Review Article

The Great Significance of Research into the Physiological Relevance between AQP4 and Vasopressin for Studying Alzheimer's Disease

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Abstract

Aquaporin 4 (AQP4), which is the predominant aquaporins (AQPs) isoform in the adult brain, is specifically localized to astrocytes. Current findings regarding AQP4 and various neurological diseases have initiated our interest in unraveling the mystery of AQP4 function in Alzheimer's disease (AD), which is a progressive neurodegenerative disorder characterized by the loss of memory and cognitive disturbances; however, far less is known regarding the precise mechanisms. Vasopressin plays an important role in the regulation of central nervous functions, including learning and memory. Research into vasopressin might contribute to clarification of the neuroprotective effect of AQP4 against AD. Currently the research regarding the functional interaction of AQP4 and vasopressin has demonstrated to be of great significance for studying AD. Here we review the interaction of AQP4 and vasopressin in astrocyte that might have a pivotal role in the regulation of distinct cellular responses directed to neuropretection against AD, as experimental results strongly emphasize the importance of this topic for future investigations.

Keywords: Alzheimer's disease; AQP4; Vasopressin; Astrocyte

Abbreviations: AD: Alzheimer's Disease; AQPs: Aquaporins; NMO: Neuromyelitis Optica; MS: Multiple Sclerosis; LTP: Long-Term Potentiation; LTD: Long-Term Depression; LRP1: Lipoprotein Receptor-Related Protein-1; OGD: Oxygen-Glucose Deprivation

Introduction

Since Alzheimer's disease (AD) prevalence is age-related and the aging population is progressively growing up, a dramatic increase of the disease is expected in the coming decades [1]. Research has indicated that 115.4 million people may be living with dementia by 2050. The pathogenesis of AD is a complex process involving both genetic and environmental factors [2]. Despite these complexities, extensive research has laid the foundation of current understanding of the etiology and pathogenesis of AD [3,4], and many hypotheses have been put forward for AD pathogenesis, including cholinergic hypothesis, tau hypothesis and amyloid cascade hypothesis [2]. Current therapies may ease symptoms by providing temporary improvement and reducing the rate of cognitive decline. More significant research efforts should be directed toward clarifying the etiology and pathogenesis of AD as well as more adequate therapies against AD. Research into the development of drugs aimed at the treatment of AD via various targets has great potential for success [5]. Aquaporins (AQPs) are water-channel proteins on the plasma membrane that play critical roles in the control of cellular water content. Aquaporin 4 (AQP4) is the predominant AQP isoform in the adult brain, which is previously demonstrated to be associated with demyelination and neuroinflammation in chronic and acute brain diseases [6-12]. The possible link between neuroinflammation and AQP4 was first suggested in Neuromyelitis Optica (NMO) [13]. And it has been suggested that the pathogenesis of many clinical diseases, such as NMO, Multiple Sclerosis (MS) and brain injuries, is related to the regulation of AQP4 expression [14]. Current evidence has indicated that brain AQP4 is involved in various astrocytic functions related to neurological diseases, including brain fluid and ion homeostasis [15-17], potassium uptake and release by astrocytes [18], astrocyte migration and glial scarring [19,20], neural signal transduction [21], pro-inflammatory factor secretion [22], astrocyte-to-astrocyte cell communication [23] and synaptic plasticity [24]. There is growing evidence that glia play a role In Long-Term Potentiation (LTP) [25-29], which could subsequently be influenced by AQP4, for that AQP4, is specifically localized to astrocytes. Recent studies have examined LTP, Long-Term Depression (LTD), and the behavior in AQP4 knockout and wild-type mice to gain additional insights into its potential roles. Thus AQP4 could be the promising target for AD treatments [30]; however, far less is known regarding the precise molecular mechanisms. It's known that the water balance and neurohormone release in the neurohypophysis are processes that are closely interconnected. Vasopressin is a nonapeptide and neurotransmitter or neuromodulator; it plays an important role in the regulation of central nervous functions, including learning and memory. Numerous studies have shown that vasopressin and its analogs can improve learning and memory-related performance in experimental animals [31]. Both AQP4 and vasopressin could play roles in preventing the impairment of cognitive function in AD patients. Recently various studies have shown functional interaction of AQP4 and vasopressin in astrocyte that might have a pivotal role in the regulation of distinct cellular responses directed to neuronal preservation and neuropretection against AD, thus a deeper research into the functional interaction of AQP4 and vasopressin could have promising significance for clearing AD pathogenesis and exploring potential target for AD treatments. Furthermore, AQP4 could be considered a molecular target for Aβ metabolism and clearance in AD [30]; more efforts directed toward clarifying their physiological relevance may help clear the promising neuroprotective effect of AQP4 and vasopressin against AD, and clarify the closely interconnected

