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Review

# The role of aquaporin-4 in synaptic plasticity, memory and disease

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ABSTRACT

Since the discovery of aquaporins, it has become clear that the various mammalian aquaporins play critical physiological roles in water and ion balance in multiple tissues. Aquaporin-4 (AQP4), the principal aquaporin expressed in the central nervous system (CNS, brain and spinal cord), has been shown to mediate CNS water homeostasis. In this review, we summarize new and exciting studies indicating that AQP4 also plays critical and unanticipated roles in synaptic plasticity and memory formation. Next, we consider the role of AQP4 in Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS), neuromyelitis optica (NMO), epilepsy, traumatic brain injury (TBI), and stroke. Each of these conditions involves changes in AQP4 expression and/or distribution that may be functionally relevant to disease physiology. Insofar as AQP4 is exclusively expressed on astrocytes, these data provide new evidence of "astrocytopathy" in the etiology of diverse neurological diseases.



**Contents**



## 1. Introduction

The aquaporins (AQPs) are a family of small integral membrane proteins that provide a pathway for water transport (Nagelhus and Ottersen 2013; Papadopoulos and Verkman 2013). Aquaporin-4 (AQP4), a bidirectional water channel protein, is the most abundantly expressed AQP4 in the central nervous system (CNS). AQP4 is primarily expressed by astrocytes and ependymal cells particularly in brain-fluid interfaces such as the blood-brain barrier (BBB) and

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ependymal-cerebrospinal fluid (CSF) barriers (Verkman 2011) and is highly polarized at the astrocyte perivascular endfeet in direct contact with blood vessels (Nielsen et al., 1997; Nagelhus et al., 2004; Oshio, et al., 2004). The heterogeneous distribution of this protein suggests an important role in fluid exchange into and out of the brain parenchyma.

Due to its ability to transport water, it is no surprise that AQP4 plays a critical role in maintaining water homeostasis. Water regulation is particularly important because increases in brain water content (edema) can lead to deleterious effects. Studies have shown that AQP4 knockout ($AQP4^{-/-}$) mice were protected from cytotoxic edema (intracellular accumulation of water across an intact BBB) and had improved neurological outcome while vasogenic edema (results from fluid leaking across a compromised BBB) was exacerbated in mice lacking AQP4 (Papadopoulos et al., 2004a,b). These studies demonstrate the significance of the bidirectional water flow of AQP4 in edema formation and elimination.

Because the brain lacks a lymphatic system alternative mechanisms must be employed to remove fluid and waste. Recently, an emerging hypothesis of brain and waste clearance has been proposed. The 'glymphatic' system suggests that parenchymal fluid and solutes can be cleared from the interstitial space through the paravascular space alongside large veins facilitated by AQP4 (Iliff et al., 2012; Thrane et al., 2014; Thrane et al., 2015). While these studies suggest a possible mechanism in fluid and waste removal, the hypothesis remains controversial. It was originally proposed that convective forces generated by hydrostatic pressure drive water movement by AQP4 (Thrane et al., 2015), however, others argue that the main driving force of water movement is provided by osmotic gradients (Smith et al., 2015).

The use of $AQP4^{-/-}$ mice has helped elucidate several other functional roles of AQP4. AQP4 plays a role in synaptic plasticity (Skucas et al., 2011), astrocyte migration (Saadoun et al., 2005), regulation of ECS volume (Binder et al., 2004b), and $K^+$ homeostasis (Binder et al., 2006a,b). Therefore, the dysregulation of AQP4 in disease can have several functional consequences. For example, $AQP4^{-/-}$ mice experience longer electrographic seizure duration (Binder et al., 2006a,b). Furthermore, changes in ECS and cell volume in response to altered extracellular osmolarity have also been associated with neuronal hyperexcitability (Traynelis and Dingledine, 1989; Schwartzkroin et al., 1998; Binder et al., 2004a; Haj-Yasein et al., 2012).

The data described thus far provide compelling evidence that AQP4 plays roles beyond regulating water balance in the CNS. In particular, the roles of AQP4 in cognition and the functional consequences of AQP4 dysregulation have not been investigated until recently. In this review, we explore these studies on how AQP4 impacts synaptic plasticity and learning and memory and its functions in various neurological disorders.

## 2. AQP4 in synaptic plasticity

Astrocytes are highly dynamic cells that play many essential roles in the CNS including regulation of the BBB (Abbott et al., 2006), providing structural and metabolic support (Barker and Ullian 2010; Scharfman and Binder, 2013), and maintaining ionic homeostasis (Simard and Nedergaard, 2004). Astrocytes can also secrete factors that can directly influence the formation of synapses (Barker and Ullian 2010) and thus are beginning to be recognized as vital players in regulating synaptic plasticity. Recent studies have identified AQP4 as a potential regulator of synaptic plasticity.

### 2.1. Impaired synaptic potentiation in $AQP4^{-/-}$ mice

Impaired LTP has been reported in $AQP4^{-/-}$ mice. In the Schaffer collateral synapse in CA1, significant reduction in LTP was observed in $AQP4^{-/-}$ slices compared to WT slices after theta-burst stimulation (TBS). Surprisingly, delayed LTD was also noted in $AQP4^{-/-}$ slices after TBS. High-frequency stimulation (HFS) did not result in any differences in LTP amplitude or LTP incidence between genotypes 60 min after stimulation. Low-frequency stimulation (LFS) was used to induce LTD due to the unexpected finding of delayed LTD after TBS. LTD was reduced in $AQP4^{-/-}$ mice and the incidence of LTD was also lower in $AQP4^{-/-}$ mice. Interestingly, delayed LTP was observed after LFS (Skucas et al., 2011).

Impaired LTP was also observed in $AQP4^{-/-}$ mice in the perforant path-dentate gyrus (PP-DG) pathway *in vivo* (Fan et al., 2013; Li et al., 2012). An initial increase in population spike (PS) amplitude was noted immediately after TBS, however, the PS amplitude was significantly lower in $AQP4^{-/-}$ mice. The potentiation of PS amplitude remained significant in both genotypes; however, $AQP4^{-/-}$ mice had significantly less LTP of PS amplitude. These studies suggest that AQP4 plays a role in TBS-induced LTP in the DG *in vivo*.

