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Content

Coagulants and Anticoagulants

- Coagulation cascade
- Coagulants
- Natural anticoagulant mechanisms
- Anticoagulants classification
- Systemic anticoagulants

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Objectives

At the end of this lecture, student will be able to

- Describe the mechanism of blood coagulation
- Explain the coagulant mechanism and therapeutic uses of Vit. K
- Describe natural anticoagulant mechanisms
- Classify anticoagulants
- Discuss pharmacology of systemic anticoagulants

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Coagulation

- Complex process - blood forms clots
- Part of hemostasis
- Damaged blood vessel wall - Covered by a platelet and fibrin-containing clot to stop bleeding
- Begin repair of the damaged vessel
- Disorders of coagulation - increased risk of bleeding (hemorrhage) or clotting (thrombosis)

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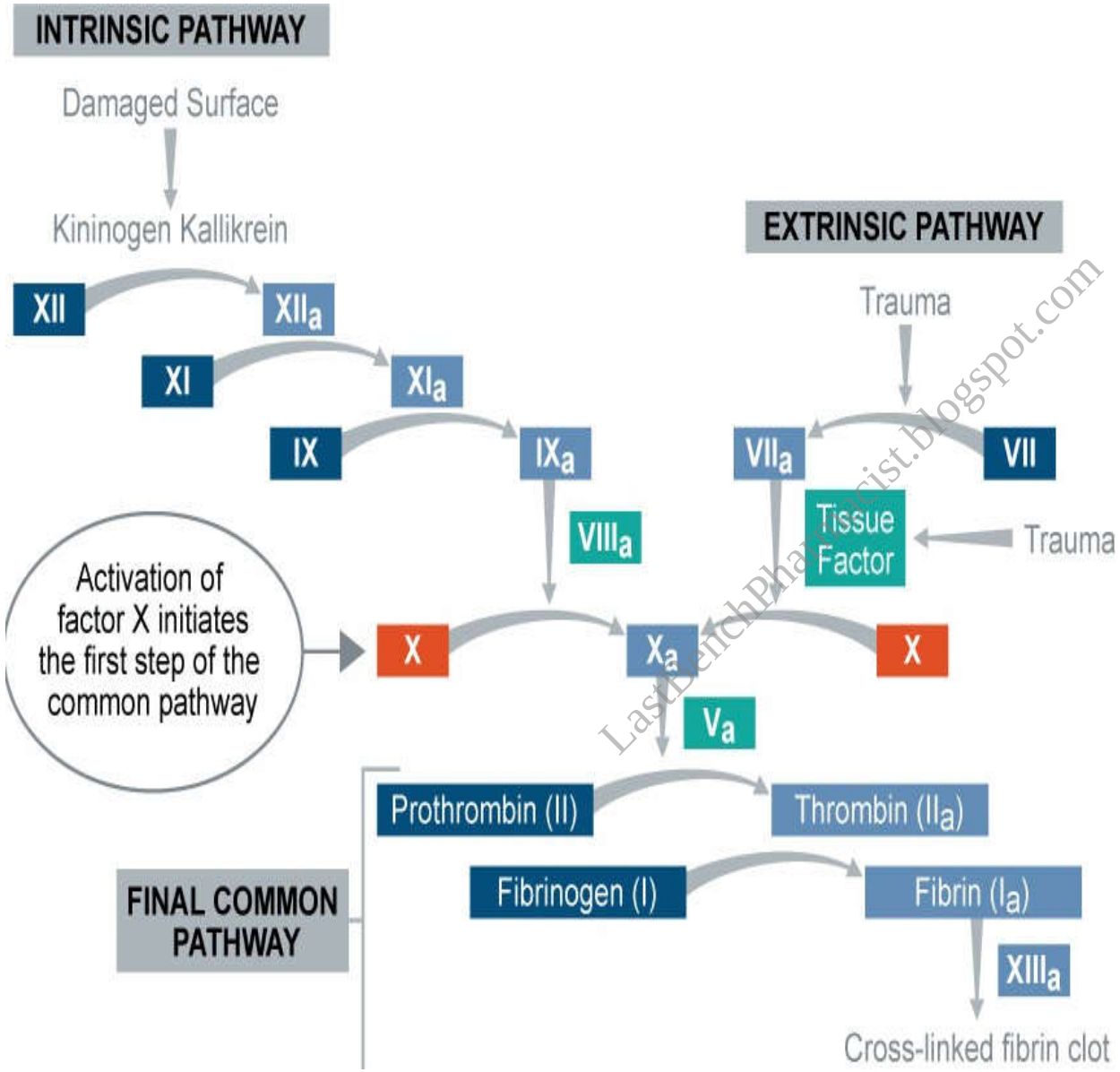
The Coagulation Cascade



Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium Ions
Factor V	Labile Factor
Factor VII	Stable Factor
Factor VIII	Antihemophilic Factor
Factor IX	Christmas Factor, or Plasma Thromboplastin Component (PTC)
Factor X	Stuart-Prower Factor
Factor XI	Plasma Thromboplastin Antecedent (PTA)
Factor XII	Hageman Factor
Factor XIII	Fibrin Stabilizing Factor

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Coagulants

- Substances promote coagulation
- Indicated in hemorrhagic states
- Therapy for deficiency of clotting factors

Vitamin K (Endogenous Systemic coagulant)

- Fat soluble vitamin
- Produced by colonic bacteria
- Required for synthesis of factor II, VII, IX and X

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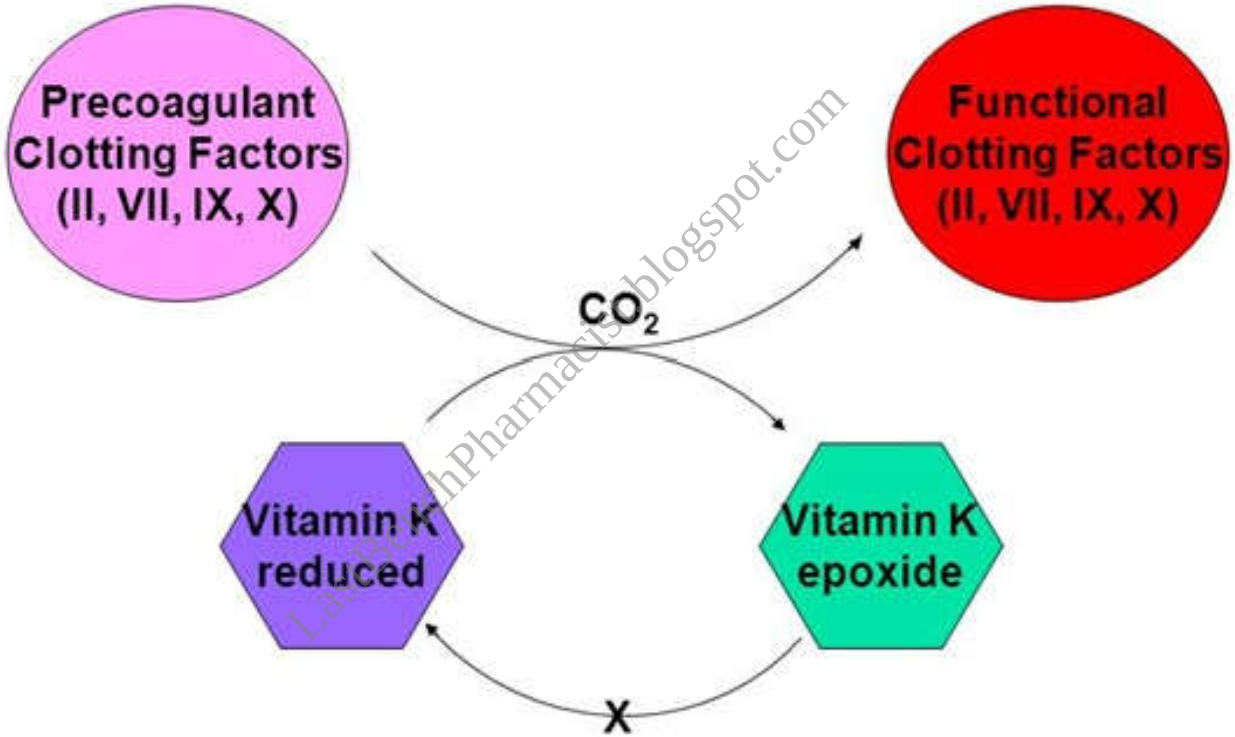
Mechanism of Action of Vitamin K

- carboxylation of glutamic acid residues



In hepatocytes

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Therapeutic uses of Vit. K

- Prolonged antibiotic use
- Overdose of oral anticoagulants
- Malabsorption syndrome
- Obstructive jaundice

