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Aquaporin-4 and Epilepsy

DEVIN K. BINDER,[1]* ERLEND A. NAGELHUS,[2] AND OLE PETTER OTTERSEN[2]
[1]*Center for Glial-Neuronal Interactions, Division of Biomedical Sciences, University of California, Riverside, California*
[2]*Centre for Molecular Biology and Neuroscience (CMBN), Centre for Molecular Medicine Norway (NCMM), Nordic EMBL Partnership, University of Oslo, 0318 Oslo, Norway*

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ABSTRACT
Recent studies have implicated glial cells in modulation of synaptic transmission, so it is plausible that glial cells may have a functional role in the hyperexcitability characteristic of epilepsy. Indeed, alterations in distinct astrocyte membrane channels, receptors, and transporters have all been associated with the epileptic state. This review focuses on the potential roles of the glial water channel aquaporin-4 (AQP4) in modulation of brain excitability and in epilepsy. We will review studies of mice lacking AQP4 (*Aqp4*$^{-/-}$ mice) or α-syntrophin (an AQP4 anchoring protein) and discuss the available human studies demonstrating alterations of AQP4 in human epilepsy tissue specimens. We will conclude with new studies of AQP4 regulation and discuss the potential role of AQP4 in the development of epilepsy (epileptogenesis). While many questions remain unanswered, the available data indicate that AQP4 and its molecular partners may represent important new therapeutic targets.

INTRODUCTION
Glial Cells and Epilepsy

Epilepsy, affecting at least 2% of the population (Hesdorffer et al., 2011), comprises a group of disorders of the brain characterized by the periodic and unpredictable occurrence of seizures. It is clear that epilepsy is a major public health problem in that those affected experience the periodic and unpredictable occurrence of seizures leading to impairment of consciousness. This handicap severely impairs the performance of many tasks and secondarily the procurement and maintenance of steady employment. Elucidating the cellular and molecular mechanisms of seizure generation may lead to novel antiepileptic drug (AED) therapies.

Most current existing AEDs act on widely expressed ion channels that directly control neuronal excitability (Rogawski and Loscher, 2004). For example, sodium channel blockers (e.g. phenytoin) reduce the rate and/or rise of neuronal action potentials and thus inhibit high-frequency neuronal firing. Gamma-aminobutyric acid GABA receptor agonists (e.g. phenobarbital) increase the efficacy of GABAergic synapses, thus increasing inhibitory synaptic transmission. These existing medications have at least two major drawbacks. First, even with optimal current AED therapy, ∼30% of patients have poor seizure control and become medically refractory. Second, as these medications act as general central nervous system depressants and must be taken chronically for seizure suppression, they also have marked effects on cognition and cognitive development.

Glial cells are involved in many important physiologic functions, such as sequestration and/or redistribution of K^+ during neural activity, neurotransmitter cycling, and provision of energy substrates to neurons (Ransom et al., 2003). Several recent lines of evidence strongly suggest that changes in glial cells potentially contribute to epilepsy (Amiry-Moghaddam et al., 2003c; Binder and Steinhäuser, 2006; Wetherington et al., 2008). First, many studies now link glial cells to modulation of synaptic transmission (Halassa et al., 2007; Halassa and Haydon 2010; Tian et al., 2005; Volterra and Meldolesi 2005; Volterra and Steinhäuser, 2004). Second, functional alterations of specific glial membrane channels and receptors have been discovered in epileptic tissue (de Lanerolle and Lee 2005; Heinemann et al., 2000; Hinterkeuser et al., 2000; Kivi et al., 2000; Seifert et al., 2006; Steinhäuser and Seifert, 2002). Third, direct stimulation of astrocytes has been shown to be sufficient for neuronal synchronization in epilepsy models (Tian et al., 2005) [although see (Fiacco et al., 2007)]. Thus, if the cellular and molecular mechanisms by which glial cells (especially astrocytes) modulate excitability are better understood, specific antiepileptic therapies based on modulation of glial receptors and channels can be contemplated (Seifert and Steinhäuser, 2011). It is likely that therapies directed to glial cells would have fewer deleterious side effects than current therapies targeting neurons.

Alteration of water and K^+ homeostasis could dramatically affect seizure susceptibility. First, brain tissue excitability is exquisitely sensitive to osmolarity and the size of the extracellular space (ECS) (Schwartzkroin et al., 1998). Decreasing ECS volume with hypoosmolar treatment produces hyperexcitability and enhanced epileptiform activity (Chebabo et al., 1995; Dudek et al., 1990; Pan and Stringer, 1996; Roper et al., 1992). At

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*Correspondence to: Devin K. Binder, MD, PhD, Center for Glial-Neuronal Interactions, Division of Biomedical Sciences, 1247 Webber Hall, University of California, Riverside, Riverside, CA 92521-0121. E-mail: dbinder@ucr.edu

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least two mechanisms could be operative: decreasing ECS volume could increase the extracellular neurotransmitter and ion concentrations and magnify ephaptic interactions among neurons due to increased ECS resistance (Wetherington et al., 2008). Conversely, increasing ECS volume with hyperosmolar treatment powerfully attenuates epileptiform activity (Dudek et al., 1990; Haglund and Hochman, 2005; Pan and Stringer, 1996; Traynelis and Dingledine, 1989). These experimental data parallel extensive clinical experience indicating that hypo-osmolar states such as hyponatremia lower seizure threshold while hyperosmolar states elevate seizure threshold (Andrew et al., 1989; Carter, 1962; Maa et al., 2011). Second, millimolar and even submillimolar increases in extracellular K^+ concentration powerfully enhance epileptiform activity in the hippocampus (Feng and Durand 2006; Rutecki et al., 1985; Traynelis and Dingledine, 1988; Yaari et al., 1986). High-K^+ reliably induces epileptiform activity in hippocampal slices from human patients with intractable temporal lobe epilepsy (TLE) (Gabriel et al., 2004).

