CNS Neuroscience & Therapeutics

REVIEW

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Involvement of Aquaporin 4 in Astrocyte Function and Neuropsychiatric Disorders

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Keywords
Aquaporin 4; Astrocytes; Central nervous system; Neuropsychiatric disorders.

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Received 2 January 2014; revision 14 March 2014; accepted 14 March 2014

SUMMARY

Aquaporin 4 (AQP4) is the main water channel in the central nervous system (CNS) and specifically localized to astrocyte processes. Recent studies indicate that AQP4 regulates various biological functions of astrocytes, including maintaining CNS water balance, spatial buffering of extracellular potassium, calcium signal transduction, regulation of neurotransmission, synaptic plasticity, and adult neurogenesis, while under neuropathological conditions, AQP4 has a role in astrogliosis and proinflammatory cytokine secretion. In addition, accumulating evidence suggests that, besides cerebral edema, neuromyelitis optica and epilepsy, AQP4 participates in the onset and progression of Alzheimer disease, Parkinson disease, depression, and drug addiction. This review summarizes recent findings and highlights the involvement of AQP4 in astrocyte function and neuropsychiatric disorders.

doi: 10.1111/cns.12267

Introduction

Aquaporins (AQP), also known as water channels, are widely expressed on cell membranes and integral for transporting water and other small molecules, such as glycerine, selectively and efficiently [1]. To date, at least 13 AQP members have been found in mammals [1]. In the central nervous system (CNS), three water channels (AQP1, AQP4, and AQP9) have been identified [2]. AQP1 is mainly localized to the apical membrane of choroid plexus epithelial cells and involved in the secretion of cerebrospinal fluid [3,4]. AQP9 expression is found in tanycytes mainly localized in the circumventricular regions and catecholaminergic neurons in the hindbrain and implicated in brain energy metabolism [5,6]. AQP4 is the predominant water channel in the CNS and distinctively expressed in astrocyte processes and the basolateral cell plasma membrane of ependymal cells throughout the brain and spinal cord [7,8]. Great progress has been made on the biological characteristics and functions of AQP4 in the CNS, compared with the relatively limited studies on AQP1 and AQP9.

Here, we review literature regarding the involvement of AQP4 in the biological function of astrocytes and the pathophysiological processes of neuropsychiatric disorders.

Regulating Astrocyte Function

Astrocytes are the most abundant glial cells in the mammal brain and responsible for a wide variety of essential functions in the physiology and pathology of the CNS. They maintain brain fluid, iron, and transmitter homeostasis, regulate neural signal transduction, and secret several neural growth factors, such as brain-derived neural factor (BDNF) and glial-derived neural factor (GDNF) [9,10]. Moreover, astrocytes undergo variable degrees of activation (reactive astrogliosis) and produce proinflammatory cytokines in respond to all forms of brain injury and disease [11].

In mice, the functions and biological features of astrocytes are altered upon AQP4 gene deletion. Evidence for the involvement of AQP4-based rapid water transport in astrocyte function is summarized below.

Establishment and Maintenance of the CNS Water Homeostasis

Astrocytes regulate water exchange between the brain, blood, and within brain compartments through AQP4 [12]. AQP4 knockout ($AQP4^{-/-}$) mice were shown to exhibit slightly increased baseline water content in the brain and spinal cord,

compared with wild-type ($AQP4^{+/+}$) littermates [13–15]. AQP4 also plays a key role in the water uptake of the brain after birth. Early studies reported that AQP4 expression levels in the rat cerebellum were extremely low in the first postnatal week, but significantly increased in the second week [16]. More recent studies revealed that increased AQP4 expression levels partially relate to decreased brain water content in postnatal mice [17,18]. Furthermore, a significant delayed decrease in brain water content occurs in the newborn systemic or conditional $AQP4^{-/-}$ mice, providing direct evidence for a role of AQP4 in postnatal brain water uptake [18,19].

Potassium Spatial Buffering

Regulating neuronal electrical activity is one of the important physiological functions of astrocytes; the process involves spatial buffering and uptake of extracellular K^+ [20]. During the repolarization process, K^+ channels on the neuronal cell membrane open, causing the concentration of K^+ to increase within the extracellular space. Astrocytes take up excess K^+ through the inward rectifier potassium channel (Kir 4.1). K^+ is then redistributed through the astroglial syncytium via gap junctions, thereby stabilizing neuronal activity [21]. AQP4 gene deletion resulted in delayed water transport coupling extracellular K^+ clearance, which subsequently affected neuroexcitation. This view is supported by the phenotype analysis of $AQP4^{-/-}$ mice that showed impaired vision [22], hearing [23] and olfaction [24], as well as reduced seizure threshold, increased seizure duration, and slowed K^+ kinetics [25–27] (Figure 1).

