Clinical Implications of Basic Research

COX Inhibitors and Thromboregulation

FROM a historical perspective, there is perhaps no more interesting therapeutic saga than that of aspirin, which began as a folk remedy, distilled from willow bark, and became a lifesaving preventive treatment for ischemic cardiovascular disease. Aspirin primarily inhibits the cyclooxygenase (COX)-dependent synthesis of eicosanoids, which are the end products of metabolism of essential fatty acids and include prostacyclin and thromboxane A_2. Numerous studies have shown the importance of eicosanoids in preserving the dynamic balance among thrombosis, hemostasis, and the fluidity of blood.

Recently, Cheng et al.[1] presented compelling evidence that cell–cell interactions, principally between platelets and endothelial cells, that are mediated by eicosanoids have a role in thrombosis. Using genetically engineered mice that either overexpressed or lacked essential components of the eicosanoid pathway — namely, receptors for prostacyclin (a platelet inhibitor and vasodilator) or thromboxane A_2 (a platelet agonist and vasoconstrictor) — they found that the response of the intima of carotid vessels to mechanical injury is exuberant and leads to obstruction in mice lacking the prostacyclin receptor. However, this response is muted in mice lacking the thromboxane A_2 receptor or both receptors. In mice lacking the prostacyclin receptor (a defect that mimics the effects of COX-2–selective

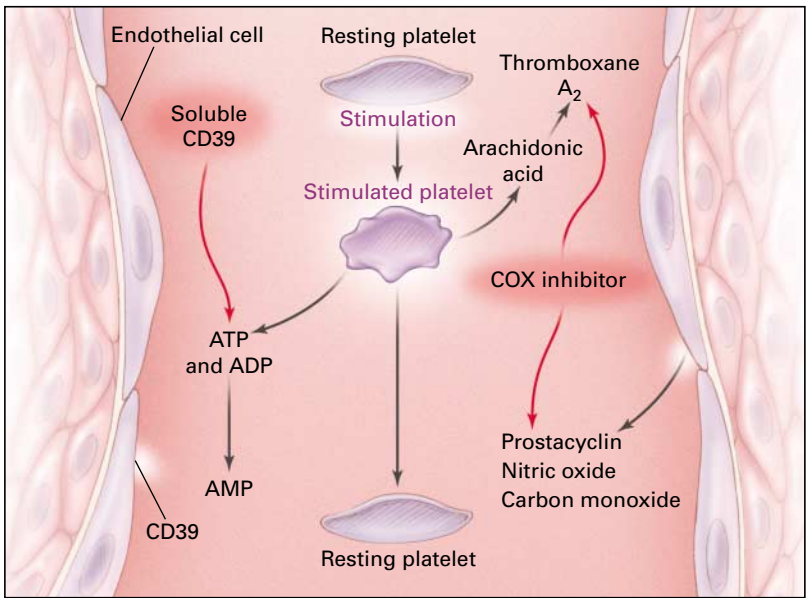

Figure 1. Effect on Platelet Reactivity of the Eicosanoids Thromboxane A_2 and Prostacyclin, the Biologic Gases Nitric Oxide and Carbon Monoxide, and the Ectonucleotidase CD39.

Resting platelets contain secretable nucleotides and esterified arachidonic acid. On stimulation, platelets release arachidonic acid, which leads to the generation of eicosanoids, and secrete adenosine triphosphate (ATP) and adenosine diphosphate (ADP). One of the eicosanoids, thromboxane A_2, is a platelet agonist and vasoconstrictor. ADP and thromboxane A_2 recruit and activate unstimulated platelets, leading to the formation of a thrombus. Cyclooxygenase (COX) inhibitors block the generation of thromboxane A_2 to a varying extent. Nearby endothelial cells generate prostacyclin, nitric oxide, and carbon monoxide, which down-regulate the reactivity of platelets in the vicinity. The synthesis of prostacyclin is also blocked by COX inhibitors, especially the COX-2–specific inhibitors, thereby creating a potentially prothrombotic condition.[1] Nonselective COX inhibitors such as aspirin and naproxen lower thromboxane A_2 levels in an antithrombotic manner. The enzyme CD39 metabolically deletes ADP released by platelets from the local milieu and renders stimulated platelets quiescent, thereby abolishing platelet recruitment. Soluble CD39 has the same biologic activity as endothelial CD39 in the systemic circulation and is a potential antithrombotic agent.

inhibitors such as rofecoxib), thromboxane A_2 was also overproduced by platelets and components of the injured vessel wall.

