Platelet Glycoprotein IIb/IIIa Receptor Antagonists and Coronary Artery Disease

Phong N. Nguyen-Ho, M.D., and Nasser M. Lakkis, M.D.

Address
Cardiology Section, Baylor College of Medicine, 6550 Fannin, SM 677, Houston, TX 77030, USA.
E-mail: nlakkis@bcm.tmc.edu

Current Atherosclerosis Reports 2001, 3:139–148
Current Science Inc. ISSN 1523-3804
Copyright © 2001 by Current Science Inc.

The importance of platelets in coronary artery disease has been better elucidated in the past 20 years with the continued understanding of their role in the development of the atherosclerotic lesion and acute coronary syndromes. The most recent therapeutic efforts have focused on blockade of the platelet glycoprotein IIb/IIIa receptor, which represents the final common pathway to platelet aggregation and arterial thrombus formation. This manuscript summarizes platelet function and pathophysiology, currently available glycoprotein IIb/IIIa inhibitors, and the important clinical trials with this new class of drugs.

Platelet Adhesion and Aggregation

Injury to the vascular wall exposes the subendothelial matrix to circulating platelets and plasma coagulation factors. A complex interaction of platelets with the subendothelium and each other is mediated by a number of membrane receptor proteins to initiate hemostasis. The most abundant receptor on the platelet surface is the glycoprotein (GP) IIb/IIIa integrin, with about 50,000 to 80,000 copies per platelet [1]. Integrins are heterodimeric receptors formed by specific combinations of an α subunit and a β subunit [2]. They recognize various macromolecular ligands, and are widely distributed throughout the vasculature. The GP IIb/IIIa integrin, however, is only found on platelets [3].

The first step in hemostasis is platelet adhesion to the site of injury to cover the breach in the endothelium. This process does not require prior activation of the platelets. The major subendothelial ligands involved in platelet adhesion are von Willebrand factor (vWF), collagen, fibronectin, and vitronectin [4]. Glycoprotein Ib (a nonintegrin) binds vWF, and is the major receptor for platelet adhesion. Other receptors include GP Ia/IIa and GP IV (a nonintegrin), which interact with collagen, GP Ic/IIa, which binds fibronectin, and αVβ3, which recognizes vitronectin, as well as other ligands that also bind to GP IIb/IIIa. Although GP IIb/IIIa is principally concerned with platelet aggregation, it can also mediate adhesion by virtue of its ability to bind vWF, fibronectin, and vitronectin [5].

Platelet activation accompanies adhesion, and is further induced by a number of agonists such as thrombin, thromboxane A2, norepinephrine, collagen, and adenosine diphosphate (ADP). These agents probably exert their effects through the second messenger, inositol triphosphate, to increase intraplatelet calcium concentrations [1,3]. This results in changes in platelet shape, with formation of pseudopodia to form a platelet mesh, exocytosis of storage granules containing ADP, thromboxane A2, and serotonin to amplify the activation process and recruit surrounding platelets, induction of the coagulation cascade, and activation of the GP IIb/IIIa receptor [3].

Activation of the GP IIb/IIIa receptor is the final common pathway leading to platelet aggregation. Under normal physiologic conditions, the GP IIb/IIIa receptor is in a resting state and has low affinity for ligands. Additionally, a pool of GP IIb/IIIa receptors exists in the membranes of storage granules and can be recruited to increase the numbers on the platelet surface by 20% [6]. Platelet agonists stimulate intracellular signals that act on the cytoplasmic domain of the GP IIb/IIIa receptor to produce a conformational change (inside-out signaling), which exposes the binding site on the extracellular domain [7]. The activated receptor now has a high affinity for fibrinogen, vWF, fibronectin, and vitronectin. Due to its high concentration relative to the other ligands, fibrinogen is the primary polypeptide that occupies the binding site; vWF may play a more important role during conditions of high shear [3]. Aggregation occurs when the divalent fibrinogen molecule cross-links adjacent platelets in multiple similar interactions.

