CORTICOSTEROIDS

DR PRADNYA ROTITHOR

Drugs widely used

and

abused

biosynthesis

-synthesized from cholesterol

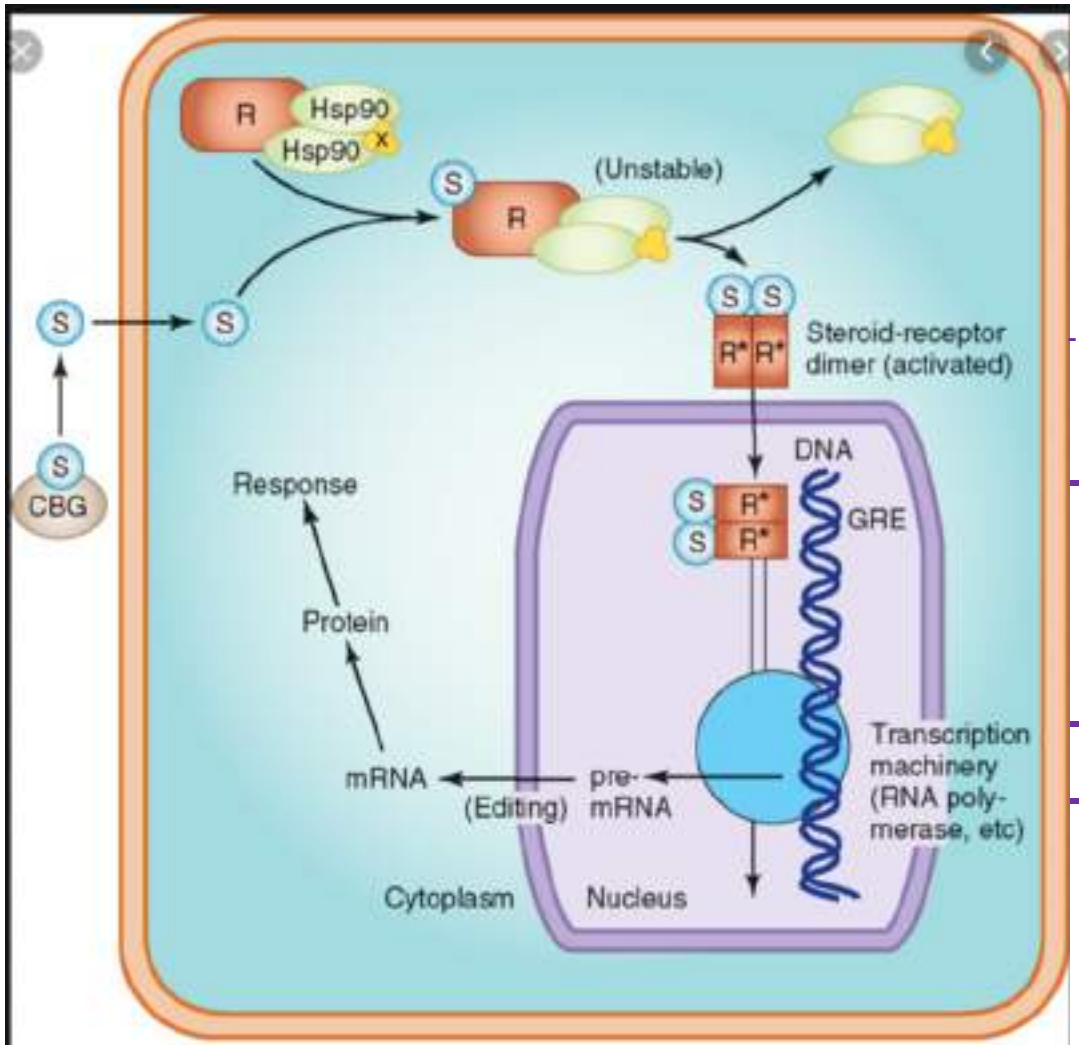
In Suprarenal gland (adrenal gland)

-Adrenal Cortex

-Zona glomerulosa – Aldosterone

-Zona fasciculata – glucocorticoids

Zona reticularis sex hormones



MOA

Nuclear receptor

MCQ

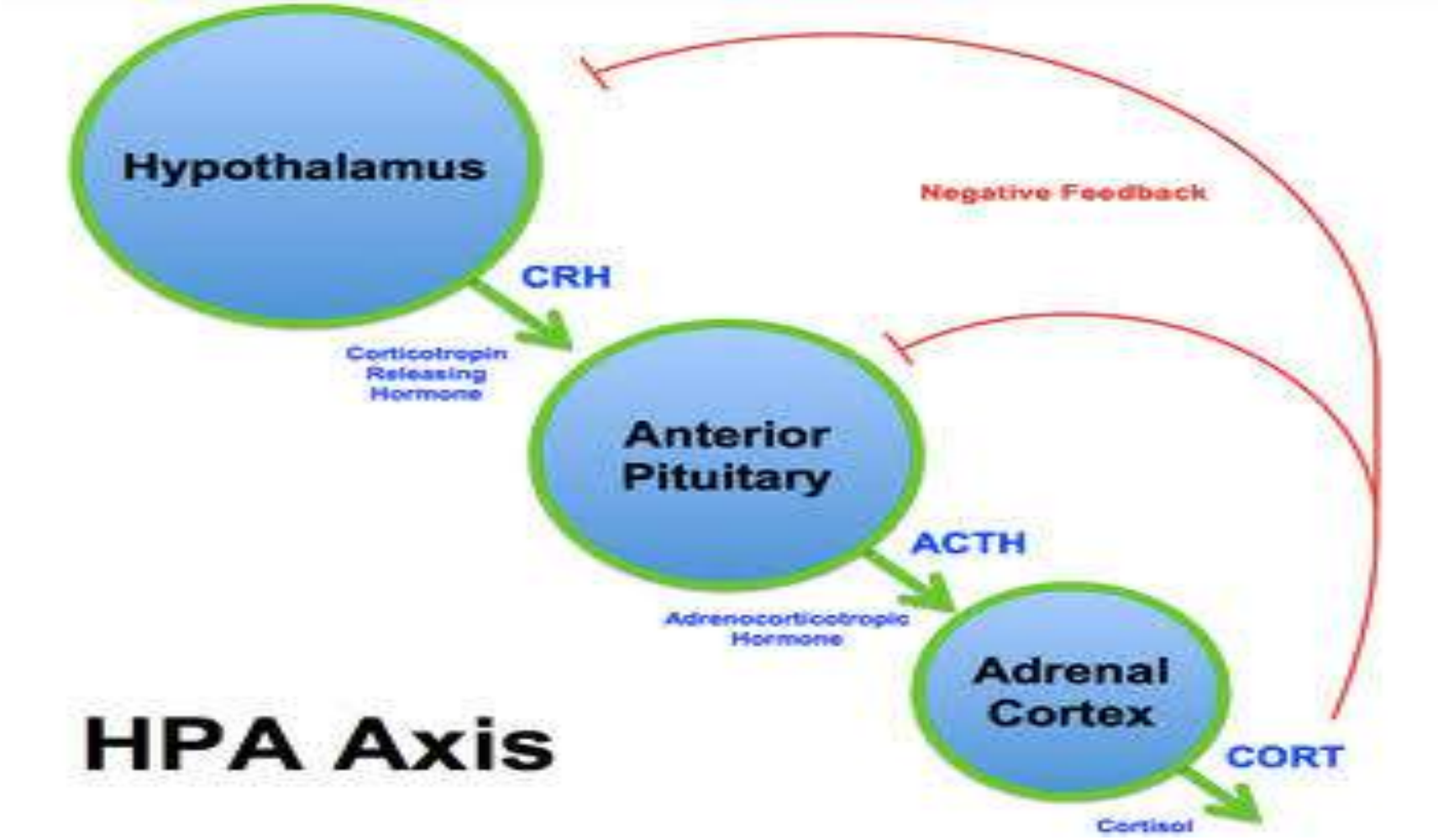
-dimerization of the receptor

-activates glucocorticoid response elements

(GRE)

-leads to gene transcription

-Protein synthesis leading to specific effects


Hypothalamus
Negative Feedback
CRH
Corticotropin Releasing Hormone
Anterior Pituitary
ACTH
Adrenocorticotropic Hormone
Adrenal Cortex
CORT
Cortisol
HPA Axis

Hypothalamus Pituitary Adrenal Axis

- Hypothalamus---acth-rh
- Ant pituitary---acth
- Adrenal cortex –steroids
- **Negative feedback on ant pituitary and hypothalamus**

Suppression of HPA axis

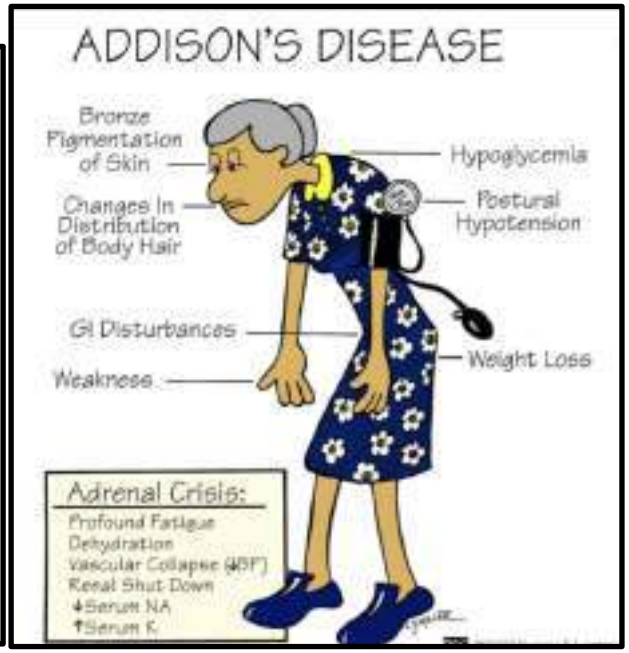
Chronic administration –exogenous steroids

↓ Endogenous steroids

→body depends on exogenous supply

ABRUPT stoppage →

ACUTE ADRENAL INSUFFICIENCY



Precautions for steroid therapy

- **1 avoid**
- **2 Minimum period**
- **3 Minimum dose possible**
- **4 Stop at the earliest**
- **5. NO ABRUPT STOPPAGE -→ TAPERING**
- ***Smallest possible dose for shortest possible duration***

Guidelines for clinical uses

- **local therapy** wherever possible—inhalation /nasal spray/cutaneous
- **Severe illness** –starting dose high ,reduce gradually after symptoms subside
- **Mild illness** –start with lowest dose and titrate upwards to correct steady dose
- Administer ***full dose*** in the ***morning***
- ***No abrupt withdrawal when given for > 2-3 weeks***
- **Increase the dose** – infection trauma, surgery or any other stress during therapy

Types of pharmacological actions

Direct

Produce effect themselves

permissive

do not act themselves but their presence facilitates other substrates to exert that action

example-pressor action by adrenaline

Pharmacological actions and ADR

1	**Hypothalamus→ (CRH/ACTH-RH)** **Pituitary → (ACTH)** **Adrenal Cortex** **Corticosteroids** Steroids decrease ACTH and CRH by negative feedback. Due to decreased CRH and ACTH, endogenous steroid secretion decreases	**Suppression of HPA axis** **Abrupt stoppage of steroids leads** **to** **ACUTE ADRENAL INSUFFICIENCY**

Pharmacological actions and ADR

1	**Decreased cortisol**	[redacted]
2	**Cbh: Glycogenolysis Gluconeogenesis** **Inhibit glucose utilization by peripheral tissues**	
3	**Fat: Redistribution (Permissive)**	
4	**Protein:catabolic antianabolic**	

Actions		ADR
5	Calcium ↓ Intestinal absorption ↑Renal excretion ↑Bone resorption	
6	Skeletal muscle: protein anti-anabolic	
7	Stomach: ↓PG synthesis: ↑ HCl secretion	
8	CVS: Na retention cardiac changes	
9	CNS: Mood swing, seizure threshold, water retention	

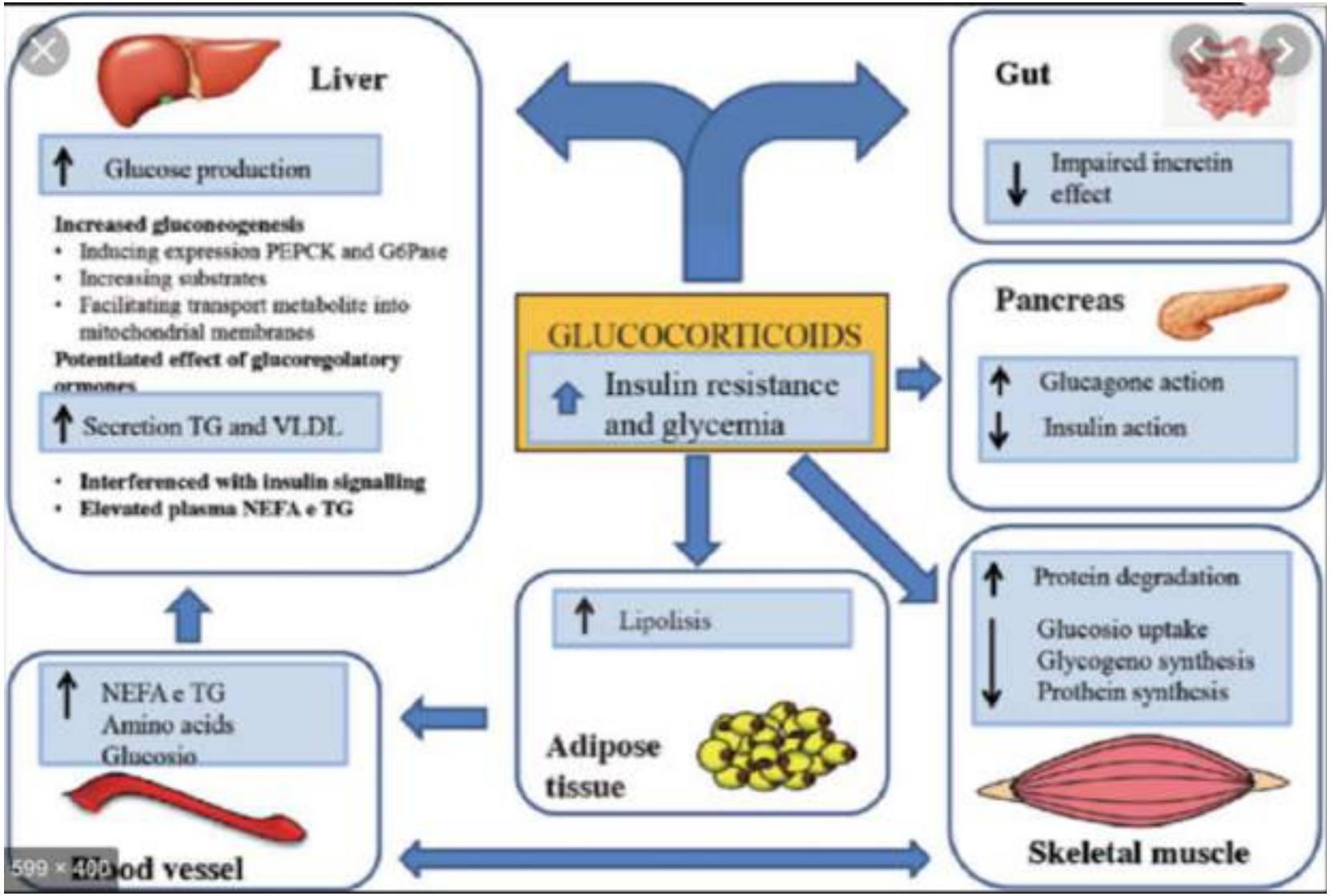
10) inflammatory responses –base of most of the clinical indications.

