



NOTTINGHAM PLATELET CONFERENCE, 2010



PGE₂ and platelet function

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Some natural agents that influence platelet function

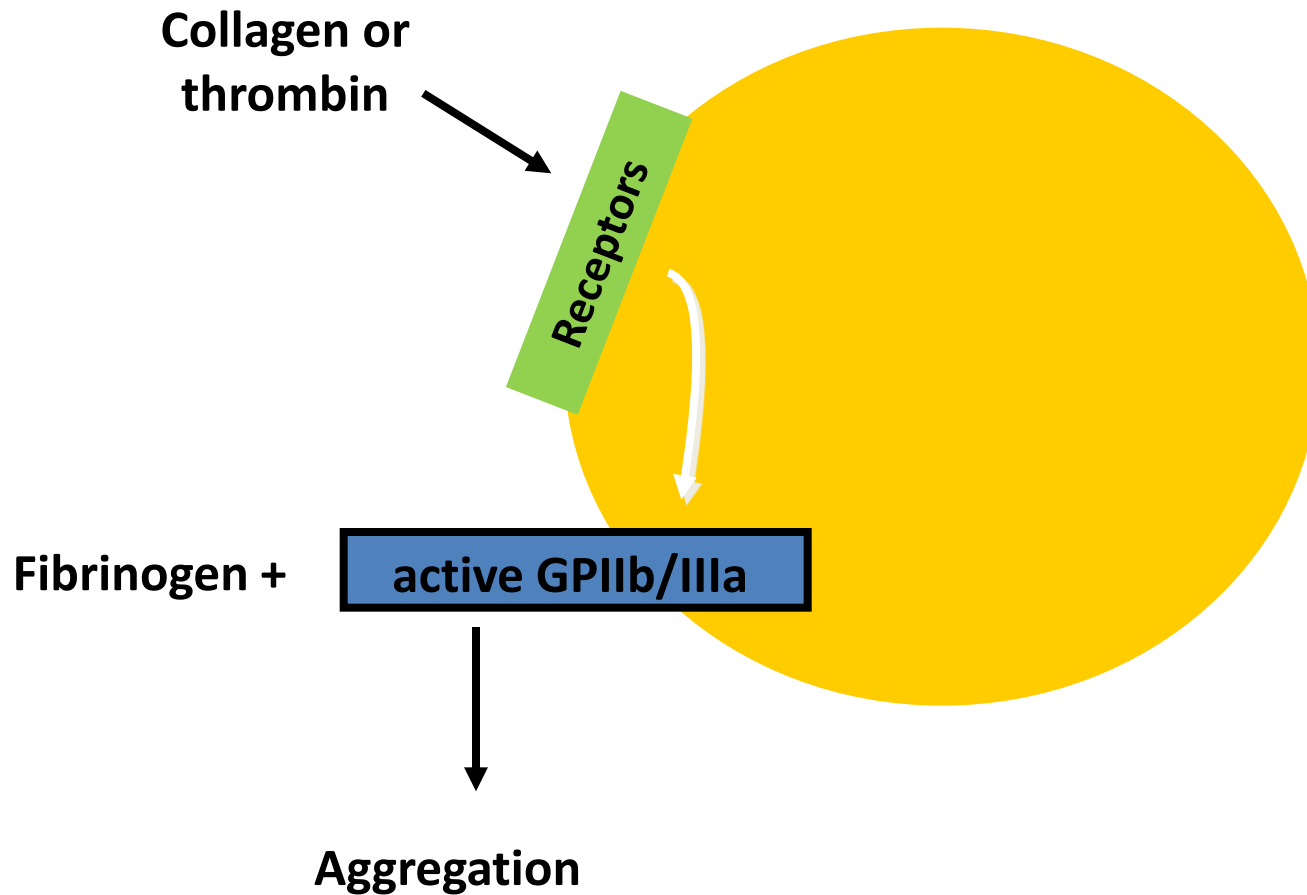
Promoters of platelet function

Thrombin
Collagen
Thromboxane A₂
Adenosine diphosphate

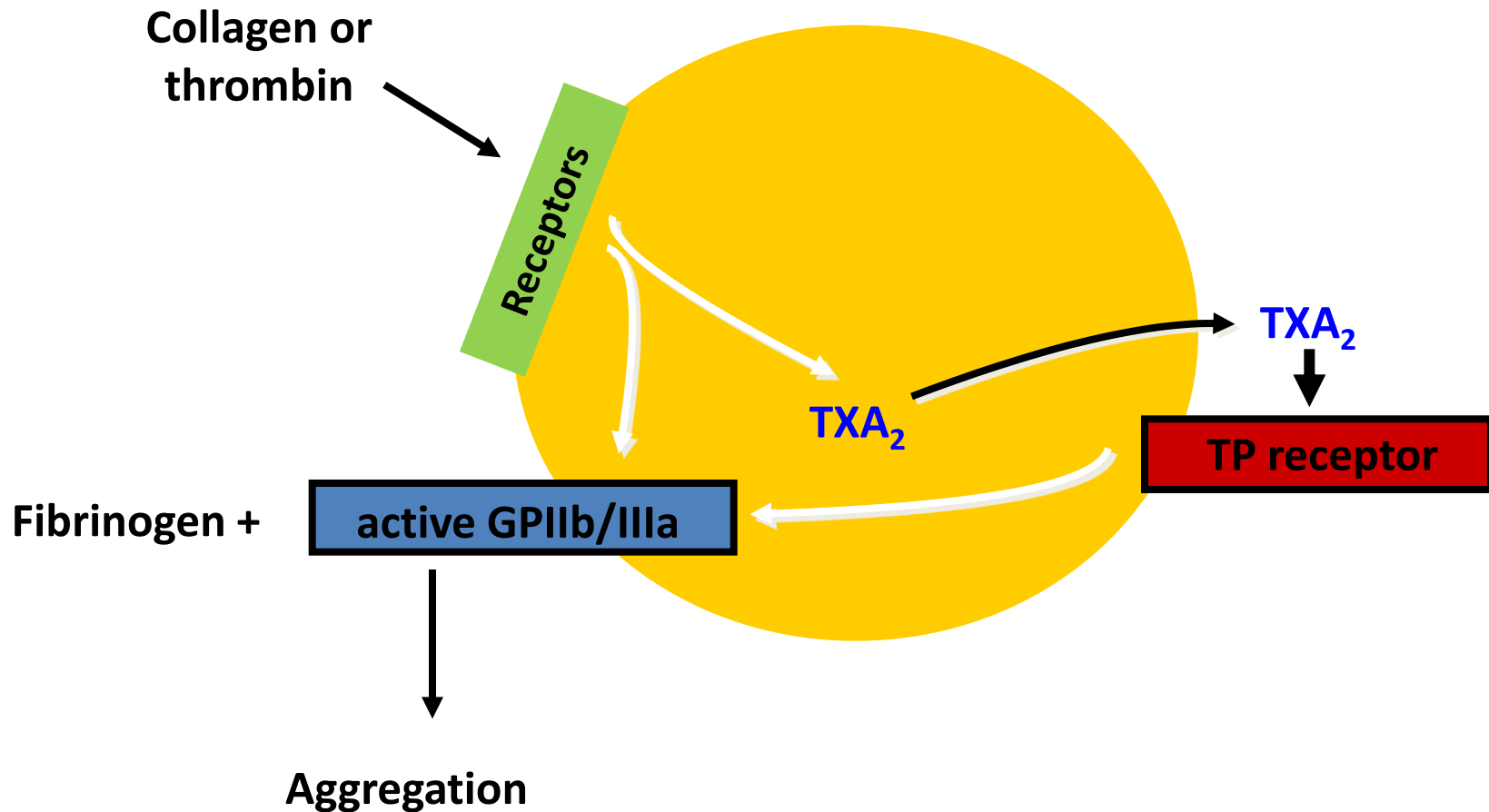
Inhibitors of platelet function

Prostaglandin I₂
Nitric oxide
Adenosine?

