BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
Course Code : BM35C7

Unit-IV

Pharmacology of Endocrine System - Part 3

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PANCREATIC HORMONES
ANTIDIABETIC DRUGS

Diabetes mellitus

Madhumeha as a disease is known for ages

Pharmacotherapy is just over 90 years old.

Presence of sugar in the urine diabetics - by Dobson in 1755.

In 1889, von Mering and Minkowski discovered that pancreatectomised dogs become diabetic in addition to developing digestive disturbances.

The non-digestive part of the pancreas, islet cells, was thought to be responsible for the substance which prevented diabetes

It was christened 'insulin' by de Mayer (1909), long before its extraction by Banting and Best in 1921.

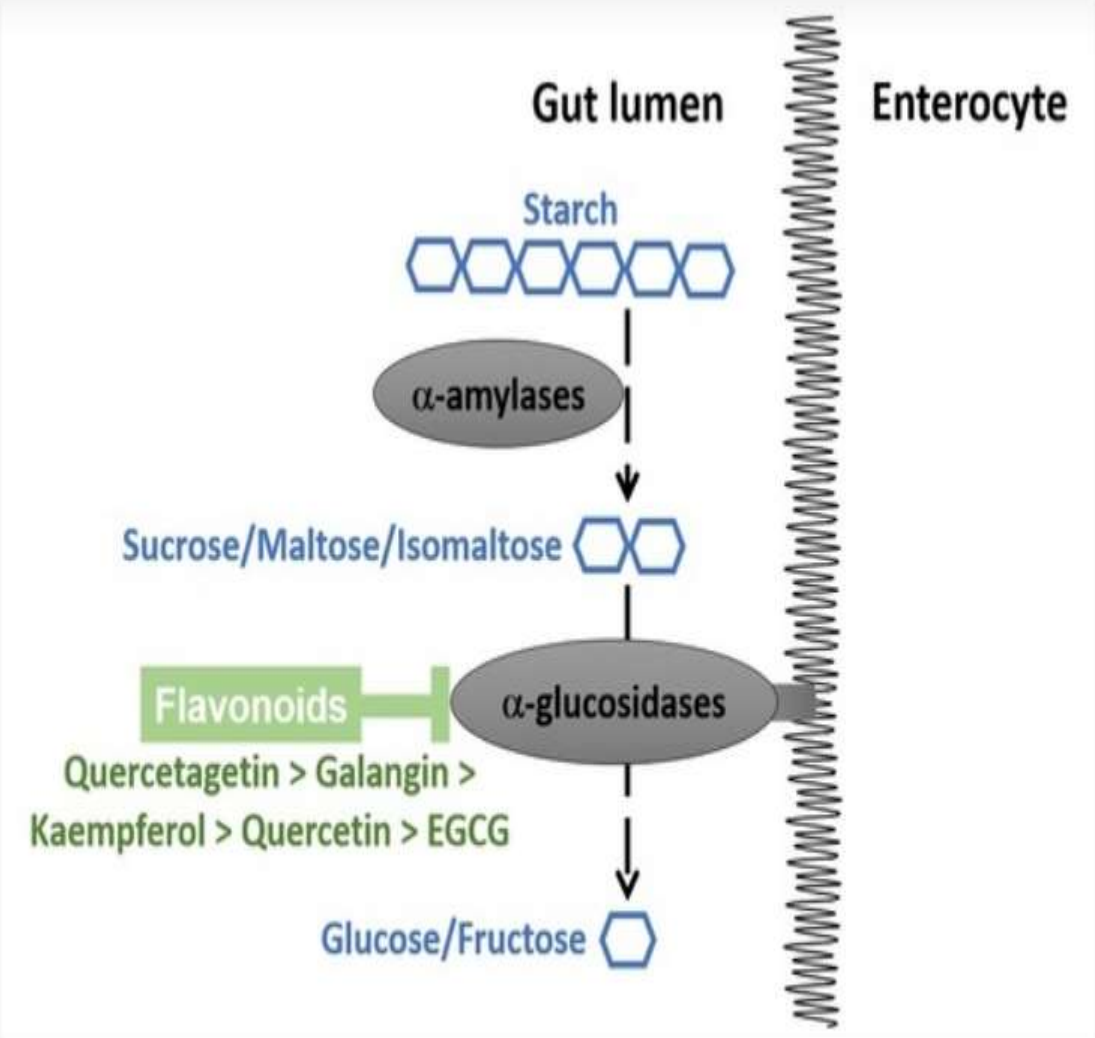
Discovery of insulin, a life saving agent.

Carbohydrates consumed by humans are starch, a polysaccharide, and sugar, a disaccharide.

Split to a small extent by the salivary amylase, but largely by the pancreatic amylase, into oligosaccharides in the duodenum and upper jejunum.

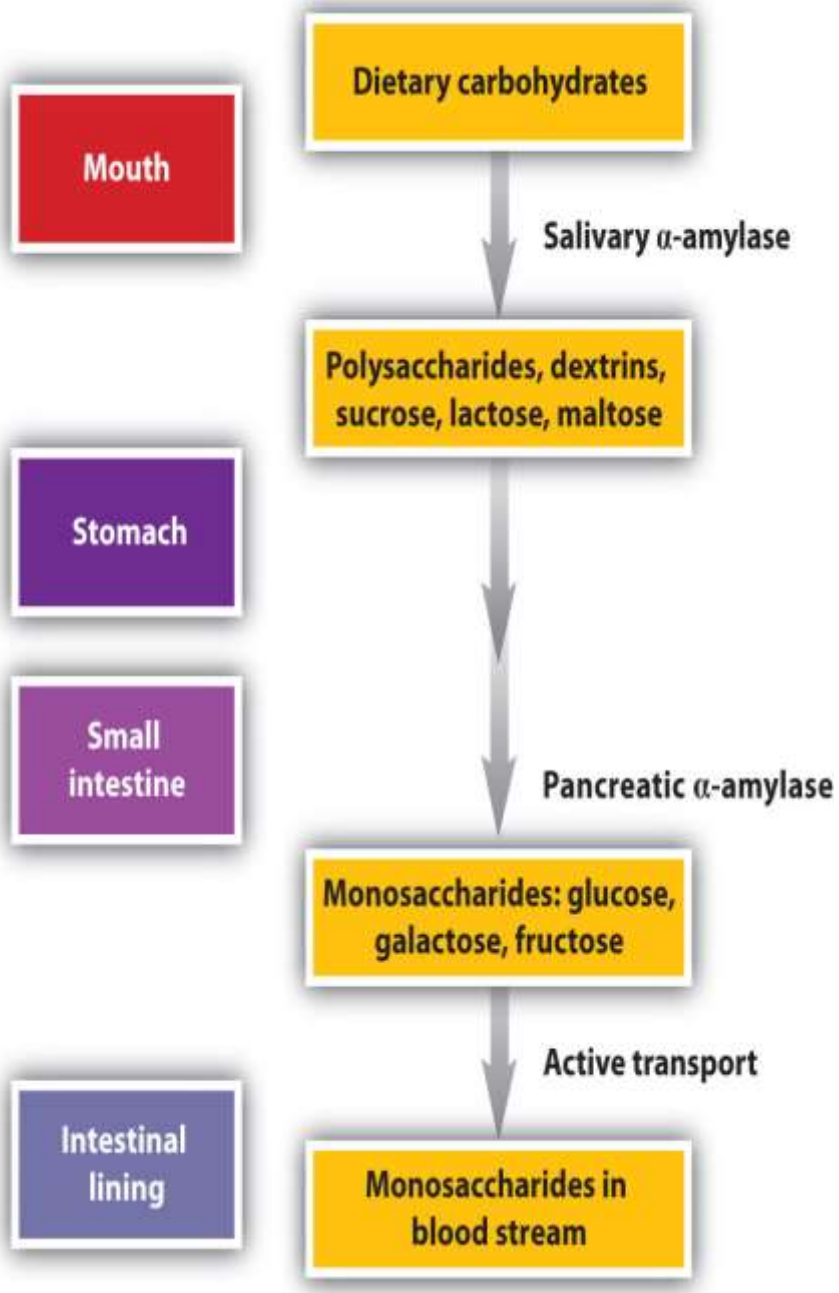
The oligosaccharides and disaccharides are cleaved by alpha-glucosidases in the brush border of the jejunal enterocytes into monosaccharides (glucose, fructose and galactose) which are promptly absorbed in the upper jejunum.

Glucose absorbed after a meal, is utilised preferentially by all tissues for energy production and/or storage.



Graphical Abstract

- Tissues differ in their dependence on glucose and free fatty acids (FFA) for energy.
- The brain utilises only glucose while most other tissues can utilise glucose as well as FFAs.
- In fact, in the fasting state, the skeletal and cardiac muscle can derive 90% of their energy from FFA.
- By facilitating the entry of glucose into the cells, insulin makes possible its utilisation by tissues at lower blood glucose levels than would be possible without insulin.
- Deficiency of insulin causes DM.


Mouth
Dietary carbohydrates
Salivary α-amylase
Polysaccharides, dextrins, sucrose, lactose, maltose
Stomach
Small intestine
Pancreatic α-amylase
Monosaccharides: glucose, galactose, fructose
Active transport
Intestinal lining
Monosaccharides in blood stream

Immediately on entry into the cell, glucose is phosphorylated by hexokinase to glucose-6-phosphate (G-6-PO4) which is further metabolised

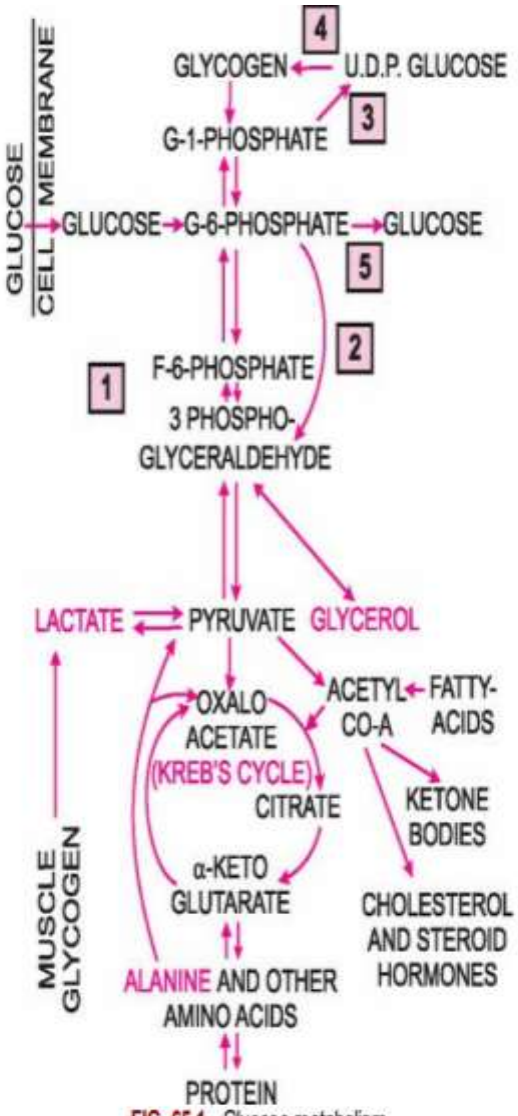


FIG. 65.1 Glucose metabolism

G = Glucose; F = Fructose

1. Glycolysis; 2. Pentose-phosphate shunt; 3. Glucu-runoic acid pathway; 4. Glycogenesis; 5. Conversion to glucose

Glycolysis-Triose phosphate pathway

- Intracytoplasmic anerobic process by which G-6-PO4 is converted to pyruvate.
- When pyruvate production exceeds the cell's oxidative capacity, it is reduced to lactate.
- When oxygen is available, lactate is converted back to pyruvate.
- It is quantitatively a major mechanism in (a) the brain, (b) the red blood cells, (c) the exercising skeletal muscle and (d) the ischemic cardiac muscle.

Pentose-phosphate shunt

- Is an aerobic multicyclic process that converts a part of G-6-PO4 to 3-phospho-glyceraldehyde by a different pathway.
- This pathway is an important source of NADPH (reduced Nicotinamide Adenine Dinucleotide Phosphate).
- NADPH is important for lipogenesis; its deficiency causes impaired lipogenesis; and consequently contributes to ketoacidosis in DM.

Glucuronic acid pathway

- Converts G-6-PO4 to uridine diphospho-glucose (UDPG) via G-1-phosphate.
- UDPG is utilised for synthesis of glycogen and muco-polysaccharides and contributes glucuronic acid required for hepatic conjugation of many substances such as bile pigments and steroids.

Glycogenesis

- Glycogen is derived from UDPG by the action of glycogen synthetase

Conversion to glucose:

- Liver and kidney are the only two organs which contain the enzyme glucose-6-phosphatase which converts G-6-phosphate to glucose.
- The reaction is irreversible.
- Muscle cannot convert glycogen to glucose but converts it by glycolysis to lactate which is either utilised locally for energy or is transported to the liver where, it is utilised for neoglucogenesis.

Glucose - daily ingested foodstuffs,

3% is stored in the liver and muscle as glycogen;

30% is converted to fatty acids;

Rest enters Kreb's cycle and is utilised partly for energy production and partly for synthesis of amino acids.

Pyruvate metabolism (Kreb's cycle) is the meeting ground for the metabolism of carbohydrates, fats and proteins.

Between meals, the liver converts the stored glycogen to glucose (Glycogenolysis) for release into circulation;

It also converts non-carbohydrate sources (lactate; glucogenic amino acids-alanine and glutamine; and glycerol) to glucose (Neoglucogenesis or Gluconeogenesis).

Insulin inhibits both, hepatic glycogenolysis and neoglucogenesis; its deficiency in DM leads to exaggerated neoglucogenesis.

- Glucose and other nutrients are more effective in invoking insulin release when given orally than i.v.
- They generate chemical signals 'incretins' from the gut which act on ß cells in the pancreas to cause anticipatory release of insulin.
- The incretins involved are glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pancreozymincholecystokinin, etc..

