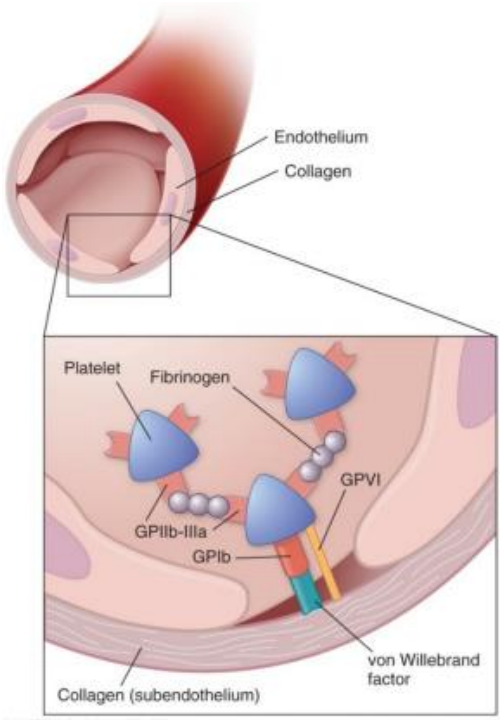
Lecture 15- pharmacology of haemostasis and thrombosis

To explain and describe the mechanisms of haemostasis (including vasoconstriction, primary haemostasis, secondary haemostasis and regulation)

The process-

- Vascular injury, endothelin released by activated endothelium, induce transient vasoconstriction (occurs immediately after vascular injury, mediated by a poorly understood reflex neurogenic mechanism, secretion of endothelin potentiates the reflex)
- Injury-induced exposure of the sub-endothelial matrix provides a substrate for platelet adhesion and activation.
- Granule release reaction; activated platelets secrete thromboxane A2 (TxA2) and ADP. TxA2 and ADP released by activated platelets cause nearby platelets to become activated
- Newly activated platelets undergo shape change and are recruited to the site of injury.
- Primary haemostasis: forms a platelet plug to stabilise the injury, platelets contain cytoplasm but lack nuclei. Haemostatic plug involves 3 reactions- adhesion, granule release action and aggregation and consolidation
- fibrin polymerises around the site of injury- forms a secondary haemostatic plug
- natural anticoagulant and thrombolytic factors limit the haemostatic process to the site of the injury
- these factors include: tissue plasminogen activator (t-PA- activates the fibrinolytic system), thrombomodulin, which activates inhibitors of the coagulation cascade, prostacyclin, which inhibits both platelet activation and vasoconstriction, surface heparin-like molecules, which catalyse the inactivation of coagulation factors.



Platelet adhesion and aggregation-

- Von willebrand factor (vWF)- a large multimeric protein, secreted by activated platelets and injured endothelium.
- vWF mediates platelet adhesion to the subendothelium by binding both to the platelet membrane glycoprotein GPIb and to exposed subendothelial collagen
- platelet adhesion to the subendothelial matrix requires direct binding interaction between GPVI and subendothelial collagen
- during platelet aggregation, fibrinogen cross-links to one another by binding to GPIIb-IIIa receptors on platelet membranes

Platelet activation-

- initiated at the site of vascular injury when circulating platelets adhere to exposed subendothelial collagen

- platelet recruitment is mediated by the release of soluable platelet factors, including ADP and thromboxane A2 (TxA2- critical component in the coagulation cascade)

Coagulation cascade-

- consists of the intrinsic pathway, extrinsic pathway and the common pathway
- intrinsic and extrinsic converge at the level of factor X activation
- intrinsic- largely in vitro
- extrinsic- largely in vivo
- Each activation requires an enzyme, a substrate and a cofactor, all of which are present on the plasma membrane of activated platelets, endothelial cells and leukocytes.

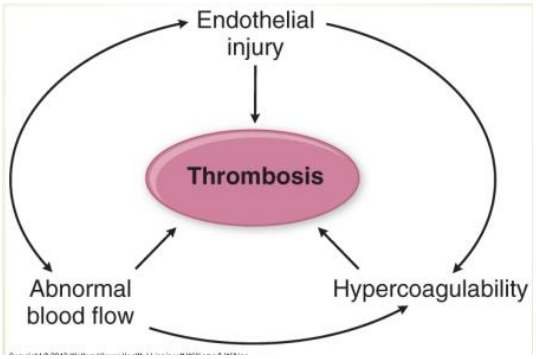
Prothrombin is cleaved to thrombin by factor Xa; factor Va and calcium act as cofactors in this reaction. Thrombin converts the soluable plasma protein fibrinogen to fibrin

Antithrombin III (AIII) inactivates thrombin and factors IXa, Xa, Xia and XIIa by forming a stoichiometric complex with these coagulation factors.

