(1)

DATE
PAGE

* Plasma Volume Expanders:
"These are high Molecular Weight substance which exert Osmotic pressure and when infused i.v. retain fluid in the Vascular department."

They are Mainly used to Collect hypovolemia due to loss of plasma / blood.

→ Desirable properties

(i) Should exert Osmotic pressure comparable to plasma.
(ii) Should remain in Circulation and not leak out in tissue.
(iii) They should be long acting.
(iv) Should not be pyrogenic or Antigenic
(v) They should be stable, easily Sterlizable and Cheap.

Examples of plasma expanders:
Human Albumin, Dextran, ~~poly~~ Gelatin polymers, polyvinyl pyrrolidone (PVP) and Hydroxy ethyl Starch.

(A) Human Albumin

- It is obtained from pooled human plasma.
- It does not show Cross Matching with blood group.
- It is free of risk of transmitting serum Hepatitis.

(B) Dextran

- It is polysaccharide obtained from sugar beat and is available in 2 forms i.e
  Dextran 70 (M.W. 70000)
  Dextran 40 (M.W 40000)
- It May Interfere with blood group and show Cross Matching.
- It is not Dextran 70 effectively expands plasma volume for Weekly 24 Hours
- Dextran 40 is faster but Sheart acting than Dextran 70.

- Dextran have long shelf life (10 years) cheap and can be easily sterilized.

(c) Gelatin polymers

They have molecular weights of 30,000 and duration of action of 12 hr.

They can remain stable for 2 years at pH 7.2 - 7.3.

They ~~does~~ donot interfere with Coagulation. blood grouping and cross-Matching.

They can rarely cause Urticaria, allergic reactions and bronchospasm.

Uses of plasma expanders

In treatment of burns hypovolemia and endotoxin shock, Severe trauma and extensive tissue damage.

(2) Hypersensitive

DATE
PAGE

* ACE Inhibitors

ACE Inhibitors block specifically the enzyme ACE and thereby decrease the angiotensin - II which is responsible for Vaso-constriction and aldosterone secretion.

- Hence, ACE Inhibitor cause Vasodilatation, increased Sodium and water retention leading to decrease in blood pressure.
- Captopril, the oldest one is having sulfhydryl group
- Enalapril, Lisinopril, Ramipril, Fosinopril are also available in India.

Classification of ACE

1) Direct action but Internalized Metabolite to disulfide group Ex. Captopril.

2) Prodrug
They have the effects when they are changed to active metabolized - Ex enalapril, benazepril.

3) Soluble in water and not change in the body Ex. Fisinopril.

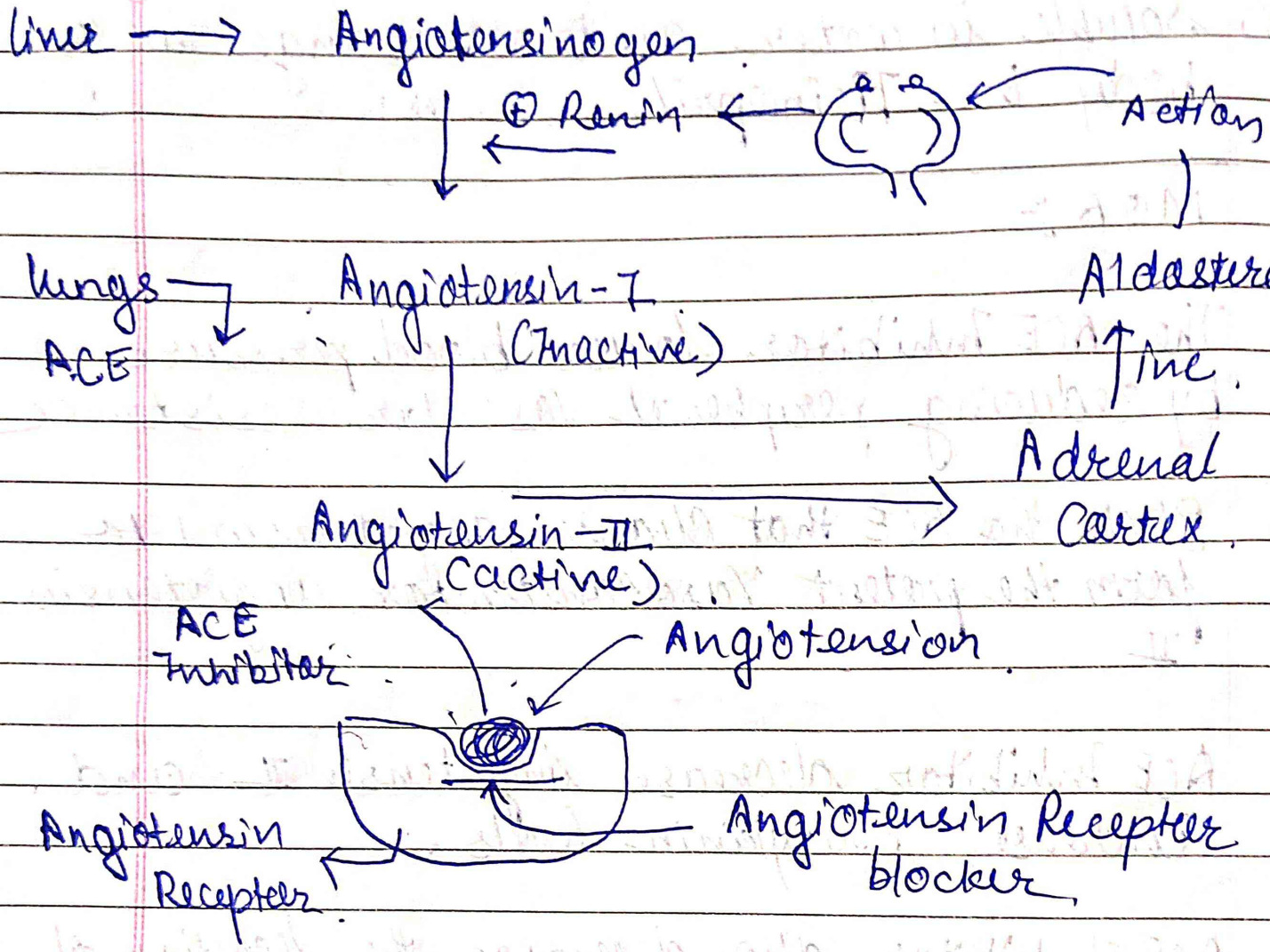
MOA :-

The ACE Inhibitor lower blood pressure by reducing peripheral vascular resistance

Block the ACE that cleaves Angiotensin I to form the potent Vasoconstrictor angiotensin II

ACE Inhibitor decrease Angiotensin II and increase Bradykinin levels.

ACE Inhibitor also decreases the secretion of aldosterone resulting in decreased sodium and water retention.



Therapeutic uses :-

1) Hypertension
2) Congestive Heart failure
3) Diabetic Nephropathy
4) Progressive renal insufficiency

Adverse effects :-

Cough, hypotension, renal failure, angioedema and hyperkalemia.

(3)

Q→ Classify NSAIDs
MOA ; therapeutic uses and adverse effects of Aspirin.

Classification.

1 Non Selective Irreversible Inhibitors of COX :-
eg :- Aspirin, Sulfasalazine, Olsalazine, Methylsalicylate.

2 Non Selective reversible Inhibitors of COX.
e.g :- Indomethacin, Ibuprofen, Mefenamic acid, Naproxen.

3 Weak Inhibitors of COX-1 and COX-2 plus Other Modes of Action :-
e.g :- Nimesulide

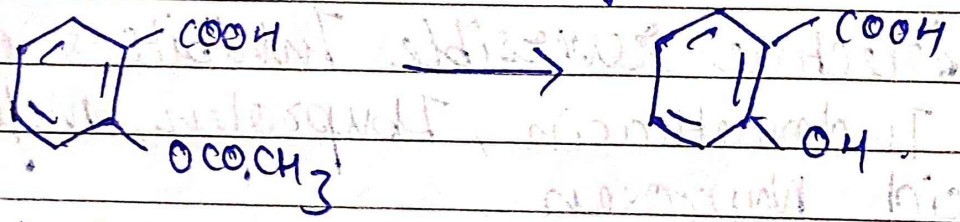
4 Preferential COX-2 Inhibitors :-
e.g :- Meloxicam. Etodolac. Nabumetone.

5 Selective COX-2 Inhibitors :-
eg :- Rofecoxib, Celecoxib, Etoricoxib.

6 Cox-3 Inhibitor
e.g :- Paracetamol.

* Aspirin

Also known as Acetyl Salicylic Acid.
- It is a prodrug.
- It firstly converted into Salicylic acid in the body then it gives their action.



Aspirin Salicylic acid.

MOA.
- It inhibits the enzyme Cox
- Which further decrease the production of Inflammatory Mediators such as PGs.
- Due to the decrease Inflammatory responses such as pain, fever etc.

- Pharmacological Action

① It gives analgeric, antipyretics and anti-inflammatory actions.

② GIT → irritate gastric Mucosa and cause peptic ulcers
- ↑ risk of GIT Bleeding
- cause Nausea vomiting.

③ Blood - Anti platlets effect by Inhibiting TXA_2

- Uses :-
- as Analgesic, antipyretics, anti-Inflammatory
- Acute Rheumatic fever and also Antiplatlets
- Rheumatoid ~~arthritus~~ arthritis and other Inflammations.

- Adverse effects →
- Nausea Vomiting
- Hypersensitivity
- ↑ risk of GI bleeding and peptic ulcer.
- ↑ risk of bleeding
- ↑ risk of renal injury.

4

* Oral hypoglycemic agents.

Oral hypoglycemic / Anti diabetes

↓ blood glucose ↓ diabetes.

These are those drugs which lowers blood glucose level in diabetes and are effective orally.

- Mostly used to treat type-2 diabetes Mellitus.

- Diabetes → A serious disease in which a person body cannot control the level of sugar in the blood.

Type-1 diabetes
- A chronic condition in which the pancreas produce little or no insulin

Type-II diabetes
- A chronic condition that affects the way the body processes blood sugar.

↓

Impairment in the way the ~~blo~~ body regulates and uses glucose as a fuel.

- Agents that are given orally to reduce the blood glucose level in ~~bi~~ diabetic patients.

- The Oral Antidiabetic drugs are of value only in the treatment of patients with type 2 diabetes Mellitus whose condition cannot be controlled by diet alone.

- These drugs may also be used with Insulin in the Management of some patients with diabetes Mellitus ~~Whose condition~~ use of an oral antidiabetic drug with Insulin may decrease the Insulin dosage in some Individuals.

- Five types of oral antidiabetic drug are currently in use:-

1) Biguanides :- Metformin, phenformin

2) Sulfonylureas :- Tolbutamide, Chlorpropamide, Glipizide, Glimepiride.

3) Thiazolidinediones :- Proglitazone, Rosiglitazone

4) Meglitinides :- Repaglinide, Nateglinide

5) Alpha-glucosidase Inhibitors :- ~~Acarbose~~ Acarbose, Voglibose.