Insulin

- Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct.
- It was first obtained in pure crystalline form in 1926 by Sanger.
- Insulin is a two chain polypeptide having 51 amino acids and MW about 6000.
- The A-chain has 21 while B-chain has 30 amino acids.

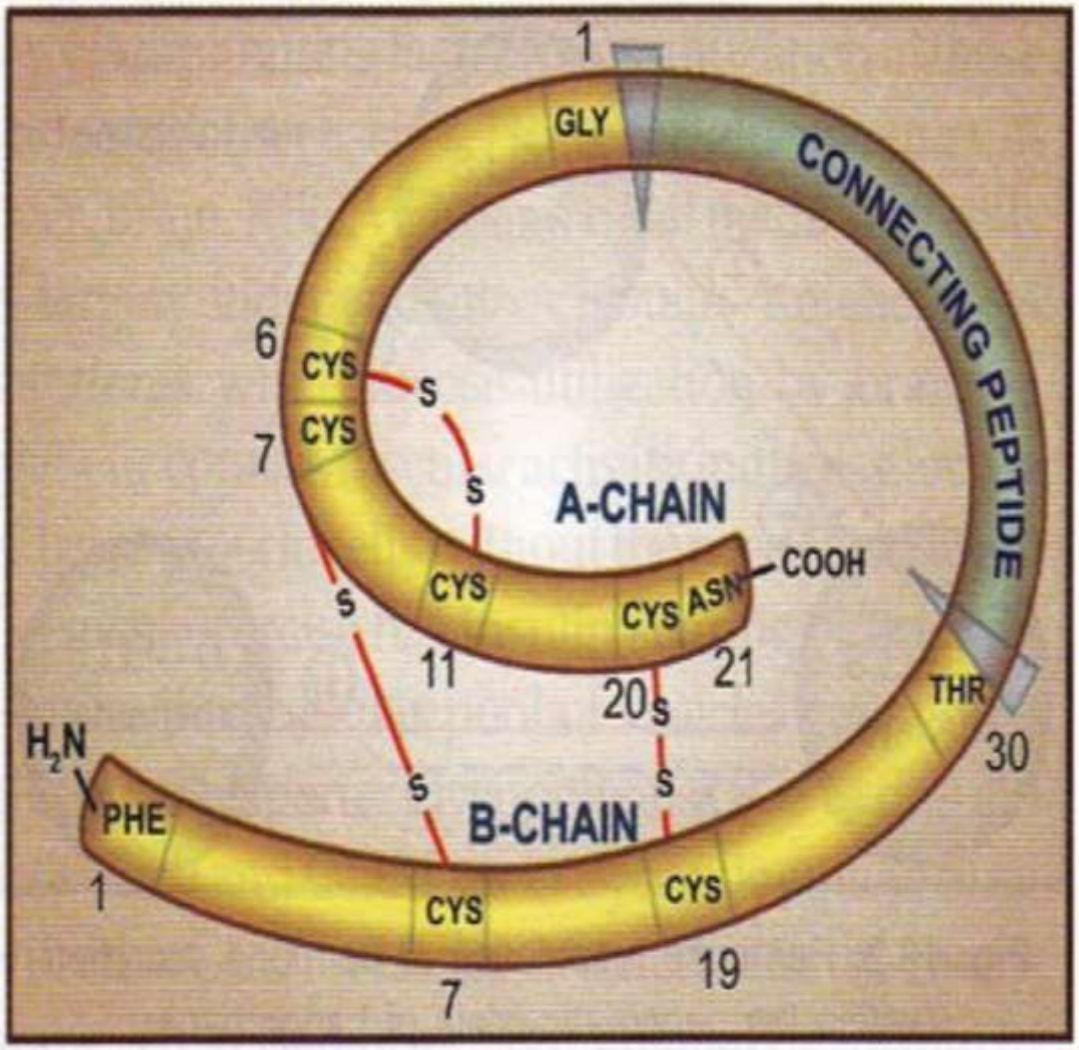


Fig. 19.1: Human proinsulin; simplified structure depicting

Insulin is synthesized in the ß cells of pancreatic islets as a single chain peptide Preproinsulin (110 AA) from which 24 AAs are first removed to produce Proinsulin (Fig.19.1). The connecting or 'C' peptide (35 AA) is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell. The C peptide is secreted in the blood along with insulin

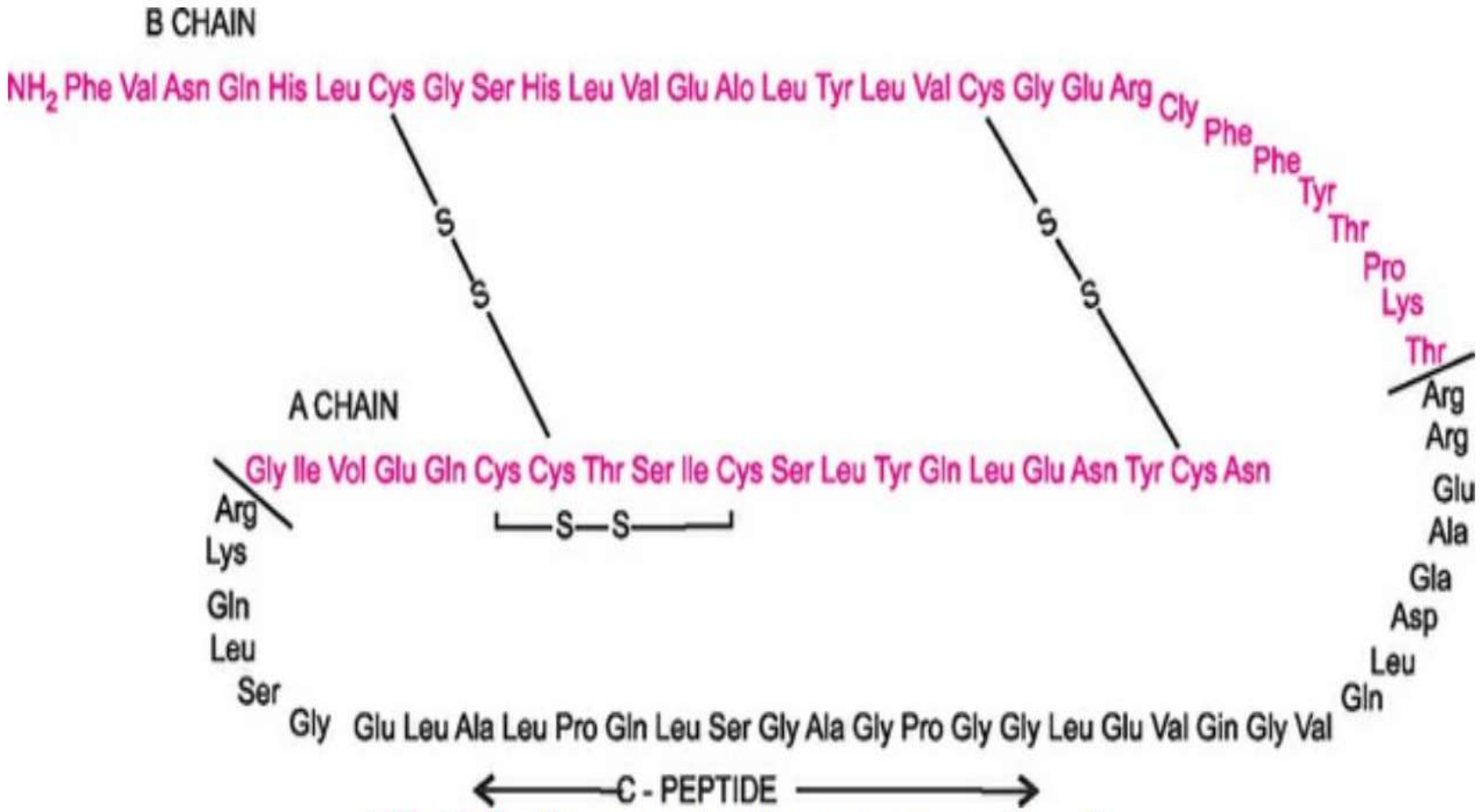


FIG. 65.2 Human proinsulin, a precursor of insulin

- Insulin is soluble in water but undergoes molecular aggregation to hexameric form at extremes of pH (3.2 and 10).
- Such aggregation is enhanced by zinc which brings about its crystallisation.
- Insulin is relatively insoluble at the pH range of 4 to 7.

SYNTHESIS AND STORAGE:

- The islets constitute 1% by weight of the pancreas.
- Alpha or A cells which secrete glucagon.
- Beta or B cells which secrete insulin.
- Delta or D cells which secrete somatostatin;
- PP or F cells which secrete pancreatic polypeptide (PP)

Regulation of insulin secretion

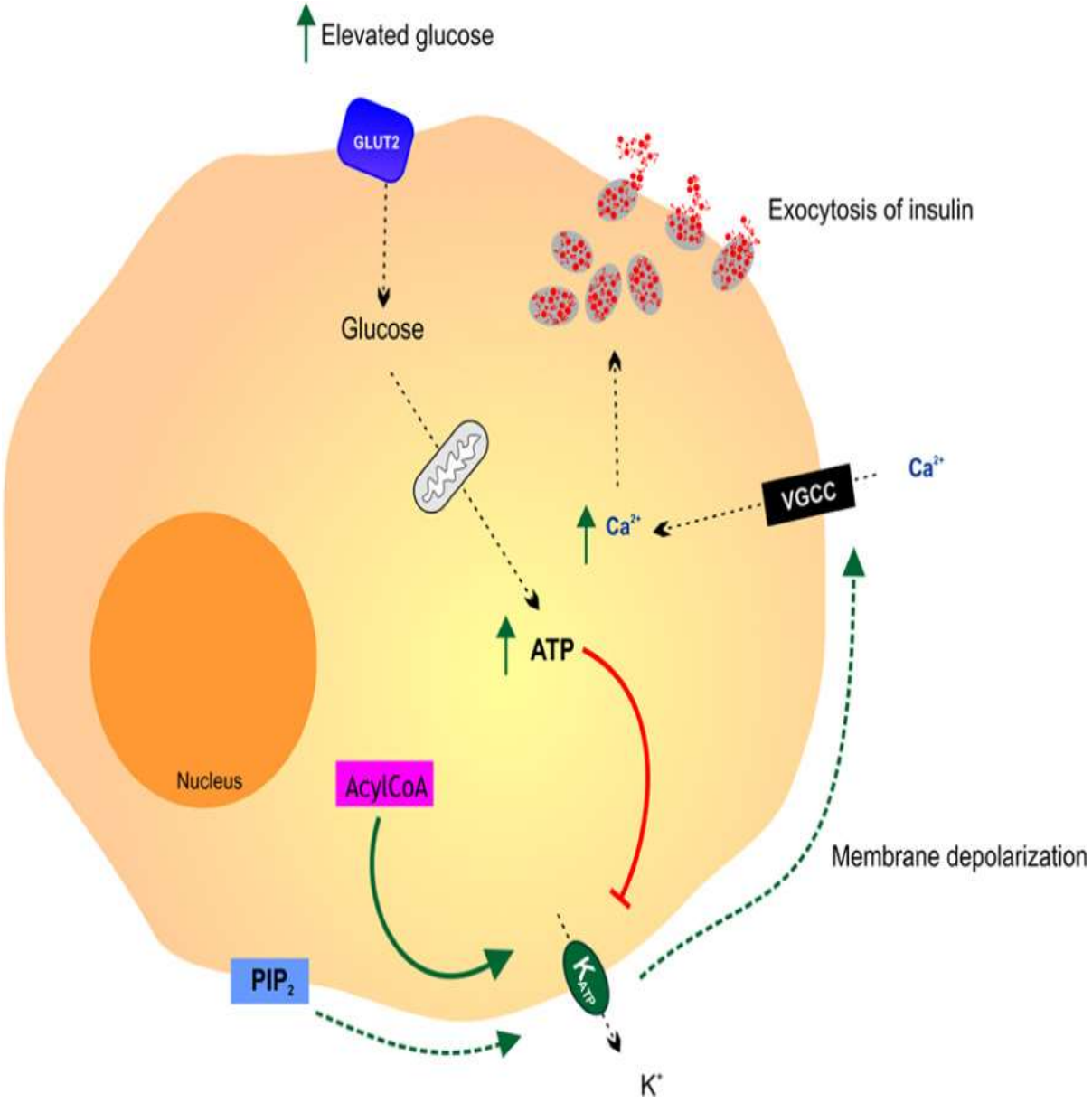
- Under basal condition – l U insulin is secreted per hour by human pancreas.
- Much larger quantity is secreted after every meal.
- Secretion of insulin from ß cells is regulated by chemical, hormonal and neural mechanisms.

