Lecture Notes

UJ | SCHOOL OF MED

PHYSIOLOGY

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019

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Hemostasis is maintained by three processes:

1. Vasoconstriction
2. Platelet plug formation: Adhesion > release reaction > aggregation > procoagulant activity > fusion of the injury
3. Clotting mechanism

- During the platelet plug formation, substances are produced:
  - There is a release of tissue thromboplastins, and activation of factor XII and production of platelet factor III (PF3) which is a phospholipid.
- When they are produced, they encourage the clotting mechanism, and this mechanism needs clotting factors, which are shown in the table below.
- Almost all of the clotting factors are produced in the liver.
- Factors II, VII, IX, and X are called <u>vitamin-k dependent factors</u>. If vitamin k is not available, these are not produced
- When vascular injury occurs, these substances are released to encourage the coagulation mechanism.

Table 10.1 Major blood clotting factors

Factor	Name (synonyms)	Site of formation
I	Fibrinogen	Liver
II*	Prothrombin	Liver
III	Tissue thromboplastins	Tissue cells (membrane protein)
IV	Calcium ions	
V•	Labile factor	Mainly liver
VII*	Stable factor	Liver
VIII•	Anti-haemophiliac globulin A (AHG)	Platelets, RES endothelial cells, liver
vWF	von Willebrand's factor	Endothelial cells, platelets
IX*	Anti-haemophiliac globulin B (Christmas factor)	Liver
X*	Stuart factor	Liver
XI	Plasma thromboplastin antecedant factor (PTA)	Liver
XII	Hageman factor	Liver
XIII	Fibrin stabilizing factor	Liver
PF3	Platelet factor 3	Platelets

Note
* vitamin K-dependent • pro-cofactors

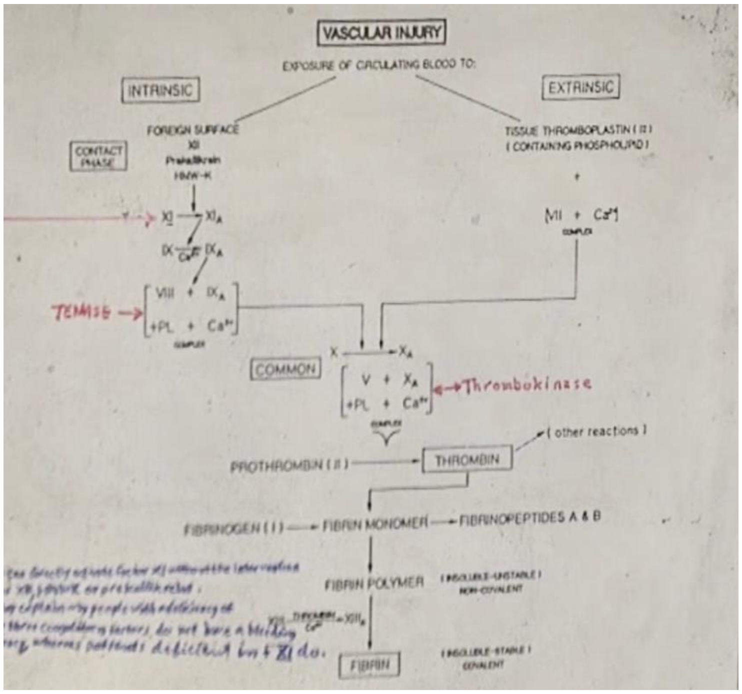
Each clotting factor has a number and a synonym (a name). You need to memorize both. ☺ and their sites of production.

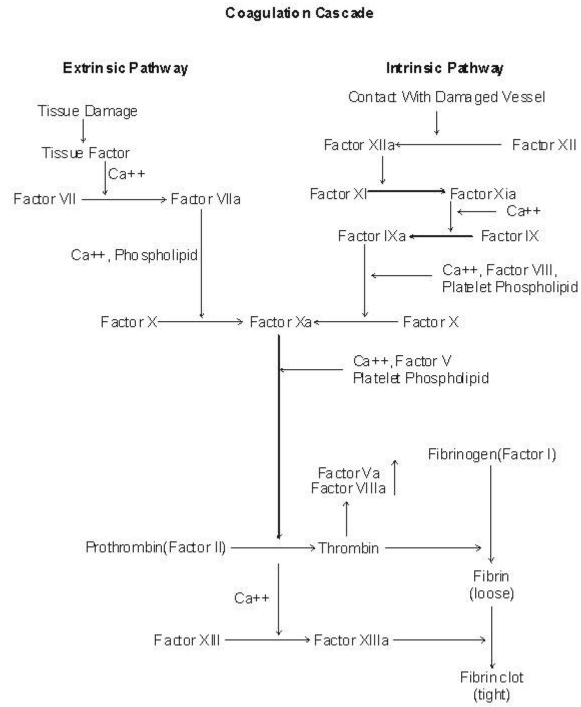
Extra:

Prekallikrein (PK), also known as Fletcher factor, is **an 85,000 Mr serine protease that complexes with high-molecular**-weight kininogen. PK is the precursor of plasma kallikrein, which is a serine protease that activates kinins. PK is cleaved to produce kallikrein by activated Factor XII (Hageman factor).

Clotting mechanism

- The clotting mechanism occurs through 3 pathways: the intrinsic, extrinsic, & common.





Notice how calcium is important

1. The intrinsic pathway begins with the activation of factor XII, prekallikrein and high molecular weight kininogen (HMW-K) after the exposure of these to the foreign surfaces, these 3 elements activate factor XI.
   - Platelets can directly activate factor XI (which is also activated by factor XII). Therefore, people with the deficiency of factor XII, prekallikrein and HMWK, they don't complain from serious bleeding problems, while people with the deficiency of factor XI suffer from moderate-severe bleeding.

- Then factor XI in the presence of calcium activates factor IX.
- Activated factor IX, factor VIII, calcium and phospholipids, they form a complex called tenase.
- Tenase activates factor X.

2. The extrinsic pathway starts by the release of tissue thromboplastin which contains phospholipids.

- Thromboplastin, factor VII and calcium form a complex that activates factor X.

✓ These 2 pathways function at the same time and both activate factor X in the end.

3. Then the common pathway begins, it is initiated when activated factor X is present.

- Activated factor X, factor V, phospholipids and calcium form an enzyme called thrombokinase, it activates prothrombin to form thrombin.
- Thrombin activates fibrinogen to form fibrin threads, but they are unstable.
- Factor XIII in the presence of thrombin and calcium stabilize the fibrin.

➢ All the components of the intrinsic pathway are present in the plasma. This pathway is usually slow, weak and takes about 6 minutes, but it is long-acting and more important.

➢ The extrinsic pathway which occurs because of the tissue damage is fast and powerful, it takes about 16 seconds.

Thrombin

The main function of thrombin is the activation of fibrinogen, to form fibrin threads. There are also other functions:

1. Activation of factor VIII
2. Activation of factor V
3. Activation of factor XIII (that stabilizes the fibrin threads).
4. Activation of platelets
5. Binds to thrombomodulin for the activation of protein C

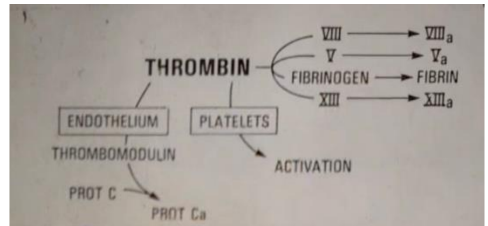


Figure 3.27. The multiple actions of thrombin in blood coagulation. *Prot C*, protein C; *Prot Ca*, activated protein C.

Calcium

****If we remove calcium from the blood, the blood does not coagulate, calcium is present in every step of the coagulation process, <u>except</u> in the first two steps of the intrinsic pathway.**

Functions of calcium:

1. Activation of platelets
2. It is also present in the platelets, it is important for the activation of enzymes and the secretion of granules especially alpha granules.
3. Contraction of the actomyosin part of the membrane.

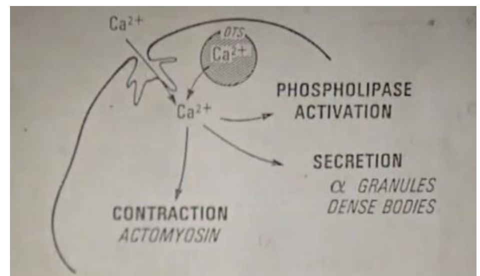


Figure 3.32. The flow of calcium into the cytoplasm of the platelet after stimulation and responses that this initiates. DTS,

