Response: Mechanism of Action of High-Dose Factor VIIa

Kenneth G. Mann, Saulius Butenas

There are two areas of disagreement between our groups concerning the mechanism of action of supraphysiological factor VIIa concentrations in hemophilia:

1. Whether high concentrations of factor VIIa can support vigorous thrombin generation in the absence of factor VIII and factor IX in a tissue factor-independent manner.

2. Whether phospholipid additions can increase the hemostatic (or thrombotic) potential of the factor VIIa/tissue factor complex.

Recombinant factor VIIa at supraphysiological concentrations has been used primarily for the treatment of bleeding episodes related to hemophilia with inhibitors. However, the “standard” dose of 90 μg/kg (=26 nmol/L) has also been used for the treatment of a variety of bleeding disorders, leading to reports of either success or failure to provide normal hemostasis. These observations emphasize the importance of knowledge related to the mechanism by which supraphysiological concentrations of factor VIIa may act to produce a desirable response.

Recombinant factor VIIa in the absence of functional factor VIII or factor IX. Thus, we are not able to obtain experimental evidence confirming a pronounced prothrombotic activity of high concentrations of factor VIIa in the absence of functional factor VIII or factor IX.

With respect to criticisms leveled at our study published in this issue of the Journal, we would like to emphasize that phospholipids were added to whole blood (normal and “acquired” hemophilia B), ie, platelets were present at 1.8 to 2.7×10⁹/mL, and their activation was not impaired by the addition of phospholipids (see Figure 3B). Osteonectin release. The increase in thrombin generation with phospholipids shown in this study is not new: a similar effect was observed for the combination of factor Xa and phospholipids (synthetic and derived from platelets) in an in vivo rabbit model. It is likely that the accumulation of platelets from flowing blood at a site of vascular damage might produce a similar result to phospholipids per se.

We are unsure of the basis for the discrepancies between our results and those observed by Monroe et al and Hoffman et al. Our experimental systems differ in the source of tissue factor, which is used to initiate the reaction; that could be the cause of some of the differences.

References


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