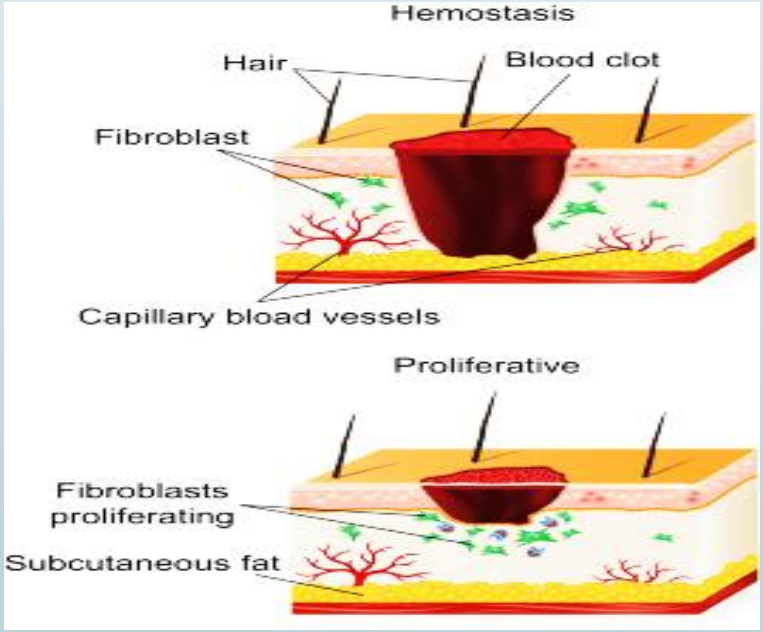
9. BLOOD LYSIS.



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*Causes of **fluidity of blood** inside the cardiovascular system [Factors against intravascular clotting]:

These factors prevent blood clotting in normal state and in cases of injury they limit the process of blood coagulation to the site of injury and help re-canalisation of thrombosed blood vessels:

1) Role of smoothness of endothelium in prevention of clotting:

a- Prevent contact activation of XII.

b- Protein that covers the endothelium has –ve charges which repels –ve charged platelet & clotting factors.

c- Protein (**thrombomodulin**) which cover endothelium binds with thrombin preventing its action and this complex activates protein- C that act as an anticoagulant.

d- Release of prostacyclin (major inhibitor of platelets aggregation) from the healthy endothelium.

2) Anticoagulant in the blood itself:

a- Blood flow: Removal of activated coagulation factors by the circulating blood and their inactivation in the liver, spleen and the bone marrow.

b- Antithrombin action of fibrin and antithrombin III:

Fibrin: adsorb about 90% of thrombin formed during this process preventing its spread into the blood causing more coagulation.

Antithrombin III (alpha globulin) Combine and inhibit the remaining thrombin and factor Xa.

c- **Protein C** & **protein S**: (Both are natural anticoagulants are formed in the liver in presence of vit.K)

Protein C: activated by thrombin and inhibits the clotting factors V and VIII and stimulate fibrinolysis.

Protein S: potentiate the effect of protein C.

d-Heparin :

- It is the most powerful anticoagulant
- It is negatively charged muco-polysaccharide.
- It is secreted by mast cells and basophile cells in minute amounts.
- **Mechanism of its action:**

1. It combines with anti-thrombin III aiding its inhibition of thrombin Also, it inhibits the activated factors IX, X and XI

2.It inhibits platelet aggregation and stimulate fibrinolysis.

3.Lipaemia clearing effect occur by activation of lipase enzyme to hydrolyse lipids and prevent its deposition in blood vessels so prevent the development of atherosclerosis.

e- Alpha2-macroglobulin: bind and inhibit coagulation factors.

f- Alpha1-antitrypsin: Inactivate factor XIa and thrombin.

g-Plasmin (fibrinolysin):causes breakdown of fibrin, fibrinogen, prothrombin, factor V ,VIII and XII.

*Prevention of blood clotting **outside** the body **[Invitro anticoagulants]**

(1) Blood is collected in silicon or paraffin coated test tube to prevent aggregation and activation of factor XII.

(2) Cooling of the blood delay clotting.

(3) Removal of Ca++ ions: by

- Precipitation of ionized calcium by addition of Na oxalate Ca++ oxalate (toxic) or by EDTA.
- Adding of Na citrate → Chelation of Ca++ and formation of non-ionized Ca++ (Ca++ citrate). This compound is not toxic, and rapidly removed from the blood so citrate is used in blood transfusion.
- EDTA (Ethelyne diamine tetraacetic acid) → Chelation of Ca++

(4) De-fibrination of blood by a glass rod.

(5) Addition of heparin as in artificial kidney machine.

*Prevention of blood clotting **inside** the body **[Invivo anticoagulants]**

Drugs are used for prevention and treatment of thrombosis as in:

1- Deep venous thrombosis or pulmonary thrombosis.

2- Myocardial infarction.

3- After cardiac surgery.

4- Rheumatic valve disease complicated with embolism.

5- In hereditary deficiency of anti-thrombin III, protein C or S.

- There are two types of anticoagulants drugs:

	Heparin	***Coumarin***
-Origin:	- Animal origin from mast cells and basophils	- Plant origin as warfarin and Dicumarol
-Mode of action:	- Anti-thrombin - Inhibits platelet aggregation - Prevent activation of IX, X, XI - Lipaemia clearing effect	- Competitive inhibition with vit K in liver. So prevent formation of factors II, VII, IX & X and protein C & S.
-Site of action	-In vivo and in vitro	-In vivo only
-Onset:	-Rapid	-Delayed onset (1-3 days)
-Duration:	-Short duration (4-6 h.) then hydrolysed by Heparinase enzyme.	-Long duration (3 days)
-Mode of administration:	-Intravenous or intra-muscular (as it is digested by the stomach)	-Orally
-Antidote:	-Protamine sulphate 1% (It has strong positive charges to neutralize the negative charges of heparin)	-Vitamin K or blood transfusion

Fibrinolytic System

*** Definition:**

- Fibrinolysis means lysis and removal of blood clot after stoppage of bleeding and healing of the vascular wall.