* Biguanides

- Metformin :- is the only drug of this class presently available in Market.
- It does not cause hypoglycaemia
- MOA :-
  They increase glucose uptake and utilisation in Skeletal Muscle (thereby reducing insulin resistance) and reduce Hepatic glucose production (gluconeogenesis)

drugs :- Metformin, phenformin

- Contra ~~Laid~~ Indications :-

- Metformin should not be given to patients with.
  Renal failure
  Hepatic disease
  Hypoxic pulmonary disease
  Heart failure or shock.

* Sulfonylureas

- 1st gen :- Tolbutamide and chlorpropamide.
- 2nd gen :- Glipizide, Glimepiride.

MOA :- Acts of B Cell Stimulating insulin secretion and thus reducing plasma glucose.

- Tolbutamide :-
  half-life :- 6-12hrs.

- Adr :- Hypoglycaemia May decrease Iodide uptake by thyroid. Contraandicated in liver failure, renal failure patients.

* Meglitinides

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

Q Hematinics.

- Hematinics are those substance which are required in the formation of Blood and are used for the treatment of anemia.
- Anemia occurs when ~~RBC~~ loss of RBC

(a) Blood loss
(b) Impaired red cell formation
(c) Bone Marrow depression, Erythropoetin deficiency
(d) ↑ destruction of RBCs.

① Iron.
It is important for body used to treat weakness

Total body iron - 2.5-5 gm.

→ It is essential for haemoglobin production

RBC Contain → Hemoglobin
- Hemoglobin Contain four iron which carry O_2 and transported it into body.

Distribution of Iron in body :-

Haemoglobin :- 66%
haemosiderin :- 25%
Myoglobin :- 3%

Iron is stored in our body in ferric form in combination with large protein apoferritin.

Fe^{3+} + Apoferritin ⟶ ferritin ⟶ aggregates ⟶ Haemosiderin

excretion :- daily 0.5-1 mg of iron excreted

Preparation of Iron

- Oral iron
- Parenteral Iron

① Oral iron.
- are available as ferrous sulphate, ferrous fumarate, ferrous gluconate, ferrous succinate.

ferrous salt are better absorbed than ferric.

- Preparation of iron hydroxyl polymaltose have been extensively marketed and claimed to better ~~tolerated~~ ~~act~~ with NO Metabolic taste.

Adv :-
- Nausea, vomiting
- Metallic taste
- Constipation etc.

② Parenteral iron.

By injection or Intravenously.

- Indication :- Non-Compliance
- Severe deficiency with bleeding.
- Severe bleeding.

- given parenterally if,
- Failure to absorb oral iron
- ~~Iron~~ oral iron is not tolerated.

Adver :-
- Headache, Joint Pain, Nausea
- Pain at the site of Injection.
- Pegmentation of skin

e.g :- Iron-dextran, ferrous Sucrase, ferric Carboxymaltose etc

Uses of Iron.

- Used in the treatment of Iron deficiency anemia
- Increased iron requirement during pregnancy professional blood donor etc.

(2) Vitamin - B_{12}

Synthesized by Microbes, liver, fish, egg yolk, Meat, Cheese.

- absorbed with help of instrinsic factors, protein secreted by stomach.
- carried in plasma by B_{12} binding Proteins called transcobalmin.

Uses →
- treatment of Vit B_{12} deficiency
- treatment of Megaloblastic anemia
- treatment of perdicious anemia.

(3) ~~Folic acid~~
function → Involved in Several Vital Metabolic reaction and is essential for Synthesis of purine & needed for DNA Synthesis.

③ folic acid.

Pteroyl glutamic acid (PGA)

↓ consist of

Pteridine + Paraminobenzoic acid + glutamic acid.

Source - green veg, liver, yeast, egg etc.

function :-

folic acid $\xrightarrow{\text{folate reductase}}$ dihydrofolic acid $\xrightarrow{\text{Dihydrofolate reductase}}$ Tetrahydro folic acid.

Uses :-

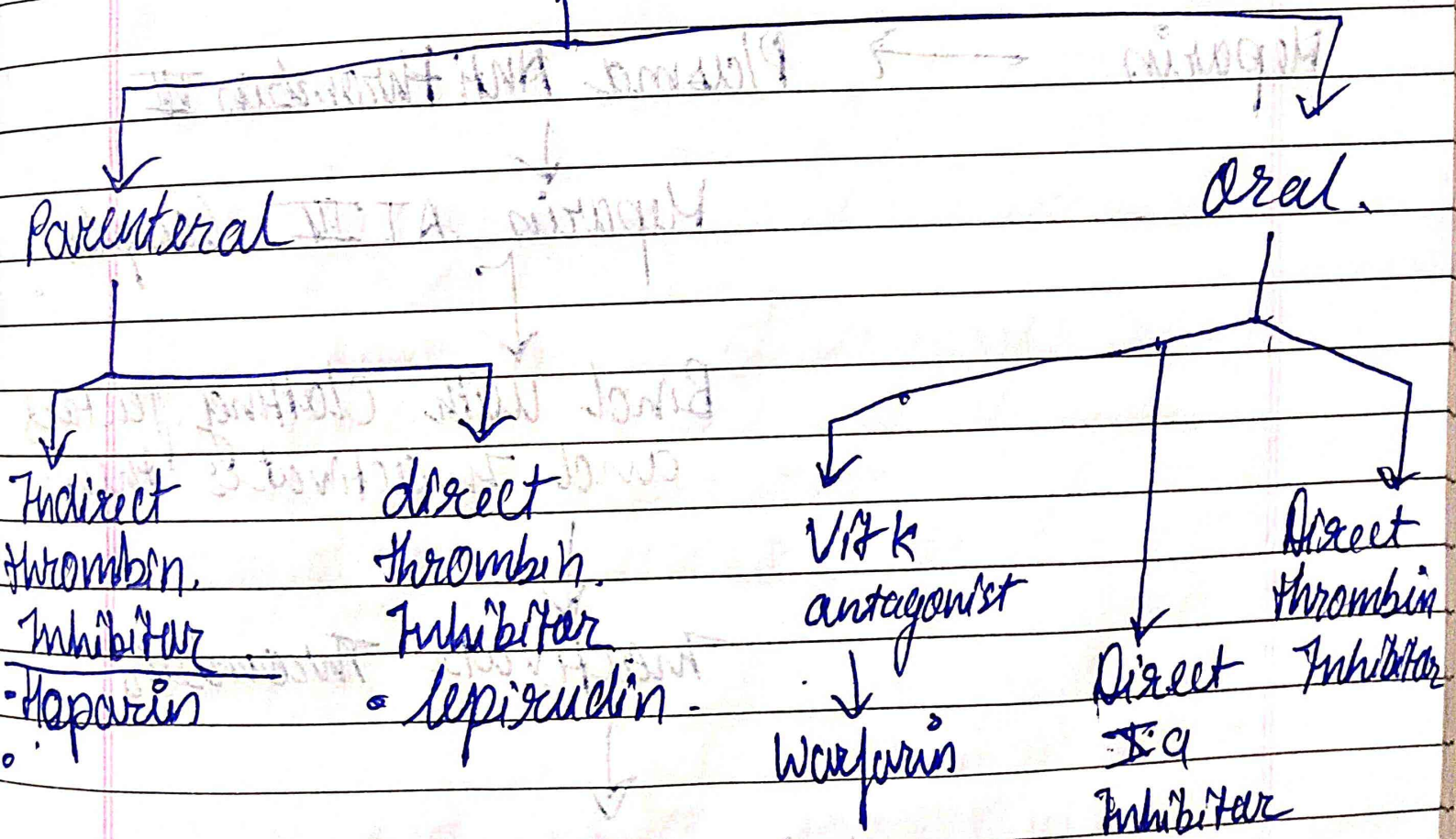
- treat Megaloblastic anemia.
- folic acid deficiency
- used during pregnancy, lactation and for growth in infants.

Q

⇒ Anticoagulant

- These drugs which prevent blood coagulation.
- They decrease the blood's ability to clot.
- Also called as Blood thinners:

Classification.



A. Parental.

→ Indirect Thrombin

Heparin
- It is obtained from liver.
- It is a Mixture of Mucopolysaccharides.
- It is found in the Mast cell of lungs, liver and intestinal Mucosa.

Mechism:-

Heparin ⟶ Plasma Anti thrombin III

↓

Heparin AT III complex

↓

Bind with clotting factors and inactivates them

↓

Inactivate Thrombin

↓

↓ fibrins ⟶ ↓ clots.

Adv-
- Bleeding, Osteoporosis.
- Hypersensitivity reaction
- Thrombocytopenia.

→ Direct Thrombin.

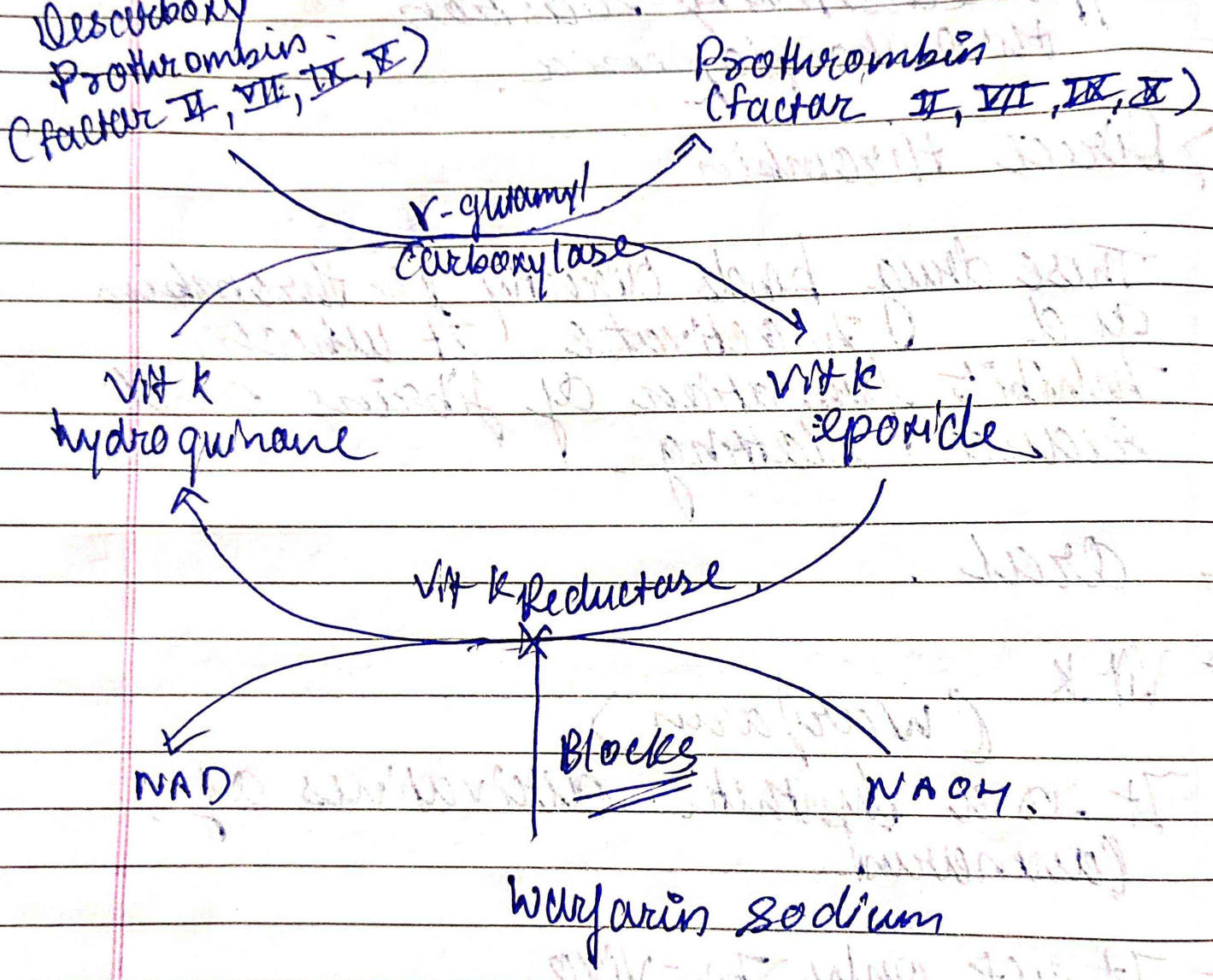
These drug binds directly to thrombin and inactivate it which inhibit formation of fibrins and reduce clotting.