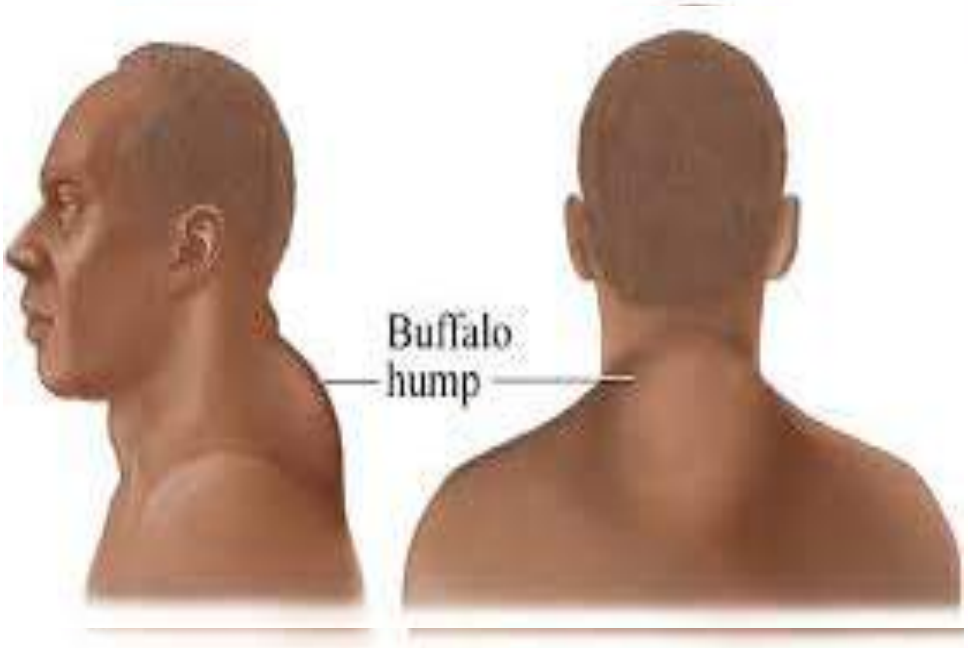
- Palliative –do not remove cause of inflammation
- Covers all components and all stages of inflammation
- Reduction of ----increased capillary permeability, PG LT PAF,
- local exudate, cellular infiltration, phagocytosis
- collagen deposition and scar formation

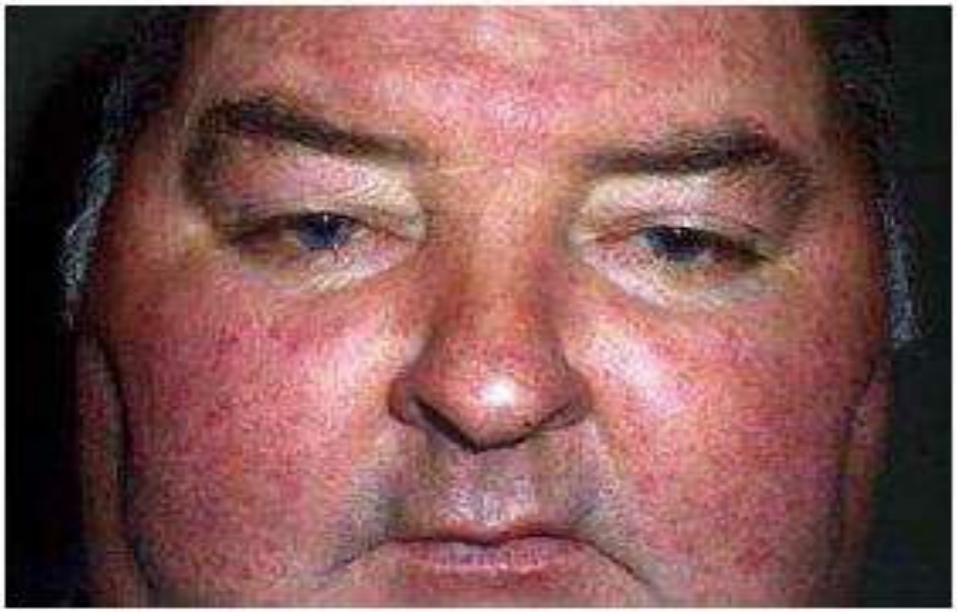
- Action is nonspecific ,direct
- All cardinal signs of inflammation are suppressed— erythema,heat,swelling and pain

11) Immunological and allergic responses

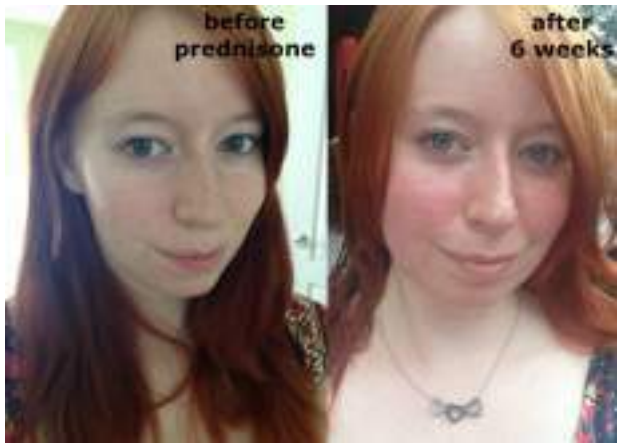
Suppress CMI at higher doses

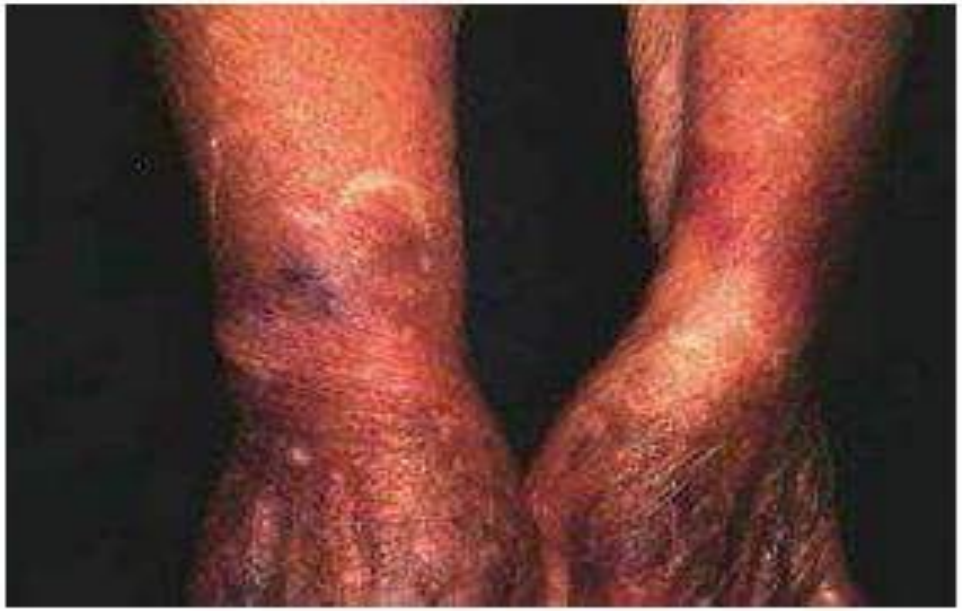

Liver
Glucose production
Increased gluconeogenesis
• Inducing expression PEPCK and G6Pase
• Increasing substrates
• Facilitating transport metabolite into mitochondrial membranes
Potentiated effect of glucoregolatory ormones
Secretion TG and VLDL
• Interferenced with insulin signalling
• Elevated plasma NEFA e TG
GLUCOCORTICOIDS
Insulin resistance and glycemia
Gut
Impaired incretin effect
Pancreas
Glucagone action
Insulin action
Lipolisis
Adipose tissue
Protein degradation
Glucosio uptake
Glycogeno synthesis
Prothein synthesis
Skeletal muscle
NEFA e TG
Amino acids
Glucosio
od vessel



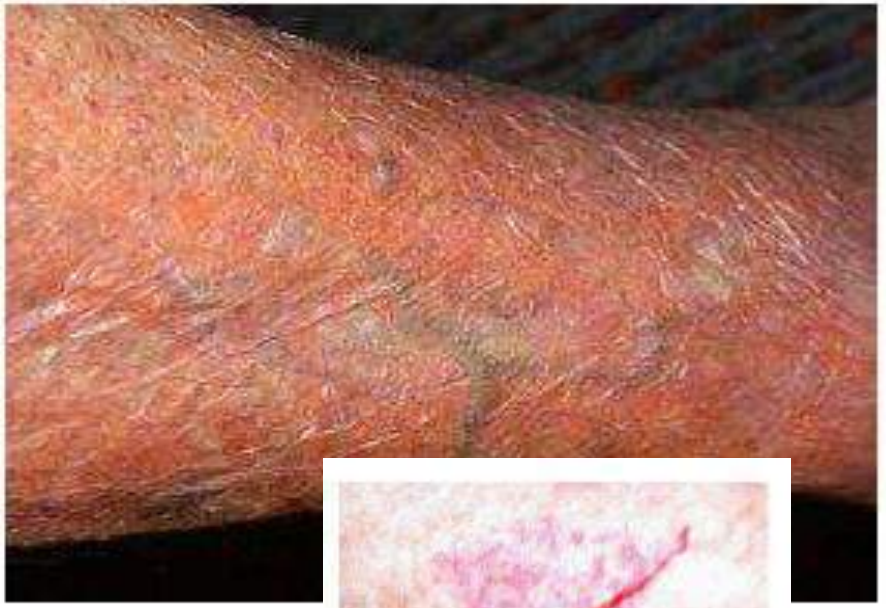


Moon face

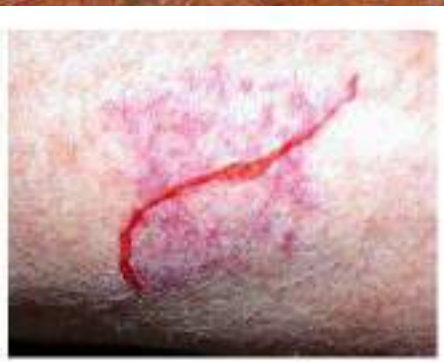




Easy bruising



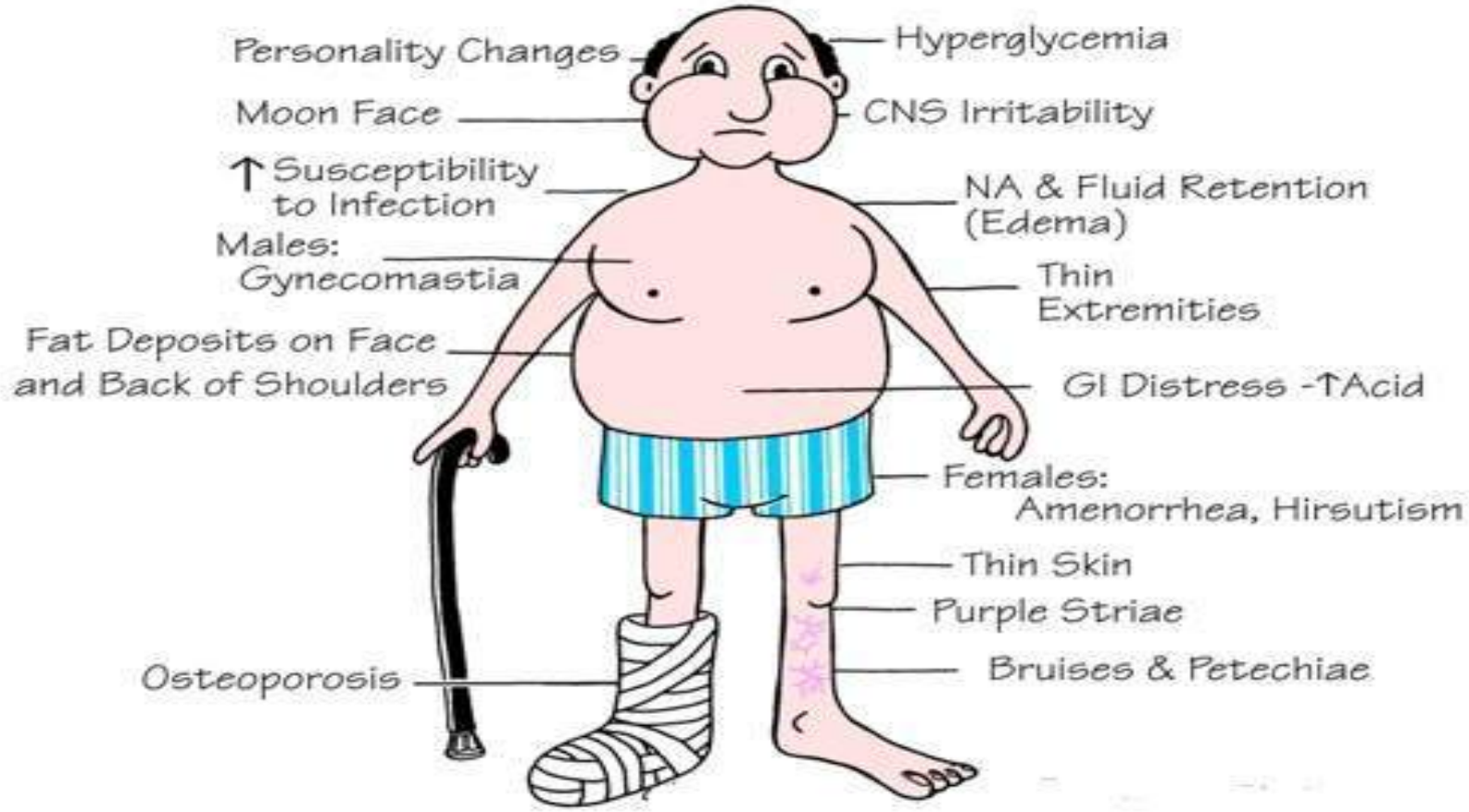
Skin thinnin



Fragile skin

Red skin syndrome – Topical steroid use

CUSHING'S SYNDROME



Synthetic steroids

- **Intermediate and long acting:**
- **Prednisone, prednisolone**
- **Methylprednisolone**
- **Triamcinolone**
- **Dexamethasone**
- **Betamethasone**

Synthetic steroids

- **NEWER**
- **Clobetasone, clobetasol**
- **Fluticasone,flunisolide,fluocinolone**
- **Mometasone**
- **Beclomethasone dipropionate**
- **Budesonide**

Advantages of synthetic steroids

- √ ↑ **More potent**
- √ **Longer acting**
- √ ↑ **glucocorticoid activity**
- √ ↓ **mineralocorticoid activity**
- √ ↓ **suppression of HPA axis**
- √ **LOCAL USES**

[minimal systemic adverse effects]

Newer synthetic steroids -indications

- skin dieases (applied locally) or

- chronic bronchial asthma (by inhalation)

- allergic rhinitis/conjunctivitis (avoiding systemic toxicity)

- intraarticular injection (joint)

Newer synthetic steroids –application 1

- **SKIN DISEASES: Creams, Ointments Betamethasone, Dexamethasone, Fluocinolone, Clobetasol, Beclomethasone**
- **Atopic eczema**
- **Contact dermatitis**
- **Lichen planus**
- **Lichen simplex**
- **Allergic dermatitis, and other….**

application2

- **Severe chronic asthma**
- **Beclomethasone dipropionate, Budesonide**
- **Inhalation**
- **To reduce bronchial hyper-reactivity**

- **Throat irritation, hoarseness**
- **Oral / oropharyngeal candidiasis: Nystatin…**

Application 3

- **Allergic rhinitis**
  - **Intranasal sprays**
  - **Beclomethasone dipropionate**
  - **50-100 mcg bid**
  - **Budesonide 200-400 mcg bid**

Glucocorticoids (systemic) -Indications-1 muhs SAQ

LIFE SAVING INDICATIONS

- **Anaphylactic shock,**
- **Status asthmaticus**
- **Circulatory collapse**
- **Acute adrenal insufficiency**
- **Acute necrotizing vasculitis**
- **Acute hypercalcemia**
- **Cerebral edema**
- **Septic shock, acute respiratory distress syndrome**
- **Water intoxication, central hyperthermia**

Indications 2 **Replacement therapy**

- **1)Acute adrenal insufficiency**
- **Hydrocortisone 100 mg IV → iv infusion 100 q 2h, then 50-100 mg q 6h for 2-3 days**
- **NaCl - 0.9% - fluid replacement**
- **Treatment and prevention of infection**
- **Fluodrocortisone - 50 mcg qd**
- 2)Addison's disease
- **Hydrocortisone 15-25 mg qd PO**
- **Fluodrocortisone 50-100 mcg qd po**
- **3)congenital adrenal hyperplasia**

Indications 3. **PHARMACOTHERAPY**

1. **Arthritides**- Rheumatoid arthritis, osteoarthritis, gout, rheumatic fever.
2. **Collagen diseases**- SLE, PAN, dermatomyositis.
3. **Allergic disorders-** Anaphylaxis, urticaria, angioneurotic edema, serum sickness.

Indications 4

- **PHARMACOTHERAPY.. Continued..**

4. **Autoimmune disorders-** AIHA, ITP, chronic active hepatitis, myasthenia gravis, nephrotic syndrome, lepra reactions
5. **Bronchial Asthma-** Status, chronic.
6. **Malignancies-** ALL, Hodgkin, other lymphomas……

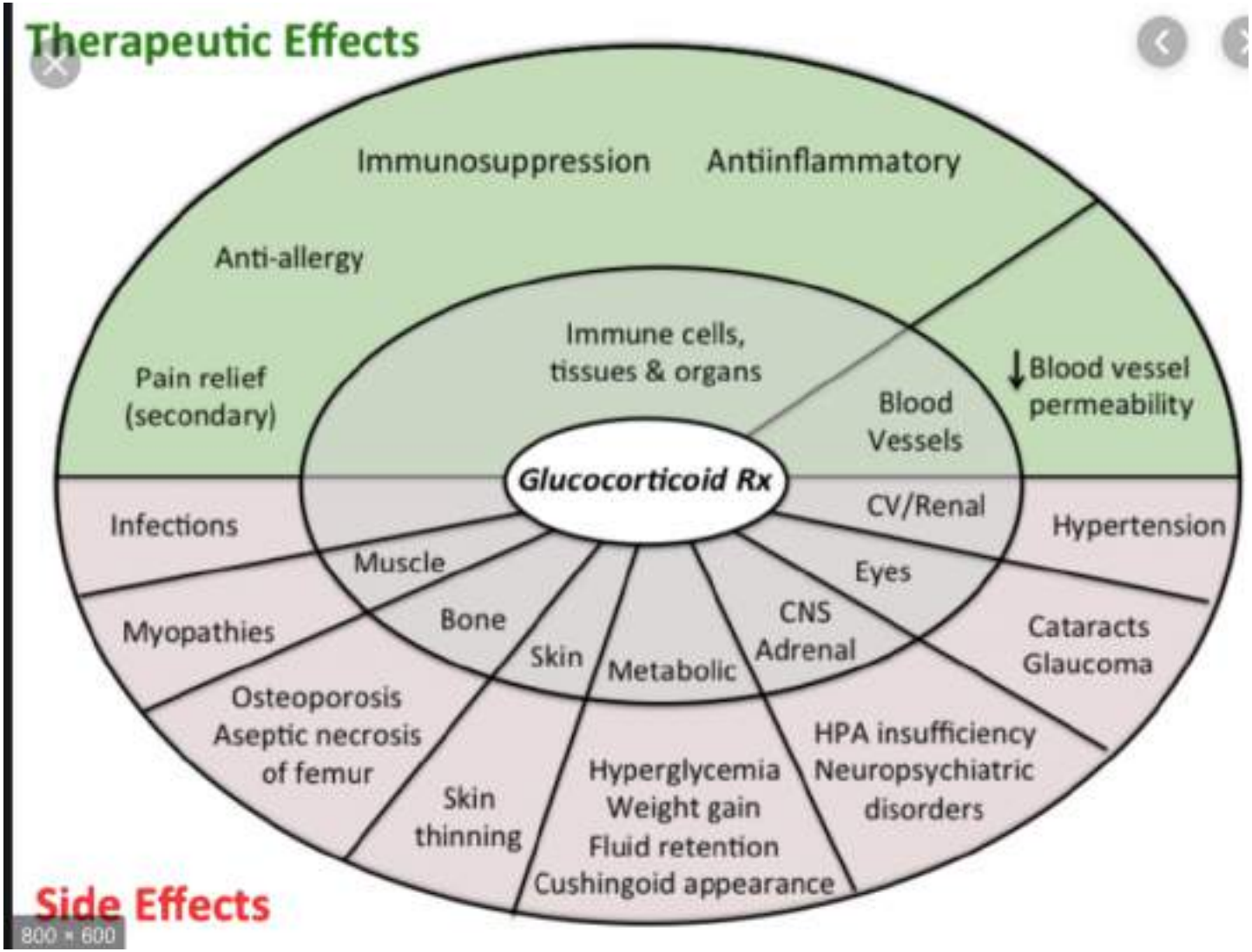
Indications 5

- **PHARMACOTHERAPY.. Continued..**

7. **Organ transplantation:** To prevent graft rejection.
8. **Shock** (circulatory collapse)
9. **Cerebral edema**
10. **Diseases of lungs, intestine, eye, skin**