Aquaporins

The aquaporins (AQPs) are a family of membrane proteins that function as water channels in many cell types and tissues in which fluid transport is crucial (Agre et al., 2002; Amiry-Moghaddam and Ottersen, 2003b; Verkman, 2005). The AQPs are small hydrophobic integral membrane proteins (~30 kDa monomer) that facilitate bidirectional water transport in response to osmotic gradients (Verkman, 2002). Multiple mammalian AQPs have been identified including AQP0, AQP1, AQP2, AQP4, and AQP5 which transport water only (AQPs), and AQP3, AQP7, and AQP9 which also transport glycerol (aquaglyceroporins) (Agre et al., 2002; Verkman, 2002).

AQP4 (Hasegawa et al., 1994; Jung et al., 1994; Yang et al., 1995) is of particular interest in neuroscience as it is expressed in brain and spinal cord by glial cells, especially at specialized membrane domains including astroglial endfeet in contact with blood vessels and astrocyte membranes that ensheath glutamatergic synapses (Nagelhus et al., 2004; Nielsen et al., 1997; Oshio et al., 2004; Rash et al., 1998) (Fig. 1). Activity-induced radial water fluxes in neocortex have been demonstrated that may represent water movement via AQP channels in response to physiological activity (Holthoff and Witte, 2000; Niermann et al., 2001). Interestingly, AQP4 is a structural component of orthogonal arrays of particles seen in freeze-fracture electron micrographs (Frigeri et al., 1995; Verbavatz et al., 1997; Wolburg and Berg, 1988; Wolburg et al., 2011; Yang et al., 1996).

Aqp4$^{-/-}$ Mice

Aqp4$^{-/-}$ mice were originally generated by targeted gene disruption in 1997 (Ma et al., 1997), and recently a glial conditional deletion of *Aqp4* has been generated (Haj-Yasein et al., 2011b). *Aqp4*$^{-/-}$ mice are grossly normal phenotypically, do not manifest overt neurological abnormalities, altered blood-brain barrier properties, abnormal baseline intracranial pressure, impaired osmoregulation, or obvious brain dysmorphology (Binder et al., 2004a; Papadopoulos et al., 2004; Saadoun et al., 2009). A mild hearing impairment has been recorded and the electroretinogram is perturbed (Li et al., 2002; Li and Verkman, 2001). Mice with *Aqp4* deletion have normal blood chemistries and hematologies, normal expression of other brain AQPs (AQP1 and AQP9) and their only non-neural phenotype is a mild impairment in maximal urine concentrating ability (Ma et al., 1997).

Interestingly, more detailed studies of brain tissue from *Aqp4*$^{-/-}$ mice demonstrated reduced osmotic water permeability as measured in isolated membrane vesicles (Ma et al., 1997), brain slices (Solenov et al., 2002), and intact brain (Thiagarajah et al., 2005). Also, water permeability was seven-fold reduced in primary astrocyte cultures from *Aqp4*$^{-/-}$ mice as measured by a calcein fluorescence quenching method (Solenov et al., 2004), and similar results were obtained with *Aqp4* RNAi knockdown experiments in wild-type astrocytes (Nicchia et al., 2003). These data directly demonstrated that AQP4 provides the predominant pathway for transmembrane water movement in astrocytes.

In vivo studies of these mice demonstrated a functional role for AQP4 in brain water transport. *Aqp4*$^{-/-}$ mice have markedly decreased accumulation of brain water (cerebral edema) following water intoxication and focal cerebral ischemia (Manley et al., 2000) and impaired clearance of brain water in models of vasogenic edema (Papadopoulos et al., 2004). A recent study indicates that clearance of seizure-induced edema may also be AQP4-dependent (Lee et al., 2011). Impaired water flux into (in the case of cytotoxic edema) and out of (in the case of vasogenic edema) the brain makes sense based on the bidirectional nature of water flux across the AQP4 membrane channel at the blood-brain barrier. The recently generated glial-conditional *Aqp4* knockout mouse line demonstrates a 31% reduction in brain water uptake after systemic hypoosmotic stress (Haj-Yasein et al., 2011b). Similarly, mice deficient in dystrophin or α-syntrophin, in which there is mislocalization of the AQP4 protein (Frigeri et al., 2001; Neely et al., 2001; Vajda et al., 2002), show attenuated cerebral edema (Amiry-Moghaddam et al., 2003a; Vajda et al., 2002).

Altered Extracellular Space in Aqp4$^{-/-}$ Mice

The ECS in brain comprises ~20% of brain tissue volume, consisting of a jelly-like matrix in which neurons, glia, and blood vessels are embedded (Sykova, 1997). The ECS contains ions, neurotransmitters, metabolites, peptides, and extracellular matrix molecules, forming the microenvironment for all cells in the brain and mediating glia-neuron communication via diffusible messengers, metabolites, and ions (Fields and Stevens-Gra-

