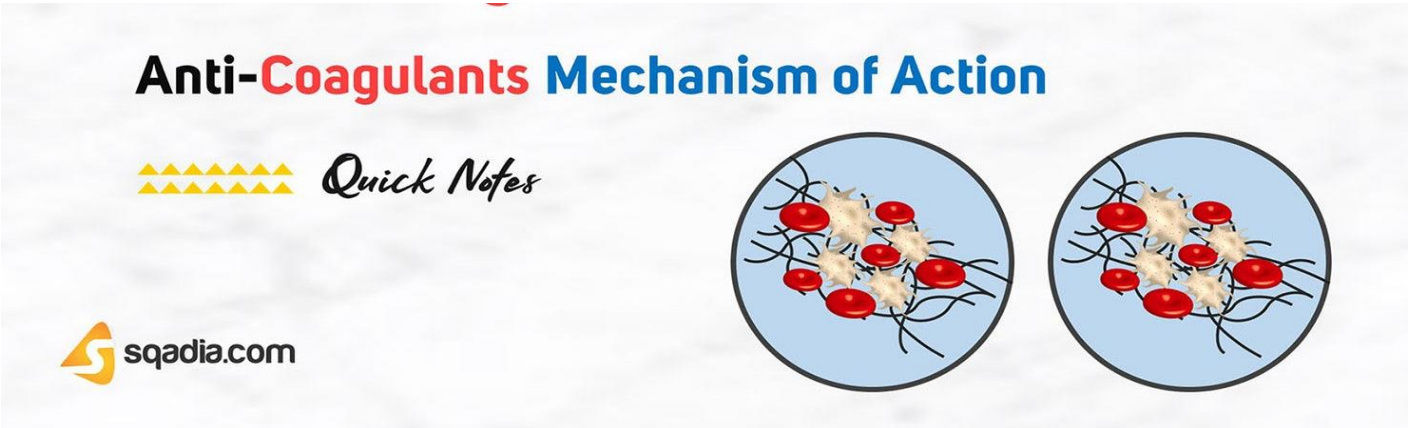
# HLS MODULE
# PHYSIOLOGY (LECTURE 9)
# BLOOD LYSIS (ANTI-COAGULANTS MECHANISMS)

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# Anticoagulant Mechanisms

It wont allow it to spread it should only be in the injured place and that the main function

- ✓ The body has **mechanisms for limiting clot formation inside blood vessels and for dissolving a clot after it has formed**.
- There are **at least three different mechanisms** that **oppose clot formation**, thereby helping to limit this process and prevent it from spreading excessively.

It should be balanced between the coagulant and anti-coagulant

- **Defects** in any of these **natural anticoagulant mechanisms** are associated with **abnormally high risk of clotting, a condition called hypercoagulability**.

# Mechanisms That Oppose Clot Formation

- **These mechanisms include:**

**1. The first anticoagulant mechanism acts during the initiation phase of clotting and utilizes the tissue factor pathway inhibitor (TFPI), which is secreted mainly by endothelial cells.**

- This substance binds to tissue factor–factor VIIa complexes and inhibits the ability of these complexes to generate factor Xa.
- **This anticoagulant mechanism is the reason that the extrinsic pathway by itself can generate only small amounts of thrombin.**

Why the extrinsic is limited and minor because it have a tissue factor inhibitor

## 2. The second anticoagulant mechanism is triggered by thrombomodulin.

- **Thrombin can bind to a thrombin-binding protein on endothelial cells known as thrombomodulin.**
- In circulating blood, thrombin is a procoagulant, but when it binds to thrombomodulin, it becomes an anticoagulant in that the thrombomodulin-thrombin complex activates protein C.
- Activated protein C (APC), along with its cofactor protein S, inactivates factors Va and VIIIa.