Lung maturity to prevent RDS for premature labour

11. **Thyroid storm –to prevent peripheral T4 to T3 conversion**
12. **Congenital adrenal hyperplasia: to decrease the production of adrenal androgens**


Therapeutic Effects
Immunosuppression
Antiinflammatory
Anti-allergy
Pain relief
(secondary)
Immune cells,
tissues & organs
Blood vessel
permeability
Blood
Vessels
Glucocorticoid Rx
Infections
CV/Renal
Hypertension
Muscle
Eyes
Myopathies
Bone
CNS
Adrenal
Cataracts
Glaucoma
Skin
Metabolic
Osteoporosis
Aseptic necrosis
of femur
HPA insufficiency
Neuropsychiatric
disorders
Skin
thinning
Hyperglycemia
Weight gain
Fluid retention
Cushingoid appearance
Side Effects
800 × 600

Contraindications

-Diabetes mellitus
-Peptic ulcer
-Epilepsy
-Glaucoma
-CHF
-Hypertension
-Osteoporosis
-Psychosis
-Pregnancy
-Severe renal dysfunction
-Tuberculosis/Active infections
-Immunodeficiency
-Cerebral malaria
-Herpes simplex keratitis…

As steroids are life saving drugs these are termed as relative contraindications

ADR SAQ/LAQ

Mineralocorticoids-sodium and water retention oedema hypokalemic alkalosis and hypertension

Glucocorticoids—

1 cushing's disorder- truncal obesity and thin limbs moon face buffalo hump

2 fragile skin with purple striae hirsutism

3 Hyperglycaemia—precipitation of DM ,iatrogenic DM

4 muscle wasting ,proximal mayopathy

5 susceptibility to infection- to all pathogens ,latent TB flares ,fungal infections

6 delayed healing : wound and surgical incisions

7 peptic ulcer

ADR --

8 osteoporosis

9 Post subcapsular cataract

10 Glaucoma

11 Growth retardation

12 Intrauterine growth retardation

13 psychiatric disturbances

14HPA axis suppression –sudden stoppage

MUHS Q

- **LAQ**
- classification
- Pharmacological actions
- MOA
- ADR
- Therapeutic uses
- Lots of SAQs. MCQs **Viva**

Pharmacotherapy of DM
Part I
Insulin

Dr Pradnya Rotithor

Pancreatic Hormones

Islets of Langerhans -

Alpha cells glucagon

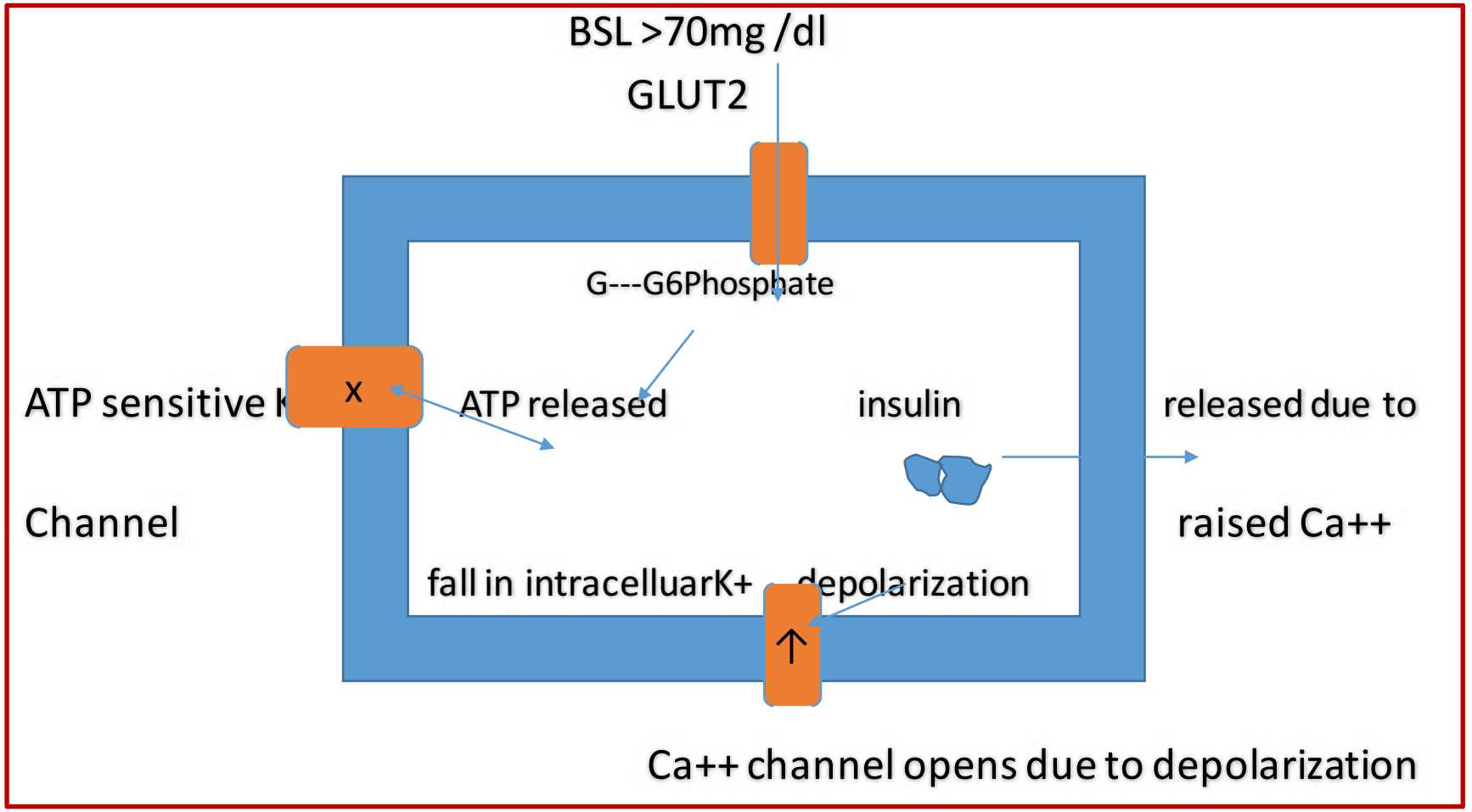
Beta cells insulin

Insulin and glucagon –opposite action on glucose

Delta cells somatostatin

P cells pancreatic polypeptides

Mechanism of insulin secretion from pancreas



Flow chart of insulin release from pancreas

Food intake –BSL>70MG/DL

↓

Enters through GLUT2 IN BETA cells

G →G6PO4 ATP is released in this process

↓

ATP blocks ATP sensitive K+ channel (MOA of OHA)

↓

Intracellular fall of K+ → membrane depolarization

↓

Opening of Ca++ channel → **intracellular high Ca++**

↓

Release of insulin from beta cells

BSL control by Insulin: liver muscle adipose tissue

•Liver

- Increases glucose uptake
- Promotes glycogen synthesis
- Inhibits glycogenolysis and glucose output
- Inhibits gluconeogenesis from Amino acids FFA pyruvate

•Muscle

- Increases glucose uptake and utilization
- Inhibits protein breakdown and release of AA lactate pyruvate

•Adipose tissue

- Increases glucose uptake and storage as fat and glycogen
- Inhibits lipolysis and release of FFA and glycerol
- Thus prevents gluconeogenesis substrates for liver

Effects of insulin deficiency

Decreased peripheral utilization of glucose

Decreased production of ATP

Decreased synthesis of glycogen in liver and muscle

Increased protein catabolism and neoglucogenesis

Increased lipolysis with raised FFA

Increased neoglucogenesis and raised hepatic glucose output

Increased ketogenesis

Depressed cell mediated immunity-CMI

Diabetes Mellitus

Metabolic disorder

Affects metabolism of carbohydrates lipids and proteins

Affecting almost all organs

Characterized by ---raised BLOOD GLUCOSE

raised glycosylated haemoglobin

Accumulation of glycosylated proteins and sorbitol in tissues and consistent high glucose leads to tissue/organ damage

HbA1c= index of protein glycosylation

(Sorbitol=reduced product of glucose)

Microcirculation adverse effects due to premature atherosclerosis and peripheral vascular insufficiency: root cause of most pathology

More frequently affected systems :

kidneys liver retina peripheral nerves

	Fasting BSL Mg/dl	**PP Mg/dl**	**HbA1C %**	**Random BSL Mg/dl**
normal	<100	<140	<5.7	
Pre diabetic	100 TO 125	140 TO 199	5.7 TO 6.4	
Diabetic ---------- Values for	126 OR more ---------- Gestational	200 or more ---------- DM are	6.5 or higher ---------- Lower in	>200 ---------- Each group

How to diagnose?

American Diabetes Association guidelines for diagnosis of DM

1)FPG >126mg/dl fasting for 8 hours

2)2 hour PP BSL > 200mg/dl
during OGTT -75 Gm anhydrous glucose dissolved in water

3)HbA1C > 6.5%

4)In a patient with classic symptom of hyperglycaemia random BSL >200mg/dl

5)For gestational DM all the parameters are set lower for strict control

Classification by ADA

Four types –I II more common

Type I Insulin dependent diabetes mellitus/early onset/juvenile --- **IDDM**

Type II noninsulin dependent/maturity onset diabetes mellitus **NIDDM**

Type III—due to other aetiology (pancreatic removal /drug induced)

Type IV –gestational diabetes mellitus

Type I--IDDM

Insulin dependent diabetes mellitus/early onset/juvenile ---**IDDM**

IA = beta cell destruction –autoimmune ,anti beta cell antibody found

IB = idiopathic

Circulating insulin =low **more prone for ketoacidosis**

Low degree of genetic predisposition

Incidence =10%

Treatment=insulin

Oral drugs ineffective

Type II

noninsulin dependent/maturity onset diabetes mellitus
NIDDM

No circulating ab found less prone for ketoacidosis

Circulating insulin =nml/low/high

Beta cell deficiency/insulin resistance

High degree of genetic predisposition

Incidence =90%

Treatment =insulin/oral drugs

Drug therapy

Oral hypo glycaemic agents

- **Type II DM**
- **Uncomplicated DM**
- **Age above 35**
- **Obese patients**

insulin

- **Type I DM**
- **Failure of oral therapy**
- **Gestational DM**
- **young age DM**
- **During complications of DM ketoacidosis/hyperglycemic or hyperosmolar coma**
- **Other complications : gangrene**
- **Surgery /trauma**

MOA OF INSULIN :
Insulin receptor -Enzyme linked R

Consists of two subunits alpha and beta

Insulin binds to alpha subunit and stimulates --

–tyrosine kinase in Beta subunit

→phosphorylation of tyrosine residues → IRS (insulin receptor series)activation of PIP3 kinase → Production and Translocation of ATP dependent glucose transporters – GLUT 4, 1 →

→ glucose transport, uptake →

Insertion of glucose transport molecules in the cell walls

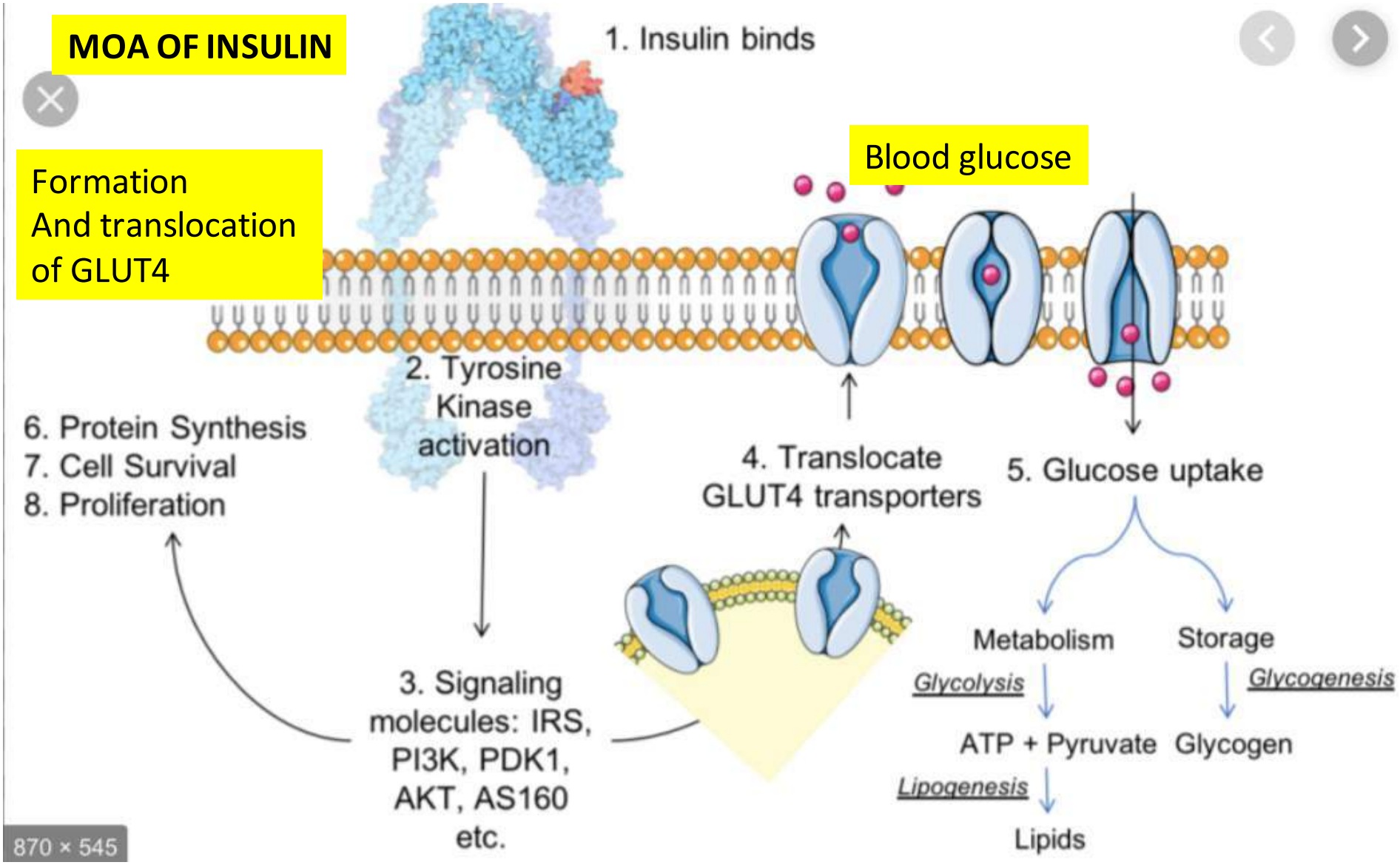
Uptake and utilization of glucose

All cells - Major target organs –

Liver , skeletal muscle, adipose tissue

MOA OF INSULIN

Formation
And translocation
of GLUT4



Actions of insulin LAQ

First write MOA in brief

Carbohydrates : Stimulates glycogen synthetase – [glucose → glycogen] and storage and inhibits glucose production

↓ glycogenolysis, ↓ gluconeogenesis

Fat: ↓ lipolysis (anti-lipolytic action) in adipose tissue, inhibits conversion of fat in to carbohydrates

Protein: ↑ amino acid . entry in to cells ---

↑ ↑ protein synthesis

↓ protein catabolism

Other actions of insulin

- Vasodilator
- Fibrinolysis
- Linear growth
- Steroidogenesis
- Anti inflammatory action –especially in vasculature

Insulin ADR SAQ

1. **Hypoglycemia.** Most common ADR

Factors precipitating hypoglycemia:

-missed meal

-inadvertent high dosage of insulin

- More exercise, exertion

Children, old patients

Patients with renal damage

How to minimise/prevent

Don't miss a meal

Do controlled exercise

Use correct dosing

understand early signs and symptoms of hypoglycemia

Always Carry glucose

Signs and symptoms of hypoglycemia

Sweating	tachycardia
Lip/tongue tingling,	hunger
anxiety	tremors
Confusion	lethargy,
difficulty in concentrating	
Drowsiness	vertigo
coma	seizures

