Angiopoietin-2 in Cerebrospinal Fluid and Serum as a Predictive Biomarker for Brain Injury.

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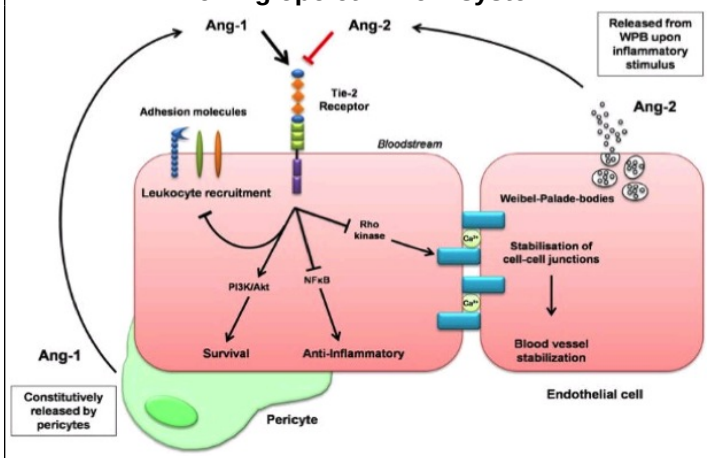
Introduction

As roles of angiopoietins in brain injury become better understood, clinical uses for Ang-2 as a vascular stress biomarker are increasingly being explored. Several studies have established serum Ang-2 as a marker of systemic illness severity, reflecting vascular injury. Less is known about how angiopoietins, e.g. pro-inflammatory Ang-2, change in other compartments in brain injury. Since Ang-2 is stable for 24 h and resists freeze-thaw cycles it may represent a reliable and durable clinical marker for brain vascular injury.

The Angiopoietin Tie-2 system



The Ang1 and Ang2 interplay is demonstrated at the Tie-2 receptor and the downstream affects of this interplay on inflammation, gap junction integrity and leukocyte recruitment.

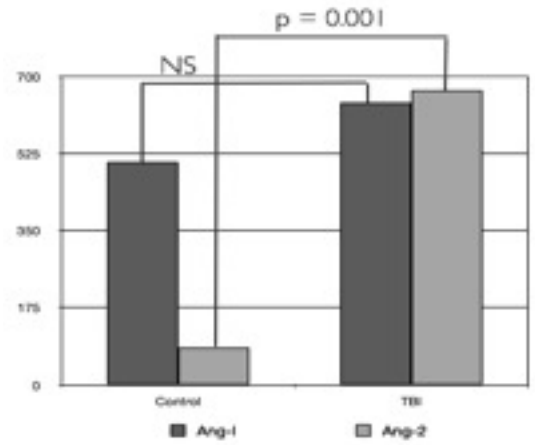
Methods

We compared Ang-2 in cerebrospinal fluid (CSF) collected from clinically defined subarachnoid hemorrhage (SAH, n=7) vs. controls (n=4) by immunoblotting.

Learning Objectives

To identify changes in CSF biomarkers (e.g. angiopoietins/ Ang-1/Ang-2 ratios) that may provide novel clinical indicators both of disease severity and mechanism. To identify changes in the ratios of Angiopoietin-1 and -2 as well as their absolute levels that may represent important targets of therapy in brain injury.

Change in angiopoietin levels in CSF of patients with TBI.



The levels of Ang1 in the control and TBI group were not significantly different (p = 0.37). However, the Ang2 levels were markedly elevated in the TBI group compared to the control group (p = 0.001).

Results

We found a large (2.66-fold) and significant (p=0.043) increase in Ang-2 (range = 8-370% of control). We also evaluated Ang-2 in serum from mice undergoing middle cerebral artery occlusion for 2h / 24 hours reperfusion, ('I/R'). We observed a significant decrease (p=0.001) in serum Ang-2 levels after I/R. Despite differences in mouse and human samples, these results suggest contrasting changes in serum and CSF Ang-2, with ischemic injury decreasing serum Ang-2 with a concomitant increase in CSF Ang-2.

Conclusions

The results suggests that serum/CSF Ang-2 ratios may be a useful biomarker of vascular stress and temporal changes in serum/CSF ratios may predict disease severity and prognosis. Further experiments to confirm serum Ang -2 in SAH and traumatic brain injury TBI are underway to validate these markers in SAH/TBI.

Change in angiopoietin levels with SAH

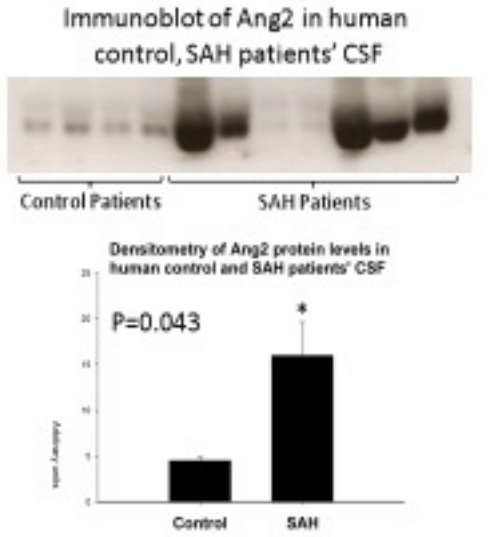


Fig-2. Ang2 levels are significantly increased in human SAH CSF samples. Western blots showed a significant increase in Ang2 levels in human SAH CSF samples compared to controls. Two way ANOVA.

Serum angiopoietin change in mouse stroke model

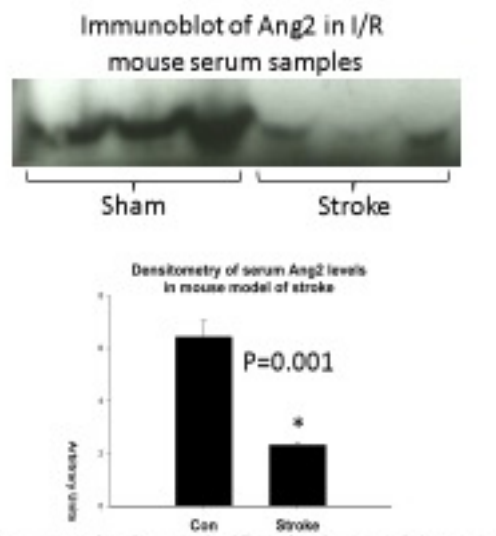


Fig-3. Ang2 levels are significantly decreased in post-stroke mouse serum. Western blots showed a significant decrease in Ang2 levels in stroke mouse serum compared to sham. Two way ANOVA.