Chemical

- The ß cells have a glucose sensing mechanism dependent on entry of glucose into ß cells **(Glucose transporter GLUT2**) and its **phosphorylation by glucokinase.**
- Glucose entry and activation of the glucoceptor indirectly **inhibits the ATP-sensitive K+ channel** resulting in partial **depolarization of the ß cells**.
- This increases intracellular **Ca2+** availability

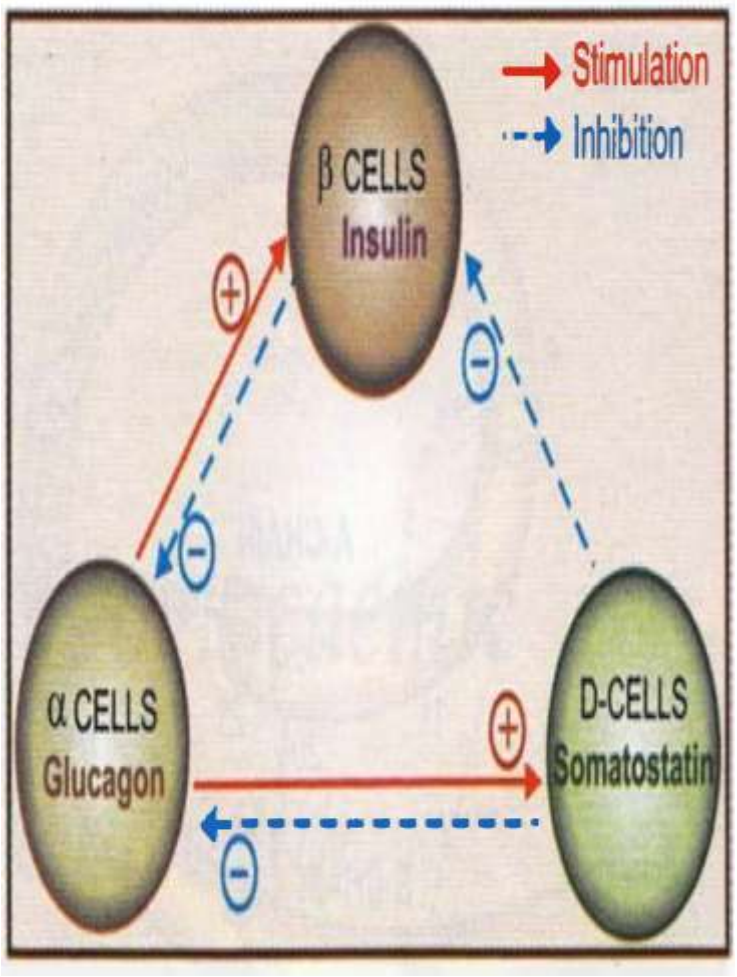
(due to increased influx, decreased efflux and release from intracellular stores)

- Exocytotic release of insulin storing granules.
- Other nutrients that can evoke insulin release are-amino acids, fatty acids and ketone bodies
- Glucose induces a brief pulse of insulin output within 2 min (first phase) followed by a delayed but more sustained second phase of insulin release


Elevated glucose
GLUT2
Exocytosis of insulin
Glucose
VGCC
Ca^{2+}
Ca^{2+}
ATP
Nucleus
AcylCoA
Membrane depolarization
PIP_2
K_{ATP}
K^+

Hormonal

- A number of hormones, e.g. growth hormone, corticosteroids, thyroxine modify insulin release in response to glucose.
- PGE has been shown to inhibit insulin release.
- More important are the **intra-islet paracrine interactions between the hormones** produced by different types of islet cells.
- Somatostatin inhibits release of both insulin and glucagon.
- Glucagon evokes release of insulin as well as somatostatin.
- Insulin inhibits glucagon secretion.



Neural

- The islets are richly supplied by sympathetic and vagal nerves.
- Adrenergic α2 receptor activation decreases insulin release (predominant) by inhibiting ß cell adenylyl cyclase.
- Adrenergic ß2 stimulation increases insulin release (less prominent) by stimulating ß cell adenylyl cyclase.
- Cholinergic-muscarinic activation by ACh or vagal stimulation causes insulin secretion through IP 3/DAG-increased intracellular Ca2+ in the ß cells.

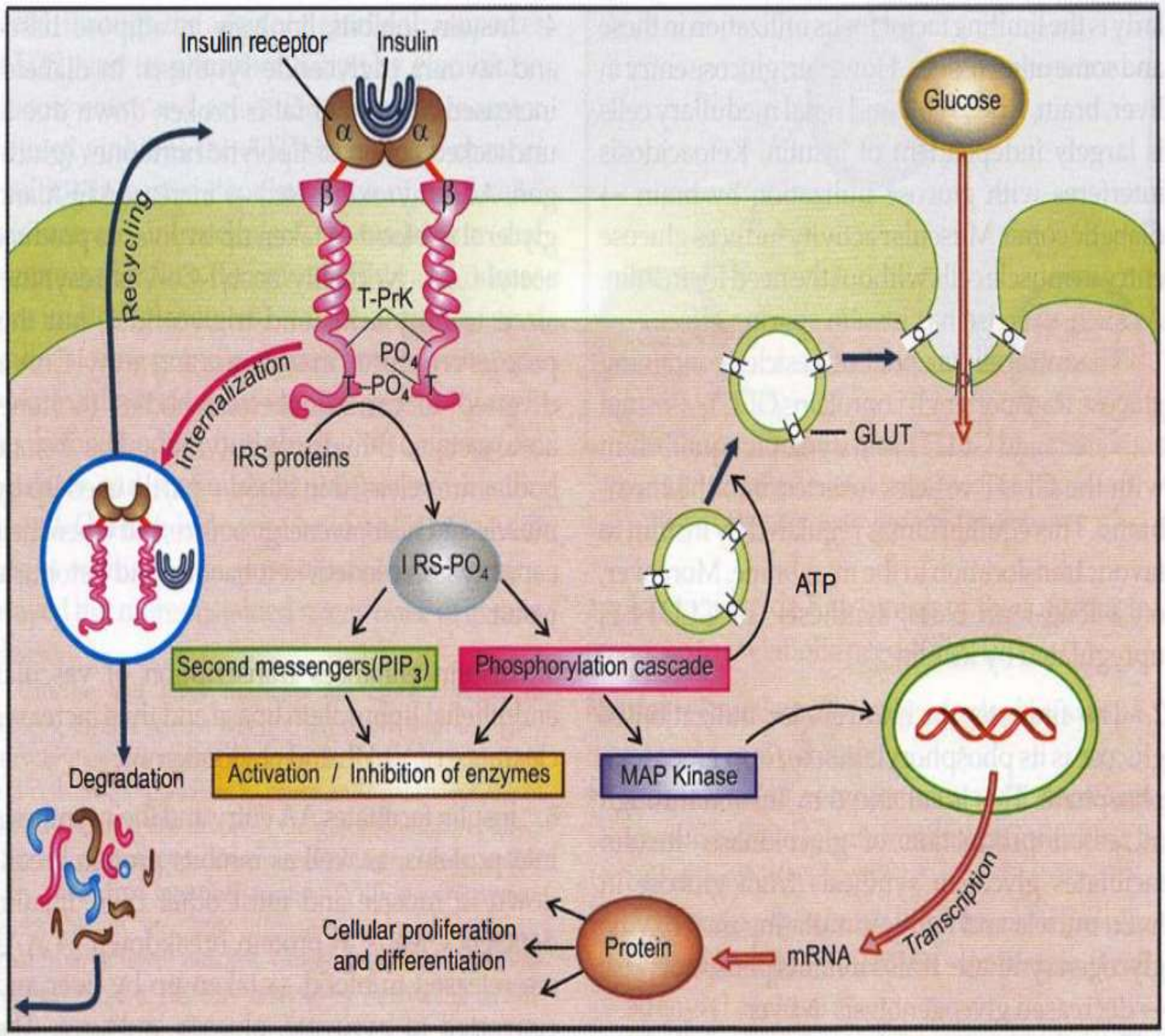
- The primary central site of regulation of insulin secretion is in the hypothalamus: stimulation of ventrolateral nuclei evokes insulin release
- whereas stimulation of ventromedial nuclei has the opposite effect.

ACTIONS OF INSULIN

- The overall effects of insulin are to favor storage of fuel.
- Insulin facilitates glucose transport across cell membrane; skeletal muscle and fat are highly sensitive
- Glucose entry in liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin
- Muscular activity induces glucose entry in muscle cells without the need for insulin.
- As such, exercise has insulin sparing effect.

Actions of insulin producing hypoglycaemia

Liver	Muscle	Adipose tissue
▲ Increases glucose uptake and glycogen synthesis	▲ Increases glucose uptake and utilization	▲ Increases glucose uptake and storage as fat and glycogen
▲ Inhibits glycogenolysis and glucose output	▲ Inhibits proteolysis and release of amino acids, pyruvate, lactate into blood which form substrate for gluconeogenesis in liver	▲ Inhibits lipolysis and release of FFA + glycerol which form substrate for gluconeogenesis in liver
▲ Inhibits gluconeogenesis from protein, pyruvate, FFA and glycerol		


Insulin receptor
Insulin
α
α
β
β
Glucose
Recycling
T-PrK
PO4
T-PO4
T
Internalization
IRS proteins
GLUT
IRS-PO4
ATP
Second messengers(PIP3)
Phosphorylation cascade
Degradation
Activation / Inhibition of enzymes
MAP Kinase
Transcription
Cellular proliferation
and differentiation
Protein
mRNA

Fate of insulin

- It is distributed only extracellularly.
- It is a peptide; gets degraded in the g.i.t. if given orally.
- Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles.
- Nearly half of the insulin entering portal vein from pancreas is inactivated in the first passage through liver.
- The plasma Half life is 5-9 min.

Diabetes mellitus

- It is a metabolic disorder
- Characterized by hyperglycaemia, glycosuria, hyperlipaemia, negative nitrogen balance and sometimes ketonaemia.

PATHOLOGICAL CHANGE

- Thickening of capillary basement membrane,
- Increase in vessel wall matrix
- Cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

Types of diabetes mellitus: Type I Insulin-dependent diabetes mellitus (IDDM), Juvenile onset diabetes mellitus:

- ß cell destruction in pancreatic islets
- Autoimmune (type lA) antibodies destroy ß cells are detectable
- Idiopathic (type lB) - no ß cell antibody is found.
- Circulating insulin levels are low or very low
- Patients are more prone to ketosis.
- Low degree of genetic predisposition.

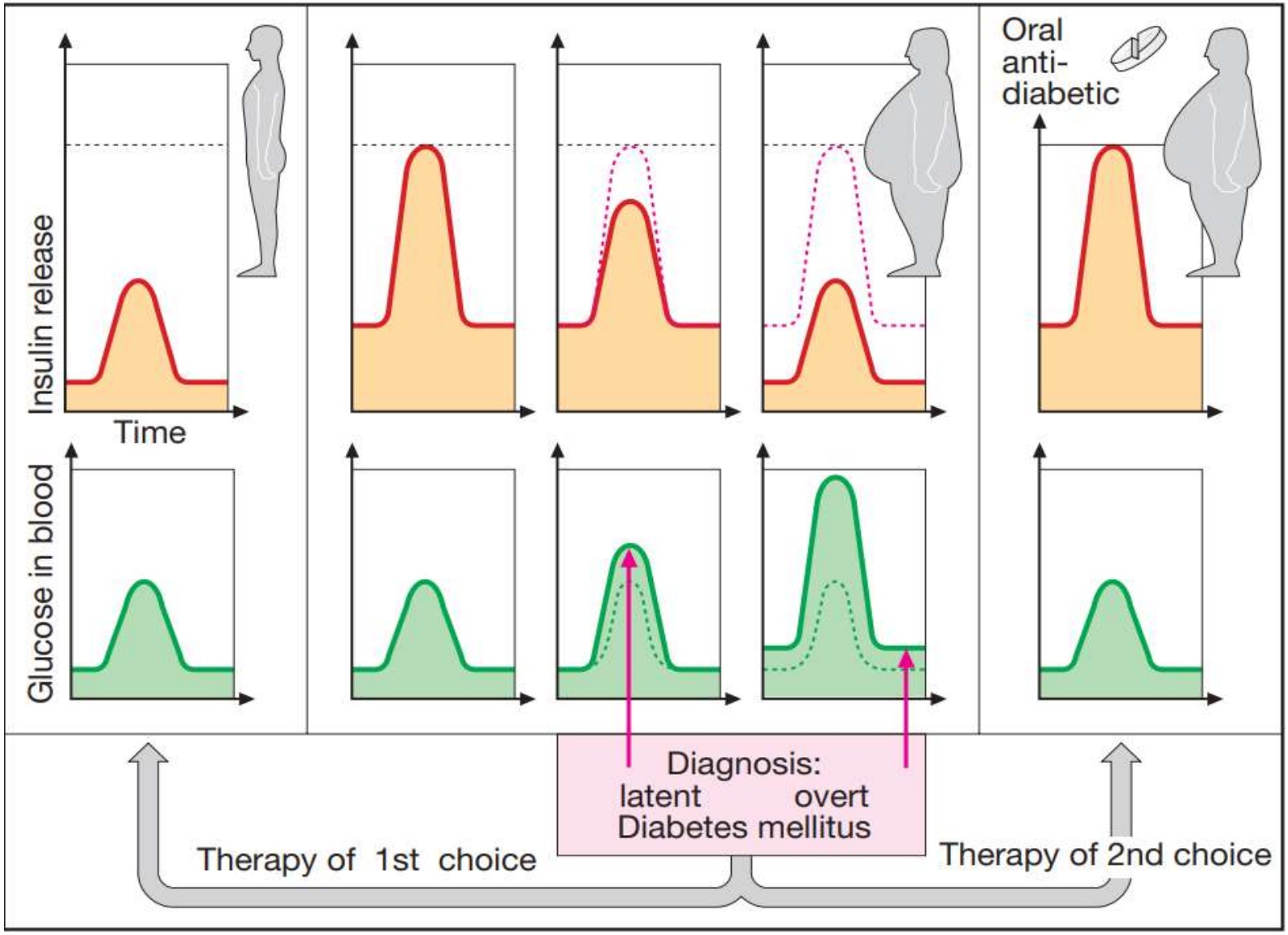
Type II Noninsulin-dependent diabetes mellitus (NIDDM), maturity onset diabetes mellitus:

- There is no loss or moderate reduction in ß cell mass
- Insulin in circulation is low, normal or even high
- No anti- ß -cell antibody is demonstrable;
- High degree of genetic predisposition;
- Late onset (past middle age).
- Over 90% cases are type 2 DM.

- Abnormality in gluco-receptor of ß cells so that they respond at higher glucose concentration
- Relative ß cell deficiency.
- Reduced sensitivity of peripheral tissues to insulin: reduction in number of insulin receptors, 'down regulation' of insulin receptors.
- Many hypertensives are hyperinsulinaemic, but normoglycaemic; exhibit insulin resistance associated with dyslipidaemia
- Excess of hyperglycaemic hormones (glucagon, etc.)
- Obesity: Cause relative insulin deficiency

Therapy of first choice is weight reduction, not administration of drugs!