Impaired LTP could be due to altered basal synaptic transmission in $AQP4^{-/-}$ mice, however, no significant differences in basal transmission between the two genotypes were found in either the hippocampus or amygdala. Neither field excitatory postsynaptic potential (fEPSP) slope nor fEPSP amplitude were different between WT and $AQP4^{-/-}$ animals (Skucas et al., 2011; Fan et al., 2013; Yang et al., 2013). Unaltered paired-pulse facilitation (PFF) was also observed in $AQP4^{-/-}$ mice (Li et al., 2012; Fan et al., 2013). The impairment in synaptic plasticity observed in $AQP4^{-/-}$ mice may, instead, be due to changes in the postsynaptic response (Li et al., 2012) or result from changes in perisynaptic astroglial physiology.

### 2.2. Impaired long-term potentiation (LTP) by NMDA receptor (NMDAR) dysregulation

LTP and LTD are known to be regulated by postsynaptic NMDA receptor (NMDAR) activation and subsequent rises in intracellular calcium (Bear and Malenka 1994; Lamprecht and LeDoux, 2004; Taniike et al., 2008; Paoletti et al., 2013). Classically, LTP induction results from new AMPA receptor (AMPAR) insertion into the postsynaptic membrane from large increases in calcium while LTD is a result of dephosphorylation of AMPAR due to small increases in calcium (Bear and Malenka 1994; Lamprecht and LeDoux, 2004; Taniike et al., 2008). Absence of AQP4 may lead to NMDA dysregulation and impair LTP. Impaired LTP from $AQP4^{-/-}$ slices could also be due to NMDAR being less activated from altered bicarbonate transport (Scharfman and Binder, 2013). During neuronal activity, NMDAR is activated by increases in extracellular pH (Sinning and Hübner, 2013). Bicarbonate acts as a pH buffering system (Sinning and Hübner, 2013) and is regulated by $Na^+/HCO_3^-$ cotransporter which drives water into astrocytes through AQP4 (Nagelhus et al., 2004). NMDAR functions are altered by changes in extracellular proton concentrations (Tang et al., 1990; Traynelis and Cull-Candy, 1991) and studies have shown that extracellular acidosis suppressed the induction of LTP which may result from the interaction of NMDAR with extracellular protons (Velíšek, 1998). Thus, AQP4 deficiency may cause NMDAR dysregulation from extracellular pH imbalance but how this is achieved remains to be resolved.

### 2.3. Potassium dysregulation and synaptic plasticity

Astrocytes play a critical role in the maintenance of potassium homeostasis by either net uptake of potassium or by potassium spatial buffering (MacAulay and Zeuthen, 2012; Bedner and Steinhäuser, 2014; Cheung et al., 2015). The net uptake of potassium involves various cotransporters such as $Na^+/K^+/Cl^-$ and active antiporter $Na^+/K^+$ pumps (MacAulay and Zeuthen, 2012; Bedner and Steinhäuser, 2014). In the spatial potassium buffering model (Orkand et al., 1966) extracellular potassium is taken up by $K_{ir}4.1$

and redistributed throughout the glial syncytium through gap junctions (Bedner and Steinhäuser, 2014). Therefore, the impaired LTP could be related to potassium dysregulation. For instance, slowed potassium reuptake was observed in AQP4$^{-/-}$ mice (Binder et al., 2006a,b) and delayed recovery of extracellular potassium was noted in α-syntrophin-null mice which was associated with AQP4 mislocalization (Amiry-Moghaddam et al., 2003). This would result in increased extracellular potassium that would depolarize neurons and glial cells which in turn leads to tonic depolarization that may improve LTP. However, tonic depolarization may also impair LTP by reducing the driving force of fEPSP or inactivating sodium channels which would decrease the postsynaptic firing during LTP induction (Scharfman and Binder, 2013). Indeed, high extracellular potassium has been shown to clear LTP (Harrison and Alger, 1993).

While the mechanistic link between potassium uptake and AQP4 permeability in astrocytes remains unclear, the colocalization of AQP4 and $K_{ir}$4.1 has suggested a possible functional interaction between the two proteins. It is hypothesized that potassium released into the ECS during neuronal activity is taken up by $K_{ir}$4.1 followed by influx of water through AQP4 in the perisynaptic space. This results in shrinkage of the ECS. Water is then extruded into the perivascular space by AQP4 located at the endfeet and ECS volume returns to its initial state (Wetherington et al., 2008). Interestingly, studies have found evidence against direct functional coupling between the two (Zhang and Verkman, 2008) while modeling studies support AQP4-dependent potassium water transport and suggest that AQP4 deficiency alone may impair potassium dynamics (Jin et al., 2013). Indeed, $K_{ir}$4.1 plays crucial roles in potassium homeostasis and the lack of AQP4 impairs potassium kinetics. Additionally, AQP4$^{-/-}$ mice also displayed increased gap junctional coupling which enhanced spatial buffering of potassium (Strohschein et al., 2011). While it is still unclear why changes in gap junctional coupling occur in AQP4$^{-/-}$ mice, studies have shown that complete disruption of astrocytic gap junctional coupling results in impaired potassium homeostasis (Wallraff et al., 2006). These data suggest that AQP4 deficiency, rather than an effect on gap junctional coupling, directly underlies impairment of potassium uptake kinetics.

### 2.4. Brain-derived neurotrophic factor (BDNF) and synaptic plasticity

The neurotrophin brain-derived neurotrophic factor (BDNF) is a central player in regulating synaptic plasticity. For example, mice with targeted disruption of the BDNF gene exhibit altered basal synaptic transmission and LTP at the SC-CA1 synapse which can be rescued by exogenous application of recombinant BDNF (Patterson et al., 1996). BDNF binds to the low-affinity receptor $p75_{NTR}$ and the high-affinity receptor TrkB (Binder and Scharfman 2004) and the BDNF-TrkB signaling pathway has been established as an underlying mechanism of LTP (Purcell and Carew, 2003; Minichiello, 2009; Park and Poo, 2013). While the role of BDNF in synaptic plasticity has been clearly demonstrated, the influence of AQP4 on activity-dependent BDNF signaling synaptic plasticity is only beginning to be elucidated.

Skucas and colleagues observed impaired LTD after LFS in AQP4$^{-/-}$ slices which was rescued by the BDNF scavenger TrkB-Fc and Trk antagonist K252a. No changes in TrkB receptor levels were identified, however, reduced levels of $p75_{NTR}$ in AQP4$^{-/-}$ mice were detected (Skucas et al., 2011). Low levels of $p75_{NTR}$ may be critical because LTD is mediated by binding of proBDNF to $p75_{NTR}$ (Pang et al., 2004; Woo et al., 2005; Yang et al., 2014). However, application of TrkB antagonist and BDNF scavenger rescued LTD suggesting that the low levels of $p75_{NTR}$ were not necessary to impair LTD in AQP4$^{-/-}$ mice (Skucas et al., 2011). Interestingly, increased mRNA and protein levels of $p75_{NTR}$ was observed in hypoosmolar conditions (Ramos et al., 2007) which is in line with an expanded ECS in AQP4$^{-/-}$ mice (Binder et al., 2004b; Haj-Yasein et al., 2012). Hence, extracellular molecules could be diluted under hypoosmolar conditions (Scharfman and Binder, 2013) which may underlie the alterations in potentiation after TBS and HFS.