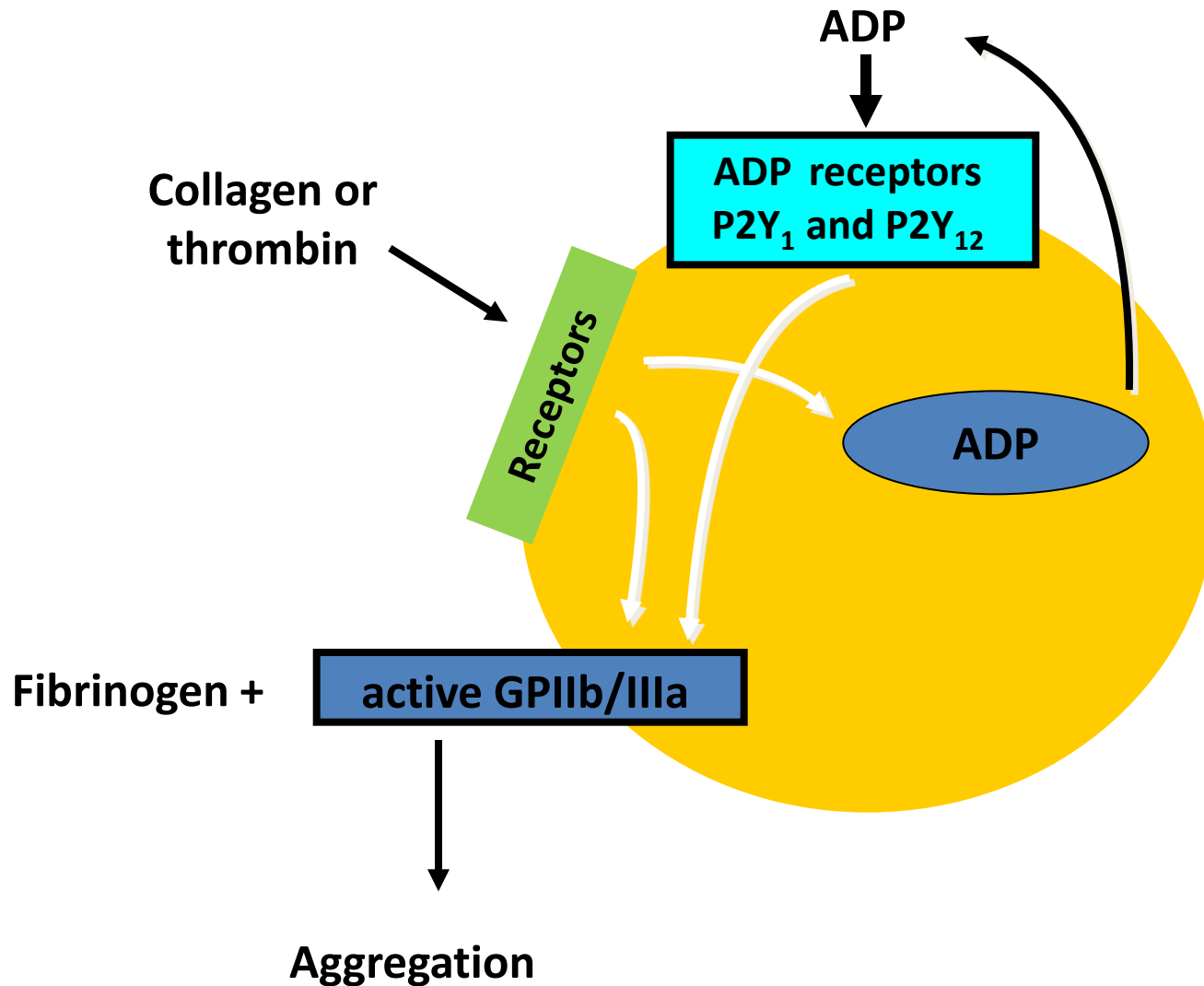
Collagen/thrombin: mechanism of action



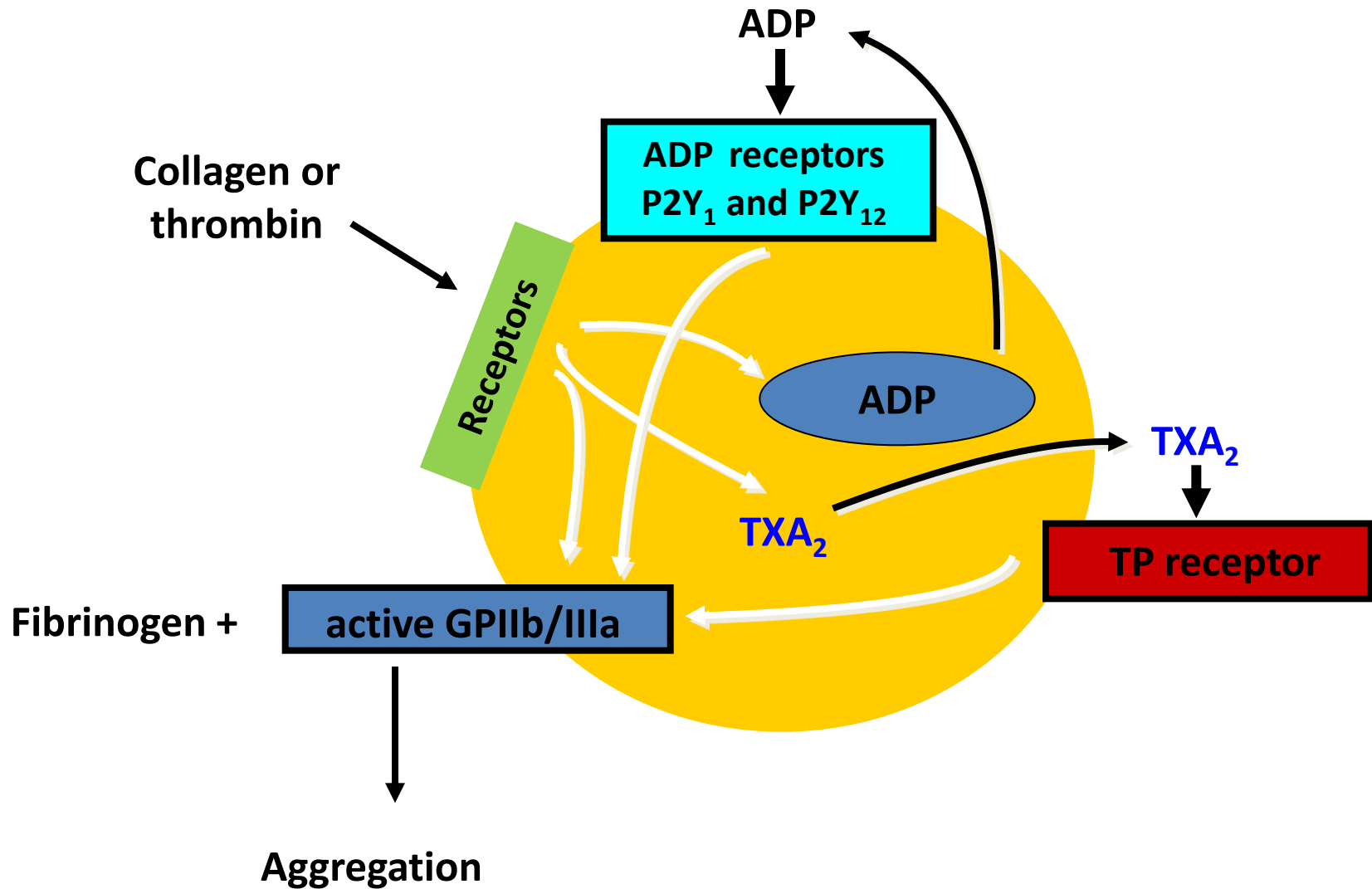
Collagen/thrombin: mechanism of action



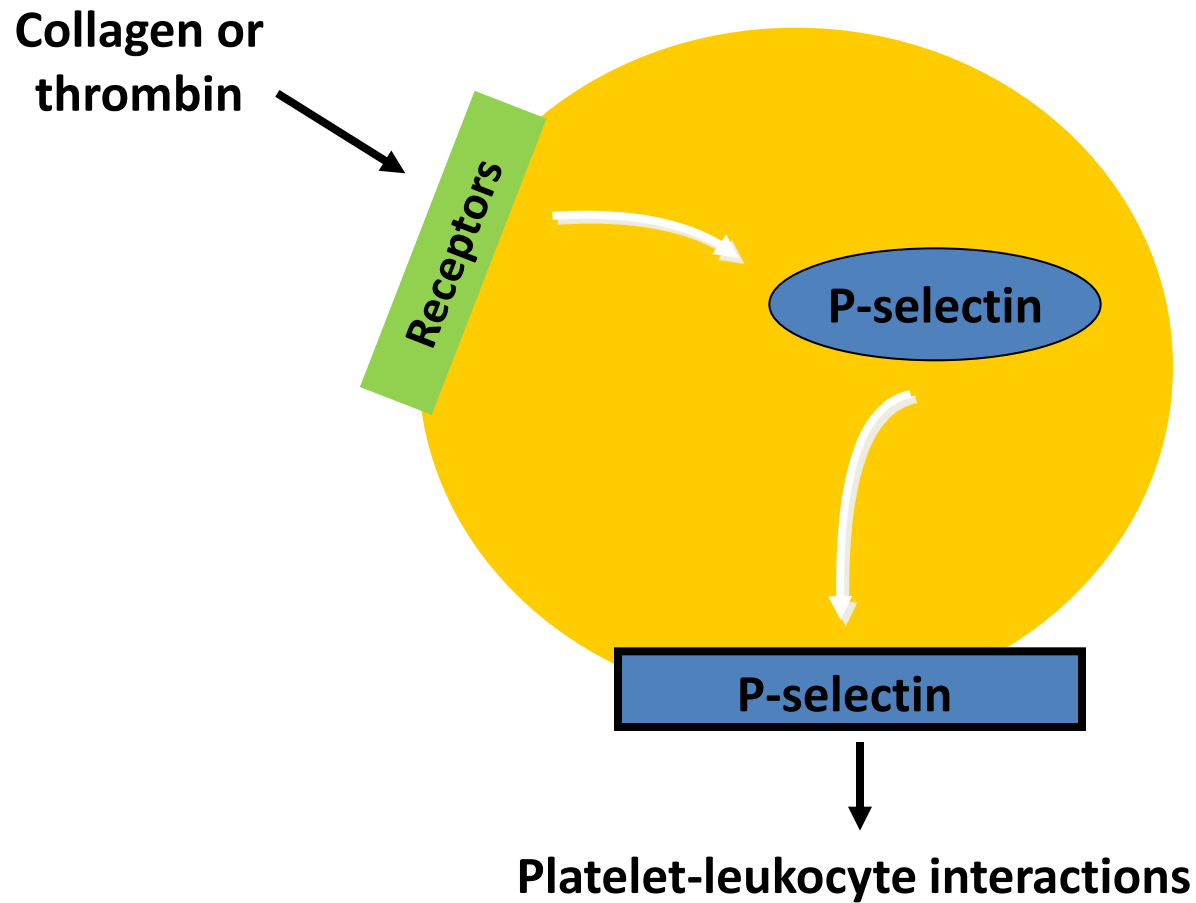