Should the diabetic condition fail to resolve, consideration should first be given to insulin replacement


Insulin release
Time
Glucose in blood
Oral
anti-
diabetic
Diagnosis:
latent overt
Diabetes mellitus
Therapy of 1st choice
Therapy of 2nd choice

Therapeutic objectives are:

(1) Prevention of life-threatening hyperglycemic (diabetic) coma;

(2) Prevention of diabetic sequelae (angiopathy with blindness, myocardial infarction, renal failure), with precise “titration” of the patient being essential to avoid even short-term spells of pathological hyperglycemia;

(3) Prevention of insulin overdosage leading to life-threatening hypoglycemic shock (CNS disturbance due to lack of glucose).

REGULAR (SOLUBLE) INSULIN:

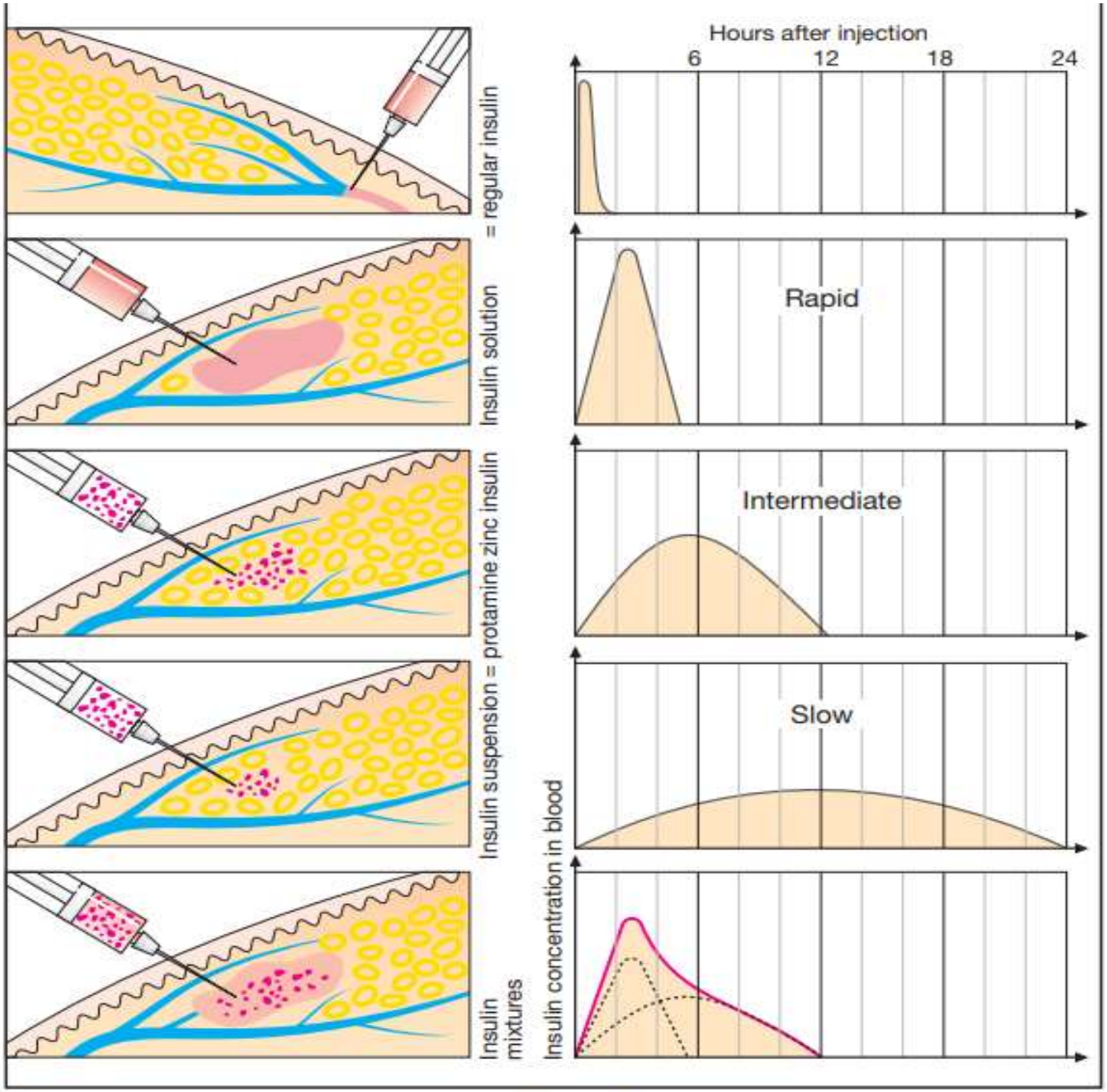
- It is a buffered solution of unmodified insulin stabilized by zinc.
- After s.c. injection, insulin monomers are released gradually by dilution, so that absorption occurs slowly.

LENTE INSULIN {INSULIN-ZINC SUSPENSION):

- The one with large particles is crystalline and practically insoluble in water (ultralente or 'extended insulin zinc suspension') is longacting.
- The other has smaller particles and is amorphous (sernilente or 'prompt insulin zinc suspension'), is short-acting.
- Their 7:3 ratio mixture is called 'Lente insulin' and is intermediate-acting.

ISOPHANE (NEUTRAL PROTAMINE HAGEDORN OR NPH) INSULIN:

- On s.c. injection, the complex dissociates slowly to yield an intermediate duration of action.



B. Insulin: preparations and blood level-time curves

Human insulins

- In the 1980s, the human insulins (having the same amino acid sequence as human insulin) were produced by recombinant DNA technology in Escherichia coli-'proinsulin recombinant bacterial' (prb) and in yeast 'precursor yeast recombinant' (pyr), or by 'enzymatic modification of porcine insulin (emp)

The human insulins are:

- Pure and stable.
- Neutral in pH and less likely to cause subcutaneous fat atrophy.
- Less antigenic.

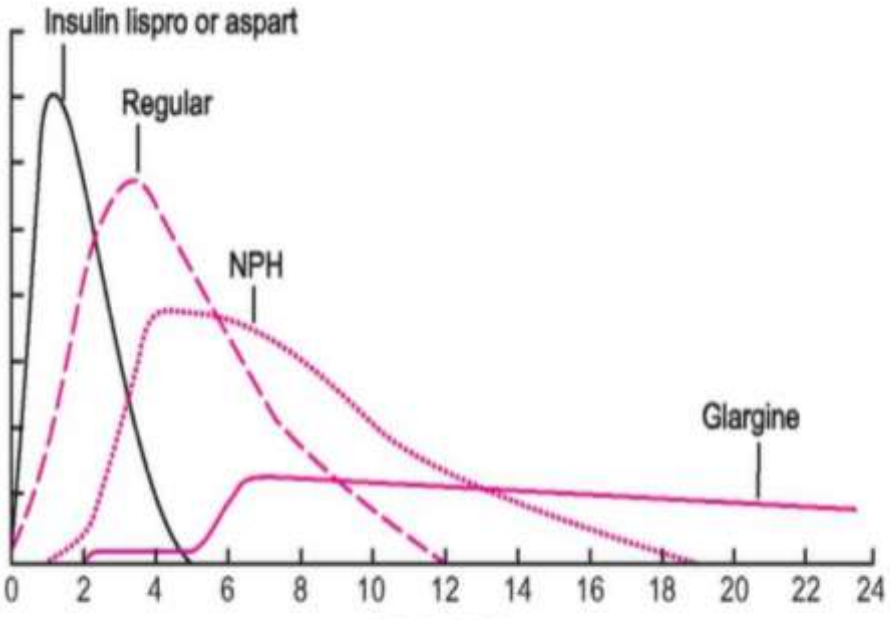
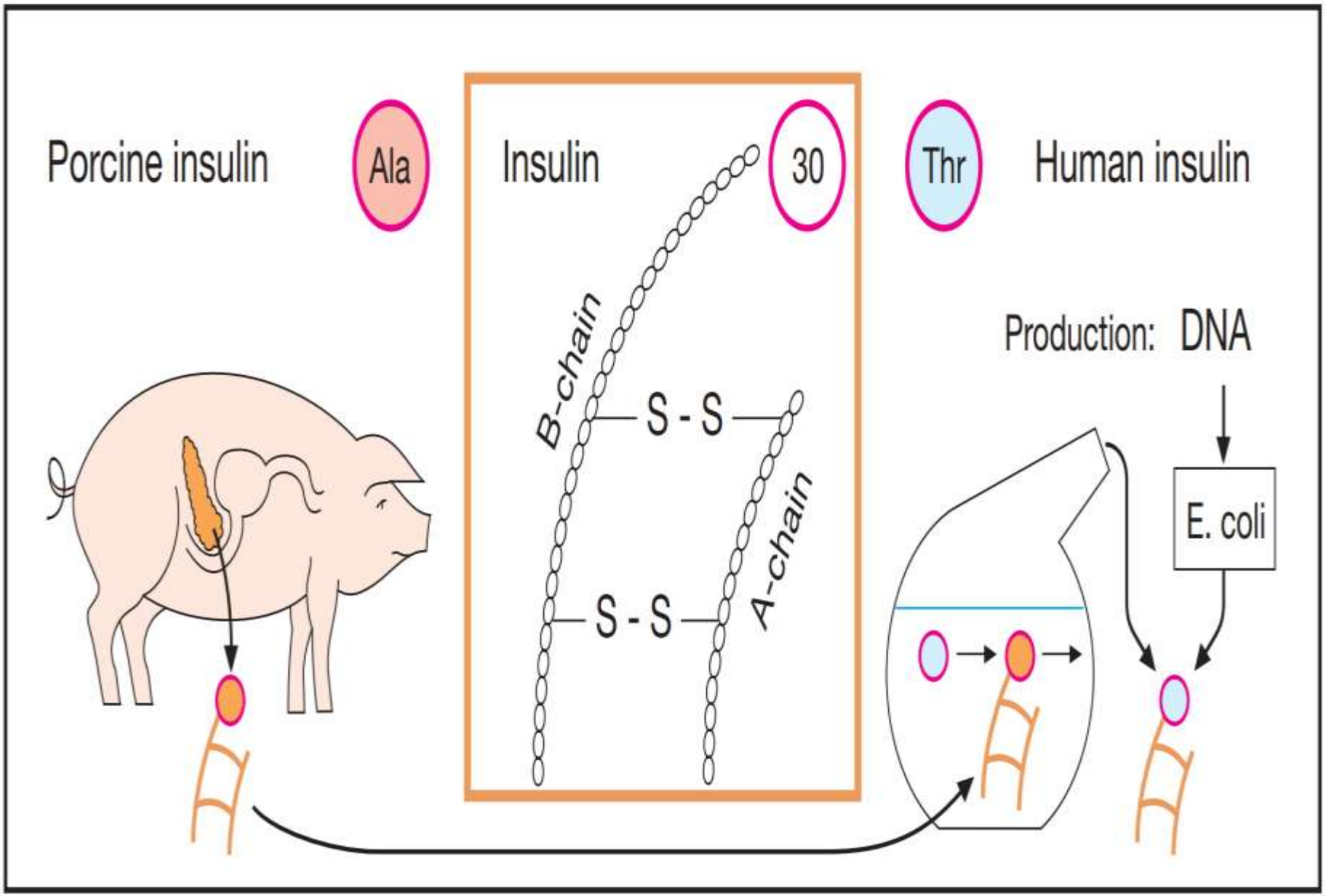


FIG. 65.3 Extent and duration of action of various types of insulin



A. Insulin production

Inhaled insulin:

- This new formulation, “Afrezza” when inhaled as dry powder is absorbed faster than injection of insulin lispro.
- It has a shorter duration of action.
- It is moderately effective in reducing HbA1C.
- Commonly it causes cough and hypoglycemia.
- It needs further evaluation.

Adverse reactions:

HYPOGLYCEMIA

(a) Too large a dose;

(b) Failure to eat;

(c) Vigorous physical exercise,

(d) Ingestion of alcohol

INSULIN ALLERGY

Allergy to insulin is IgE- mediated.

It may consist of local itching, redness, swelling and pain

Insulin lipodystrophy

This occurs at the site of injection and is of two types:

(1) LIPOHYPERTROPHY

presents as a spongy lump and is due to the lipogenic property of insulin injected repeatedly into the same area. The skin around the growth becomes anaesthetised, and this may encourage further injections in the same area. It is advisable to rotate the site.

(2) **LIPOATROPHY**

in which there is a loss of fat tissue, is probably of immunological origin.

OBESITY:

Insulin therapy without dietary restriction and exercise may increase the body weight (2-4 kg). This increases the insulin requirement.

INSULIN PRESBYOPIA:

When hyperglycemia is rapidly controlled with insulin, the patient develops loss of visual accommodation due to alterations in the physical properties of the lens. It is reversible.

INSULIN NEUROPATHY:

In an occasional patient, rapid control of hyperglycemia with insulin either precipitates peripheral neuropathy or worsens a pre-existing one.

EDEMA may be seen in some patients on initiating insulin therapy.

HEPATOMEGALY due to glycogen deposition occurs rarely.

