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The Role of Betaine in Fluid Osmoregulation in Post-Traumatic Syringomyelia

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Purpose

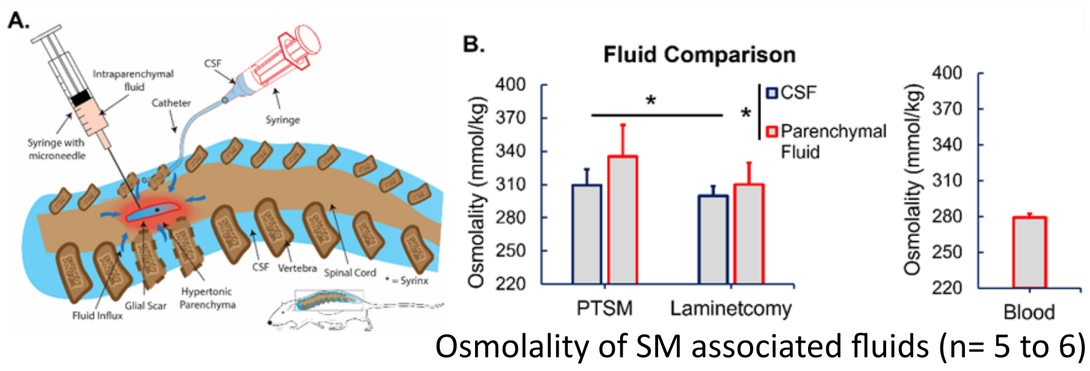
Syringomyelia (SM) is clinically treated depending on the severity of symptoms using surgical interventions, however, there are high failure rates and unsatisfactory outcomes. This motivates a need to better understand the biological and molecular underpinnings of SM with a goal of ultimately developing non-surgical interventions. We have previously performed metabolomics and transcriptomics studies on post-traumatic SM (PTSM) rat models to uncover molecular targets associated with syrinx formation. Notably, betaine upregulation and dysregulation of the betaine-associated channel (betaine/γ-aminobutyric acid (GABA) transporter 1 (BGT1)) and synthesis enzyme (choline dehydrogenase (CHDH)) in injured spinal cord tissue after 6 weeks of injury motivated us to further investigate the role of betaine on fluid osmoregulation in PTSM pathophysiology.

Methods

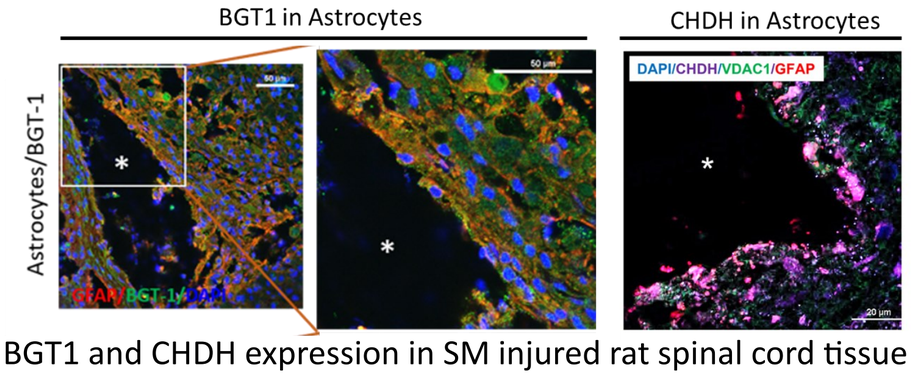
Our molecular investigations were conducted using different approaches. First, a PTSM rat model was used to understand the osmotic conditions of the fluids associated with SM and the expression of BGT1 and CHDH in the SM environment. Also, *in vitro* studies using liver (HepG2) cells and astrocytes were conducted to study the potential osmoprotectant role of betaine transport through BGT1 and betaine synthesis via CHDH under different osmotic conditions. Moreover, the direct osmotic contributions of betaine were evaluated using a combination of experimental as well as simulation approaches.

Results

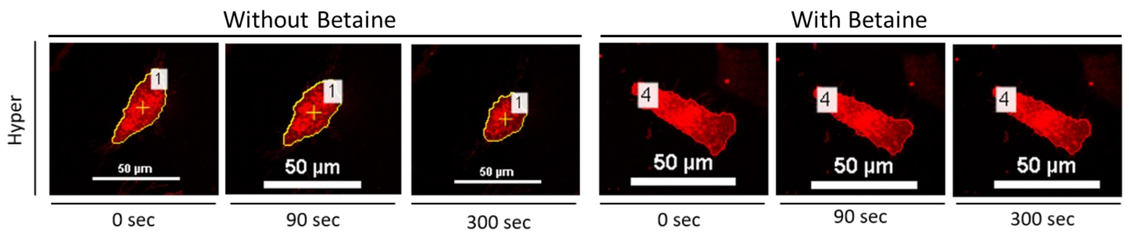
PTSM parenchymal fluid had the greatest osmolality, which was higher than CSF osmolality in the same animals. This establishes an osmotic gradient in an injured spinal cord to drive more fluid into the tissue. We also showed upregulation of BGT1 and CHDH near the vicinity of the syrinx area in PTSM animals, as confirmed using immunohistochemistry analysis. This confirms betaine-focused osmoregulation activities in the osmotically disturbed spinal cord. We corroborated our *in vivo* observations using *in vitro* astrocyte cell assays under different osmotic conditions. Cells upregulated betaine transport through BGT1 and betaine synthesis via CHDH during osmotic disturbances suggesting an endogenous osmoprotectant role. Finally, a simulation study of the osmotic contribution of betaine showed that betaine does increase osmotic pressure, and thus imposes forces directly on spinal cord tissues.