Collagen/thrombin: mechanism of action



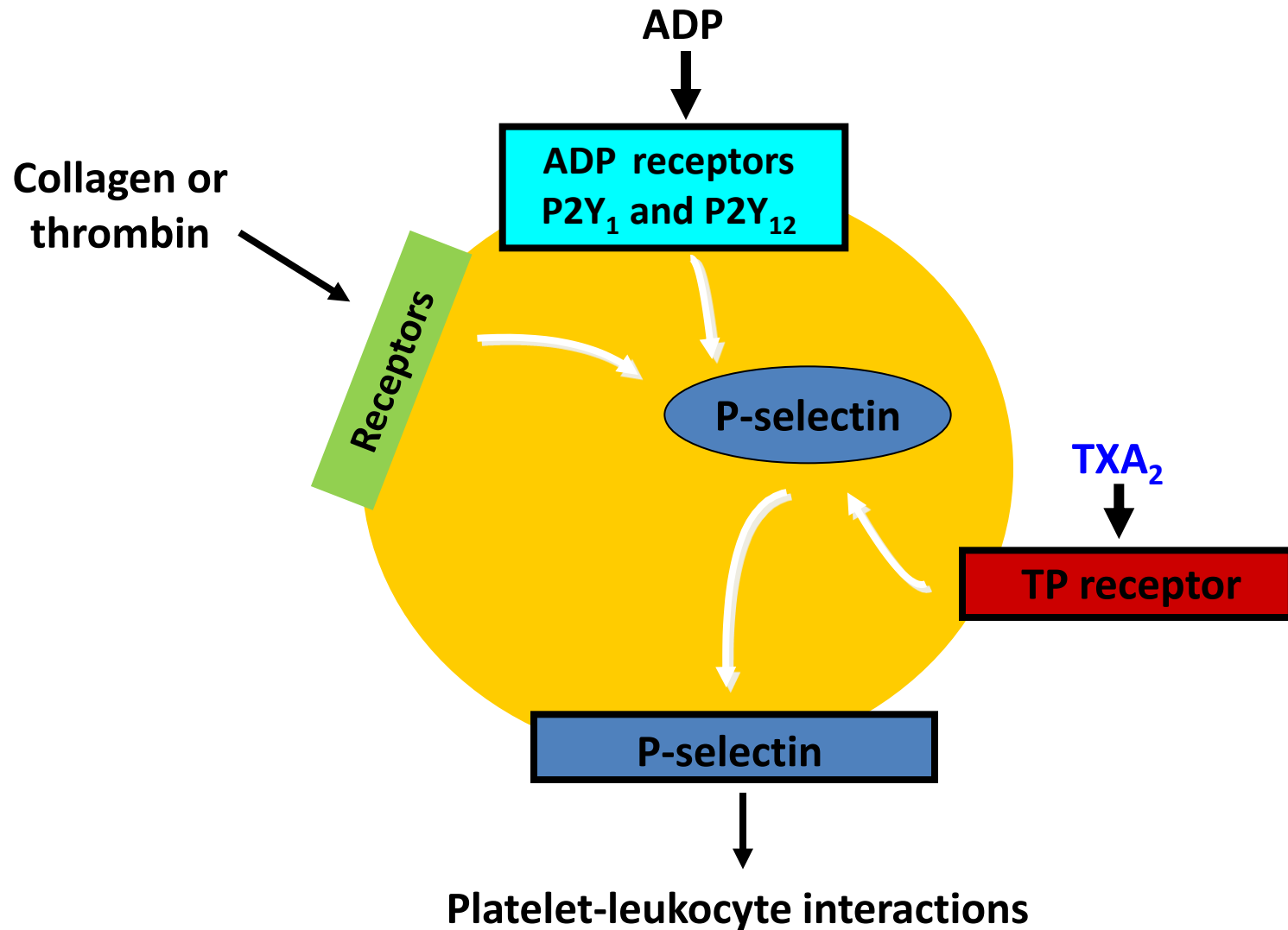
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Some natural agents that influence platelet function