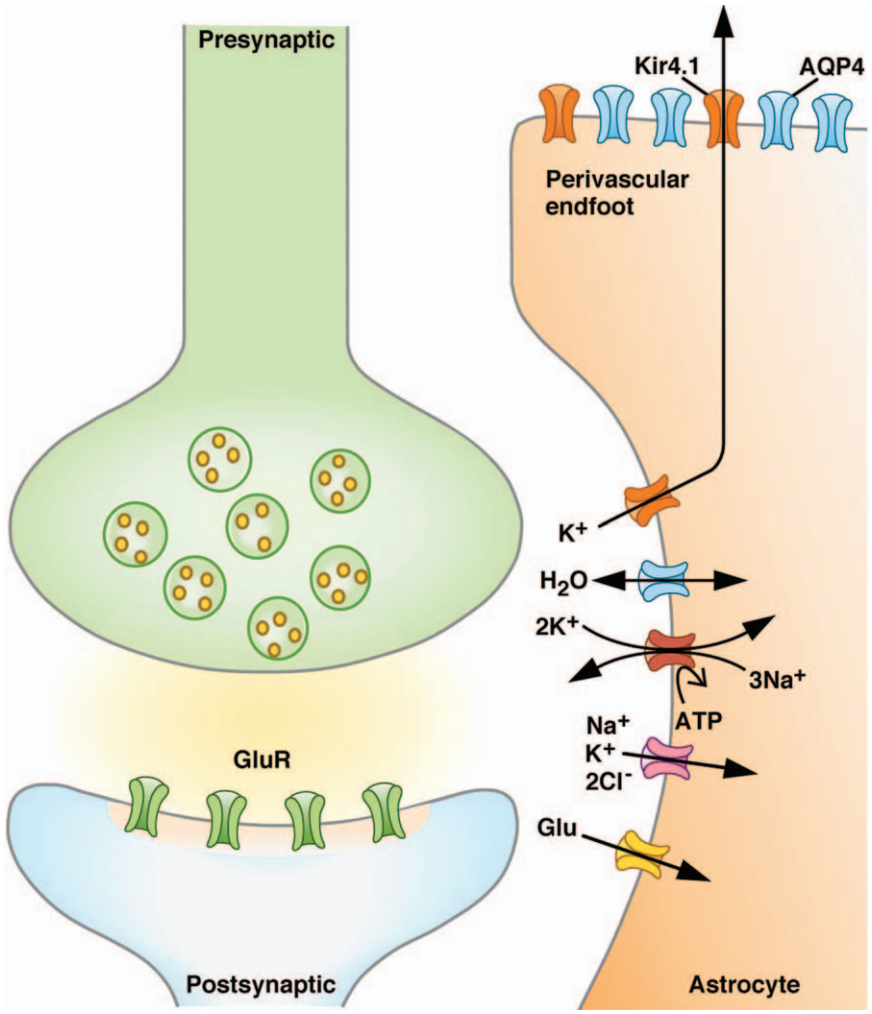

Fig. 1. Schematic of AQP4 distribution at the "tripartite" synapse. In addition to its well-known perivascular location on astrocyte endfeet, AQP4 is also localized in perisynaptic astrocyte processes. Depicted here are the presynaptic (axon) and postsynaptic (dendrite) components of the synapse as well as the perisynaptic astrocyte process (together forming the "tripartite" synapse). Multiple channels and transporters (e.g., AQP4, Kir4.1, Na^+-K^+-ATPase, chloride cotransporters, glutamate transporters) are located on the perisynaptic astrocyte membrane.

ham, 2002). The size of the ECS is likely largely controlled by astrocytic mechanisms (Andrew et al., 2007; Østby et al., 2009; Risher et al., 2009).

The ECS of *Aqp4*$^{-/-}$ mice was assessed using a cortical fluorescence recovery after photobleaching method to measure the diffusion of fluorescently labeled macromolecules in the cortex (Binder et al., 2004b). ECS in mouse brain was labeled by exposure of the intact dura to fluorescein-dextrans (M_r 4, 70, and 500-kD) after craniectomy, and fluorescein-dextran diffusion was detected by fluorescence recovery after laser-induced cortical photobleaching using confocal optics. The cortical fluorescence recovery after photobleaching method was applied to brain edema, seizure initiation, and AQP4 deficiency. In contrast to the slowed diffusion produced by brain edema and seizure activity, ECS diffusion was faster in *Aqp4*$^{-/-}$ mice, indicating ECS expansion in AQP4 deficiency (Binder et al., 2004b). Similar results were obtained with follow-up studies using the TMA^+ method (Yao et al., 2008).

Seizure Phenotype of Aqp4$^{-/-}$ Mice

Seizure susceptibility of *Aqp4*$^{-/-}$ mice was initially examined using the convulsant ($GABA_A$ antagonist) pentylenetetrazol (PTZ) (Binder et al., 2004a). At 40 mg/kg PTZ (i.p.), all wild-type mice exhibited seizure activity, whereas six of seven *Aqp4*$^{-/-}$ mice did not exhibit seizure activity. At 50 mg/kg PTZ, both groups exhibited seizure activity; however, the latency to generalized (tonic-clonic) seizures was longer in *Aqp4*$^{-/-}$ mice (Binder et al., 2004a). Since seizure propensity is exquisitely sensitive to ECS volume (Schwartzkroin et al., 1998), the expanded ECS in AQP4 deficiency is consistent with the increased seizure threshold. Thus, more intense stimuli (e.g. higher PTZ doses or a longer time after PTZ) may be required to overcome the expanded ECS of *Aqp4*$^{-/-}$ mice in order to initiate a seizure.

In order to analyze the seizure phenotype of the *Aqp4*$^{-/-}$ mice in greater detail, *in vivo* electroencephalographic (EEG) characterization with stimulation and re-

