The small peptide ATN-161 as a novel potential therapeutic for vascular disease.

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Abstracts will be considered for both poster and platform presentations

Stroke/Neurovascular

Endothelial cell integrin receptors, specifically the β1 subtype, play a direct role in inflammation and blood-brain barrier (BBB) dysfunction, both of which are implicated in stroke and Vascular Cognitive Impairment and Dementia (VCID). We hypothesize that inhibition of a particular β1 integrin subtype, α5β1, (a pro-angiogenic fibronectin receptor upregulated after brain injury) with the small peptide ATN-161, could be therapeutically effective via BBB stabilization. To model ischemic stroke, mice (3-month-old, male, C57BL/6J) underwent transient middle cerebral artery occlusion for 1 hour. ATN-161 was then administered intraperitoneally at 1 mg/kg upon reperfusion and on post stroke days (PSD)1 and 2. Analysis showed administration of ATN-161 led to a reduction in infarct volumes (TTC, T2-weighted MRI) and edema (T1-weighted MRI) as well as an improvement in functional outcome (11-point Neuroscore) at PSD3. The BBB appeared to be stabilized with increased expression of the tight junction protein, Claudin-5 (immunohistochemistry, qPCR), decreased extracellular matrix proteinase (MMP-9; qPCR), reduced inflammatory cytokine (IL-1β; qPCR), reduced leukocyte infiltration (CD45; immunohistochemistry), and reduced integrin α5β1 expression (immunohistochemistry) on PSD3 following ATN-161 treatment. The in vitro stroke model, oxygen-glucose deprivation (OGD, 8 hrs) resulted in increased expression of tight junction proteins (Claudin-5; immunocytochemistry) with decreased monolayer permeability (FITC-dextran migration assay) with 10 μM ATN-161 administration upon completion of the OGD. In a model of VCID, bilateral carotid artery stenosis (BCAS), ATN-161 was administered at 1 mg/kg via intraperitoneal injection the day of surgery and continuing every other day for 14 days. This resulted in comparable results with a decrease in integrin α5β1 expression, decreased astrocyte activation (GFAP) by immunohistochemistry and improved functional outcome (y-maze). In conclusion, the small peptide ATN-161 appears to be a new potential therapeutic option for treating ischemic stroke and preliminary results suggest it could also be a novel therapeutic to target the early changes occurring in VCID.