دفعة يقين 2025

HLS

PHARMACOLOGY فارما

LECTURE المحاضرة

3

BY إعداد

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EDITED تعديل

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#معكم_خطوة_بخطوة

Thrombosis

"The formation of unwanted clot within a blood vessel"

- Myocardial Infarction (MI) (cardiac ischemia caused by occlusion of coronary arteries by clot)
- Deep Venous Thrombosis (DVT)
- Pulmonary Embolism (PE) (occlusion by embolus in the Pulmonary circulation)
- Cerebrovascular Accident (CVA) (occlusion of blood vessels that supply the brain)

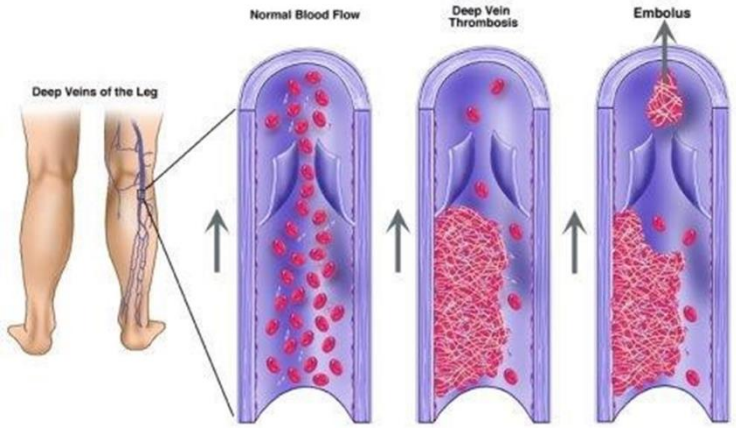
Thrombus vs Embolus

- What is the difference?
-

thrombus :the formation of blood clot in the blood vessels at the primary site

embolus: fragmentation and dislodgment of the thrombus to the blood stream

ممكن يروح يسكر مكان ثاني



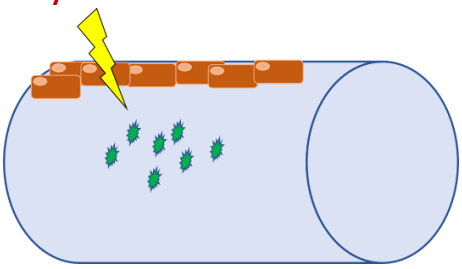
Arterial thrombosis vs venous thrombosis

- What is the difference?

- Arterial thrombosis: platelet-rich clot
- Venous thrombosis: blood stasis/pathological activation of the coagulation cascade

Platelet Response to Vascular Injury

Physical Trauma



يعني اذا بدنا نصلح ال damage اللي صار بال blood vessels لازم نعمل activation لل:

Three main players:

1. **Endothelium**
2. **Platelets**
3. **Coagulation Pathway**

vasospasm → formation of platelet-fibrin plug → thrombus formation

اول اشي بصير vasospasm يعني الـblood vessel بصير فيه contraction بالـsmooth muscles عشان نقلل الـblood loss

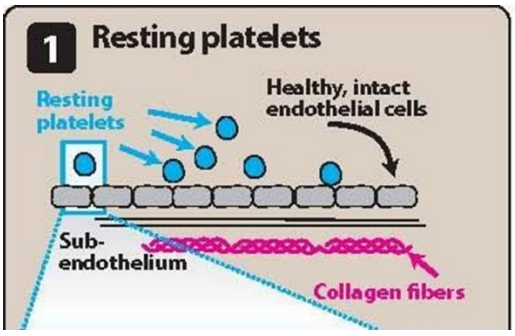
Resting Platelets

بالوضع الطبيعي الـplatelets بكونوا inactive لانو ما في bleeding ولا tissue damage

والـendothelium بكون intact

والـcollagen بكون متخبي not exposed

وحدة من الاشياء المهمة اللي بتخلي الـplatelets



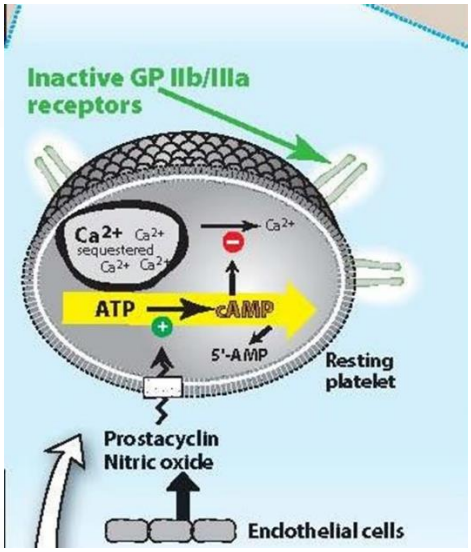
بالـresting state هو الـ $PG\ I_2$

Monitor the integrity of the vascular endothelium

Prostacyclin PG I_2:

- Synthesized by intact endothelial cells
- Inhibits platelet aggregation (bind to receptors on the platelets)

- Prostacyclin binds to platelet membrane receptors, causing synthesis of cAMP.
- cAMP stabilizes inactive GP IIb/IIIa receptors and inhibits release of granules containing platelet aggregation agents or Ca^{2+}.



بمنع الCa^{2+} من انو يطلع بالتالي بمنع الactivation of platelets

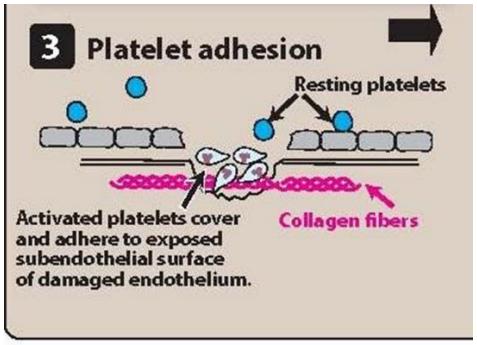
What else can bind to the resting platelet?

كلهم بشتغلوا عكس الPG بالتالي بعملوا activation للplatelets

- Thrombin
  - Thromboxanes
  - Exposed collagen

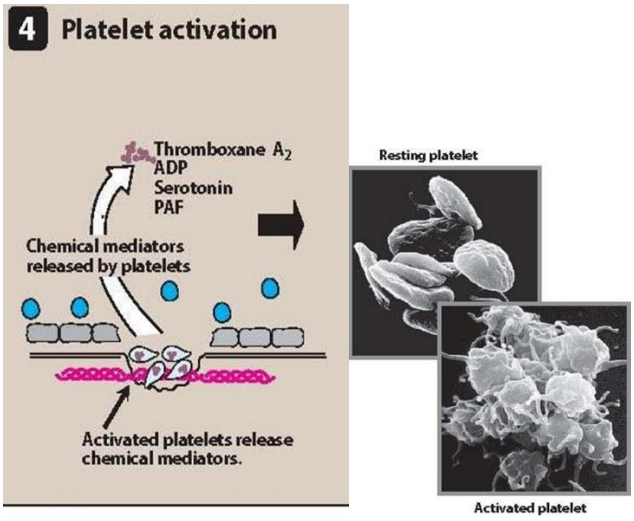
Platelet Adhesion

- Platelets adhere to exposed collagen
- Collagen binding results in platelet activation



Platelet Activation

- **Activated platelets release:**
  secreted immediately from the كلهم
  activated platelets



-Adenosine Diphosphate (ADP)

(as a signaling molecule بشتغل)

-thromboxane A_2

-serotonin

-Platelet Activating Factor (PAF)

-thrombin

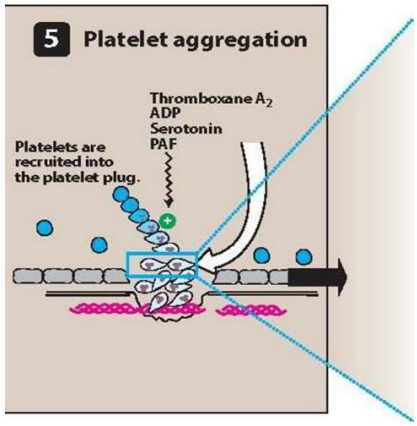
Platelet Aggregation

- Binding of these signaling molecules
  results in:

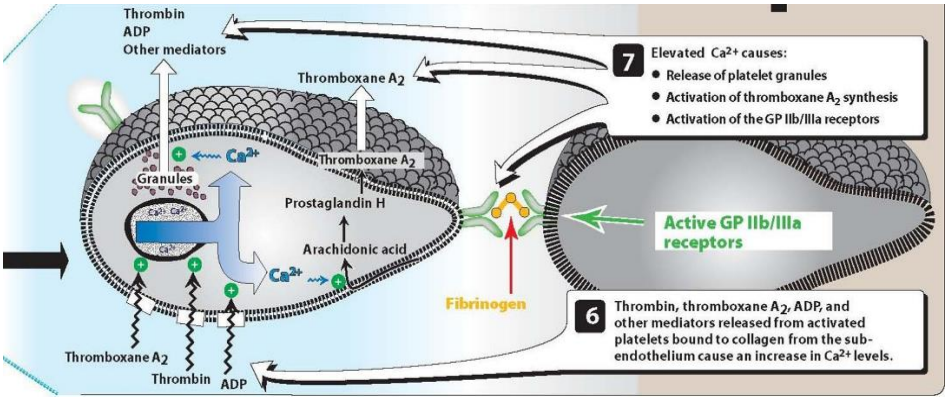
(PG I_2 عكس ال)

↓ cAMP

↑ Ca^{++}

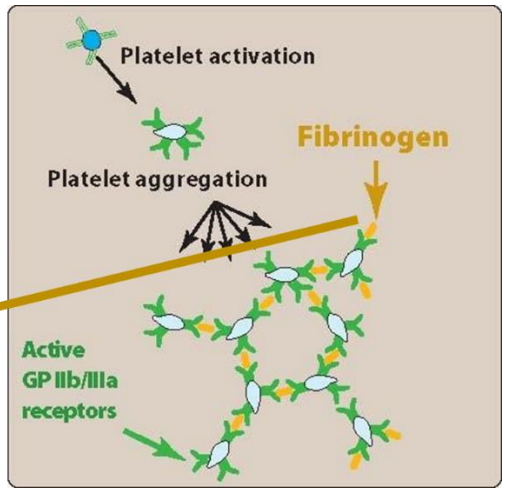


Platelet Aggregation



Glycoprotein IIb/IIIa Receptors

- Bind **fibrinogen**
- Regulate platelet-platelet interaction and thrombus formation
- Fibrinogen is a soluble plasma glycoprotein



الCa بعمل activate group of receptors اسمهم GP IIb/IIIa بكون موجود على الsurface تبع الplatelets وبحالة الplatelets resting بكون inactive بس لما يصيرplatelets activation والCa يزيد بعمله activation

وظيفة هذا ال receptor هي ربط الfibrinogen وبستخدمه كsticking material عشان يرتبط مع another platelet

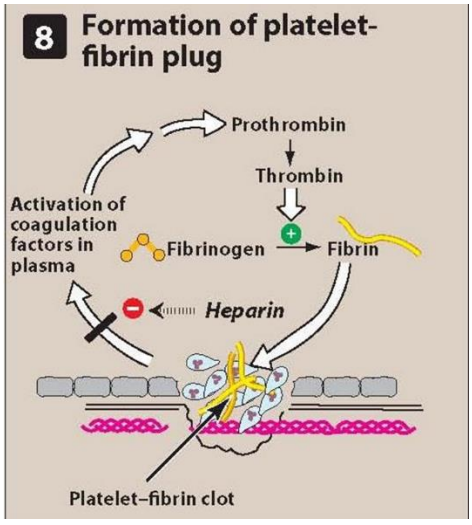
Formation of Plug

- Tissue factors + activated platelets →

prothrombin → thrombin

Thrombin (IIa): is a serine protease that catalyzes:

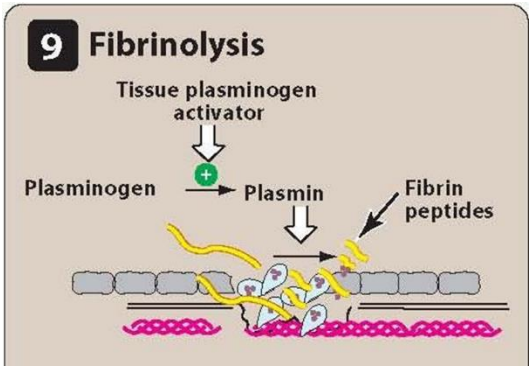
fibrinogen → fibrin



Fibrinolysis

بتشتغل بالعكس عشان نعمل control للsize of the thrombus

- tPA converts plasminogen to plasmin
  - Plasmin limits the growth of the clot and dissolves the fibrin network



The glycoprotein that facilitates platelets aggregation and is cleaved to form fibrin clot is Fibrinogen

The serine protease that is involved in the formation of the fibrin clot is Thrombin

The enzyme that is responsible for dissolving the fibrin clot is

Plasmin

What happens if:

- You pharmacologically interfere with the increase in platelet intracellular calcium upon tissue injury?