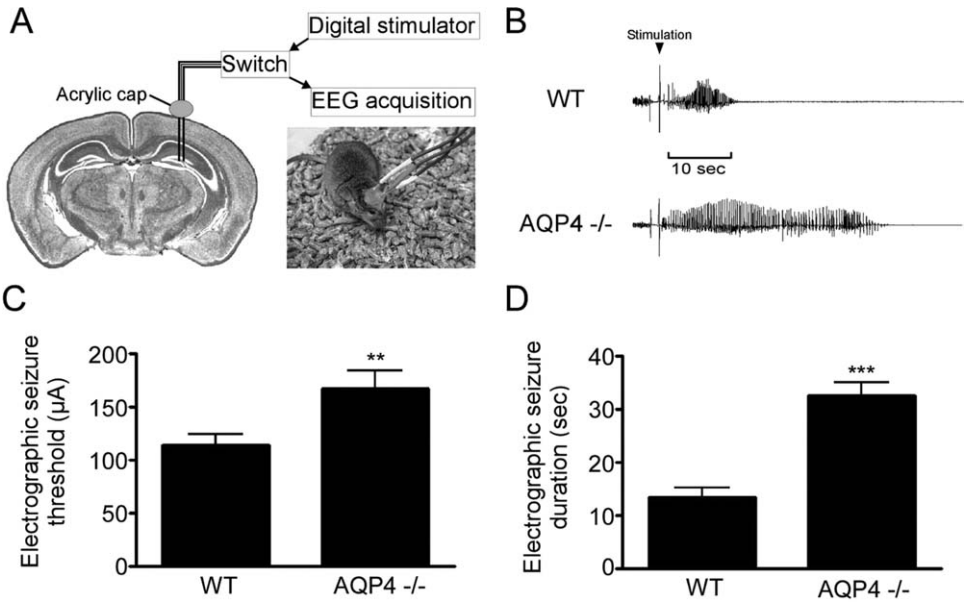

Fig. 2. Electrographic seizure threshold and duration in wild-type *vs*. AQP4$^{-/-}$ mice. **A**. Bipolar electrodes implanted in the right hippocampus were connected to a stimulator and digital EEG acquisition system. Mice were awake and behaving normally at the onset of stimulation (*inset*). **B**. Representative electroencephalograms from WT and *Aqp4*$^{-/-}$ mice. Baseline EEG prior to stimulation is similar (*left*). Hippocampal stimulation-induced electrographic seizures are shown for a WT mouse (*top*) and an *Aqp4*$^{-/-}$ mouse (bottom). The WT mouse had an 11-second seizure, whereas the *Aqp4*$^{-/-}$ mouse had a much longer seizure (37 seconds). Behavioral arrest was observed in both animals during the seizure. Postictal depression is evident on the EEG in both cases. **C**. Electrographic seizure threshold (μA) (mean ± SEM) in WT *vs. Aqp4*$^{-/-}$ mice. *Aqp4*$^{-/-}$ mice had a higher electrographic seizure threshold than wild-type controls. **D**. Electrographic seizure duration (sec) (mean ± SEM) following hippocampal stimulation in WT *vs. Aqp4*$^{-/-}$ mice. *Aqp4*$^{-/-}$ mice had remarkably longer stimulation-evoked seizures compared to wild-type controls. (From Binder et al., 2006, 53, 631-636, Glia, reproduced by permission).

cording was employed (Binder et al., 2006) (Fig. 2). *Aqp4*$^{-/-}$ mice and wild-type controls were implanted in the right dorsal hippocampus with bipolar electrodes. Following postoperative recovery, electrical stimulations were given to assess electrographic seizure threshold and duration. *Aqp4*$^{-/-}$ mice had a higher mean electrographic seizure threshold than wild-type controls, consistent with the prior PTZ studies (Binder et al., 2004a). However, *Aqp4*$^{-/-}$ mice were also found to have remarkably prolonged stimulation-evoked seizures compared to wild-type controls (Binder et al., 2004a).

Altered K^+ Homeostasis in Aqp4$^{-/-}$ Mice

Because of the colocalization of AQP4 and inwardly rectifying K^+ channels in glial endfeet, the hypothesis arose that AQP4 was indirectly involved in K^+ reuptake (Nagelhus et al., 1999; Nielsen et al., 1997). Impaired K^+ clearance from the ECS following the intense neuronal activity accompanying the seizure would lead to prolonged depolarization of neurons and inhibit seizure termination (Rutecki et al., 1985; Steinhäuser and Seifert, 2002; Traynelis and Dingledine, 1988; Yaari et al., 1986). Indeed, in addition to modulation of brain water transport, AQP4 and its known molecular partners have been hypothesized to modulate ion homeostasis (Manley et al., 2004; Simard and Nedergaard, 2004). During rapid neuronal firing, extracellular $[K^+]$ increases from ~3 mM to a maximum of 10-12 mM; and K^+ released by active neurons is thought to be primarily taken up by glial cells (Heinemann and Lux, 1977; Somjen, 2002; Sykova, 1997; Xiong and Stringer, 1999). Such K^+ reuptake into glial cells could be AQP4-dependent, as water influx coupled to K^+ influx is thought to underlie activity-induced glial cell swelling (Walz, 1987, 1992). In support of this possibility was the known subcellular colocalization of AQP4 with the inwardly rectifying K^+ channel $K_{ir}4.1$ in the retina (Connors et al., 2004; Nagelhus et al., 1999; Nagelhus et al., 2004). *K_{ir}4.1*$^{-/-}$ mice, like *Aqp4*$^{-/-}$ mice (Li et al., 2002; Li and Verkman, 2001), demonstrate abnormal retinal and cochlear physiology presumably due to altered K^+ homeostasis (Kofuji et al., 2000; Marcus et al., 2002; Neusch et al., 2001; Rozengurt et al., 2003). $K_{ir}4.1$ is thought to contribute to K^+ reuptake and spatial K^+ buffering by glial cells (Newman, 1986, 1993; Newman et al., 1984; Newman and Karwoski, 1989), and pharmacological or genetic inactivation of $K_{ir}4.1$ leads to impairment of extracellular K^+ regulation (Ballanyi et al., 1987; Djukic et al., 2007; Haj-Yasein et al., 2011a; Kofuji et al., 2000; Kofuji and Newman, 2004; Neusch et al., 2006; Seifert et al., 2009).

To address the possibility that AQP4 deficiency was associated with a deficit in K^+ homeostasis, K^+ dynamics were examined *in vivo* in *Aqp4*$^{-/-}$ mice (Binder et al., 2006). Neither baseline $[K^+]_o$ nor the "Lux-Heinemann ceiling" level of activity-induced $[K^+]_o$ elevation (~12 mM) (Heinemann and Lux, 1977; Somjen, 2002) were altered in AQP4 deficiency, indicating that basic

K^+ homeostasis was intact. Based on K^+ measurements made from cortex with double-barreled K^+-sensitive microelectrodes, stimulation-induced rises in $[K^+]_o$ were quite different in *Aqp4*$^{-/-}$ compared to wild-type mice; in particular, there was a markedly slower rise and decay time for post-stimulus changes in $[K^+]_o$ in *Aqp4*$^{-/-}$ mice (Binder et al., 2006). A similar delay in K^+ kinetics was observed following cortical spreading depression in *Aqp4*$^{-/-}$ mice using a fluorescent K^+ sensor (Padmawar et al., 2005).

Slowed $[K^+]_o$ rise time is consistent with increased ECS volume fraction in *Aqp4*$^{-/-}$ mice (Binder et al., 2004b). Slowed $[K^+]_o$ decay is possibly due to impaired K^+ reuptake into *Aqp4*$^{-/-}$ astrocytes. Interestingly, there is no difference in expression of $K_{ir}4.1$ protein (Binder et al., 2006) or $K_{ir}4.1$ immunoreactivity (Hsu et al., 2011) in *Aqp4*$^{-/-}$ mice nor AQP4 immunoreactivity in *Kir4.1*$^{-/-}$ mice (Hsu et al., 2011). In addition, no alterations were observed in membrane potential, barium-sensitive $K_{ir}4.1$ K^+ current or current-voltage curves in Aqp4$^{-/-}$ retinal Müller cells (Ruiz-Ederra et al., 2007) or brain astrocytes (Zhang and Verkman, 2008). Lack of alteration of K_{ir} channels in *Aqp4*$^{-/-}$ mice suggests the interesting possibility that the slowed $[K^+]_o$ decay may be a secondary effect of slowed water extrusion ("deswelling") following stimulation, but this has not been directly demonstrated.

