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Aptamer Inhibition of Von Willebrand Factor Reduces Ischemic Stroke Burden in a Gender-Dependent Manner

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Introduction

A clear gender difference exists in stroke, with increased morbidity and mortality in women, although the underlying mechanisms remain unknown. As the focal point of platelet adhesion and aggregation, the interaction between von Willebrand factor (VWF) and glycoprotein Ib-IX-V may play a role in the observed gender gap. Aptamers are a class of RNA molecules that bind and inhibit proteins. An aptamer targetting VWF was recently developed, preventing platelet adhesion and aggregation. Previous work with the VWF aptamer has demonstrated efficacy in thrombolysis in a gender-dependent manner (Figure 1).

Figure 1

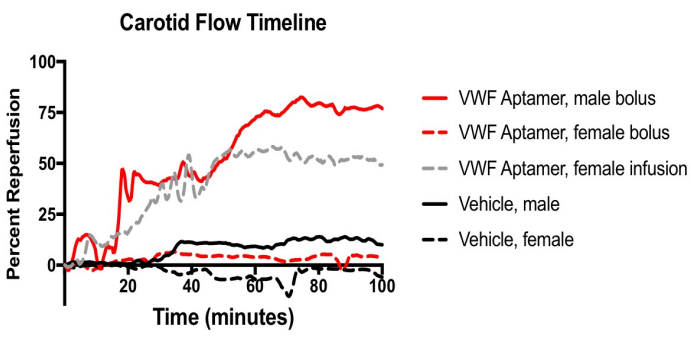


Figure 1. Thrombolysis of carotid occlusion in a gender-dependent manner

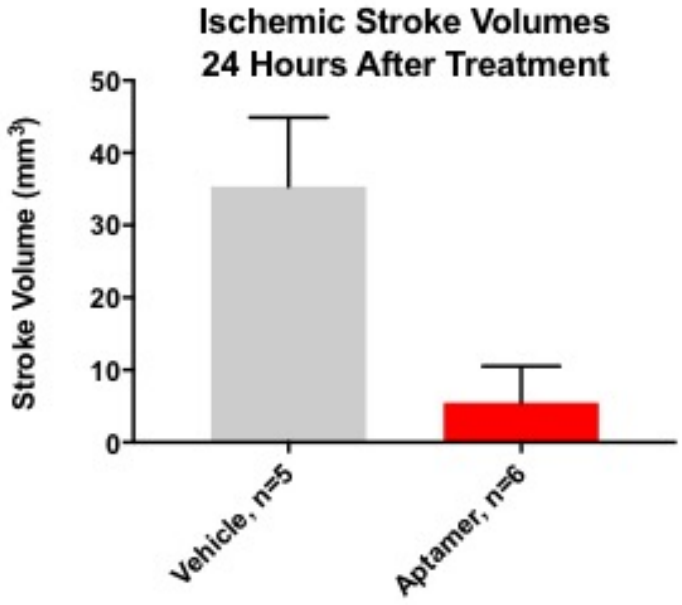
Methods

Male and female wild-type (C57BL/6J) mice were anesthetized, and the right carotid artery was exposed. A 32-gauge intracranial catheter was advanced within the carotid artery. Murine autologous blood was then mixed with 0.9% normal saline and murine thrombin, was allowed to stabilize, and was then injected into the MCA. Laser -doppler flowmetry monitoring measured decreased flow following embolus injection. Treatment with vehicle or VWF aptamer (0.5 mg/kg) was initiated 20 minutes after thrombus injection. An MRI was obtained at 24 hours to assess ischemic stroke volumes.

Results

Ischemic stroke volume was significantly decreased in female mice (Figure 2) treated with VWF aptamer (n=6, 5.49 ± 5.01 mm3) compared to vehicle (n=6, 35.34 ± 9.57 mm3, $p<0.05$). No significant difference was observed when comparing male mice treated with VWF aptamer (n=11, 18.73 ± 6.95 mm3) or vehicle (n=7, 13.32 ± 2.67 mm3, $p=0.56$).

Figure 2

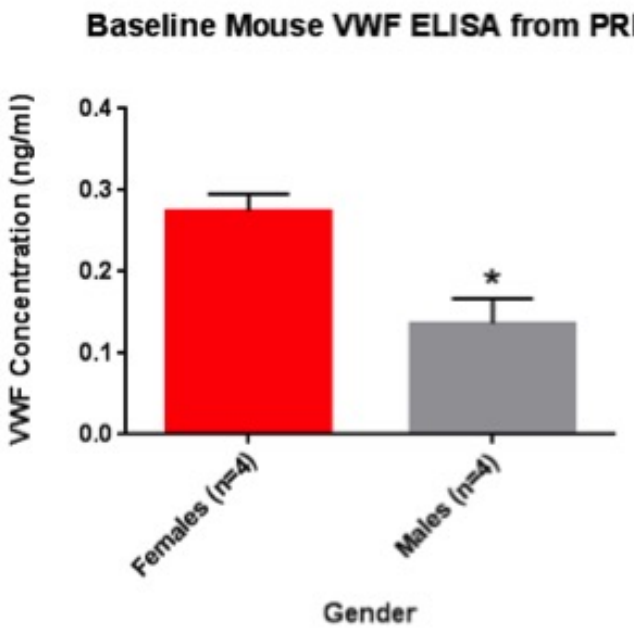


Ischemic stroke volumes between vehicle and aptamer-treated female mice

Results

An ELISA assay was used to assess VWF levels in murine whole blood. ELISA analysis of murine whole blood revealed significantly higher VWF expression in female mice (0.27 ± 0.01 ng/mL) compared to males (0.14 ± 0.02 ng/mL, $p<0.001$)(Figure 3).

Figure 3



Baseline VWF levels in wild-type male and female mice

Conclusions

Aptamer inhibition of VWF decreases stroke volume in a murine model of embolic stroke in female mice. At the same dose of VWF aptamer, this did not yield significant stroke reduction in male mice. Given the gender discrepancies in VWF expression and thrombolysis with VWF inhibition, the VWF-GP IB-IX-V axis may play a role in the gender differences observed in stroke outcomes, and VWF inhibition may result in improved stroke outcomes in females.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the gender differences in outcome following ischemic stroke. 2) Discuss the potential benefits of VWF inhibition in ischemic stroke and the role for novel reversible anti-platelet agents in this setting.