LTP at the SC-CA1 synapse is modulated by mature BDNF (Kang and Schuman 1995; Jiang et al., 2003). Previous studies have shown that release of mature BDNF leads to LTP (Kang and Schuman 1995), inhibits LTD (Jiang et al., 2003), and is suppressed by LFS (Aicardi et al., 2004; Yang et al., 2013). Therefore, the delayed LTP in AQP4$^{-/-}$ mice was a surprising finding (Skucas et al., 2011). Mature BDNF is also released by glial cells (Parpura and Zorec, 2010; Perea and Araque, 2010), thus, excessive release of mature BDNF after LFS in AQP4$^{-/-}$ slices may explain the observed LTP after LFS (Scharfman and Binder, 2013). These data indicate a tight regulation of pro- and mature BDNF release for the competition of either LTP or LTD and that BDNF release in regulating synaptic plasticity may be modulated by AQP4.

## 3. AQP4 and cognition

Since AQP4 appears to be required for basic mechanisms of synaptic plasticity, it is plausible that deficiency of AQP4 could lead to specific cognitive impairments (Lu et al., 2008). The influence of AQP4 on cognition has been investigated and the behavioral studies below present interesting findings that further elucidate the potential impact of AQP4 in synaptic plasticity and cognitive functions.

### 3.1. Memory deficits as assessed by Morris water maze (MWM)

A disruption in memory consolidation was discovered in AQP4$^{-/-}$ mice. They displayed a shorter swim path, reduced velocity, and reduced motivation to escape compared to WT mice (Fan et al., 2013; Zhang et al., 2013). The probe tests also revealed impaired spatial retention in AQP4$^{-/-}$ animals (Fan et al., 2013). The aversive motivation may lie in levels of dopamine in the CSN. Dopamine is well known to play an essential role in learning and motivation (Dayan and Balleine 2002; Wise 2004) and previous studies suggest that dopamine may be regulated by AQP4 (Fan et al., 2005; Fan et al., 2008). For instance, AQP4$^{-/-}$ mice were reported to have increased basal extracellular levels of dopamine (Fan et al., 2005; Ding et al., 2007). However, the relationship between increased levels of dopamine and motivation warrants more investigation (Cagniard et al., 2006; Treadway et al., 2012).

AQP4$^{-/-}$ mice displayed a clear dissociation between memory acquisition and spatial retention. The DG not only plays a fundamental role in memory storage and acquisition but is also the site of neurogenesis (Kee et al., 2007; Jessberger et al., 2009; Fan et al., 2013). Studies have shown newly matured neurons incorporating into the spatial memory circuits (Kee et al., 2007) and inhibition of neurogenesis in the DG results in impaired spatial and object recognition (Jessberger et al., 2009). AQP4 is expressed in adult neural stem cells (ANSCs) and is involved in neurogenesis (Zheng et al., 2010). Thus, the lack of AQP4 could potentially block the recruitment of ANSCs to the spatial memory circuits in the DG to stabilize the memory trace. This may also result as a consequence in the absence of AQP4 in promoting cell migration and proliferation (Fan et al., 2013). Although these intriguing findings support a critical role of AQP4 in neurogenesis and memory determination of the exact mechanisms require further investigation.

### 3.2. Fear and object placement (OP) memory deficits

Contextual fear conditioning (CFC) revealed that AQP4$^{-/-}$ mice exhibit significant reductions in immobility and therefore impaired

associative fear memory formation (Li et al., 2012; Yang et al., 2013). However, Skucas et al. (2011) observed an increase in freezing behavior in both WT and AQP4$^{-/-}$ that was not statistically significant. The dissimilarities in findings may reflect different fear conditioning protocols. The hippocampus is known to be dependent on contextual fear memories while the lateral amgydala is dependent on cued fear memories. Thus, the mechanisms for fear memory retrieval for the hippocampus *vs.* lateral amgydala are different (Phillips and LeDoux, 1992; Hall et al., 2001; Li et al., 2012).

Object placement (OP) tests revealed that AQP4$^{-/-}$ did not show preference towards the moved object compared to WT mice (Skucas et al., 2011). These findings indicate that WT mice can differentiate between objects in a familiar and new location while AQP4$^{-/-}$ mice exhibited a deficit in object placement memory (Scharfman and Binder 2013). These memory impairments may be related to different neural circuits. For example, the OP task relies more on prefrontal cortical inputs (Ennaceur et al., 1997; Luine and Frankfurt, 2013). Interestingly, memory performance in the OP task has been previously linked to altered levels of BDNF (Bekinschtein et al., 2007; Francis et al., 2012; Luine and Frankfurt, 2013).

## 4. AQP4 in disease

Given that AQP4 plays a significant role in cognition, it is interesting that AQP4 is also dysregulated in several neurological disorders. Because cognitive impairment often accompanies neurological disorders, we believe there may be a link between disease progression and AQP4 regulation. In the following section, we will discuss the role of AQP4 in Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Multiple Sclerosis (MS), Neuromyelitis optica (NMO), epilepsy, traumatic brain injury (TBI), and stroke. A summary of the role in AQP4 in each disease can be found in Table 1.

### 4.1. Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder that manifests as progressive cognitive decline in middle or old age. Reports of reactive astrocytes in AD have been accompanied with either increased (Yang et al., 2011; Hoshi et al., 2012) or no change (Rodríguez et al., 2006; Pérez et al., 2007) in AQP4 frontal cortex expression. Many patients with AD have amyloid deposits in the walls of the vasculature, a condition known as cerebral amyloid angiopathy (CAA). Both increased (Moftakhar et al., 2010) and decreased (Wilcock et al., 2009) AQP4 immunoreactivity in patients with CAA have been reported. Wilcock et al., 2009 found that as the severity of CAA increased, the levels of AQP4 and dystrophin mRNA levels as well as AQP4 staining around blood vessels decreased (Wilcock et al., 2009). Furthermore, they confirmed the loss of AQP4 localization at astrocytic endfeet in 4 different mouse models of AD with CAA. While no overall changes in AQP4 protein or mRNA levels were noted in any of the transgenic mice, an increase in vascular amyloid deposits was associated with decreased AQP4-positive blood vessels as well as decreased overall dystrophin 1 mRNA and protein levels in the frontal cortex (Wilcock et al., 2009). Therefore, CAA may result in AQP4 mislocalization.

