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Mini Review

The Spectrum of Thrombin in Acute Coronary Syndromes

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ABSTRACT

The role of thrombin in vascular physiology and pathophysiology continues to impact our understanding of many cellular processes and systems including the function of platelets, endothelial cells, smooth muscle cells, leukocytes and the regulation of the coagulation cascade. Recent acute coronary syndrome clinical trial results that have compared the use of parenteral or oral anticoagulants versus or in combination with anti-platelet agents have forced a reexamination of the importance of thrombin activity in influencing patient outcomes, particularly in the area of secondary prevention. The debate of the need to include oral anticoagulation as a concomitant or replacement therapy to an antiplatelet regimen as a means to improve patient outcomes requires further examination and larger prospective clinical trials.

Contents

Introduction

The discovery of thrombin was made as early as the end of the 19th century by Buchanan, a Scottish physiologist [1]. Thrombin belongs to a class of enzymes known as serine proteases which cleave peptide bonds in proteins [2]. Thrombin or Factor IIa is one of the key enzymes in the coagulation cascade and exerts a dual role of both procoagulant and anticoagulant functions, hence regulating the activity of the coagulation cascade [3]. Because of this central regulatory position, the formation of thrombin is often regarded as one of the most crucial steps in coagulation cascade [4]. The utilization of agents that inhibit the generation or activity of thrombin as a means to prevent secondary events in ACS is under intense investigation.

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Generation of Thrombin

Thrombin is generated through a complex process that can broadly be divided into initiation, propagation and amplification stages [5]. The circulating precursor protein, called the prothrombin, is synthesized in the liver and converted to thrombin at sites of tissue injury. Exposure of tissue factor in response to tissue injury activates Factor VII leading to initial thrombin generation in picomolar concentrations [6]. This initially formed thrombin, then activates factors V and VIII, leading to enhanced formation of the prothrombinase complex consisting of prothrombin, Factor Xa, Factor Va and phospholipids with calcium ions [Fig. 1]. The prothrombinase complex is the primary activator of thrombin. Thrombin then amplifies its own generation by activation of platelets and Factors V, VIII and XI [6]. The end result is the rapid conversion of fibrinogen to fibrin and securing of hemostasis [7].

Role of Thrombin in Coagulation Cascade

While thrombin is crucial in the conversion of fibrinogen to fibrin, it also activates factor XIII that serves to stabilize the fibrin formation [8]. Thrombin also takes part in the generation of thrombin-activatable fibrinolysis inhibitor [TAFI] which serves to retard clot lysis by removing the binding sites of tissue plasminogen activator to fibrin for subsequent fibrinolysis [8].

Thrombin also participates in the endogenous anticoagulant pathways. The thrombin generated around endothelial surface binds another protein called thrombomodulin [TM]. This binding then activates Protein C which, along with Protein S as a cofactor, inactivates several clotting factors including V and VIII [9]. In addition, there are several inhibitors of thrombin such as antithrombin, alpha 1 antitrypsin, heparin cofactor II as well as α2 macroglobulin, that serve to keep the anticoagulant activity of thrombin under close regulation [8].