processes of water balance and neurohormone release in anti-AD neuroprotective mechanisms.

AQP4 Is associated with alzheimer's disease

LTP is a persistent strengthening of synapses based on recent patterns of activity. Impaired LTP have a role in AD. Skucas et al. [24] have investigated hippocampal synaptic plasticity and spatial memory function in mice with a deletion of the astrocyte-specific channel AQP4, and it was the first to demonstrate that LTP changed in AQP4 knockout mice using electrophysiology. The study of Scharfman et al. [32] was the first study to demonstrate the direct effect of AQP4 on specific forms of activity-dependent plasticity. Thereafter, studies that have investigated the effect of AQP4 on AD have gradually increased. AQP4 may mediate the clearance of amyloid beta peptides (Aβ) and exert neuroprotection against AD [33]. Low-density Lipoprotein Receptor-Related Protein-1 (LRP1) is expressed in the perivascular end feet of astrocytes and brain microvascular endothelial cells; it mediates a continuous efflux of brain Aβ into the circulation [34]. MAPKs are a family of serine/threonine kinases that comprise 3 major subgroups: ERK, JNK and p38 MAPK. The ERK pathway plays a major role in the regulation of cell growth and differentiation, whereas the JNK and p38 MAPK cascades are most frequently associated with astrocyte activity [35]. Aβ has been demonstrated to activate G-protein-coupled transmembrane receptors, which induces a transient increase in the phosphorylation of ERK1/2 [36]. Moreover, the internalization of Aβ results in mitochondrial dysfunction, which induces the generation of reactive oxygen species and, in turn, causes a sustained upregulation of phospho-p38 MAPK and phospho-JNK [37,38]. Intriguingly, several studies have demonstrated that the expression of AQP4 is regulated by MAPKs in response to changes in osmolality [39-41]. Hyperosmotic stress has also been reported to increase AQP4 through a p38 MAPK-dependent pathway in cultured rat astrocytes [40]. Nito et al. [42] examined the role of MAPK pathways in AQP4 regulation in rat primary astrocytes using Oxygen-Glucose Deprivation (OGD) injury and the immunoreactivity of p38 MAPK and AQP4 in brain edema formation; the authors further hypothesized that MAPK pathways, particularly p38 MAPK, mediate AQP4 expression in cortical astrocytes after in vitro and in vivo ischemic brain injuries. Yang et al. [33] demonstrated that AQP4 deficiency decreases LRP1 upregulation and Aβ uptake, which thus attenuates changes in MAPK signaling pathways and ultimately reduces astrocyte activity. Therefore, AQP4 may be significantly important in the upregulation of LRP1 and the clearance of Aβ (Figure 1). Thus, AQP4 is a molecular target for AD, and it is significant to explore the novel roles of AQP4 in the pathogenesis of neurological disorders.

In addition, AQP4 may influence potassium (K^+) and calcium (Ca^{2+}) ion transport which plays decisive roles in the pathogenesis of AD [30,43]. AQP4 deficiency may impair learning and memory, in part, through glutamate transporter-1 (GLT-1) [44-46]. Furthermore, AQP4 knockout is involved in neuroinflammation and interferes with AD [47-50]. Ample evidence has indicated that the regulation of astrocyte functions via AQP4 may offer a new therapeutic option for AD [51].