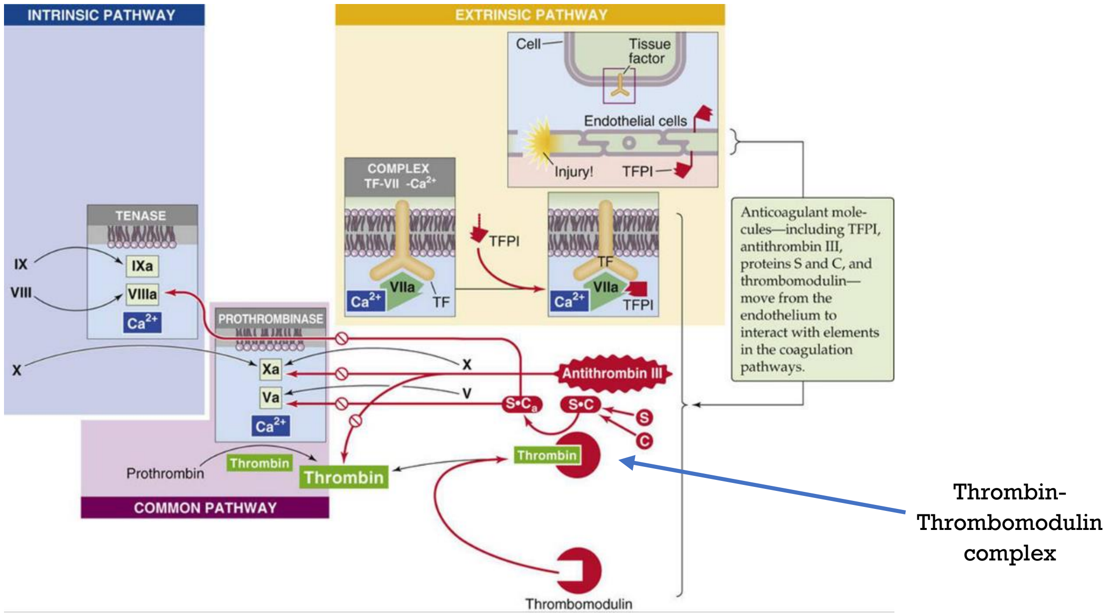
Fluidity of the blood

If the blood clots too easily the result will end up with thrombosis, but if it takes too long to clot the result will be hemorrhage. Therefore, we need the blood to flow normally.

Factors which maintain the normal fluidity of the blood:

- ✓ **Heparin**: the most important factor (it's produced by the basophils mainly)
- ✓ The clotting factors (such as prothrombin and fibrinogen):
  - ➢ They are present in plasma in the inactive form.
  - ➢ During the circulation, they are removed by the liver and by this process, their concentration will be reduced.
- ✓ **Endothelial lining** of blood vessels is smooth and negatively charged so it rejects the adhering of the platelets with cells.
- ✓ **Antithrombin III**: inhibits the action of thrombin as well as the activated factors IX,X,XI,XII.
- ✓ Thrombin binds with thrombomodulin forms a complex that activates **protein C+S** which inactivates factor V and VIII in the presence of calcium.
  - ➢ Protein C+S requires vitamin K.

  (Extra: Don't get confused: yes, thrombin alone does activate factors V, VIII, and XIII. And no, it's not made up by dr Saleem. So thrombin is a multitasker (better than us :))
- ✓ **Alpha 2 macroglobulin** and **alpha 1 anti-trypsin** also contribute to the anti-thrombin effects of the plasma and the fibrinolytic system.
- ✓ In every person, there are minor clottings that dissolve immediately which results in **fibrin or fibrinogen degradation products** that work as anti-coagulant. It inhibits the fibrin threads and platelets aggregation.
- ✓ Fibrinolytic system



Fibrinolytic System (fibrinolysis)

The essential step in this system is the production of plasmin

- Plasmin causes lysis of fibrinogen, fibrin and activated factors V and VIII.
- Fibrin and fibrinogen degradation products act as anticoagulants; they inhibit the fibrin threads and the platelet aggregation