A recent study investigated the impact of AQP4 on stimulus-induced alterations of $[K^+]_o$ in hippocampal slices. Antidromic stimulation evoked smaller increases and slower recovery of $[K^+]_o$ in the stratum pyramidale of *Aqp4*$^{-/-}$ mice, consistent with the previous *in vivo* studies in cortex. Interestingly, astrocyte gap junction coupling as assessed with tracer filling during patch clamp recording demonstrated enhanced tracer coupling in *Aqp4*$^{-/-}$ mice, and laminar profiles indicated enhanced spatial redistribution of K^+ (Strohschein et al., 2011). The functional consequences of alterations in gap junctional coupling are not completely clear; however the complete absence of astrocytic gap junctions impairs K^+ homeostasis (Wallraff et al., 2006). To further assess the direct link between AQP4 and K^+ homeostasis, it would be interesting to perform similar studies in the new glial-conditional *Aqp4* knockout mouse line (Haj-Yasein et al., 2011b).

Anchoring of AQP4 by the Dystrophin-Associated Protein Complex (DAPC)

AQP4 in endfeet membranes is anchored to α-syntrophin, a dystrophin-associated protein (Neely et al., 2001). Accordingly, mice deficient in α-syntrophin show marked loss of AQP4 from perivascular and subpial membranes as judged by quantitative immunogold electron microscopy (Amiry-Moghaddam et al., 2003a). Similarly, dystrophin-deficient (*mdx*) mice exhibit a dramatic reduction of AQP4 in astroglial endfeet surrounding capillaries and at the glia limitans (cerebrospinal fluid-brain interface) despite no alteration in total AQP4 protein (Vajda et al., 2002). These studies clearly suggest that alterations in components of the DAPC may affect the subcellular targeting and function of AQP4. A recent study also demonstrates that dystrophin localization at the astrocytic endfoot is dependent on syntrophin (Bragg et al., 2006).

What are the functional consequences to seizure susceptibility of loss of dystrophin or syntrophin? Amiry-Moghaddam et al., (2003) were the first to report a possible association between AQP4 and epilepsy by demonstrating an increased severity of hyperthermia-evoked seizures in α-syntrophin-deficient mice. These mice exhibited a deficit in extracellular K^+ clearance following evoked neuronal activity (Amiry-Moghaddam et al., 2003c). Dystrophin-deficient mice were found to have altered seizure susceptibility in response to various chemical convulsants; in particular, *mdx* mice showed enhanced seizure severity and a shorter latency in the development of chemical kindling produced by administration of PTZ (De Sarro et al., 2004). It is interesting to note that there is an increased incidence of epilepsy in forms of human muscular dystrophy in which the dystrophin complex is affected (Tsao and Mendell, 2006). Taken together, these data suggest that AQP4 and its molecular partners together comprise a multifunctional "unit" responsible for clearance of K^+ and/or water following neural activity and that alterations in expression of this complex can lead to alterations in seizure susceptibility.

Human Tissue Studies

The most common pathology in patients with medically intractable TLE is mesial temporal sclerosis (MTS), characterized by marked neuronal cell loss in specific hippocampal areas, gliosis, and microvascular proliferation (Blümcke et al., 1999). Emerging work also demonstrates dysregulation of water and K^+ homeostasis in patients with mesial TLE. First, imaging studies demonstrate abnormal T2 prolongation by magnetic resonance imaging in the epileptic hippocampus, possibly partially due to increased water content (Mitchell et al., 1999). This is accompanied by alterations in apparent diffusion coefficient with diffusion-weighted magnetic resonance imaging (Hugg et al., 1999). Second, the expression and subcellular localization of AQP4 have been shown to be altered in sclerotic hippocampi obtained from patients with MTS. Using immunohistochemistry, rt-PCR and gene chip analysis, Lee et al. demonstrated an overall increase in AQP4 expression in sclerotic epilepsy tissue (Lee et al., 2004). However, using quantitative immunogold electron microscopy, the same group found that there was mislocalization of AQP4 in the human epileptic hippocampus, with reduction in perivascular membrane expression (Eid et al., 2005) (Fig. 3). Thus, although there was an overall increase in AQP4 content by Western blot, rt-PCR and gene chip analysis, the subcellular distribution of AQP4 in mesial TLE tissue had changed. Their hypothesis was