Calcium Signal Transduction

Ca^{2+} signaling is a characteristic form of cellular excitability that serves as a mediator of bidirectional interactions between neurons and astrocytes [9]. Astrocytic Ca^{2+} signaling also plays a role in neuronal death following ischemia [28]. Now there is evidence for a critical role of AQP4 in astrocyte Ca^{2+} signal transduction. Using *in vivo* two-photon imaging, Thrane and colleagues demonstrated that conditional deletion of AQP4 reduced hypoosmotic stress-evoked Ca^{2+} signaling in astrocytes [29]. Their *in vitro* experiments further suggested that AQP4-dependent Ca^{2+} signal transduction is mediated in part by autocrine purinergic signaling [29]. Apart from affecting the pathological outcome of cerebral edema, AQP4-dependent Ca^{2+} signals may mediate astrocyte–astrocyte or astrocyte–neuronal communication in normal physiological conditions, hereby providing a sophisticated means for information exchange in the CNS (Figure 1).

Regulation of Neurotransmission

Glutamate is the most prominent neurotransmitter in the brain. Astrocytes mediate glutamate uptake by excitatory amino acid receptors [30]. Glutamate uptake is also accompanied by water

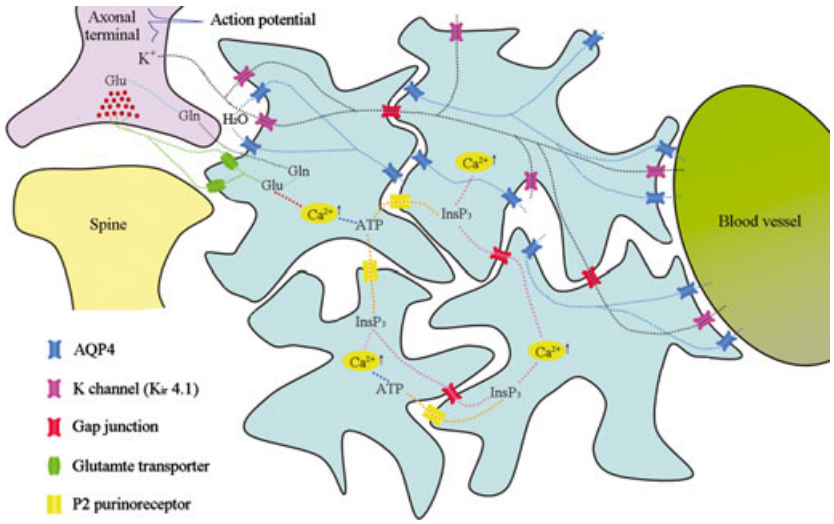

Figure 1 AQP4 involvement in the regulation of CNS water, iron, and glutamate homeostasis and glial calcium wave propagation. (1) Potassium is released into the extracellular space (ECS) during repolarization of the action potential. Astrocyte processes surrounding the synapse take up excess K^+ through inward rectifier potassium channels Kir 4.1 (local potassium buffering), redistribute the K^+ through the astroglial syncytium via gap junctions (spatial potassium buffering), and release K^+ through Kir 4.1. (2) Glutamate released during synaptic activity is removed from the ECS mainly by glutamate transporters on the astrocyte processes. After entering the astrocytes, glutamate is converted into glutamine, which is then transported back to the presynaptic terminal for synthesizing glutamate. The glutamate–glutamine shuttle allows for sustained glutamatergic synaptic transmission and prevents postsynaptic neurons from glutamate excitotoxicity. (3) Intracellular glutamate can also activate calcium signals in astrocyte processes enwrapping synaptic contacts. Calcium signals propagate through the astroglial syncytium via ATP-P2 purinoreceptor-inositol trisphosphate ($InsP_3$) pathway. (4) AQP4 facilitates water entry into astrocyte processes surrounding the synapse, transports water through the astroglial network, and releases distantly into the ECS surrounding microvessels. The AQP4-mediated rapid transport of intercellular water would drive reuptake of K^+ and glutamate and Ca^{2+} signaling transduction by astrocytes, because water serves as transport medium for these substances.

transport, which can cause astrocyte processes to swell around the synapses, resulting in a reduction in the extracellular synaptic space during synaptic transmission and processing [31]. To restore extracellular space volume, astrocytes transport water further into the surrounding capillary via AQP4 located in the perivascular endfeet (Figure 1). Both *in vitro* and *in vivo* evidence indicates that AQP4 gene deletion in mice downregulates glutamate transporter 1 expression and impairs glutamate uptake ability [32–35]. Previous studies have also suggested an involvement of AQP4 in the metabolism of dopamine, serotonin, and other neurotransmitters [36,37].

