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Current Concepts in Secondary Hemostasis.

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ABSTRACT

Hemostasis which is the arrest or stoppage of bleeding involves the primary and secondary stages. The conventional teaching in medical colleges regarding the secondary hemostasis is about the two pathways - the intrinsic and the extrinsic pathways. According to the current view of hemostasis these pathways are only an in vitro model of hemostasis and what actually happens in vivo is the tissue factor pathway of coagulation.The tissue factor which is present on the surface of non vascular cells is exposed when there is injury, activates factor VII and forms a complex with it on the surface of stimulated cells. This complex further activates other coagulation proteins to bring about clot formation. Knowledge of this in vivo model of coagulation makes the understanding of coagulation disorders like Disseminated intravascular coagulation easier.

Keywords: Hemostasis, current concepts, tissue factor, factor VII

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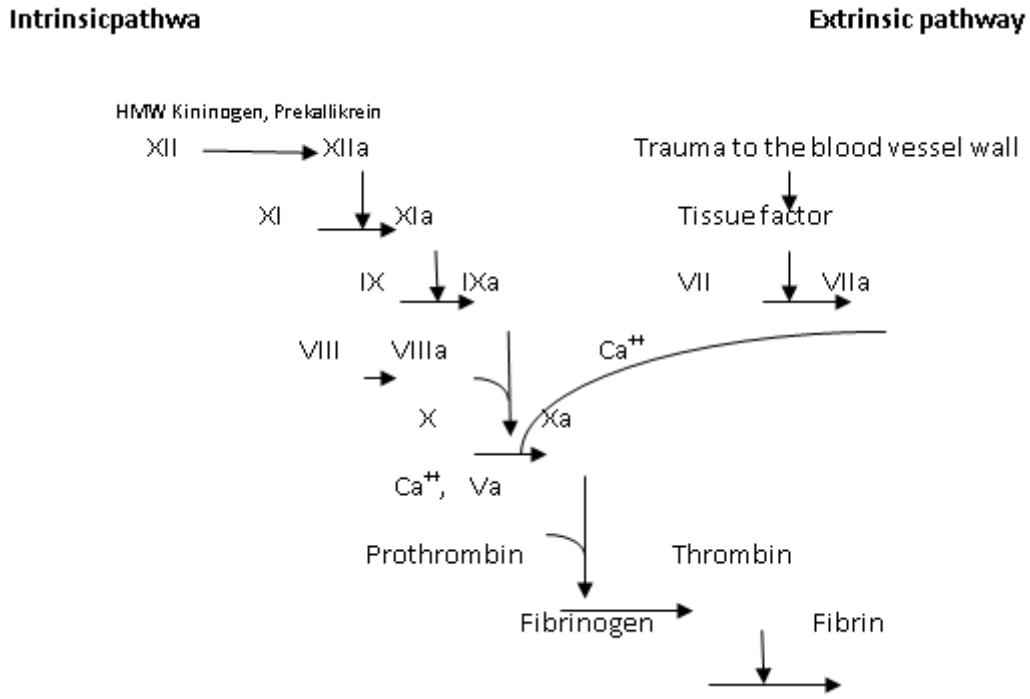
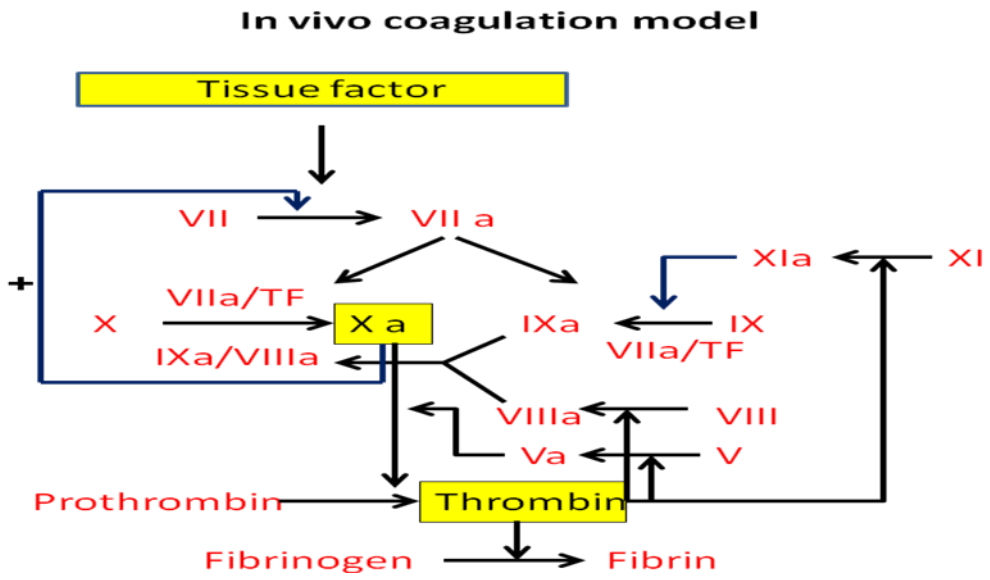
INTRODUCTION

