Novel snake venom-based hemocoagulase bypasses coagulation to enhance hemostasis and limit bleeding in murine model of hemophilia A

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INTRODUCTION

Hemophilia A is a hereditary bleeding disorder and FVIII replacement is the mainstay of treatment. However, there is an unmet need for novel therapies to prevent and treat bleeding. We recently reported that slounase, a thrombin-like enzyme batroxobin from a snake venom containing Factor X activator, enhances platelet-fibrin clot formation in heparin-anticoagulated mice, suggesting slounase may bypass coagulation to restore hemostasis. The effect of slounase on hemostasis and bleeding was determined in FVIII- mice, with and without inhibitors, using intravital microscopy hemostatic models, thromboelastography and bleeding assays.

METHODS

- Laser-induced cremaster arteriole thrombosis model, with and without inhibitors
- Saphenous vein hemostasis model
- FeCl3-induced carotid artery thrombosis model
- Tail bleeding and hepatic bleeding models
- Thromboelastography using blood from FVIII- mice

RESULTS

FVIII- mice are able to form hemostatic clots due to a severe defect in platelet accumulation and absence of fibrin formation at the site of vascular injury, as confirmed in hemostatic models under real-time intravital microscopy. Prophylactic intravenous treatment of 1U/kg slounase in FVIII- mice significantly enhanced platelet activation, accumulation, and fibrin formation in response to vascular injury resulting in stable hemostatic clot formation in the cremaster artery and saphenous vein laser ablation hemostasis models. Platelet-fibrin hemostatic clots also formed following ferroc chloride injury to the carotid artery in FVIII- mice treated with anti-FVIII antibodies and slounase. Furthermore, the hemostatic effect of slounase was confirmed by in vitro thromboelastography and in vivo bleeding assays.

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CONCLUSIONS

Our data indicates slounase is a novel bypassing agent that promotes platelet procoagulant activity and fibrin formation, to restore hemostasis and limit bleeding in hemophilia A, with and without inhibitors.