Adult Neurogenesis

Adult neurogenesis mainly occurs in the subventricular zone (SVZ) of the lateral cerebral ventricle and the subgranular zone (SGZ) of the dentate gyrus, where a large number of neural stem/progenitor cells reside [38]. In both locations, astroglia are the stem elements that produce neurons. These "stem" astrocytes differ from "classical" mature astrocytes by radial morphology, specific expression of the protein nestin, and for some astrocytes, the formation of cilia [39]. *In vitro* experiments showed that AQP4 gene deletion in mice impaired proliferation, migration, and neuronal differentiation of adult neural stem cells [40]. The deletion also disrupted fluoxetine treatment-induced adult mouse hippocampal neurogenesis under both basal and chronic mild stress-evoked depressive conditions [41]. In physiological conditions, adult $AQP4^{-/-}$ mice showed altered neurogenesis in SVZ, but not in SGZ, compared with $AQP4^{+/+}$ controls [41]. The discrepant roles of AQP4 in adult SGZ and SVZ neurogenesis may be due to the different microenvironments; further studies are necessary to explore the underlying mechanisms.

Neurotrophin-dependent Synaptic Plasticity

Astrocytes mediate synaptic plasticity via secretion of neurotrophic factors such as BDNF and GDNF [9]. Recent studies have shown that AQP4 is involved in the regulation of neurotrophic factor-dependent synaptic plasticity. $AQP4^{-/-}$ mice demonstrate impaired BDNF-dependent long-term potentiation (LTP) [42] and long-term depression (LTD), which could be rescued by a scavenger of BDNF or blockade of Trk receptors [42]. In addition, AQP4 gene deletion in mice was shown to exacerbate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic degeneration associated with inhibited astroglial proliferation and GDNF protein synthesis [43]. Adult $AQP4^{-/-}$ mice exhibited defects in consolidation memory and location-specific object memory [42,44,45], which is consistent with impaired neurotrophin-dependent synaptic plasticity. These findings highlight that AQP4 has a role in synaptic plasticity and cognitive function, although the exact mechanisms warrant further investigation.

Astrocyte Migration and Reactivation

Reactive astrogliosis and glial scar formation are hallmarks of all brain injuries and diseases and therefore may exert a number of essential beneficial functions in response to CNS insults [11]. Astrocyte migration toward the lesion is the key step toward glial scar formation and is regulated by various factors, including growth factors, cytokines, and mediators of innate immunity [46]. There is compelling evidence from *in vitro* and *in vivo* studies that suggest a critical role for AQP4 in astrocyte migration. Compared with $AQP4^{+/+}$ controls, primary cultured astrocytes from $AQP4^{-/-}$ mice were shown to have similar morphology, adhesion, and proliferation, but significantly impaired migration ability in the wound healing assay and the transwell Boyden chamber assay [47]. Consistent with these results, using the mouse cortical stab injury model, implanted $AQP4^{-/-}$ astrocytes, prelabeled with a fluorescent dye, showed greatly impaired migration toward the injured site [48]. AQP4-mediated astrocyte migration may facilitate water influx across lamellipodia at the leading edge of a migrating cell and promote membrane protrusion, although the exact mechanism remains unclear [49,50]. AQP4 gene deletion in mice appeared to inhibit astrocyte proliferation, reactivation, and scar formation in severe traumatic brain and spinal cord injuries [48,51], and in chemical agent-induced neurodegeneration [43,52,53]. Taken together, these results suggest that AQP4 is a unique target for regulating astrocyte activation in various CNS disorders and pathologies.

Secretion of Proinflammatory Cytokines

In response to different kinds of stimulation, reactive astrocytes can exert either pro- or antiinflammatory potential, which is determined by context-specific signaling mechanisms [46]. *In vitro* cultured studies have shown that lipopolysaccharide (LPS)-induced TNF-alpha and IL-6 secretion was reduced in $AQP4^{-/-}$ astrocytes, while increased in adenovirus transfected AQP4 overexpression astrocytes [54]. Likewise, attenuated neuroinflammation was observed in $AQP4^{-/-}$ mice following intracerebral injection of LPS [54]. These results demonstrate the role of AQP4 in promoting cytokine secretion from reactive astrocytes. However, other studies have shown AQP4 gene deletion in mice to increase secretion of proinflammatory factors in the heart following treatment with a β-receptor agonist, isoproterenol, resulting in the aggravation of cardiac failure and arrhythmias [55]. These discrepant results indicate that AQP4 plays different proinflammatory roles in different pathological conditions. The mechanism still requires further analysis.