Both from the liver

Instrinsic

Common that emerge with 10

- **Thrombin directly activates factors VIII and V when the endothelium is damaged. But, it indirectly inactivates them via protein C in areas where the endothelium is intact.**

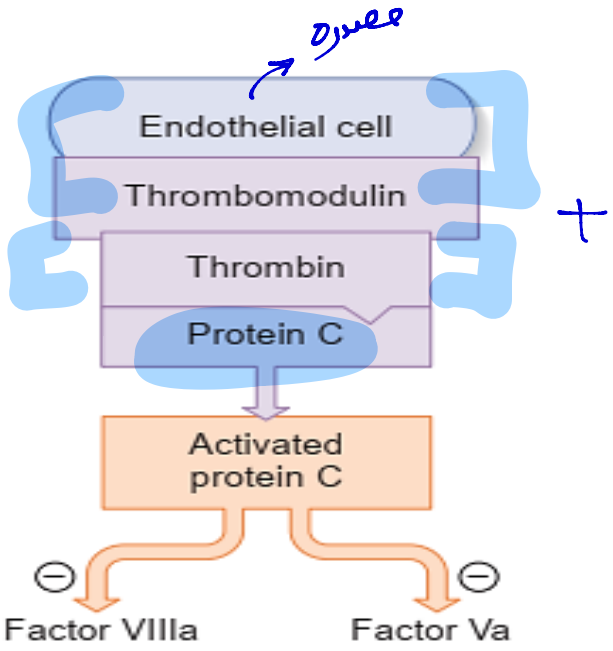


**Figure 12.78** Thrombin indirectly inactivates factors VIIIa and Va via protein C. To activate protein C, thrombin must first bind to a thrombin receptor, thrombomodulin, on endothelial cells; this binding also eliminates thrombin's procoagulant effects. The ⊖ symbol indicates inactivation of factors Va and VIIIa.

## 3. A third naturally occurring anticoagulant mechanism is a plasma protein called anti-thrombin III.

## Anti-thrombin III:

- The activity of anti-thrombin III is greatly enhanced when it binds to heparin. So, it is called anti-thrombin III or anti-thrombin-heparin cofactor.
- It inactivates thrombin and active forms of clotting factors IX, X, XI, and XII.
- Anti-thrombin III prevents the spread of a clot by rapidly inactivating clotting factors that are carried away from the immediate site of the clot by the flowing blood.

Natural anti coagulation

It all work together because its considered as a positive feedback mechanism

# The Fibrinolytic System

To stop the wide spread

- TFPI, Activated Protein C (APC), and Anti-thrombin III all function to limit clot formation.
- The fibrinolytic system, however, dissolves a clot after it is formed.
- Clots are dissolved by a process called fibrinolysis.
- A fibrin clot is a temporary fix until permanent repair of the vessel occurs.
- The fibrinolytic (or thrombolytic) system is the principal effector of clot removal.
- The physiology of fibrinolytic system constitutes a plasma proenzyme, plasminogen (or profibrinolysin), which can be activated to the active enzyme plasmin (fibrinolysin) by plasminogen activators.
- Once formed, plasmin digests fibrin, thereby dissolving the clot.

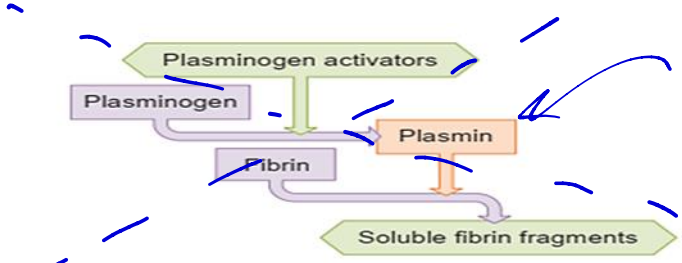


**Figure 12.79** Basic fibrinolytic system. There are many different plasminogen activators and many different pathways for initiating their activity.

# Plasmin (Fibrinolysin)

- Plasmin (fibrinolysin) is the active component of the plasminogen (fibrinolytic) system.
- This enzyme lyses fibrin and fibrinogen, with the production of fibrinogen degradation products (FDPs).
- Over a few days, plasmin slowly breaks down the fibrin.
- Plasmin is formed from its inactive precursor, plasminogen, by the action of thrombin and tissue-type plasminogen activator (t-PA)

Vascular endothelium but the first origin location was from the tissue so its named after it

- The injured tissues and vascular endothelium very slowly release t-PA that a few days later, after the clot has stopped the bleeding, eventually converts plasminogen to plasmin, which in turn removes the remaining unnecessary blood clot.
- Plasminogen is also activated by urokinase-type plasminogen activator (uPA).

