ANTIPLATELET DRUGS AND THROMBOLYTICS

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Objectives

- Platelet plug formation
- Prostaglandin synthesis/ degradation pathway
- Mode of action, types, uses and main side effects of anti-platelets

- Thrombolytic pathway
- Mode of action, uses and main side effects of thrombolysics

Platelets support haemostasis in 3 ways

1. Physical
2. Activation of coagulation proteins
3. Vasoconstriction

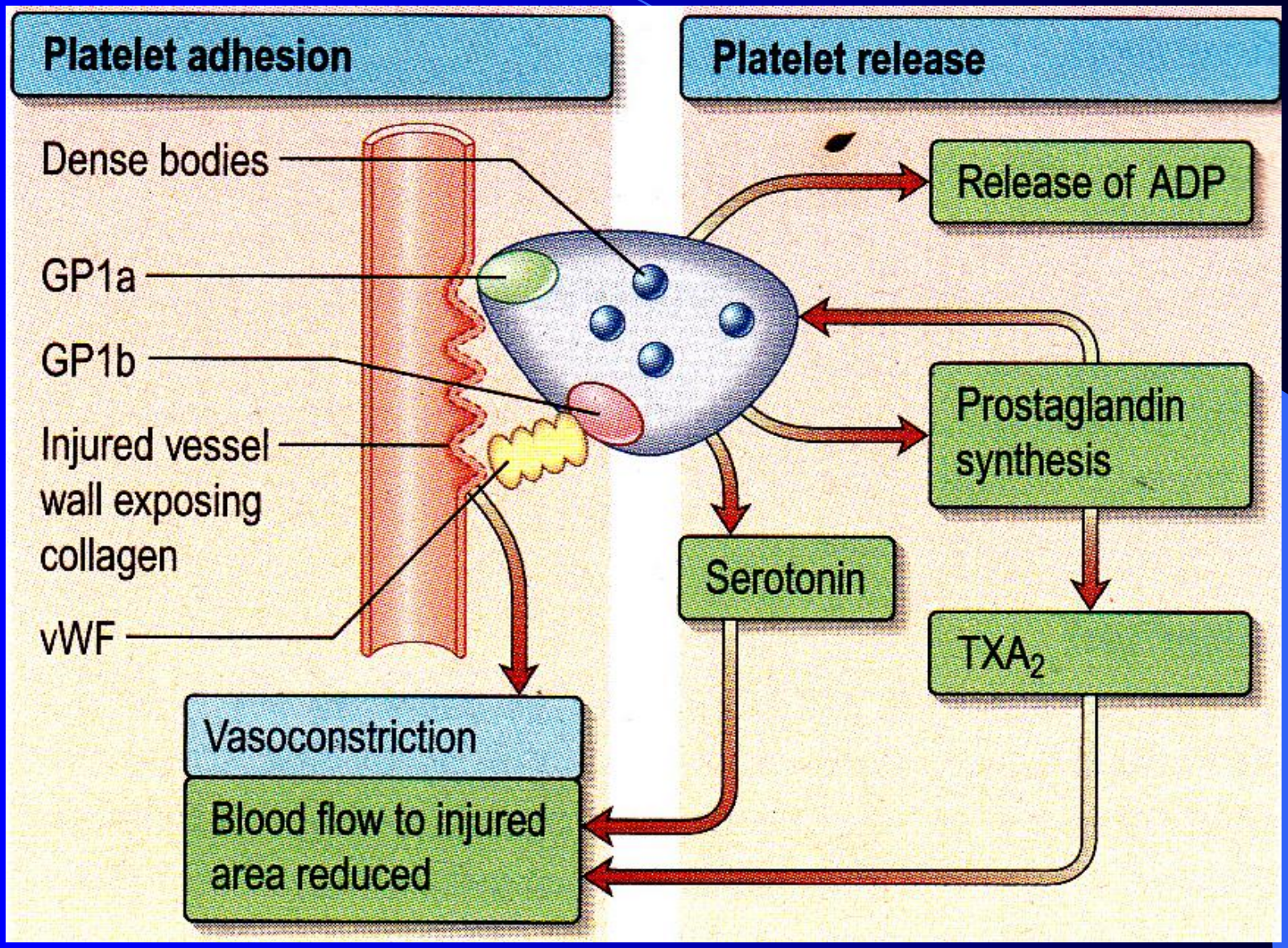
Platelets do not aggregate