A hallmark of AD is the accumulation of β-amyloid (Aβ) plaques within the brain. Aβ-42 is the major species present in AD whereas Aβ-40 is often found in the arteriolar walls affected by CAA. AQP4 immunoreactivity was absent on the classic Aβ-42 plaques in the dense core but was enhanced at the marginal rims (Hoshi et al., 2012). Larger vessels and capillaries with CAA (Aβ-40-positive vessels) exhibited various degrees of AQP4 expression; intense immunoreactivity was seen around larger vessels showing mild to moderate Aβ-40 positivity compared to Aβ-40-negative vessels (Hoshi et al., 2012). In fact, a loss of AQP4 polarization occurred just after the appearance of the first plaques in the tg-ArcSwe (Yang et al., 2011), PDAPP (Zago et al., 2013), and APP/PS1 (Xu et al., 2015) mouse models of AD. Specifically, downregulation of AQP4 at astrocytic endfoot membranes at sites of perivascular amyloid deposits coincided with an upregulation of AQP4 in the soma and at sites of neuropil surrounding amyloid deposits (Yang et al., 2011; Zago et al., 2013; Xu et al., 2015). Thus, Aβ deposits may alter the expression patterns of AQP4 during the development of AD.

The neurovascular unit (NVU) is a multicellular site of communication composed of a myriad of cell types, including capillary endothelial cells, neurons, astrocytic endfeet, and pericytes. Aβ plaques intercalate and spatially disrupt the astrocytic membrane architecture found within the NVU (Zago et al., 2013). This is undoubtedly related to disruptions in AQP4 polarization. In a mouse model of AD involving an ovariectomy followed by 8 weeks of D-galactose injections, mice exhibited increased hippocampal AQP4 protein expression, astrogliosis, and microarchitectural damage in the neuronal-glial and gliovascular units (Liu et al., 2010; Liu et al., 2012). AQP4$^{-/-}$ mice also exhibit increased Aβ production (Liu et al., 2012) and accumulation (Xu et al., 2015). This may be a direct result of reduced interstitial solute clearance in AQP4$^{-/-}$ mice, including an inability to effectively clear Aβ-40 from the CNS (Iliff et al., 2012).

AQP4$^{-/-}$ mice exhibit exacerbated memory impairment in mouse models of AD. After D-galactose injections, AQP4$^{-/-}$ mice experienced more severe brain oxidative stress, cognitive deficits, and loss of synapse-related proteins (Liu et al., 2012). AQP4$^{-/-}$

**Table 1**
Summary of AQP4 regulation in various neurological disorders.

| Disease | Summary |
|---|---|
| Alzheimer's disease | • AQP4 expression is mislocalzed in the presence of β-amyloid (Aβ) deposits<br>• AQP4 deficiencies may result in reduced ability to clear Aβ and reductions in BDNF production |
| Amyotrophic lateral sclerosis | • Increased levels of AQP4 accompanied by decreased levels of $K_{ir}4.1$<br>• Disruption of BBB integrity, water and $K^+$ homeostasis |
| Parkinson's disease | • AQP4 expression was reduced in blood samples<br>• Reduced levels of AQP4 resulted in a disruption of the inflammatory response |
| Multiple sclerosis | • Both increased AQP4 expression around lesions and stage-dependent loss of AQP4 have been reported |
| Neuromyelitis optica | • Often defined by the presence of anti-AQP IgGs<br>• Heterogeneous expression changes reported |
| Epilepsy | • Mislocalization of AQP4 expression<br>• AQP4$^{-/-}$ mice have prolonged seizure threshold, increased seizure severity, delayed $K^+$ kinetics, and increased edema |
| Traumatic brain injury | • Downregulation of AQP4 expression coincided with maximal vasogenic edema<br>• AQP4$^{-/-}$ mice had reduced water accumulation, intracranial pressure, and lesion volume suggesting a protective role for AQP4 in cellular edema |
| Stroke | • AQP4 expression is altered in a region-specific manner<br>• AQP4 expression may be regulated by HIF-1α |

APP/PS1 mice experienced exacerbated symptoms of AD, including increased Aβ accumulation, CAA, astrogliosis, cognitive deficits, as well as loss of BDNF protein and IL-1β production in the hippocampus and cortex (Xu et al., 2015).

Impaired cognitive function in animal models of AD could be associated with a decreased expression of the presynaptic vesicle protein synaptophysin (SYP) and the postsynaptic density protein-95 (PSD-95) (Liu et al., 2012; Xu et al., 2015). SYP and PSD-95 are known to be altered in the hippocampus and cause memory deficits during the progression of AD (Sze et al., 1997; Xu et al., 2015) which may be linked to pathways that includes PSD-95, BDNF, and NMDAR. For instance, NMDAR stimulation recruits TrkB to the synapse and initiates BDNF signaling to transport new PSD-95 to the synapse (Yoshii and Constantine-Paton, 2010). Decreased expression of SYP and PSD-95 was observed in AQP4$^{-/-}$ OVX-treated mice which is consistent with the decline in spatial learning and memory (Liu et al., 2012). Interestingly, mechanisms underlying memory performance have been previously linked to BDNF (Bekinschtein et al., 2007; Francis et al., 2012; Luine and Frankfurt, 2013). For example, AQP4$^{-/-}$ APP/PS1 mice had lower levels of BDNF in the hippocampus and in the cortex compared to APP/PS1 controls. The deficits in cognition could be attributed to the lack of new PSD-95 to further strengthen the responsiveness of the synapse to BDNF to promote LTP.

The cholinergic system has been previously linked to cognitive deficits in AD (McKinney, 2005; Schliebs and Arendt, 2006) and is also vulnerable to oxidative damage (McKinney, 2005). Cholinergic neurons have also been associated with endogenous levels of estrogen (Gibbs, 1998) which have been correlated to BDNF and memory functions (Bekinschtein et al., 2007; Francis et al., 2012; Luine and Frankfurt, 2013). Thus, the OVX treatment could reduce levels of BDNF through activation of CREB (Shieh et al., 1998; Tao et al., 1998) and sublethal accumulation of Aβ has been shown to suppress CREB activation (Tong et al., 2004). Indeed, AQP4$^{-/-}$ mice exhibited a significant reduction in cholinergic neurons, increased brain oxidative stress, and decreased antioxidant capabilities. Thus, an increase in Aβ and brain oxidative stress with a decrease in SYP, PSD-95, and cholinergic neurons can be attributed to the absence of AQP4 (Liu et al., 2012).

