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Platelet–leukocyte interactions link inflammatory and thromboembolic events in ischemic stroke

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Abstract

Stroke is a common and often fatal event, and, in survivors, it is accompanied by a high risk of recurrence. Ischemic stroke is associated with abnormal platelet activity and thrombus formation. In addition to their roles in the development of acute thrombi, platelets serve as a bridge for leukocytes within the vasculature. Myeloid leukocytes are critical mediators of atherosclerosis and atherothrombosis. Interactions between platelets and leukocytes foster an inflammatory and thrombotic milieu that influences lesion progression, facilitates plaque rupture, and triggers thrombus formation and embolization. Accordingly, antiplatelet agents, including aspirin, dipyridamole, and clopidogrel, are recommended therapies for most patients with a history of stroke. In addition to mitigating thrombosis, antiplatelet drugs have direct and indirect effects on inflammation, which may translate to enhanced clinical efficacy.

Keywords

platelets; leukocytes; stroke; antiplatelet agents

Introduction

The American Heart Association has reported that approximately 795,000 people in the United States suffer from a stroke every year and 23% of these individuals will eventually develop a recurrent cerebrovascular event. Approximately 15–30% of recurrent stroke victims become permanently disabled, often requiring institutionalized care. In addition, the estimated direct and indirect costs of stroke are \$73.7 billion annually. Understanding safe and effective ways to prevent ischemic stroke from occurring (or recurring) is paramount.

Although there are many etiologies for ischemic stroke, established risk factors include tobacco use, high blood pressure, diabetes mellitus, hypercholesterolemia, and physical inactivity.¹ Many of these risk factors are associated with key biological consequences, including abnormal platelet function. Circulating platelets have long been recognized for their importance in modulating recurrent stroke and related cardiac syndromes. Hence,

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Conflicts of interest

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current therapies for the prevention of secondary stroke include aspirin, clopidogrel, and dipyridamole, either alone or as combination therapy. All of these drugs dampen platelet activation and aggregation. Prospective, randomized studies have demonstrated that antiplatelet regimens are associated with a reduced incidence of secondary stroke.²

By limiting platelet activation, agents such as aspirin, clopidogrel, and dipyridamole decrease interactions of platelets with inflammatory leukocytes. In addition, select agents such as dipyridamole appear to directly influence the inflammatory function of leukocytes and will be discussed later.³ Interactions between platelets and leukocytes are particularly relevant in secondary stroke and contribute to the development of plaque and narrowing arteries.⁴ Understanding these relationships and how current antiplatelet agents may modulate platelet–leukocyte function is critical to understanding cerebrovascular disease. The purpose of this brief review is to discuss platelet–leukocyte interactions and their influence on inflammatory and thrombotic processes that occur in stroke situations. We also discuss how current clinical practice strives to modulate these interactions to decrease the risk of recurrent stroke.

Platelet–leukocyte interactions in stroke

The events that lead to secondary stroke are precipitated by an array of thrombotic and inflammatory processes. Among these are multifaceted interactions between cells in the bloodstream and neighboring endothelium. Circulating platelets are critical effectors in the development, progression, and resolution of stroke, not only due to their direct effects upon the endothelium but also by acting as a “bridge” for other cells within the vascular system. For example, upon vessel injury (i.e., plaque rupture or laceration) platelets readily adhere to damaged endothelium.⁵ This binding event facilitates activation and discharge of activating factors stored in platelet granules. Platelet secretory components include membrane ligands and several chemokines that play a role in recruitment of leukocytes, additional platelets, or other blood cells to the vessel wall.⁶ The interplay between platelets and leukocytes is critical for hemostasis, host defense, and the function of interfacing endothelial cells (Fig. 1). Overactive interactions can also lead to a gratuitous recruitment of blood cells to and through the vessel wall.⁷

In addition to the key roles played by platelets, the recruitment of monocytes to the vessel wall is critical for all stages of atherogenesis. Monocytes migrate, differentiate, and reside in the subendothelial milieu and monocyte-derived macrophages avidly engulf lipoproteins and oxidized LDL. This process contributes to the development of lipid-rich foam cells and fatty streaks commonly associated with atherosclerotic lesions.⁸ In addition, macrophages and other leukocyte subsets release numerous proinflammatory factors that influence smooth muscle migration and proliferation as well as the deposition of a collagen-rich matrix in the fibrous core and cap. Secretion of matrix-degrading proteins also contributes to thinning of the fibrous cap, which leads to decreased plaque stability with subsequent plaque rupture and thrombosis formation.⁹