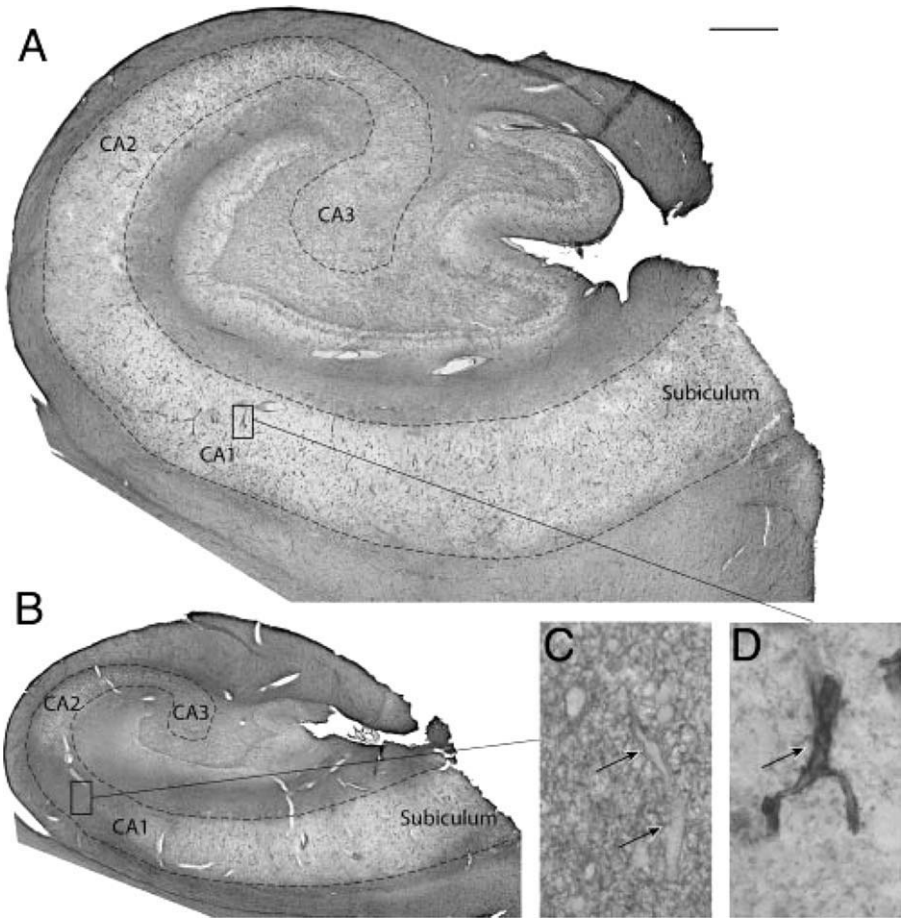

Fig. 3. Altered AQP4 distribution in mesial temporal lobe epilepsy (MTLE). Although AQP4 is preferentially distributed around blood vessels in the non-MTLE hippocampus, this localization is lost in MTLE. AQP4 is demonstrated by preembedding immunohistochemistry on Vibratome sections of a representative non-MTLE (**A** and **D**) and MTLE (**B** and **C**) hippocampus. A. In the non-MTLE hippocampus, immunoreactivity for AQP4 in the pyramidal layer of Ammon's horn (the area within the dashed line) is preferentially distributed around blood capillaries (scale bar, 1 mm). D. This finding is demonstrated in the high-power field of CA1, where the arrow indicates a strongly immunopositive capillary amidst a weakly labeled neuropil (magnification, ×6 selected portion of A). B. In the MTLE hippocampus, the preferential distribution of AQP4 around blood capillaries is lost in the pyramidal layer in areas of sclerosis (such as CA1). Scale is the same as in A. C. In the high-power field of CA1, moderate immunolabeling for AQP4 is present throughout the neuropil and also around blood capillaries, which are indicated by arrows (magnification, ×6 selected portion of B). (From Eid et al., 2005, 102, 1193-1198, Proc Natl Acad Sci U S A, reproduced by permission).

that reduction in perivascular AQP4 expression would lead to water and K^+ dysregulation in the epileptic hippocampus, potentially contributing to hyperexcitability.

Recently, Medici et al., reported AQP4 expression in tissue from patients with focal cortical dysplasia (FCD) type IIB, normal-appearing (cryptogenic) epileptic cortex, and nonepileptic control tissue (Medici et al., 2011). AQP4 expression and distribution in the cryptogenic cases were similar to control cases, i.e. with intact perivascular immunoreactivity. In the patients with FCD type IIB, the pattern was different, with strong AQP4 immunoreactivity around dysplastic neurons but with very weak immunoreactivity for AQP4 around blood vessels (Medici et al., 2011).

Disruption of the DAPC has also been demonstrated in human epileptic tissue. In the study in which reduced perivascular membrane expression of AQP4 was noted (Eid et al., 2005), these authors also studied perivascular dystrophin expression. Like AQP4 expression, perivascular dystrophin expression was also reduced in tissue from the sclerotic epileptic hippocampus (Eid et al., 2005). The more recent study also demonstrated reduced perivascular dystrophin expression in FCD type IIB (Medici et al., 2011). Thus, subcellular alteration in AQP4 expression may result secondarily from alterations in dystrophin and/or other members of the DAPC.

Dysfunction of astroglial K_{ir} channels has also been found in specimens from patients with TLE (Heinemann et al., 2000; Steinhäuser and Seifert, 2002). First, using ion-sensitive microelectrodes, Kivi et al., demonstrated an impairment of glial barium-sensitive K^+ uptake in the CA1 region of MTS specimens (Kivi et al., 2000). Second, using patch-clamp analysis, Hinterkeuser et al., demonstrated a dramatic reduction in astroglial K_{ir} currents in MTS tissue (Hinterkeuser et al., 2000). Reduction in K_{ir} currents would be expected to contribute to hyperexcitability; evidence for this comes from the finding of stress-induced seizures in conditional $K_{ir}4.1^{-/-}$

mice (Djukic et al., 2007). For further details as to the role of Kir channels in epilepsy see the article by Steinhäuser et al., in this Special Issue (Steinhäuser et al., 2012).

Methodological Issues

In assessing the contribution of AQP4 and its molecular partners to epileptogenesis, it is critical to examine the methodology in the reported studies. First, studies of human tissue represent the "endpoint" of an already long-standing epileptogenic process. A sclerotic hippocampus with significant neuronal cell loss and gliosis may show many molecular changes in glial cells including the reported altered distribution of AQP4 (Eid et al., 2005; Lee et al., 2004), but what is unclear from these studies is whether AQP4 dysregulation represents a cause or consequence of epileptogenesis. Appropriate animal models of epilepsy permit dissection of the process of epileptogenesis in greater detail. In particular, in such models it is possible to examine the transition from a normal to an epileptic brain as assessed by *in vivo* electrophysiological recordings of spontaneous seizures following an initial epileptogenic insult. Description of molecular changes in glial cells during epileptogenesis (Binder and Steinhäuser 2006) will be facilitated by studies in such *in vivo* models. Unlike *in vivo* models, studies with *ex vivo* slices enable the delineation of tissue and synaptic physiology in greater detail (Amiry-Moghaddam et al., 2003c), but at the expense of isolating only a part of the *in vivo* network. Thus, a fruitful combination of methodologies for future study will include *in vivo* electrophysiologic recording for validation of epileptogenesis, *ex vivo* slice physiology, and examination of the cellular and molecular changes in glial cells leading up to the development of spontaneous seizures.