### 4.2. Amyotrophic lateral sclerosis (ALS)

Also known as Lou Gehrig's disease, amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that results in motor neuron deterioration and subsequent muscle weakness and paralysis. Increased AQP4 expression has been reported in the brainstem (Bataveljić et al., 2012), cortex (Bataveljić et al., 2012), and gray matter of the spinal cord (Nicaise et al., 2009; Cui et al., 2014) at the end stages of ALS in the mutant SOD1 transgenic mouse model. Increased AQP4 expression was associated with swollen astrocytic processes surrounding vessels (Nicaise et al., 2009). Alterations in AQP4 expression combined with decreased levels of $K_{ir}$4.1 (Bataveljić et al., 2012) in ALS may result in disrupted water and $K^+$ homeostasis as well as loss of BBB integrity. These changes may alter the microenvironment that normally ensures neuronal health.

### 4.3. Parkinson's disease (PD)

As a result of the loss of dopaminergic neurons in the substantia nigra, Parkinson's disease (PD) causes the slow, progressive loss of motor function coordination. Cardinal motor findings in PD are tremor, rigidity, bradykinesia, and postural instability. Reduced levels of AQP4 were found in blood samples from patients with AD compared to healthy controls (Thenral and Vanisree 2012). To replicate this condition in a mouse model, intraperitoneal injections of methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are used to reproduce the dopaminergic neuron loss and motor symptoms in mice.

AQP4 expression was discovered in the mouse thymus, spleen, and lymph nodes (Chi et al., 2011). When sub-populations of cells, such as B cells, natural killer cells, dendritic cells, macrophages, and T cells, were purified from the spleen and lymph nodes, AQP4 RNA was detected in all cells and subpopulations (Chi et al., 2011). AQP4$^{-/-}$ mice, which do not express AQP4 mRNA in any of these cell types, had lower numbers of CD4$^+$ CD25$^+$ regulatory T cells (Chi et al., 2011). After treatment with MPTP, AQP4$^{-/-}$ mice exhibited a more robust inflammatory response, a greater amount of dopaminergic neuron loss, increased activation of the NF-κB pathway in the midbrain, and elevated levels of both astrogliosis and microgliosis compared to WT mice (Chi et al., 2011; Sun et al., 2016; Zhang et al., 2016). Therefore, AQP4 may be a key regulator of the immune response in PD.

### 4.4. Multiple sclerosis (MS) and neuromyelitis optica (NMO)

Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination throughout the CNS. Neuromyelitis optica (NMO), also known as Devic's disease, is an inflammatory disease of the CNS that selectively affects both the optic nerve and the spinal cord. In Japanese populations, MS involving both the optic nerve and spinal cord is called opticospinal MS (OSMS). Therefore, NMO in Western populations exhibits the same clinical features as OSMS (Tanaka et al., 2007a). In NMO, the immune system develops antibodies (NMO-IgGs), which were discovered to bind to AQP4 but not the related dystroglycan complex proteins (Lennon et al., 2005).

The presence of anti-AQP4 immunoglobulin G (IgG) antibodies is considered a biomarker for NMO (Takahashi et al., 2006; Paul et al., 2007; Hayakawa et al., 2008). Patients with NMO have more lesions than patients with MS and levels of anti-AQP4 antibody positivity correlate with linear lesions (Lu et al., 2010). In fact, patients who were seropositive for anti-AQP4 antibodies showed a higher clinical severity, increased annual relapse rate, higher frequency of brainstem lesions, and hypercomplementemia compared to those without anti-AQP4 antibodies (Matsuoka et al., 2007; Tanaka et al., 2007b; Doi et al., 2009; Asgari et al., 2013). The correlation between anti-AQP4 antibodies and relapse rates, however, has been debated (Chanson et al., 2013; Isobe et al., 2013). Furthermore, anti-AQP4 positive patients showed female preponderance and had a higher age of onset. Therefore, more females also had a recurrent form of NMO (Ketelslegers et al., 2011).

Several studies have tried to elucidate the mechanistic consequences of serum NMO antibodies binding to AQP4. An *in vitro* study determined that the binding of NMO-IgG to astrocytes caused the internalization of AQP4 and altered its expression polarization (Vincent et al., 2008). NMO-IgG also increased BBB permeability and caused natural killer (NK) cell degranulation (Vincent et al., 2008). Hinson et al. reported that NMO IgG causes AQP4 to be endocytosed, which led to a loss of glutamate clearance through the concomitant loss of glutamate transporter-1 (GLT1) (Hinson et al., 2007; Hinson et al., 2008). These findings, however, were refuted by Ratelade et al. (2011). They found that NMO-IgG and AQP4 were rapidly internalized in transfected cell cultures, but no internalization of NMO-IgG, AQP4, or GLT1 occurred in primary astrocyte cultures or *in vivo*. Glutamate uptake by GLT1 was entirely unaffected by NMO-IgG exposure (Ratelade et al., 2011).

AQP4 tetramers are composed of two different splice variants, one long (M1) and one short (M23). The M23 isomer alone is capable of forming orthogonal arrays of particles (OAPs) whereas the M1 isomer is not. Hinson et al. (2012) found that NMO-IgG causes internalization of the M1, but not M23, isomer. This resulted in larger OAPs, impaired AQP4-dependent water flux, tissue swelling,

and increased complement-dependent cytotoxicity (CDC) (Hinson et al., 2012). Although M1 isoform removal and reduced water permeability was confirmed *in vitro* (Melamud et al., 2012), a separate study used super-resolution imaging to show that serum from NMO patients did not alter AQP4 OPA formation in astrocyte cultures (Rossi et al., 2012a). Furthermore, technical concerns of the work done by Hinson et al. (2012) were raised because of the use of N-terminus GFP-labeled AQP4 in clonal singly transfected HEK293 cells after exposure to NMO-IgG. The addition of a fluorescent tag to the N terminus of the M23 isoform affects OAP assembly and prevents the NMO sera from binding to AQP4 (Pisani et al., 2011). In a letter to PNAS, Rossi et al. (2012b) further challenged this work stating that differential internalization is unexpected because M1 and M23 isoforms of AQP4 form tight heterodimers within the membrane. Instead, Rossi et al. found that M1 and M23 exhibited similar single molecule water permeability and it was unaltered after NMO exposure (Rossi et al., 2012b). In transfected cells expressing only M1 or only M23, NMO IgG did cause a more rapid internalization of M23 than M1. When these isoforms were both expressed in cells, M1- and M23-AQP4 commingled in OAPs and were internalized together in response to NMO IgG. In fact, a separate study confirmed that OAP assembly was required for NMO-IgG to recognize and pull down AQP4 (Nicchia et al., 2009). Furthermore, NMO-IgG were able to bind to both the M23 and M1 isoforms (Crane et al., 2009), although NMO-IgG showed a greater affinity to M23 over M1 (Crane et al., 2011). This difference, however, was credited to OAP assembly rather than difference in the M1 and M23N termini (Crane et al., 2011). Finally, NMO sera did not alter OAP size (Rossi et al., 2012b).