Initial interactions between platelets and leukocytes are primarily attributed to P-selectin, an adhesive molecule that is stored in alpha granules and, in response to activating signals, translocated to membranes of platelets. P-selectin glycoprotein ligand-1 (PSGL-1), the key receptor for P-selectin, is constitutively expressed on the surface of most leukocytes.¹⁰ Several clinical studies have shown increased soluble P-selectin, surface P-selectin expression, and/or platelet–leukocyte aggregates (PLA) in whole blood isolated from stroke patients or patients with hypercholesterolemia and atherosclerotic carotid arteries.^{11–14} Furthermore, atherosclerotic lesions are far less prevalent in P-selectin deficient mice that lack apolipoprotein E^{15–17} as are the number of leukocytes present in atherosclerotic

lesions.¹⁸ Together, these and other data suggest that P-selectin, PSGL-1, and PLAs modulate atherogenesis and may be important biomarkers in identifying patients at increased risk for stroke.

In addition to adhering to target leukocytes via P-selectin/PSGL-1, activated platelets also release an array of prothrombotic and proinflammatory mediators. One of these mediators, soluble CD40 ligand (sCD40L), binds to CD40 on endothelial cells and induces the expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin) involved in leukocyte trafficking.^{19,20} Activated platelets also release regulated upon activation, normal T cell expressed and secreted (RANTES), which binds to atherosclerotic endothelium and forms a chemoattractant surface for monocytes.²¹ RANTES functions in parallel with P-selectin to induce monocyte chemoattractant protein 1 (MCP-1) expression in monocytes.²² Platelets also generate thromboxane A₂, which promotes platelet and endothelial activation, and platelet-activating factor (PAF), a player in juxtacrine signaling and adhesion of leukocytes to other cells.^{23–25}

Adherence to leukocytes and subsequent release of factors is a unique mechanism used by platelets to induce inflammatory gene expression in target monocytes. For example, monocytes adherent to P-selectin bearing platelets synthesize MCP-1 and interleukin-8 (IL-8). MCP-1 and IL-8 are necessary for leukocytes to migrate into subendothelial layers and proliferate.^{22,26} In addition, activated platelets upregulate and induce monocyte production of cyclooxygenase-2 (COX-2).²⁷ COX-2 is an enzyme responsible for the synthesis of proinflammatory eicosanoids and is upregulated in chronic inflammatory conditions.²⁸ Platelets coincubated with monocytes also express IL-1 β , IL-6, and tumor necrosis factor- α (TNF- α).^{27,29} IL-1 β and IL-6 have numerous roles in inflammation where they activate leukocytes and endothelial cells and increase expression of several proinflammatory mediators.^{24,30} TNF- α is a potent inflammatory factor inducing cell activation and apoptosis.⁷ Activated platelets also increase matrix metalloproteinase-9 (MMP-9) production by human monocytes.³¹ MMP-9 degrades fibrillar collagen within atherosclerotic plaques and contributes to plaque instability.³²

Several of the proinflammatory mediators described earlier are implicated in ischemic stroke. For example, patients with stroke have higher expression of MCP-1, IL-8, and IL-1 β .^{33,34} In addition, stroke patients with high concentrations of plasma IL-6, TNF- α , or soluble VCAM-1 (a leukocyte adhesion molecule expressed by activated endothelium) may be at higher risk of recurrent stroke.^{35,36} Increased blood concentrations of MMP-9 and elevated urine concentrations of thromboxane A₂—an eicosanoid indicative of platelet or mononuclear cyclooxygenase activity—have been observed in ischemic stroke patients as well.^{37–39} These data suggest that platelet–leukocyte interactions regulate atherothrombosis and accompanying inflammatory events.