Explain and broadly describe the pathogenesis of thrombosis-

Virchow's Triad

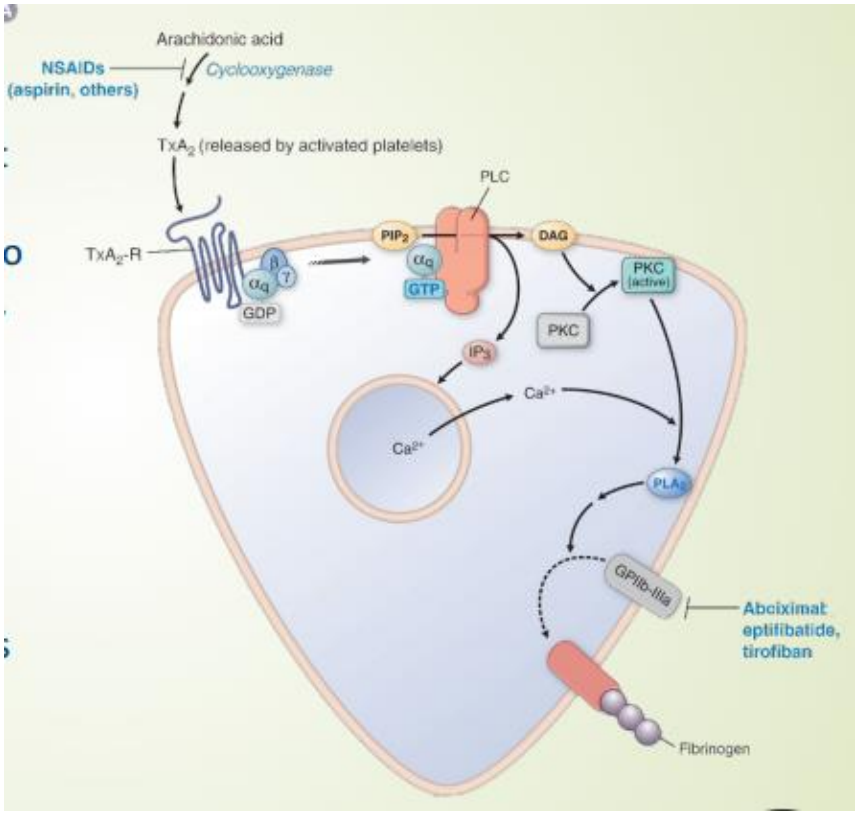
Thrombosis- pathological extension of haemostasis, coagulation reactions inappropriately regulated= clot uncontrollably enlarges and obstructs blood vessel. 3 factors-



Explain and describe pharmacologic classes and agents-

3 classes:

1. antiplatelet agents
2. anticoagulants
3. thrombolytic agents



Mechanism of action of anti-platelet agents-

- aspirin inhibits cyclooxygenase by covalent acetylation of the enzyme near its active site, leading to decreased TxA2 production (effect is profound because platelets lack the ability to synthesise new enzyme molecules)
- aspirin inhibits the synthesis of prostaglandins inhibiting platelet granule release action interfering with normal platelet aggregation
- clopidogrel, ticlopidine, prasugrel etc inhibit steps in ADP-mediated platelet activation. All of these are antagonists of the P2Y(ADP) receptor

Warfarin-

- vitamin K is a necessary cofactor in the post-translational carboxylation of glutamate residues on factors II, VII, IX and X
- during the carboxylation reaction, vit K is oxidised to the inactive 2,3-epoxide
- warfarin acts on the carboxylation pathway not by inhibition but by blocking the epoxide reductase that mediates the regeneration of reduced vitamin K

Lecture 16: pharmacology of heart disease

Explain and describe the pathophysiology of hypertension: Specifically the role of CO and SVR.
Primary hypertension: unknown cause.
Secondary hypertension: linked to a defined cause (eg thyroid problems, adrenal gland tumours, defects in blood vessels, sleep apnoea, kidney problems, illegal drugs, alcohol abuse etc).

Cardiac function-
high cardiac output hypertension, seen mainly in young people. Involves increased cardiac output and normal systemic vascular resistance (SVR). Treatment with β-antagonists is ideal in this population.

Vascular function-
vascular resistance based hypertension (normal cardiac output but increase SVR). Seen mainly in the elderly, vasculature is abnormally responsive to sympathetic stimulation, circulating factors or local regulators. Presents as a predominant elevation of systolic blood pressure. Thiazide diuretics are the preferred treatment option for this group.