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Review Article

Potential blood clotting factors and anticoagulants

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ABSTRACT

Hemostasis initiates a wound healing process and stops bleeding of blood within a damaged tissue, an important process in human and animal systems. However, this process needs to revert temporarily during surgery and analyze the clotting mechanism. In the past decade, heparin has been used widely as an anticoagulant in surgery to prevent unwanted blood clotting as it is not expensive, not difficult to control, lack of suitable replacement as well as less harmful to the human. However, heparin has several disadvantages, which include thrombocytopenia and non-specific plasma binding. Moreover, using heparin it may lead dysfunction and platelet aggregation. In this overview, potential clotting factors and anticoagulants are reviewed and special focus was given to get more insights.

Contents

1. Introduction

Hemostasis, a process promoted by damaged blood vessel during injury, is vital for human being and animal to prevent excessive bleeding [1]. Generally, there are three main hemostatic mechanisms are engaged in reducing loss of blood, which comprise

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vascular spasm, platelet plug formation, and coagulation. Vascular spasm, also called vasoconstriction, is the initial response to the injury that induces systole of smooth muscle [1]. Formation of platelet plug is the following process of vascular spasm after exposed to collagen, forming plugs to block the gap and minimize the bleeding in the damaged vessel. The crucial process in hemostasis will be blood clotting, which is playing the transformation role of blood state from liquid to solid by the assistance of clotting factors. There are about 30 types of interacting proteins engaged in this process, leading to the formation of a hemostatic plug after injury. In the formation of prothrombin, two pathways are involved and named as intrinsic and extrinsic pathways, highly connected to generate the factor Xa [2]. Extrinsic pathway takes place for 8–15 s when there is a damage of tissue outside the vessel, while intrinsic pathway takes place for 1–6 min when there is a damage to the blood vessel [1]. In extrinsic pathway, factor VII will be activated by the factor III released from damaged tissue to become factor VIIa with the assistance of cofactor Ca^{2+} (Fig. 1). Subsequently, Tissue Factor (TF) (also called factor III, platelet tissue factor, and thromboplastin) will bind to factor VIIa, forming a heterodimer which functions as a proteolytic with factor IX and X [3]. TF is on the surface of the cell and receptor for the serine protease. TF is glycoprotein also act on factor X. TF pathway inhibitor (TFPI) is important in regulating TF-initiated blood coagulation. Transcriptional activation of TF and TEPI have been regulated by PAK1 (p21-activated Kinase-1) as revealed by Sánchez-Solana et al. [4]. Involvement of TF leads thrombin generation and fibrin formation. Activation of factor XI by the factor XII released from platelets will induce intrinsic pathway (Fig. 2). Fig. 3 showed the common blood clotting process when there is an injury. As a Hageman factor, factor XII is circulating in the blood and it is activated by the contraction of blood with collagens in tissue space. After the activation of factor XI by factor XII, a serine protease, the factor IXa will activate factor IX. Subsequently, factor IXa will be the activator to active on factor X. As a protease, prothrombinase is formed after binding and activation of factor V with factor X, which is then converting prothrombin to thrombin. Then, soluble fibrin molecules are formed by the breaking of fibrinogen by thrombin. At the same time, thrombin activates factor XIII to XIIIa, which is then used to transform soluble fibrin into insoluble fibrin meshwork, called 'clot'.

The historical perspectives and clear picture of the research on coagulation factors have been viewed by Saito et al. [5], are well described the groundbreaking events. In the very beginning, it was believed that the substances thrombokinase (derived from damaged tissue), prothrombin, fibrinogen, and calcium are involved in the classic clotting [6]. After that, the remarkable understanding on the proteins and recombinant DNA technology, facilitated the crystallographic studies on the clotting factors and revealed the insights into the clotting system. These developments were further supported by *in vivo* studies, and currently progresses in stem-cell technologies are making the future directions [5]. Antihaemophilic factor, antihaemophilic globulin or factor VIII and vitamin K were discovered in late 1930 [7,8]. During the period of 1940s and 1950s several major factors involved in the clotting pathways have been discovered and these factors include V, VII, IX, X, XI, XII and XIII [5]. With these developments, anticoagulants such as antithrombin, protein C were also discovered [9,10]. Another interesting and potent anticoagulant was from snake venom and it could bind with factors IX and X [11]. After the invention of the aptamer technology in the year 1990 [12], several anticoagulant aptamers have been generated to be potential agents [13].

Obviously, clotting factors play crucial roles in the hemostatic system. Lack of blood clotting factor may arise diseases, which include von Willebrand disease, hemophilia A, hemophilia B and hemophilia C [14]. However, excessive clotting can also be a severe problem as it will leads to blocking blood vessel, cause strokes, and heart attacks, as well as pulmonary embolism [15]. Until now, there are several interests on anticoagulants growing for the prevention of excessive bleeding during cardiovascular surgery. For instant, the most general anticoagulants used are heparin and warfarin, which are taken by injection and ingestion, respectively. Although snake venom also contain the factor (IX and X) binding protein that leads to anticoagulant, but it is not suitable for use due

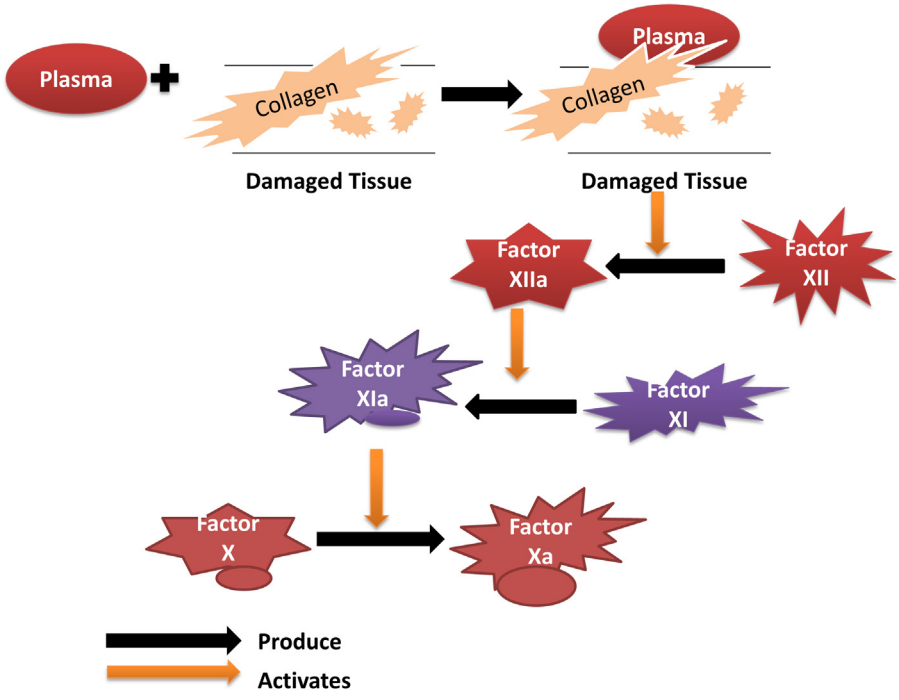

Fig. 1. Intrinsic pathway. Intrinsic pathway is mainly lead by factor XIa, converts factor IX to factor IXa.