Glycoprotein IIb/IIIa Receptor Structure

The GP IIb/IIIa integrin is composed of a 136-kDa α subunit (GP IIb) and a 92-kDa β subunit (GP IIIa), which
Coronary Heart Disease

are noncovalently bound to each other and maintained in the heterodimeric state by calcium [7••,8]. The GP IIb subunit contains an extracellular heavy chain linked by a disulfide bond to a light chain, which spans the cell membrane and has a short cytoplasmic tail. The GP IIIa subunit is a single polypeptide that is 90% extracellular. The intracellular tail interacts with the \( \alpha \) subunit to form the cytoplasmic domain that regulates GP IIb/IIIa activation [7••].

The GP IIb/IIIa receptor recognizes two peptide sequences within fibrinogen. The first sequence is the lysine-glutamine-alanine-glycine-aspartate-valine (KQAGDV) amino acid residue on the \( \gamma \) chain of fibrinogen. This sequence is found only in fibrinogen, specific for the GP IIb/IIIa receptor, and essential for the binding of fibrinogen [1,7••]. The other peptide sequence contains arginine-glycine-aspartate (RGD), and was first identified as the adhesive sequence in fibronectin [9]. Subsequently, it has been found in fibrinogen, vWF, and vitronectin. This sequence is not specific for GP IIb/IIIa, however, as it is also recognized by other integrins. The exact role of RGD in the binding of fibrinogen to GP IIb/IIIa is not clear, but synthetic peptides with this sequence are potent inhibitors of the fibrinogen-GP IIb/IIIa interaction [10].

Platelets and Coronary Artery Disease

Atherosclerosis is a chronic disease that affects the medium and large arteries. It begins as fatty streaks that can develop into fibrous plaques over a patient's lifetime. The clinical manifestations of this disease reflect progressive plaque growth resulting in a flow-limiting stenosis (chronic angina), and plaque rupture leading to thrombosis (acute coronary syndrome).

Fatty streaks are the earliest lesions of atherosclerosis and occur in all populations. They begin in the aorta in infancy, and appear in the coronary arteries by 10 to 14 years of age [11]. Chronic injury to the endothelium by hemodynamic shear-stress induces monocytes and lymphocytes to attach to, and migrate between, the endothelial cells. In the subintimal space, the monocytes transform into macrophages, accumulate lipids, and become foam cells. In susceptible individuals, the fatty streaks increase in size and the endothelial layer is disrupted, exposing the subendothelium to circulating platelets. At these sites, the platelets initiate formation of mural thrombi, and along with the endothelium and macrophages, release cytokines and growth factors that lead to the migration and proliferation of smooth muscle cells from the arterial media. The smooth muscle cells are responsible for the deposition of fibrous connective tissue. This pattern of injury and wound healing (response to injury hypothesis) can be repetitive, and leads to development and progression of the fibrous plaque [12]. A fibromuscular cap of collagen and smooth muscle cells overlies a fatty core composed of foam cells, free cholesterol, and necrotic, calcified debris.

Acute coronary syndromes occur when the fibrous cap of an unstable atherosclerotic plaque ruptures and exposes the highly reactive lipid core. Platelets become activated and form a nidus of thrombosis within the plaque. The coagulation cascade is initiated, and fibrin deposition further expands the thrombus, both intra-intimally and intra-luminally. Pathologically, acute arterial thrombi tend to be platelet rich and are described as white thrombi [13]. Several events can follow. The fibrinolytic process can limit the growth of, and eventually disperse, the clot, such that no limitation in blood flow occurs, and the patient remains asymptomatic. The fissure can reseal with some clot debris incorporated in the plaque to lead to further stenosis. If the resultant thrombus is larger but nonocclusive, it can transiently interrupt coronary blood flow and cause unstable angina (Fig. 1). As in the previous situation, thrombus is often incorporated into the plaque after the acute event. More severe thrombosis with occlusion of the artery results in acute myocardial infarction (MI) [14,15].

Glycoprotein IIb/IIIa Receptor Antagonists

The preceding discussion has highlighted the role of platelets in the development of atherosclerotic lesions and the manifestations of coronary artery disease (CAD). Previously, the drugs available to inhibit platelet function and treat clinical syndromes were relatively weak, as each targeted only one of the many platelet activators. The most commonly used drug, aspirin, only blocks thromboxane \( A_2 \) activation, and the newer thienopyridines, ticlopidine and clopidogrel, block ADP activation. The other platelet triggers (thrombin, norepinephrine, and collagen) cannot be readily inhibited with either aspirin or