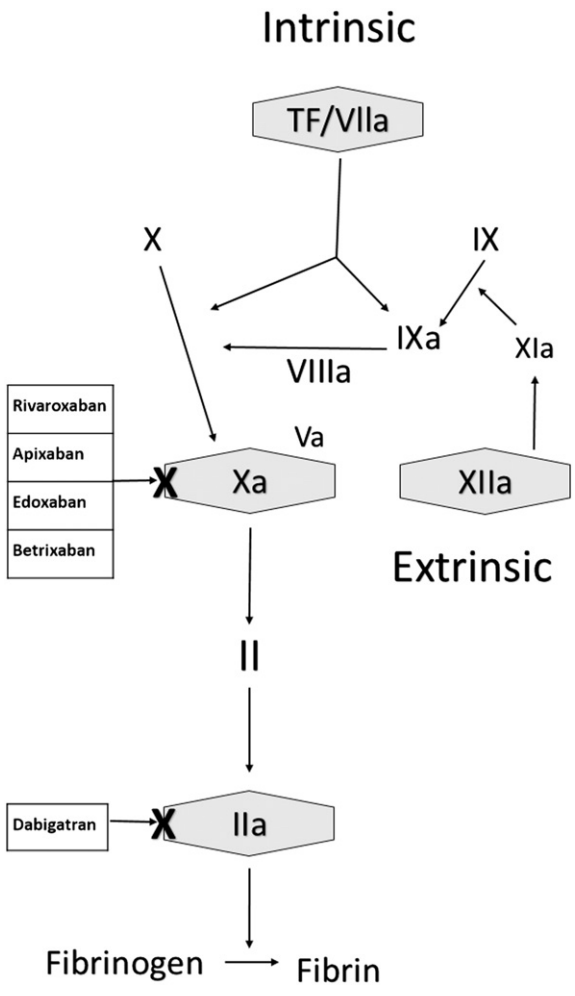

Fig. 1. Blood coagulation is traditionally designated as two pathways called the intrinsic and the extrinsic pathways. The intrinsic pathway is well-defined as a cascade that utilizes only factors that are soluble in the plasma, whereas the extrinsic pathway entails some factors that are insoluble in the plasma, e.g., membrane-bound factors such as factor VII. Both the intrinsic and the extrinsic pathways proceed through a common pathway by forming FXa. Generated thrombin cleaves fibrinogen to form fibrin monomers. These monomers then aggregate to form a clot. Sites of action of selected anticoagulant drugs are indicated by X. Anticoagulant drugs and their targets are shown in boxes.

Cellular Effects of Thrombin

Thrombin exerts effects on other cells including platelets, endothelial cells and vascular smooth muscle cells through protease-activated receptors (PAR) 1, 3 and 4. The PAR family of proteins is a novel class of G-protein coupled receptors (GPCR) that are activated by the proteolysis of the N-terminal exodomain (Fig. 2). Upon proteolysis, the newly formed N-terminus acts as a tethered ligand that activates the receptor and initiates multiple signaling cascades via heterotrimeric G-proteins [10]. While PAR1 is the major receptor through which thrombin exerts the majority of its cellular actions, little is known about the functions of PAR 3 and PAR 4 receptors in humans. PAR 1 mediates thrombin-induced proinflammatory response, endothelium dependent vasorelaxation and plays a major role in vascular remodeling and atherosclerosis [11,12]. PAR 3 has been reported to contribute the pro-inflammatory

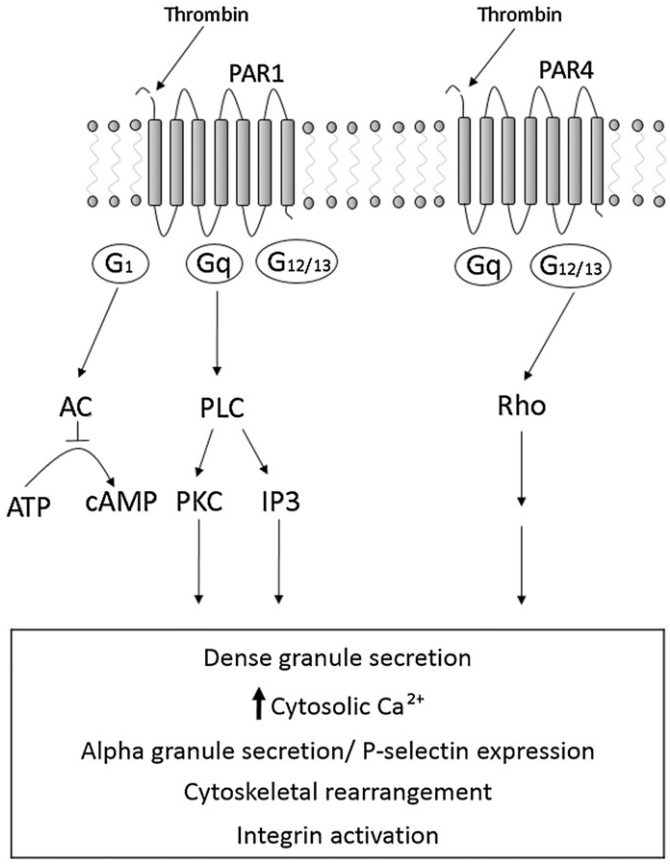

Fig. 2. Protease-activated receptor type 1 receptors are the principal thrombin receptors in humans. PAR-1 and PAR-4 activation in platelets stimulates a system of G-protein coupled signaling pathways that involve phospholipase C (PLC)-inositol triphosphate (IP3)-[Ca2+] pathway or inhibition of adenylate cyclase (AC) resulting in decreased cAMP generation, dense granule secretion and calcium mobilization via the dense tubular system (DTS). Thrombin action on PAR-4 also stimulates calcium release, cytoskeletal rearrangement and platelet activation as measured by p-selectin (CD62) expression.