

Role of aquaporin channels in spinal cord and implications for treatment of syringomyelia

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Background. Trans-membrane water movement in the central nervous system is facilitated by the water channel protein aquaporin 4 (AQP4), expressed primarily in astroglia at the tissue-blood or tissue-CSF interfaces. AQP4 has been implicated in hydrocephalus and vasogenic oedema in the brain, and in spinal cord disorders. After spinal cord injury, an increase in AQP4 expression is associated with increased oedema in the cord. AQP4-knockout animals suffering spinal cord injury have improved neurological outcomes compared to wild-type animals, with decreased neuronal death and reduced cord swelling.

Syringomyelia is a disorder of the spinal cord consisting of fluid cysts within an expanded central canal (canalicular syringomyelia) or outside the central canal (extracanalicular syringomyelia). Canalicular syringomyelia forms in association with Chiari malformation, a hindbrain abnormality with herniation of the cerebellar tonsils into the spinal canal. Extracanalicular syringomyelia forms in association with spinal cord injury and spinal arachnoiditis. The origin of syringomyelia fluid and the mechanisms of fluid accumulation in both types of syringomyelia are unknown. Treatment is often unsuccessful or carries high risk.

It has been hypothesised that aquaporins, and in particular AQP4, might play an important role in syrinx formation or enlargement.

Methods. Rat models of canalicular and extracanalicular syringomyelia were used. All procedures were conducted under Isoflurane inhalational anaesthesia, including terminal aldehyde perfusion. Spinal cord tissues were removed after death. Canalicular syringomyelia was induced using an injection of kaolin suspension into the cervical spinal cord dorsal columns. Extracanalicular syringomyelia was modelled using excitotoxic (intraparenchymal injections of quisqualic acid) and contusional models of spinal cord injury, each in combination with arachnoiditis induced with a subarachnoid injection of kaolin. AQP4 function was modulated using the agonist AqF026 and the antagonist AqB050. AQP4 expression was examined using immunohistochemistry and Western blotting, and the effect of aquaporin modulation was assessed using measurements of syrinx dimensions on axial cord sections.

Results. AQP4 expression in animals with canalicular syringomyelia was not significantly different from controls. In extracanalicular (post-traumatic) syringomyelia, the expression of AQP4 increased after 3 weeks, particularly adjacent to the syrinx cavity. Syrinx cavities were smaller in animals treated with the AQP4 agonist than in the antagonist group. AQP4 expression was higher in the antagonist group than in the agonist group.

Conclusions. AQP4 expression is increased around syrinx cavities in extracanalicular syringomyelia but not in canalicular syringomyelia. The effects of AQP4 modulation suggest that AQP4 is assisting with fluid clearance in this condition rather than contributing to the fluid load. Systemic modulation of AQP4 function is promising as a therapeutic option for syringomyelia patients.