Treatment of hypoglycemia

1)Oral glucose

2) 25 or 50% glucose IV 20-50 ml

Or IV Drip of Dextrose

3)Glucagon injection 0.5-1 mg IV / 1 mg SC OR IM /Inhalation

4)IV dexamethasone(prevents cerebral edema), Epinephrine 0.2 mg sc

Immunological adverse effects

insulin antibodies –allergic reactions

Human insulin is less antigenic

Resistance: > 200 units/day

Decreased receptor number/sensitivity

Resistance - less with human insulin

Local reactions and other A/E

Lipodystrophy- hypertrophy or lipoatrophy: subcutaneous fat

Much less with newer insulins

Presbyopia

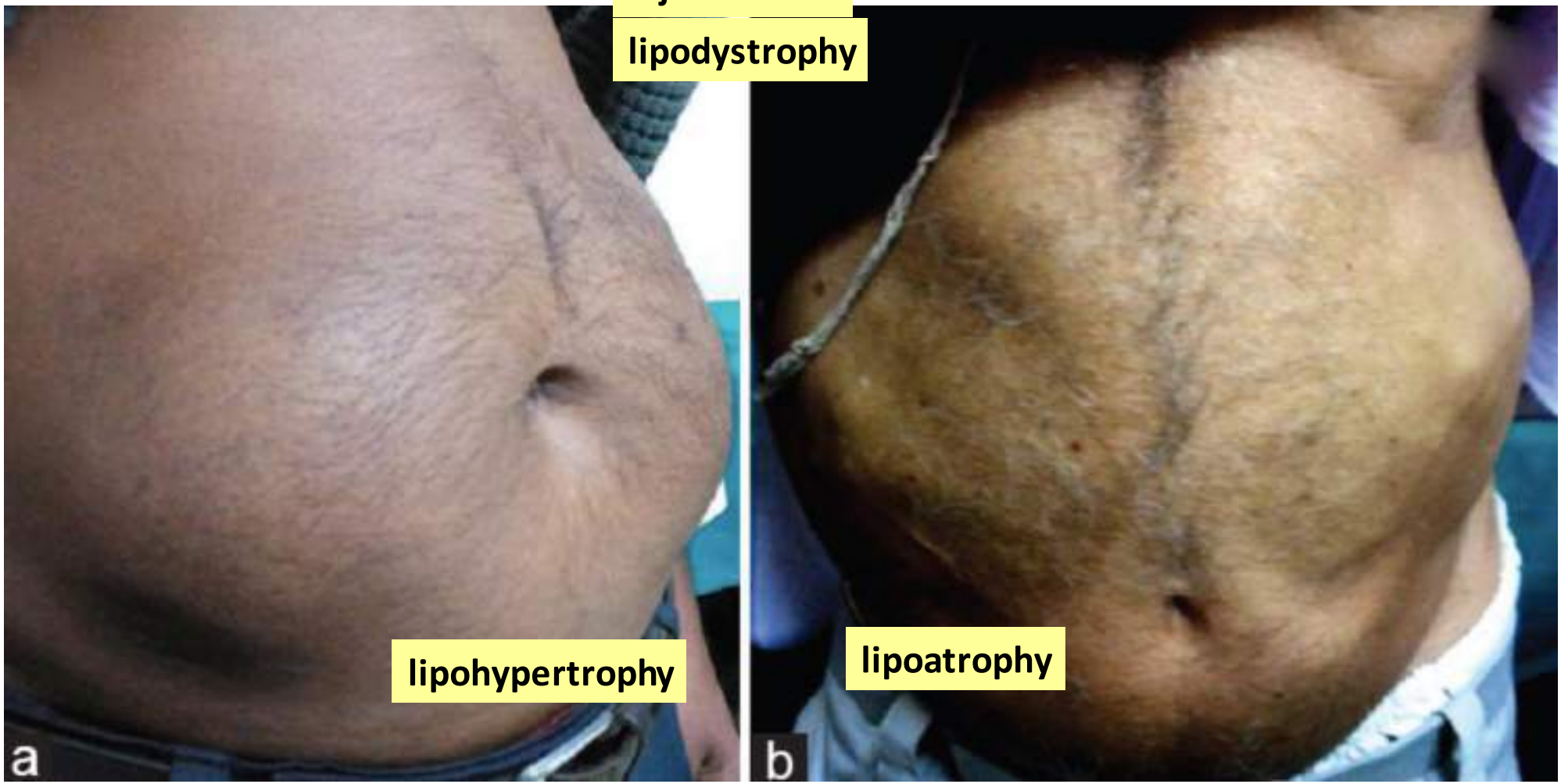
Neuropathy

Weight gain, edema

Local injection site reactions

Disturbed sleep, morning headaches

Injection site lipodystrophy



Drug interactions

Beta blockers → hypoglycemia unresponsiveness MCQ

Beta blockers prolong hypoglycemia by inhibiting compensatory mechanisms operated through beta adrenergic receptors

Warning signals of hypoglycemia such as palpitation Tremors anxiety are masked

Unopposed action on alpha R by released Adrenaline leads to rise in BP

Other Drug interactions

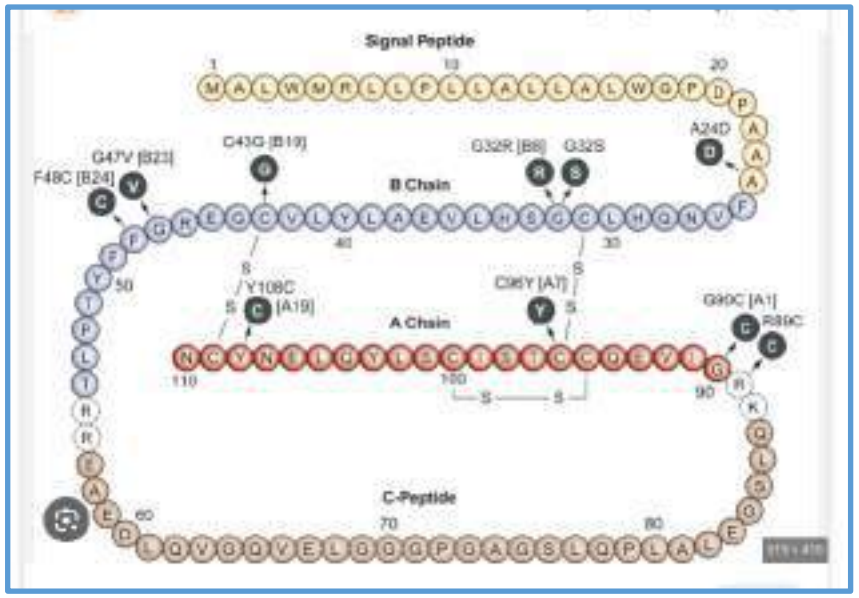
Thiazides, loop diuretics, corticosteroids, OCP salbutamol nifedipine→ Increase blood sugar → opposite effect

High dose aspirin lithium theophylline →hypoglycaemia

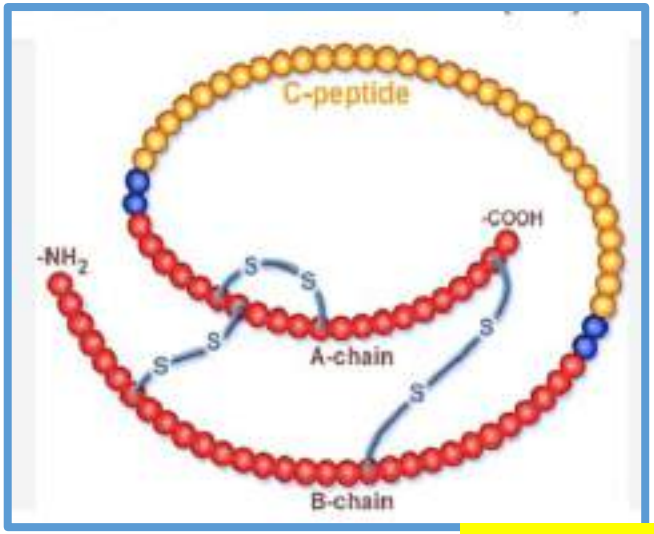
Acute alcohol ingestion - hypoglycemia

Stages of insulin production and structure

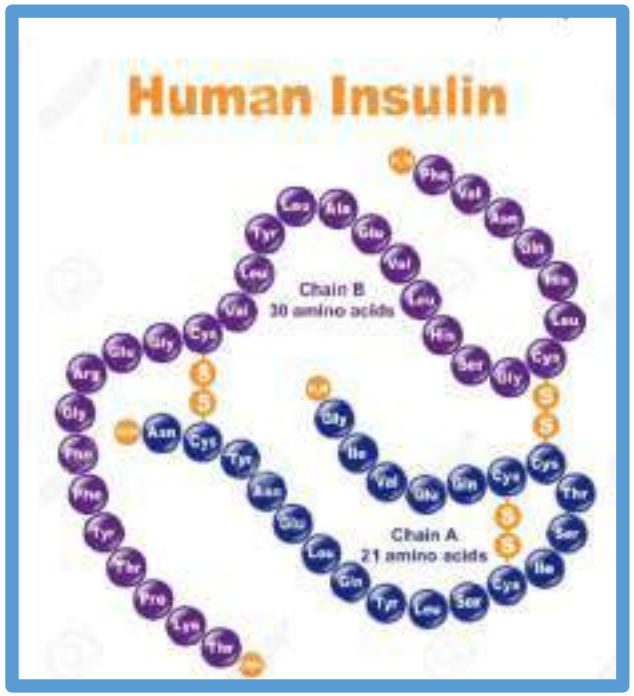
- Preproinsulin – 4 parts alpha chain beta chain connector peptide and signal peptide
- Proinsulin – 3 parts alpha chain beta chain connector peptide
- Insulin- 2 parts alpha chain beta chain with disulfide bonds
- Alpha chain- 21 amino acids
- Beta chain - 30 amino acids
- Modification in sequence of amino acids yields different varieties of insulin
- Addition of zinc and protamin makes it longer acting



preproinsulin



proinsulin



Production of human insulin

By genetic engineering

Human beta cell DNA -extracted

Incorporated – E coli or yeast nucleus

Start producing insulin –exactly matching with human insulin

Later from these rapidly multiplying E coli or yeast large amount of human insulin is extracted

non antigenic

Insulin preparations

Older

Source : Animal

More antigenic

Impure/less pure

Less stable

Less potent

More allergic reactions

High dose requirement

More pH incompatibility

More lipodystrophy

Hardly used currently

Newer

Source: animal human and recombinant

Less antigenic

More pure

More stable

More potent, better BSL control

Less allergic

Less dose requirement

Less pH incompatibility

Less lipodystrophy

Progress of insulin production-
first isolated by Benting and Best in 1921

1)Older(conventional) insulins –beef and pork pancreas

potentially antigenic pork is more close to human

No more used/manufactured

---

2)highly purified pork/beef insulin monocomponent (MC)

stable less resistance less lipodystrophy

Immunogenicity of pork MC insulin = recombinant human insulin less or not used now

---

3)recombinant human insulin

4) insulin analogues

3 and 4 are currently in use

Human insulin and analogues

- Standard recombinant human insulin

➢ **Insulin analogues –same as human insulin but sequence of amino acids is different**

➢ **These are termed as designer insulin**

- **To make retard preparations insulin is complexed with protamine or excess zinc**

- **Absorption –fastest from abdominal wall**
- **less rapid –arm**
- **slowest –thigh**
- ***Rate of absorption of v rapid insulin is independent of site of injection***

Methods of modification

Ultra rapid acting **Lispro, Aspart, Glulisine**

1----------21 alpha chain

1----------28—29 --30 beta chain

pro lys this sequence in interchanged –lispro

1----------21 alpha chain

1----------28— --30 beta chain

proline replaced by aspartic acid Aspart

1----------21 alpha chain

1----------23--------—29 --30 beta chain Glulisine

Lysine replaces aspargine at B23 and glutamic acid replaces lysine at B29

By making these changes hexamer of insulin becomes weak and acts faster

-control post prandial sugar better

Modification to get long acting insulin

Glarglin-

1---------21 alpha chain –at 21 glycin replaces aspargine

1----------------30 beta chain. 2 additional arginine -32 beta chain

Detimir addition of fatty acid at B29 (lysine)

Degludec longest acting insulin preparation

These modifications make hexamer dissolve slowly making them long acting

Long acting insulin controls basal sugar

classification

1)Older(conventional) beef pork –not used

2) 2)highly purified pork/beef insulin monocomponent (MC) not used

3)recombinant human insulin

4) insulin analogues

3 and 4 are currently in use

Regular insulin is modified to get analogues by changing sequence of amino acids –ultra short acting

Regular insulin is modified by adding amino or fatty acids to get analogues –long acting

Regular insulin contains small amt of zinc

By adding more zinc or protamin intermediate acting insulin is obtained

final Classification

1)Ultra short acting – **Lispro, aspart, glulisine** monomers

2)Short acting – **regular insulin** –soluble only iv preparation
hexamer with small amount of zinc

3)intermediate acting –

a)insulin zinc suspension **lente insulin** –ultralente+semilente 7:3
hexamer with more amount of zinc

b) insulin + protamin –Neutral Protamine Hagedorn –**NPH (isophane)**
protamine added instead of zinc

4) Long acting –**glargine detemir degludec**

1 and 4 are analogues

2 and 3 are standard

MCQ

Shortest or most rapidly acting insulin- Aspart

Longest acting insulin –degludec

Only iv insulin/emergency use/used in pregnancy – regular insulin

Insulin with acidic pH and can not be mixed with other insulin -glargine

Classification of Insulin Preparations

Insulin Preparation	Hours after Subcutaneous Administration		
	Onset	Peak	Duration (h)
Very rapid–acting			
Lispro	5–15 min	45–75 min	2–4
Insulin aspart	5–15 min	45–75 min	2–4
Glulisine	5–15 min	45–75 min	2–4
Rapid-acting			
Regular	30 min	2–4 h	6–8
Intermediate-acting			
NPH	2 h	4–12 h	18–28
Long-acting			
Detemir	2 h	3–9 h	6–24
Glargine	1.5 h	None	20–>24
Ultra long-acting			
Degludec	2 h	None	>40

Time of administration

Ultra short acting 5 min before each meal

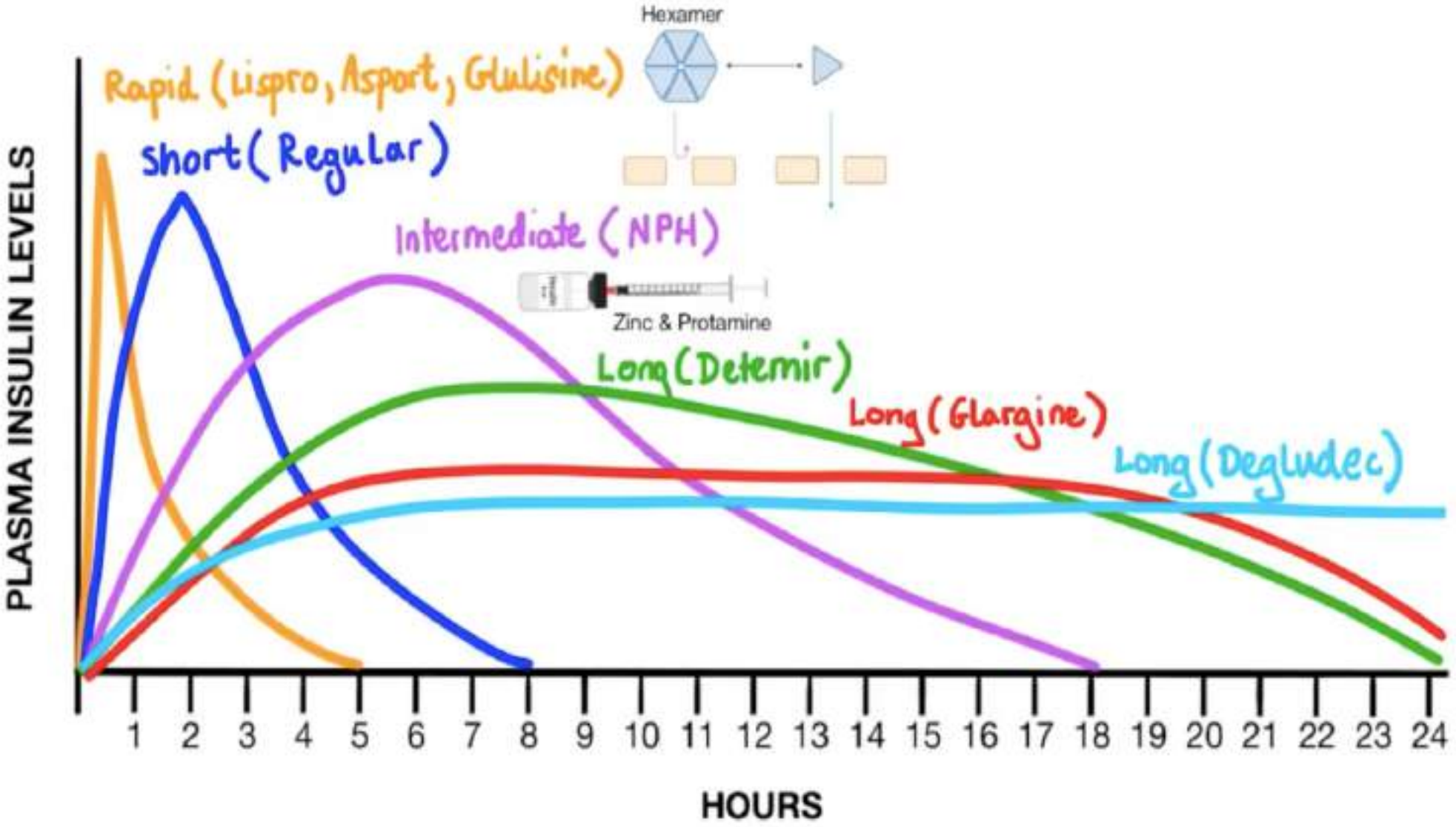
Short acting –half hour before meals

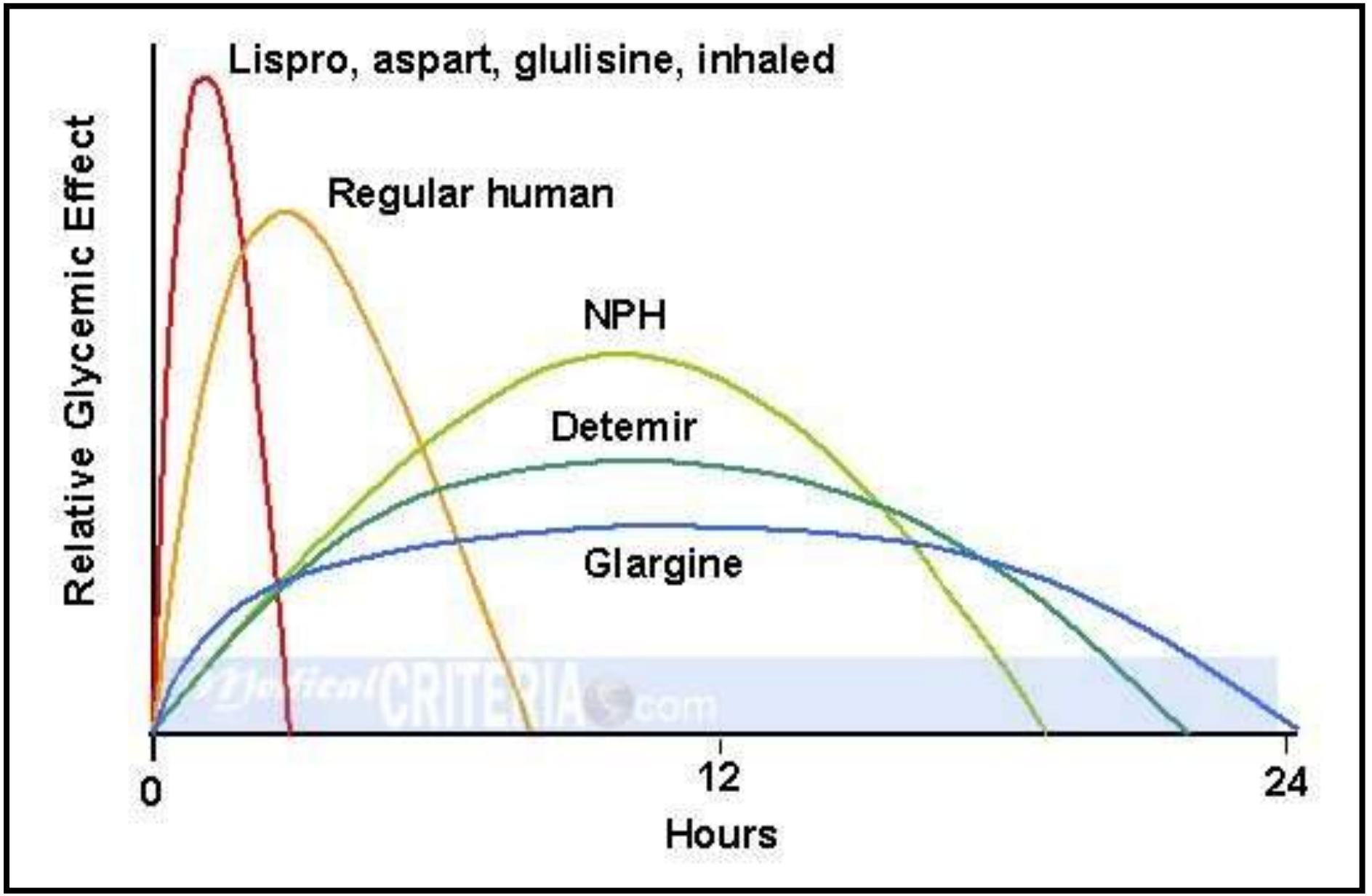
Long acting –once a day but at the same time every day

