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A capillary hemostasis mechanism regulated by sympathetic tone and activity via factor VIII or von Willebrand's factor may function as a ''capillary gate'' and may explain angiodysplasia, angioneurotic edema, and variations in systemic vascular resistance

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Summary The sympathetic nervous system (SNS) may directly or indirectly govern the release of von Willebrand's factor (VWB), which may be a hormone, from the vascular endothelium, which may be a gland. VWB is known to stabilize the labile VIIIC component of Factor VIII complex, and may thereby determine its half-life and activity level in the blood. Rising blood levels of Factor VIII may increase the speed of thrombin production during the ''propagation'' phase of blood coagulation and thereby elevate peak levels and duration of thrombin activity to produce and stabilize insoluble fibrin in quantities necessary to initiate clot formation. At the capillary level, microvascular receptor sites may bring fibrinogen and fibronectin, which are basic ''building blocks'' of insoluble fibrin, into close proximity with rising levels of Factor VIII to facilitate insoluble fibrin production and serve as binding sites for an expanding mass of insoluble fibrin that adheres to blood components to cause capillary hemostasis. Capillary hemostasis may serve as a ''capillary gate mechanism'' (CGM) that increases systemic vascular resistance and blood pressure and decreases cardiac output in accord with increased tone and activity levels of the SNS by obstructing capillary bed flow. Angiodysplasia may be caused by persistent defects in the VWB molecule that impair CGM function and cause visible capillary damage. Angioneurotic edema may be caused by sudden complement system attack on VWB that results in widespread paralysis of CGM function and sudden shift of blood from arteries and arterioles to capillaries to cause tissue edema and hypotension. The hypothesis may offer improved insight into the nature of circulatory physiology, the surgical stress syndrome, ''vasoactive'' drugs, and numerous disease states. It may be tested by using videomicroscopy to monitor changes in bowel capillary flow in response to stepwise increases of VWB or Factor VIII intravenous boluses in animals anesthetized using combined epidural-general technique to minimize SNS activity levels.

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A recently published hypothesis [1] suggests an explanation of how insoluble fibrin, the final product of coagulation pathways, may initiate blood clot formation by damping turbulence and mixing in systemic circulation and then binding blood components into a clot, but this does not explain capillary hemostasis. At the capillary level, turbulence and mixing is arguably so minimal as to exert little effect on capillary hemostasis. I hypothesize that capillary hemostasis may be partially explained by the presence of receptor sites for fibrinogen, fibronectin and Factor VIII in the microvasculature [2]. Fibrinogen and fibronectin are the two primary ''building blocks'' of insoluble fibrin, the final product of the coagulation system. Factor VIII is an enzyme that accelerates thrombin formation as an integral part of the coagulation process [3,4]. Thrombin induces the activation of Factor XIII and the conversion of fibrinogen to insoluble fibrin that involves the incorporation of fibronectin cross-links in the structure of the insoluble fibrin to create a three-dimensional molecular mass. By accelerating thrombin production, I hypothesize that Factor VIII induces peak levels of thrombin necessary to simultaneously produce and stabilize [5] insoluble fibrin in quantities necessary to initiate clot formation.

I hypothesize that the capillary receptor sites bring these components of the coagulation system into close proximity so as to facilitate the formation of insoluble fibrin at the capillary level, and then serve as ''attachment sites'' for an enlarging mass of three-dimensional insoluble fibrin that binds to red blood cells and other blood components to form a barrier to capillary flow, and thereby effect capillary hemostasis.

Capillary hemostasis may function as a ''capillary gate mechanism'' (CGM) that affects capillary blood flow in a variety of circumstances and may thereby offer improved explanations for a number of medical and physiological mysteries, including angiodysplasia and angioneurotic edema (anaphylactic shock). These syndromes may be partially explained in terms of the dual nature of Factor VIII, which consists of two components, VIIIC and von Willebrand's factor (VWB), that have separate origins but circulate together and exert their effects in concert. The labile, sex-linked VIIIC component originates in the liver and participates in the production of thrombin. The fluctuating VWB component is produced by the vascular endothelium and stabilizes the VIIIC component, so that both the half life and activity level of the Factor VIII complex may be determined by VWB levels.

All forms of angiodysplasia, an age-related bleeding diathesis characterized by visible capillary damage, appear to involve damage to the largest multimers of the VWB molecule [6–15]. The defect in VWB function may interfere with the operation of the CGM so as to cause visible capillary damage and bleeding that can be treated with transfusions of VWB or Factor VIII. In contrast, angiodysplasia does not occur in classical hemophilia, where there is a defect in VIIIC production [16,17] but VWB levels remain normal. Meanwhile, hemophilia patients suffer from an unexplained form of exercise intolerance that may be caused by a less severe defect in CGM function caused by impaired VIIIC function. They are also subject to anaphylactic shock [18,19], which differs from other forms of shock in that it appears to involve sudden immune system activation after repeated exposure to foreign antigen, notably protamine and bee venom, in which the complement cascade suddenly attacks the VWB molecule [20], and there is a rapid swelling of membranes and tissues and simultaneous drop in blood pressure while cardiac output and other clotting factors are minimally affected [21]. The membrane swelling may cause sudden airway obstruction and death. The syndrome may be treated effectively with epinephrine, which increases blood levels of Factor VIII. Angioneurotic edema may thus be explained by a sudden collapse of the CGM due to rapid paralysis of VWB function that causes a sudden shift of blood and fluid from the large vessels to capillary beds. These facts suggest that Factor VIII may play an important role at the capillary level.

Unique among coagulation elements, both VWB and Factor VIII fluctuate constantly in association with stressful stimuli, sympathetic nervous system (SNS) activity levels, systemic vascular resistance (SVR), blood pressure (BP), blood coagulability and blood viscosity [22]. Because it affects the speed of thrombin production, Factor VIII levels may affect the activity level of the CGM. VWB may be released from the vascular endothelium under the direct or indirect control of the SNS so as to control the activity level and half-life of Factor VIII. This may explain the relationships between SNS activity, SVR, and BP. This hypothesis might be tested using the Sielenkamper rat model, by exposing the epiduralized animal subjects to stepwise increases of either Factor VIII or VWB concentrates while monitoring for changes in bowel capillary flow [23].

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