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Systemic Procoagulants

- Plasma fractions
- Desmopressin
- Antifibrinolytic
- Aminocaproic and Tranexamic acid
- Aprotinin
- Miscellaneous – Rutin and Ethamsylates

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Natural anticoagulant mechanism

- Clot do not extend beyond a wound site
- Fibrin absorbs thrombin into clot & inactivates it

* Prostacycline (PGI_2) – inhibits platelet aggregation
* Anti thrombin III (AT III) – blocks action of factor XII, XI, IX, X &II
* Protein C – inactivates factor V & VIII, degrades fibrin
* Heparan sulphate – acts as co factor, ↑activity of AT III

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Anticoagulants

- Prevent the clotting (coagulation) of blood
- Prevent new clots from forming or an existing clot from enlarging
- Don't dissolve a blood clot
- Given to those with artificial heart valves or who have atrial fibrillation

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Classification

Parenteral anticoagulants

1. Heparin
2. Low mol. wt heparin – Enoxaparin, Dalteparin, Tinzaparin, Ardeparin, Nadroparin, Reviparin
3. Synthetic heparin derivatives – Fondaparinux
4. Thrombin inhibitors – Lepirudin, Bivalirudin, Desirudin, Argatroban, Danaparoid

Oral – Dabigatran, Rivaroxiban, Apixaban

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Classification

Oral anticoagulants

1. Coumarin derivatives – Warfarin, Acenocumarol, Ethyl biscoumacetate and Dicumarol (rarely used)
2. Indanedione group – Phenindione and Anisindione

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Heparin

- Mixture of sulfated mucopolysaccharide
- Mol. wt 10,000 – 40,000
- Strongly electronegatively charged acidic polymer
- Present together with histamine
- Richest source – Lungs, Liver & intestinal mucosa

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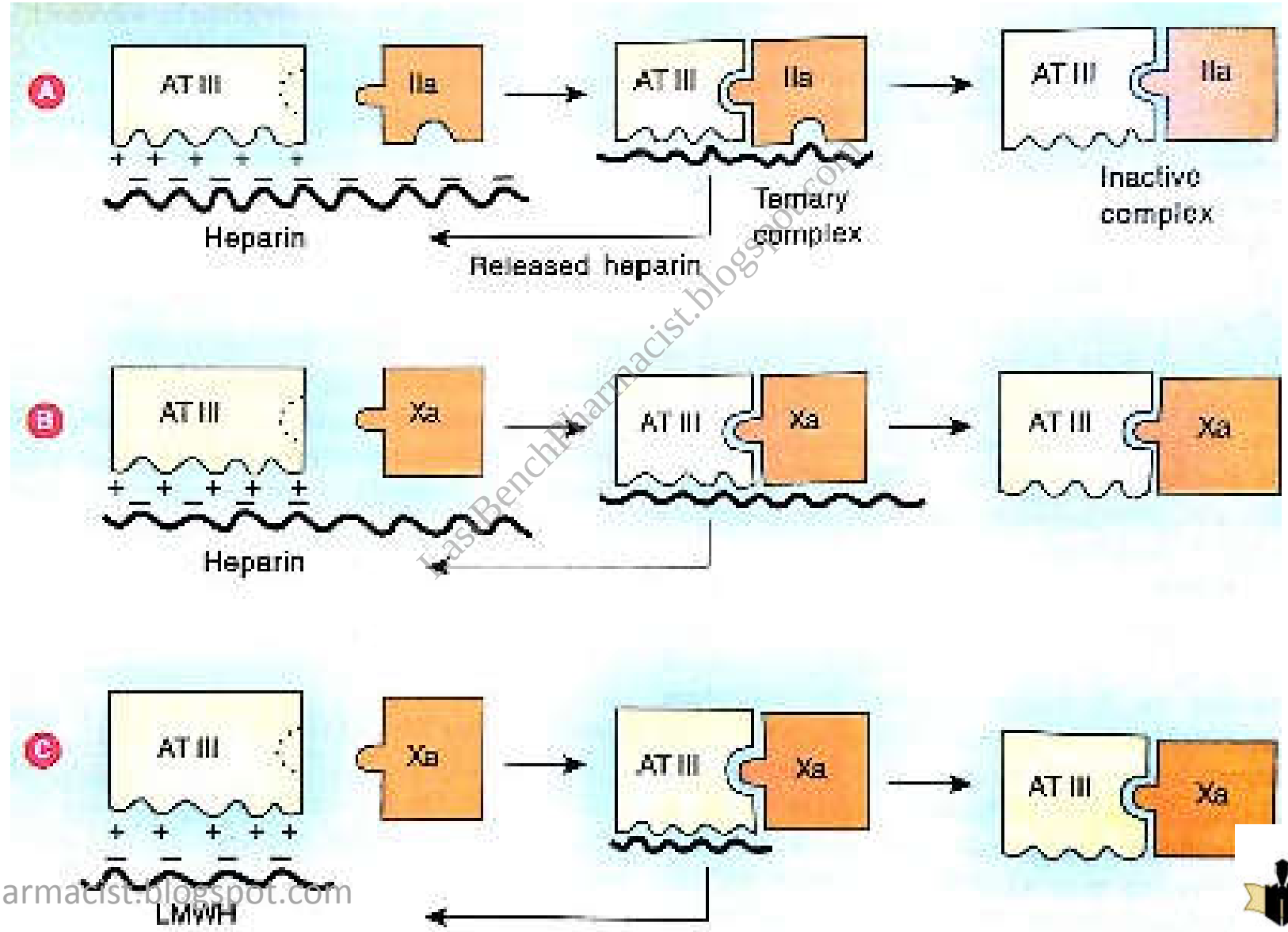
Mechanism of Heparin and Low mol.wt heparins action