- If CAMP level is high
- When GPIIB IIIA receptor is in resting state

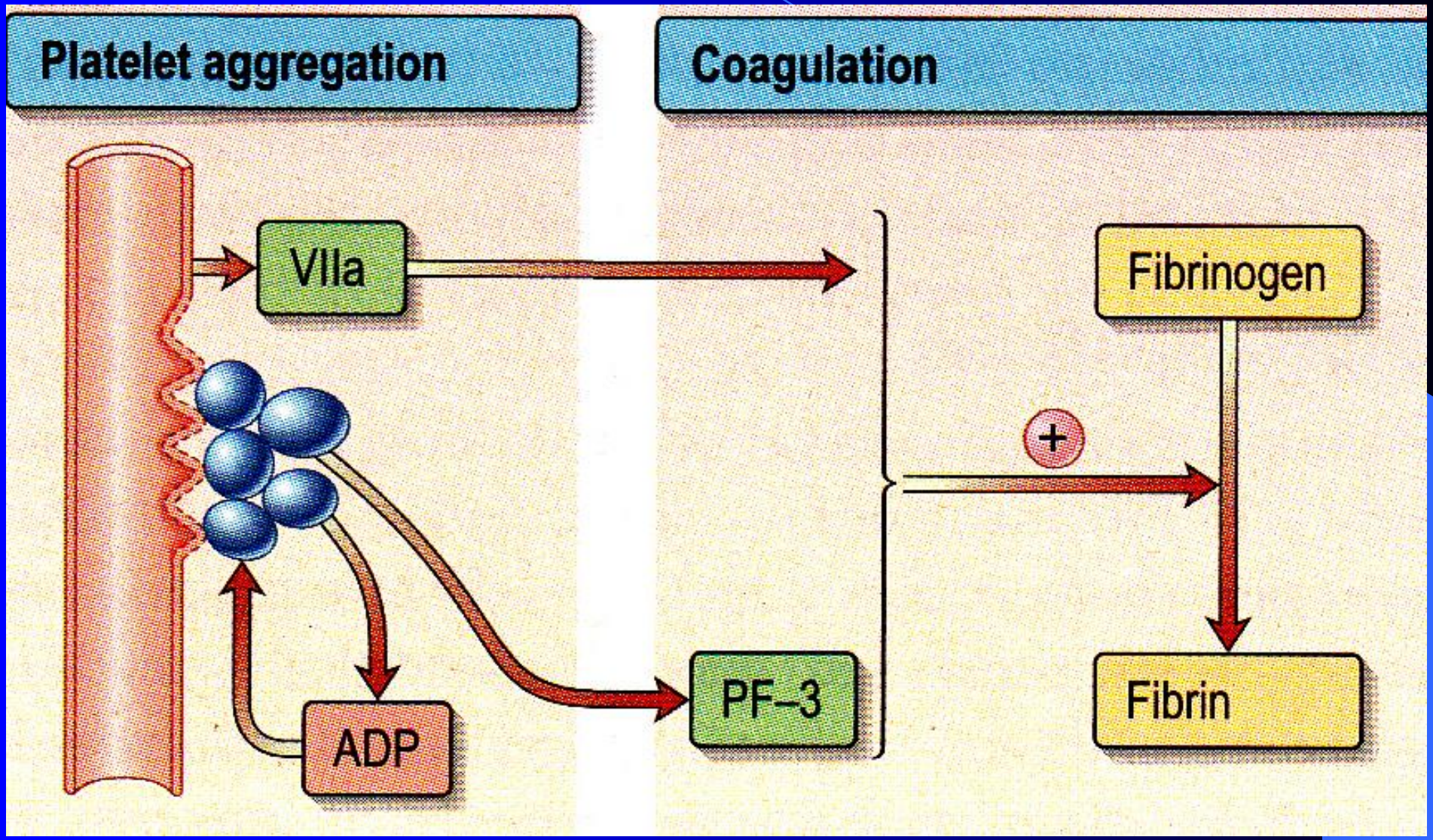
Formation of haemostatic plug 4/4

- Blood vessel damage - exposes collagen
- Platelet adhesion to collagen - via GP Ia / Ib receptors and vWF
- Platelet release – ADP, serotonin, TxA2…
- Platelet aggregation – by ADP induced conformational change in GP IIb IIIa receptors
- Fibrin strands formed by clotting factor stimulation
- Clot formed by binding platelets and RBC to fibrin mesh, stabilized by F XIII

