Brain Research Bulletin xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

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

Jacqueline A. Hubbard, Jenny I. Szu, Devin K. Binder*

Center for Glial-Neuronal Interactions, Division of Biomedical Sciences, School of Medicine, University of California, Riverside, United States

ARTICLE INFO

Article history:
Received 4 November 2016
Received in revised form 27 February 2017
Accepted 28 February 2017
Available online xxx

Keywords:
AQP4
Astrocyte
Cognition
Epilepsy
Neuromyelitis optica
Stroke

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

* Corresponding author at: 1247 Webber Hall 900 University Avenue, University of California, Riverside, CA 92521, United States.
E-mail address: dbinder@ucr.edu (D.K. Binder).

http://dx.doi.org/10.1016/j.brainresbull.2017.02.011
0361-9230/

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 $K_{ir}4.1$

Please cite this article in press as: Hubbard, J.A., et al., The role of aquaporin-4 in synaptic plasticity, memory and disease. Brain Res. Bull. (2017), http://dx.doi.org/10.1016/j.brainresbull.2017.02.011