Mechanism of Action of High-Dose Factor VIIa
Points of Agreement and Disagreement

Dougald M. Monroe, Harold R. Roberts

In an article in this issue of the *Arteriosclerosis, Thrombosis, and Vascular Biology,* Butenas and colleagues report studies looking at pharmacologic levels of factor VIIa in a model system of hemophilia. Understanding the mechanism by which high-dose factor VIIa increases thrombin generation and enhances hemostasis is important because it is currently being used very effectively in treatment of patients with hemophilia, especially those with inhibitors. Factor VIIa is also being tested in other clinical settings of uncontrolled bleeding. Previously, Mann and coworkers developed a model for studying coagulation that involved reassembling purified coagulation factors with phospholipid vesicles. They examined not only thrombin generation but also the precise sequence of events leading to thrombin generation. Subsequently, this group has looked at the mechanisms of coagulation using tissue factor initiation and surfaces of: phospholipid vesicles, isolated platelets, and platelets in whole blood. These studies provided the impetus for many of the current studies on the mechanisms of coagulation and surfaces of: phospholipid vesicles, isolated platelets, and platelets in whole blood. This body of work has resulted in important observations that have helped define the mechanisms of the hemostatic process including demonstration of: the pivotal role of the tissue factor complex in initiating coagulation, the important role of initial thrombin generation in activating platelets, and the role of coagulation cofactor interactions.

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In the present article by Butenas and coworkers, the effects of pharmacologic doses of factor VIIa on hemophilia were studied in whole blood that was supplemented with phospholipids. They state that it is established that thrombin generation profiles are similar for platelets and phospholipids at appropriate concentrations. While this is true, there is disagreement about the extent to which phospholipids can mimic the contribution of platelets to the procoagulant process. It is clear that phospholipid vesicles support procoagulant reactions through accumulation of the individual reactants on the lipid surface and that this accumulation of reactants is similar to the mechanism by which complexes are formed on the platelet surface. Thus this work is valuable for the insight that it provides into conditions at high levels of surface such as at the site of a lesion. It does not, however, follow as a consequence of this study that lipids can replace platelets in vivo. Previous studies that directly compared platelets and phospholipids showed that platelets have complex activities that are not identical to what is seen on phospholipids. Also, the kinetics of procoagulant reactions on platelets showed some significant differences with the kinetics seen on lipid surfaces. Furthermore, a number of investigators have shown that the activity of activated protein C/protein S on platelets is significantly different from the activity on phospholipid vesicles. Nevertheless, the data presented by Butenas et al clearly leads to some important conclusions.

In the studies reported in this issue, Butenas et al initiated coagulation with a catalytic amount of tissue factor. Under these conditions, there was a clear difference between hemophilic and normal blood. While either high doses of factor VIIa or added phospholipid could shorten the clotting time, only the combination of both increased factor Xa generation to the levels required for near normal thrombin generation. This work differs from cell-based model systems of coagulation where, in addition to the required tissue factor initiation, factor VIIa enhanced thrombin generation by binding to activated platelets where it can directly activate factor X. This factor Xa, in the presence of factor Va from activated platelets, forms the prothrombinase complex. Increasing doses of factor VIIa lead to increased thrombin generation which, while not reaching normal levels, nevertheless exhibit a significant dose-dependent increase. The system used by the Mann et al, on the other hand, does not show a dose dependence of factor VIIa above the amount required to compete with zymogen factor VII and to saturate tissue factor. There are however many points of agreement between assays with cell-based models and the studies from Mann and coworkers. For example, both models suggest that tissue factor is required for high-dose factor VIIa to initiate coagulation by generating a priming dose of thrombin that is important for subsequent reactions. Both models also indicate that a surface is required to assemble the coagulation reactions. Both models support the idea that high-dose factor VIIa alone cannot restore thrombin generation to normal. Overall, the work of Butenas and colleagues provides further data that support the idea that the safety and efficacy of high-dose factor VIIa arises as a consequence of localizing its action to sites of vascular injury. These sites will contain tissue factor to initiate the coagulation reactions and a mechanism for recruiting surface, in the form of activated platelets, on which to propagate thrombin generation.

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