Relationship of vasopressin and alzheimer's disease

Aβ is crucially involved in AD as the main component of the amyloid plaques found in the brains of Alzheimer patients. It is interesting that vasopressin and its receptors are present in the same brain regions as Aβ deposits. There are several studies that have demonstrated vasopressin and its analogues, in contrast to Aβ, may function as memory-facilitating peptides and can improve learning and memory-related performance in experimental animals [31]. For example, in the 1990s, [Arg8]-vasopressin (AVP) administered systemically or centrally was demonstrated to
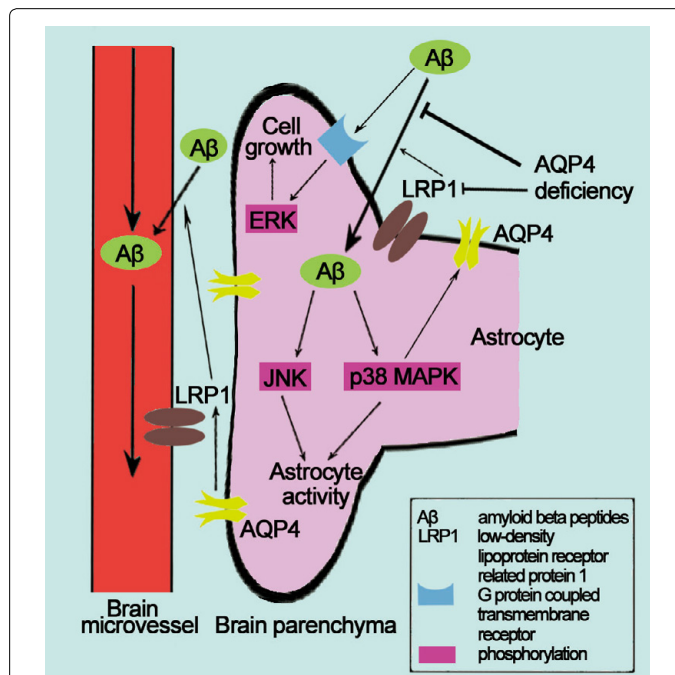

Figure 1: The involvement of AQP4 and LRP1 in Aβ clearance from the brain to the circulation. Aβ could activate G-protein-coupled transmembrane receptors, which thus increases ERK1/2 phosphorylation. AQP4 may increase LRP1 and mediate the internalization of Aβ, which, in turn, causes sustained upregulation of phospho-p38 MAPK and phospho-JNK. Furthermore, p38 MAPK may mediate AQP4 expression in cortical astrocytes, which has been demonstrated in in vitro models and in vivo ischemic brain injuries. The increase in ERK1/2 phosphorylation plays a major role in the regulation of cell growth and differentiation, whereas the upregulation of phospho-p38 MAPK and phospho-JNK induces astrocyte activity.