B. Oral.

→ Vit K (warfarin)
- It is a synthetic derivatives of Coumerin.
- It acts only in-vivo

Meachism:-
- It interfere with Vit K dependent synthesis of clotting factors in liver by blocking the Vit K reductase.

Mechism :-



Ad

- Bleeding
- warfarin poisoning
- ability to cross placenta during pregancy.

Pharmacokinetics
- Completely absorb orally
- Slow onset action (1-3 day)
- Metabolized by glucoronide conjugation.

→ Direct Inhibitor of activated factor x.

eg:- Rivaroxaban
(used in deep vein thrombosis)

→ Orally:- Direct thrombin Inhibitor

eg:- Dabigatran etexilate.

Uses:- Anticoagulant

- Prevent the extension of thrombus
  - Heparin - rapid (for Initiation)
  - warfarin - slow (for Maintenance)
- Deep vein thrombosis
- Rheumatic heart diseases

Anti Hypertensive

- Persistent of rise of blood pressure above the upper limit of Normal level according to the age and sex of the Individual is called Hypertension.

Normal limit of B.P

Systolic :- 100 - 140 mm Hg.

Diastolic :- 60 - 90 mm Hg.

* Cause.

1) Primary hypertension (90-95 %)
- also called as Essential hypertension
- Unknown Etiology or Idiopathic

2) Secondary hypertension (5-10 %)
- Renal disease
- Endocrine disease
- Cushing's Disease.
- Vascular causes (Contraction of aorta).

- Drugs (Sympathomimetic, NSAIDs, Steroid, Contraceptive Pills)

* Risk factors
  - Age
  - Alcohol consumptions
  - Anxiety
  - Salt Intake
  - Obesity

* Special patient group:
  - Race
  - Diabetes
  - Renal disease
  - Stroke
  - Pregnancy
  - Oral Contraceptic

* Management of Hypertension
  - Non-

Classification :-

(A) Diuretics.

- (1) Carbonic anhydrase Inhibitors
  - Acetazolamide
- (2) loop diuretics
  - Furosemide
  - Ethacrynic acid
- (3) Thiazide
  - Amiloride
  - Spironolactone
- (4) Osmotic diuretics
  - Mannitol

(B) Sympatholytics

(1) Centrally acting
- Methyl dopa
- Clonidine

(2) Beta blockers :-
Atenolol
Metaprolol

③ Alpha blockers
- prazocine

④ Adrenergic Neurone blockers :-
- Guanethidine
- Reserpine.

⑤ Direct vasodilators

(1) Arteriolar dilators
- Diazoxide
- Minoxidil.

(2) Vasodilators (non-selective)
- Nitroprusside.
- prazosine.

⑥ calcium channel Blockers

- Nifedipine
- Verapamil.

(E) Angiotensin Converting Enzyme (ACE)

- Captopril
- Enalapril
- Lisinopril
- Ramipril

Q/ Calcium channel blockers

- Calcium is the chief ion required for cardiac contraction.

- Smooth musele contraction
- Propagation of cardiac impluse

* classification of Ca^{++} channel blockers.

1) Dihydropyridine family.
   - Nifedipine
   - Nicardipine
   - Visoldipine.

2) Miscellaneous
   - Verapamil
   - Deltiazem
   - Bepridil.

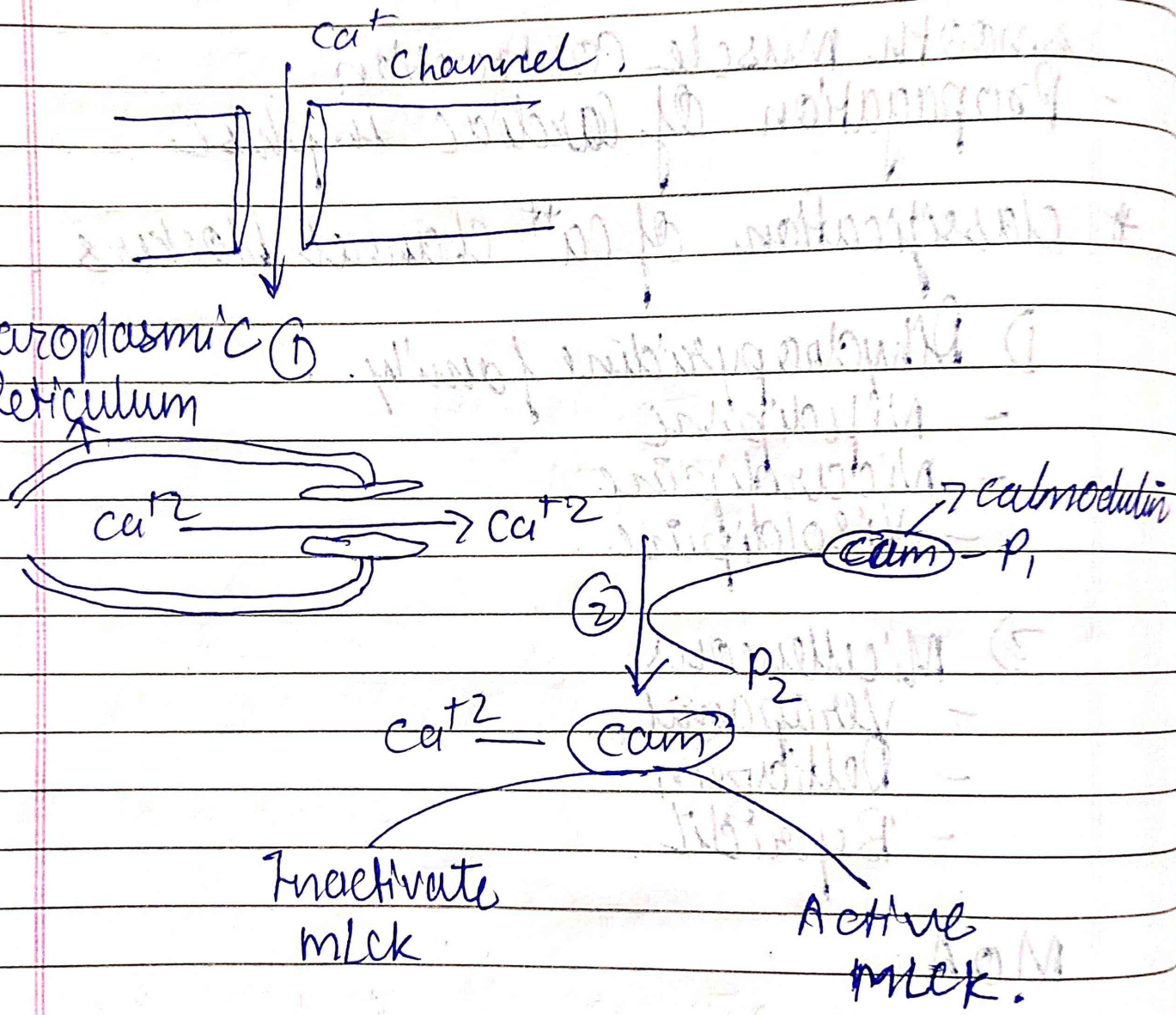
MoA.

Calcium channel blockers bind with voltage dependent Ca^{++} b Channel in depolarised Membrane

↓

MLCK:
Myosin light chain kinase

The resultant effect is relaxation of the smooth Muscles and Negative ionotropic and Chronotropic action in heart.



* Pharmacological action

1) CNS

Dilates main coronary vessel

↓

Improves Myocardial perfussion

② Negative chronotropic effect
↓
cardiac Slowin (Heart beat ↓)
A.V. block

③ Vasodilation → ↓ Se total peripheral resistance

Smooth Muscle

- Vascular smooth Muscle :- relaxation
- Coronary Vasodilation :- Anti anginal action

Adverse effect

- Due to Vasodilation.
- Postural hypotension reflex tachycardia.
- Bradycardia, palpitation
- Headache, flushing, dizziness ankle edema
- Constipation.
- Nausea
- Vomiting ; Gum hypertroph.

Q4

Classify Anti-Anginal drugs

- It is a pain syndrome due to Induction of an adverse oxygen supply or demand situation in a portion of the Myocardium

Classification :-

① Nitrates :-

→ Amyl Nitrate
Sodium Nitrate
Octyl Nitrate

① Short acting
Glyceryl Trinitrate

② long acting
Psosorbide dinitrate
Psosorbide Mononitrate

② β-blockers
Propranolol
Metaprolol
Atenolol..

(3) ~~Ca~~ Calcium channel blockers :-

(a) Phenyl alkylamine
Verapamil

(b) Benzothiazepine
Diltiazem

(c) Dihydropyridine

Nifedipine.
Nimodipine.
Amlodipine
Lacidipine.

(4) Potassium channel ~~open~~ opener.
Nicorandil

(5) Other
- dipyridamole
~~Tri~~metazidine

Q Nitrates.

MOA.

Nitrates is involve in Nitrate receptor the are present in vascular smooth muscles.

↓

Nitrate receptor posses -SH group which reduce Nitrate to Nitrite and Nitric oxide (NO).

↓

NO is converted into Nitrosothiol.

↓

Which activate intracellular guanylate cyclase to converted GTP to CGMP

↓

(Ca++) Ca-mp.

↓

Vascular smooth muscle relaxation

↓

Inhibition of Ca^{+2} entry via L-type Ca^{+2} channel.

↓

cGMP activate of dephosphorylation of Myosin light chains (PO_4) to MLC.

↓

which prevent Interaction of Myosin with actin, lead to vascular smooth Muscle relaxation

↓

formation of PGE_2 or PGI_2 and membrane Hyperpolarization.

Adver :-

- flushing of face
- Syncope
- postural Hypotension
- Headache -

* Contraindication.

- Glucoma
- Migraine
- Organic Nitrate tolerance.

Uses :-

- used for prophylaxis of Angina
- Myocardial Infarction
- CHF
- Cyanide poisoning.

Q8

Anti-dysrhythmic agent.

- Definition :- The disorder in rate and rhythm of cardiac contraction due to myocardial damage is known as cardiac arrhythmias.

- These drug are use to prevent or treat irregularities of cardiac rhythm.

* Classification :-

1 Class - I [Na^+ Channel blockers]

(a) Group A :-
ex :- Quinidine
- Procainamide

(b) Group B :-
ex :- Lidocaine
Tocainide.
Phenytoins.

