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Drugs of the Future

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Review Article

Progress in the design of inhibitors of coagulation factor Xa

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Introduction

Myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism accounted for approximately 2 million deaths in the United States in 1996 (1). The formation of an occlusive thrombus is causally related to the pathology of these conditions. As such, antithrombotic therapy is a crucial component in both acute intervention procedures and chronic prevention strategies for treatment and management of these diseases.

Effective antithrombotic therapy often requires administering a combination of antiplatelet and anticoagulant agents. Aspirin and heparin represent the current mainstay of combination therapy for the treatment of coronary syndromes (2). The shortcomings of each have driven intense efforts within the pharmaceutical industry to identify and develop more effective and safer antiplatelet and anticoagulant agents. Significant advances have been made in the development of more potent and effective antiplatelet agents (3, 4); however, the clinical need for improved anticoagulant agents is arguably greater. Current treatment options are limited to unfractionated heparin (UFH), low molecular weight heparins (LMWHs) and warfarin. The challenge remains to achieve consistent, predictable and clinically effective levels of anticoagulation while minimizing the risk of bleeding complications.

Recent approaches to identify anticoagulant agents with improved safety and efficacy have focused on developing specific inhibitors of enzymes within the coagulation cascade (5). Thrombin remains the most extensively investigated of these targets. Two decades of experience in the design of thrombin inhibitors has led to the development of highly potent and selective inhibitors, several of which have been investigated in large-scale clinical studies (6-10). In general, the results of these studies have fallen short of expectations, demonstrating no clear advantage over heparin in the treatment of coronary syndromes (11). More encouraging clinical results have been obtained in the treatment of venous thromboembolism (12).

Factor Xa inhibitors, the subject of this review, represent a more recent and rapidly evolving approach toward the development of anticoagulant agents. Theoretically, direct inhibition of factor Xa activity should provide a potent anticoagulant devoid of the potentially limiting side effects observed with thrombin inhibitors (5, 13).

Background

To develop superior anticoagulant strategies requires an understanding of the biochemical and biophysical mechanisms activating and regulating blood coagulation. The process of normal hemostasis requires maintaining a delicate balance between the dynamic processes of pro- and anticoagulant activities in circulating blood. Both are governed by a finely tuned and highly integrated cascade of enzymatic processes that amplify the response to vascular injury preventing hemorrhage and initiating the repair processes. An abbreviated scheme highlighting the key aspects of these processes is presented in Figure 1.

Two convergent procoagulant pathways have evolved, each capable of being activated in response to different stimuli. The intrinsic and extrinsic coagulation pathways consist of a cascade composed of serine proteases which effectively amplify the initial stimulus to provide a strong and rapid signal to initiate the coagulation process (14). These pathways ultimately converge upon the formation of factor X and its conversion to factor Xa in the prothrombinase complex.