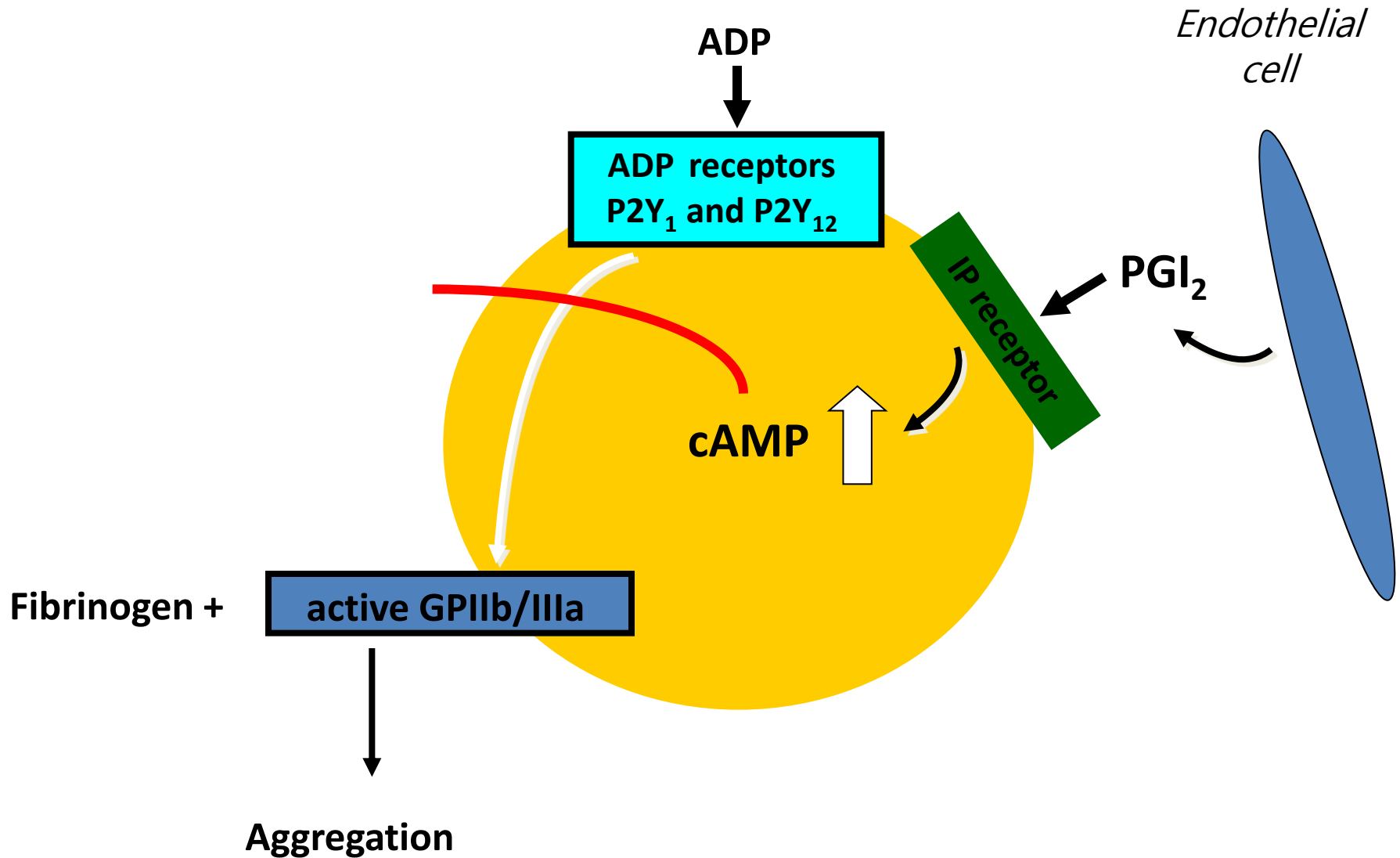
Promoters of platelet function

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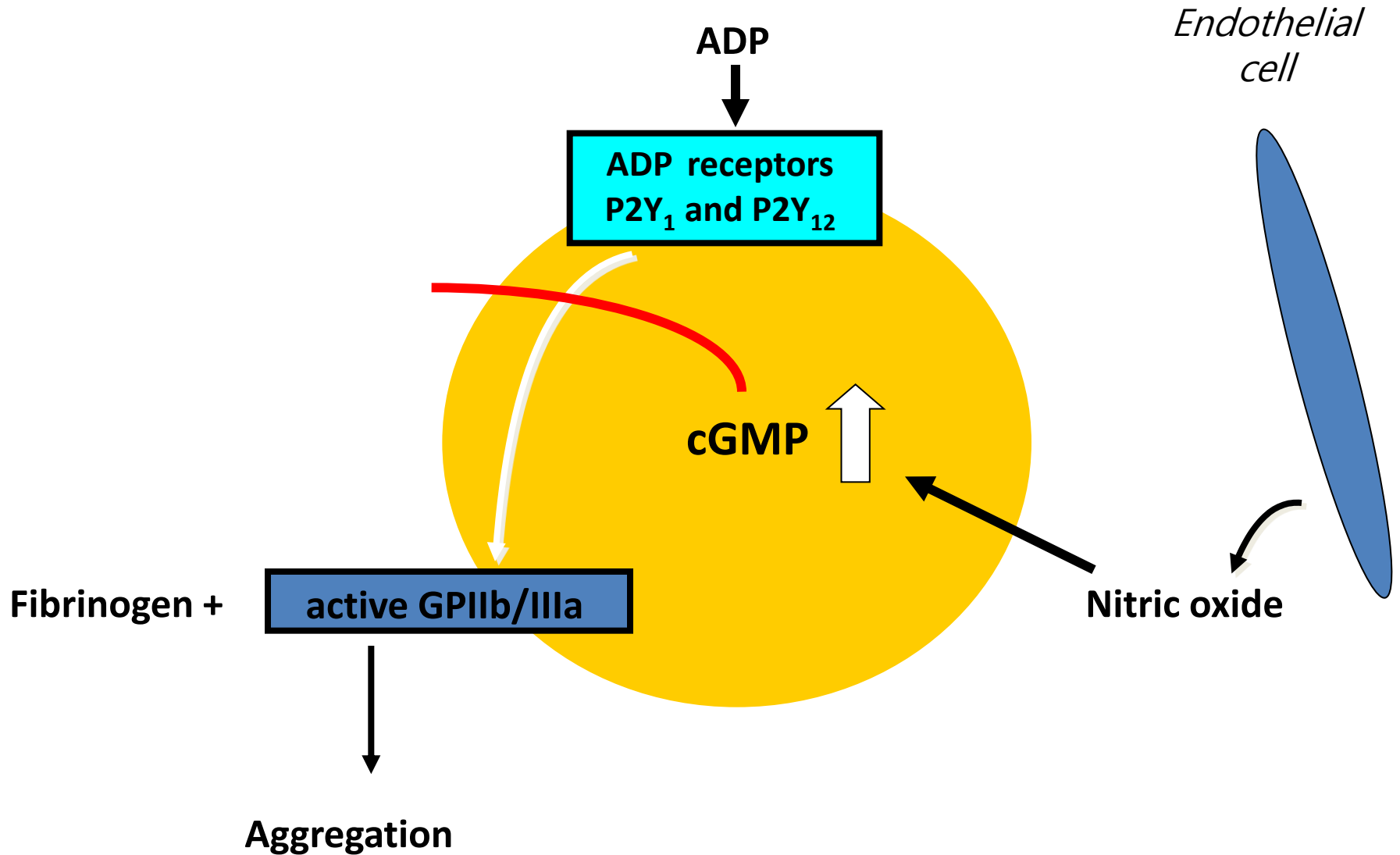
Inhibitors of platelet function

Prostaglandin I₂
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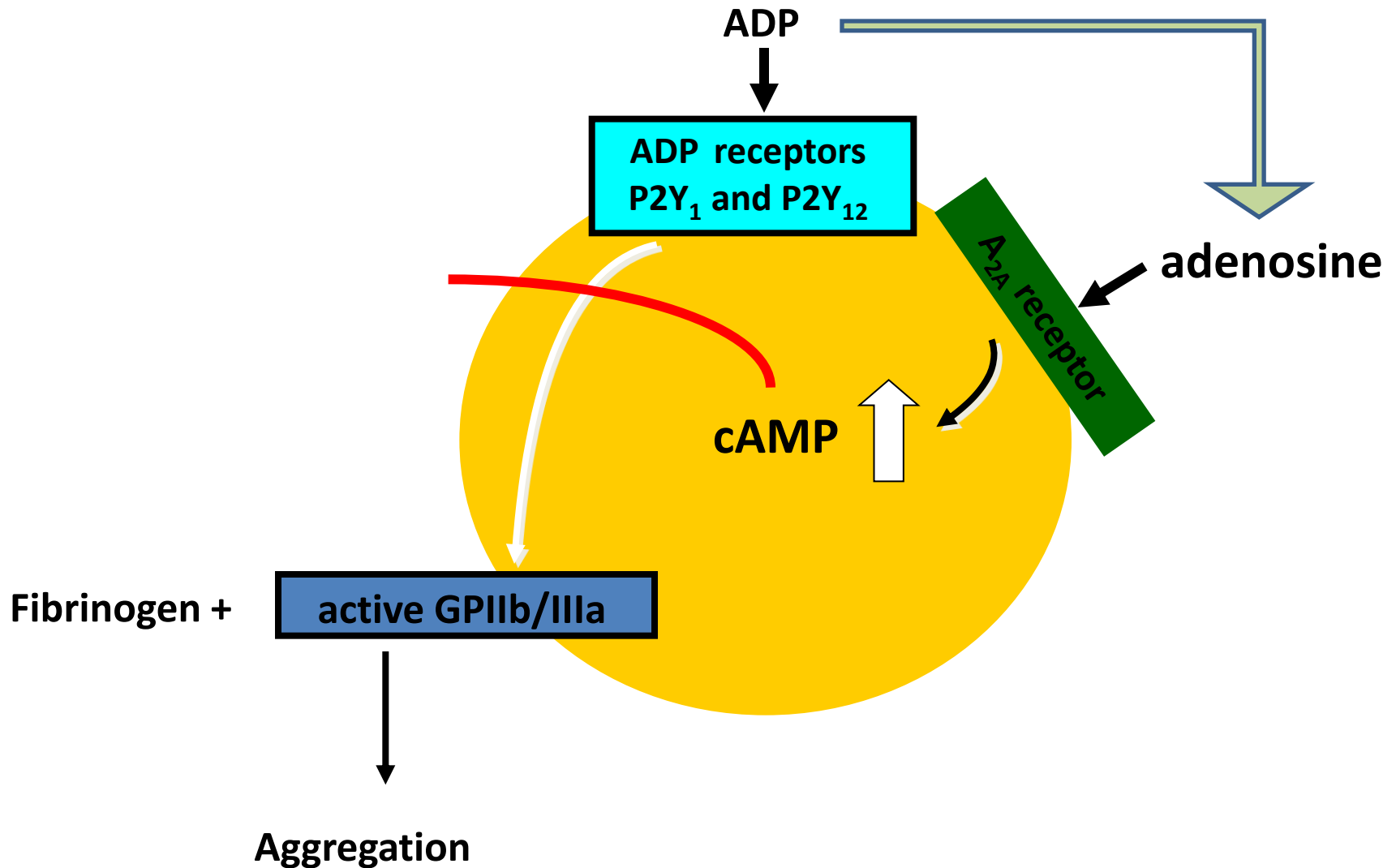
PGI₂: mechanism of action



