A novel approach to the treatment cerebral oedema following trauma: modulation of Aquaporin 4 water channels

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Traumatic brain injury (TBI) is a significant health problem worldwide and despite best neurosurgical intervention and critical care management, it is associated with high levels of mortality and morbidity. This is largely attributed to the development of life-threatening cerebral oedema and complications such as elevated intracranial pressure (ICP) and herniation syndromes. Cerebral oedema, the abnormal accumulation of fluid within the brain tissue, is recognized as a leading cause of death within one week of trauma and is a predictor of poor outcome in surviving individuals. Despite this, the pathophysiology of cerebral oedema genesis remains poorly understood and clinical treatments are largely ineffective given that they generally target the symptoms only rather than the underlying cause of the swelling. However, the recent discovery of the aquaporin (AQP) family of water channels may provide a new potential avenue for treatment. AQP channels are bi-directional water channels found throughout the body in tissues such as the kidney. To date, 13 different AQP channels have been identified, of which AQP4 is most abundant within the brain tissue. Specifically, AQP4 is primarily located in the astrocytic end feet encompassing the cerebral vasculature, within ependymal cells in periventricular regions and within the glia limitans. Given the location of AQP4 at brain-fluid interfaces, it has been implicated in pathological swelling to the brain. Accordingly, we sought to delineate the role of AQP4 in the genesis and resolution of cerebral oedema following acute brain injury through the use of specific AQP4 modulators in both diffuse and focal models of experimental TBI. These modulators specifically block (antagonist; AqpB013; 0.8 mg/kg) or increase the function (agonist; AqpF026; 0.2 mg/kg) of the AQP4 channel.

In the diffuse TBI studies in adult male Sprague-Dawley rats, cerebral oedema was found to be maximal at 5h following injury. The AQP4 agonist, antagonist or vehicle were administered at 30min, 5h, 12h, 24h or 48h following injury and cerebral oedema assessed 5h after drug administration in order to determine the optimal treatment time for each agent. An AQP4 antagonist was found to be most effective when administered at 5h post-TBI and the AQP4 agonist at 48h post-TBI. The AQP4 antagonist was also shown to reduce neuronal injury and albumin extravasation, which is indicative of blood-brain barrier dysfunction. Subsequent studies administering the sequential treatment with both of the AQP modulators at each of these time points demonstrated an even greater efficacy in ameliorating injury-induced brain swelling and motor deficits when compared to either agent alone. These findings suggest that an AQP4 antagonist would be most effective when administered early after injury in order to prevent the flow of water into the brain whereas an AQP4 agonist would be most effective when administered late after injury in order to facilitate the resolution of oedema and efflux of fluid from the brain. Nevertheless, sequential treatment of the antagonist at 5h and the agonist at 48h provided the greatest benefit.

In the focal TBI studies adult male Sprague-Dawley rats were subject to the cold lesion injury and treated with either intravenous AQP4 agonist, AQP4 antagonist or equal volume vehicle at 30 mins post-trauma. The focal injury model was shown to produce maximal oedema formation at 24h post injury. Following trauma, administration of the AQP4 agonist was shown to improve water clearance post-injury and reduce cerebral oedema. In contrast, treatment with an AQP4 antagonist was shown to exacerbate post-traumatic cerebral oedema. Given that the AQP4 antagonist was ineffective in reducing oedema in this focal model suggests that water may gain access to the brain tissue via a route independent of the AQP4 channels. Indeed, it is well documented that tight junction disruption occurs in the cold lesion model and in this scenario, blocking the influx of water will not have a significant effect on cerebral oedema given that water may still gain access to the parenchyma via the disrupted tight junctions.

Taken together these findings suggest that modulation of AQP4 activity may represent a novel therapeutic target in the treatment of cerebral oedema. However, the effect of AQP4 modulation is largely dependent upon both the type of brain injury and the time following injury onset. Specifically, in settings where the tight junctions are disrupted blocking AQP4 with an antagonist is not useful in reducing oedema as water may still enter through the tight junctions. In this instance an AQP4 agonist is most beneficial in order to facilitate the clearance of oedema fluid from the brain parenchyma. Alternatively, in diffuse TBI where the tight junctions remain intact an AQP4 antagonist is effective when administered early in order to prevent water movement into the brain and an AQP4 agonist is effective when administered late to facilitate clearance of oedematous fluid from the brain parenchyma. As such, AQP4 modulation following TBI influences the flux of water into and out of the brain and has the potential to profoundly reduce cerebral oedema and improve survival and outcome.