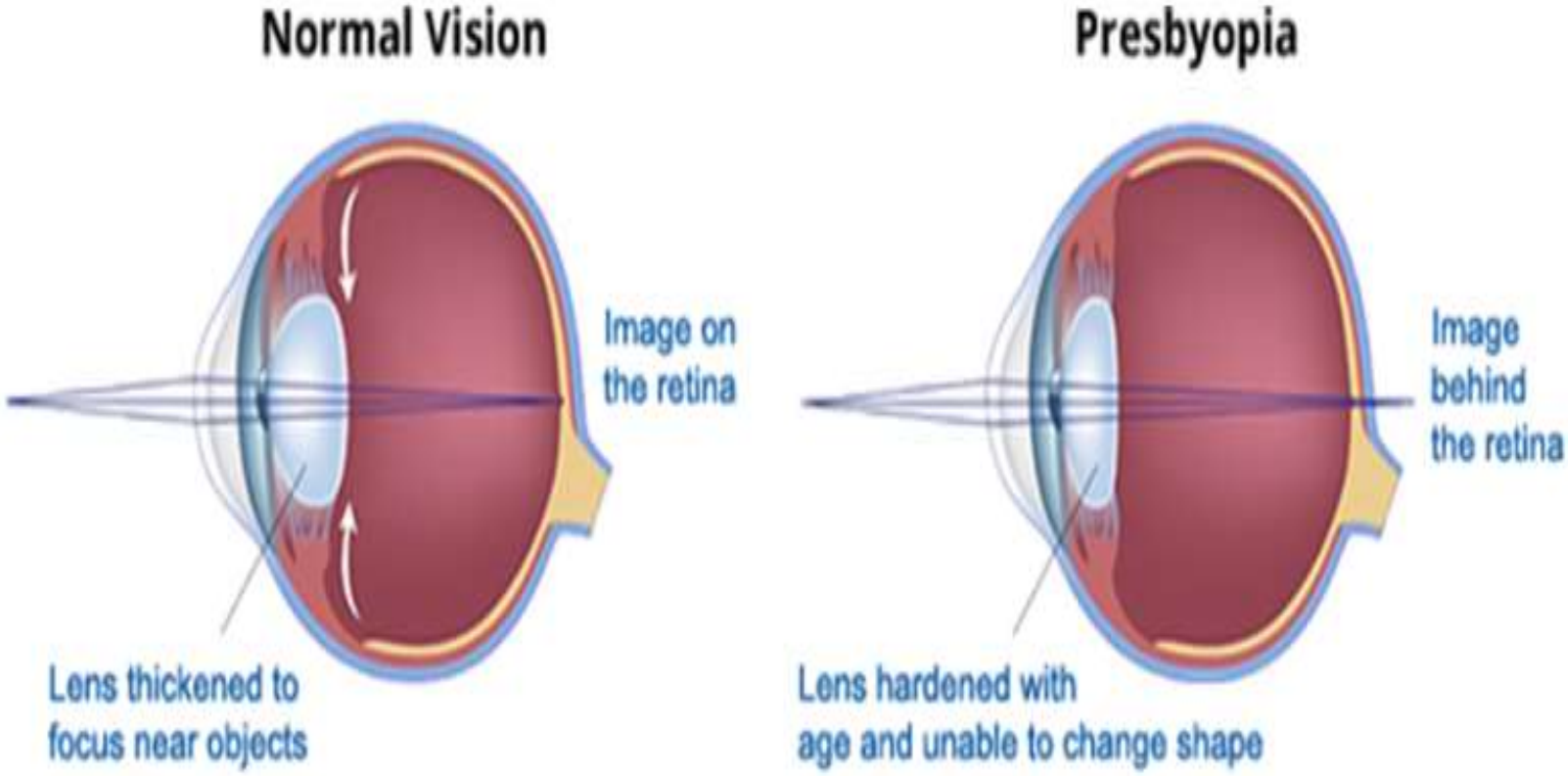
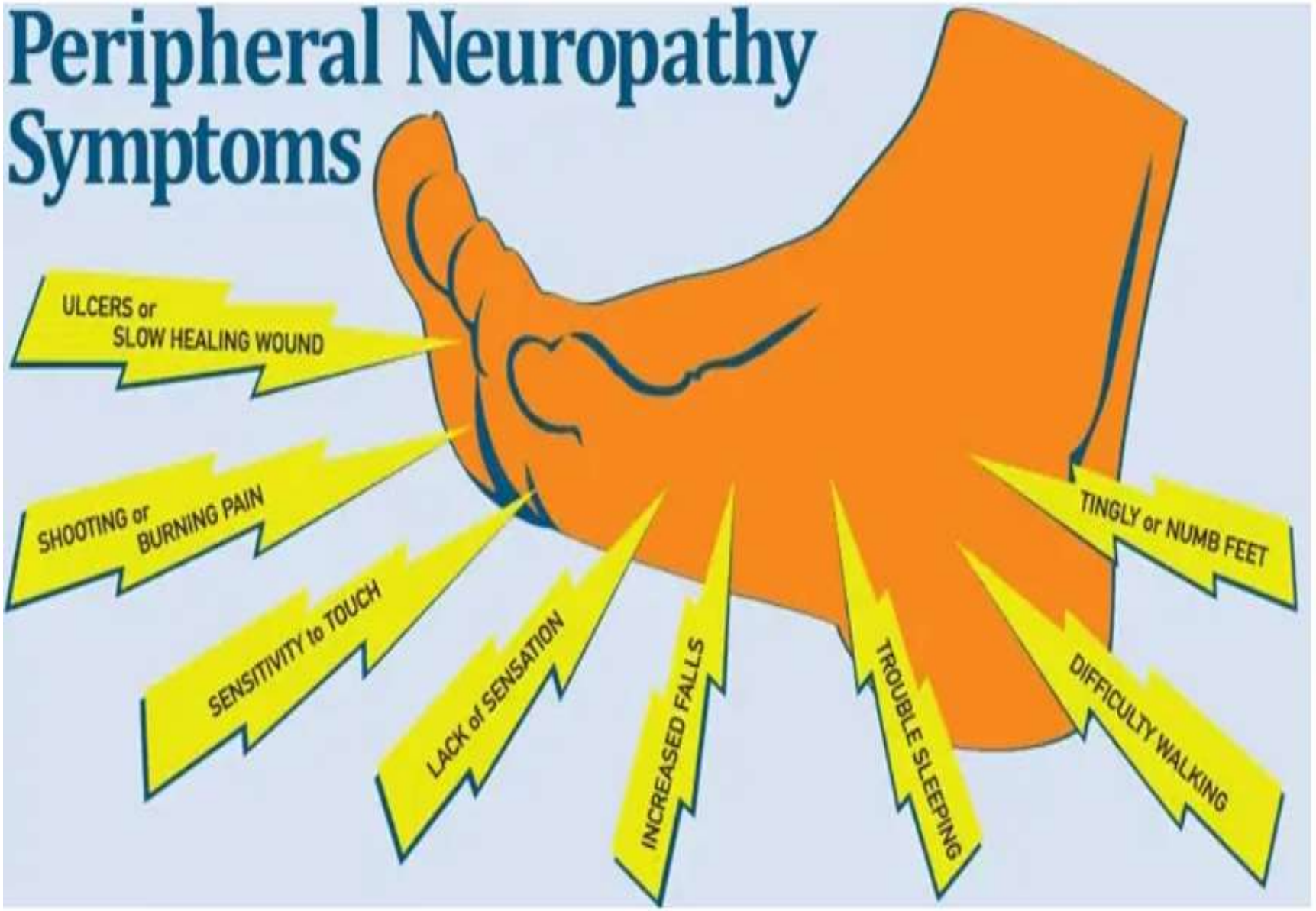


Figure 1: The Normal Eye And Presbyopia


Peripheral Neuropathy Symptoms
ULCERS or SLOW HEALING WOUND
SHOOTING or BURNING PAIN
SENSITIVITY to TOUCH
LACK of SENSATION
INCREASED FALLS
TROUBLE SLEEPING
DIFFICULTY WALKING
TINGLY or NUMB FEET

Drug interactions

- **ß adrenergic blockers** prolong hypoglycaemia by inhibiting compensatory mechanisms operating through ß 2 receptors
- **Thiazides, furosemide, corticosteroids, oral contraceptives, salbutamol, nifedipine** tend to raise blood sugar and reduce effectiveness of insulin.
- **Acute ingestion of alcohol** can precipitate hypoglycaemia by depleting hepatic glycogen.
- **Salicylates, lithium and theophylline** may also accentuate hypoglycaemia

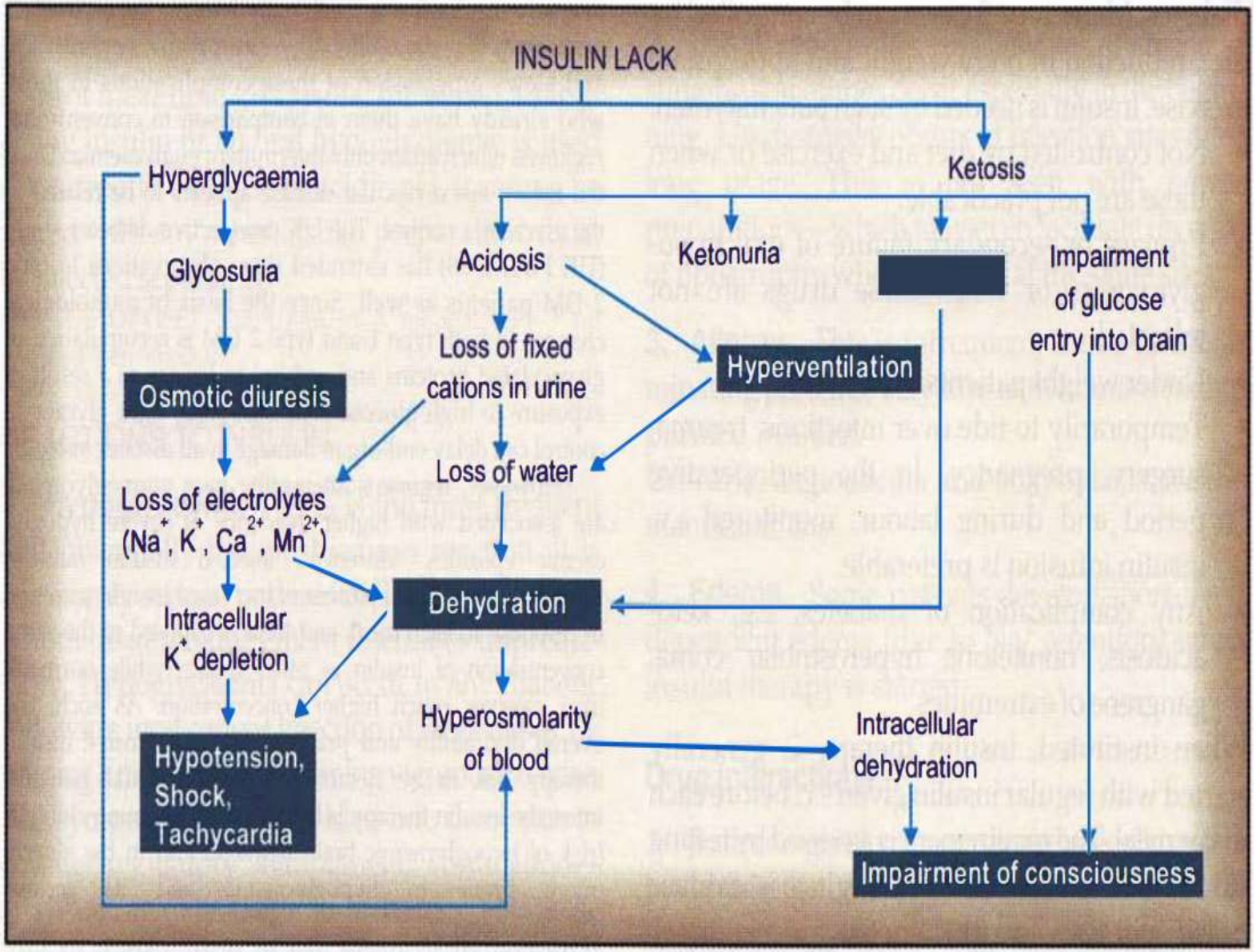


Fig. 19.4: Schematic depiction of the development of diabetic ketoacidosis due to insulin lack. Symptoms produced are shown within boxes

Non-Insulin Antidiabetic Drugs

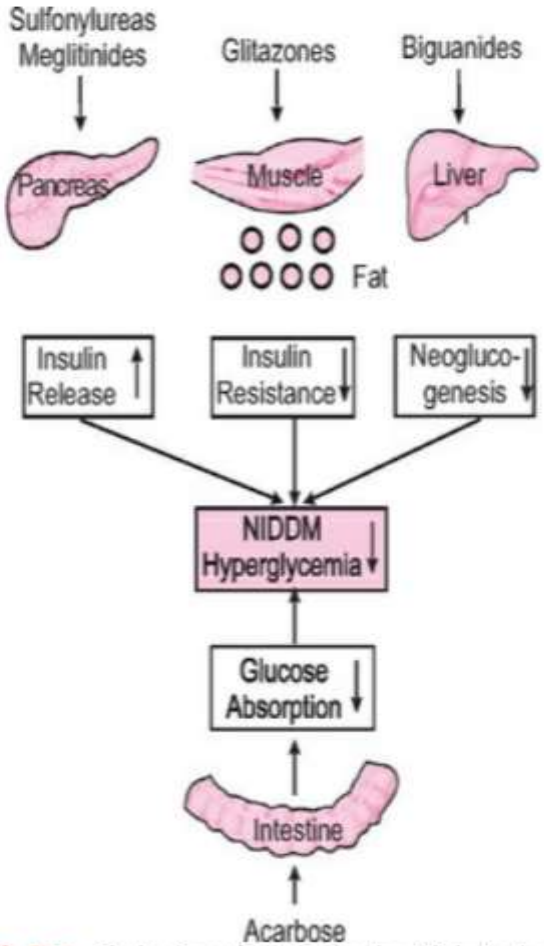


FIG. 65.4 Mechanism of action of oral antidiabetic drugs

SULFONYLUREAS

First generation	*Second generation*
Tolbutamide	Glibenclamide
Chlorpropamide	(Glyburide)
	Glipizide
	Gliclazide
	Glimepiride