Involvement in Neuropsychiatric Disorders

Reactive astrocytes play either a primary or contributing role in CNS disorders, either via loss of normal astrocyte functions or gain of abnormal effects [56]. Protection of astrocyte function has been implicated as a far more effective strategy than direct protection of neurons in neurological disorders [10]. Thus, identifying molecular targets for functional regulation of astrocytes and elucidating their therapeutic potential have important theoretical and practical significance. There are several in-depth, extensive reviews on the role of AQP4 in astrocyte dysfunction under various neuropathological conditions, such as stroke, cerebral edema, neuromyelitis optica, and epilepsy [57–61]. Here, we

only summarize the pathophysiological roles of neurodegenerative diseases including Alzheimer disease (AD), Parkinson disease (PD), and psychiatric disorders, such as depression and drug addiction.

Alzheimer Disease

Alzheimer disease is the most common neurodegenerative disease among the elderly and characterized by beta-amyloid (Aβ) plaque deposition, neurofibrillary tangles, and neuronal and synapse loss in learning and memory related regions [62]. Recent studies have suggested that AQP4 is an important functional regulator on astrocyte plasticity and involved in the progression of AD. Altered AQP4 expression in astrocytes has been observed in the brain tissues of patients with AD and several AD models, for example, upregulated expression around Aβ plaques, or loss of expression from endfoot membranes at vascular amyloids [63–66]. *In vitro* experiments have shown that $A\beta_{1-42}$ increases AQP4 expression in cultured mouse cortical astrocytes when present at low concentrations, but decreases AQP4 expression when at high concentrations. AQP4 gene deletion reduces $A\beta_{1-42}$-induced astrocyte activation and apoptosis, which is associated with a reduction in the uptake of Aβ via decreased upregulation of low-density lipoprotein-receptor-related protein-1 [67]. *In vivo* studies on APP/PS1 transgenic AD model mice further revealed that AQP4 gene deletion impairs exogenous Aβ clearance from brain parenchyma [68] and exacerbates spatial learning and memory defects associated with more severe Aβ plaque deposits and synaptic protein loss (unpublished data). These *in vitro* and *in vivo* results highlight that AQP4 can be considered a molecular target for Aβ metabolism and clearance in AD.

Parkinson Disease

Parkinson disease is another common neurodegenerative disease that generally strikes middle-aged adults. To date, there are several hypotheses on the pathogenesis of PD, of which include the neuroinflammatory hypothesis [69]. Evidence from several recent studies indicates an involvement of AQP4 in the onset and progression of PD. AQP4 mRNA levels were shown to be significantly downregulated in the plasma of PD patients, compared with normal subjects [70]. AQP4 gene deletion caused severe dopaminergic neuronal loss and microglial inflammation induced by systemic MPTP injection [43]. Further studies revealed that AQP4 deficiency decreases CD4(+) CD25(+) regulatory T cells, resulting in hyperactive immune responses, potentially contributing to the increased severity of PD [71]. The specific mechanism of AQP4 in PD pathogenesis warrants further investigation.

Depression

Increasing evidence indicates that adult hippocampal neurogenesis plays a key role in the pathogenesis of depression [72]. Fluoxetine is a common antidepressant drug, and its therapeutic action is mainly via promoting hippocampal neurogenesis [73]. As mentioned earlier, AQP4 gene deletion suppresses fluoxetine-induced hippocampal neurogenesis in the CMS mouse model of depression [41]. *In vitro* experiments also showed that AQP4 deficiency inhibits fluoxetine-induced proliferation of cultured NSCs [41]. AQP4 might therefore serve as a new target for antidepressant therapy.

Addiction

Addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug or the practice of a harmful activity. Studies have reported that cocaine-induced addiction mainly results from alterations in dopaminergic neurotransmission from the ventral tegmental area to the nucleus accumbens [74,75,76]. $AQP4^{-/-}$ mice have shown to exhibit reduced spontaneous activity and extracellular dopamine levels in nucleus accumbens following exposure to cocaine [77]. Repeated cocaine administration significantly decreased cellular proliferation in the hippocampal SGZ, and AQP4 gene deletion resisted this reduction. Further studies have suggested that AQP4 is involved in the negative regulation of neurogenesis by cocaine via PKC-mediated signal transduction [78].

Concluding Remarks

Accumulating evidence supports the notion that glial water channel AQP4 not only plays important physiological functions in the normal CNS, but also participates in a variety of neuropsychiatric disorders. AQP4 may serve as a functional regulator of astrocytes for the treatment of CNS diseases or injuries. AQP4 regulates multiple functions of astrocytes and is also extensively expressed in peripheral organs and tissues; thus, the potential side effects of AQP4 drugs, such as agonists, antagonists, as well as opening or blocking agents, should be noted for treatment of CNS diseases associated with astrocyte dysfunction.

Acknowledgements

This work was supported by grants from the National Nature and Scientific Foundation of China (No. 81271210).

Conflict of Interest

The authors declare no conflict of interest.

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