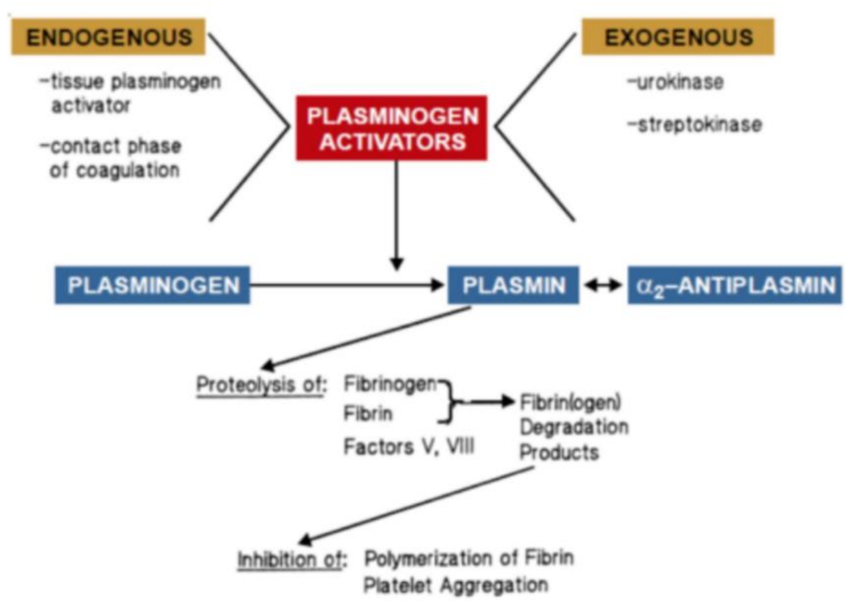
So fibrolytic system or fibrolysis means the <u>production of plasmin</u>.

Fibrinolysis like coagulation, it's a normal hemostatic response to a vascular injury.

Activators of Plasmin production (plasminogen activators):

1. Exogenous activators:
   - Urokinase: presents in plasma and urine
   - Streptokinase from streptococcus bacteria
2. Endogenous activators:
   - Tissue Plasminogen activators
   - Contact phase of coagulation

When the plasmin is produced, there is another protein enzyme that controls the normal concentration of it, which called alpha-2 antiplasmin



Clot Retraction

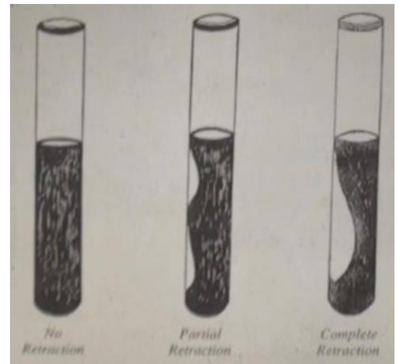


Fig. 149. Retraction of the blood clot

- The clot retraction time measures the ability of the blood clot to retract.
- If we take blood in a tube and leave it for more than one hour, clot retracts (partially or fully retraction). It shrinks to about 50% of the original size. In normal blood, the clot retracts as follows:
  - After 2 hours, there's partial retraction of the clot.
  - After 24 hours, there's complete retraction of the clot
- If we remove the clot, the remaining is serum that doesn't contain coagulation factors, so it doesn't clot while the plasma clots.
- Factors of clot retraction: Platelets and Calcium.
- When the platelet count is decreased, the clot retraction time is increased.
- The clot retraction time is used in the diagnosis of hemorrhagic diseases.

Thrombosis & embolism

- Sometimes unwanted clotting is formed in the blood vessels, which called thrombosis, the clot itself is thrombus/thrombi
- This clot may dissolve (minor clotting dissolve immediately)
- The clot may be removed from its attachment (if they are not dissolved) and carried with blood, this circulating clot is called embolus/emboli, the condition is called embolism. Embolus may be clot, bubble of air, fat from broken bones or piece of debris.
  - Emboli can be swept by the blood through the heart and pulmonary artery to lodge in and obstruct a small artery in the lung.
  - Thrombi in arteries are more dangerous than in veins, especially when the artery is one that carries blood to vital regions such as the brain or heart muscle.
  - Arteriosclerosis or atherosclerosis (conditions related to embolism and thrombosis): these are the conditions underlying most heart attacks.

    **Atherosclerosis: accumulation of lipids in blood vessels

    **Arteriosclerosis: related to loss of elasticity & flexibility of the walls of arteries

Causes of thrombosis in Man:

- Injury to a blood vessel by trauma, or application of an irritating substance, which activate the intrinsic or extrinsic coagulation route
- Infection: in the vicinity of cellulitis and abscesses the endothelium becomes injured through inflammatory responses, these induce platelet adhesion to injured endothelium, with ADP release to increase the platelet aggregation.
- Slowing of the blood stream: After major surgery or childbirth, there's an increased risk of developing thrombosis and embolism. This may be due to the fact that the flow of blood in veins becomes sluggish, that results in platelet deposition and clotting.
- Changes in the blood composition: After operation or childbirth, both the number of platelets and the level of fibrinogen are increased. An important factor leading to thrombosis is probably an alteration in platelet stickiness, associated with alterations in the endothelium and slowing of blood flow.

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ولمسة رنيم ;)