Hemostasis, which is the arrest or stoppage of bleeding, as we all know involves both primary and secondary stages, the primary consisting of vasoconstriction and platelet plug formation and the secondary consisting of the process of coagulation. The platelet plug formation involves the adhesion of the platelets to the underlying exposed subendothelium and the aggregation of the platelets to each other. (6, 8, 14)

Flow chart 1: Present concept of coagulation*a refers to activated Factors*



Flow chart -2: Current concept of coagulation in vivo a refers to activated factors



The conventional teaching in medical colleges at the first year of Medicine regarding secondary hemostasis is about the two different pathways involved – the intrinsic and extrinsic pathways. These pathways are named so depending on the mode of activation of the pathways. According to the conventional teaching the intrinsic pathway is activated by the contact of the blood to negatively charged surfaces like

collagen etc and the extrinsic pathway is activated when there is trauma to the blood vessel wall resulting in the release of tissue factor. (6, 8) Substances intrinsic to whole blood are required for the activation of the intrinsic pathway whereas exogenous tissue factor is the one which initiates the extrinsic pathway. As we all know a cascade of reactions occur (flowchart-1) resulting in activation of thrombin which further converts fibrinogen to fibrin. (6, 8)

DISCUSSION

Patients with deficiencies of factor XII, Prekallikrein and HMW Kininogen which are involved in the intrinsic pathway have prolonged Partial thromboplastin time (PTT) but no bleeding tendencies (2, 3, 12, 14, 15) whereas deficiency of factor VIII which is also involved in the intrinsic pathway results in severe bleeding disorder and prolonged PTT. This suggests that factor XII, Prekallikrein and HMW Kininogen may not be required for hemostasis although they have a role in wound healing and inflammation and factor VIII forms an essential cofactor of hemostasis. (7, 9, 14) Hence it is suggested that the intrinsic and extrinsic pathways apply only to the in vitro model of hemostasis and what actually happens in vivo is an entirely different pathway. (3, 7, 9, 14) Understanding of this in vitro model is essential for the diagnostic purpose and for the laboratory monitoring of anticoagulation therapy hence these pathways cannot be neglected.

According to the suggested in vivo model the one which triggers the coagulation cascade is the tissue factor-factor VIIa complex. (4, 7, 11, 14) Tissue factor is present on the surface of non vascular cells, monocytes and also in the circulating blood as leukocyte-derived microparticles in an inactive form. In case of vessel wall injury this tissue factor accumulates in the area of injury and activates factor VIIa and forms a complex with it. This complex in turn activates factor X and factor IX. (7, 9, 11, 14) Activated factor X converts prothrombin to thrombin and by positive feedback mechanism activates more and more factor VII. (14) It is postulated that this coagulation cascade occurs on membrane surfaces of stimulated cells but it is still unclear on which surface this occurs. (14) Tissue factor which is present on the surface of non vascular cells and circulating leucocytes is exposed after cell injury and binds to protein VIIa in the presence of calcium ions and initiates the coagulation cascade. The thrombin which is formed initially in small quantities activates factors V, VIII and XI. (7, 14) Activated platelets express binding sites for activated factors VIII and V hence platelet membranes act as binding surfaces for coagulation proteins VIIIa and Va. Activated factor VIII on the platelet membrane binds to factor IXa forms a tenase complex and activates factor X in addition to the initial activation by factor VIIa-TF complex. (7,13,14) Activated factor XI is an added mechanism of activation of factor IX. Similarly factor Va binds to the surface of activated platelets and forms a complex with factor Xa to form the prothrombinase complex which converts prothrombin to thrombin. This Thrombin now converts fibrinogen to fibrin monomer which polymerizes further to form the fibrin clot. (7)

This vicious cycle continues till the activation of the fibinolytic system. This tissue factor pathway is inhibited by a protease inhibitor, tissue factor pathway inhibitor (TFPI). TFPI forms a complex with factor Xa and inhibits the activity of factor VIIa-TF thereby prevents the extension of the clot. (1) Factor Xa is also inhibited by other protease inhibitors like antothrombin III. (5)

SUMMARY

Understanding of coagulation disorders especially DIC (disseminated intravascular coagulation) becomes easier now with this current concept of coagulation. Any condition which results in expression of tissue factor or tissue factor-like activity results in thrombotic tendencies. Mechanical injuries to organs like brain and placenta like gun shot injuries to the brain and abruptio placenta result in accelerated coagulation due to overexpression of tissue factor finally resulting in consumption coagulopathy or disseminated intravascular coagulation. (14) Other conditions which can increase tissue factor expression are malignancy where tissue factor-like activity is increased and sepsis where endotoxins increase tissue factor expression.

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