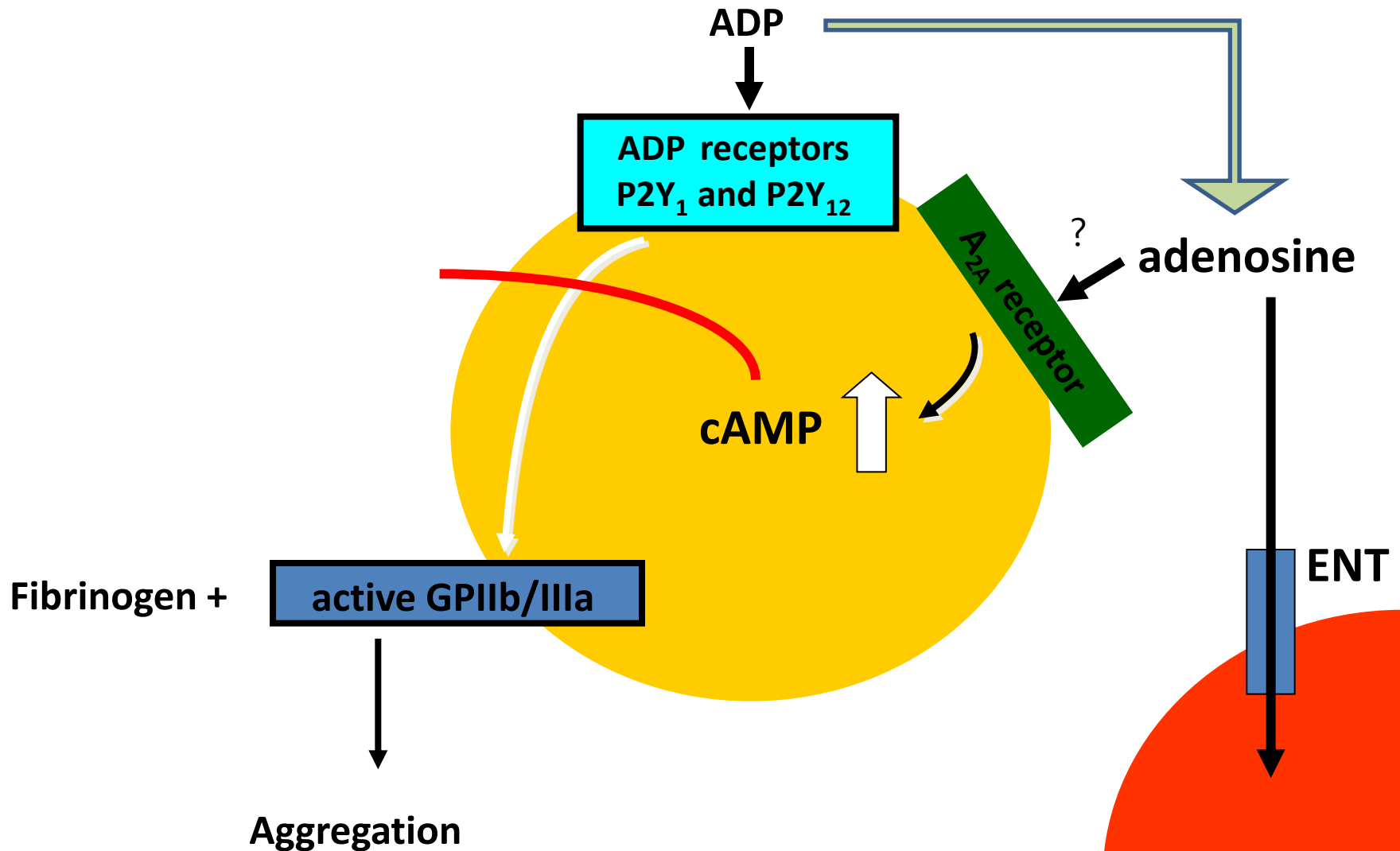
Nitric oxide: mechanism of action



Adenosine: mechanism of action



Adenosine: mechanism of action



Some natural agents that influence platelet function

Promoters of platelet
function

Thrombin
Collagen
Thromboxane A₂
Adenosine diphosphate

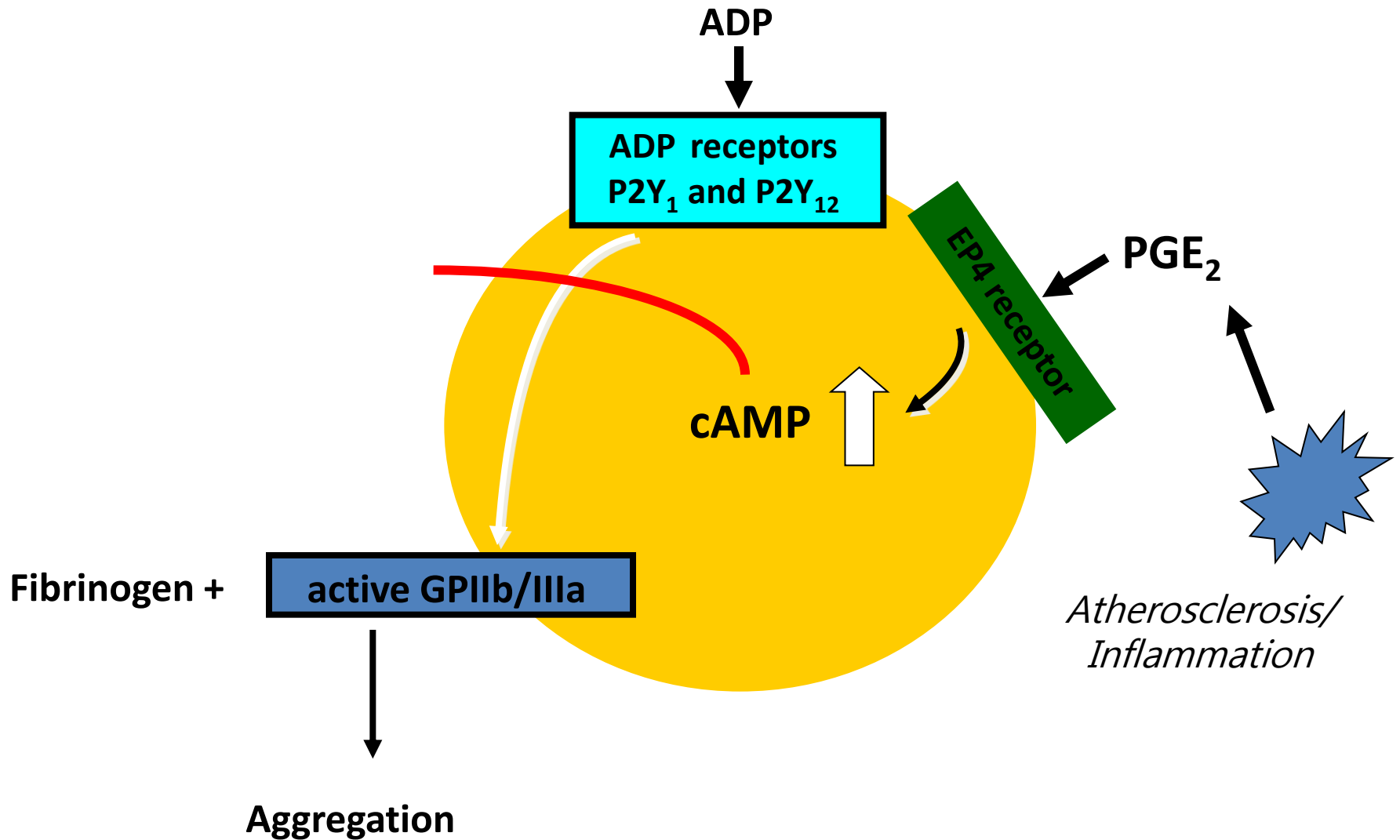
Inhibitors of platelet
function

Prostaglandin I₂
Nitric oxide
Adenosine?

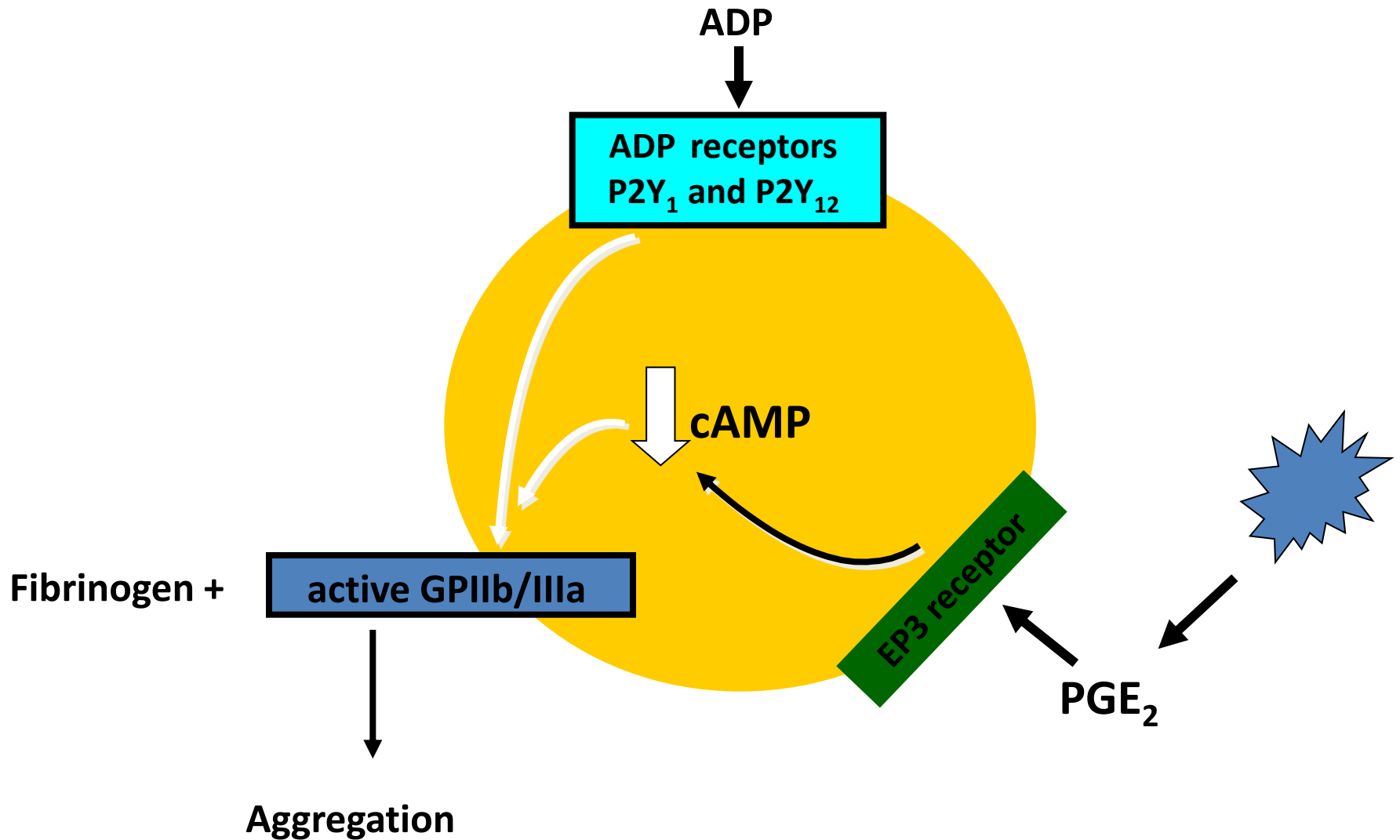
Promoter and inhibitor of platelet function