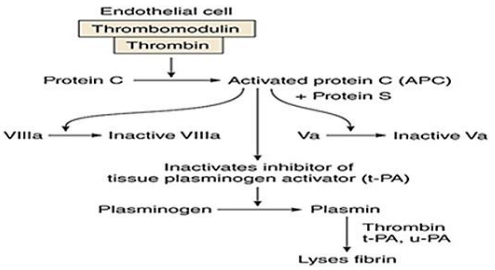


**FIGURE 31–13 The fibrinolytic system and its regulation by protein C.** u-PA, urokinase-type plasminogen activator.

# Clinical Impact of Fibrinolysis

- A heart attack (myocardial infarction) can occur when a clot blocks blood vessels that supply the heart.
- One treatment of heart attack is to inject certain chemicals into the blood that activate plasmin.
- Unlike aspirin and anticoagulant therapies, which are used to prevent heart attacks, plasmin activators quickly dissolve the clot and restore the blood flow to cardiac muscle, thus reducing damage to tissues.
  - **Human t-PA is produced by recombinant DNA techniques for clinical use in myocardial infarction and stroke.**
  - **Streptokinase, a bacterial enzyme, is also fibrinolytic and is also used in the treatment of myocardial infarction.**

# Anticoagulant Roles of Endothelial Cells

**The endothelium of the blood vessels plays an active role in preventing the extension of clots.**

- It normally provides an **intact barrier between the blood and subendothelial connective tissue …… prevents platelet aggregation and contact activation of clotting system (intrinsic system).** (1)
- **Synthesize and release $PGI_2$ and nitric oxide ……These inhibit platelet activation and aggregation.** (2)
- **Secrete tissue factor pathway inhibitor (TFPI)**…….. This **inhibits the ability of tissue factor–factor VIIa complexes to generate factor Xa.** (3)
- **Bind thrombin (via thrombomodulin), which then activates protein C……Activated protein C inactivates clotting factors VIIIa and Va.** (4)
- **Secrete tissue plasminogen activator…… Catalyzes the formation of plasmin, which dissolves clots.** (5)

# ANTICOAGULANTS

## (1) Heparin

- It is a naturally occurring powerful anticoagulant. But its concentration in the blood is normally low.
- Heparin is formed by the mast cells and basophil cells.
- Heparin is used in vivo and in vitro.
- It is given only by injection (IV or S.C.). So, its action is rapid.
- Mechanism of action:

Short duration

It exerts anticoagulant effect mainly by facilitating action of anti-thrombin III.

↑Dose

Bleeding.

✓ The highly basic protein protamine forms an irreversible complex with heparin and is used clinically to neutralize heparin (antidote).

## (2) Coumarin derivatives such as dicumarol and warfarin

- ✓ They are effective **anticoagulants (in vivo anticoagulants)**.
- ✓ They are **given orally**. So, onset of action is slow (after 12-24 hours).
- ✓ Normal coagulation usually returns 1 to 3 days after discontinuing coumarin therapy.
- ✓ **Factors II (prothrombin), VII, IX, and X are vitamin K–dependent**. They **inhibit the action of vitamin K in the liver** (by competitive inhibition).
- ✓ They cause this effect by competing with vitamin K for reactive sites in the enzymatic processes for formation of prothrombin (II) and the other three clotting factors, thereby blocking the action of vitamin K.
- ✓ So, the **antidote of coumarin derivatives is vitamin K**.

Why its slow ti act due to the factor
Thats why the factor should be firstly removed

Calcium important in clottig

## (3) Low Plasma $Ca^{2+}$ level

In vivo, a plasma $Ca^{2+}$ level low enough to interfere with blood clotting is incompatible with life, but clotting can be prevented in vitro if $Ca^{2+}$ is removed from the blood.

