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 hemo-
static (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.

Our data using both a synthetic coagulation model (in the presence of either phospholipids or platelets) and minimally altered fresh blood suggest that factor VIIa at the pharmacological concentration attained (~10 nmol/L) does not restore normal thrombin generation in hemophilia A and hemophilia B blood. However, the addition of anionic phospholipids together with 10 nmol/L factor VIIa to “acquired” hemophilia B blood increases thrombin generation to the extent observed in normal blood at the same tissue factor concentration.

We agree and have reported that the role of platelets in blood coagulation is more complex than that of phospholipids. However, phospholipid preparations composed of 75% phosphatidylcholine and 25% phosphatidylserine at 1 to 2 μmol/L produce equivalent thrombin generation as platelets at their mean physiological concentration (2×10⁷/mL) in the presence or absence of factor VIII. The addition of factor VIIa (up to 40 nmol/L) in the absence of factor VIII has little effect on thrombin generation in the presence of either platelets or 2 μmol/L phospholipids. Similarly, the addition of 10 nmol/L factor VIIa to congenital hemophilia A and “acquired” hemophilia B blood, which contains all peripheral blood elements, including platelets (which appears to be a physiologically relevant system) has only a marginal effect on thrombin generation. 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; osteonecrotin 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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Arterioscler Thromb Vasc Biol. 2003;23:10
doi: 10.1161/01.ATV.0000047646.64969.8B
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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