The studies discussed above suggest novel roles for AQP4 in control of seizure susceptibility (Amiry-Moghaddam et al., 2003c; Binder et al., 2004a; Binder et al., 2006), K^+ homeostasis (Amiry-Moghaddam et al., 2003c; Binder et al., 2006; Padmawar et al., 2005), and ECS physiology (Binder et al., 2004b). These findings together with the changes in human epileptic tissue (Eid et al., 2005; Lee et al., 2004) lead to the unifying hypothesis that AQP4 and its molecular partners may play a functional role in epilepsy (Dudek and Rogawski, 2005; Wetherington et al., 2008). In this context, and based on the recent burgeoning literature on glial-neuronal interactions and gliovascular interactions, a number of fascinating unanswered issues arise.

Expression and Regulation of AQP4 During Epileptogenesis

Early studies demonstrated the perivascular localization of AQP4 (Badaut et al., 2002; Badaut et al., 2000; Nagelhus et al., 2004; Nielsen et al., 1997) but did not examine region-specific expression of AQP4 in the brain in detail. A recent study examined subregional expression pattern of AQP4 within the mouse hippocampus, a structure critical to epilepsy (Hsu et al., 2011). AQP4 immunohistochemistry revealed a developmentally regulated and laminar-specific pattern, with highest expression in the CA1 stratum lacunosum-moleculare and the molecular layer of the dentate gyrus. AQP4 was also ubiquitously expressed on astrocytic endfeet around blood vessels.

This study also addressed the cell type-specificity of AQP4 expression in the hippocampus. The description of novel classes of hippocampal glial cells (classical astrocytes *vs*. NG2 cells) with different morphology and functional properties (Jabs et al., 2005; Matthias et al., 2003; Nishiyama et al., 2005; Wallraff et al., 2004) makes it particularly important to clearly identify which "glial cell" expresses AQP4. While AQP4 is thought to be expressed predominantly by "classical" astrocytes, some have reported expression in other cell types, such as activated microglia (Tomas-Camardiel et al., 2004). However, a recent study found no AQP4 expression in resting microglia of the neocortex (Eilert-Olsen et al., 2012) and conditional *Aqp4* deletion driven by the human glial fibrillary acidic protein promoter completely removed AQP4 from brain (Haj-Yasein et al., 2011b). In line with the latter studies, AQP4 was found to colocalize with the astrocyte markers glial fibrillary acidic protein and S100β in the hippocampus, and electrophysiological and postrecording RT-PCR analyses of individual cells revealed that AQP4 and $K_{ir}4.1$ were coexpressed in nearly all CA1 "classical astrocytes." In NG2 cells, AQP4 was detected at the transcript level but not with immunohistochemistry (Hsu et al., 2011).

Seizure activity is accompanied by a variety of changes in gene expression, and repeated or prolonged seizure activity leads to glial changes, ultimately including the proliferation of "reactive" astrocytes (gliosis). The human studies indicated an upregulation and altered distribution of AQP4 protein in sclerotic tissue resected from patients with mesial TLE (Eid et al., 2005; Lee et al., 2004). However, it is unclear whether AQP4 is upregulated by seizure activity *per se* and/or by other processes occurring during epileptogenesis (development of epilepsy), such as cell death, inflammation or gliosis (Vezzani and Granata, 2005). AQP4 is known to be dramatically upregulated in reactive astrocytes following injury (Badaut et al., 2003; Saadoun et al., 2002; Vizuete et al., 1999) but may also be regulated by physiologic stimuli (Saito et al., 2005).

Kim et al., studied regulation of various AQPs in the rat pilocarpine model of epilepsy (Kim et al., 2009, 2010). In control animals, AQP4 immunoreactivity was detected diffusely in the piriform cortex and hippocampus, with greatest expression at astrocyte endfeet. Following status epilepticus in this model the authors describe an "AQP4-deleted area" in the piriform cortex, associated with decreases in immunoreactivity for dystrophin and α-syntrophin, members of the DAPC (Kim et al., 2010). Further studies will need to address the

coordinate regulation of AQP4 and other relevant astrocyte molecules such as $K_{ir}4.1$ in these models.

Of course, whether AQP4 dysregulation precedes or follows epileptogenesis impacts its functional role as cause or consequence. To address this question will require studies of AQP4 regulation with concurrent video-EEG monitoring during epileptogenesis to determine the exact timing of onset of spontaneous seizures relative to changes in AQP4 and its molecular partners. Finally, distinct epilepsy models in which epileptogenesis occurs in the absence of detectable cell death would prove useful in determining the threshold for AQP4 regulation (Bender et al., 2004; Dubé et al., 2007).

FUTURE DIRECTIONS

Subcellular Alteration in AQP4 Distribution: A Common Disease Mechanism?

The hallmark of AQP4 expression in the CNS is its polarized expression at astrocyte endfeet ensheathing blood vessels (Nagelhus et al., 2004, 1998; Nielsen et al., 1997). Loss of such polarization is associated with pathology in mesial TLE as discussed earlier (Eid et al., 2005). During seizures, there is focal swelling in the area of the seizure focus (Binder et al., 2004b; Traynelis and Dingledine 1989); and the putative effect of loss of the perivascular pool of AQP4 would be to slow water egress from astrocyte to capillary leading to local astrocyte swelling, ECS constriction and increased excitability (Wetherington et al., 2008).

Interestingly, a similar loss of AQP4 polarization has been observed in distinct models of neurological diseases. For example, in a mouse model of Alzheimer's disease, loss of AQP4 from endfoot membranes at sites of perivascular amyloid deposits was observed (Yang et al., 2011). Such subcellular alterations could lead to perturbation of local water and K^+ homeostasis in affected brain regions, and thus contribute to cognitive decline and seizure susceptibility. Similarly, Badaut et al., found loss of polarization of AQP4 expression on astrocyte endfeet following subarachnoid hemorrhage (SAH) and in peritumoral tissue (Badaut et al., 2003); thus, post-traumatic epilepsy and tumor-associated epilepsy (Rajneesh and Binder, 2009) could be associated with alterations in AQP4 expression and distribution. Further studies will require careful determination of perivascular/perisynaptic AQP4 expression ratios in a variety of conditions.