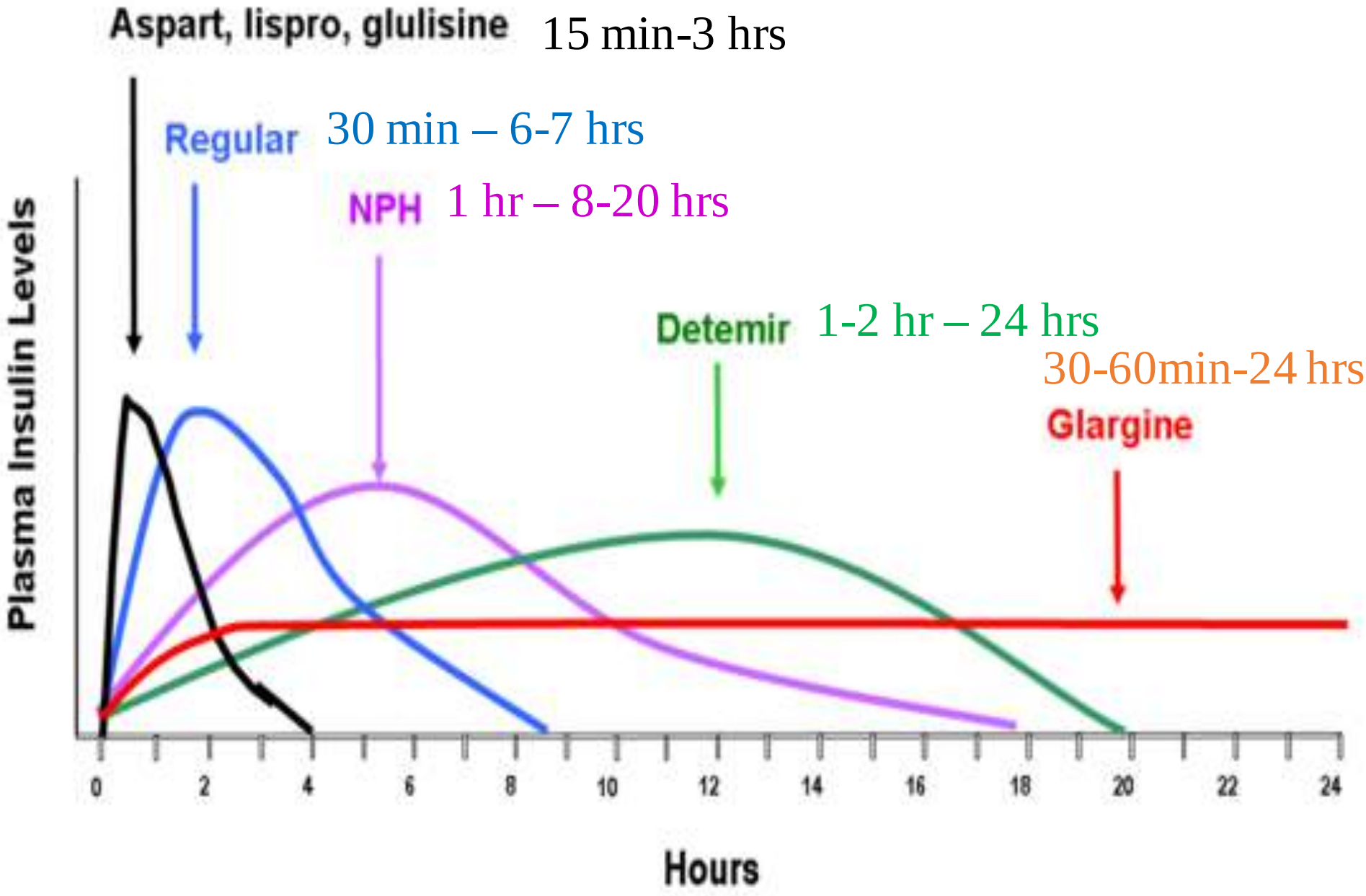
(every 24 hours)

OR

(every 12 hours)


Hexamer
Rapid (Lispro, Aspart, Glulisine)
Short (Regular)
Intermediate (NPH)
Zinc & Protamine
Long (Determir)
Long (Glargine)
Long (Degludec)
PLASMA INSULIN LEVELS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
HOURS


Lispro, aspart, glulisine, inhaled
Regular human
NPH
Detemir
Glargine
Relative Glycemic Effect
0
12
24
Hours


Aspart, lispro, glulisine
15 min-3 hrs
Regular
30 min – 6-7 hrs
NPH
1 hr – 8-20 hrs
Detemir
1-2 hr – 24 hrs
30-60min-24 hrs
Glargine
Plasma Insulin Levels
0
2
4
6
8
10
12
14
16
18
20
22
24
Hours

Newer insulin delivery devices

SC : conventional disposable needle-syringe

Newer systems):-expensive but convenient

Prefilled disposable syringes containing specific type of insulin

Portable pen-sized injectors- with insulin cartridges

Continuous SC insulin infusion devices—implantable pumps

Programmable pumps- constant 24-hour basal rate

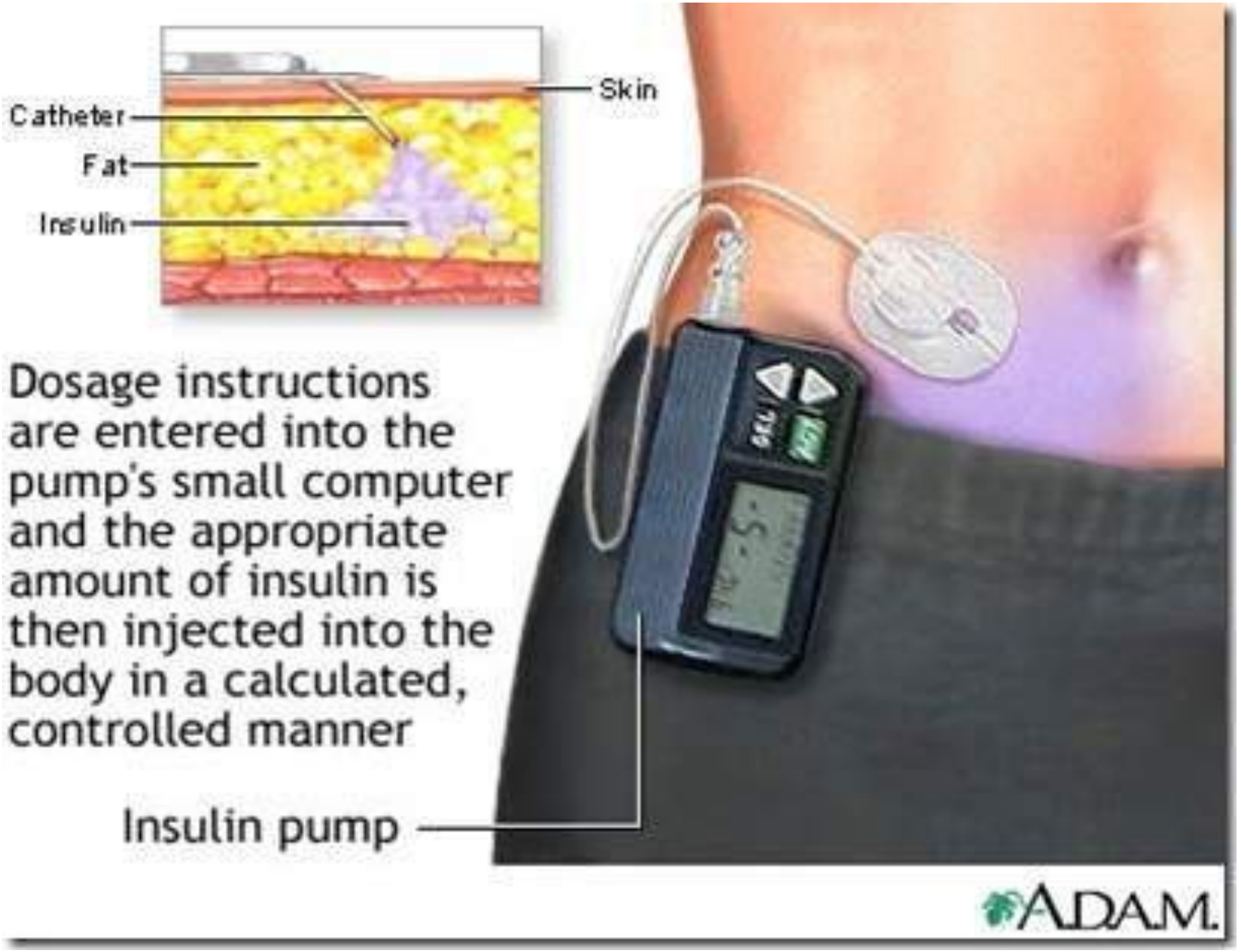
Inhaled/buccal spray/oral insulin/intraperitoneal -future

Cut-section view of skin

Insulin pen injector

Insulin jet injector

A.D.A.M.


Skin
Catheter
Fat
Insulin
Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner
Insulin pump
A.D.A.M.

Mixed insulin preparations

- Intermediate + Short/ Rapid
  - NPH + regular (Premixed available)
  - NPH + insulin lispro
  - NPH + insulin aspart
- You can mix in same syringe
- Premixed are also available only for NPH + regular
- Protamine + Insulin lispro -> NPL
- Protamine + Insulin aspart-> NPA
- Long acting should not be mixed

Take home advice

Types of insulin preparations

Vary in onset and duration of action:

1.Ultrashort acting insulins e.g. Lispro, aspart

very fast onset and short duration

2. Short acting insulins (Regular)e.g.Humulin R

fast onset and short duration.

3. Intermediate acting insulin e.g. NPH, lente

slow onset and relative long duration.

4. Long acting e.g. glargine, detemir

slow onset and long duration.

Pharmacotherapy of DM

Oral Hypoglycamic agents

OHA

Dr Pradnya Rotithor

Pancreatic Hormones

Islets of Langerhans contains -

Alpha cells glucagon

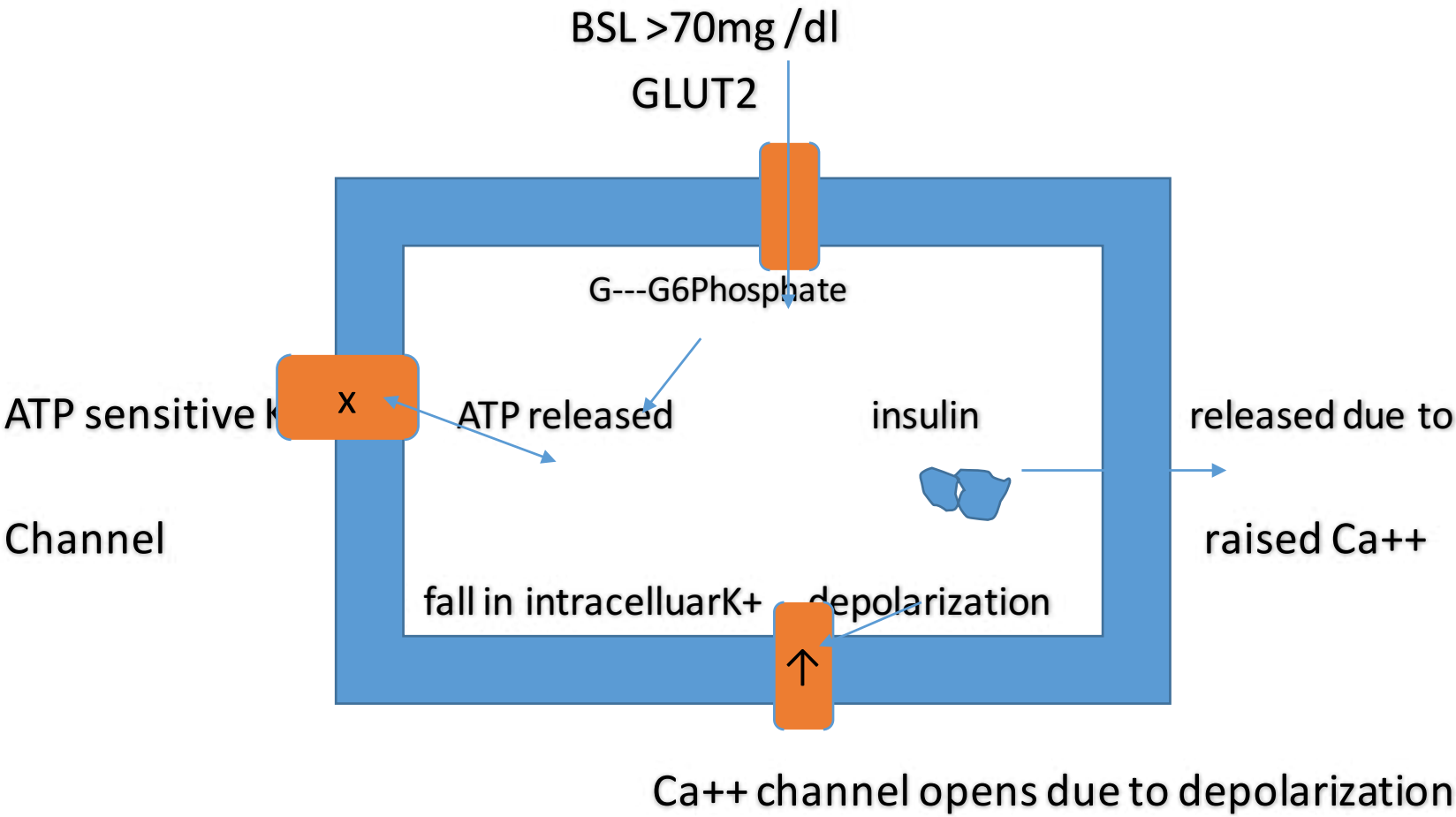
Beta cells insulin

Insulin and glucagon –opposite action on glucose

Delta cells somatostatin

P cells pancreatic polypeptides

Mechanism of insulin secretion from pancreas



Flow chart of insulin release from pancreas

Food intake –BSL>70MG/DL

↓

Enters through GLUT2 IN BETA cells

G →G6PO4 ATP is released in this process

↓

ATP blocks ATP sensitive K+ channel (MOA of OHA)

↓

Intracellular fall of K+ → membrane depolarization

↓

Opening of Ca++ channel → **intracellular high Ca++**

↓

Release of insulin from beta cells

BSL control by Insulin: liver muscle adipose tissue

•Liver

- Increases glucose uptake
- Promotes glycogen synthesis
- Inhibits glycogenolysis and glucose output
- Inhibits gluconeogenesis from Amino acids FFA pyruvate

•Muscle

- Increases glucose uptake and utilization
- Inhibits protein breakdown and release of AA lactate pyruvate

•Adipose tissue

- Increases glucose uptake and storage as fat and glycogen
- Inhibits lipolysis and release of FFA and glycerol
- Thus prevents gluconeogenesis substrates for liver

Effects of insulin deficiency

Decreased peripheral utilization of glucose

Decreased production of ATP

Decreased synthesis of glycogen in liver and muscle

Increased protein catabolism and neoglucogenesis

Increased lipolysis with raised FFA

Increased neoglucogenesis and raised hepatic glucose output

Increased ketogenesis

Depressed cell mediated immunity-CMI

Diabetes Mellitus

Metabolic disorder

Affects metabolism of carbohydrates lipids and proteins

Affecting almost all organs

Characterized by ---raised BLOOD GLUCOSE

raised glycosylated haemoglobin

Accumulation of glycosylated proteins and sorbitol in tissues and consistent high glucose leads to tissue/organ damage

HbA1c= index of protein glycosylation

(Sorbitol=reduced product of glucose)

Microcirculation adverse effects due to premature atherosclerosis and peripheral vascular insufficiency: root cause of most pathology

More frequently affected systems :

kidneys liver retina peripheral nerves

	Fasting BSL Mg/dl	**PP Mg/dl**	**HbA1C %**	**Random BSL Mg/dl**
normal	<100	<140	<5.7	
Pre diabetic	100 TO 125	140 TO 199	5.7 TO 6.4	
Diabetic ---------- Values for	126 OR more ---------- Gestational	200 or more ---------- DM are	6.5 or higher ---------- Lower in	>200 ---------- Each group

How to diagnose?