facilitate the consolidation and retrieval processes of active [52], working and reference memory in the radial maze [53]. With respect to the electrophysiological mechanism of AVP in the improvement of memory function, one of the most important research techniques focuses on central synaptic plasticity, such as hippocampal LTP. Although inconclusive, many experiments support a facilitatory action of AVP on LTP [54,55]. Jing et al. [56] indicated for the first time that AVP, as a memory-facilitating peptide, could effectively protect against Aβ-induced impairment of LTP via the upregulation of synaptic plasticity in the hippocampal CA1 region. The authors suggested that pretreatment with various concentrations of AVP dose-dependently prevented the Aβ-induced suppression of LTP and enhanced high frequency stimulation (HFS)-induced LTP in the hippocampal CA1 region instead of affecting baseline synaptic transmission. These results are supported by the study of Pan et al. [57] who demonstrated that centrally administered AVP protects against Aβ-induced memory decline in the Morris water maze test. Intriguingly, a recent study conducted by Varga et al. [58] identified increased levels of AD-related markers; memory deficits were only observable in vasopressin-deficient animals. Furthermore, the tissue samples were obtained from the parietal cortex, in which dysfunction is an important characteristic of early AD [59]. Thus, the study by Varga is a canonical paper in support of the beneficial effect of central AVP in the prevention and treatment of AD.
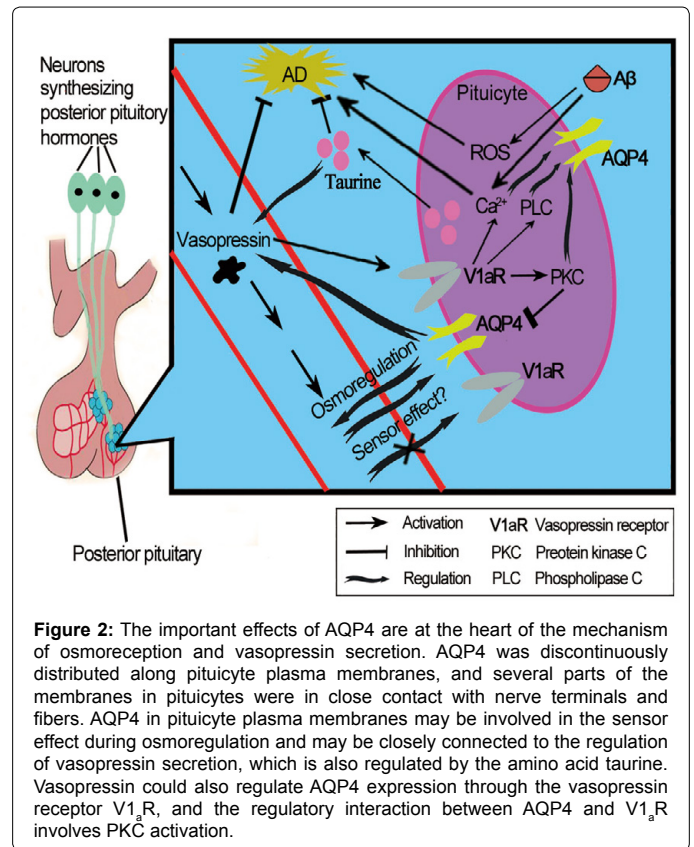
Vasopressin might be one factor in the explanation of the neuroprotective mechanisms of AQP4 against alzheimer's disease

Although the main function of AVP is antidiuresis in the kidney, it

plays a key role in stress-related psychiatric diseases, such as depression [60], which is a marked symptom in preclinical AD as previously discussed. A study conducted by Mesbah-Benmessaoud et al. [61] was the first study to describe the distribution of AQP4 throughout the neural lobe of the adult mouse hypophysis, and they demonstrated that AQP4 is abundant in the mouse hypophysis, mainly in the neural lobe, which was recently described in the rat pituitary gland [62,63]. AQP4 was discontinuously distributed along plasma membranes of pituicyte, which is one kind of astrocyte. Some parts of the pituicyte membranes were in close contact with nerve terminals and fibers. After salt loading, the staining was more intense. This finding implicates AQP4 water channels in neurohypophyseal neuroglial interactions that affect water homeostasis during pathologies, such as brain edema, as well as physiological conditions [61]. Furthermore, pituicytes appear to be key elements in the osmoregulation process [64]; these cells are sensitive to osmolar changes and have been recently described as osmotic sensors [65]. In addition, they could modulate neurohormone output [65] that may be locally controlled by the amino acid taurine, which is produced by pituicytes [66]. Taurine is a naturally occurring β-amino acid in the brain, which has been demonstrated to have neuroprotective properties. Pretreatment with taurine significantly attenuated Aβ-induced neuronal death [67]; similarly, taurine reversed mitochondrial function in the presence of Aβ. Moreover, taurine attenuated the intracellular Ca^{2+} and ROS generation induced by Aβ. And the effective maintenance of intracellular Ca^{2+} homeostasis and ROS generation during exposure to neurotoxic insults are considered to be mechanistic components of neuroprotection against AD [68,69]. As a ubiquitous osmolyte involved in the regulation of cell volume, taurine is also a regulator of vasopressin release in the hypothalamo-neurohypophyseal system [70]. Thus, water balance and neurohormone release in the neurohypophysis are processes that are closely interconnected. Vasopressin exerts its effects via a family of G protein-coupled receptors. The most prominently expressed are the $V1_a$ and the V2 type ($V1_aR$ and V2R) [71]. The V1aR is found in a number of tissues including brain; it has been detected in neurons, glial cells, and endothelial cells of the blood-brain barrier [72], while The V2R has a more restricted distribution, and is predominantly expressed in the kidney [73]. Interestingly, the most recent published data demonstrated that V1R and V2R respond directly to vasopressin exposure, but they do not have an ability to act as osmo- or volume sensors when exposed to an osmotic gradient in the absence or presence of vasopressin [74], although regrettably this study was exerted in *Xenopus* oocytes or in mammalian cells. Therefore, AQP4 in pituicyte plasma membranes may be involved in this sensor effect during osmoregulation instead [61] and may also be closely connected to the regulation of vasopressin secretion. This research indicates that the movement of water regulated by AQP4 may lie at the heart of the mechanism of osmoreception and AVP secretion (Figure 2). However, because the absence or presence of AVP did not influence the levels of AD-related markers, the clearance of Aβ or other aggregated agents of AD might not be a factor in the explanation of the neuroprotective mechanisms of AQP4 via AVP.