Prostaglandin E₂

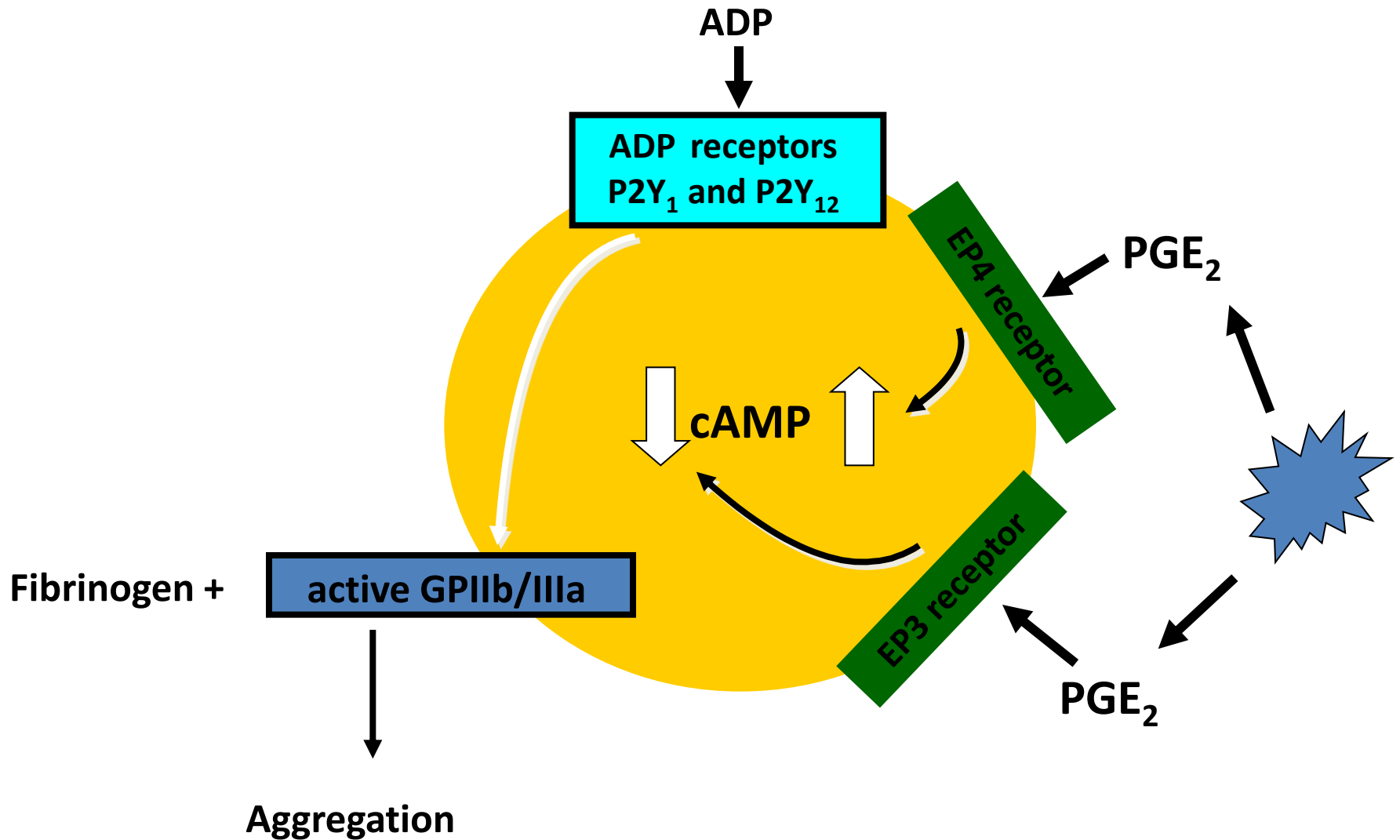
PGE₂: mechanism of action



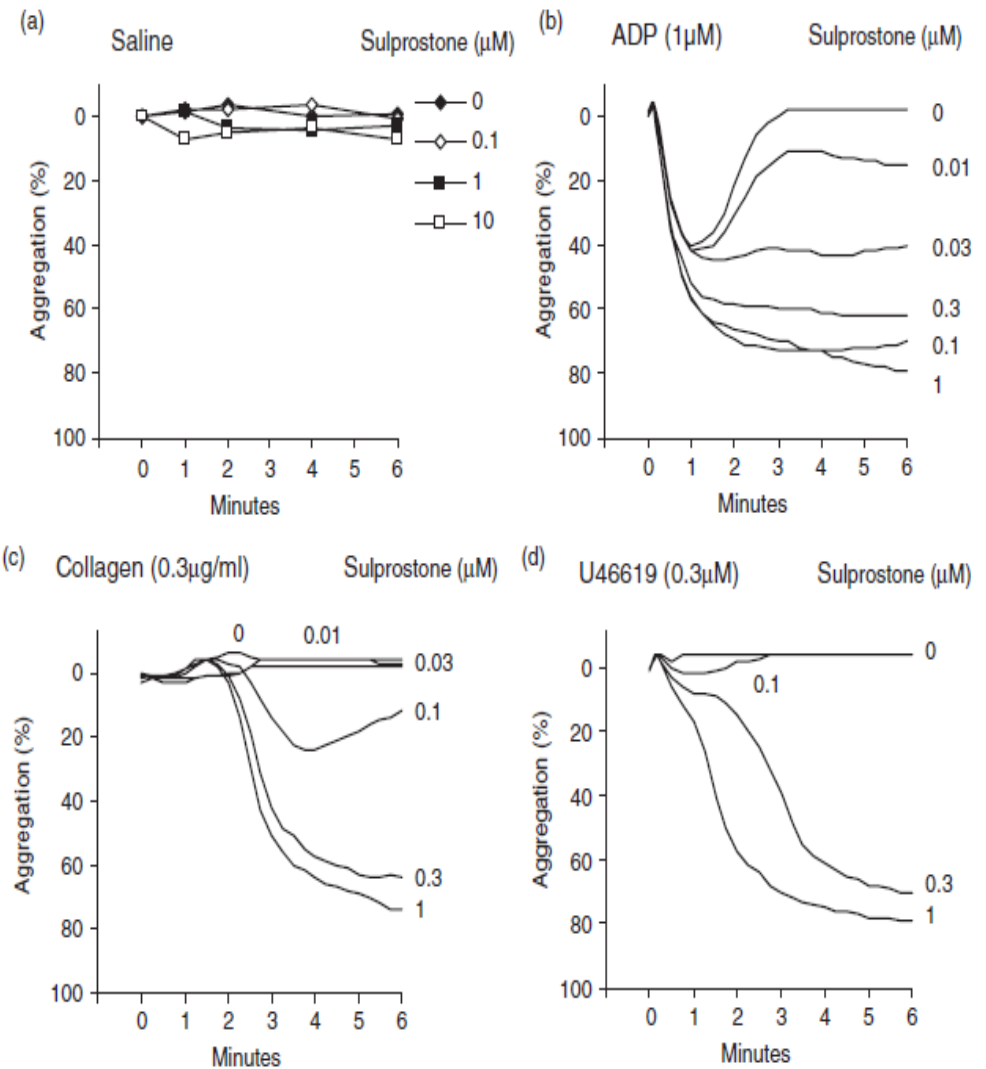
PGE₂: mechanism of action



PGE₂: mechanism of action

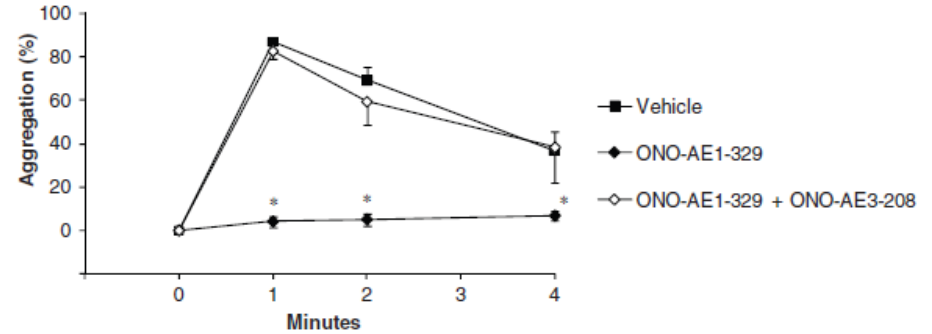


- The EP3 agonist sulprostone promotes platelet function induced by other agonists

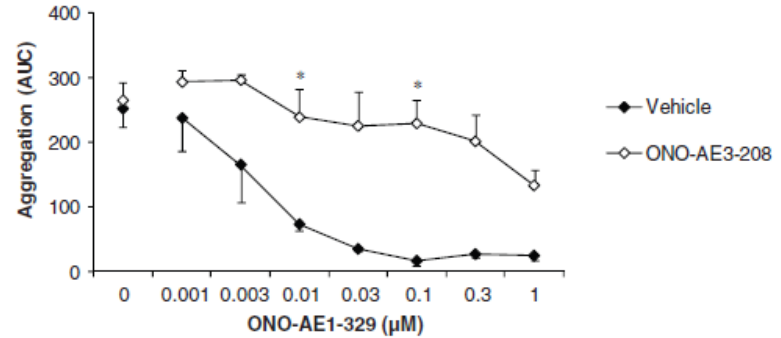


- A selective EP4 agonist inhibits platelet function via increased levels of cAMP

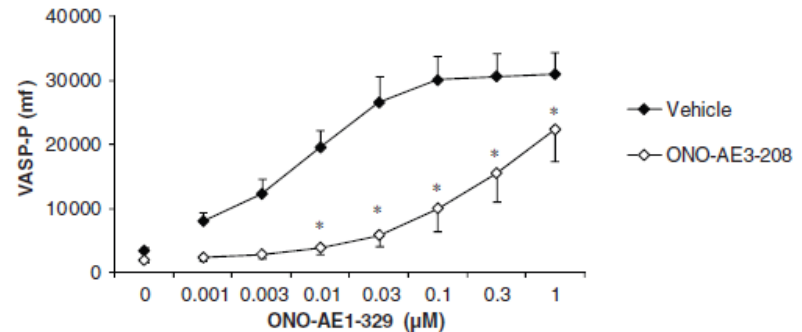
(a) Effects of the EP4 agonist ONO-AE1-329 and the EP4 antagonist ONO-AE3-208 on platelet aggregation (% aggregation)