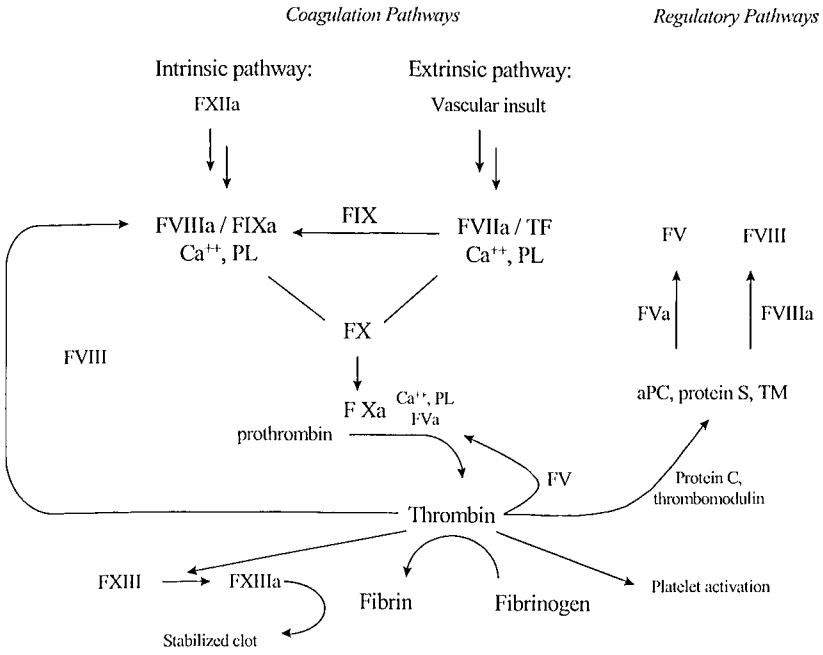

Fig. 1. Schematic diagram of the enzymatic processes of procoagulant and anticoagulant activities in circulating blood. FXa = factor Xa, PL = phospholipid, TF = tissue factor, TM = thrombomodulin, aPC = activated protein C.

The intrinsic pathway is stimulated by the contact of flowing blood with foreign surfaces or upon vascular injury and exposure of subendothelial matrix collagen (15). Three circulating factors, high molecular weight kininogen, prekallikrein and factor XII, bind together on the surface to yield the catalytically active serine protease, factor XIIa. This branch of the coagulation cascade ultimately produces factor IXa. Factor IXa combines with factor VIIIa, phospholipid, Ca^{2+} and factor X in the intrinsic Xase complex to afford factor Xa.

The extrinsic pathway is initiated following vascular injury and the resulting exposure of tissue factor (TF) onto the surface of endothelial cells and macrophages (16, 17). Tissue factor binds to factor VII and catalyzes its conversion to factor VIIa. This complex, in the presence of Ca^{2+} and phospholipid, converts factor X to factor Xa. Factors XI and IX can also be activated by tissue factor/factor VIIa, thus providing a link with the intrinsic pathway.

Factor Xa, generated by either pathway, combines with the nonenzymatic cofactor Va and Ca^{2+} on the phospholipid surface of platelets or endothelial cells to form the prothrombinase complex. The catalytic activity of factor Xa in this complex is increased 300,000-fold relative to its activity in solution. Factor Xa in the prothrombinase complex converts prothrombin (factor II) by limited proteolysis to release catalytically active thrombin (factor IIa) (18).

Thrombin holds a central position in control of coagulation processes. It catalyzes the cleavage of fibrinogen to fibrin, thus initiating the process of clot formation and activates factor XIII which cross-links fibrin monomers to stabilize the developing clot. Thrombin binds avidly to fibrin and remains catalytically active within the growing thrombus (19). Thrombin also catalyzes the formation of cofactors Va and VIIIa and thus provides a positive feedback mechanism for its continued generation and the progression of clot development (20). In addition to its direct actions on the coagulation cascade, thrombin is also a potent agonist of platelet activation. The direct activation of platelets is an important first response to maintain normal hemostasis, allowing the generation of a homeostatic plug following injury (20). Prolonged activation and recruitment of platelets will further potentiate the development of clot formation.

Thrombin also plays a key role in the initiation of inhibitory pathways to downregulate the coagulation process. Upon release from the prothrombinase complex, thrombin can bind to thrombomodulin, a glycoprotein present on the surface of endothelial cells (22, 23). Thrombin has high affinity for thrombomodulin which alters its substrate specificity from fibrinogen and the procoagulant factors V, VIII and XIII to protein C. Cleavage of protein C bound to thromomodulin affords activated protein C. This complex, in the presence of the nonenzymatic cofactor protein S, cleaves the procoagulant cofactors Va and VIIIa, thus providing a mechanism of inactivating the intrinsic coagulation pathway. In addition, active protein C activates the fibrinolytic system by stimulating the release of tissue plasminogen activator from endothelial cell, which provides a physiologically important link between anticoagulant and fibrinolytic pathways (24).

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