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Pharmacokinetics of heparin

- Large & highly ionised molecule – not absorbed from GIT
- Does not cross BBB or placental barrier
- Ca^{2+} Na^{+} of heparin given I.V. infusion or I.V. injection
- I.M. not administered – avoid haematoma
- Low dose S.C. for prophylaxis
- Metabolised in liver (heparinase)
- $t_{1/2}$ increases with increasing dose

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Low Molecular Weight Heparin (LMWH)

- Unfractionated heparin (UFH) – MW 5000 – 40,000
- Fractionation releases – HMWH & LMWH
- LMWH – shorter polymer
  - inhibits factor X preferably
  - Lesser effect on thrombin
  - Thrombocytopenia is less frequent

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Heparin Antagonist

Protamine sulfate

- Specific antagonist for heparin overdose
- Used to terminate heparin action immediately
- As in cardiac/ vascular surgeries
- Basic protein given I.V. neutralizes acidic heparin wt by wt (1 mg of protamine sulfate for 100 U of heparin)
- Incomplete neutralization of LMWH
- HS reaction, flushing & bronchoconstriction can occur

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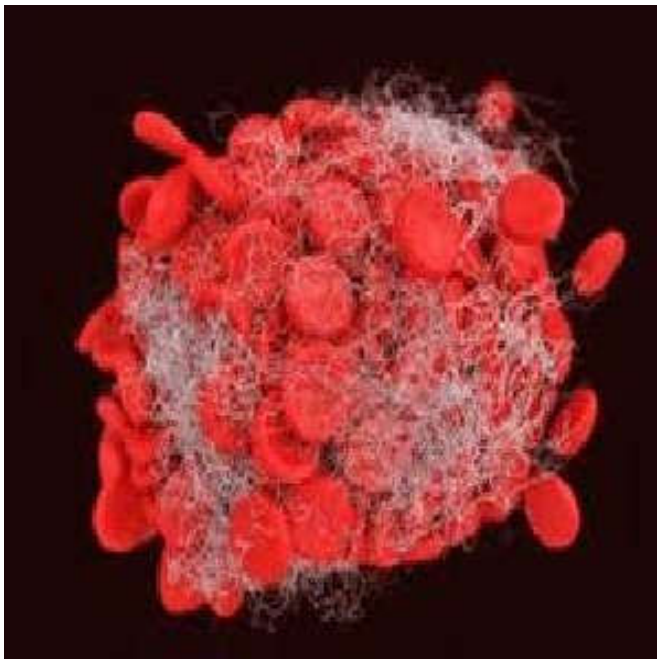
Thrombin inhibitors

- Bind to thrombin directly
- Inhibit thrombin effect in coagulation cascade
- Do not bind to AT III or plasma proteins like platelet factors



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Summary

- Coagulation is a complex process where blood forms clots
- Coagulants are the substances that promote coagulation
- Vit. K is the endogenous coagulant
- Natural anticoagulant mechanism prevent the extension of clot beyond the wound site
- Anticoagulants are the drugs the prevents the clotting of blood
- Heparin and LMWH are most important parenteral anticoagulants

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