(b) Effects of the EP4 agonist ONO-AE1-329 and the EP4 antagonist ONO-AE3-208 on platelet aggregation (area under the curve)

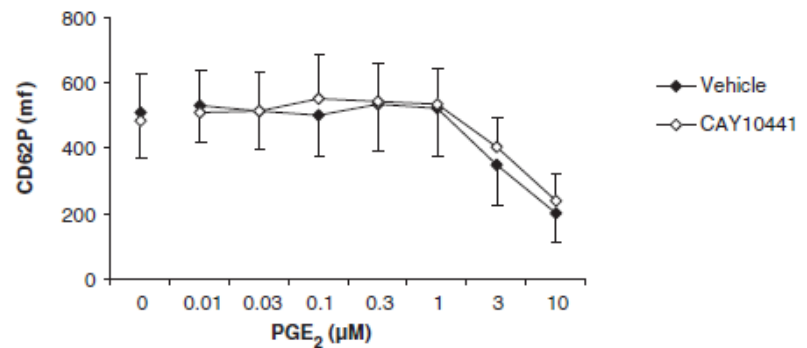


(c) Effects of the EP4 agonist ONO-AE1-329 and the EP4 antagonist ONO-AE3-208 on platelet VASP-phosphorylation

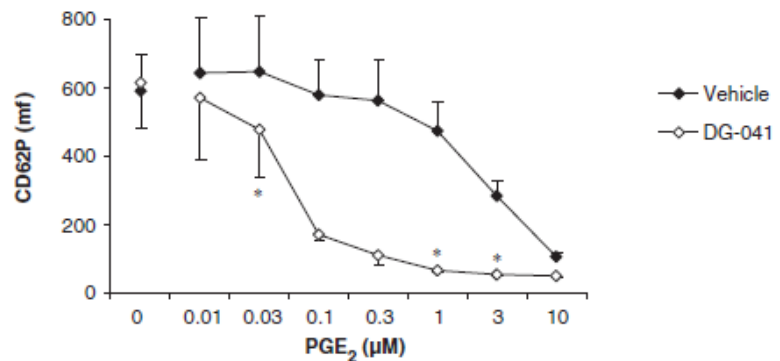


- IP receptor antagonist does not modify the effects of PGE₂ on platelet function
- EP3 receptor antagonist promotes inhibition of platelet function by PGE₂
- EP4 receptor antagonist negates inhibition of platelet function by PGE₂

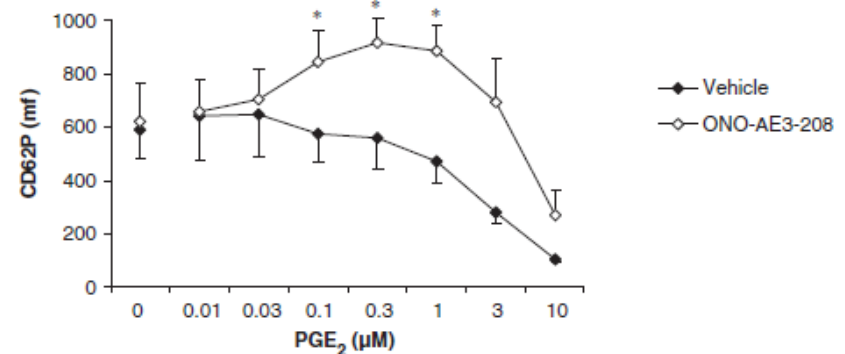
(a) Platelet P-selectin expression: effects of PGE₂ and CAY10441 (IP antagonist)



(b) Platelet P-selectin expression: effects of PGE₂ and DG-041 (EP3 antagonist)



(c) Platelet P-selectin expression: effects of PGE₂ and ONO-AE3-208 (EP4 antagonist)