The earlier considerations lead to a new potential therapeutic opportunity: restoration of water and K^+ homeostasis by regulation of AQP4 targeting and distribution. Whether such a therapeutic approach in epilepsy may be reasonable is an open question. However, increasing understanding of the molecular partners involved (such as the DAPC) could lead to such approaches. For example, the extracellular matrix protein agrin may be a critical regulator of AQP4 membrane trafficking and polarity (Noell et al., 2007). Astrocytes cultured with the neuronal agrin isoform A4B8 but not with the endothelial and meningeal isoform A0B0 demonstrated increases in the M23 splice variant of AQP4, increased water transport capacity, and increased membrane density of orthogonal arrays of particles (Noell et al., 2007).

AQP4 and the Gliovascular Junction

Another area of astrocyte biology of potential importance for epilepsy is the "gliovascular junction" (Simard and Nedergaard, 2004). Recent studies have shown the close relationship between astrocyte endfeet ensheathing blood vessels, the targeted expression of AQP4 and $K_{ir}4.1$ on astrocyte endfeet, and the role of astrocytes in blood-brain barrier permeability (Abbott, 2002) and control of cerebrovascular tone (Gordon et al., 2007; Metea and Newman, 2006; Mulligan and MacVicar, 2004; Takano et al., 2006; Zonta et al., 2003). Molecular and cellular alterations in the gliovascular junction could perturb blood flow, water and K^+ regulation, and therefore local tissue excitability. Interestingly, recent studies have shown that transient opening of the blood-brain barrier is sufficient for focal epileptogenesis (Ivens et al., 2007; Seiffert et al., 2004). For further details as to the role of blood-brain barrier disruption in epilepsy see the article by Heinemann et al. in this Special Issue (Heinemann et al., 2012).

Just as alterations in the perivascular pool of AQP4 on existing blood vessels could affect local water and K^+ regulation, it is also the case that many new blood vessels can be formed in epileptic tissue. MTS is characterized by neuronal cell loss in specific hippocampal areas, gliosis, synaptic reorganization, but also significant microvascular proliferation (Blümcke et al., 1999). How does the regulation of AQP4 relate to angiogenesis during epileptogenesis? The increased number of microvessels in epileptic tissue may in part be due to upregulation of vascular endothelial growth factor following seizures (Croll et al., 2004; Nicoletti et al., 2008; Rigau et al., 2007). Vascular endothelial growth factor administration itself has been shown to upregulate AQP4 (Rite et al., 2008), but it is unclear whether AQP4 distribution and/or function may be unique in "epileptic vasculature." Alterations in cerebrovascular tone in epileptic vasculature would be another interesting topic of investigation.

A Role for AQP4 at the Synapse?

It was clear from early immunogold studies of AQP4 localization that while the most abundant pool was localized at astrocyte endfeet, there was also a significant concentration in non-endfeet membranes, including those astrocyte membranes that ensheath glutamatergic synapses (Nagelhus et al., 2004; Nielsen et al., 1997). Given the role of AQP4 in rapid water fluxes and K^+ homeostasis, more specific roles of AQP4 in synaptic transmission, plasticity, and behavior have begun to be tested.

Skucas et al., evaluated long-term potentiation (LTP) and long-term depression (LTD) in hippocampal slices

from *Aqp4*$^{-/-}$ mice (Skucas et al., 2011). Interestingly, *Aqp4*$^{-/-}$ mice mice exhibited a selective defect in LTP and LTD without a change in basal synaptic transmission or short-term plasticity. The impairment in LTP in *Aqp4*$^{-/-}$ mice was specific for the type of LTP that depends on the neurotrophin brain-derived neurotrophic factor (BDNF), which is induced by stimulation at theta rhythm [theta-burst stimulation-LTP], but there was no impairment in a form of LTP that is BDNF-independent, induced by high-frequency stimulation. LTD was also impaired in *Aqp4*$^{-/-}$ mice, which was rescued by a scavenger of BDNF or blockade of Trk receptors. The *Aqp4*$^{-/-}$ mice also exhibited a cognitive defect in location-specific object memory but not Morris water maze or contextual fear conditioning. These results suggest that AQP4 channels in astrocytes may play an unanticipated role in neurotrophin-dependent plasticity and influence behavior.

Genetic Studies of AQP4 and Epilepsy

Based on the idea that AQP4 and $K_{ir}4.1$ act in concert to regulate water and K^+ homeostasis in the brain, the hypothesis arose that variants of the *AQP4* and *KCNJ10* (*$K_{ir}4.1$*) genes may be associated with forms of epilepsy. In a study of 218 Norwegian patients with TLE and 181 controls, Heuser et al., found several single nucleotide polymorphisms (SNPs) in the *KCNJ10* and *AQP4* genes associated with TLE (Heuser et al., 2010). In a mouse model with glial-specific deletion of *Kcnj10*, delayed stimulation-associated K^+ clearance in CA1 stratum radiatum was observed (Haj-Yasein et al., 2011a).

CONCLUSIONS

Compelling evidence indicates that the glial water channel AQP-4 plays a fundamental role in water transport in the brain. AQP4 is expressed in astrocytes, and along with the inwardly rectifying K^+ channel $K_{ir}4.1$ is thought to be responsible for water and K^+ homeostasis during neural activity. Because osmolarity and K^+ have powerful effects on seizure susceptibility, AQP4 and its molecular partners may represent novel therapeutic targets for control of seizures. Transgenic mice lacking AQP4 have significantly prolonged seizure duration, associated with alterations in extracellular K^+ clearance and gap junctional coupling. Dysfunctional K^+ homeostasis and upregulation and altered subcellular distribution of AQP4 have been observed in human epileptic tissue. The relevance of these findings to hippocampal epileptogenesis and also to human epilepsy requires further study. Restoration of water and K^+ homeostasis in epileptic tissue constitutes a novel therapeutic concept. AQP4 occupies a pivotal position: concentrated in both astrocytic endfeet and in astroglial processes investing synapses, AQP4 may be involved in glio-neuronal interaction of water and ion fluxes and also in glio-vascular interactions across the blood-brain barrier and thus play a critical role both during active tissue metabolism and in pathophysiologic states. New data further indicate that AQP4 may be involved in osmosensing, acting in concert with the transient receptor potential vanilloid channel TRPV4 (Benfenati et al., 2011) and in Ca^{2+} signaling in astrocytes (Thrane et al. 2011). The relevance of these findings in the context of epilepsy is currently under investigation.

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