Targeting von Willebrand Factor as a Novel Treatment Approach in Acute Ischemic Stroke, Arterial Thrombosis and Endovascular Endothelial Injury

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CNS 2016 ANNUAL MEETING San Diego CALIFORNIA SEPTEMBER 24-28, 2016

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

Introduction

Stroke remains a major cause of morbidity and mortality. While recombinant tissue plasminogen activator (TPA) has been efficacious in establishing reperfusion, re-occlusion remains a significant problem, especially after endothelial injury from mechanical thrombectomy. Aptamers are a class of RNA molecules that bind and inhibit proteins. An aptamer was recently developed which binds von Willebrand factor (VWF) and inhibits its interaction with glycoprotein Ib-IX-V, preventing platelet adhesion and aggregation. VWF aptamer has previously been shown to prevent thrombus formation following intimal injury (Figure 1).

Methods

Adult male wild-type (C57BL/6J) mice were anesthetized, intubated and ventilated using a mouse respirator. A midline incision was made, and the right carotid artery was exposed. Baseline carotid flow was obtained using a Doppler flow probe (Model 0.5 VB, Transonics Systems). Thrombosis was induced by placing a ferric chloride patch proximal to the flow probe for 3 minutes with clot stabilization for 20 minutes. Mice were then infused via intravenous catheterization vehicle (platelet binding buffer), TPA or VWF aptamer. Carotid flow was monitored for a total of 100 minutes. Two-way ANOVA was utilized for statistical analysis.

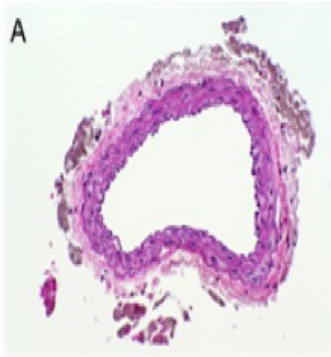

Figure 1. Carotid artery histology (H&E staining) A. patency in VWF aptamer treated mice and B. occlusion in negative controls

Results

Treatment groups:

- No perfusion group: n=2
- Control group: n=10
- TPA group: n=6
- VWF aptamer group: n=7

Time to clot stabilization was not significantly different among the three groups.

Following carotid occlusion and initiation of infusion:

- Animals treated with no perfusion or control did not experience reperfusion following occlusion.
- Mice treated with TPA established minimal reperfusion, although this was not statistically significant.
- Animals treated with VWF aptamer underwent reperfusion, which demonstrated statistical significance (Figure 2) compared to control 48 minutes after initiation of aptamer infusion ($p<0.05$).

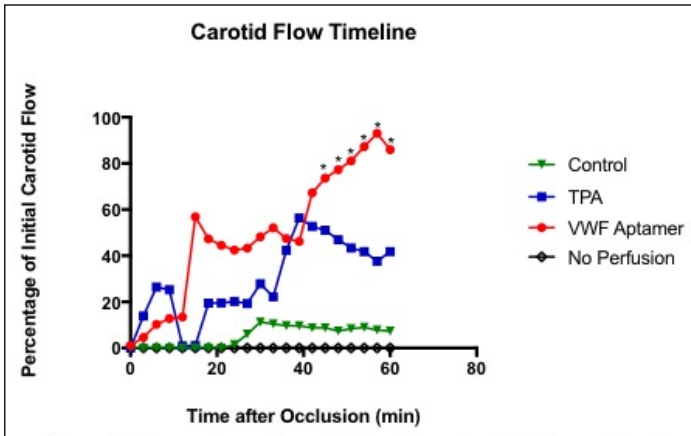

Figure 2. Percentage of carotid flow (based on initial recordings) following occlusion and infusion of drug.

Conclusions

Targeting the VWF-GP-Ib-IX-V interaction effectively inhibits platelet adhesion and aggregation. In addition to preventing thrombus formation, VWF aptamer successfully establishes reperfusion following carotid thrombus formation and vessel occlusion compared to control with greater efficacy than TPA. Targeting this interaction between VWF and GP-Ib-IX-V would also be expected to prevent new platelet adhesion to exposed VWF in the endothelium in the setting of stroke or endovascular endothelial injury.

Learning Objectives

1) Describe the need for new anti-platelet modalities in the setting of acute ischemic stroke and endovascular endothelial injury

2) Discuss the utility of an anti-vWF aptamer to contribute to thrombolysis and protect against re-occlusion

3) Identify new ways to utilize such an aptamer in endovascular treatment of acute ischemic stroke

References

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