

Oral presentation

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

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from 50th Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida  
Cambridge, UK. 30 August – 2 September 2006

Published: 21 December 2006

Cerebrospinal Fluid Research 2006, 3(Suppl 1):S11 doi:10.1186/1743-8454-3-S1-S11

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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 ( $L_{p_{ave}}$ ) for AG cells perfused B→A was  $4.49 \pm 0.53 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$  ( $n = 17$ ) with average perfusion pressure ( $\Delta P_{ave}$ ) across the cell layer of 3.15 mmHg which was statistically higher ( $p < 0.001$ )

than  $L_{p_{ave}}$  for cells perfused A→B (non-physiologic direction),  $0.28 \pm 0.16 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$  ( $n = 6$ ) with  $\Delta P_{ave}$  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  $L_{p_{ave}}$  of  $1.05 \pm 0.15 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$  ( $n = 20$ ). The  $L_{p_{ave}}$  of tissue perfused in the A→B direction was  $0.11 \pm 0.03 \mu\text{L}/\text{min}/\text{mmHg}/\text{cm}^2$  ( $n = 3$ ).

### 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.