BIGUANIDES

Metformin

MEGLITINIDE / PHENYL ALANINE ANALOGUES

Repaglinide Nateglinide

THIAZOLIDINEDIONES

Rosiglitazone Pioglitazone

α GLUCOSIDASE INHIBITORS

Acarbose Miglitol

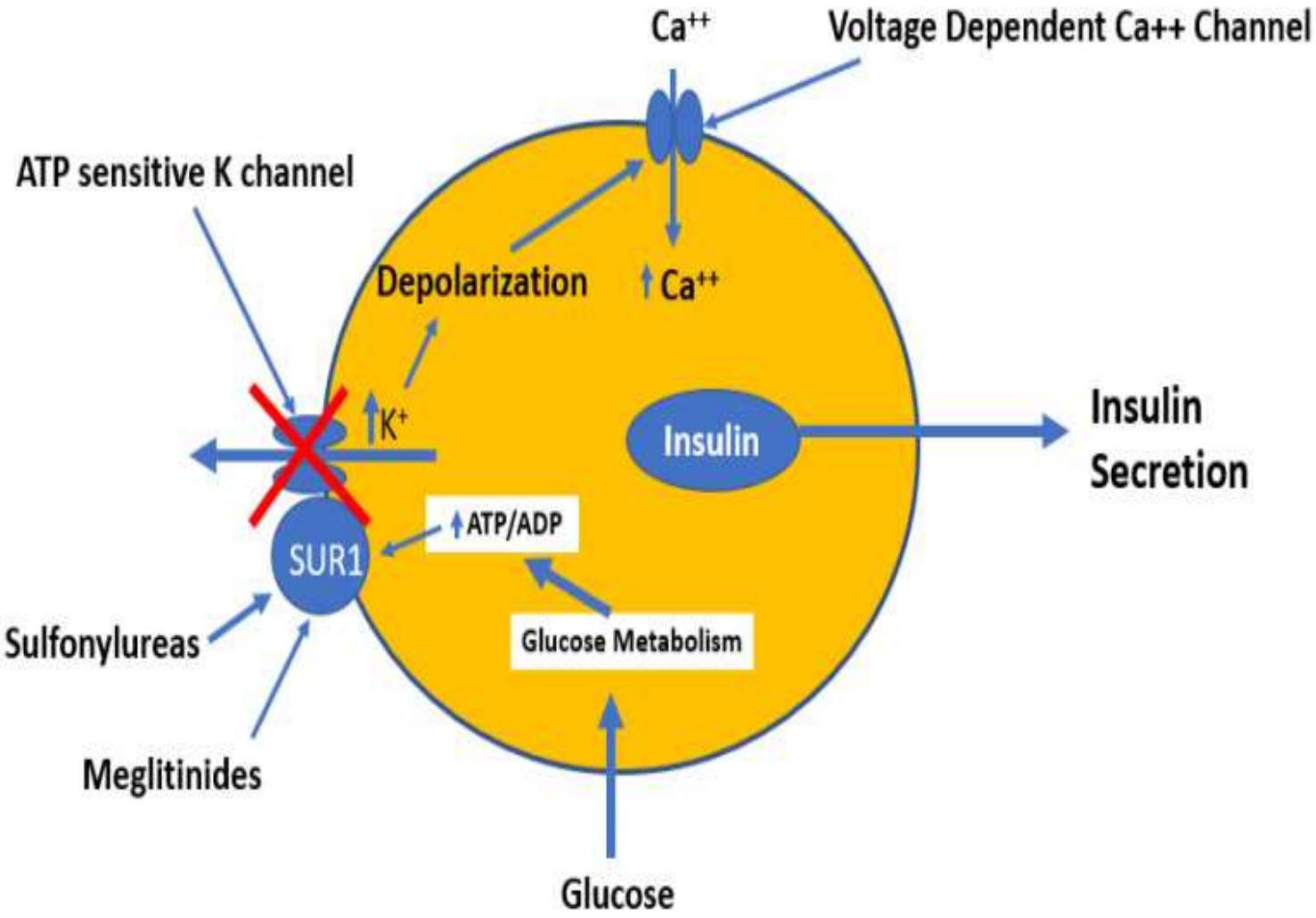
SULFONYLUREAS:

PANCREATIC BETA CELLS

They act on sulphonylurea receptors (SUR) linked to the ATP dependent K channels (KATP) in the cell membrane of the islet beta cells.

Activation of the receptors causes the K channels to close and the cell membrane to depolarise.

This results in a calcium influx into the cell, with release of stored insulin


Ca++
Voltage Dependent Ca++ Channel
ATP sensitive K channel
Depolarization
Ca++
K+
Insulin
Insulin Secretion
SUR1
ATP/ADP
Sulfonylureas
Glucose Metabolism
Meglitinides
Glucose

Choice of the sulfonylurea preparation

- Tolbutamide is well tolerated and is relatively safe. But it has to be taken 2-3 times a day.
- Chlorpropamide controls hyperglycemia in a single daily dose.
- Glipizide is intermediate between tolbutamide and chlorpropamide.
- Glibenclamide is effective in a single daily dose and may be effective in patients who are not controlled by maximum doses of chlorpropamide.
- Gliclazide, glipizide and tolbutamide are largely metabolised by the liver and are hence preferred in patients with renal impairment.

Absorption, fate and excretion

Sulfonylureas are rapidly absorbed from the GI tract when taken on empty stomach.

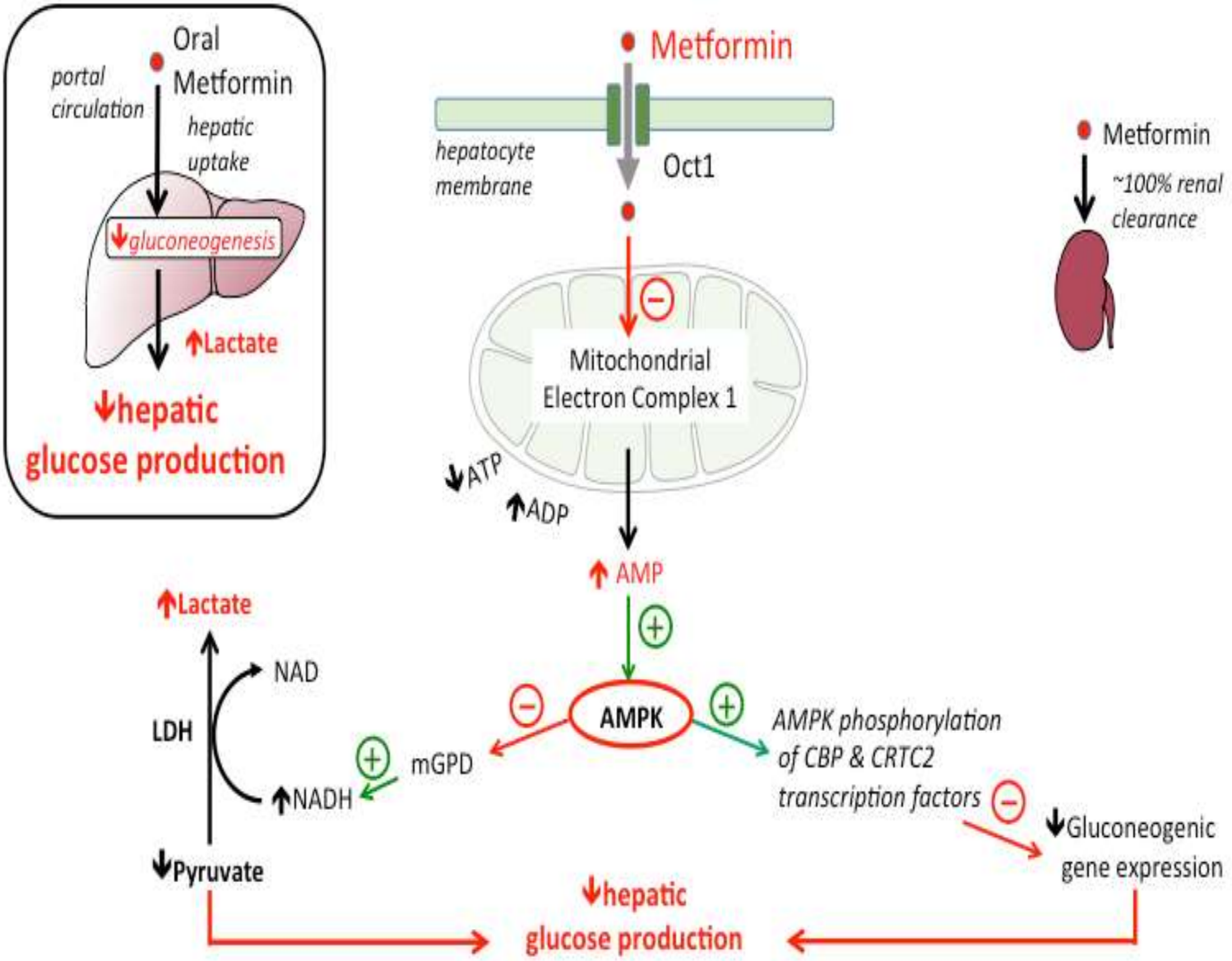
They are absorbed within 1-2 hours and peak levels are achieved in 4-6 hours.

Food reduces their absorption.

They are all extensively (>90%) protein bound and are mainly metabolised in the liver

Metformin (Biguanide)

- Mechanism of action of metformin is not clear.
- Inhibits hepatic neoglucogenesis and decreases hepatic and renal glucose output.
- It acts on adenosine monophosphate activated protein kinase (AMPK).
- Increases the peripheral glucose utilisation by enhancing anaerobic glycolysis, and increases the activity of glucose transporters (GIUT-4).
- Acts as insulin sensitisers in the muscle and adipose tissue, and reduces hyperinsulinemia
- Delays glucose absorption
- Reduces the appetite, which may be helpful in obese subjects.

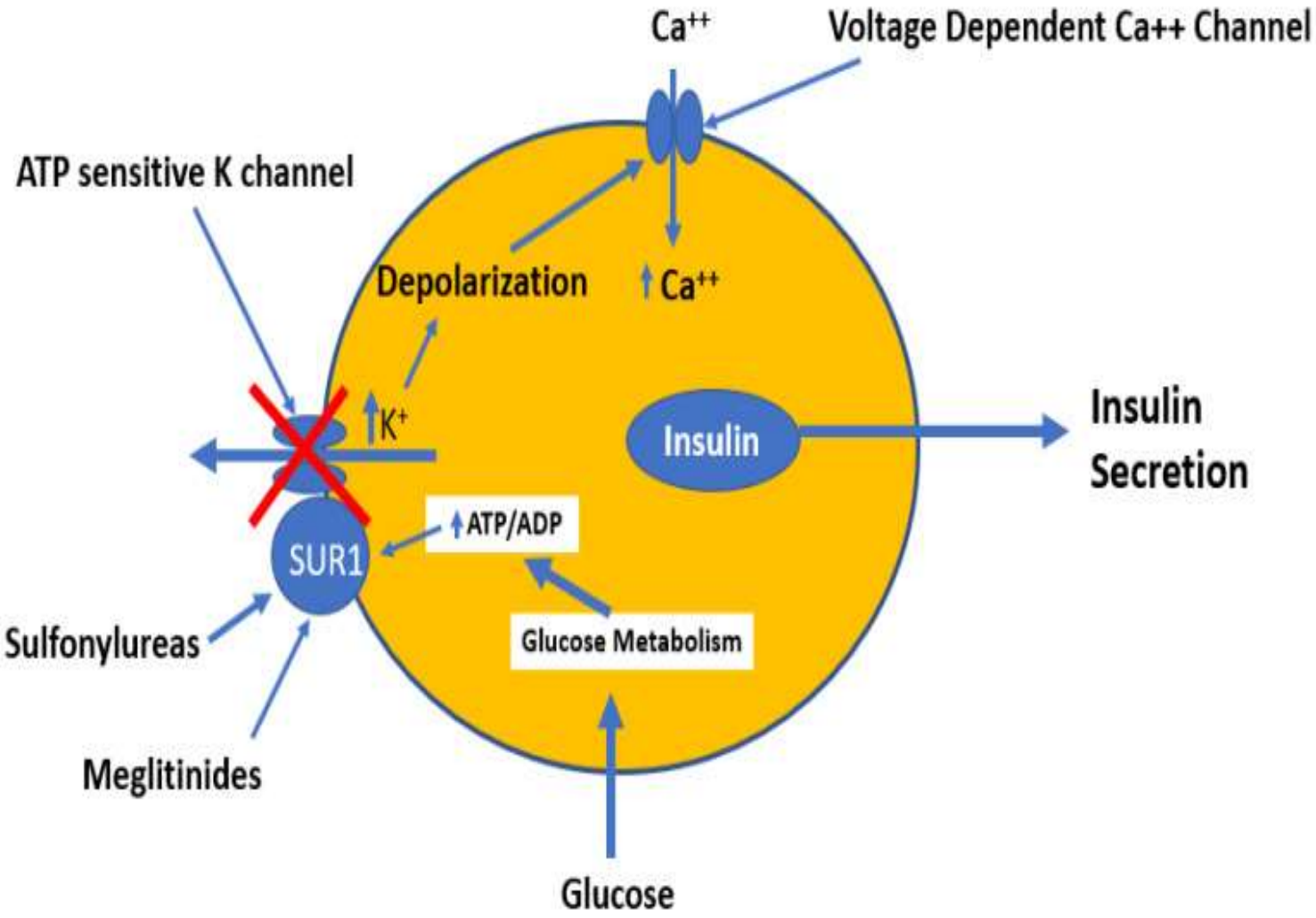

Oral
Metformin
portal circulation
hepatic uptake
gluconeogenesis
Lactate
hepatic glucose production
Metformin
hepatocyte membrane
Oct1
Mitochondrial Electron Complex 1
ATP
ADP
AMP
Metformin
~100% renal clearance
Lactate
NAD
LDH
NADH
mGPD
AMPK
AMPK phosphorylation of CBP & CRTC2 transcription factors
Gluconeogenic gene expression
Pyruvate
hepatic glucose production

Pharmacological actions: Metformin

- Does not lower the blood sugar in normal subjects.
- By itself, it does not produce hypoglycemia in diabetics.
- However, it potentiates the hypoglycemic action of insulin and sulfonylureas.