(c) Group C :-
ex :- Flecainide
Encainide.

(2) Class II [β-blockers]

- Propranolol
- Atenolol
- Metaprolol.

(3) Class III [Repolarising prolonging]

ex:- Amidarone.

(4) Class IV [Ca^{+2} Channel blockers]

ex:- Verapmil.
- Deltizem.

Q. Quinidine

→ Quinidine is dextro isomer of the anti-Malarial alkaloid quinine. found in cinchona bark.

- At high doses it can precipitate arrhythmias.

↓

which leads fatal Ventricular fibrillation.

MOA

Quinidine bind to open and in activated Na^+ channel.

↓

Prevent Na^+ influx.

↓

Showing the rapid uptake during phase-0.

↓

It also (decs) the slope of phase-4 Spontaneous depolarization.

Therapeutic use :-

- Quinidine effective in many atrial and ventricular arrhythmias, it is rarely used now.

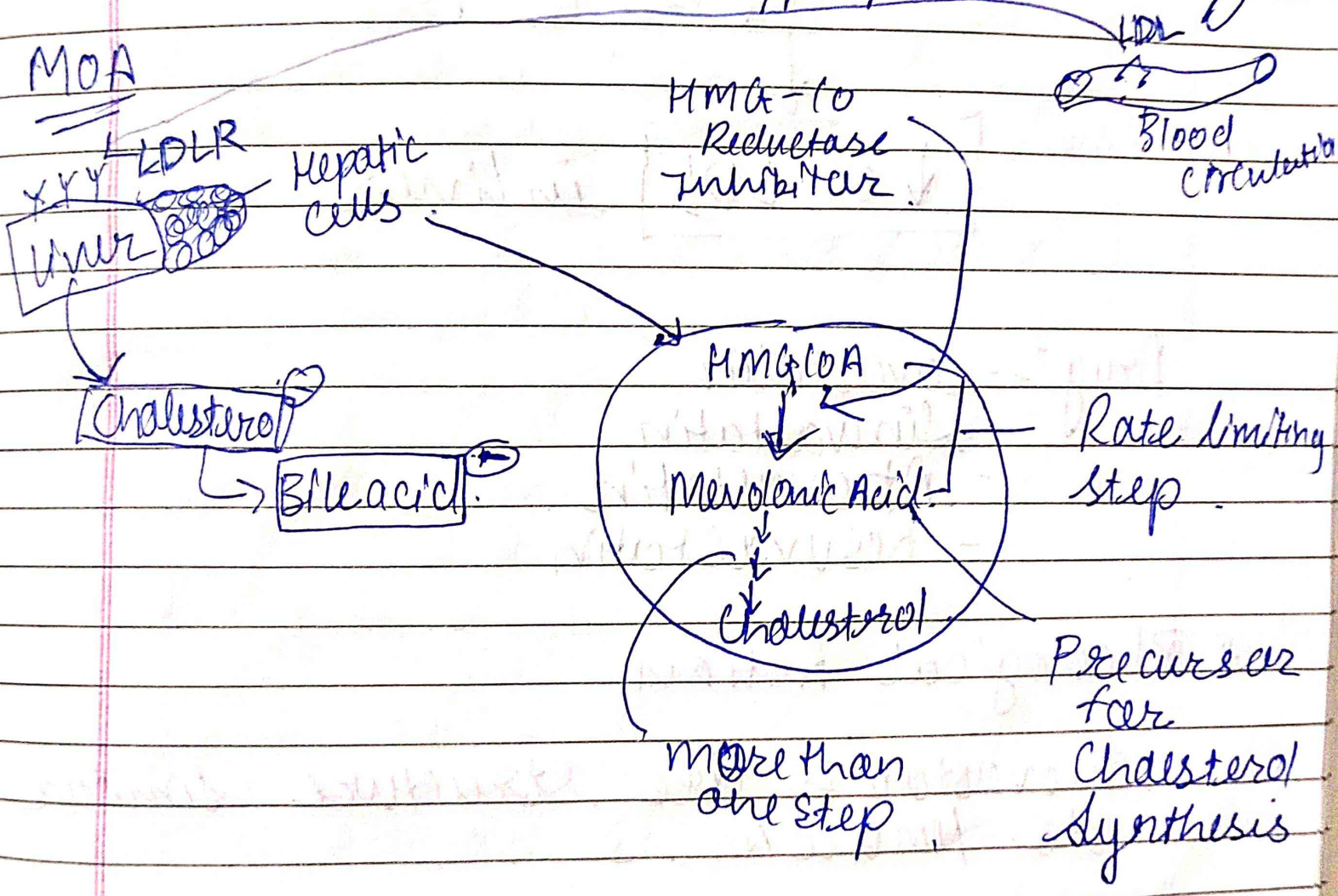
- Because of risk of adverse effects sudden cardiac arrest or ventricular fibrillation (VF), vascular collapse, thrombocytopenia etc.

[statins]

HMG-CO-Reductase Inhibitor.

- These are the drug which lower the level of lipids and lipoprotein in blood. Called as Hypolipidemic drug.

MOA



Statins.

↓

Inhibit HMG CO.A reductase

↓

↓es Mevalonate

↓

↓es Synthesis of Cholesterol

↓

↓es LDL in liver

Drug :- - lovastatin
- Simvastatin
- Atorvastatin
- Rosuvastatin

* Pl cological Action

- Atorvastatin are structure similar to HMG-COA.

- Competitively Inhibit HMG-COA reductase And leads to Inhibit Conversion of HMG-COA to Mevalonic acid.

- Therapeutic dose cholesterol synthesis by 20-50%.
- Result in fall in LDL and Triglyceraldehyde
- To attened Maximum effect these are Administrated at Night, because HMG-COA Reductase activity is Maximum At night.

*- Adverse effect.

- Headache, Nausea, bowel upset, rashes, sleep disturbances.
- Myopathy
- Contra Indicated in pregnancy.
- Rarely :- Cough, dizziness, skin rashes.
- Therapeutical uses :-
- lowering plasma cholesterol level in All types of Hyperlipidemia.

- Atherosclerosis.

- In Patients with MI, Angina pectoris, stroke transient ischemic Attack to lower Cholesterol level.

Q. Classify Anti-hyperlipidemics

Anti-Hyperlipedemic

(1) HMG CO Reductase Inhibitor
- Livastain
- Rosuvastain
- Atorvastain
- Simastain.

(2) Lipoprotein lipase activators
- Clofibrate
- Benzafibrate.

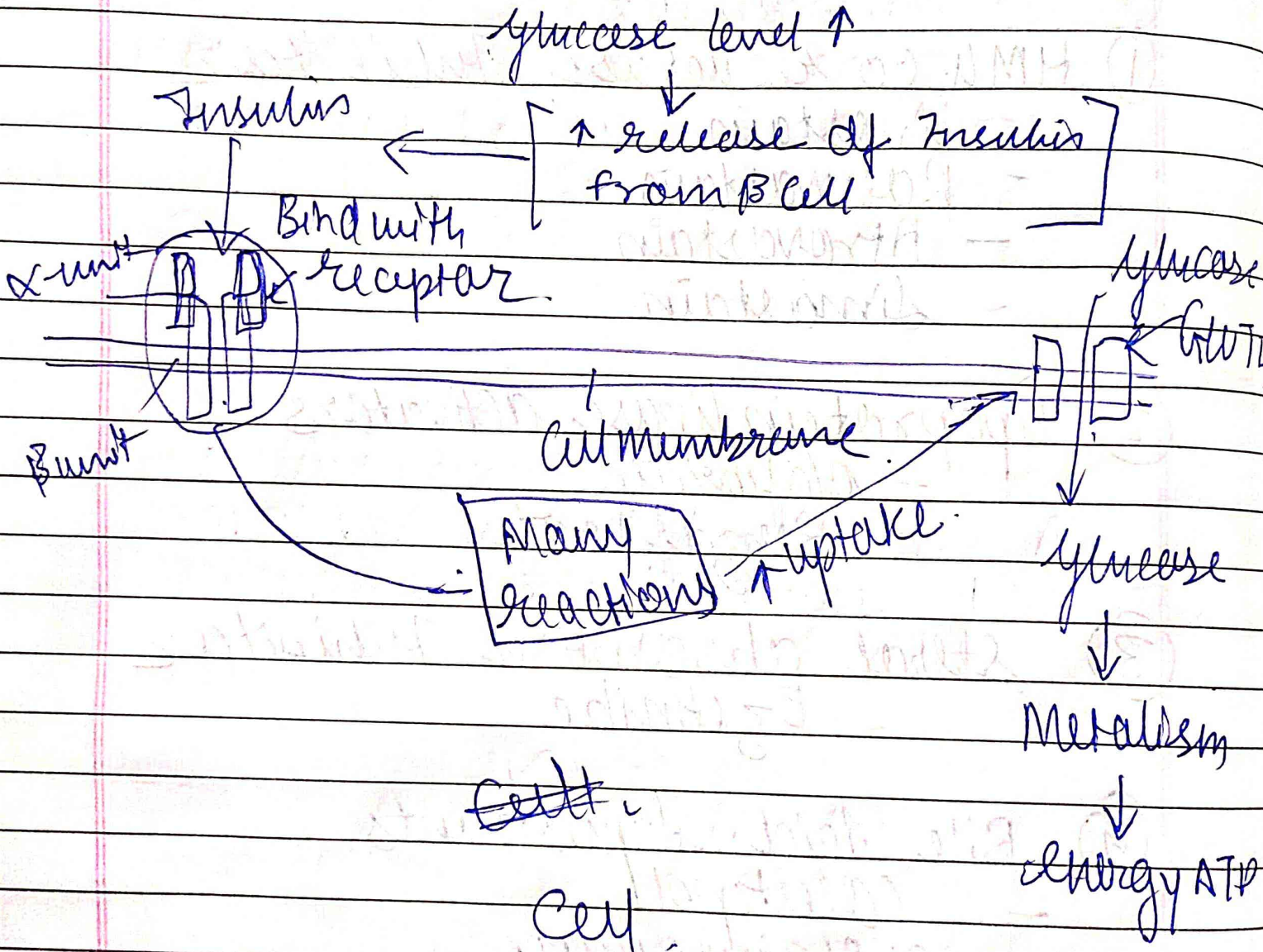
(3) Steral absorbtion Inhibitor
- Ezetimibe.

(4) Bile Acid Sequestrants
- Colestipol
- Cholestyramine.

(5) Lipolysis and triglyceride synthesis Inhibitor
- Nicotinic Acid.

Q

110A and pharmacological Action of Insulin



~~Cell~~.

Cell.

- Insulin receptor in Mammalian cell is large trans Membrane glycoprotein

↓

It composed of 2 α subunit and 2-β subunits

↓

linked by disulfide bonds to constitute β-α-α-β Heterotetramer

↓

β-subunit contains tyrosine kinase ~~acid~~ residues

↓

When Insulin bonds to the α-subunits at Outside of cell surface

↓

* Tyrosine kinase activity in β-subunit is stimulate

↓

Adjacement β-subunit and phosphoryl-ation of tyrosine residue

↓

present on a Cytoplasmic proteins

called as Insulin receptor substrate I.

↓

generated by phosphorylation of IRS-2 (phospholipase-II activate)

For 2nd messengers such as IP3s and DAGs.

