

Leptomeningeal vasodilation modulates intracranial pressure influencing barrier dysfunction in ASDH with hemorrhagic shock

Marica Pagliarini, Zongren Zhao, Florian Olde Huevel, Peter Radermacher, Thomas Kapapa¹, Francesco Roselli^{2,3}

¹ Department of Neurosurgery, Ulm University Medical Center, 89081 Ulm, Germany, ² Dept of Neurology, Ulm University, Germany, ³ DZNE Ulm, Ulm, Germany

Background: Acute subdural hematoma (ASDH) frequently co-occurs with hemorrhagic shock (HS), creating a “double hit” of systemic hypotension and cerebral metabolic debt that accelerates intracranial pressure (ICP) surges and secondary injury. Therapies that stabilize the endothelial barrier and preserve cerebral perfusion pressure (CPP) with less vasoactive load are urgently needed. Adrenomedullin (ADM), signaling via CALCRL with RAMP2/3, tightens endothelial junctions and counters inflammatory and oxidative injury, positioning the ADM axis as a mechanistic handle for edema and ICP control.

Methods: In human-sized pigs, we combined ASDH with standardized HS and delivered 48 h of humanized ICU care (mechanical ventilation, hemodynamic management, continuous ICP/CPP monitoring). We then performed bulk RNA-seq from injured and contralateral hemispheres and integrated: (i) modular cell-type deconvolution, (ii) ligand–receptor mapping, (iii) leptomeningeal histology, and (iv) ADM protein assays in meninges, brain, and serum. Cell response associations were computed for ICP, CPP, and survival.

Results: The injured hemisphere showed robust transcriptional remodeling enriched for extracellular matrix, vessel morphogenesis, hemostasis/platelet programs, and interleukin/Toll-like receptor signaling. Deconvolution highlighted vascular leptomeningeal cells (VLMCs) as principal responders linked to ICP at 24–48 h, focusing attention on the meninges as a modifiable compartment. Enrichment tied ICP to ECM, endothelial junctions, hemostasis, and mechanosensing; CPP and survival mapped to distinct endothelial and oligodendroglial modules. Ligand–receptor analysis prioritized 62 pairs, highlighting ADM–CALCRL/RAMP2. ADM mRNA rose with ICP at 48 h; co-varying genes clustered in hypoxia, NF- κ B, and cytokine pathways. Histology showed vessel dilation and increased cellularity without angiogenesis, implicating barrier dysregulation. ADM protein increased in meninges and was detectable in brain and serum. Notably, meningeal ADM associated negatively with ICP, while brain ADM associated positively.

Conclusions: ASDH+HS activates a pressure-relevant leptomeningeal–vascular program converging on ADM–CALCRL/RAMP2. Multi-modal data nominate a targetable pathway, motivating translational testing of barrier-stabilizing strategies to reduce ICP with lower pharmacologic burden.