adipose tissue -- Facilitates glucose uptake by adipocytes
      -- Increases triglyceride synthesis .
2. **ON PROTEIN METABOLISM**
   a. Liver – Inhibits proteolysis and oxidation of AA
   b. Muscles -- Enhance protein synthesis and uptake of AA.
3. **ON FAT METABOLISM**
   a. Liver – Enhance lipogenesis
   b. Adipose tissue – Inhibit lipolysis, increase fatty acid and triglyceride formation

4. **OTHER ACTIONS**

- Enhance clearance of VLDL and chylomicrons by activating vascular endothelial lipoprotein.
- Facilitates the transport of Ca 2+, K+ into the cell.
- Decreases fibrinolysis.
- Exerts vasodilatory effect.

INSULIN PREPARATION

1. **CONVENTIONAL PREPARATION OF INSULIN**

A. Soluble/Neutral insulin

-- Fast acting -- Peak plasma level – 2 hrs

-- Reduce within 4-8 hrs. -- Stabilized by zinc in buffered soln

B. Isophane insulin

-- Equimolar complex of protamine and insulin

-- Each ml provide 40, 80 or 100 units of insulin activity.

c. Lente insulin

-- 7:3 mixture of crystalline long acting and amorphous short acting zinc preparation of insulin.

2. **HIGHLY PURIFIED INSULIN PREPARATION**

-- Advance purification is done.

-- pork insulin is used for purification

-- Carried out by ion-exchange chromatography.

a. Highly purified [MC] pork regular insulin

-- e.g.. Actrapid (40 U/ml inj) [MC= Monocomponent]

b. Highly purified [MC] lente insulin

-- e.g.. Lantard, monotard (40 U/ml inj)

c. Highly purified [MC] pork isophane insulin

-- e.g.. Insulatard (40 U/ml inj).

3. **HUMAN INSULIN**

-- Produced by employing recombinant DNA technology in E.choli.

a. HUMAN REGULAR INSULIN

-- Quick onset of action. E.g. Actrapid

-- 100 U/ml

b. HUMAN LENTE INSULIN

-- E.g. Human monotard inj.

-- 40 U/ml, 100 U/ml.

c. HUMAN ISOPHANE INSULIN

-- Human insulated inj.

-- 40 U/ml

4.**INSULIN ANALOGUES**

-- Prepared by using recombinant DNA technology.

-- Greater stability and consistency

-- Superior pharmacokinetic profile upon SC inj.

a. INSULIN LISPRO

-- Produced by the exchange of proline and lysine at B28 and B29 on carboxy terminus of human insulin .

--e.g. Humalog 100 U/ml

b. INSULIN ASPART

-- Produced by replacing the B28 proline of human insulin with aspartic acid

-- E.g. Novolog 100 U/ml.

ORAL HYPOGLYCAEMIC AGENTS

- These are agents that are given orally to reduce the blood glucose levels in diabetic patients.
- They are effective orally and have longer duration of action than insulin and its preparation.

Effective in following patients–

- Age > 40 years at onset of disease
- Fasting blood sugar < 200 mg/dl
- Obesity
- Disease duration < 5 yrs when initiating therapy
- Insulin requirement < 40 U/day
- No ketoacidosis or any other complication

CLASSIFICATION

1. **SULFONYL UREAS**
   - A. 1ST generation - Tolbutamide, chlorpropamide
   - B. 2nd generation – Glipizide, Glimepride, Glicazide, Glibenclamide

2. **BIGUANIDES** – Metformin, phenformin

3. **MEGLITINIDES/ PHENYLALANINE ANALOGUES**
   - Repaglinide, Nateglinide

4. **THIAZOLIDINEDIONES** -- Rosiglitazone,, Pioglitazone

4. **α- GLUCOSIDASE INHIBITORS** -- Acarbose, Migitol

1. SULFONYL UREAS

--Promote the release of insulin from ß- cells.

-- Also called insulin secretogogues, chemically related to sulfonamides.

MOA – Binds to SUR-1 receptors present on the ATP- sensitive K+ channels and block k+ efflux, causing membrane depolarization and increased Ca2+ efflux. This activates sensitive proteins resulting in release of stored insulin.

PHARMACOKINETICS

-- Well absorbed orally.

-- Highly protein bound.[1st generation are less protein bound]

-- Metabolized in liver

-- Excreted in urine.

PHARMACOLOGICAL EFFECTS

- Decrease blood sugar levels.
- Restore normal metabolic status
- Decrease elevated plasma FFA levels
- Correct the abnormalities of platelets and coagulation.

ADVERSE EFFECT

- Hypoglycemia, Weight gain, Hypersensitivity, Nausea and vomiting, Headache and Hypoglycemia.