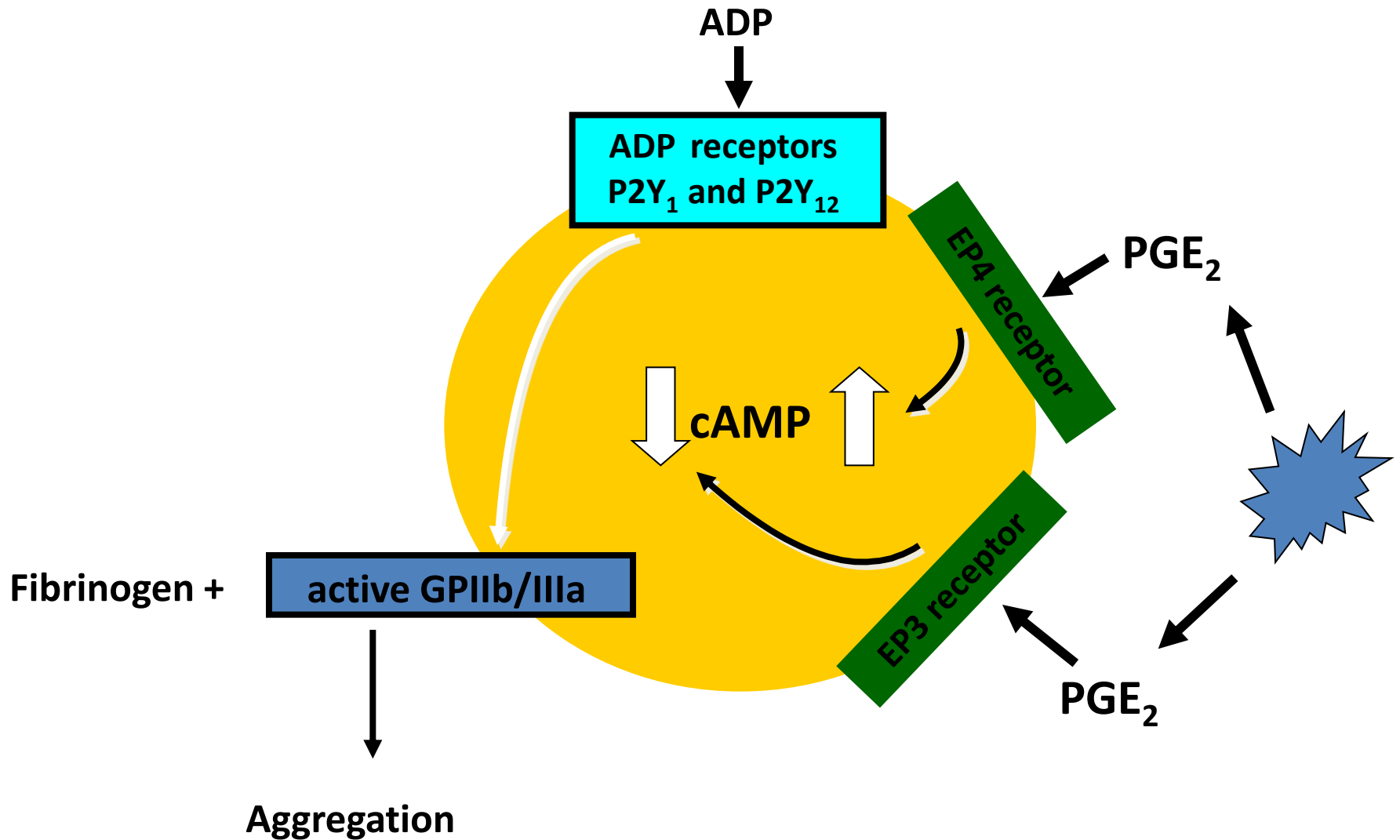


Some pharmacological agents used as antithrombotic therapy

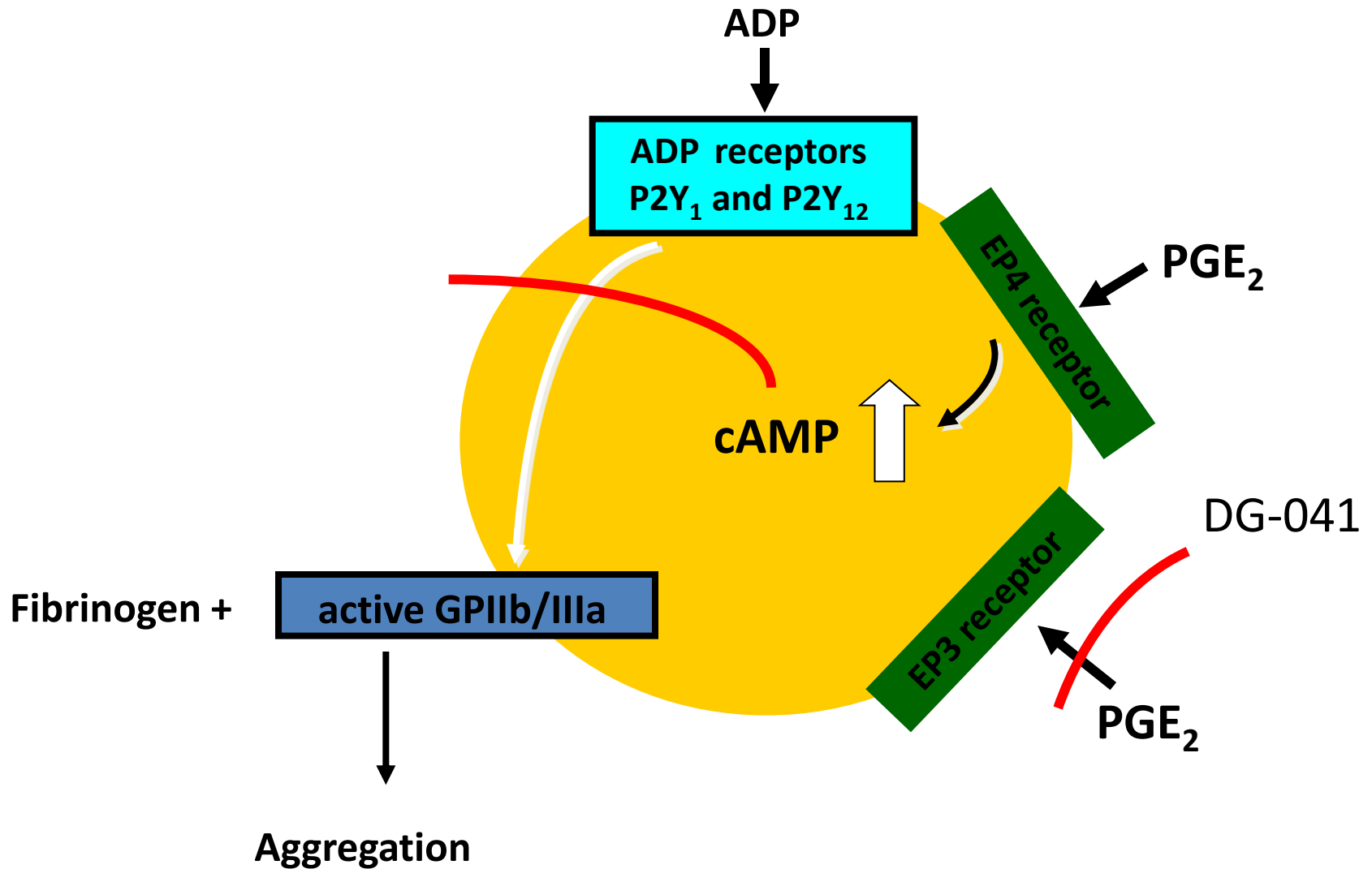
- Aspirin - inhibition of TXA₂ synthesis via COX-1
- P2Y₁₂ antagonists – clopidogrel, prasugrel, ticagrelor, cangrelor
- GPIIb/IIIa antagonists - tirofiban, eptifibatide, abciximab
- Dipyridamole - inhibition of adenosine uptake into erythrocytes

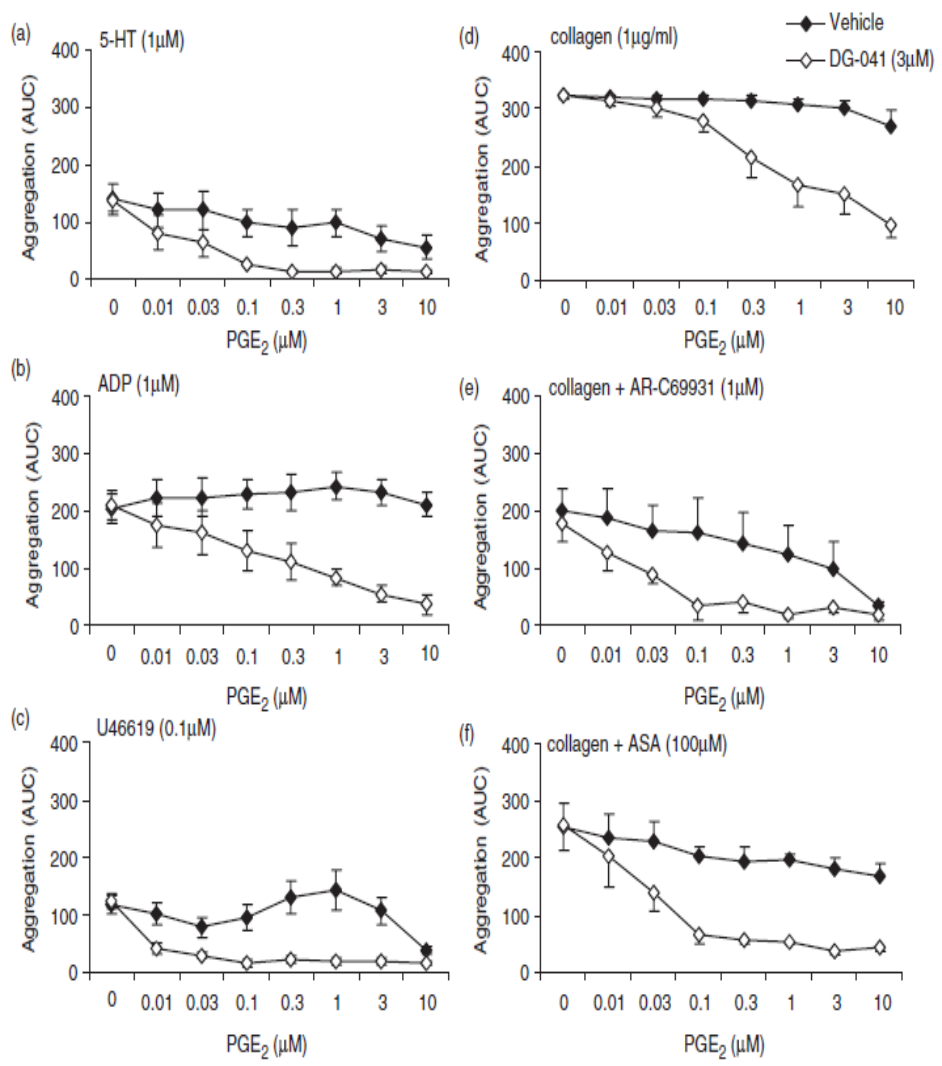
- EP3 antagonist – DG-041 ?

PGE₂: mechanism of action



EP3 antagonist: mechanism of action

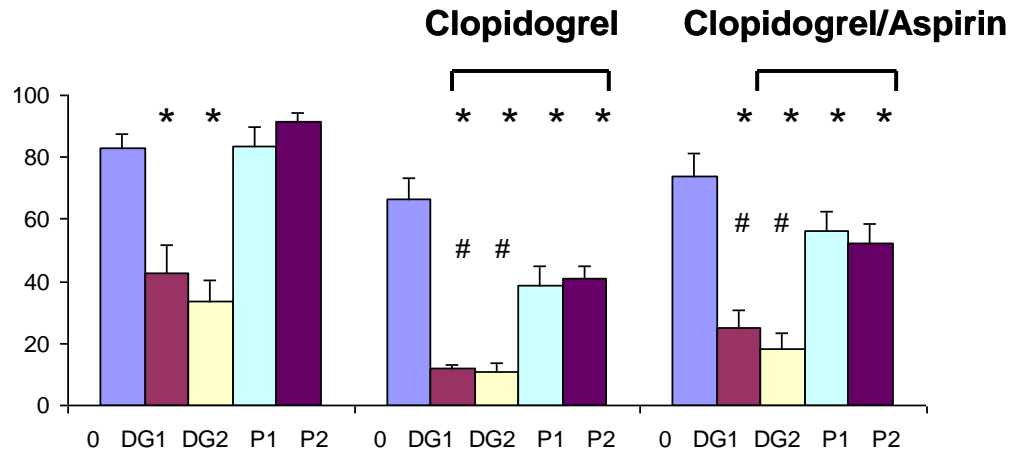




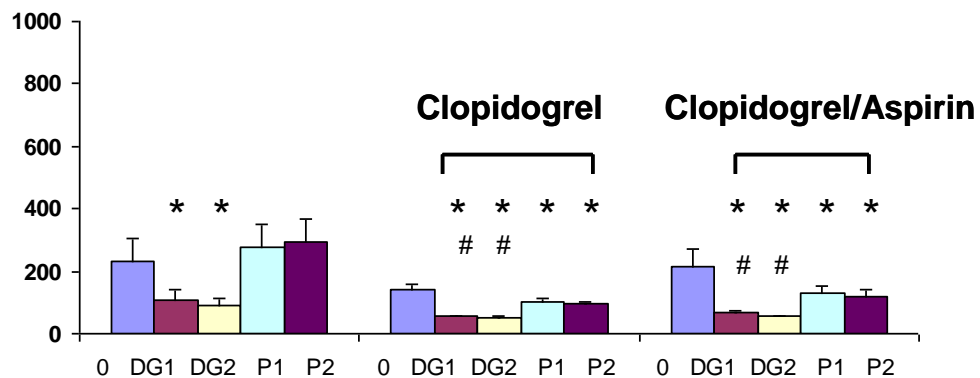
- DG-041 enhances inhibition of platelet function in the presence of PGE₂

U46619 + PGE₂

Platelet aggregation



P-selectin



- DG-041 in the presence of PGE₂ inhibits platelet function ex vivo after administration to man.
- DG-041 in the presence of PGE₂ adds to the inhibition brought about by co-administration of other antiplatelet agents.

PGE₂ and platelet function - conclusions

- PGE₂ is a natural agent derived for inflammatory and atherosclerotic tissue
- PGE₂ inhibits platelet function via EP4 receptors
- PGE₂ promotes platelet function via EP3 receptors
- An EP3 antagonist enhances inhibition of platelet function in the presence of PGE₂ both in vitro and ex vivo
- An EP3 antagonist adds to the inhibitory effects of a P2Y₁₂ antagonist and aspirin
- This may provide a new approach to antithrombotic therapy