

## Therapy of Brain Edema

### Potential Pharmacologic Regulation of Aquaporin 4

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Inhibition or downregulation of AQP4 may aid in therapy of cytotoxic edema while activation or upregulation of AQP4 may aid in therapy of vasogenic brain edema (Saadoun & Papadopoulos 2010). In using mice null for AQP4, studies showed that AQP4 facilitates edema production manifested by astrocytic swelling under experimental conditions producing cerebral ischemia, hyponatremia, water intoxication or other hypoosmotic conditions, or meningitis. The AQP4 or  $\alpha$ -syn null animals show less edema than do the respective wild types. In  $\alpha$ -syn null animals, the deficit is in the number of OAPs, not in AQP4 monomers. The AQP4-null mice also exhibit prolonged seizures and delayed  $K^+$  reuptake from the ECF during cortical spreading depression, which reveals the loss of  $K^+$  flow through Kir4.1 channels and loss of water flow through AQP4 channels. These experimental paradigms show that AQP4 facilitates edema production manifested by astrocytic swelling under conditions that produce cerebral ischemia, hyponatremia, meningitis, water intoxication, or other hypoosmotic conditions. These are all examples of *cytotoxic edema*.

In contrast to the above-mentioned conditions, brain tumors or brain abscesses in animals null for AQP4 produced more edema than in the wild type, indicating that AQP4 facilitates removal of this type of edema. These are examples of *vasogenic edema*. Other examples of vasogenic edema in AQP4-null mice include intracerebral hemorrhage (Tang et al., 2010) and subarachnoid hemorrhage (Tait et al., 2010). This type of edema is produced independently of AQP4 (which has been ablated in the null animals) but requires AQP4 for its elimination through the three available AQP4 routes: perivascular endfeet around intraparenchymal vessels, the

subpial glia limitans, and ependyma. In human edematous brain tumors, astrocytes adjacent to the tumor show increased expression of AQP4 throughout the astrocyte plasmalemma, not only at endfeet. This upregulation of AQP4 may be a protective mechanism.

Animals with overexpression of AQP4 in the endfeet develop more brain edema after water intoxication than do the wild type. Thus, AQP4 in the astrocytic endfeet is rate limiting for osmotic water movements across the blood–brain barrier. AQP4 is also important in spinal cord edema but fewer data are available (see references in Saadoun & Papadopoulos, 2010; Yukutake & Yasui, 2010 for further reading and methodology).

Recent reports along these lines are notable: arylsulfonamide AqB013 is an antagonist of AQP1 and AQP4 (Yool et al., 2010); phorbol myristate acetate, which is an activator of PKC, results in downregulation of AQP4 after cerebral ischemia in rats (Fazzina et al., 2010); in a study of water permeability of *Xenopus* oocytes expressing AQP4 and the vasopressin G protein-coupled receptor V1(a)R, the permeability was reduced in a vasopressin-dependent manner as a result of V1(a)R-dependent internalization of AQP4 (Moeller et al., 2009). It is notable that this interaction with vasopressin involves PKC activation and is reduced by mutation of Ser<sup>180</sup> on AQP4 to alanine, as reported by Moeller and colleagues (Moeller et al., 2009), just as in studies with dopamine-dependent inhibition of mammalian astrocyte AQP4 described in this chapter. Edaravone, a free radical scavenger used in Japan for treatment of acute ischemic stroke, has been found to reduce the infarct area, improve neurologic deficit scores and markedly reduce AQP4 immunoreactivity and protein levels in the infarct area of rat brain after experimental cerebral ischemia (Kikuchi et al., 2009). The recently made discoveries of regulatory pathways for AQP4 that are sensitive to dopamine, glutamate and vasopressin provide strategies for continued investigation in the therapy of cytotoxic edema. Although the precise means of

regulating water homeostasis in brain under all conditions are not yet fully understood, the available data point to certain processes meriting investigation regarding AQP4 function: channel gating, regulation by kinases, and OAP formation (Yukutake & Yasui, 2010).

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