American Diabetes Association guidelines for diagnosis of DM

1)FPG >126mg/dl fasting for 8 hours

2)2 hour PP BSL > 200mg/dl
during OGTT -75 Gm anhydrous glucose dissolved in water

3)HbA1C > 6.5%

4)In a patient with classic symptom of hyperglycaemia random BSL >200mg/dl

5)For gestational DM all the parameters are set lower for strict control

Classification by ADA

Four types –I II more common

Type I Insulin dependent diabetes mellitus/early onset/juvenile --- **IDDM**

Type II noninsulin dependent/maturity onset diabetes mellitus **NIDDM**

Type III—due to other aetiology (pancreatic removal /drug induced)

Type IV –gestational diabetes mellitus

Type I--IDDM

Insulin dependent diabetes mellitus/early onset/juvenile ---**IDDM**

IA = beta cell destruction –autoimmune ,anti beta cell antibody found

IB = idiopathic

Circulating insulin =low **more prone for ketoacidosis**

Low degree of genetic predisposition

Incidence =10%

Treatment=insulin

Oral drugs ineffective

Type II

noninsulin dependent/maturity onset diabetes mellitus
NIDDM

No circulating ab found less prone for ketoacidosis

Circulating insulin =nml/low/high

Beta cell deficiency/insulin resistance

High degree of genetic predisposition

Incidence =90%

Treatment =insulin/oral drugs

Drug therapy

Oral hypo glycaemic agents

- **Type II DM**
- **Uncomplicated DM**
- **Age above 35**
- **Obese patients**

insulin

- **Type I DM**
- **Failure of oral therapy**
- **Gestational DM**
- **young age DM**
- **During complications of DM ketoacidosis/hyperglycemic or hyperosmolar coma**
- **Other complications : gangrene**
- **Surgery /trauma**

How insulin is normally secreted and released from pancreas

- **Glucose is principal regulator of release as well as synthesis of insulin**
- **Others -Amino acids fatty acids ketones**
- Basal condition-1 U insulin/hr Much larger quantity after every meal
- **Mech of release** –
- Glucose enters beta cells thru GLUT1
- Phosporylated by glucokinase
- **ATP sensitive k+ ch are blocked**
- Leading to partial depolarization
- Which increases intracellular Ca++
- Leading to exocytosis of granules containing insulin –release of insulin
- **First phase** –within 2 min
- **Second phase** –delayed but more sustained release of insulin

Oral hypoglycaemic agents

--Stimulate insulin release

(insulin secretogogues)

(insulin releasers)

-- Increase receptor sensitivity

(insulin sensitizers)

--Other MOA

MOA by which drugs may act—
basis for classification

Insulin secretion and release from pancreas

Utilization by tissues is another component

more glucose uptake by tissues means less blood glucose

Thus drugs can act on ---promoting release from pancreas

promoting uptake by tissues

Few other MOA--

decrease absorption of dietary sugars from GIT which leads to less requirement of insulin

decrease glucagon secretion which causes hyperglycaemia

prevent renal tubular reabsorption of glucose

classification

Sulphonylureas k+ ch inhibitor
Meglitinides- nataglinide

Enhance insulin secretion

GLP1 R agonist liraglutide stimulate beta cells
Dpp 4 inhibitors sitagliptin prolong action of incretins

This group requires presence of functioning beta cells in the pancreas

---

Biguanides -metformin
Thiazolidineodiones-pioglitazone
This group does not act on beta cells

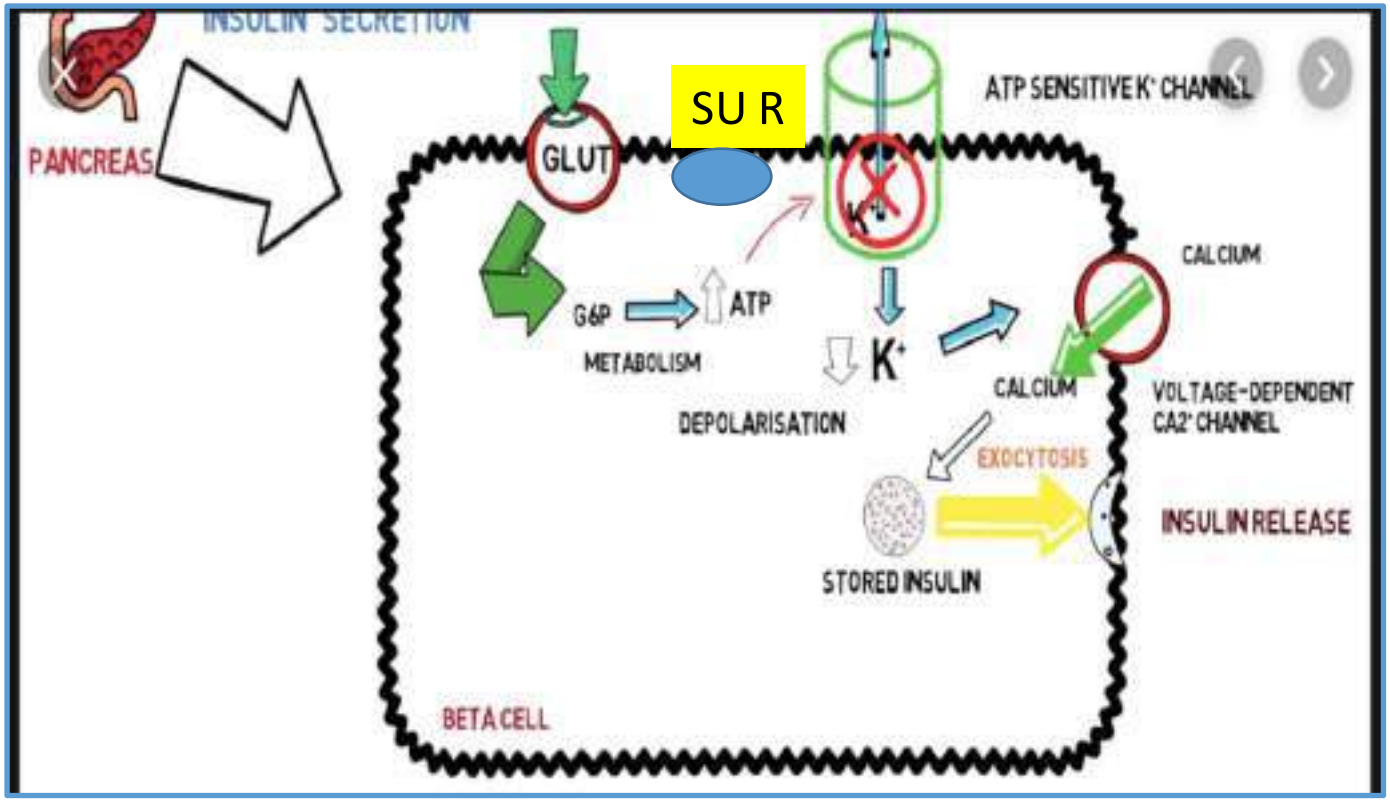
Overcome insulin resistance

Alpha glucosidase inhibitors— acarbose ✖ absorption of sugar from intestine
SGLT2 inhibitor- canagliflozine ✖ renal reabsorption of glucose

Amylin analogues-decrease glucagon secretion
D2 agonist -bromergocryptin

Oral antidiabetics-1. K ch inhibitor

Insulin secretogogues (releasers): {Pancreas} used in NONOBESE diabetics		
Sulfonylureas long acting Block ATP-sensitive K channels → ↑ Ca channels ↑ Insulin release	Gen I:not use now Chlorpropamide Tolbutamide GEN II: Glyburide Gliclazide Glipizide Glimeperide	HYPOGLYCEMIA WEIGHT GAIN Hepatic dysfunction Renal dysfunction Alcohol intolerance (Disulfiram-like reaction) Cholestatic jaundice
Meglitinides rapid onset, short action	Repaglinide, Nateglinide	Hypoglycemia Weight gain


INSULIN SECRETION
PANCREAS
GLUT
SU R
ATP SENSITIVE K+ CHANNEL
K+
CALCIUM
G6P
ATP
METABOLISM
K+
CALCIUM
VOLTAGE-DEPENDENT
CA2+ CHANNEL
DEPOLARISATION
EXOCYTOSIS
INSULIN RELEASE
STORED INSULIN
BETA CELL

MOA SU


GLUCOTROL XL
GLIPIZIDE GITS
5 mg
30 Tablets

Oral antidiabetics –1 stimulate beta cells

1. GLP-1 (glucagon-like-peptide) analogs

Incretin mimetics (Incretin=GLP1)

Bind to GLP1 R and stimulate glucose dependent insulin release from beta cells

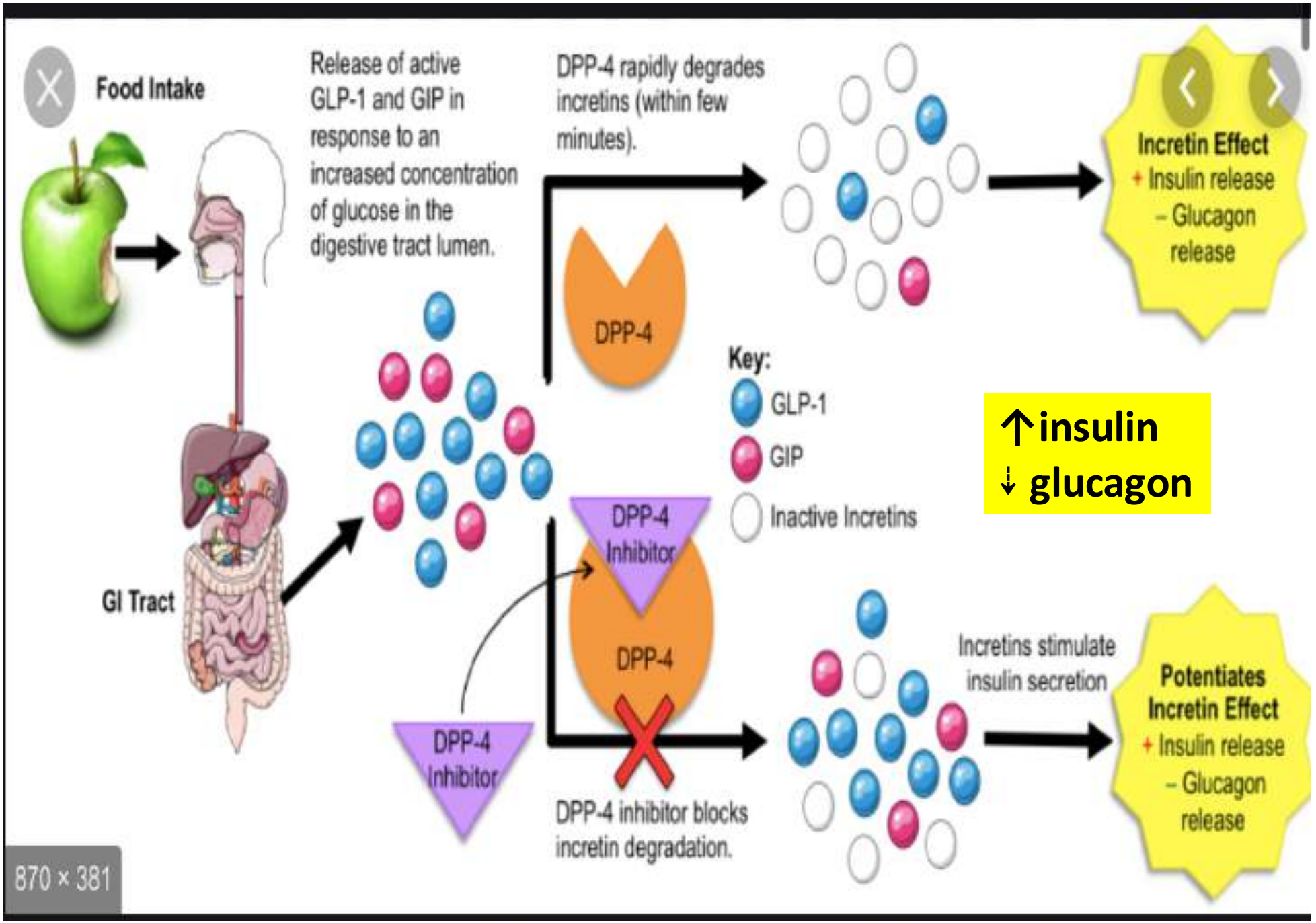
s/c inj

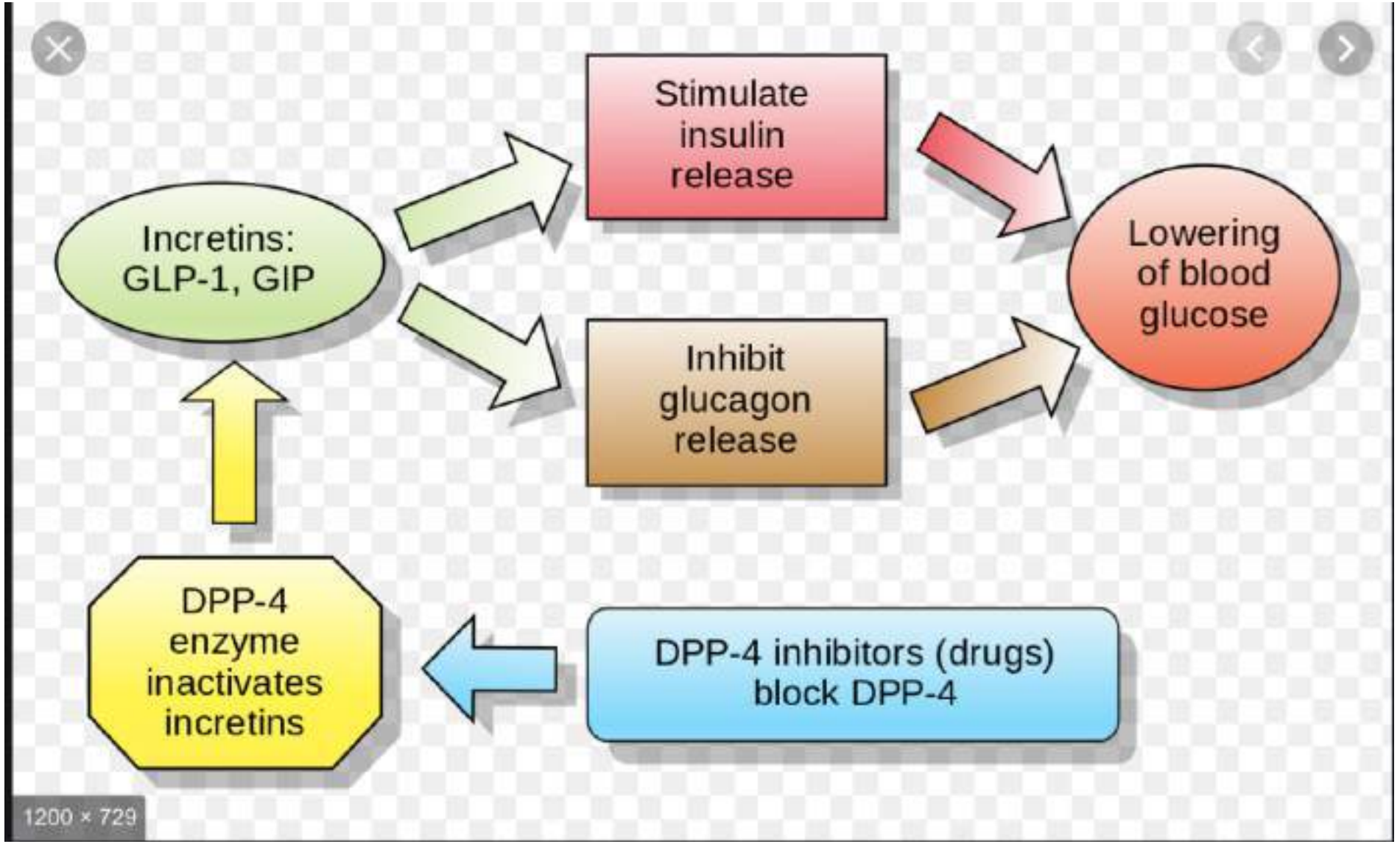
-Exenatide, Liraglutide

2. DPP-4 (DiPeptidyl Peptidase)inhibitors: oral

Block DPP4 that destroy incretins

-Gliptins: Sitagliptin, saxagliptin, vildagliptin

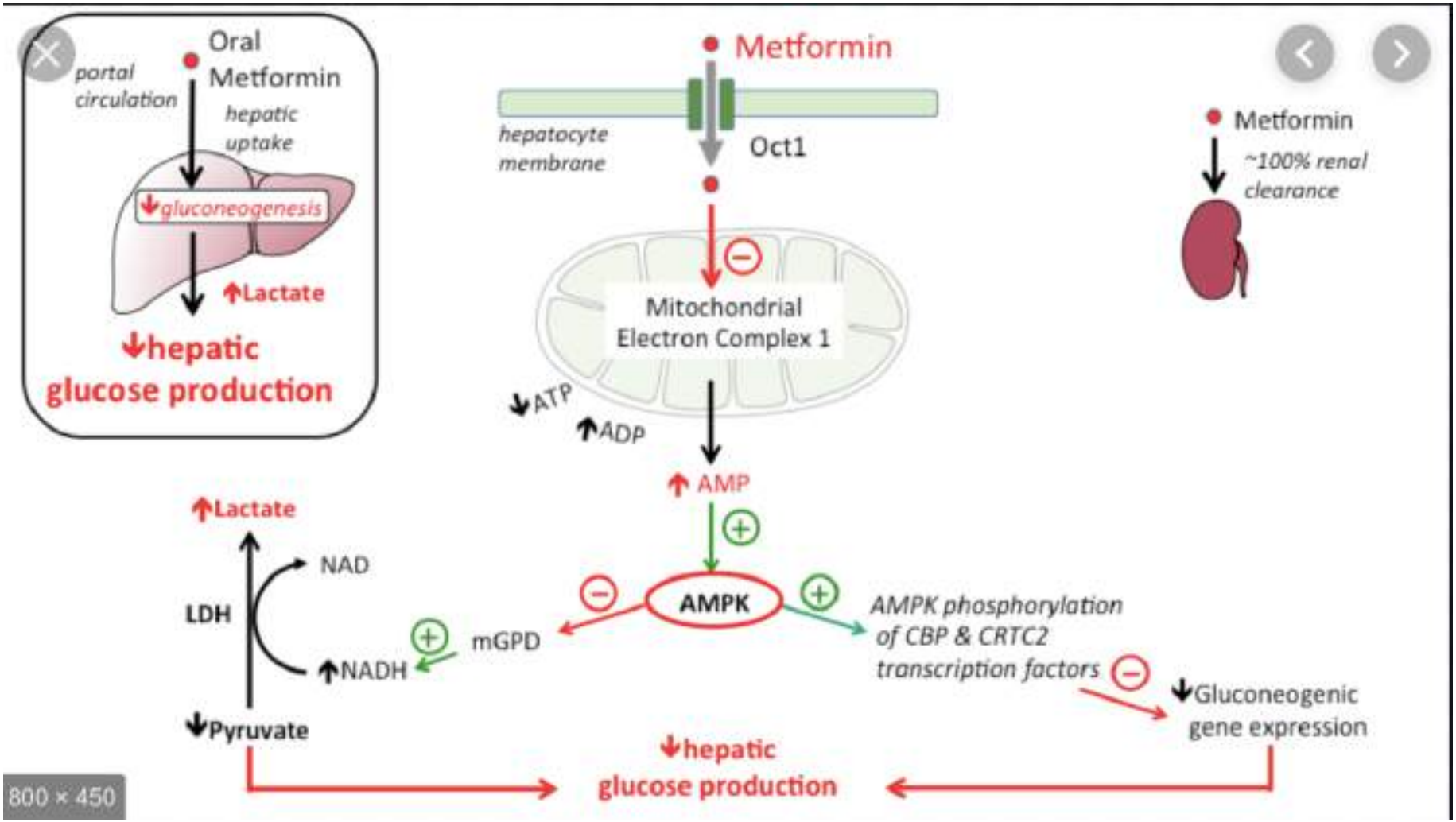

Food Intake
Release of active GLP-1 and GIP in response to an increased concentration of glucose in the digestive tract lumen.
DPP-4 rapidly degrades incretins (within few minutes).
Incretin Effect
+ Insulin release
– Glucagon release
DPP-4
Key:
GLP-1
GIP
Inactive Incretins
↑insulin
↓ glucagon
GI Tract
DPP-4 Inhibitor
DPP-4
DPP-4 Inhibitor
DPP-4 inhibitor blocks incretin degradation.
Incretins stimulate insulin secretion
Potentiates Incretin Effect
+ Insulin release
– Glucagon release
870 × 381