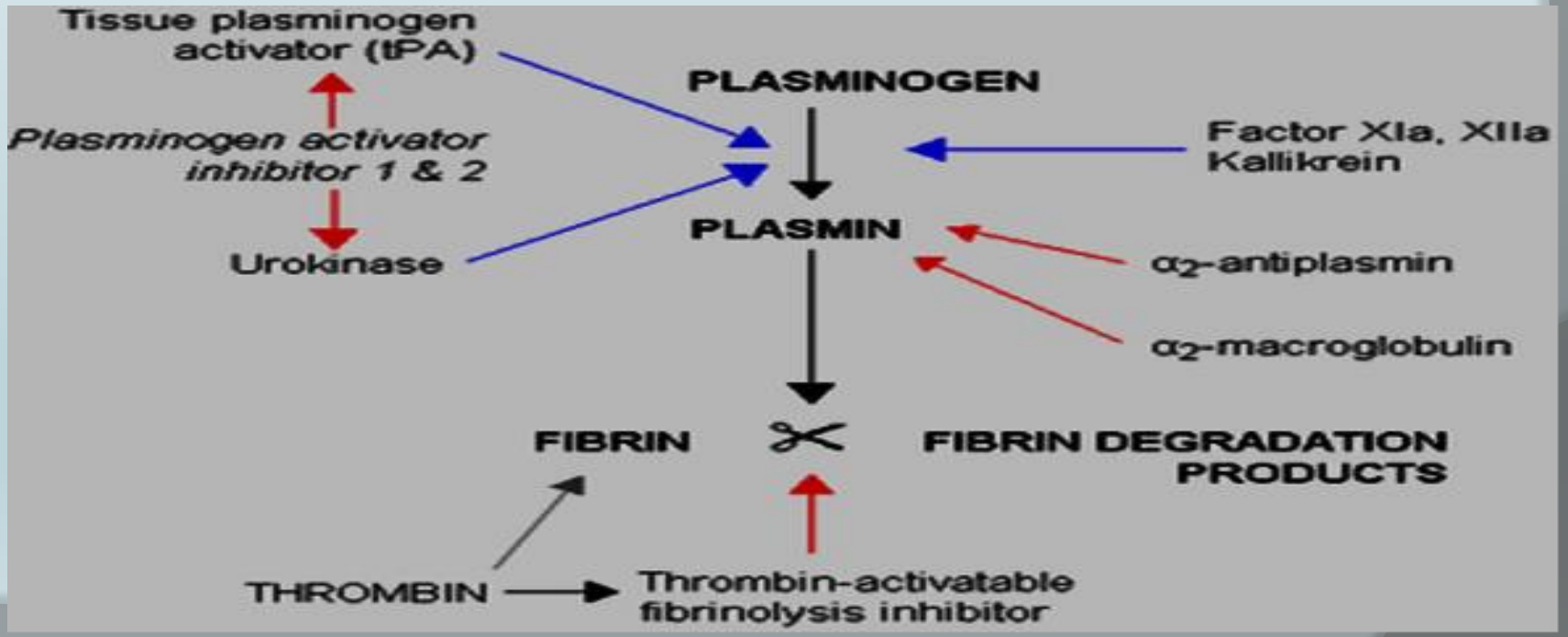
- This is produced by enzyme called plasmin (fibrinolysin) which present in plasma as inactive plasminogen (pro-fibrinolysin).

*** Mechanism:**

- After the blood clotting stops the bleeding, tissue plasminogen activator (t-PA) converts plasminogen into plasmin which lyses the blood clot into fibrin degradation products (FDP).

- After lysis of the blood clot, plasmin, t-PA and FDP are removed by the phagocytic cells.

- Then the inhibitor to t-PA limit its effect to site of blood clot only.



- ***Activation of plasminogen & fibrinolysis:**

- (1) Tissue plasminogen activator: (t-PA): Released from injured tissue & endothelium but the plasma contains a physiological inhibitor to the t-PA to balance its effect.
- (2) Factor XII, Kallikrein & thrombin.
- (3) Other physiological activators as:
- a- Urokinase enzyme in the urine to lyse blood clots in the urine.
- b-Enzymes in pleural, peritoneal & uterine cavities to prevent blood clot in these sites and passage of uterine blood to outside.
- (4) Exogenous activators: as streptokinase enzyme from bacteria to treat acute myocardial infarction to dissolve clot.

- ***Inhibition of fibrinolysis:**
- (1) Inhibition of plasmin: by α 2 Anti-plasmin , α-2-macroglobulin & α-1 anti-trypsin.
- (2) Inhibition of tissue plasminogen activator.
- *** Significance of fibrinolysis:**
- 1- Lysis of blood clots & reopening the blood vessels and prevent closure of capillaries by sluggish circulation.
- 2- Cleaning of the tissue from the blood clots formed outside the blood vessels
- 3- Removal & prevent bl. clots in the urinary tract (to prevent blocking of renal tubules), pleural, uterine & peritoneal cavities.
- 4-Treatment of early stages of myocardial infarction by:
- - Injection of tissue plasminogen activator.
- - Streptokinase & urokinase injection [direct on the clot].

Thank You