Meglitinides (Glinides):

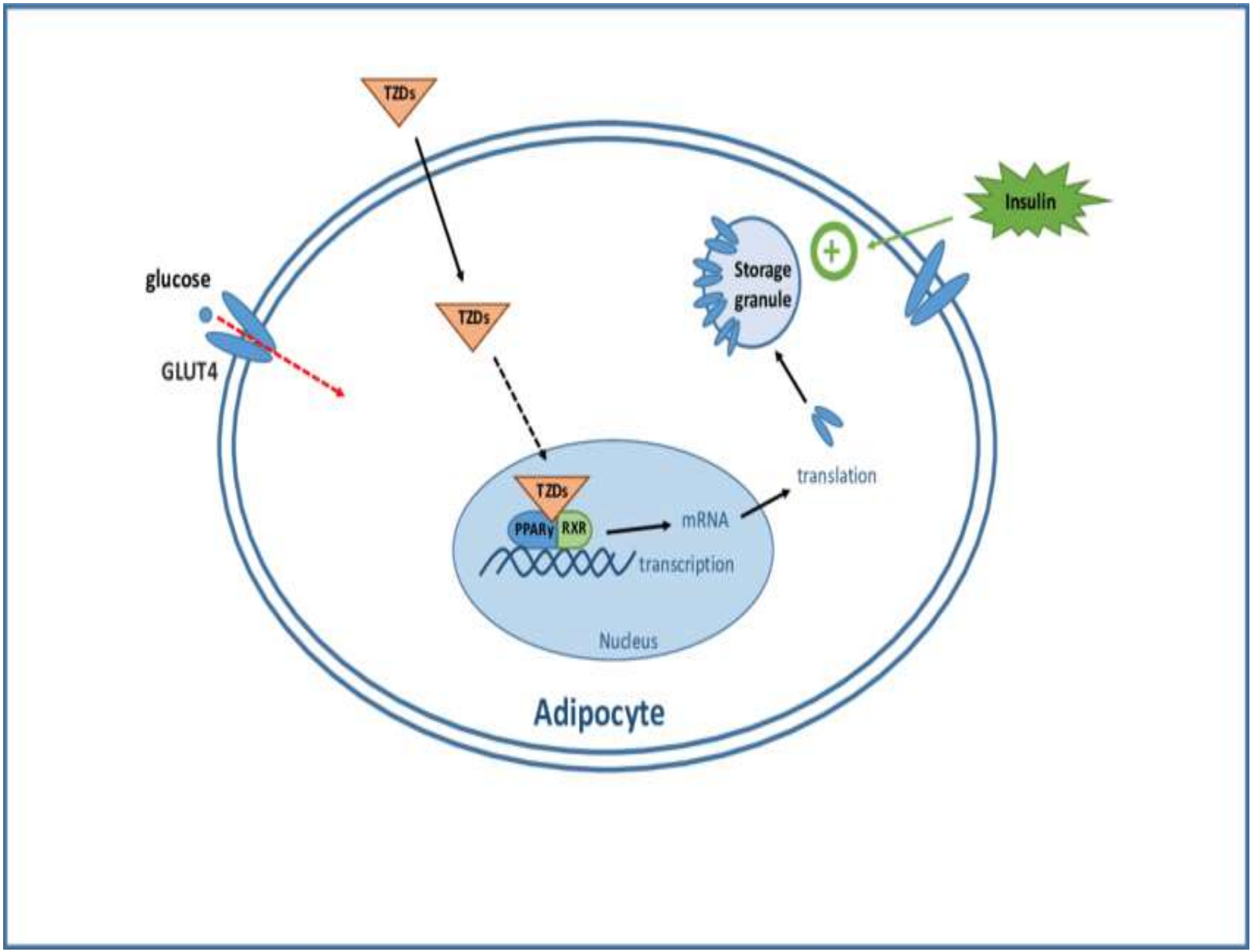
- These drugs, chemically unrelated to sulfonylureas, have the same mechanism of action.
- They bind to a site adjacent to SUR and stimulate insulin secretion.
- They can be used in patients with decreased renal function.


Ca++
Voltage Dependent Ca++ Channel
ATP sensitive K channel
Depolarization
Ca++
K+
Insulin
Insulin Secretion
SUR1
ATP/ADP
Sulfonylureas
Glucose Metabolism
Meglitinides
Glucose

THIAZOLIDINEDIONES (Glitazones)

MOA

- Potent agonists (stimulants) of the nuclear receptors Peroxisome Proliferator-Activated Receptors gamma (PPARγ),
- Abundantly present in the adipose tissue and also present in the liver, heart and skeletal muscle.
- After binding to the receptor PPARγ, glitazones modulate **gene expression involved in glucose and lipid metabolism, insulin signal transduction, and adipocyte differentiation and proliferation**.
- Thus they reduce peripheral insulin resistance.


TZDs
Insulin
glucose
GLUT4
TZDs
Storage granule
translation
TZDs
PPARγ
RXR
mRNA
transcription
Nucleus
Adipocyte

Pharmacological actions:

Reduce peripheral resistance to insulin and increase the insulin sensitivity of the adipose

Increase the subcutaneous, small-adipocyte mass, and divert the triglyceride storage from the visceral adipocytes to the subcutaneous adipose tissue.

Lower the hepatic fat content and ameliorate dyslipidemia.

Lower the hepatic glucose production and increase glucose uptake by skeletal muscle.

Absorption, fate and excretion:

- Pioglitazone is generally prescribed for use once daily.
- It is completely absorbed and is metabolised extensively by the liver.
- The metabolites of pioglitazone are more active and are excreted in the bile.

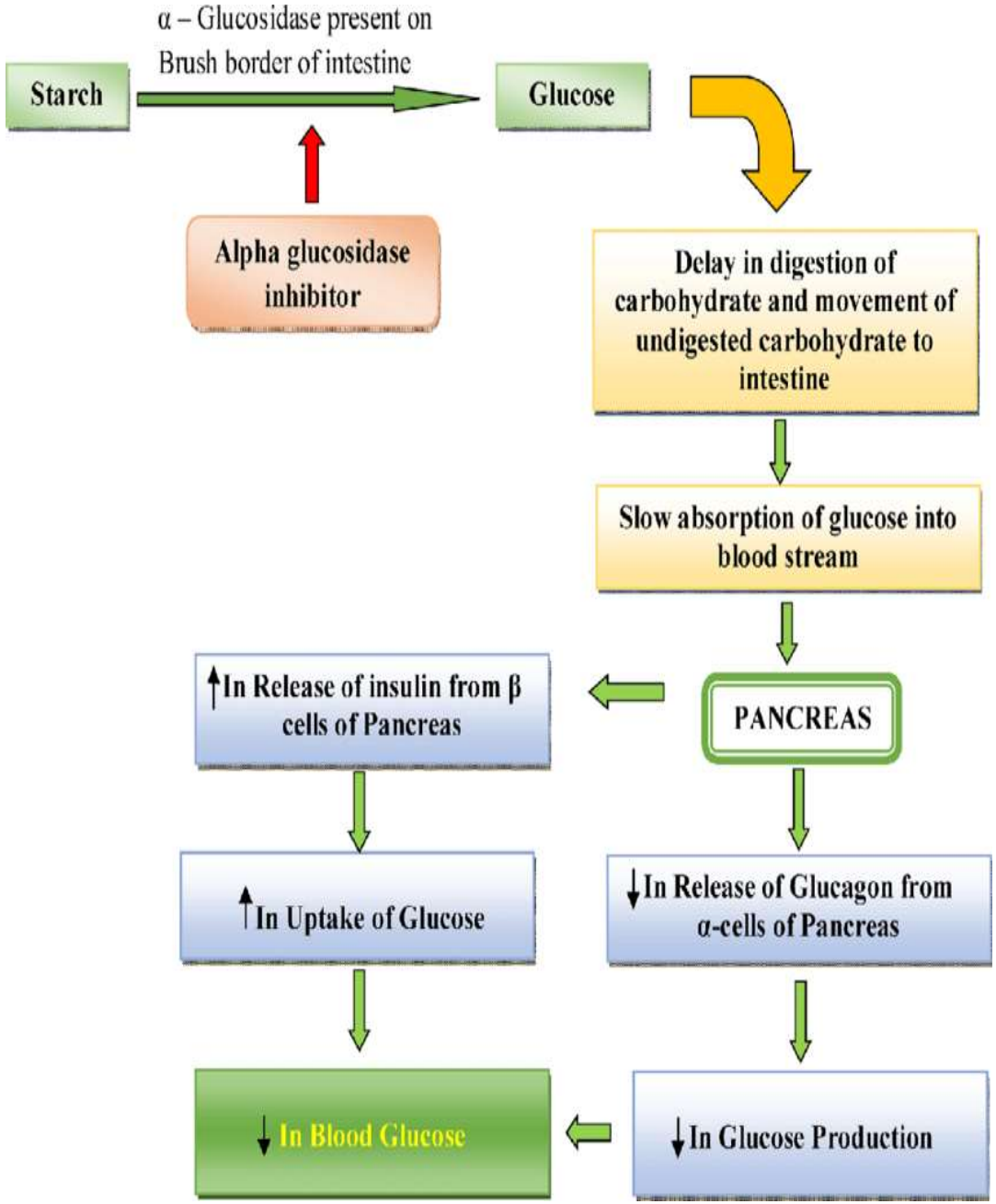
α GLUCOSIDASE INHIBITORS

Acarbose is an oligosaccharide of microbial origin.

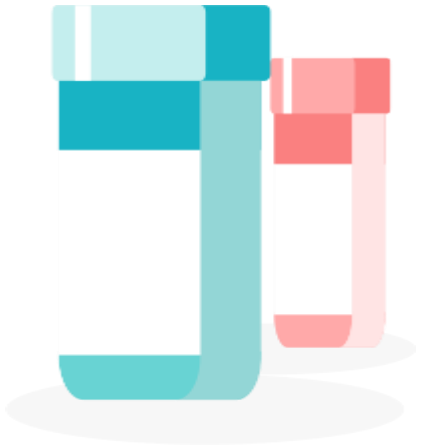
MECHANISM OF ACTION:

It binds competitively to carbohydrate binding sites of alpha glucosidases enzymes in the brush border of the enterocytes in the jejunum.

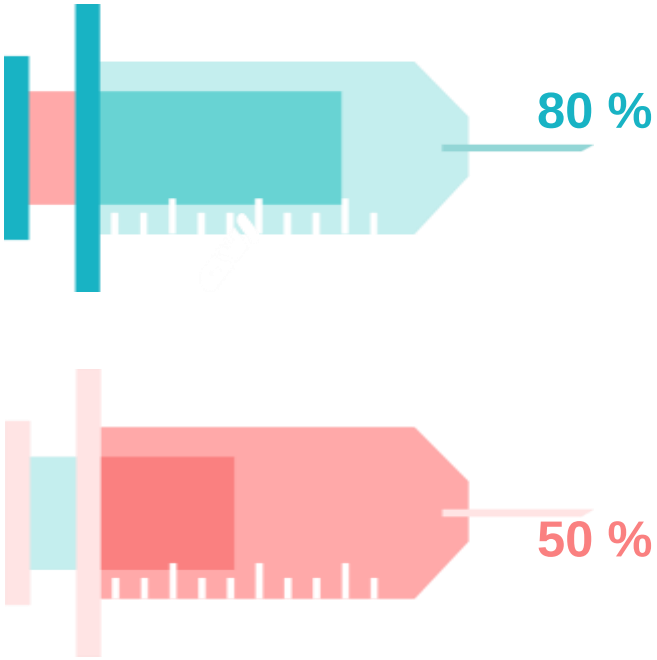
It thus **inhibits the absorption of carbohydrates but not of glucose** because it does not interact with the intestinal sodium dependent glucose transporter.


α – Glucosidase present on
Brush border of intestine
Starch
Glucose
Alpha glucosidase inhibitor
Delay in digestion of carbohydrate and movement of undigested carbohydrate to intestine
Slow absorption of glucose into blood stream
PANCREAS
In Release of insulin from β cells of Pancreas
In Uptake of Glucose
In Release of Glucagon from α-cells of Pancreas
In Blood Glucose
In Glucose Production

GLUCAGON



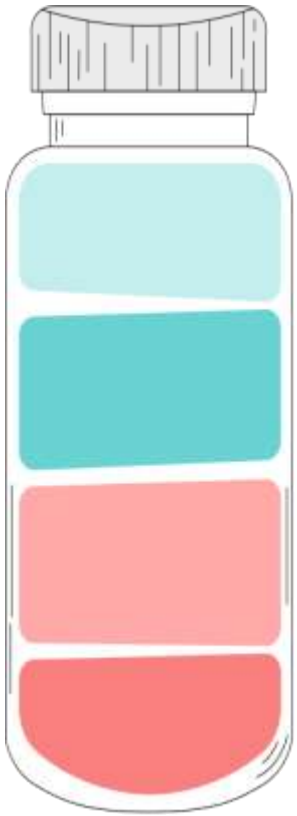
INTRODUCTION:



- Glucagon is a hormone that your pancreas makes to help regulate your blood glucose (sugar) levels.
- Glucagon increases your blood sugar level and prevents it from dropping too low, whereas insulin, another hormone, decreases blood sugar levels.
- Glucose is very important because it’s the primary source of energy for your brain.