DRUG INTERACTIONS

- Phenylbutazone, salicylates, sulfinpyrazone and sulfonamides displace sulfonylurea from protein binding sites and enhance their action.
- Cimetidine, acute alcoholism, sulfonamides, warfarin and chloramphenicol inhibit metabolism of sulfonylureas and enhance their action.
- Phenytoin, phenobarbitone, chronic alcoholism and rifampicin induce the metabolism of sulfonyureas and decrease their action.

- Thiazides , corticosteroids, oral contraceptives and diazoxide suppress insulin release.

THERAPEUTIC USES

- Useful in type-2 diabetes mellitus
- Used in diabetes insipidus.

DOSAGE

TOLBUTAMIDE – 0.5-2 g

CHLORPROPAMIDE – 100-500 mg

GLIBENCLAMIDE – 2.5 – 15 mg

GLIPIZIDE – 2.5 – 40 mg

GLIMEPIRIDE – 1 – 6 mg

GLICAZIDE - 40 – 320 mg

2. BIGUANIDES [Metformin]

- CALLED AS INSULIN SENSITIZERS

MOA – The exact mechanism by which biguanides act is unclear. They decrease hepatic and renal glucose output and increase peripheral glucose uptake .

PHARMACOLOGICAL EFFECTS

- Reduce elevated blood sugar levels in diabetes.
- Reduce glycogen content in hepatocytes.
- Reduce VLDL and LDL levels and increase HDL levels.
- Suppress appetite and hence unlike sulfonylureas do not cause weight gain.

PHARMACOKINETICS

- Well absorbed orally.
- Plasma t 1/2 life – 1.5-4 hrs.

- Action persists for 6-10 hrs.
- Excreted unchanged in urine.

ADVERSE REACTION

- Anorexia, Nausea, Metallic taste, Mild diarrhea, abdominal pain and tiredness

THERAPEUTIC USES

- Drug of choice in obese type-2 diabetes.
- Can be given along with sulfonylureas in secondary sulfonylureas failure.

CONTRAINDICATIONS

- Metformin should not be given to patients with-

  Renal failure,

  Hepatic disease,

  Hypoxic pulmonary disease and Heart failure or shock.

3. MEGLITINIDES

- Also called Phenylalanine Analogues.
- Quick and short acting hypoglycemic activity.
- Drugs include Repaglinide and nateglinide.

MOA – Same as of sulfonylureas. They enhance insulin secretion by binding to same ATP-sensitive K+ -channels in beta-cells.

- Onset of action of 1 hr and duration of about is 4-5 hrs.
- Given before a meal to control postprandial hyperglycemia and do not cause serious hypoglycaemia.
- Given orally, rapidly metabolized by liver enzymes.
- **A/E** – Headache, weight gain, dyspepsia and arthralgia.
- **USES** - Used to control postprandial glucose rise in type-2 diabetic patients either alone or along with metformin or long acting insulin.
- **DOSE** – Nateglinide – 180-540 mg and Repaglinide – 1-16 mg.

4. THIAZOLIDINEDIONES / GLITAZONES

- Currently marketed Thiazolidinediones are Rosiglitazone and Pioglitazone.

MOA – They bind to PPAR-$^{\gamma}$ (Peroxisome proliferator activator receptor -$^{\gamma}$) and increase the transcriptions of genes essential for insulin sensitivity and carbohydrates and lipid metabolism. These genes cause an increase in the uptake of glucose and fatty acids, differentiation and proliferation of adipocytes and enhance lipogenesis.

PHARMACOLOGICAL EFFECTS

- They increase insulin sensitivity of adipose tissue, liver and muscle and reduce hyperinsulinaemia.
- Inhibit hepatic gluconeogenesis and promote glucose uptake in muscles via GLUT-4 and thus reduce hyperglycaemia.
- Improve Beta cells and vascular function by reducing inflammation

- Reduce fat content in the liver and decrease dyslipidemia.

PHARMACOKINETICS

- They are completely absorbed.
- Their action persists for more than 24 hrs
- They are metabolized in the liver and excreted in urine.

ADVERSE EFFECTS

-- Weight gain, Fluid retention and plasma volume expansion, headache, myalgia and mild anaemia.

DRUG INTERACTION

- Ketaconazole inhibits the metabolism of pioglitazone.
- Pioglitazone increases the metabolism of oral contraceptives and decrease their action.

THERAPEUTIC USES

- First line drugs in type-2 DM and also used in non-alcoholic steatohepatitis.

- Used in insulin resistant conditions such as polycystic ovary syndrome.

DOSE – Pioglitazone – 15-30 mg
Rosiglitazone – 4-8 mg

5. α-GLUCOSIDASE INHIBITORS

-- Acarbose and Miglitol belong to the class of these types.