Stimulate insulin release
Incretins: GLP-1, GIP
Lowering of blood glucose
Inhibit glucagon release
DPP-4 enzyme inactivates incretins
DPP-4 inhibitors (drugs) block DPP-4
1200 × 729

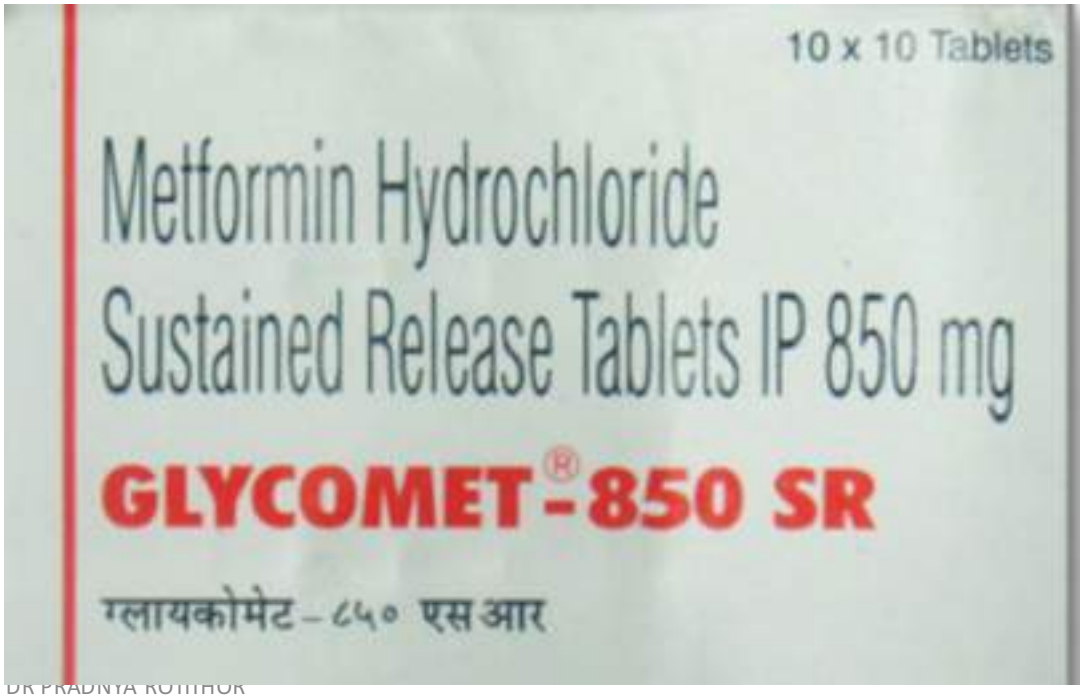
Oral antidiabetics-2. do not act on beta cells

Insulin sensitizers: {Liver, Tissues } **(called euglycemics)** **used in OBESE diabetics DOC**		
↓Gluconeogenesis ↓glucose prodⁿ activates AMP-activated Protein Kinase (AMPK) (hepatocytes), ↑insulin sensitivity ↑ glucose uptake	***Biguanides*** **Metformin** 500-3000 bd / tds SR also available	Anorexia, WT LOSS, Vit B12 deficiency Metallic taste Abdominal discomfort RARE lactic acidosis Liver/renal impairment

MOA OF METFORMIN



Also used in PCOD patients



Oral antidiabetics-2

Thiazolidinediones (Glitazones) **PPAR analogs**		
↓ Insulin resistance ↑ glucose uptake ↓ gluconeogenesis	Pioglitazone 15-30 qd/bd ? Bladder cancer	Cardiotoxicity Weight gain edema , CHF fluid retention, ***Monitor liver function***

WHAT IS PIOGLITAZONE?

- Oral antidiabetic drug
- Belongs to the Thiazolidinedione class
- 2 members currently available – Pioglitazone & Rosiglitazone
- Ligand of the nuclear receptor - peroxisome proliferator activator receptor-γ (PPAR-γ) in liver, muscle and adipose tissue

PRIMARY ACTION

PIOGLITAZONE → PPAR-γ receptors in the nucleus → Regulates genes related to glucose & lipid metabolism → Increased insulin sensitivity

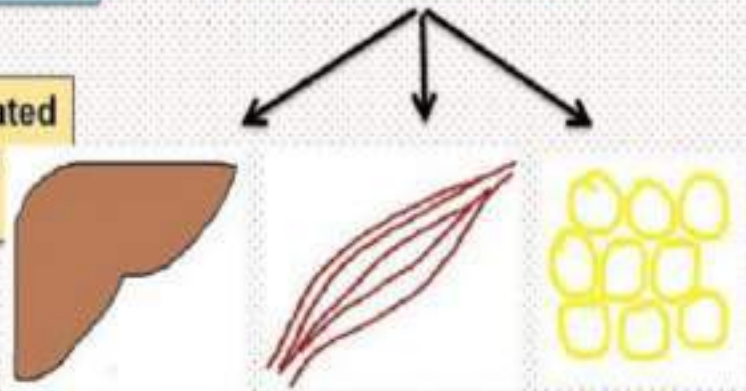
INSULIN SENSITIZER

OTHER ACTIONS

Pioglitazone also activates PPAR-α

- Decrease triglycerides
- Increase HDL cholesterol
- Decrease plasma fatty acid level

Increase insulin-mediated glucose uptake by around 30-50%



★★ PIOGLITAZONE REQUIRES THE PRESENCE OF INSULIN FOR ITS PHARMACOLOGICAL ACTIONS

1280 × 720

Classification3 -- Alpha glucosidase inhibitors

Alpha glucosidase inhibitors: (acarbones)

{ Intestine } Brush border

Complex sugars --------//---------> Glucose

↓

glucose absorption

Insulin-sparing effect

↓ dose req of insulin

Acarbose, miglitol

½ hr before meals

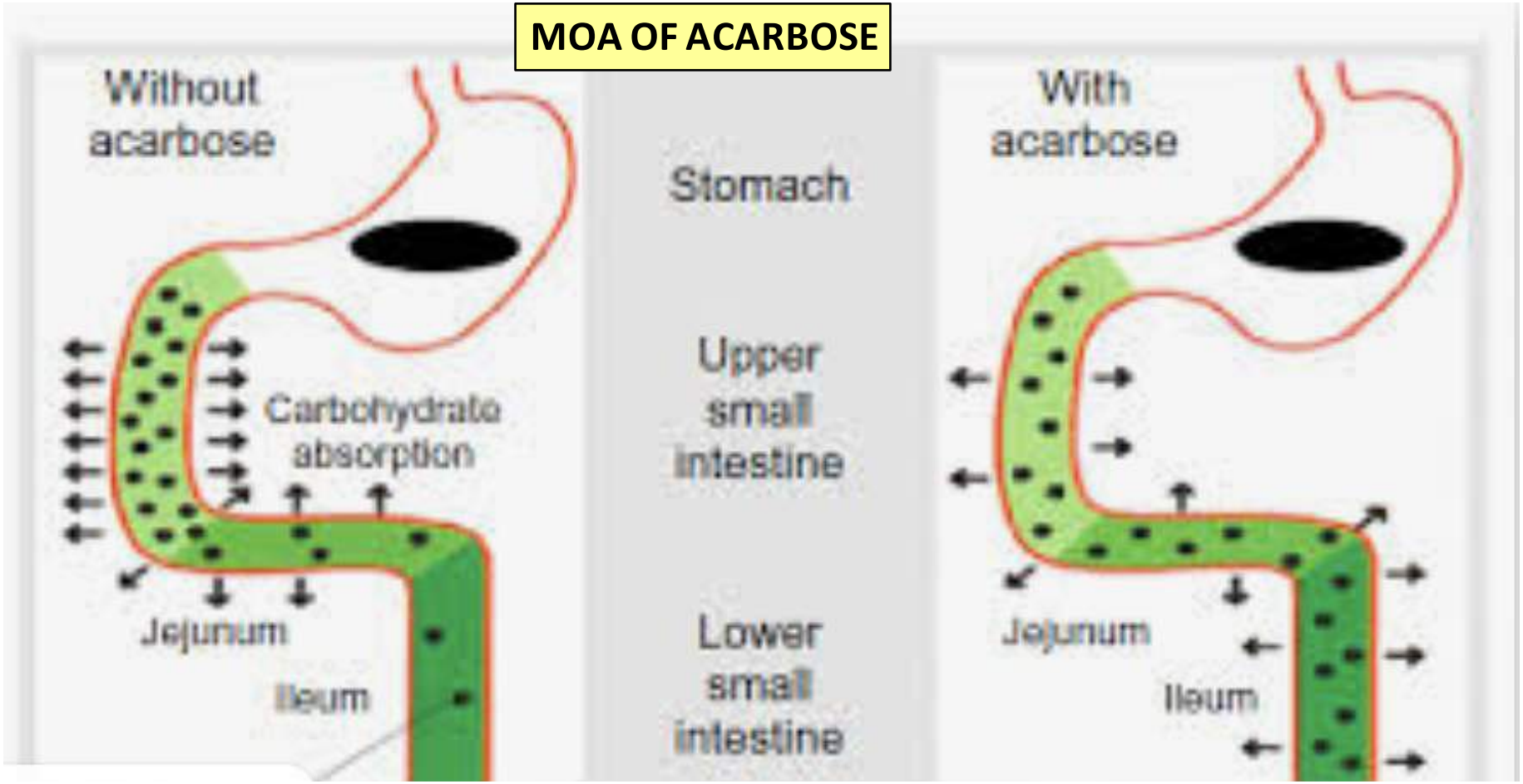
50-100 mg tds/qid

GI discomfort,bloating Diarrhea, flatulence -

Hypoglycemia not corrected by sucrose

X cirrhosis, malabsorption, renal impairment

MOA OF ACARBOSE



Classification3 SGLT2 INHIBITORS

- Sodium Glucose cotransport inhibitors – prevent renal tubular reabsorption of glucose
- Canagliflozin empagliflozin dapagliflozin
- Reduce plasma glucose without stimulating beta cells –insulin sparing action
- ADR –high incidence of UTI as urine sugar is high

Complications of DM

- **Ketoacidosis --diabetic coma**
- **Hyperosmolar coma**

Diabetic ketoacidosis (diabetic coma)

- **More frequent with IDDM (Type 1)**
- **Precipitated by:** infection, trauma, stroke, stress, pancreatitis, inadequate insulin dosages
- → **Polyuria, polydipsia, fatigue, dehydration, "fruity" breath**

  Kussmaul breathing – (deep, rapid, respiration)

treatment

- **HOSPITALIZATION**
- **IV INSULIN**
- **low dose continuous insulin infusion**

- **1. Regular insulin 0.1-0.2 units/kg IV followed by 0.1 unit/kg/h by infusion**
- **(Double the rate if no response in 2-3 h)**
- **When BSL < 300 mg%, (After 4-6 h), rate reduced to 2-3 units/h**

Treatment

- **2. IV fluids:**
- **normal saline 1 lit/h, then 0.5 lit every 4 hours, then ½N saline**
- **3. KCl 10-20 mEq/Hr**
- **4. IV NaHCO3 to treat acidosis - 50 mEq**
- **5. Na-K phosphate 5-10 mmol/h**
- **6. Antibiotics**
- **7. Ventilatory support**

Hyperosmolar non ketotic coma

- **Common in elderly NIDDM**
- severe diuresis, dehydration, glucose accumulation (may be > 800 mg%)
- **Treatment Same as DM coma**
- **- low-dose continuous insulin**
- **Faster fluid replacement**
- **Prophylactic heparin—due to high viscosity**
- **Antibiotics may not be needed**

- **High mortality rate**

Thyroid Hormone and Inhibitors

Dr. Pradnya Rotithor

Step 1)Iodine uptake I^- **iodide (ion inhibitors –thiocynate)**

peroxidase **(thioamides –PTU Methimazole)**

oxidation I^+ **Iodinium**

Step 2)Tyrosil residue + iodine ---MIT /DIT in **TG**

Coupling ---peroxidase **thioamides**

MIT + DIT = T_3

DIT + DIT = T_4

TSH influences both iodine uptake and coupling

SYNTHESIS

TG containing T3 T4 -stored as colloid in the interior of thyroid cell

Endocytosis of TG containing t3 t4 -----

lysosomal proteases

T3 T4 released into blood (iodides)

MIT DIT are de iodinated ---------I – is reutilized

Release of hormones

T_4 to T_3 at periphery

Mainly by liver kidney Target tissues take up T3

T3 is the only active component

Highly protein bound ---TBG

FREE T3 –ONLY 0.3 % OF TOTAL PLASMA T3

Only free hormone is available for uptake

rT_3 –byproduct of mono-de iodination of T4 at periphery

_ metabolically inactive

Brain and pituitary take up T4 and convert to T3 within their own cells

Thiouracils propranolol corticostroids lower peripheral conversion of T4 to T3

HYPO VS HYPER

↓levels of thyroid hormones→ **Hypothyroidism**

R_X T4, T3 substitution/replacement - **Preferred –T4**

↑levels of thyroid hormones → **Hyperthyroidism**

R_X - reduce actions of thyroid hormone
prescribe -Thyroid Inhibitors

Anti-thyroid drugs-carbi/methimazole PTU
Lugol's iodine
Radioactive iodine

Beta blockers –no action on thyroid gland function, offer symptomatic relief in thyrotoxic crisis

Physiological Functions of t3/t4

Growth, development, function, and maintenance of all body tissues

– Nervous, skeletal, reproductive tissue

↑ BMR, ↑ cellular metabolism,

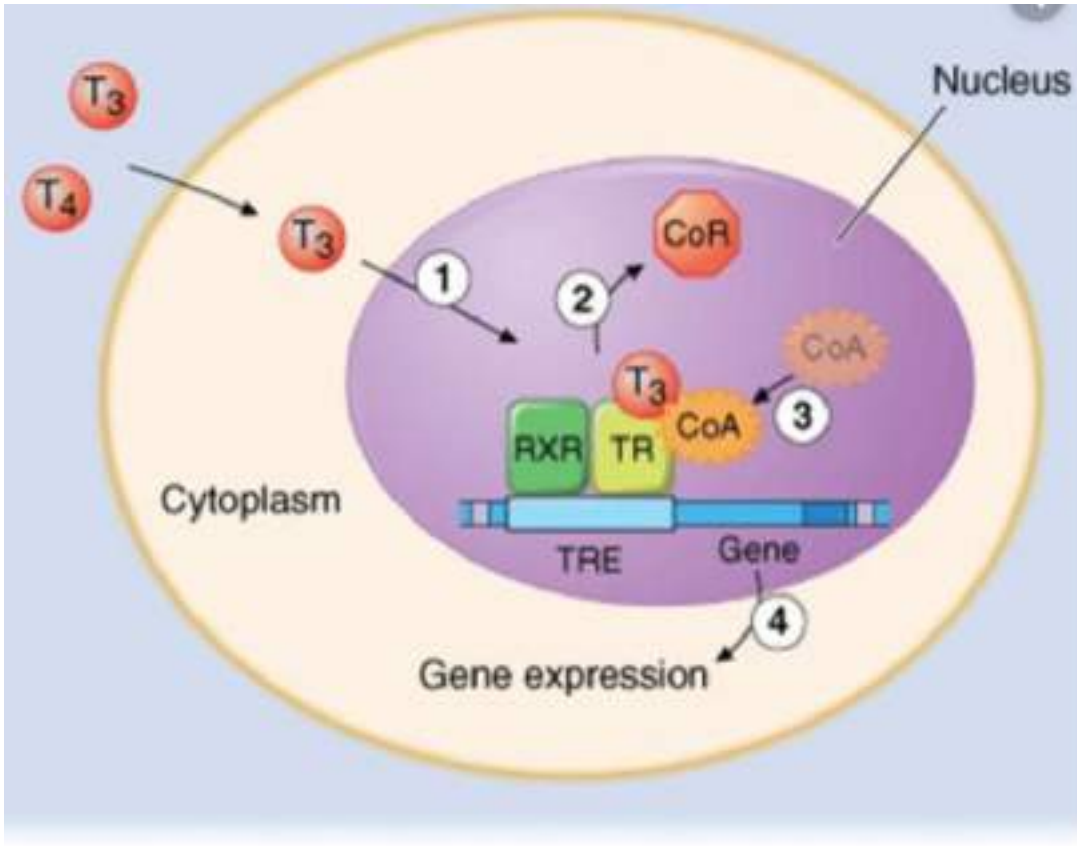
↑ ↑ calorigenesis,

Temperature regulation

↑ metabolism of Carbohydrates, lipids, proteins, vitamins

A/E of T3/T4

- Excessive action of thyroid hormones lead to --
- Tachycardia, palpitation,
- arrhythmias
- tremors
- Weight loss
- insomnia, heat intolerance
- Headache, Diarrhoea,



Key steps in receptor activation: Endogenous thyroid hormone T3 crosses mitochondrial membrane (1) binding thyroid receptor TR, dissociating co-repressor CoR (2). Subsequent binding of co-activator CoA (3) results in altered gene expression (4). RXR: retinoid X receptor; TRE: thyroid response element.

