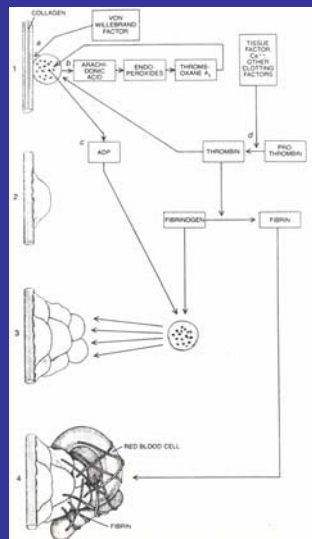


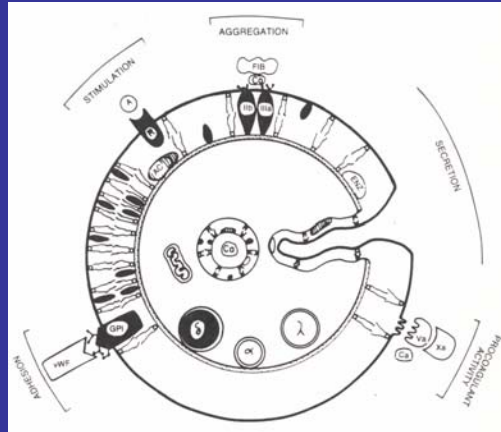
Anti-platelet Therapy

- Thrombi – aggregated platelets + fibrin deposit
- Aspirin
- ADP receptor antagonists
- Fibrinogen receptor antagonists
- Dipyridamole

Thrombus Formation



Platelet Membrane Receptors



Platelet Aggregation

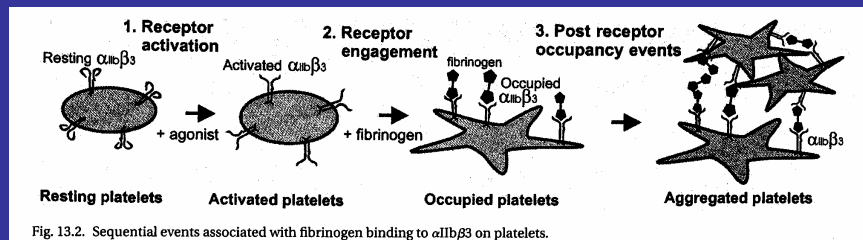
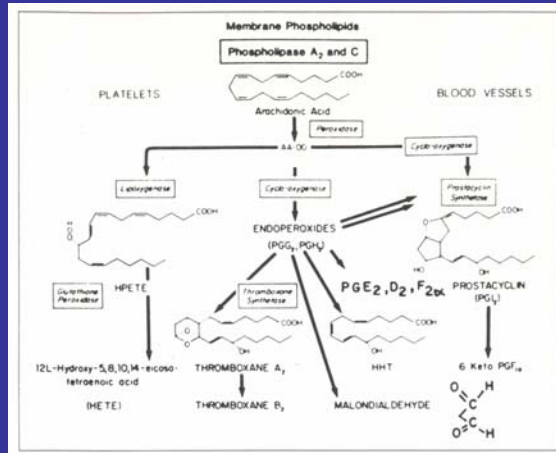


Fig. 13.2. Sequential events associated with fibrinogen binding to $\alpha_{IIb}\beta_3$ on platelets.

Cyclooxygenase Pathway



Inhibition of the Cyclooxygenase Pathway

- Phospholipase A₂
Anti-malarial drugs (quinacrine and mepacrine)
Non-specific
- Cyclooxygenase
Aspirin
Effective at low doses

Inhibition of the Cyclooxygenase Pathway

- Thromboxane synthetase
Dazoxiben, U63557A
No effect because PGH_2 also activates platelets
- TXA_2 / PGH_2 receptor antagonists
Being evaluated
Promising

ADP Receptor Antagonists

- Clopidogrel (PLAVIX)
- Ticlopidine (TICLID)
- Useful in aspirin-intolerant patients
- Side effects include nausea, dyspepsia, diarrhea, hemorrhage, leukopenia
- Clopidogrel has fewer side effects

GPIIb-IIIa Antagonists

- Abciximab (REOPRO)
- Eptifibatide (INTEGRILIN)
- Tirofiban (AGGRASTAT)

- Blocks fibrinogen binding and platelet aggregation
- Administered parenterally
- Oral drugs not active