↓

Insulin stimulates the glucose transport across cell membrane by ATP dependent translocation of GLUT-4 to plasma membrane

↓

* IRS-1 also stimulate PK activation and other kinase are important for regulation of proliferation and differentiation of several cell type.

↓

Insulin receptor complex is internalised

by endocytosis.

↓

followed by degradation of Insulin and recycling of the receptor to cell surface

↓

* Physiological Action

→ Insulin promotes the uptake and storage of glucose, fats and protein through effect on liver, muscles and adipose tissue.

- Excess secretion of Insulin lead to hypoglycemia, lack of insulin release leads to Hyperglycemia.

On liver cells

- ↓es glycogenolysis Inhibiting glycogen phosphorylase and ↑se glycogenesis by activate glycogen synthetase.

* On Muscle :-

Glucose uptake by promoting translocation of GLUT-4

It promote glycogen synthesis and res glycolysis.

Uses :-

- Used as the specific replacement therapy in diabetes Mellitus.
- Used in emergency treatment of diabetic ketoacidosis.

Adv :-

- Hypoglycemia
- Allergic reaction

Q. ⇒ Corticosteroids.

Corticosteroids are steroid hormones secreted by the adrenal cortex of adrenal gland.

- The adrenal cortex of adrenal gland synthesis numerous steroids hormons which are ~~collecting~~ collectively called as Corticosteroids.

There are two types :-

Glucocorticoids

Mineralocorticoids

- They have various Metabolic function and some are used to treat inflammation.

Action of Corticosteroids.

- Aldosterone is the prototype of Mineralo corticoid effects.

- Act on the distal tubule to enhance absorption of Na^+.
- Increase excretion of K^+ and H.
- Similar effect occur in colon, sweat gland and salivary gland.

→ Deficiency of Mineralocorticoid action lead to :-

- dilutional hyponatraemia, hyperkalaemia, acidosis, Massive loss of Na^+ and decreased ECF volume.
- Hyperaldosteronism :-
  Positive Na^+ Balance, expansion of ECF, increased plasma Na, hypokalaemia, alkalosis and progressive rise in BP - hypertension, Myocardial, fibrosis etc.

Therapeutic uses :

- A Number of diverse disease states respond to ACs.

- Physiologic doses of corticosteroids are used for replacement therapy in primary and secondary adrenal insufficiency such as Addison's disease.

- Supraphysiologic doses are used for their anti-inflammatory effect in arthritis, asthma and inflammatory bowel disease.

Adv =

Glucocorticosteroids

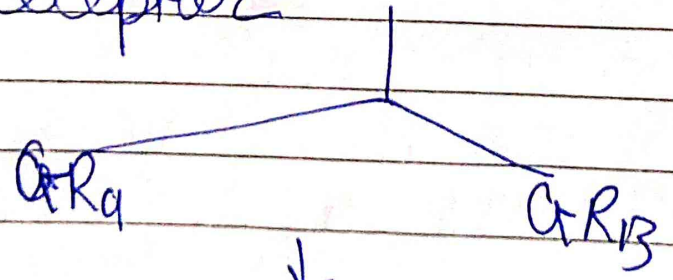
- Glucocorticoids refers to steroidal hormons secreted by the adrenal cortex of adrenal gland.

These corticosteroids control carbohydrate, fat and protein Metabolism.

- They show anti-corticosteroids control carbohydrate, fat and protein Metabolism. They show anti-inflammatory action by inhibiting phospholipid released.

MOA

→ Glucocorticoids action steroid Nuclear recepter



↓

These receptors passess 3 domains.



↓ Glucocorticoid Binding domain

↓ DNA Binding domain

↓ Regulatory domain

- Glucocorticoids enters into the cells and Bind to the receptors in Cytoplasm

↓

They get activated and undergo Conformational change and enter into the Nucleus.

↓

And also bind to Chromatin there and repress or induce transcription of genes which.

↓

Modifies Protein Synthesis.

* Pharmacological Actions :-

1) Carbohydrate Metabolism

Main effect of Carbohydrate Metabolism

and Hunel, called glucocorticoids

- They produce both Insulin like and Anti Insulin.

- Like Insulin :- They stimulate formation of glycogen in liver and Muscle and increased gluconeogenesis in liver

- Unlike Insulin :- They depress glucose uptake and it's oxidation by tissue. & Help in Absorption of dyes

(2) Protein Metabolism :-

↑es the rate of deamination and Break down of tissue proteins to amino acid.

↓

Thus body protein are loss and ↑es Nitrogen excretion.

- They also ↓es protein Synthesis by interfering with Nucleic

Acid Metabolism

→ Adv :-

- Gastritis, peptic Ulceration and Intestinal perforation.
- Epilepsy in Children.
- Glaucoma.
- loss of Hair, Hirsutism, etc.
- Myopathy and Osteoporosis.

→ Therapeutic uses

- used to Endocrine disorder.
- Also used to treat many allergic reaction
- It is used as anti inflammatory or Immune suppressive agent.

Q Replacement Therapy by Corticosteroids

→ Adrenal Insufficiency - acute / chronic.

- Abrupt withdrawal of steroid therapy.
- Chronic Infections - Tuberculosis.
- Auto immune adrenal disease
- Surgery - Hemorrhage and APDS.

→ Congenital adrenal hyperplasia.

- Congenital disorder due to deficiency of 21-hydroxylase enzyme - no Cortisol but ACTH - increased androgen production.

→ Acute adrenal insufficiency

- IV replacement of Sodium Chloride and fluid.
- IV hydrocortisone 100 mg Stat

followed by 100 mg every 8 hrs - Maximal daily rate of secretion.

→ Chronic adrenal insufficiency.

- Hydrocortisone
- Prednisolone or dexamethasone - long acting
- Fludrocortisone for Mineralocorticoid effects.

→ Congenital adrenal hyperplasia.

- Hydrocortisone 0.6 mg / kg in divided doses - to maintain feedback suppression.

Q Anti-rheumatic drug [DMARDS]

→ An auto-immune disease in which there is joint inflammation synovial proliferation and destruction of articular cartilage

Immune complexes

↓

Composed of Igm

↓

Activate compliment

↓

release cytokines

↓

Which are chemotactic for Neutrophils

* Normal and Arthritic Joints :-

- The Inflammatory cells secrete lysosomal enzymes which damage cartilage and erode bone while PGs produced in the process cause vasodilator

Drug for Rheumatoid Arthritis :-
- NSAIDS
- corticosteroids - DMARDS.
and Pain.

→ classification of Rheumatoid arthritis :-

① - Disease Modifying Anti-rheumatoid drugs

Ⓐ non-biological drugs.

- Immune suppressants
  - Methotrexate
  - Azathioprine
  - Cyclosporine
- Sulfa salazine
- Chloroquine
  - Hydroxy chloroquine
- Leflunomide

Ⓑ Biological drugs.

- TNF-α-Inhibitors
  - Adalimumas
  - Infliximab.
- IL-1 Anatagonist
  - Anakinra.

(2) Adjuvant drug

↓

Prednisolone and other glucocorticoids

* DMARDs:

- Methotrexate :-
  - 1st Chaice DMARDs for R.A
  - It is folate antagonist
  - Inhibit folate reductase, lymphocyte proliferation, production of cytokines
- ADR: nausea - mucosal ulcer - Hepatotoxicity

Folic acid $\xrightarrow[\text{synthetase}]{\text{Dihydropteroate}}$ DHFA $\xrightarrow[\text{reductase}]{\text{DMFA}}$ THFA $\xrightarrow{\text{Thymidylate}}$ Thymidylate → Purine synthesis → DNA.

* Sulfasalazine :-

- It have anti-inflammatory activity in the bowel and useful in ulcerative colitis
- It is a compound of sulfapyridine and 5-amino salicylic acid.

VISION DATE : PAGE NO.

* Hydroxychloroquine

→ Anti malarial drug.
- low toxicity but also low efficacy.
- Doesn't prevent bone destruction
- Inhibit B lymphocytes.

* TNFα Inhibitor
- Etanercept
↓
Competitive Inhibitor of TNFα receptor located on T-cells, Macrophage
↓
Anti-Inflammatory activity
- quicker than non-biological drug
Anakinra
↓
Competitive Inhibitor of IL-1 receptor → Anti Inflammatory activity.

Teacher's Signature

Anti thyroid drugs

- Anti thyroid drug are the drug which are used in the treatment of Hyperthyrodism.
- These drugs control over production.

Classification

(A) Thio Amide derivatives
- Propylthiouracil.
- Carbimazol
- Methimazole

(B) Radioactive Iodine.
- Iodine ^{131}

(C) Iodinated Contrast Media.
- Oral Ipodate and Ipanoic acid
- Diatrizoate (IV).

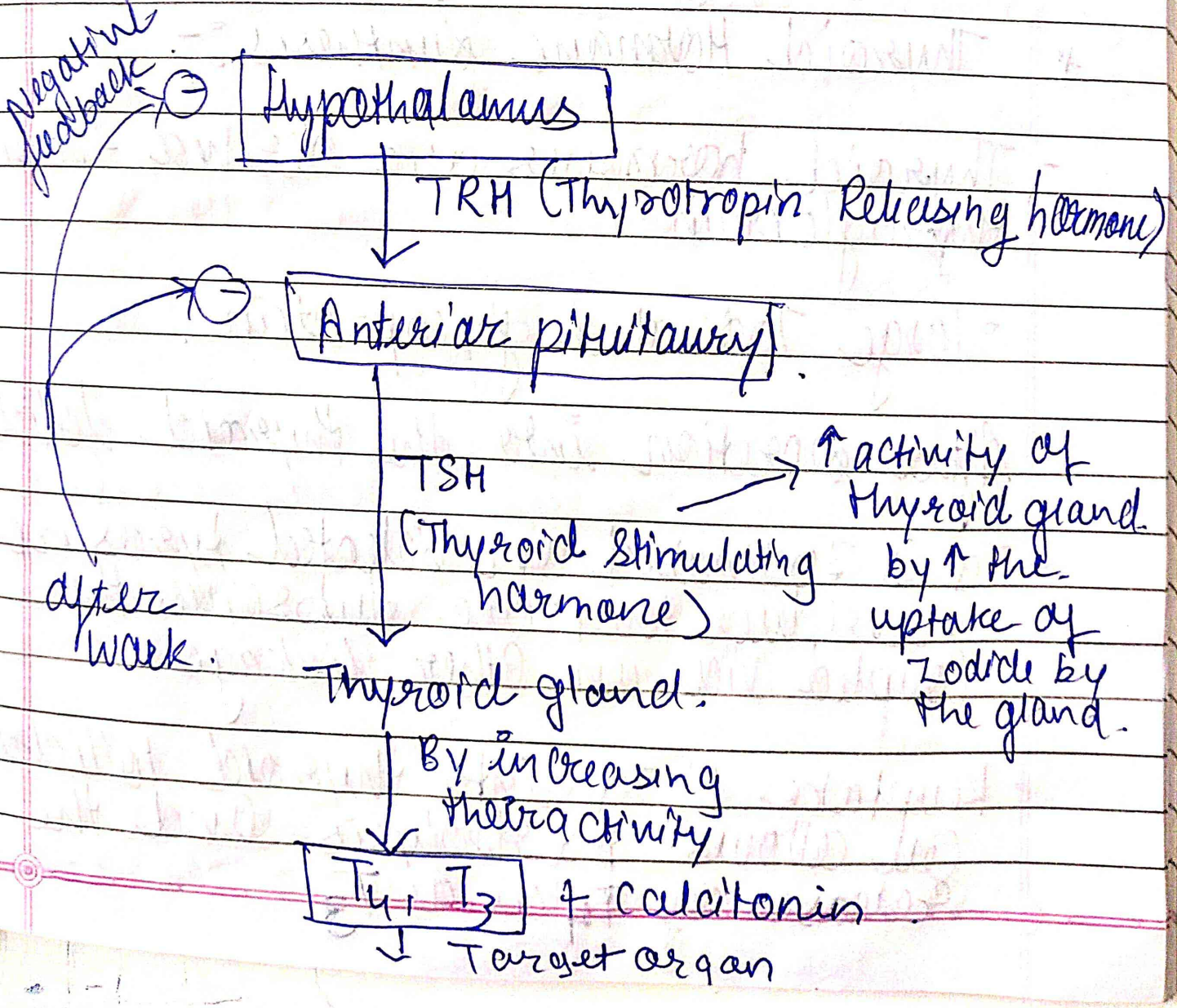
(D) Iodides
- Aqueous potassium Iodide Solution.