AQP4 immunoreactivity is found throughout the healthy rodent brain, particularly on astrocytic endfeet facing abluminal surfaces (Nielsen et al., 1997; Rash et al., 1998; Oshio et al., 2004). In MS, however, increased AQP4 immunoreactivity was observed around lesions (Aoki-Yoshino et al., 2005; Pittock et al., 2006; Sinclair et al., 2007) and preserved AQP4 expression was found within demyelinating lesions (Misu et al., 2006). AQP4 mRNA and protein levels were also upregulated in periplaque demyelinated lesions (Lieury et al., 2014), although stage-dependent loss of AQP4 in MS has been reported (Roemer et al., 2007). Lesions in NMO, on the other hand, exhibited a loss of AQP4 expression, particularly in the perivascular lesions where GFAP staining was weak and IgGs and complements were deposited (Misu et al., 2006; Misu et al., 2007; Roemer et al., 2007). AQP4 expression was increased in reactive astrocytes surrounding the lesions (Misu et al., 2007) Later studies determined that a subset of NMOSD and MS cases exhibited a loss of AQP4 expression in demyelinating lesions whereas other cases showed preserved AQP4 expression in lesions (Matsuoka et al., 2011; Brück et al., 2012; Masaki et al., 2013). Therefore, AQP4 expression changes around lesions are heterogeneous in both MS and NMO. AQP4 exhibits heterogeneous regulation in other spinal cord injuries as well, a topic extensively reviewed in (Yonan and Binder 2016).

The complement system is required to create models of NMO. Lesions were not observed in spinal cord slice cultures (Zhang et al., 2011) or in mice (Saadoun et al., 2010) unless they were exposed to both NMO-IgG and complement. Lesions were also absent in NMO models using AQP4$^{-/-}$ mice (Saadoun et al., 2010; Zhang et al., 2011; Ratelade et al., 2012), suggesting both an AQP4- and complement-dependent pathogenesis. In fact, an activated complement pathway may only be present in NMO (anti-AQP4)-IgG positive patients (Chen et al., 2014). The severity of NMO increased with the inclusions of neutrophils, NK cells, macrophages, TNF-α, IL-6, IL-1β, or interferon-γ (Zhang et al., 2011; Ratelade et al., 2012). A separate study, however, found that injections of human recombinant monoclonal NMO-IgG and human NK-cells caused the loss of AQP4 and GFAP with little myelin loss, suggesting a possible complement-independent pathogenesis (Ratelade et al., 2012).

Targeting the complement pathway exhibits promising therapeutic effects for the treatment of NMO. Neutralizing monoclonal antibodies against C1q prevented NMO-induced CDC and complement-dependent cell-mediated cytotoxicity (CDCC) produced by NK cells *in vitro* (Phuan et al., 2013). Furthermore, anti-C1q antibodies prevented astrocyte damage, precluded demyelination, and reduced inflammatory demyelinated lesions (Phuan et al., 2013). Interestingly, human IgG reduced the size of neuroinflammatory demyelinating lesions, NMO-IgG-mediated CDC, and NMO-IgG-mediated ADCC following the addition of NMO-IgG and human complement to cells *in vitro* (Ratelade et al., 2014). Human IgG had no effect NMO-IgG binding to AQP4, AQP4 cell surface expression, or OAP assembly (Ratelade et al., 2014).

In a proof of concept study, Tradtrantip et al. (2012) developed non-pathogenic recombinant monoclonal anti-AQP4 antibodies that selectively block NMO-IgG binding to AQP4. This prevented complement- and cell-mediated cytotoxicity as well as the development of NMO lesions in an *ex vivo* spinal cord slice model of NMO (Tradtrantip et al., 2012). The bacterial IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS) and the bacteria-derived endoglycosidase S both reduced NMO lesions and abolished complement- and antibody-dependent cell-mediated cytotoxicity without affecting NMO-IgG binding to AQP4 (Tradtrantip et al., 2013a,b). These are promising therapeutic options for treating patients with NMO and their efficacy should be further explored.

### 4.5. Epilepsy

Epilepsy is a group of conditions characterized by the periodic and unpredictable occurrence of seizures due to abnormally synchronized activity among neurons. The most common form is temporal lobe epilepsy (TLE), which is characterized by seizures that originate in the temporal lobe. Early studies using AQP4$^{-/-}$ mice greatly helped elucidate the role of AQP4 in seizure generation and spread. AQP4$^{-/-}$ mice had a greater seizure threshold in the pentylenetetrazol (Binder et al., 2004a) and electrical stimulation (Binder et al., 2006a,b) seizure models. Furthermore, AQP4$^{-/-}$ mice had prolonged electrically-induced seizure duration compared to their WT counterparts (Binder et al., 2006a,b). In the intrahippocampal kainic acid (IHKA) epilepsy model, AQP4$^{-/-}$ mice had more seizures per day than WT mice (Lee et al., 2012b). AQP4$^{-/-}$ mice also had greater tissue edema after kainic acid-induced SE (Lee et al., 2012a). Taken together, these data suggests that although it is harder to induce a seizure in AQP4$^{-/-}$ mice, the seizure phenotype (increased number and duration of seizures) is worse, potentially due to the limited ability to regulate fluid homeostasis.