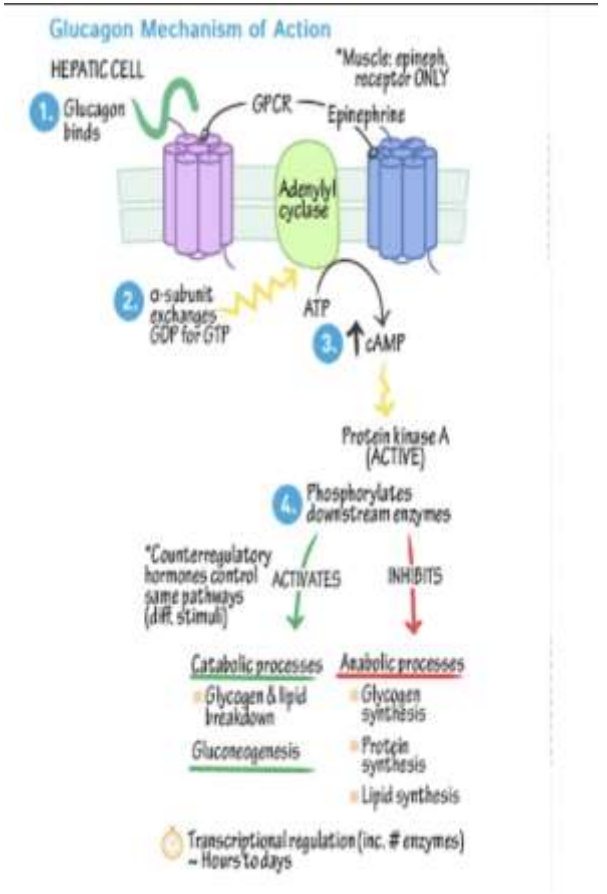
- Glucagon and insulin are both important hormones that play essential roles in regulating your blood glucose (sugar).
- Both hormones come from your pancreas — alpha cells in your pancreas make and release glucagon, and beta cells in your pancreas make and release insulin.

- The difference is in how these hormones contribute to blood sugar regulation.
- Glucagon increases blood sugar levels, whereas insulin decreases blood sugar levels

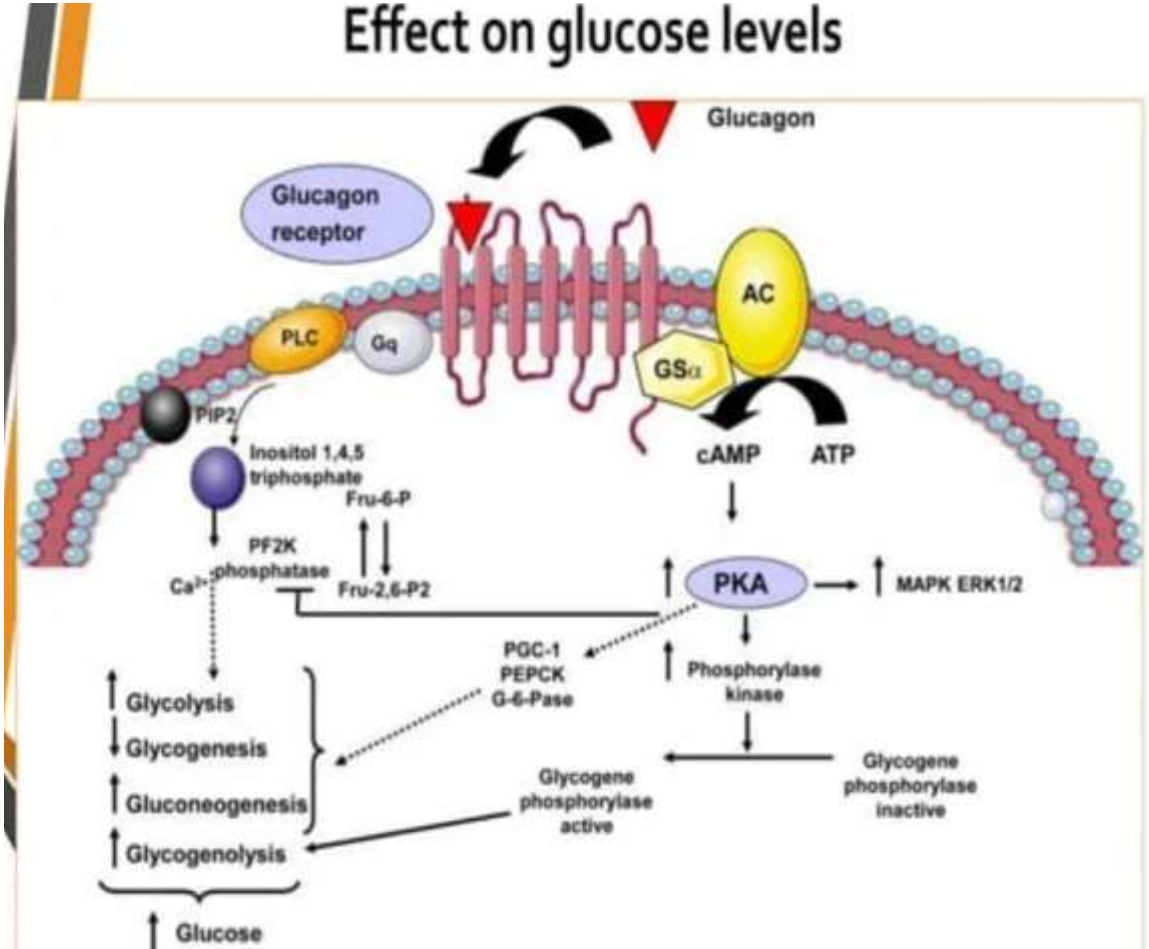


THE MECHANISM OF ACTION OF GLUCAGON IS AS FOLLOWS:

1. Binding to Receptors: Glucagon binds to glucagon receptors (G protein-coupled receptors) on the surface of target cells, primarily in the liver.
2. Activation of Adenylyl Cyclase: Upon binding to its receptor, glucagon activates the enzyme adenylyl cyclase via the Gs protein.
3. Increase in cAMP: Adenylyl cyclase converts ATP to cyclic AMP (cAMP), increasing intracellular cAMP levels.
4. Activation of Protein Kinase A (PKA): Elevated cAMP activates protein kinase A (PKA), which then phosphorylates various target proteins within the cell.



5. Glycogenolysis: PKA phosphorylates and activates enzymes like glycogen phosphorylase, leading to the breakdown of glycogen into glucose (glycogenolysis).
6. Gluconeogenesis: PKA also promotes gluconeogenesis by activating key enzymes involved in the production of glucose from non-carbohydrate sources, such as amino acids and lactate.
7.Inhibition of Glycogenesis: PKA inhibits glycogen synthase, which prevents the formation of glycogen, conserving glucose in its usable form.



Pharmacological Uses of Glucagon

Glucagon is primarily used in the following clinical setting

Treatment of Hypoglycemia:

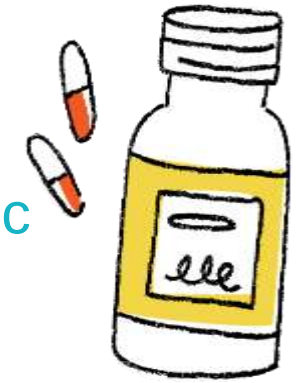
- Glucagon is a rapid-acting agent that can quickly reverse hypoglycemia, especially in patients who are unconscious or unable to take oral glucose.
- It is administered intramuscularly or subcutaneously.

Diagnosis of Insulinoma:

- An insulinoma is a rare tumor of the pancreas that produces excess insulin, leading to hypoglycemia.
- Glucagon is used as a diagnostic test. If the blood glucose level rises significantly after glucagon administration, it suggests the presence of an insulinoma.

Management of Beta-blocker Overdose:

- Beta-blockers can inhibit the release of glucagon, leading to hypoglycemia.
- Glucagon can be used to counter the hypoglycemic effects of beta-blocker overdose.



Adverse Effects

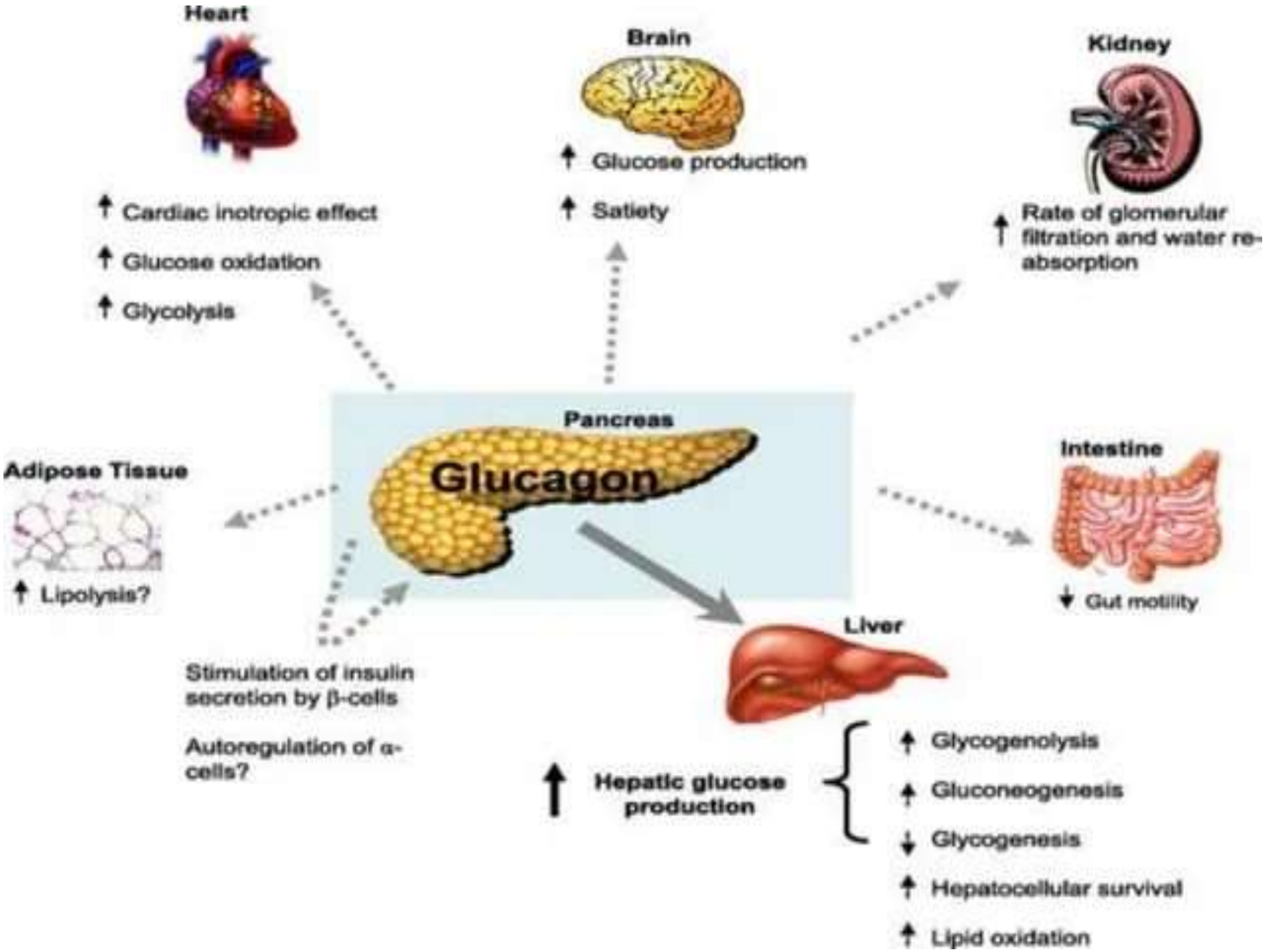
- **Nausea and Vomiting:** These are common side effects of glucagon administration.
- **Tachycardia and Arrhythmias:** In rare cases, glucagon can cause rapid heart rate or irregular heart rhythms.

Common Side Effects:

1. Nausea and Vomiting: This is the most frequently reported side effect, especially after glucagon is injected.
2. Headache: Some individuals experience headaches after receiving glucagon.
3. Dizziness: A feeling of lightheadedness may occur, particularly after blood sugar levels rapidly increase.
4. Injection Site Reactions: Pain, swelling, or redness may occur at the site where the glucagon was injected.

Less Common or Rare Side Effects:

- **Hyperglycemia:** Since glucagon raises blood glucose levels, it can lead to excessively high blood sugar.
- **Tachycardia (Increased Heart Rate)**
- **Hypokalemia (Low Potassium Levels)**
- **Allergic Reactions.**


Heart
↑ Cardiac inotropic effect
↑ Glucose oxidation
↑ Glycolysis
Brain
↑ Glucose production
↑ Satiety
Kidney
↑ Rate of glomerular filtration and water re-absorption
Pancreas
Glucagon
Adipose Tissue
↑ Lipolysis?
Intestine
↓ Gut motility
Stimulation of insulin secretion by β-cells
Autoregulation of α-cells?
Liver
↑ Hepatic glucose production
↑ Glycogenolysis
↑ Gluconeogenesis
↓ Glycogenesis
↑ Hepatocellular survival
↑ Lipid oxidation

ROUTES OF ADMINISTRATION:

Glucagon can be administered through the following routes:

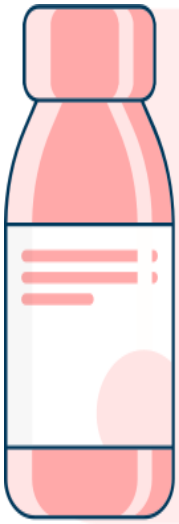
- **Intramuscular (IM):** This is the most common route for emergency treatment of severe hypoglycemia. The injection is given into a muscle, usually the thigh or upper arm.
- **Subcutaneous (SC):** This route is also used for emergency treatment of severe hypoglycemia. The injection is given under the skin, usually in the abdomen or upper arm.

- **Intravenous (IV):** This route is used in healthcare settings for diagnostic purposes or in cases of severe hypoglycemia that do not respond to IM or SC administration.
- **Intranasally:** This route is relatively new and involves administering glucagon as a nasal spray. It is approved for the emergency treatment of severe hypoglycemia in adults and children aged 6 years and older.

PHARMACOKINETICS

Absorption

- **Route of administration:** Glucagon is typically administered via injection (subcutaneously, intramuscularly, or intravenously).
- **Absorption rate:** It is rapidly absorbed from the injection site.



Distribution

- **Distribution:** Glucagon is distributed throughout the body, with a preference for the liver.
- **Protein binding:** It has a low protein binding affinity, meaning it's more freely available to exert its effects.

Metabolism

- **Metabolism:** Glucagon is primarily metabolized in the liver and kidneys.
- **Half-life:** The half-life of glucagon varies depending on the route of administration, but it's generally around 30-45 minutes.

Excretion

- **Excretion:** The majority of glucagon metabolites are excreted through the kidneys in urine.

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.