Antiplatelet agents for secondary stroke prevention

Because platelets are key effector cells that contribute to the prothrombotic and proinflammatory milieu in stroke, antiplatelet agents are first-line treatment modalities for the prevention of recurrent stroke. These therapies include aspirin, dipyridamole, and clopidogrel, all of which reduce the risk of recurrent cerebrovascular (and cardiovascular) events,⁴⁰ although there are several important differences with regards to their mechanisms of action and clinical efficacy (Tables 1 and 2). A full review of the different agents used for secondary stroke prevention and their clinical safety and efficacy is beyond the scope of this review, but key data are briefly summarized later. The reader is referred to the joint 2006 American Heart Association–American Stroke Association (AHA–ASA) Guidelines⁴¹ and

the 2008 American College of Chest Physician Guidelines for a more comprehensive review.⁴²

Aspirin is an older agent that inhibits cyclooxygenase-1 (COX-1)-induced production of thromboxane A₂ and is commonly used for the prevention of recurrent stroke. In trials in patients with a history of stroke or transient ischemia attack (TIA), aspirin reduced the risk of subsequent stroke by 15–18% compared with placebo.^{43,44} Given this efficacy, its low cost and acceptable side-effect profile, aspirin as monotherapy (50–325 mg/day) is recommended for the prevention of stroke in patients with a history of stroke or TIA.⁴⁵ Newer agents and combination therapy may be superior to aspirin monotherapy, although definitive data are still lacking and aspirin still retains a strong recommendation for use in patients with a history of stroke or TIA (Table 2).⁴⁶

Dipyridamole, which inhibits phosphodiesterase activity and increases extracellular adenosine levels, is associated with greater stroke risk reduction when used in combination with low-dose aspirin. For example, in ESPS2, patients treated with extended-release dipyridamole (200 mg twice a day) plus aspirin (50 mg daily) had a significant reduction in serious vascular events compared to aspirin alone.⁴³ These findings were confirmed in the large (>6,000 patients) ESPRIT trial,⁴⁶ and recent meta-analyses data support the higher efficacy of combination therapy over aspirin alone.⁴⁷ Although the mechanisms to explain the apparent superiority of combination therapy over aspirin monotherapy are not entirely known, the 2008 ACCP guidelines do recommend dual therapy with extended-release dipyridamole plus aspirin over aspirin monotherapy alone for select patients.⁴⁵

Clopidogrel is a prodrug that requires activation in the liver by cytochrome P450 enzymes. The active metabolite of clopidogrel prevents platelet aggregation by specifically and irreversibly inhibiting the P2Y₁₂ subtype of ADP receptor on platelet membranes. Blockade of the ADP receptor dampens signaling events in platelets that promote platelet hyperactivity, including subsequent activation of the glycoprotein IIb/IIIa receptor.⁴⁸

CAPRIE was a large, randomized, controlled trial comparing clopidogrel (75 mg daily) to aspirin (325 mg daily) for the prevention of stroke, myocardial infarction, or vascular death. Overall, clopidogrel was more effective in reducing this composite endpoint. When analyzed by intention-to-treat analysis encompassing more than 19,000 patients, the annual risk of combined vascular complications in patients randomized to receive clopidogrel was lower compared to patients randomized to receive aspirin (5.32% vs. 5.83%, respectively; RRR of 8.7% in favor of clopidogrel, $P = 0.043$).⁴⁹ Overall safety, including bleeding, appeared to be similar between clopidogrel and aspirin, although major bleeding was minimally higher in patients taking aspirin (1.55% vs. 1.38%).⁴⁹ Clopidogrel has also been compared to combination therapy with extended-release dipyridamole plus aspirin. These recent data from the very large (>20,000 stroke patients) PROFESS trial suggest that aspirin plus extended-release dipyridamole and clopidogrel alone may have similar safety and efficacy profiles.^{50,51} Aspirin plus clopidogrel is generally not recommended for the intervention of secondary stroke (Table 2).

The antithrombotic properties of agents such as aspirin, dipyridamole, and clopidogrel clearly play an important role in reducing the risk of recurrent stroke, as evident in the clinical studies cited earlier. However, as discussed earlier, inflammatory pathways also modulate the development of atherosclerosis and thromboembolic events, including stroke and TIA. Adherence of platelets to mononuclear phagocytes induces the synthesis of proinflammatory mediators, including MCP-1, IL-1, IL-8, and matrix metalloproteinases²² and these factors, among others, serve to promote atherosclerosis and enhance thrombus formation and subsequent embolization.⁵²

