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LETTER TO THE EDITOR

To the Editor: Is von Willebrand Factor a Hormone that Regulates a Coagulation Mechanism?

A hypothesis: von Willebrand factor is a hormone that is released into the bloodstream by the vascular endothelium in accord with the tone and activity levels of the sympathetic nervous system and regulates blood coagulability as an integral part of a physiological mechanism that controls blood clot formation.

A recently published hypothesis[1] explains how clot formation may be initiated via elevations of ''insoluble'' fibrin that reduces turbulence and mixing, but it fails to explain how coagulation is localized to the site of stress or injury. I believe that von Willebrand factor (VWF) indirectly regulates blood levels of insoluble fibrin.

Numerous studies have observed that both VWF and factor VIII activity fluctuate in accord with the severity of stressful stimuli such as disease, injury, and surgical procedures,[2] with the tone and activity levels of the sympathetic nervous system (SNS), and with blood coagulability and viscosity. The apparent relationship among these observations is unexplained.

Factor VIII is known to consist of VWF and VIIIC components, which have separate origins but circulate together and exert their effects in concert. Like other coagulation enzymes, the labile sex-linked VIIIC component is produced in the liver, and its blood level is genetically determined. It facilitates the production of thrombin. Unique among coagulation proteins, VWF is produced by the vascular endothelium, predominantly in the lung, and its blood levels fluctuate. It stabilizes the VIIIC component, which is inactive in its absence. Defects in the quality and quantity of VWF account for the wide range of bleeding manifestations in von Willebrand syndrome.

Insoluble fibrin, the final product of the coagulation system, is unstable. Its molecular structure incorporates plasminogen, which spontaneously converts to plasmin, which in turn attacks the structure of insoluble fibrin to reduce it to ''fibrin split products'' (FSP). However, thrombin stabilizes plasminogen[3] as it converts fibrinogen to insoluble fibrin.[4] Localized thrombin levels may therefore simultaneously induce the production of insoluble fibrin and inhibit its self-destruction.

The ''initiation'' phase of blood coagulation occurs with the activation of factor VII. This normally occurs when a localized disruption of the vascular endothelium exposes circulating factor VII to underlying tissue factor (TF).[5,6] Factor VII activation may explain how clot formation is localized to areas of stress and tissue damage, but it produces only small amounts of thrombin that are insufficient to induce clot formation. The ''propagation'' phase of blood coagulation involves the interaction of systemic coagulation factors VIII, IX, and X with activated factor VII to ''amplify'' the thrombin production of the ''initiation'' phase and activate factor XIII to generate insoluble fibrin in quantities sufficient to initiate clot formation. Levels of factors IX and X are stable and genetically determined, but factor VIII levels fluctuate in accord with SNS tone and activity level. Systemic factor VIII blood levels may regulate the speed of the propagation phase enzymatic activity via its interaction with factors IX and X, although the ultimate quantity of thrombin produced is little changed by factor VIII levels, provided it is present in minimal concentrations.[7,8] By increasing the speed of the propagation phase reaction, elevated blood levels of factor VIII may increase localized ''peaks'' in thrombin levels to facilitate clot formation.

I hypothesize that VWF is a systemic hormone that is released from the vascular endothelium under the direct or indirect nervous control of the SNS, that it regulates both the activity level and half-life of the factor VIII complex, and that the combined local effects of factor VII activation and systemic effects of factor VIII blood levels control blood clot formation.

In the presence of stress-related elevations of factor VIII, otherwise benign amounts of TF present in systemic

circulation may cause elevations in blood levels of thrombin and insoluble fibrin that induce increases in systemic blood viscosity and coagulability.[9] Most thrombin production occurs after coagulation is complete, and it exerts diverse effects in addition to fibrin generation that may be explained by a yet-unrecognized common mechanism involving calcium and an energy source.[10] Thrombin may induce inflammation, mitosis, angiogenesis, chemotaxis, hypertrophy, collagen production, and morphological changes.[11,12] Surgical procedures may induce simultaneous elevations in circulating TF and VWF that enhance the coagulation mechanism and thereby explain the various manifestations of the "surgical stress syndrome."[13]

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Lewis S. Coleman, MD

506 Vista Verde Way,
Bakersfield, CA 93309
e-mail: lewiscoleman@bak.rr.com

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