ACARBOSE – An inhibitor of intestinal α- glucosidase is used in type – diabetes

MOA – It delays carbohydrates absorption, reducing the postprandial increase in blood glucose.

A/E – Flatulence, Abdominal discomfort and diarrhea, bloating.

USE – Helpful in type 2 patients and it can be co administered with metformin. [1-3 gm]

MIGLITOL

--Synthetic agent.

-- Natural oligosaccharides obtained from the microorganism Actinoplanis utahensis.

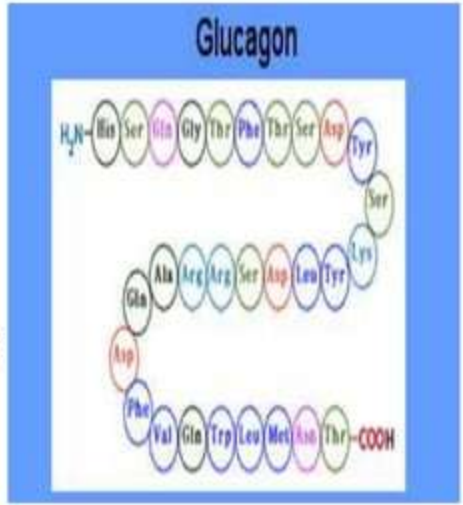
MOA – It binds to α – glucosidase enzyme in the brush borders of jejunum and prevents the breakdown and absorption of carbohydrates in blood.

- Elimination half life – 2 hrs.
- Renal excretion

GLUCAGON

Glucagon is an animal hormone which is synthesized, stored and secreted by the alpha (α) cells of islets of Langerhans of pancreas in the body.

Glucagon possess hyperglycemic properties and plays an important role in the carbohydrate metabolism.



. **STRUCTURE**

- Described by Kimball and Murlin in 1923 and its amino acid sequence was described in the 1950s.
- Glucagon is a 29-amino acid containing single chain polypeptide with a molecular weight of 3485 Daltons

MOA

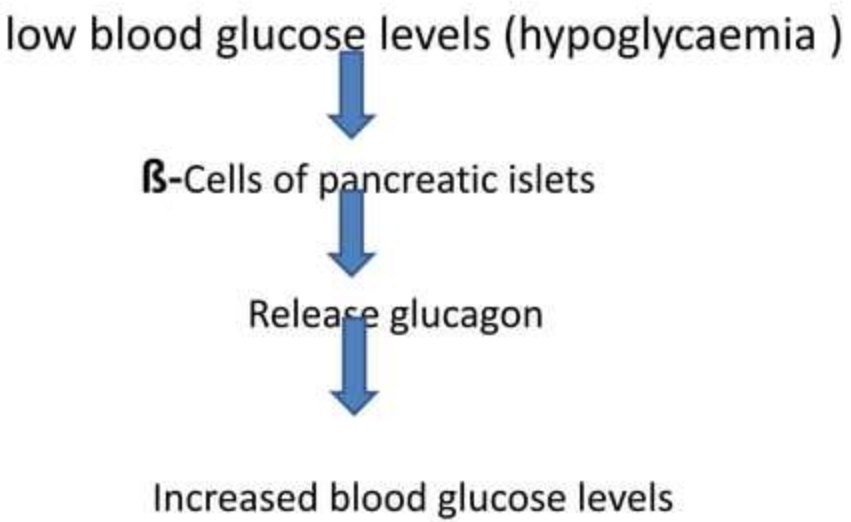
- It increases blood glucose levels which is achieved by –
- Increasing the rate of glycogenolysis i.e., conversion of glycogen to glucose especially in the liver and skeletal muscles.
- Increasing the rate of gluconeogenesis i.e., synthesis of glucose from lactic acid, amino acid etc., in blood.

PHARMACOLOGICAL ACTIONS

- Glucagon reduces the uptake of glucose by the muscle and adipose tissue.
- Glucagon inhibits gastric acid production and simultaneously causes relaxation of gastric smooth muscles.
- Glucagon raises the concentration of free fatty acids and ketoacids in the blood.
- On heart, glucagon exerts positive inotropic and chronotropic effects.

- Glucagon increases the production of urea in the body.
- It acts as a stimulant for the secretion of insulin.
- Both the mechanisms (glycogenolysis and gluconeogenesis) causes increases in the blood sugar level during hypoglycemic conditions.

REGULATION



PHARMACOKINETICS

- It is rapidly absorbed following parenteral injections.
- Plasma half-life of 3-6 hrs.
- Gets destroyed by proteolytic enzymes when taken orally.
- Metabolized in kidney, liver and plasma.

THERAPEUTIC USES

- Administered in a dose of 1 mg by i.m. route to treat severe hypoglycaemia.
- It is given by i.v. route to treat hypoglycaemia coma caused by insulin in type 1 diabetes.