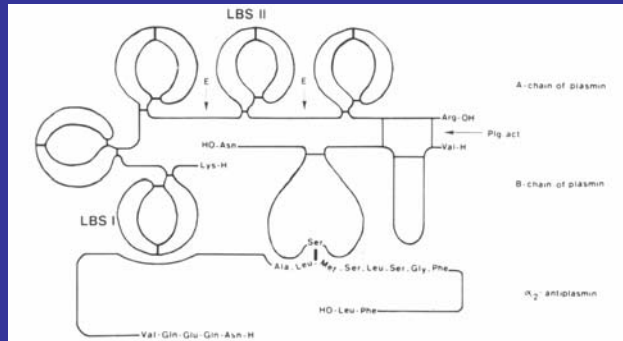
Increase of Platelet Cyclic AMP



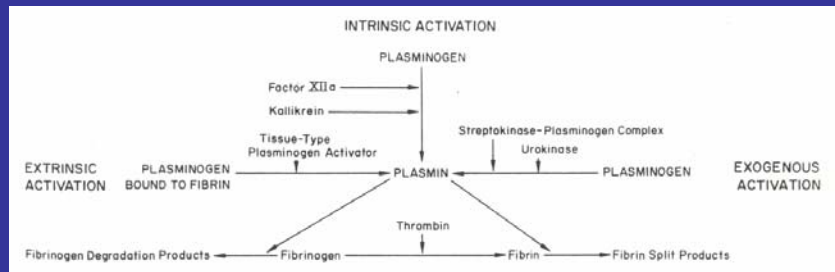
- \uparrow [cAMP] results in \downarrow [Ca^{2+}]
- PGI_2 , PGE_1 , adenosine – stimulate adenylate cyclase
- Dipyridamole – inhibits cAMP phosphodiesterase
- Not effective by itself
- Used with warfarin to prevent thromboembolisms in patients with prosthetic heart valves

Thrombolytic Therapy (Plasminogen Activators)

Plasminogen → Plasmin
(single chain) (two chain)



Plasminogen Activators



Tissue Plasminogen Activator (t-PA)

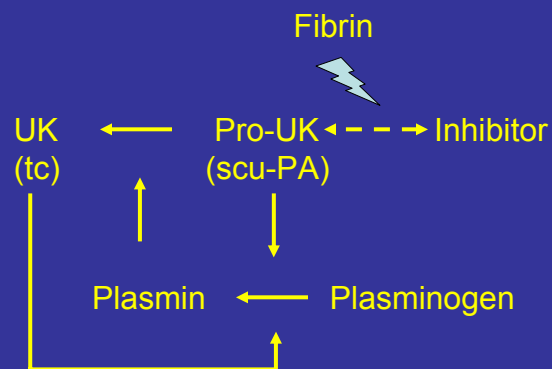
- Serine protease (68 kDa)
- Synthesized by endothelial cells
- Not a zymogen; t-PA exists in single- and two-chain forms. In the presence of fibrin, both forms are active.
- t-Pa binds to fibrin and activates plasminogen more efficient.
- Inactivated by plasmingen activator inhibitor
- Cleared by hepatic metabolism; half-life ~3 min

t-PA Therapy

- Recombinant t-PA (ACTIVASE)
- Coronary thrombolysis
10 mg (bolus injection)
followed by 3 h continuous infusion of 50 mg/h (first hour); 20 mg/h (second and third hour)

Urokinase (UK)

- Serine protease (54 kDa)
- Synthesized by kidney, excreted in urine
- Zymogen known as pro-UK or single chain urokinase-type plasminogen activator (scu-PA)
- In plasma, pro-UK forms a complex with an inhibitor; fibrin displaces the inhibitor
- Pro-UK is ~5% active
- Fibrin formed converts pro-UK to UK by hydrolysis of Lys¹⁵⁸-Ile¹⁵⁹ bond.
- Metabolized by the liver (15-20 min)



Urokinase Therapy

- UK (ABBOKINASE) lacks fibrin specificity
- Loading dose 1,000 – 4,500 U/kg iv followed by 4,500 U/kg/h
- Pro-UK (scu-PA, saurplase) is fibrin specific and is under investigation

Streptokinase (SK)

- A 47 kDa protein produced by β -hemolytic streptococci
- SK forms a complex with plasminogen, altering its conformation and exposing its active site
- SK-plasminogen complex cleaves plasminogen to plasmin
- Highly antigenic; loading dose 250,000 units to overcome anti-SK antibodies
- Half-life ~ 80 min
- Fibrin non-specific
- Apsac complex (anistreplase, EMINASE)

SK + Plg \longrightarrow SK-Plg

SK-Plg \longrightarrow SK-Plg'



Plasminogen \longrightarrow Plasmin