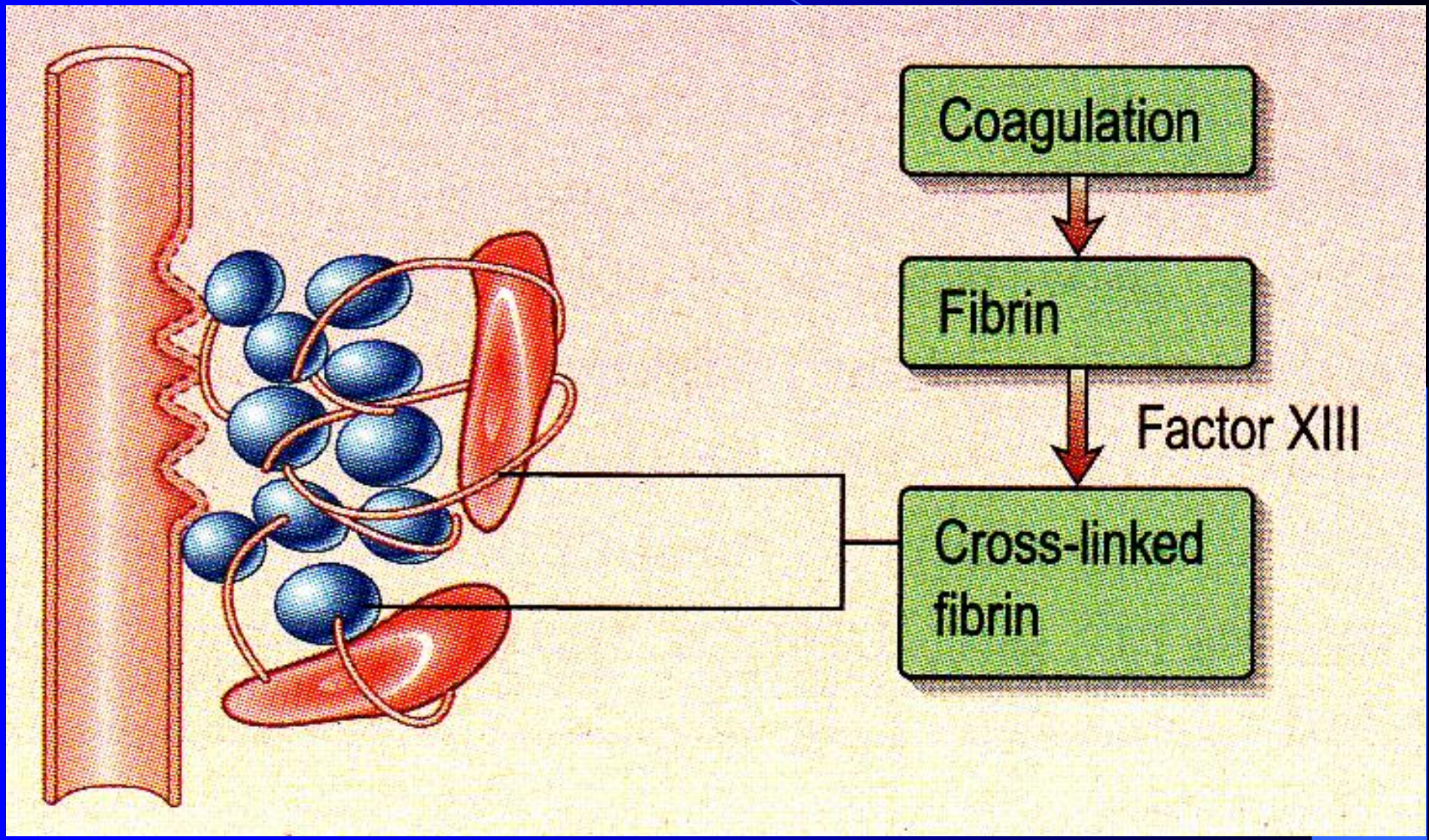
Formation of haemostatic plug 1/4



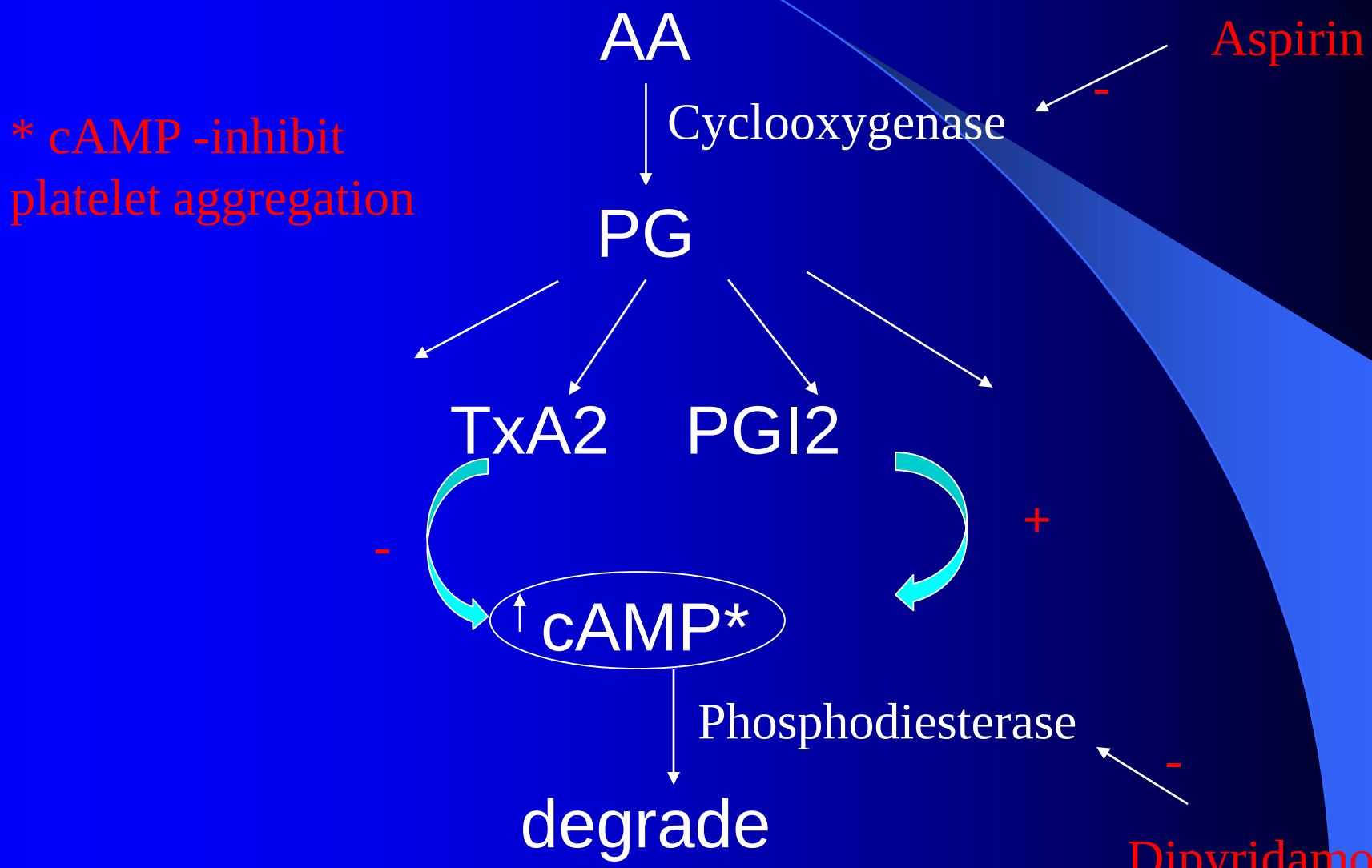
Formation of haemostatic plug 2/4



Formation of haemostatic plug 3/4



Prostaglandin synthesis & degradation pathway



Antiplatelet drug types

- Cyclooxygenase (COX) inhibitors
  - Aspirin
- ADP related activation inhibitors
  - Clopidogrel, ticlopidine
- Phosphodiesterase inhibitors
  - Dipyridamole
- Glycoprotein II b/IIIa inhibitors
  - Abciximab, tirofiban, eptifibatide

Aspirin

- MOA - **Irreversibly** inactivates COX
  - So effect last for the lifetime of platelet
  - Antiplatelet action is by low dose aspirin (75-100mg OD); as it selectively inhibits COX in platelets but not in endothelial cells
- Indication –
  - Treatment of arterial thrombosis (ACS, Ischaemic stroke/TIA, PVD)
  - Secondary prevention of CVD
  - Primary prevention of CVD – Should be an individual clinical decision considering risks and benefits
- SE – peptic ulceration and GI bleeds
  - hypersensitivity, angioedema
  – asthma

Clopidogrel

- MOA –Inhibit ADP mediated platelet aggregation
- Very much Similar to aspirin but more efficacious and more expensive

- Indication – treatment / prevention of arterial thrombosis (ACS, Ischaemic stroke/TIA, PVD)

- SE – GI bleed

Ticlopidine

- Inhibit ADP mediated platelet aggregation
- Not routinely used
- Cause sever neutropaenia on long term use, so monitoring of WBC needed