(e) Anion Inhibitor
ex :- Perchlorates
- Thiocynates.

Thyroid hormones ...

- Those hormones which are secreted from thyroid glands and are responsible for body's growth and work.

Thyroid gland :- A butterfly shaped gland which present on neck in front of trachea.



* Regulation of thyroid hormone synthesis.

T_4 and T_3 feed back to inhibit.

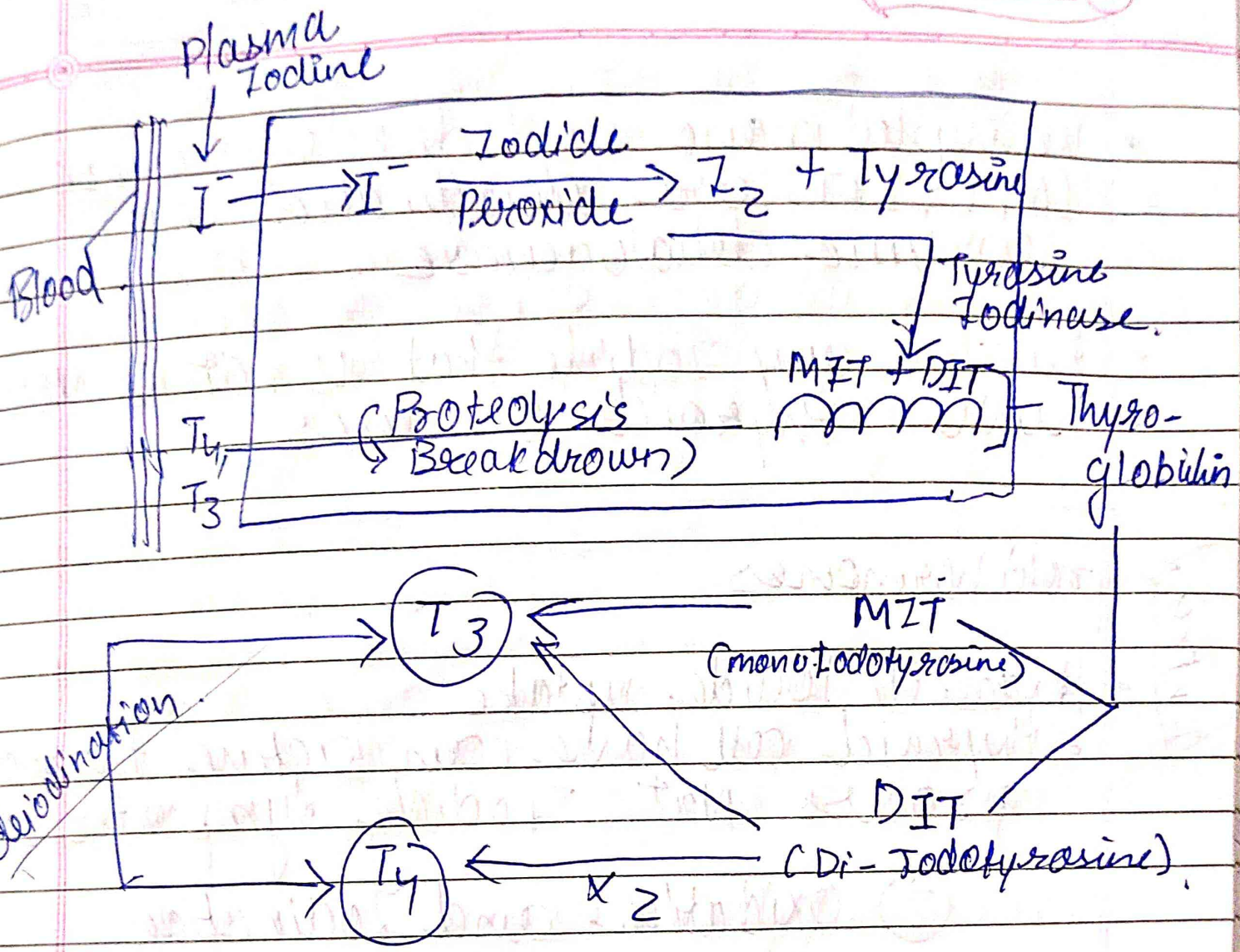
- Hypothalamic production of thyrotropin releasing hormone (TRH).
- Pituitary production of thyroid-stimulating hormone (TSH).

* Thyroid Hormone Synthesis :-

- Thyroid hormones are derived from thyroglobulin
  - large Iodinated glycoprotein.

After secretion into the thyroid follicle.

- Tg is Iodinated on selected tyrosine residues that are subsequently coupled via an ether linkage.
- Reuptake of Tg into thyroid follicular cell allows proteolysis and the release of T_4 and T_3



Storage, Release

- After Coupling, Tg, is taken back into thyroid cell
- It is processed in lysosome to release T_4 and T_3.

- Uncoupled mono- and di'odotyrosine (MIT & DIT) are deiodinated by enzyme dehalogenase.
- Recycling any Iodide that is not converted into thyroid hormones.

Thyroid hormones

- ~~Hormones~~ (1) Iodide uptake
  - Thyroid cell have an active transport process Na^+: Iodide symporter (NIS)

(2) Oxidation and Iodination

- Iodide trapped by follicular cells is carried across the apical membrane by another transporter termed 'pendrin' and oxidized by the membrane bound thyroid peroxidase enzyme to
  - Iodium (I+) ions or
  - hypoiodous acid (HOI) or
  - enzyme linked hypoiodate (E-OI) with the help of H_2O_2.

③ Coupling

- Normally much more T_4 than T_3 is formed
- Oxidation of Iodide and coupling are both stimulated by TSH

Q/ Write A Note On Selective estrogen receptor Modulator [SERMs]

→ Serms are non-Steroidal Synthetic agent whose against or Antagonist activity On estrogen receptor [ER] are tissue Selective.

- They produce estrogenic effect in Certain Organ / tissues [bone, brain and liver] and prevent deleterious estrogenic effect in some organs or tissue by BY exhibiting Antagonistic or no activity On ER.

Examples Of SERMs :-

- Clomiphene
- Ormeloxifen
- tamoxifen
- Idoxifen
- Juloxifen

→ estrogen Antagonists

* Clomiphene

- Orally active SERM
- Acts as competitive antagonist of ER in hypothalamus
- Inhibits negative feedback effects on the release of GnRH
- Increases the ~~of~~ pulse frequency of GnRH.

Uses
- Infertility due to ~~anvo~~ anovulation.
- In vitro fertilization.

Adver:-
twins or even Multiple pregnancy
- Ovarian enlargement
- Poly Cystic Ovaries
- Hot flushes
- Weight gain.

TAMOXIFEN

- Potent ER antagonist at
  - Breast
  - Blood vessel.

- ER agonist at
  - Uterus
  - Bone
  - Liver

MOA

Competitive Inhibitor of estradiol binding to the ER.

- Binding of estradiol and SERM to the estrogen binding sites of the ER's initiate a change in conformation of the ER, dissociates the ER form heat shock protein and Inhibition of ER dimerisation.

- Up regulates Transforming growth factors B

- Decreases total serum Cholestrol.

- Decreases LDL cholesterol.

Uses :-
- Breast carcinoma - Pre and postmenopausal.
- Prevent post-Menopausal osteoporosis
- Improves bone density

Adv :-
- Hot flushes
- Menstrual irregularities
- Nausea
- Vomiting
- Anorexia
- Hair loss

Q. Oral Contraceptive.

* classification of Oral Contraceptive:

(1) Combined Oral Contraceptive
[estrogen and progesterone]

(a) Monophasic pills
- Drospirenone

(b) Multiphasic pills.
- Norgestimate.

(2) Progestin only pills.
eg: Norethindrone.

(3) Emergency Contraceptives pills.

(a) levonorgestrel
(b) Ulipristal.

MoA :-

Estrogen.

Maintain steady state level of estrogen and progesterone

Inhibit the FSH secretion.

Inhibit the LH secretion.

Inhibit the Ovulation.

Progesteron.

Thicken the cervical mucus.

Prevent the entry of sperm.

Alter the endometrium

Prevent the Implantation

Adverse effects :-

- esterogen :-
  - Nausea, Migraine,
  - Breast tenderness
  - Cholestatic Jaundice
  - Hepatic adenoma
  - edema
  - Break through bleeding
  - Depression

Progesterone :-

- ↑ appetite
- Weight gain
- Virilism
- Acne
- ↓ es in libido.
- Hypertension.

* Uses :-
  - Menstraual irregularities
  - Dysfunctional uterine bleeding
  - Acne
  - Contraception.

Q. Principle and Application of Bioassay.

Estimation of the Potency of an active Principle in a unit quantity of preparation or detection and Measurement of the Concentration of the substance in a preparation using biological Method is known as Biological Assay.

Principle of Bioassay :-

- The basic principle of bioassay is to Compare Test substance with the standard preparation of the same and to find out How much test substance is produce same biological effect as produce by the standard.

- Standard are the Internationally Sample of the drug Maintained and recommended by the expert committee of the Biological Standardization of WHO

- They represent the fix units of Activity for drug.

- In India std drug are Maintained in Central drug research institute, Lucknow and central drug laboratory Kolkata.

- The problem, biological Variation must be Minimized as possible.

- For that should keep uniform experimental condition and assure the reproducibility of the response.

* Application of Bioassay :-

- Bioassay Compared to other Method of Assay are less accurate, less elaborate, More laborious, And more expensive.

- Bioassy when Carried out in whole Animal the effect of drug like Metabolism, Nervous Control, blood supply etc.

=> Bioassay is the only Method of Assay under following condition :-

(1) Active principle of drug is unknown or cannot be pin pointed.

eg :- Insulin, Streptokinase.

(2) Chemical Method is either not available or if available Complex and Insensitive or required Higher dose.

eg :- acetylcholine, glucagon.

(3) Chemical composition is not known.

eg :- Vaccines, Antitoxin, toxin and hirbal preparation.