467

MOA

thyroid receptor (TR)- Nuclear R

Activated by T3

affinity of TR to T3 – 10 times of T4

Protein synthesis -→ to produce various physiological actions

T4 Iodothyronine deiodinase→ T3 at periphery

rT_3-- inactive

Simple Goitre

A diffuse, chronic enlargement of the thyroid gland

Endemically in certain localities (soil is low in iodine)

and sporadically elsewhere.

Thyroid Gland enlargement
Of different aetiologies

Emergency in hypothyroidism

usually caused by:-
removal or
loss of functioning thyroid tissue

- **-Relatively hard oedema of subcutaneous tissue –due to ↑mucin in oedema fluid**
- **(proteoglycans) –non pitting oedema is charactristic feature of hypothyroidism**

- **-Somnolence, slow mentation, -Dryness and loss of hair**
- **-Increased fluid in body cavities such as the pericardial sac**
- **-Hypothermia, hoarseness, muscle weakness, and slow return of a muscle to the neutral position after a tendon jerk**

1)l-thyroxine sodium(T4) (Levothyroxine)
100 mcg – Longer half life --- Maintenance
50-100 mcg OD → then increase by 25-50 mcg every 15 days

Taken on empty stomach early in the morning

Inj Levothyroxine sodium—200/500 mcg

2. Liothyronine (T3): 5, 25 mcg- Shorter half life - Rapid action – Useful for emergency (Cytomel)

Inj liothyronine sodium 10mcg/ml

---

3. Combined T4 +T3 LIOTRIX: (T4: 80 mcg + T3: 25 mcg)

Thyroid extract and thyroglobulin are no more used

Thyroid preparations and dosage

DR

Therapeutic uses of thyroid hormone

- ***T4 is preferred as T3 causes arrhythmias***
- Cretinism – sporadic - endemic
- Adult Hypothyroidism (Thyroiditis / Thyroidectomy / Simple goiter with iodine deficiency / Idiopathic)
- Nontoxic goiter – endemic / sporadic
- Papillary carcinoma of thyroid
- Benign thyroid nodules
- Emergency management of myxoedema coma

myxoedema coma

Emergency in hypothyroidism –

l-thyroxine (200-500 mcg iv -→ 100 mcg IV / day till oral therapy can be started. (or T3 - 100 mcg IV, then 25 mcg q 6h)

+ Hydrocortisone

Empirical uses

-Resistant anemias

-Menstrual disturbances

-Infertility

-Chronic resistant ulcers

-Chronic constipation

T4	T3
Is an inactive form	Is an active form
Less potent	More potent
Less toxic	More toxic
Preferred	Less preferred
Less risk of arrhythmias	More risk of arrhythmias
Long t ½	Short t ½

---

affinity of TR to T3 – 10 times of T4

Brain and pituitary take up T4 and covert to T3 intra cellularly

rT3 –inactive T3

Hyperthyroidism high serum levels of thyroid hormone

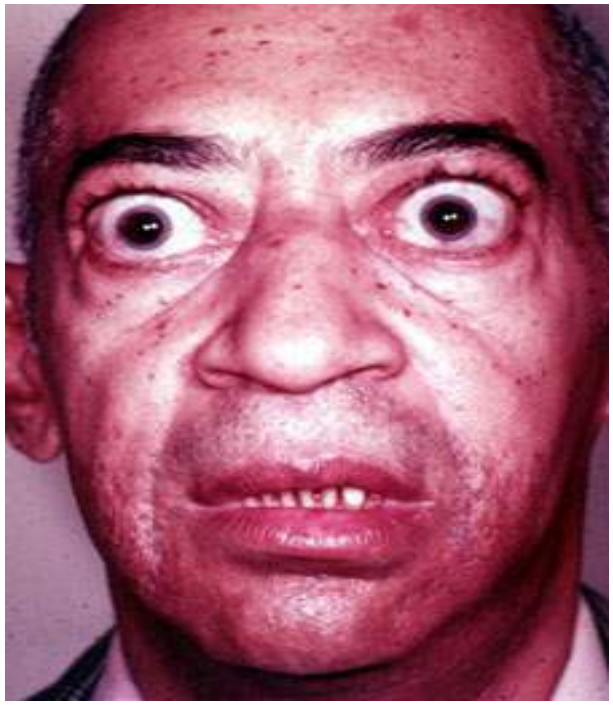
Counter with Thyroid Inhibitors

-Anti thyroid drugs

-Lugol's iodine

-Radioactive iodine

Beta blockers for symptomatic relief only



Hyperthyroidism/Thyrotoxicosis

Graves disease

Toxic nodular goiter

Emergency is called as --

thyrotoxic crisis / thyroid storm

Thyroid storm/ Thyrotoxic crisis/Thyrotoxicosis

Severe, acute condition in hyperthyroidism

Exacerbation of symptoms of hyperthyroidism

Severe tachycardia –characteristic feature

Rapid pulse (140–170/minute), nausea, diarrhea, fever, loss of weight, extreme nervousness, and a sudden rise in the metabolic rate, tremors, anxiety

Occasionally, profound prostration, weakness, and collapse.

Coma and death

Thyroid inhibitor agents

The drugs used to lower the functional capacity of thyroid.

Used for conditions associated with HYPERACTIVITY OF THYROID GLAND.

Thyroid inhibitors –classification SAQ

1)Anti-Thyroid Drugs: drugs that decrease thyroid hormone synthesis

Thioamides: Propyl-thiouracil, Methimazol, Carbimazol

MOA:-Peroxidase inhibitors and prevent coupling

2)Drugs decreasing hormone release

lugol's Iodine, NaI, KI

fastest acting thyroid inhibitor-KI MCQ

Thyroid constipation

3)Drugs destroying thyroid tissue - radioactive iodine

131-I, 125-I, 123-I

4)Drugs decreasing iodide trapping/uptake - Ionic Inhibitors

SCN, ClO4, NO3

Anti thyroid drugs

Propylthiouracil	**Carbimazole→Methimazole**
Less potent (Tab:25, 50 mg)	3 times more potent *Tab:2.5,5,10 mg*
More PPB	Less PPB
Penetrate less: Placenta, Milk	√ Placenta, Milk
t 1/2: 1-2 hours	t 1/2: 6-10 hours
BD/TID(50-100 tid) (25-50bd/tid)	OD / BD (5-10tid) → (5-15 od/bd)
Rapidly acting	Slow acting, long lasting
MOA--Decrease tyrosine iodination, coupling, blood T3, T4 levels	
T4---/-/----→T3	No effect
Thyrotoxic crisis/ thyroid storm	Hyperthyroidism Long term management

Anti-thyroid drugs

propylthiouracil

Safe to use in pregnancy

carbimazole

Therapeutic uses of anti thyroid agents

Hyperthyroidism/thyrotoxicosis associated with –

Toxic nodular goiter

Graves disease, for –

1. Definitive therapy
2. Preoperative preparation (before surgery)
3. Along with radioactive Iodine treatment (131-I)

ADR of anti thyroid drugs

Hypothyroidism

GI, skin rash (maculopapular rash), fever
Alopecia, graying of hair
Liver damage
Agranulocytosis, hypoprothrombinemia

Both cross placental barrier,
but propylthiouracil is **safer** in pregnancy (extensively protein-bound)

Advantages of anti thyroid drugs

No Surgical risk

No Scar

No risk of Injury to recurrent laryngeal nerve

suitable for children/young patients

Disadvantages of anti thyroid drugs

Long term treatment required

X Unconscious, uncooperative patients

Toxicity problems

Can cause hypothyroidism

Points to note---

Propylthiouracil in thyroid storm/ thyrotoxic crisis

(Rapid action, Also: Inhibits Peripheral conversion of T4 → T3 by inhibiting 5'deiodinase)

Propranolol/atenolol/nadolol in hyperthyroidism

Block sympathetic outflow, prompt symptomatic relief

Tremors, palpitation, ↑BP, ↑ heart contractility, automaticity)

Also, T4------//---5' deiodinase -⁄⁄-→T3 to some extent

Propranolol has NO EFFECT on thyroid gland function

Drugs ↓ hormone release - Iodine, NaI, KI, Ipodate, Ipanoic acid

Fastest Acting Thyroid Inhibitor: KI (mcq)
PEAK:10-15 DAYS

Gland shrinks
Becomes firm, less fragile, less vascular.—advantage for surgery

Effect is short-lasting- **thyroid escape**

Lugol's Iodine/Lugol' solution (5% iodine in 10%KI)
Dose : 5 to 15 drops per day

Inhibition of release → "**thyroid constipation**"

Sodium and potassium iodide

NaI KI

Fastest acting thyroid inhibitor

Available as tab/liquid/IV preparation

Indications-

1)Pre-operative preparation for thyroidectomy (start at least 15 days prior to surgery)

2)Can be used in THYROID STORM (fast acting) NaI or KI – IV or Oral to stop further release of T3, T4

3)For prophylaxis of endemic goiter (IODIZED SALT)

Expectorants contain NaI KI

Tincture iodine –local antiseptic for cuts And wounds

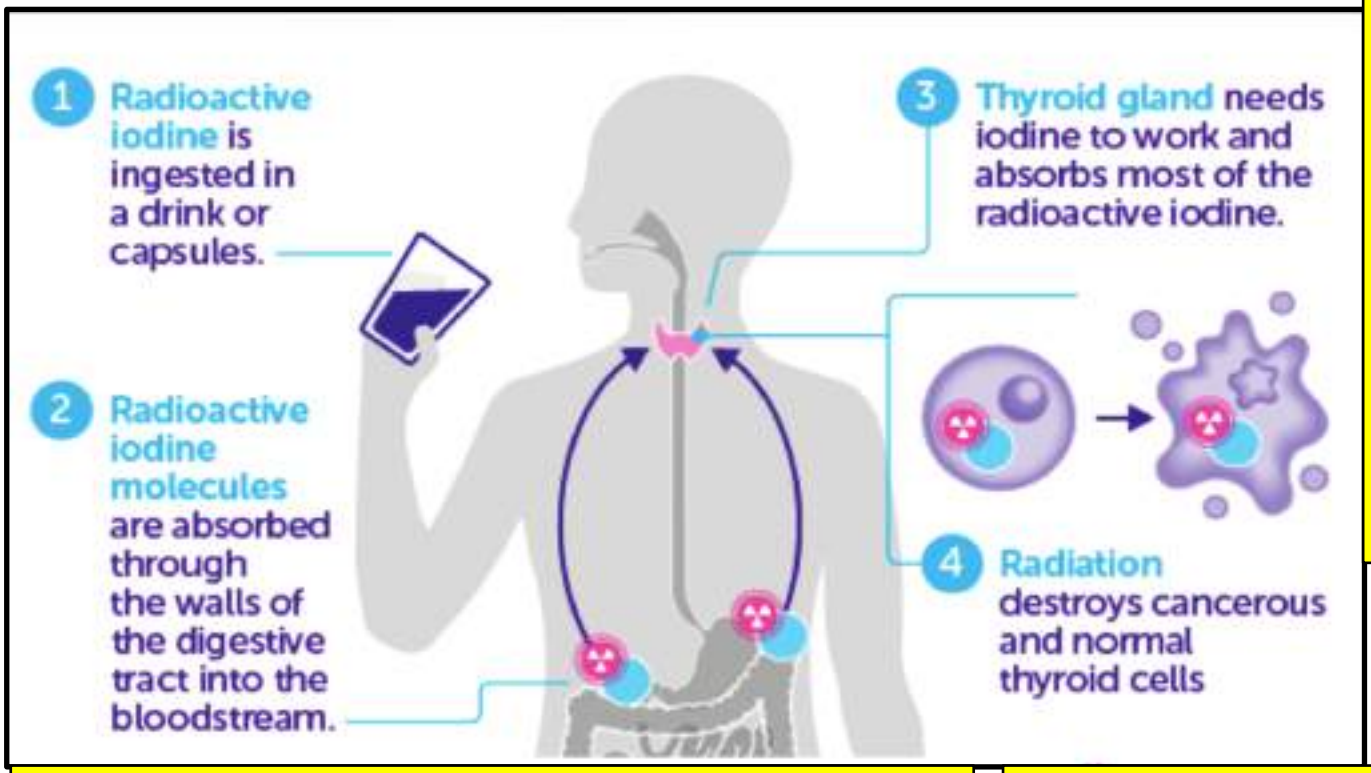
Radioactive iodine

- To **destroy** the thyroid tissue
- ^{131}I, ^{125}I, ^{123}I mcq
- ^{131}I: Dose: 3-5 m curie – given as sodium salt of ^{131}I dissolved in water and given orally on empty stomach /light BF

MOA:

- Emits beta particles upto depth =0.5 to 2mm
- → destroy the thyroid tissue from within
- Without damaging peripheral tissues

Radioactive Iodine treatment



Suitable for

1) middle aged patients
2)After reproductive age
3)When surgery is contraindicated

Advantages of ^{131}I

No surgical risk
No scar
No risk of injury to recurrent laryngeal nerve

Simple OPD based low cost treatment

Indications

1)Hyperthyroidism
2)Grave's disease
3)Toxic multi-nodular goitre
4)Postoperative for Ca Thyroid –to prevent recurrence

^{131}I Disadvantages

- Adverse effect of hypothyroidism
- Delayed results--LONG LATENT PERIOD to get response --2-3 months
- X Younger patients (reproductive system damage, impotence, sterility, infertility)
- X Pregnancy

Thyroid storm management

- **Medical emergency**
- **HOSPITALIZE the patient**

- **Propylthiouracil**
- **Beta blockers- symptomatic relief by blocking sympathetic outflow**
- **Potassium iodide (KI)- fastest acting thyroid inhibitor**
- **Ipodate or ipanoic acid**
- **Corticosteroids**

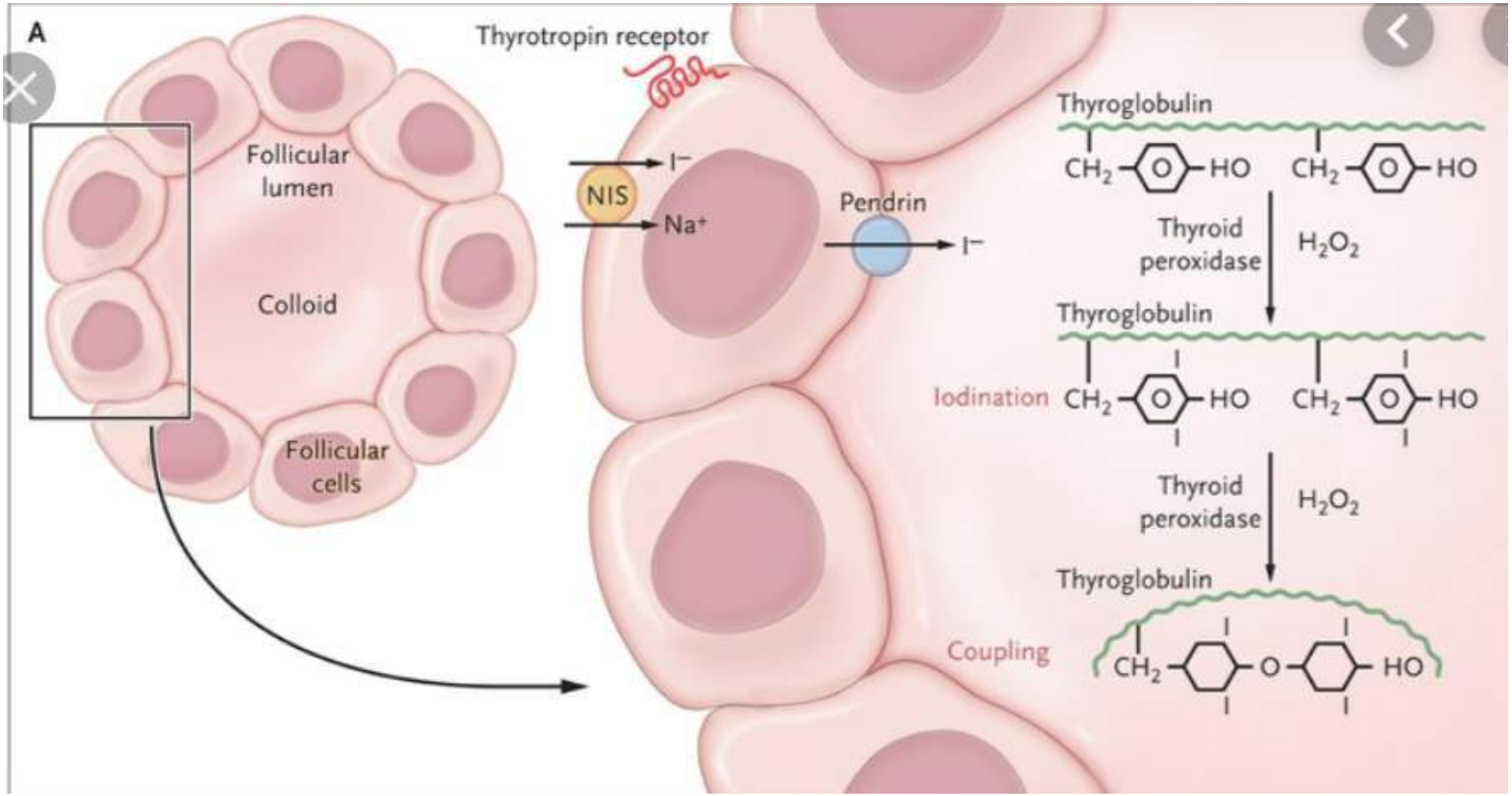
- **Antibiotics**
- **Cooling, antipyretics**
- **Antipsychotics / anticonvulsants as needed**

Role of steroids in thyroid disorders

- Myxedema coma
- Thyrotoxic crisis
- Schmidt syndrome
- Sub acute thyroiditis
- Graves ophthalmopathy

IMP FOR EXAM

- **SAQs**
- **Classify thyroid inhibitors with examples**
- **Adverse effects of antithyroid drugs**
- **Compare and contrast: Propylthiouracil – Methimazole**
- **T4 – T3**
- **MCQs**
- **Propylthiouracil in thyroid storm**
- **Beta blockers in hyperthyroidism—viva**
- **Propylthiouracil – Hyperthyroidism with pregnancy**
- **Lugol's iodine/KI---fastest acting thyroid inhibitor**


A
Thyrotropin receptor
Follicular lumen
Colloid
Follicular cells
NIS
I⁻
Na⁺
Pendrin
I⁻
Thyroglobulin
CH2 O HO
CH2 O HO
Thyroid peroxidase
H2O2
Thyroglobulin
Iodination
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Thyroid peroxidase
H2O2
Thyroglobulin
Coupling
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