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Mechanism of CSF outflow through human arachnoid granulations using *in-vitro* and *ex-vivo* perfusion models

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Background

In communicating hydrocephalus and also idiopathic intracranial hypertension, disturbed CSF dynamics may result from an increased resistance to CSF outflow at the arachnoid granulations (AGs). To better understand the mechanism of CSF egress, we modeled the outflow of CSF through human AGs using both cell culture (*in-vitro*) and whole tissue (*ex-vivo)* perfusion models.

Materials and methods

Human AG tissue was harvested within 24 hours post-mortem and used to isolate AG cells for growth on filter inserts or fit into an Ussing perfusion chamber. Cell phenotype was identified in culture with immunocytochemical staining. Cells and/or tissue were perfused at a physiologic pressure drop. Cells/tissue were perfused with fluorescent microparticles and then fixed under experimental pressure. Fixed tissue was processed for TEM or cryo-sectioned and stained for visualization.

Results

In-vitro permeability results showed flow through the AG cells was uni-directional in the physiologic direction from the basal to apical (B→A) cell membrane. The average cellular hydraulic conductivity (Lp_{ave}) for AG cells perfused B→A was 4.49 ± 0.53 μl/min/mmHg/cm^2 (n = 17) with average perfusion pressure(ΔP_{ave}) across the cell layer of 3.15 mmHg which was statistically higher ($p < 0.001$) than Lp_{ave} for cells perfused A→B (non-physiologic direction), 0.28 ± 0.16 μl/min/mmHg/cm^2 (n = 6) with ΔP_{ave} of 3.33 mmHg.

Cells perfused physiologically (*in-vitro* model), showed extra-cellular cisternal spaces between overlapping AG cells suggesting a pathway for para-cellular fluid transport. Several vacuoles within the cytoplasm were shown and suggest a trans-cellular pathway for fluid flow.

Ex-vivo perfusion experiments performed at 5 mmHg pressure in the physiological direction (B→A) resulted in Lp_{ave} of 1.05 ± 0.15 μL/min/mmHg/cm^2 (n = 20). The Lp_{ave} of tissue perfused in the A→B direction was 0.11 ± 0.03 μL/min/mmHg/cm^2 (n = 3).

Conclusion

AG perfusion results in both *in-vitro* and *ex-vivo* models showed that flow was uni-directional and physiologic. Electron microscopy showed large intracellular vacuoles and extra-cellular cisternal spaces. These structures may represent two distinct mechanisms by which AG cells move fluid: 1: Trans-cellular transport via intra-cellular vacuoles, 2: Para-cellular transport via extra-cellular cisterns.