Coagulant & anticoagulants

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Homeostasis, thrombosis & coagulation of blood

• Homeostasis is the automatic process of cessation of bleeding from a cut or wound blood vessel.

• A thrombosis occurs if the endothelium lining of the blood vessels is damaged or removed.

• These two processes work simultaneously to stop blood loss from a cut or damaged site by forming a stable homeostatic plug or fibrin.
Homeostasis, thrombosis & coagulation of blood

• The process involves the blood vessels, platelet and plasma proteins that cause formation of platelet aggregate and ultimately a stable clot.
• This process is called the coagulation of blood.
• Homeostasis occurs in a series of distinct phases.
• The first phase of homeostasis begins in platelets. Platelets are disc shaped anucleate fragments of cells circulating in the blood.
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• They are not responsive and non sticky.
• At the injury they change their shape and bind to the extracellular matrix.
• They can stop bleeding by themselves.
• Cyclooxygenases become activated and synthesise thromboxanes A$_2$ (TXA$_2$).
• The Thromboxane-A$_2$ potentiates platelet aggregation and causes vasoconstriction.
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- The platelets swell up and adhere to adjacent platelets and eventually build a platelet mass.
- The plasma coagulation factors except, factor III (tissue thromboplastin), circulates as an inactive proenzyme.
- The trauma initiates activation of the proenzymes to active enzymes.
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• The active enzymes start acting on platelet surfaces to form fibrin, which stabilizes the platelet plug.

• The final common pathway starts as the Prothrombin activator is formed, then Prothrombin is converted to thrombin and the thrombin catalyses the conversion of fibrinogen into soluble fibrin.

• Factor XIII as activated by thrombin and calcium stabilize the fibrin polymers with covalent bond cross links.
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• The blood coagulation process completes in a series of steps to form a fibrin clot.
• Blood coagulation occurs either in an intrinsic pathway, which is a slow process of clot formation, or in an extrinsic pathway that occurs at a faster rate to form a fibrin clot.
• There is a common pathway for both intrinsic and extrinsic pathways for the conversion of Prothrombin to thrombin and subsequent fibrinogen to the insoluble fibrin formation.
Coagulants

• The agents, which are used to promote the coagulation, are called Coagulants.
• They are used to stop bleeding in various conditions from external bleeding to internal bleeding in post operative surgery, in intracranial hemorrhages, or as adjunctive therapy in hemophilia.
Coagulants

• The coagulants used in these cases are Vitamin K$_1$, Vitamin K$_2$, Protamine, Romiplostim, Eltrombopag, Aminocaproic acid, Tranexamic acid and Aprotinin.

• These drugs have different mechanism of actions.

• The protamine is a heparin antagonist.

• Romiplostim and Eltrombopag are Thrombopoietin receptor agonist, while Aminocaproic acid, Tranexamic acid and Aprotinin are antifibrinolytic agents.
Coagulants

- The antihemophilic blood Factor VIII deficiency below 5% cause spontaneous bleeding.
- The factor VIII is produced by recombinant DNA technology is safe from infection risks associated with blood transfusions and can be used effectively.
- It is used in the treatment of bleeding of the hemophiliac patients.
Anticoagulants

• On the other hand a thrombus formation (blood clot) in an undamaged blood vessel is injurious to the homeostasis that can affect the flow of blood.

• It is very important to maintain an internal environment within the cardiovascular system for free flowing of blood to supply nutrients and oxygen to the cells.

• So the thrombus formation should be reduced or blocked.
Anticoagulants

• The agents used to prevent unwanted coagulation (thrombus) formation are called anticoagulants.

• The anticoagulants can be classified into parenteral anticoagulants and Oral anticoagulants.

• The parenteral anticoagulants includes heparin, Lepirudin, Desirudin, Bivalirudin and Argatroban.
Anticoagulants

- Heparin is a natural anticoagulant synthesised in mast cells and released into the blood.
- Heparin is a negatively charged mucoplyysaccharide.
- It binds plasma proteins, including antithrombin III.
- The binding of heparin to antithrombin III cause a conformational change of antithrombin III, which increases its ability to inhibit clotting.
Anticoagulants

- The oral anticoagulants are again divided into Coumarin derivatives and 1, 3-Indandione derivatives.
- The Coumarin derivatives include the drugs like Warfarin sodium and Bishydroxycoumarin derivative, the Dicoumarol.
- They are vitamin K antagonists.
- Warfarin sodium is a 3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium salt. It can also be taken by intramuscular, intravenous and rectal routes.
Anticoagulants

Warfarin

Bishydroxy Coumarin (Dicoumarol)

Anisindione
Anticoagulants

- Dicoumarol can be used alone or in combination to heparin in the prophylaxis and treatment of intravascular clotting. It is useful in postoperative thrombus formation in pulmonary and peripheral arteries.

- The 1, 3-indandiones used as oral anticoagulants are phenindione and anisindione. They act by the same mechanism to the Warfarin as vitamin K antagonist. They have hepatic and renal toxicity.
Anticoagulants

• The antiplatelet drugs are also used to prevent coagulation or thrombus formation.
• They prevent platelet aggregation.
• These agents inhibits secondary pathways of platelet aggregation such inhibition of cyclooxygenase enzyme to prevent synthesis of ThromboxaneA$_2$.
• The drugs included are Aspirin, Triflusal, Indobufen, or the phosphodiesterase inhibitors (that degrades cAMP to AMP) and the antiplatelet drugs are, Dipyridamole and Ticlopidine.
References