Because inflammation mediates atherosclerosis progression, plaque rupture, and thromboembolism, agents that inhibit these processes and, in parallel, reduce inflammation may enhance clinical efficacy. For example, *in vitro* investigations have demonstrated that dipyridamole, at a concentration similar to peak plasma concentrations achieved with administration *in vivo* to patients, inhibits inflammatory gene expression in platelet–monocyte aggregates. Dipyridamole attenuated nuclear translocation of NF- κ B and delayed IL-8 synthesis in platelet–monocyte aggregates. In addition, dipyridamole blocked the synthesis of MCP-1 and decreased translation of MMP-9 mRNA into protein.⁵³

Clopidogrel, through inhibiting ADP-mediated platelet aggregation, indirectly influences inflammatory events elicited by platelet–leukocyte aggregates. In isolated human platelets, clopidogrel reduced P-selectin expression and circulating platelet–leukocyte aggregates.^{54,55} In addition, the active metabolite of clopidogrel reduces platelet–leukocyte aggregate formation and immunoreactive tissue factor exposure on platelet and leukocyte surfaces.

In summary, current guidelines support the use of any one of three therapeutic regimens— aspirin or clopidogrel as monotherapy or the use of extended-release dipyridamole plus low-dose aspirin—as acceptable first-line antiplatelet therapeutic regimens for secondary stroke prevention.^{41,42} Emerging data suggests that combination therapy with extended-release dipyridamole plus aspirin may be superior to aspirin alone (and is strongly recommended by the ACCP; Table 2). Pleiotropic effects of current therapies, although incompletely understood, may provide additional risk reduction and, once better understood, may help us improve on standard therapies and develop new drugs with improved clinical benefit.

Conclusion

Stroke is a common and often devastating event characterized by a widespread, systemic, inflammatory, and thrombotic milieu. Platelets and leukocytes (including monocytes and macrophages) mediate atherothrombosis through a series of processes. These key effector cells modulate cellular activation and adhesion (both to one another and to endothelial cells), the release of cytokines, and the synthesis and release of other factors that promote the progression of atherosclerosis and the development of an acute thromboembolic event. Current therapies to reduce secondary stroke target different pathways in platelets. Select agents, in addition to their direct inhibition of platelet function, also modulate inflammatory responses of other cells. Inhibition of dysregulated inflammation may translate to improved clinical efficacy, but further data are clearly needed to understand the complexities of secondary stroke and to optimize current treatments.

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Figure 1.

Schematic depicting interactions of platelets and leukocytes in a vulnerable atherosclerotic vessel. In normal situations, endothelial cells lining the vasculature provide an anti-inflammatory barrier that prevents platelets (light blue) and leukocytes from adhering to the vessel wall. In advanced atherosclerotic lesions, however, endothelial dysfunction and/or plaque rupture triggers abnormal platelet adherence to the damaged area. Display of P-selectin on the surface of adherent platelets and inflamed endothelium, in combination with exposed extracellular matrix, triggers a cascade of events that include monocyte adherence and emigration into the vascular wall. Adherence of platelets to monocytes also triggers the synthesis of proinflammatory mediators that may impact atherothrombotic events in secondary stroke and related cardiovascular disorders.

Table 1

Mechanisms of action of antiplatelet agents

Antiplatelet agent	Primary mechanism of action	Dose
Aspirin	Inhibits cyclooxygenase-1 (COX-1)–dependent synthesis of thromboxane A ₂	50–325 mg/day
Dipyridamole	Inhibits phosphodiesterase enzymes that break down cAMP and cGMP; increases extracellular adenosine levels	200 mg BID
Clopidogrel	Thienopyridine that specifically and irreversibly inhibits the P2Y ₁₂ ADP receptor	75 mg/day

Table 2

2008 ACCP guidelines for the prevention of recurrent stroke

Recommendation	Grade of evidence^a
Treatment with antiplatelet drugs	1A
Aspirin monotherapy, extended-release dipyridamole with aspirin as combination therapy, or clopidogrel monotherapy	1A
Combination extended-release dipyridamole with aspirin preferred over aspirin monotherapy	1A
Clopidogrel monotherapy over aspirin monotherapy	2B
Clopidogrel for patients allergic to aspirin	1A
Avoidance of long term use of aspirin plus clopidogrel combination therapy	1B

^aGrade definitions: 1A, strong recommendation, high quality evidence; 1B, strong recommendation, moderate quality evidence; 2B, weak recommendation, moderate quality evidence.