Dipyridamole

- MOA - **Reversibly** inhibits phosphodiesterase
  - So not so effective as aspirin
  - BD dose
- Indication – used for Ischaemic stroke/TIA prevention in combination with aspirin
- SE – headache
  - GI bleeds

Glycoprotein II b/IIIa antagonists

- MOA – Competitively block receptors on platelet for fibrinogen and vWF and inhibit platelet binding at final common pathway
  - More effective than other antiplatelets but expensive
  - IV preparations
  - Dose dependant effect

- Indication – Adjunct in invasive Coronary Intervention (PCI)
  - Refractory angina patients

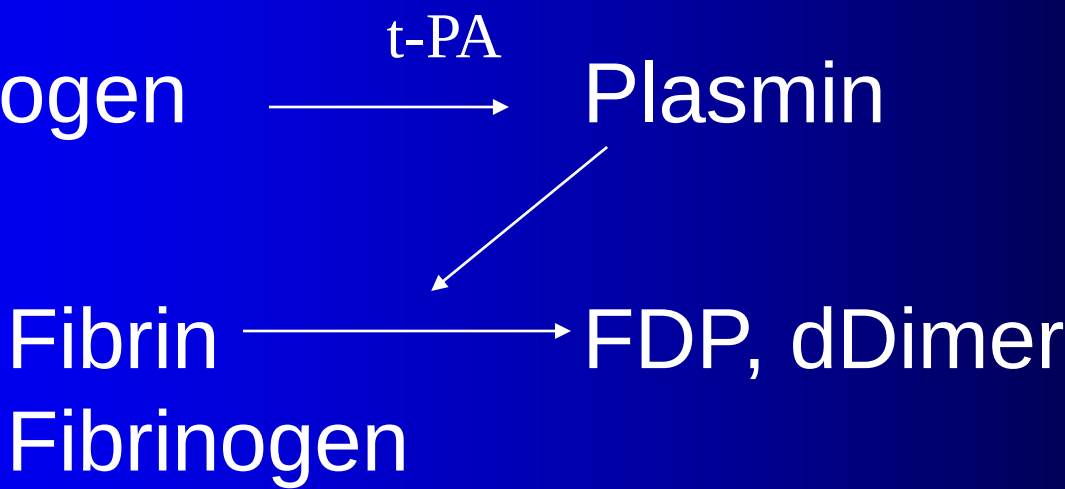
- SE – Excessive bleeding
  - Thrombocytopenia

- Murine-human chimeric Ab and synthetic preparations available eg. Abciximab, tirofiban, eptifibatide

Thrombolytic drugs

Thrombolysis/ Fibrinolysis

- Lysis of blood clot
- Important to restore vessel wall patency
- Caused by activating plasmin either by
  - intrinsic factors (e.g. CF XII, prekallikrein)
  - extrinsic factors (tissue type PA, urokinase)



Thrombolytics

- Non-fibrin selective
  - streptokinase
  - urokinase

- Reduce fibrinogen level
- Increase generalized bleeding

- Fibrin selective

Recombinant plasminogen activators

  - Alteplase
  - Reteplase
  - Tenecteplase

Streptokinase

- Derived from beta-haemolytic streptococci, hence antigenic and cause allergic reaction
- Indication –
  - STEMI in developing countries
  - Pulmonary embolism
- SE –
  - Allergic reaction
  - Hypotension
  - Increase bleeding tendency
  - Reperfusion arrhythmias

Trombolytics cont

Contra indications

- Alergy to streptokinase
- History of hemorrhagis stroke
- Head trauma or brain surgery within 6m
- Known intracranial neoplasm
- Intenai bleeding within 6 weeks
- Active bleeding in a non compressitle site
- Major surgery, trauma, or bleeding within 3 weeks
- Traumatic cardiopulmonary resuscitation within 3 weeks

Recombinant PA

- Plasminogen activators produced by recombinant DNA technology
- Non-antigenic , non-allergic
- Indication –
  - Acute cerebral infarction within 4.5hrs
  - Pulmonary embolism
  - Extensive DVT
- SE – Bleeding especially high risk of ICH than with streptokinase

* Therefore should consider contraindications before giving

Summary

- Anti-platelet drugs:
  - Inhibit platelet adhesion, release or aggregation
  - There are different types depending on there mode of action
  - Used in prevention and treatment of vascular events
- Anti-Thrombotic drugs:
  - Cause lysis of fibrin clot by activating plasminogen
  - Used in lysis of a pre-formed fibrin clot hence for treatment of mainly arterial thromboses
- Bleeding is the main side effect of both groups