Can you think of components of the platelet activation pathway that can be drug targets?

- COX-1
- GP IIa/IIIb
- ADP receptors

Medication	Adverse Effects	Drug Interactions	Monitoring Parameters
Oral Agents:			
Aspirin	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	*ketorolac*—increased bleeding *cidofovir*—nephrotoxicity *probenecid*—decreased uricosuric effects	CBC LFT
Cilostazol	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
Clopidogrel	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (*e.g., omeprazole*)	CBC LFT
Dipyridamole	Bleeding Dizziness GI discomfort Rash	Salicylates Thrombolytic agents	None for oral administration
Prasugrel	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants Other antiplatelets	CBC
Ticlopidine	Abnormal LFT Bleeding Dizziness GI disturbances SJS	Antacids—decreases levels *Cimetidine*—reduces clearance	CBC LFT platelet count
Ticagrelor	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (*e.g., ketoconazole*) Strong CYP3A4 inducers (*e.g., rifampin*)	CBC LFT
Injectable Agents:			
Abciximab *Eptifibatide* *Tirofiban*	For all agents: Hypotension Nausea Vomiting Thrombocytopenia	For all agents: Increased bleeding: *Ginkgo biloba* Antiplatelets Salicylates SSRIs and SNRIs	For all agents: APTT clotting time H/H platelet count thrombin time

APTT=activated partial thromboplastin time, CBC=complete blood count, GI = gastrointestinal, H/H=hemoglobin and hematocrit, LFT=liver function test, SCr=serum creatinine, SJS=Stevens–Johnson Syndrome, SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor

Platelet Aggregation inhibitors

Main effects

- Decrease the formation of platelet-rich fibrin clot
- Interfere with chemical signals that promote platelet aggregation

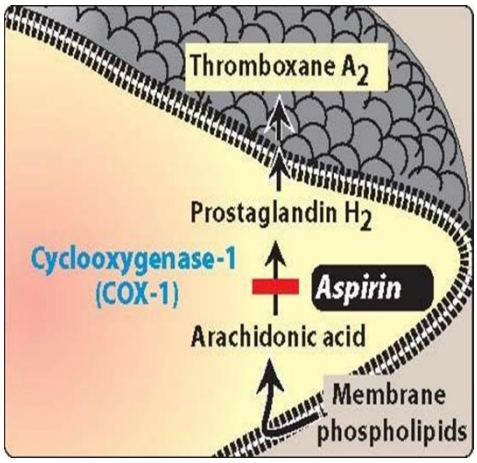
Can antiplatelets dissolve a formed fibrin clot?

Therapeutic uses:

1. Prevention and treatment of occlusive cardiovascular diseases
2. Maintenance of vascular grafts and arterial patency
3. Treatment of MI (adjunct)

Can you use antiplatelets solely for the immediate management of myocardial infarction?

Mechanism of Action

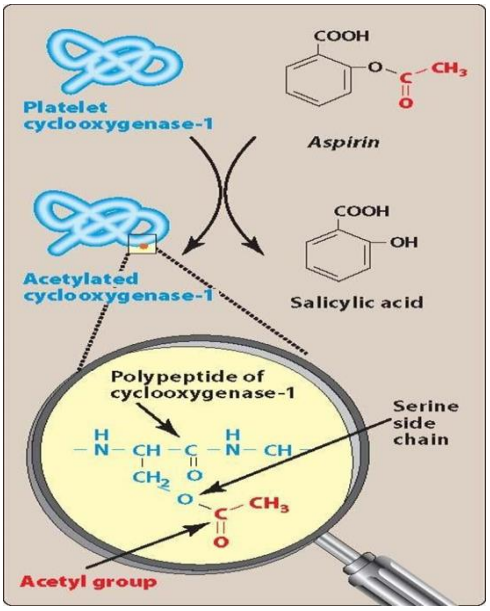


- Platelet stimulation by ADP, thrombin, exposed collagen leads to:

membrane phospholipase → arachidonic acid release → prostaglandin synthesis

- Thromboxane A_2 → platelet activation/aggregation/plug formation

aspirinال بعملblock لل1-COX بالتالي بمنع ال PG and thromboxane formation



- What does aspirin do?

Irreversibly inhibits COX-1 by acetylation of a serine residue on its active site

- ❖ Rapid
- ❖ Prolonged (lasts up to 7-10 days)