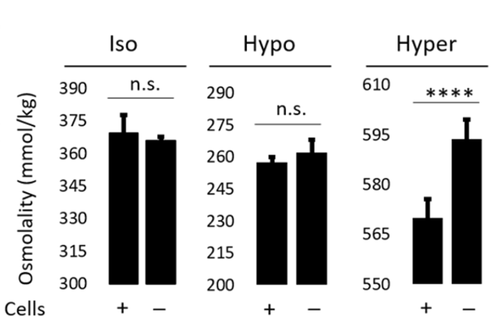
Osmolality of SM associated fluids (n= 5 to 6)



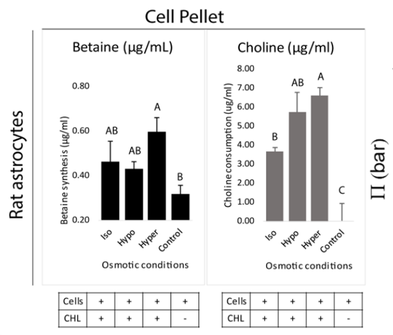
BGT1 and CHDH expression in SM injured rat spinal cord tissue



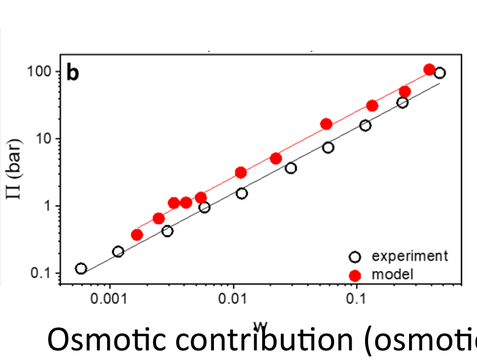
Osmoprotective role of betaine under hypertonic conditions in astrocytes



Betaine transport through BGT1 under different osmotic conditions in astrocytes



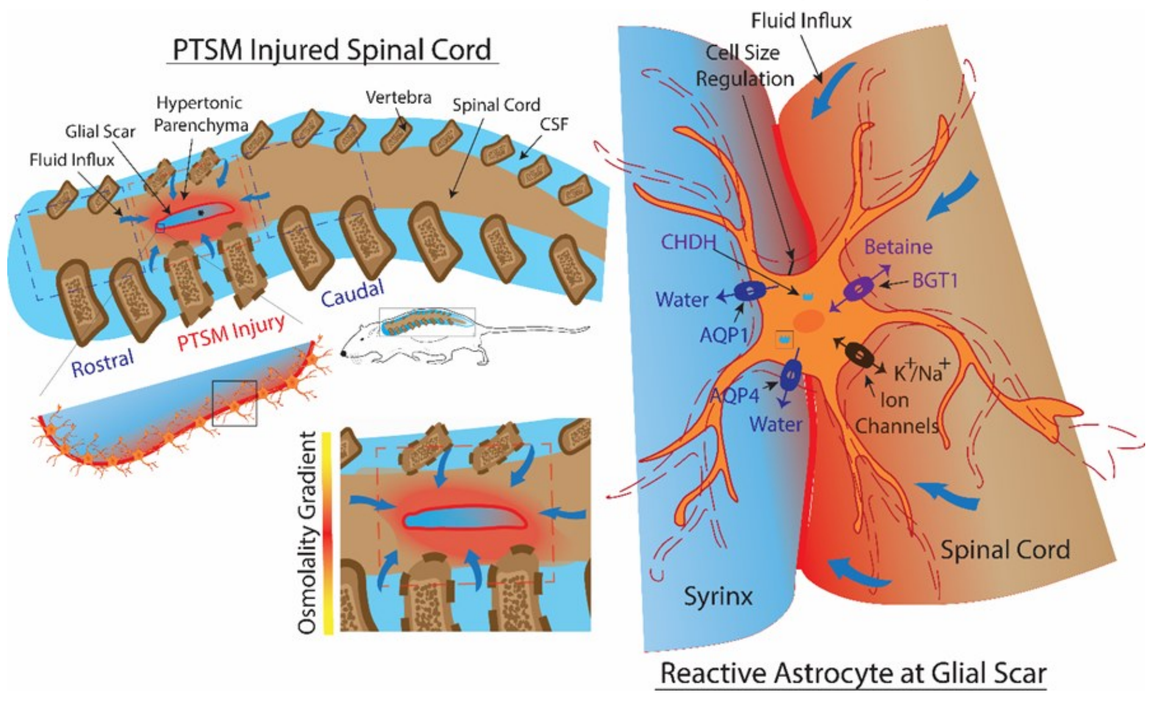
Betaine synthesis via CHDH under hypertonic condition in astrocytes



Osmotic contribution (osmotic pressure) of betaine

Conclusions

Overall, the results presented here direct us towards further confirming the involvement of betaine in osmoregulation in SM pathophysiology. Results suggest betaine fluid osmoregulation could be a potential mechanisms for syrinx formation/expansion, suggesting future drug targets for non-surgical treatment options. However, we acknowledge that considering the complexity of SM pathology and secondary insults after SCI, further comprehensive *in vitro* and *in vivo* investigations studying fluid osmoregulation-focused specific processes are required.



Schematic representation of potential PTSM fluid osmoregulation mechanisms

References

- Mohrman AE et al., J of Neurotrauma, DOI: 10.1089/neu.2015.4341
- Pukale DD et al. ACS Chem Neurosci. doi:10.1021/acschemneuro.1c00056