Taken together, the data suggest that in vivo, prostacyclin modulates interactions between platelets and the vessel wall that are mediated by thromboxane A_2. These findings assume particular importance given recent concern that unlike aspirin, selective COX-2 inhibitors may promote (or at least fail to inhibit) thrombotic cardiovascular events.[2] Selective COX-2 inhibitors block the formation of prostacyclin without affecting the COX-1–mediated generation of thromboxane A_2 by platelets. By contrast, nonselective COX inhibitors such as naproxen and aspirin inhibit the formation of both prostacyclin and thromboxane A_2.

As important as eicosanoid metabolism and its modulation by nonsteroidal antiinflammatory drugs may be, the dynamic nature of thromboregulation at the endothelial surface requires additional forms of communication at the interface between cells in the circulation and the vessel wall. During the formation of a thrombus, three functionally independent pathways mediate the interactions between circulating blood cells and cells of the vessel wall. These pathways involve the eicosanoids (prostacyclin and thromboxane A_2), biologic gases (nitric oxide and carbon monoxide), and the ectonucleotidase CD39 (Fig. 1). In addition to prostacyclin, endothelial cells produce nitric oxide (endothelium-dependent relaxing factor) and carbon monoxide, which are also platelet antagonists and vasodilators. Whereas eicosanoids, nitric oxide, and carbon monoxide are fluid-phase mediators, CD39 is an integral membrane protein with a luminally oriented active site. This enzyme metabolically deletes adenosine triphosphate and adenosine diphosphate, which are released on platelet stimulation, from the platelet–endothelial milieu, thereby abolishing and even reversing the recruitment of platelets.[3] In contrast to thromboxane A_2 and prostacyclin, nitric oxide and CD39 are unaffected by aspirin (Fig. 1). Moreover, even in the absence of prostacyclin and nitric oxide, CD39 completely inhibits the recruitment and activation of platelets in vitro[3] and in vivo.[4]

Elucidation of these three pathways has added to our understanding of the mechanisms underlying thrombotic events in the endovascular milieu, but uncertainties remain regarding the value of selective COX-2 inhibitors as opposed to nonselective COX inhibitors in the management of arthritic disorders. The work of Cheng et al.[1] in mice and the clinical observations of Bombardier et al.[2] make the choice of COX inhibitor especially important for patients with a predisposition to thrombosis.

We recommend aspirin for the prevention and treatment of coronary artery disease, but there are other possibilities. Whereas a nitric oxide donor (isosorbide dinitrate) does not have therapeutic efficacy in patients with suspected acute myocardial infarction,[5] it does have highly efficient antiplatelet activity in vitro. Thus, nitric oxide and carbon monoxide could have a role in the management of arterial thrombosis. CD39 has not yet been administered to patients, but it ameliorated platelet-driven thrombosis in mice that had had a stroke. Soluble CD39 reduced both the extent of thrombosis and the size of the infarct in wild-type mice after occlusion of the middle cerebral artery. Soluble CD39 also counteracted the defect in mice lacking the enzymatically active region of CD39, even when it was administered three hours after the induction of stroke.[4] These results suggest that novel enzyme-based therapies for arterial occlusion may be close at hand.

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REFERENCES

1. Cheng Y, Austin SC, Rocca B, et al. Role of prostacyclin in the cardiovascular response to thromboxane A_2. Science 2002;296:539-41.
2. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8.
3. Marcus AJ, Broekman MJ, Drosopoulos JHF, et al. The endothelial cell ecto-ADPase responsible for inhibition of platelet function is CD39. J Clin Invest 1997;99:1351-60.
4. Pinsky DJ, Broekman MJ, Peschon JJ, et al. Elucidation of the thromboregulatory role of CD39/ectoapyrase in the ischemic brain. J Clin Invest 2002;109:1031-40.
5. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. Lancet 1995;345:669-85.