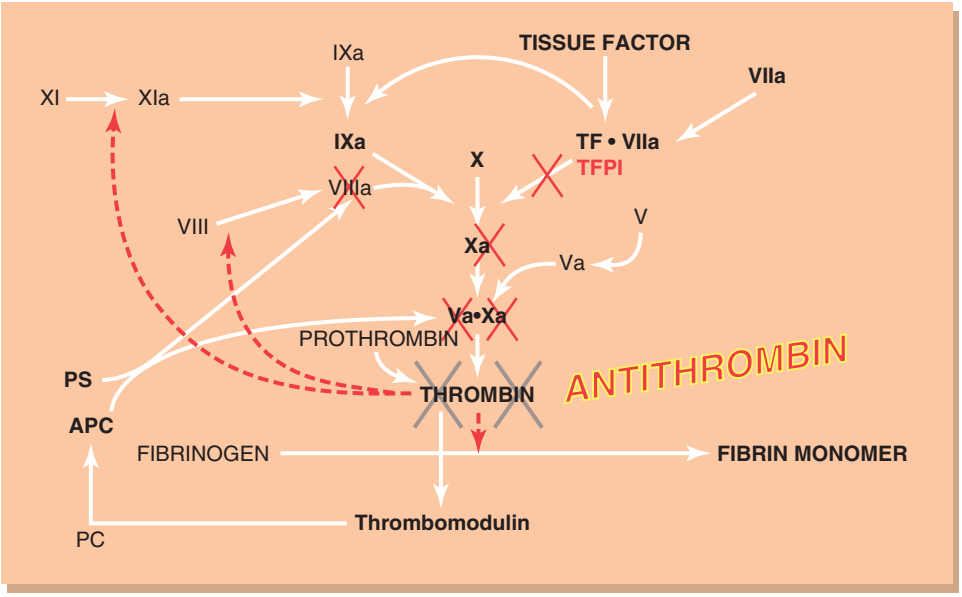

FIGURE 50-3 Endogenous anticoagulant pathways. Tissue factor pathway inhibitor (TFPI) shuts off tissue factor (TF) stimulation and blocks the TF-VIIa-X complex; in addition, the clotting cascade is further downregulated by the natural anticoagulants. This inhibition is partly generated by thrombin, which activates thrombomodulin. Circulating antithrombin inhibits thrombin activity and Xa generation of thrombin. The complex of thrombin and thrombomodulin activates protein C (PC) to become activated protein C (APC), which combines with protein S (PS) to cleave and inactivate VIIIa and Va, further blocking thrombin generation.

cleavage of arachidonic acid and then released into the clot milieu. TXA_2 is both a platelet agonist and a vasoconstrictor, and it is rapidly degraded to its inert byproduct, thromboxane B_2.

Platelet COX1 activity is *irreversibly* inhibited by aspirin, which blocks TXA_2 formation for the lifetime of that platelet. Aspirin irreversibly and covalently binds to a specific serine residue on COX1 and causes steric hindrance of the active site, a tyrosine molecule across from the serine residue. Nonsteroidal anti-inflammatory drugs (NSAIDs) do not covalently bind through acetylation at serine. Instead, they reversibly and competitively bind at the active, catalytic tyrosine site. Therefore, in contrast to aspirin, the antiplatelet effects of NSAIDs are dependent on the continual presence of plasma levels of the NSAID.

COX2 is an induced isoform within leukocytes that mediates inflammation and pain. Because mature platelets do not appear to possess COX2 activity, one rationale for development of the highly selective COX2 inhibitors for inflammatory diseases was to avoid the bleeding caused by platelet dysfunction by not affecting platelet COX1 activity. However, it appears that vascular ECs use COX2 activity to synthesize the antithrombogenic compound, prostacyclin (see Table 50-1 and Chapter 50). Downregulation of EC prostacyclin, coupled with preserved platelet prothrombotic function, may tip the hemostatic balance in favor of clot formation, and large-scale clinical trials have now shown that some highly selective COX2 inhibitors increase the likelihood of hypertension and vascular arterial events, including myocardial infarction and stroke.

Other platelet agonists are liberated into the extracellular fluid by fusion of the dense granules and alpha granules with the platelet canalicular membrane, and the result is extrusion of granule contents (see Fig. 50-1B). The dense granules contain serotonin, which, like TXA_2, is both a platelet agonist and a vasoconstrictor. Another dense granule constituent, ADP, acts purely as a platelet agonist through the G protein–linked P2RY12 receptor and has no vasoactive properties (see Table 50-2). The importance of TXA_2- and serotonin-induced vasoconstriction is not entirely clear. However, by decreasing the vessel diameter, vasoconstriction may increase shear stress and thereby facilitate recruitment of platelets to the injured site.

The importance of dense-granule release to the maintenance of hemostasis is underscored by the severe bleeding seen in patients with congenital dense-granule deficiencies (e.g., Hermansky-Pudlak syndrome). Platelet activation therefore serves to amplify platelet adhesion and to optimize the platelet surface for interaction with soluble coagulation factors, resulting in the explosive generation of thrombin and fibrin (see later discussion). Finally, other components present in platelets, such as cytosolic factor XIII, are also released into the vascular space on activation. In this case, factor XIII serves as a clot stabilizer, once again reflecting the additional role that activated platelets play in promoting hemostasis.

SOLUBLE COAGULATION

Coagulation Models

The classic "cascade" model of soluble coagulation (see Fig. 50-2A), as first described more than 40 years ago, features two starting points that converge to a common pathway leading to thrombin and fibrin generation. This model allowed great strides to be made in identifying the proteolytic reactions that culminate in fibrin clot, and it dovetailed well with the prothrombin time (PT) and activated partial thromboplastin time (aPTT) assays that guide warfarin and heparin dosing, respectively. Although the model is workable for some clinical scenarios, bleeding in a disease such as hemophilia contradicts its prediction that when