AQP4 expression is altered in several epilepsy models. Vasogenic edema and areas devoid of AQP4 were observed in the piriform cortex, but not the hippocampus, in a pilocarpine model (Kim et al., 2010). In the chronic phase of the pilocarpine model, AQP4 immunoreactivity was decreased in vacuolized CA1 astrocytes but increased in non- vacuolized astrocytes (Kim et al., 2009). Dorsal hippocampal AQP4 expression was downregulated during the latency period in the IHKA model of TLE (Lee et al., 2012b; Hubbard et al., 2016). AQP4 protein levels were elevated in the sclerotic hippocampus during the chronic phase in this model (Hubbard et al., 2016), which matched what was observed in human tissue from patients with epilepsy (Eid et al., 2005; Das et al., 2012). Total AQP4 protein levels, however, were unaltered at any time point (latency or chronic) examined in the IHKA model (Hubbard et al., 2016). These data suggested a mislocalization of AQP4, rather than a complete up- or down-regulation. To support this, reduced AQP4 adluminal expression with stable or slightly increased abluminal expression were previously reported in the latency phase

(preceding seizures) in the intraperitoneal kainic acid model in rats (Alvestad et al., 2013). Immunogold analysis of the sclerotic hippocampus from patients with TLE also revealed a similar mislocalization of AQP4 expression (Eid et al., 2005). Although an overall increase in AQP4 protein was reported, reduced levels of perivascular AQP4 were found (Lee et al., 2004; Eid et al., 2005). Interestingly, the mislocalization of AQP4 was not restricted to TLE, but was also found in tissue from patients with focal cortical dysplasia type IIB (Medici et al., 2011). In this tissue, staining of AQP4 was weak around the vessels but was strong around the neuropil (Medici et al., 2011). This new distribution of AQP4 would result in less functionally relevant protein throughout the CNS. For more detailed information about AQP4 and epilepsy please see (Binder et al., 2012).

ECS volume and $K^+$ kinetics are largely controlled by astrocytes with AQP4 being a major player in both. Faster ECS diffusion, and therefore ECS expansion, was observed in AQP4$^{-/-}$ mice (Binder et al., 2004b). Furthermore, despite $K_{ir}4.1$ expression and baseline $K^+$ dynamics being unaltered in AQP4$^{-/-}$ mice, delayed K+ kinetics after electrical stimulation (Binder et al., 2006a,b) or cortical spreading depression (Padmawar et al., 2005) were observed. It is possible that the dysregulation of AQP4 in epilepsy may result in slowed de-swelling and therefore slowed decay of extracellular $K^+$ after seizures.

### 4.6. Traumatic brain injury (TBI)

An abrupt impact causing damage to the brain, traumatic brain injury (TBI) results in a broad spectrum of symptoms ranging from mild to severe, depending on the severity of the damage to the brain. AQP4$^{-/-}$ mice exhibited a different disease course compared to WT mice after brain injury. In various models, AQP4$^{-/-}$ mice had reduced intracranial pressure, cell death, water accumulation, astrogliosis, and lesion volume in the acute stage of micro TBI compared to WT mice (Liang et al., 2015; Yao et al., 2015b). As expected, glymphatic pathway dysfunction was worsened in AQP4$^{-/-}$ mice (Iliff et al., 2014).

The role of AQP4 in TBI will depend on the stage of the disease. Zhang et al. (2015) found that in TBI, vasogenic edema occurred first and was then followed by cellular edema. AQP4 expression was downregulated during vasogenic edema but was then upregulated during cellular edema (Zhang et al., 2015). Therefore, the lack of AQP4 during the acute (vasogenic edema) stage of TBI would result in a reduced ability to remove excess water from the brain whereas the lack of AQP4 during a later (cellular edema) stage may prevent cellular damage and swelling.

In various TBI models, including CCI, penetrating ballistic-like brain injury (PBBI), and weight drop models, edema was maximal at the 1 day time point, which coincided with a downregulation of AQP4 mRNA, protein, and immunoreactivity (Ke et al., 2001; Ke et al., 2002; Kiening et al., 2002; Zhao et al., 2005; Cartagena et al., 2014; Liu et al., 2015). AQP4 levels remained downregulated until 48 h in the CCI model (Kiening et al., 2002). More specifically, AQP4 expression was downregulated in regions where edema and BBB disruption were maximal and AQP4 levels were unaltered where the BBB remained intact (Ke et al., 2001). It is possible that AQP4 downregulation also coincided with vasogenic edema following TBI (Zhang et al., 2015).

Many studies have reported increases in AQP4 expression at early time points after injury that coincide with peak increases in brain water content (Taya et al., 2010; Lu et al., 2013; Lopez-Rodriguez et al., 2015; Gupta and Prasad, 2016). Neurological deficits were observed as early as 24 h after injury but neurological scores and AQP4 expression levels recovered by 2 weeks (Lopez-Rodriguez et al., 2015). At later time points, loss of perivascular AQP4 polarization in astrocytic endfoot processes was noted (Iliff et al., 2014). Future studies should focus on the functional consequences of AQP4 expression changes.

Very few human studies on the role of AQP4 in TBI have been conducted. Biopsy specimens from patients with TBI revealed an increase in AQP4 expression from 15 h to at least 8 days after injury whereas no change was observed from 6 to 14 h after injury (Hu et al., 2005). The CSF from patients with severe TBI were taken at the time of hospitalization as well as 3 and 6 days after hospitalization. AQP4 protein was significantly elevated compared to healthy controls (Lo Pizzo et al., 2013). It has been established that patients who suffer from TBI often have cognitive impairment. Therefore, future studies should focus on determining the relationship between AQP4 expression and cognition in patients after injury.

### 4.7. Stroke

A stroke can result when blood flow, and consequently oxygen, to the brain is blocked (ischemic stroke) or by a ruptured blood vessel causing intraparenchymal hemorrhage (hemorrhagic stroke). Ischemic cerebral edema contributes significantly to morbidity and mortality (Sherman and Easton 1980). AQP4 likely plays a role in the pathology of stroke due to the location of AQP4 water channels at the perivascular astrocytic endfeet and hence the control of brain water balance and edema.

In a simple acute water intoxication model of edema, AQP4$^{-/-}$ mice have improved survival and reduced edema compared WT mice (Manley et al., 2000). Similarly, AQP4$^{-/-}$ mice have reduced edema, neuronal cell death, and mortality compared to WT mice in the transient MCAO (Manley et al., 2000; Yao et al., 2015a; Hirt et al., 2017), 4-vessel transient occlusion (Akdemir et al., 2014), and transient bilateral carotid artery occlusion (BCAO) (Katada et al., 2014) models of stroke. Other studies found conflicting results; AQP4$^{-/-}$ mice had higher mortality, neuronal cell loss, gliosis, and brain atrophy after transient MCAO (Shi et al., 2012a,b; Zeng et al., 2012). Similar symptoms, including worsened neurological deficits, brain edema, cell death, and blood-brain barrier leakage were observed in AQP4$^{-/-}$ mice in a mouse model of intracerebral hemorrhage (ICH) (Tang et al., 2010). Therefore, further clarification is necessary.