- Stability conducted by bioAssay
- Bioassay also measure any toxicity.
- Bioassay is help in diagnosis of various condition

eg :- gonadotrophins for pregnancy.

Q

Fibrinolytics.

"These agents are those drugs which lyse the clot or thrombus by dissolving the fibrin."

* Mechanism of Action

Plasminogen is a protein, circulates in the plasma and also some of it is Bound to fibrin.

Plasminogen (Inactive)

↓ fibrinolytic drugs

Plasmin (Active form)

↓

Fibrin → degradation → fibrin degraded products.

Thereby by breaking fibrin into degraded products they dissolve the clot.

* Classification

(1) First generation drugs

eg:- streptokinase, Urokinase

(2) Second generation drugs

- Also known as Tissue plasminogen activator

e.g :- Alteplase, Reteplase, Duteplase.

* Streptokinase.

→ It is an enzyme obtained from streptococci
- It combines indirectly with plasminogen and activates fibrinolytic system.

Advantages :-

(a) It is least expensive
(b) Heparin is not required
(c) It is very much effective in reducing Infarct size.

disadvantages :-

a) It is antigenic
b) It may produce hypotension.
c) It is least clot selective.

* Urokinase.

- It is isolated from human kidney cells
- It combines directly with plasminogen and activates fibrinolytic systems.

Advantages
a) It is non-antigenic
b) It is Modest clot selective
c) It doesnot produce hypotension.

Disadvantages :-
a) It is very expensive
b) Heparin administration is required

* Tissue plasminogen activator (tPA)

- They are produced by recombinant DNA technology Hence, also known as rtPA.

It has remarkable specificity for interaction with plasminogen bound to fibrin. Hence it is highly clot selective.

- It doesn't produce hypotension and is non-antigenic but simultaneous heparin administration is required.

* Alteplace

Is very short acting (8 min Half life) while Tenecteplase is longer acting, and can be given as IV bolus injection. Its ability to bind fibrin is also better than Alteplace.

- Bleeding tendencies are also Negligible with these drugs but they are very expensive.

Uses of fibrinolytic drug

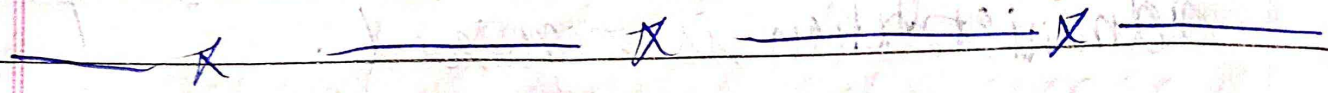
(1) Acute Myocardial Infarction

- Intravenous thrombolytics are given within

12 Hours but Preferably immediately to reduce Mortality rate.

(2) Deep Vein Thrombosis

(3) Pulmonary embolism



Oxytocics

"They are the drugs which stimulate the uterine contractions".

- They are also called as uterine stimulants
- They include oxytocin ergometrine and prostaglandins and mostly useful in ~~obstetrics~~ Obstetrics.

(1) Oxytocin

"It is a hormone synthesized in hypothalamus and secreted by posterior pituitary gland along with ADH.

Action

(a) Uterus :-

→ Oxytocin contracts the uterus.

→ Both force and frequency of contructions are enhanced by oxytocin and there is full relaxation in between the contractions which allows adequate blood supply to the foetus.

→ Estrogen enhances the synthesis of oxytocin receptors. Hence uterus

DATE
PAGE

becomes highly sensitive to Oxytocin at full term.

b) Mammary gland.

- Oxytocin facilitates Milk secretion by contraction of Myoepithelium in Mammary gland.
- Sucking stimulates the release of Oxytocin.

c) Oxytocin has Mild diuretic action.

* Uses

1) Induction of labour when uterine ~~contra~~ contractions are inadequate.

2) Post-Partum Haemorrhage.

- Bleeding after delivery can be reduced by administration of oxytocin.

3) Milk secretion

- When Milk secretion is impaired intranasal Oxytocin spray can be used

(2) Ergometrine.

- Ergometrine is Natural alkaloid derived from ergot alkaloids
- Ergometrine and its derivative - Methyl ergometrine are used as uterine stimulants.

Action.

- It is a powerful uterine stimulant.
- All parts of uterus get contract and there is no relaxation in between contractions.
- Ergometrine also cause some vasconstriction which helps to reduce bleeding from uterus in post-partal state.

* uses -

1) Post partum haemorrhage
- ergometrine is used over oxytocin to control and prevent PPH.

2) Ergometrine is also used to prevent uterine atony after caesarean section.

(5) Prostaglandins

- They play a significant role Menstruation as well as parturition.
- PGE_2 and $PGF_{2\alpha}$ stimulate the contraction of both pregnant and non-pregnant uterus through. Sensitivity is high during pregnancy.
- Prostaglandins produced by foetal tissue mediate initiation and progression of labours

⇒ Prostaglandins are also involved in the pathogenesis of dysmenorrhoea and Menorrhagia. Hence NSAIDs are useful in these conditions.

* uses

(a) Abortion.

- used as vaginal Suppositories to induce abortion
- PGs are also used with Mifepristone in termination of Pregnancy upto 9

Weeks.

(b) PPH
- used as alternative to ergometrine.
- Carboprost can be used.

(c) Cervical Priming
- gels are used intravaginally to soften the cervix and for cervical ripening prior to Induction of labour.

Q// Cardiac glycosides.

- Cardiac glycosides are those glycosides which have specific action to the failing heart.
- increase the force of contraction of failing heart and lowers the heart rate and thereby maintain an effective circulation

* Classification of Cardiac glycoside :-

1) Natural glycoside

(A) Plant Source
- from leaves of fox gloves :-

① - Digitalis lanata :-
- Digoxin, Digitoxin.

② - From the seeds of foxgloves
(a) Strophanthus Hombe :-
- Cymarin, Cymerol

(b) Strophanthus gratus :-
- Ouabain Spw4.

(B) animal source :-

- Toad Venom :- Bufotoxin.

Synthetic :-

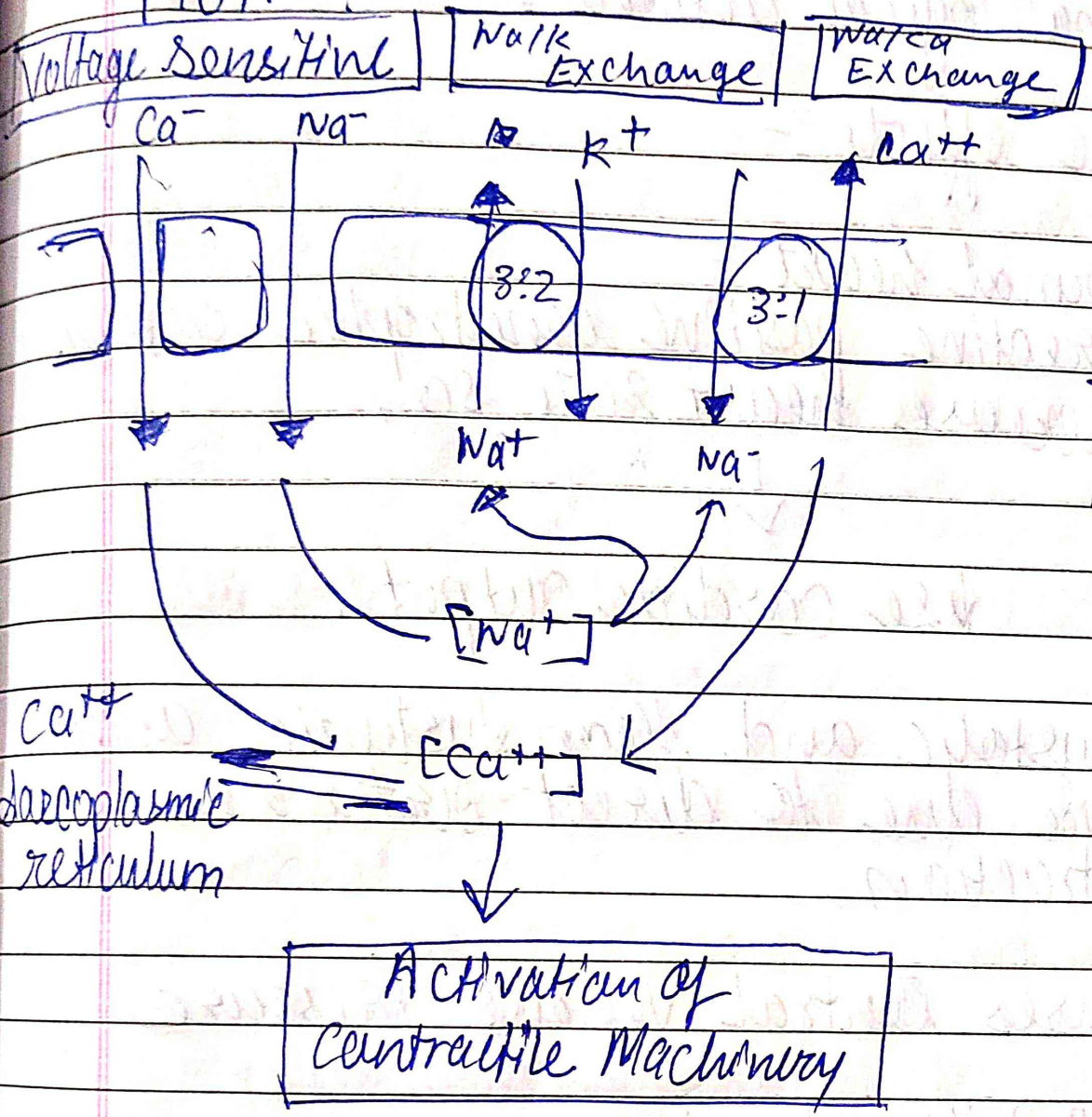
- Digitoxigenin
- Digoxigenin
- Gitoxigenin

Digitalis :-

Digitalis is a powerful Inhibitor of Na^+/K^+ ATPase.

As a result They increases the Efficiency of failing heart increasing Na^+ Conc^n within cell membrane; which Enhances Ca^{+2} availbility to the contractile apparatus and Increases the Contractility.

MOA



Glycoside

↓

Inhibition of Na/k exchange

↓

Increased [Na⁺]

↓

decreased Na/Ca exchange

↓

Increased [Ca⁺⁺]

↓

Increased Contraction

* Pharmacological actions :-

(A) Cardiac effects :-

On Normal heart :-

- directive positive ionotrophic action
- decrease heart rate so,

↓

↓se cardiac output.

↑se systolic and Mean Systemic artrial pressure due to direct Arteriolar contraction

- decreases Central Venous pressure

(B) on a failing heart.

- Direct action :- Positive inotropic action

Indirect action and decrease since Nute so decrease heart rates.

diuretics

classification

1) loop diuretics
   - Furosemide
   - Bumetanide
   - Torasemide

2) Benzothia-diazines
   - Hydrochlorothiazide
   - Benzthiazide

3) Thiazide
   - Chlorthalidone
   - Metalozone
   - Clopamide

4) Carbonic Anhydrase Inhibitor
   - Acetazolamide

5) Potassium Sparing diuretics
   - Spironolactone
   - Eplerenone
   - Amiloride

⑥ Osmotic diuretics.
- Mannitol
- Glycerol.