**Anticoagulants that act on $Ca^{2+}$ (in vitro anticoagulants)**

- **Sodium oxalate:**

**It precipitates (insoluble $Ca^{2+}$ oxalate), so blood calcium level is decreased.**

- **Na citrate:**

**It binds $Ca^{2+}$ (forming unionized forms of $Ca^{2+}$), so blood calcium level is decreased.**

**Citrate anticoagulants have an important advantage over the oxalate anticoagulants because oxalate is toxic to the body, whereas moderate quantities of citrate can be injected intravenously.**

# Abnormalities of Hemostasis

## Platelet disorders: Purpura

A bleeding disease characterized by occurrence of small punctate hemorrhages throughout tissues specially in skin where they appear as purplish blotches.

Causes:

**Thrombocytopenia** Decrease in the blood platelets

**Thrombocytopenic purpura** is due to decreased number of platelets (below 50,000/$mm^3$).

As in bone marrow disease, platelet production is affected leading to the deficiency of platelets.

**Idiopathic thrombocytopenia**

Thrombocytopenia of unknown cause.

In most of these people, it has been discovered that for unknown reasons, specific antibodies have formed and react against the platelets themselves to destroy them.

**Treatment:**

Fresh whole blood transfusions that contain large numbers of platelets.

Also, splenectomy is often helpful, sometimes.

## Vitamin K deficiency

## Vitamin K is called anti-hemorrhagic vitamin.

Vitamin K is necessary for liver formation of Prothrombin (II), Factor VII, Factor IX, Factor X.

In the absence of vitamin K, subsequent insufficiency of these coagulation factors in the blood can lead to serious bleeding tendencies.

**Causes of vitamin K deficiency:**

- Failure of absorption (obstructive jaundice). Bile salts
- Deficient intestinal bacteria : Due to prolonged use of antibiotics and in newborns.

Natural and main source or origin of vit K other than food

# Hemorrhagic diseases produced by selective deficiencies of the clotting factors.

## Hemophilia:

- A bleeding disease that occurs almost exclusively in males. Transmitted by X chromosome
- It is caused by congenital deficiency of certain clotting factors:
  - ✓ **Hemophilia A (about 85 %)**, which is caused by factor **VIII deficiency**, is relatively common.
  - ✓ **Hemophilia B (about 15%)**, which is caused by factor **IX deficiency**.
- It leads to marked bleeding after minor injuries, wounds or operations (e.g. tooth extraction).
- **Treatment:**

It is treated with factor VIII–rich preparations made from plasma, or, more recently, factor VIII produced by recombinant DNA techniques.

## von Willebrand disease:

**Due to von Willebrand factor (vWF) deficiency thus** reducing platelet adhesion.

**Treatment:**

Some patients with von Willebrand disease are treated with desmopressin, which stimulates production of factor VIII.

## Formation of clots inside blood vessels (thrombosis).

- ✓ Thrombosis is a major medical problem.
- ✓ They are particularly prone to occur where blood flow is sluggish because the slow flow permits activated clotting factors to accumulate instead of being washed away.
- ✓ They also occur in vessels when the intima is damaged by **atherosclerotic** plaques.
- ✓ They frequently occlude the arterial supply to the organs in which they form, and **bits of thrombus (emboli)** sometimes break off and travel in the bloodstream to distant sites, damaging other organs.
- ✓ An example is obstruction of the pulmonary artery or its branches by thrombi from the leg veins (pulmonary embolism).
- ✓ **Congenital absence of protein C** leads to uncontrolled intravascular coagulation and, in general, death in infancy.
- ✓ **Resistance to activated protein C** is another cause of thrombosis, and this condition is common. It is due to a point mutation in the gene for factor V, which prevents activated protein C from inactivating the factor.

**Treatment:**

Anticoagulants as heparin and t-PA.

## Disseminated intravascular coagulation (DIC)

- It is another serious complication of septicemia, extensive tissue injury, and other diseases in which fibrin is deposited in the vascular system and many small- and medium-sized vessels are thrombosed.
- The increased consumption of platelets and coagulation factors causes bleeding to occur at the same time.
- The cause of the condition appears to be increased generation of thrombin due to increased tissue factor or thromboplastin (factor III) activity without adequate TFPI activity.