AQP4 expression may be altered after a stroke. Human patients had increased AQP4 expression in ischemic cortex (Aoki et al., 2003; Mogoanta et al., 2014). This, however, was region-specific. In ischemic grey matter, perivascular AQP4 immunoreactivity was decreased and microvessel expression was weaker, suggesting a loss of polarization compared to healthy controls (Stokum et al., 2015). AQP4 expression in white mater, however, was significantly upregulated (Stokum et al., 2015). After transient MCAO, AQP4 was upregulated in the ischemic cortex, bordering the lesion, and in the lesion core for up to several days after injury (Taniguchi et al., 2000; Okuno et al., 2008; Zheng et al., 2008; Yang et al., 2009; Lee et al., 2013). AQP4 levels were also elevated after ICH (Wu et al., 2010) and in rat pups after MCAO (Badaut et al., 2007). In general, peaks of AQP4 expression may be correlated with peaks of brain swelling after stroke (Ribeiro Mde et al., 2006; Yang et al., 2009). Brain water content was increased after occlusion (Taniguchi et al., 2000; Akdemir et al., 2016) and AQP4 increases were induced during periods of active edema (Badaut et al., 2007).

Many studies did not observe a stroke-induced upregulation of AQP4. This may be because AQP4 regulation varies with time. For example, AQP4 expression was not significantly different from sham control levels at 6, 24, and 168 h after MCAO injury (Ribeiro Mde et al., 2006) or 12–24 h after a 4-vessel occlusion (Akdemir et al., 2014). Lower levels of AQP4, however, were reported in the ischemic cerebral cortex 72 h after transient MCAO (Liu et al., 2008) and in the acute phase after subdural hematoma (Wajima et al., 2013).

The heterogeneity of AQP4 regulation reported in stroke may be due to region-specific dysregulation and/or redistribution of AQP4, rather than a complete loss or gain of protein expression. In support of this, patches of reduced AQP4 expression in the ischemic cortex, but an overall maintenance of AQP4 levels, were found 8 h after transient MCAO (Friedman et al., 2009). Moreover, a loss of perivascular AQP4 expression in the ischemic cortex and striatum was found after transient MCAO (Frydenlund et al., 2006; Stokum et al., 2015) with a partial recovery by 72 h (Frydenlund et al., 2006). The loss of functionally-relevant perivascular AQP4 can have significant consequences for water redistribution throughout the brain.

Transient MCAO models used in these studies vary in the length of occlusion and of reperfusion. For example, AQP4 levels were significantly decreased after MCAO with reperfusion compared to rats that just underwent occlusion (Lu et al., 2011). Both of these factors will also affect the type of edema (vasogenic or cellular) that is occurring. Shorter reperfusion times were correlated with the prevalence of mixed (cerebral intracellular and vasogenic) edema. When the reperfusion time was postponed, cerebral intracellular edema was alleviated while vasogenic edema was not significantly changed (Lu et al., 2011). AQP4 may help reduce vasogenic edema, but the decrease in brain tissue extracellular space may result in a compensatory increase in astrocyte pressure and subsequently cytotoxic edema (Mohamed Mokhtarudin and Payne, 2016). Swelling levels will also depend on extracellular ionic concentrations, which are likely altered after an ischemic stroke (Mohamed Mokhtarudin and Payne, 2016). Details of the model used should all be considering when determining the role of AQP4 in stroke pathology.

The majority on neurological disease research, such as on epilepsy, TBI, and stroke, are done on male rodent models. Sex differences, however, are present. Female mice had a smaller infarct volume and less edema after MCAO (Shin et al., 2011). AQP4 expression in the ischemic cortex was downregulated in male mice but was mostly preserved in female mice (Shin et al., 2011), suggesting an entirely different mechanism of pathology. These sex differences disappeared after females were ovariectomized and were reversed again by estrogen replacement (Shin et al., 2011). Ovariectomized female mice with physiologically relevant restoration of progesterone exhibited decreased survival and increased brain water content after MCAO (Coomber and Gibson 2010). AQP4 protein levels, however, were unaffected (Coomber and Gibson 2010). Cultured rat astrocytes exposed to oxygen glucose deprivation exhibited increased AQP4 expression; this was attenuated by progesterone (He et al., 2014). The sex differences in neurological disorders and the effects of hormones on disease progression need to be explored further.

It is no surprise that hypoxia plays a major role in the pathology of stroke. HIF-1α expression was upregulated after MCAO in rats (Higashida et al., 2011; Lee et al., 2013). Inhibition of HIF-1α by 2-methoxyestradiol (2ME2) suppressed edema and ischemia-induced expression of AQP4 (Higashida et al., 2011). The anesthetic propofol reduced edema, BBB disruption, AQP4 and HIF-1α overexpression, infarct volume, and neurologic deficits after MCAO (Zheng et al., 2008; Lee et al., 2013). These studies stress the importance of HIF-1α in stroke, but the exact mechanisms of HIF-1α regulation and its potential as a therapeutic target remain incompletely understood.

In summary, AQP4 expression is likely altered after a stroke. How AQP4 expression changes, however, is seemingly contradictory from one study to the next. The reason for the heterogeneity in these findings may be accounted for by (i) variations in the stroke models used, (ii) the consequential types of edema formed, (iii), times points examined, (iv) region of the brain explored, (v) type of expression (protein, mRNA, or immunoreactivity) examined, and (vi) the sex (predominately male) used in each model. Furthermore, these factors will affect the therapeutic potential of the numerous treatment strategies that have been tested thus far. Nonetheless, AQP4 is a promising therapeutic target and should be considered in future studies on stroke.

## 5. Conclusion

Alterations in synaptic plasticity and cognition have been implicated in diverse neurological diseases. For example, patients with AD have problems encoding new memories and declarative and nondeclarative memories both decline gradually (Selkoe 2002). In PD, visuospatial, memory, and executive functions are impaired and are connected to changes in dopaminergic and cholinergic systems (Dubois and Pillon, 1997). Patients with epilepsy also experience marked cognitive and behavioral deficits (Helmstaedter et al., 2003). The studies reviewed above give a glimpse into how diminished expression and/or altered localization of AQP4 may affect cognitive function in pathogenesis. AQP4 deficiency-promoted decrease in BDNF signaling is just one potential mechanism linking AQP4 to cognitive impairment in the diseased brain. It will be interesting in future studies to further investigate how AQP4 impacts distinct types of memory and whether memory impairments observed in AQP4$^{-/-}$ mice can be rescued. Understanding of astrocytic AQP4-dependent synaptic plasticity and memory mechanisms may lead to new therapeutic strategies and astrocyte-based “nootropics” (memory-enhancing or “smart” drugs).

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