Thiazide diuretics -

MOA :-

Act as a distal convoluted tubule

↓

Inhibit Na^+Cl^- Co-transporter

↓

Inhibit reabsorption of Na^+

↓

Inhibit reabsorbtion of water

↓

↑ se urine output

↓

↓es blood volume

↓

↓es blood pressure.

Adverse effect

- Hypokalemic.
  Metabolic alkalosis
- Hypercalemia
- Hyperuricemia.
  Hypotension
- Hyperlipidemia.

* Uses = Hypertension
  - Les Blood pressure
- Congestive Heart failure
- Pulmonary oedema.
- Nephrotic Syndrome.

H1 receptor Antagonists →

First generation

- Diphenhydramine
- Trepridine
- Promethazine

Second generation

- Cetirizine
- levocetirizine

These are those drugs which Inhibit the action of histamine.

Pharmacological actions :-

General Antihistamine actions :-

- All antihistamines blocks histamine induced vasodilation, allergy, Anaphylaxis, triple response, contraction of smooth Muscles, hypotension, headache etc.

Central Nervous System :-

Most of the antihistamines produce CNS depression of varing degree - It may be sedation, drowsiness or even sleep.

- Promethazine and diphenhydramine are more patent as sedative.

* Therapeutic uses:-

1 Supression of urticaria, pruritis, sneezing, rhinorrhoea and other allergic reactions

2 As sedative and hypnotic

3 Parkinsonism

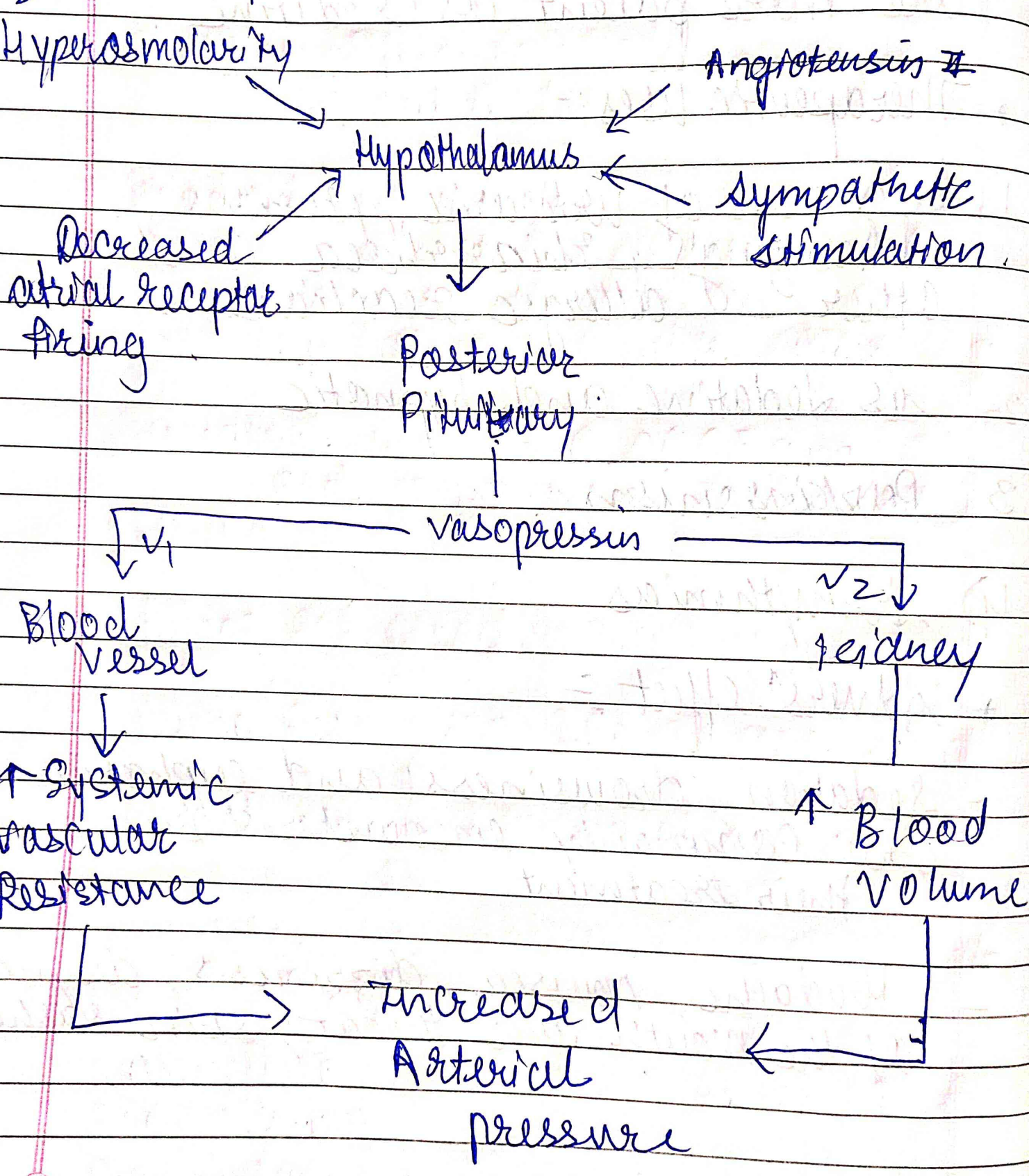
4) Arrhythmias

* Adverse effect :-

- Sedation drowsiness and euphoria are commonly encountered by their treatment.

- Headache nausea, dizziness, dryness of the mouth and throat, skin rashes

Vasopressin (ADH)



- Vasopressin is also known as Anti-diuretic

- It is a ~~hor~~ nano-peptide hormone which formed in hypothalamus then transported via axons to the posterior pituitary wherein store and release.

- Major site of action :- kidney and Blood Vessels
- It has a vasopressor action i.e can stimulate Contraction of arteries and capillaries. Hence the name Vasopressin.

Bioassay

Bioassay is defined as estimation of the concentration or potency of a substance by measuring its Biological response in a living system.

Principle :- Potency of vasopressin injection is determined by comparing test activity with that of standered preparation of Vasopressin.

Activity :- Blood pressure response

Model :- 1) Albino Rat Model
2) Cat Modes

Standard preparation :- It is a dried Acetone extract of posterior lobes of pituitary gland of Oxen or any other suitable preparation.

Standard unit :- 0.0005 gm of std preparation (20 unit/mg)

Albino Rat Model.

- Albino Rats (200-250 g) are selected
- Anaesthetized by suitable agent
- Cannulate the trachea for artificial respiration
- Cannulate the Carotid artery for BP Monitering
- Cannulate the Femoral Vein for Drug Injection

↓

Heparin (2004/100g) is Injected.

↓

A suitable hypotensive agent is given into tail vein to produce a constant basal pressure of 50 torr.

↓

Std and test preparation are diluted for the administration:

↓

2 doses of std are selected so low dose produce 30 torr B.P. higher dose produces 50 torr B.P.

↓

Test doses are selected according to Standard doses.

↓

Doses are added at intervals of 3-5 min. in a random order.

↓

Record rise in B.P in response to each dose.

Bioassay of Insulin

→ Rabbit Model.
→ Mice model.

- Standard Solution.
It is prepared by using pure, dry and crystalline insulin and one unit contains 0.04082 mg or 40.82 µg.

Preperation of std solution.

20 unit pure insulin is dissolved in small volume normal saline and Acidify it with HCl to PH 2.5.

0.5% phenol is added as preservative

Add 1.4% to 1.8% Glycerin

- Final solution contains 20 unit/ml.

Store the solution in a cool place and use it within six month.

Rabbit moduls.

Animal Selection :-

- Experiment Procedures should be approved prior to the Experiment by IAEC.*
- Thereafter healthy rabbit (2-3 kg) are selected
- After that animal are kept in fasting for 18 h before performing the assay.

Std and Test Sample dilution.

1 IU/ml and 2 IU/ml solution is freshly prepared from stock solution of standard and test solutions.

Principle :- The potency of a test sample is estimated by comparing the hypoglycemic effect of the sample with that of the Std. preparation of Insulin.

Animal are divided into 4 group and each containing 3-5 animals.

↓

Initial Blood sugar level.

↓

A sample of Blood is withdrawn from marginal ear vein of each rabbit.

↓

group No	group Name	Treatment
I	Std-1	Std dilution - S.C.
II	Std- 2	Std dilution-2 S.C.
III	Test-1	Test dilution-1 S.C
IV	Test-2	Test dilution-2 S.C.

After std and test Insulin injection from each rabbit.

↓

A sample of blood is withdrawn up to 5hrs at the interval of 1hr each.

Blood sugar is determined again.

↓

Cross over Test

- Same animals are used for the second part after one week.
- Again animals are fasted and initial blood sugar is determined.
- The grouping is reversed. animals which received the std are given test

~~std~~ test to std.

Bioassay of oxytocin

Principle :-

Potency of oxytocin is determined by comparing its specific activity with std preparation of oxytocin by using specific biological assay Method.

Activity
- Contraction of uterus
- Depression of BP
- Milk Ejection pressure

Std :-
It contain freeze dried synthetic oxytocin peptide with human albumin and citric acid.

Bioassay Methods -

Method A :- B.P lowering effects on - chicken

Method B :- Contraction of Uterine Muscle On isolated rat Uterus Model.

Method C :- Milk Ejection pressure in lactating rats.

Method A

- Young Male Chickens (1 to 2 kg) are selected.
- Expose Gluteus primus Muscle and locate popliteal artery and Crural vein.
- Cannulate the popliteal artery for BP Monitoring and Crural Vein for Infusion of Test / Std Oxytocin
- Inject (0.1ml to 0.5ml) 1st dose of Std dilute solution of Oxytocin
- Record B.P response.
- Required dose for decrease in BP. 20 - 100 mU.
- 3 - 10 min after 1st dose, 2nd dose of Std solution injected and record the Blood Pressure.

test solution injected and recorded the BP.

So as to obtain responses similar to those obtained with the std.

~~calcu~~ the ratio between the two dose of Test should be the same as std.

- ~~Repeated~~ Repeated the procedure at least 6 responses.

- and Calculate Mean result of each dose of Test and std.

Bioassay of Digitalis

- It is a cardiac glycoside.
- digitalis are the cardiotonic drug, which are used in the treatment of CHF
- digitalis mainly affects the ion transport system and electrophysiology on Myocardial tissue

Principle :-
Potency of the test sample of digitalis is compared with that of the std. preparation of digitalis by determining the action on the cardiac muscle like cardiac arrest.

Extract preparation of std and Test

- Exact amount of the powder is extracted with dehydrated alcohol in a continuous extraction apparatus for six hours.
- The final extract should contain 10 ml per

10g of digitalis powder

- And it should be stored in between 5 to -5°C

* Preparation of Std and Test

- Std and test sample extracts are diluted with Normal Saline.

Animal Models

1) Guinea pig Model (End point Method)
2) Pigeon Model.

Antiplatelet drugs

1) TXA_2 synthase Inhibitors
   - Aspirin.

2) Adenosine di phosphate (ADP) receptor Inhibitor
   1) Irreversible - Ticlopidine.
   2) Reversible - Ticagrelor, Cangrelor

3) Phosphodiesterase Inhibitors.
   - Dipyridamole.

4) Glycoprotein IIb/IIIa Inhibitor :-
   Tirofiban, Defibrotide.