The neuroprotective effects of vasopressin against alzheimer's disease could be partly through regulating AQP4 expression via binding to v1ar

The effects of AVP regulation on AQP4 have also been investigated by Moeller et al. [75]. First, they demonstrated the co-expression of AQP4 and the vasopressin receptor $V1_aR$. Furthermore, they demonstrated that the regulatory interaction between AQP4 and $V1_aR$ involves protein kinase C (PKC) activation. A PKC-dependent reduction

Figure 2: The important effects of AQP4 are at the heart of the mechanism of osmoreception and vasopressin secretion. AQP4 was discontinuously distributed along pituicyte plasma membranes, and several parts of the membranes in pituicytes were in close contact with nerve terminals and fibers. AQP4 in pituicyte plasma membranes may be involved in the sensor effect during osmoregulation and may be closely connected to the regulation of vasopressin secretion, which is also regulated by the amino acid taurine. Vasopressin could also regulate AQP4 expression through the vasopressin receptor $V1_aR$, and the regulatory interaction between AQP4 and $V1_aR$ involves PKC activation.

of the water permeability of AQP4 has previously been identified in oocytes [76] and mammalian cells [77]; however, the mechanism must be elucidated. Furthermore, Ser^{180} (numbering from the M1 isoform) is a strong PKC consensus site in AQP4 [78] and is involved in the PKC-dependent down regulation of AQP4, as previously reported [77], via direct phosphorylation or an unknown regulatory protein. The binding of AVP to $V1_aR$ leads to the increased generation of inositol trisphosphate (IP3), the activation of phospholipase C (PLC) and the release of Ca^{2+} and PKC [78,79], which could play important roles in the regulation of AQP4 expression. Furthermore, $V1_aR$ antagonism led to the upregulation of AQP4 and attenuated water content, injury, and cerebral edema [80]. Therefore, it can be hypothesized that the down regulation of AVP may upregulate AQP4 via the upregulation of PKC activation. Importantly, the future manipulation of AQP4 expression through AVP receptor antagonism may serve as an important therapeutic target for neurotoxicity and ischemia-evoked cytotoxic cerebral edema. It has been previously demonstrated that the $V1_aR$-mediated down regulation of AQP4 membrane expression levels and proposed that this down regulation might be beneficial during periods of dehydration in an attempt to limit the loss of water from the brain [75]. Vasopressin-dependent short-term down regulation of AQP4 may play a role in normal and pathophysiological conditions that induce AD or other neurological disorders. Future studies on mammalian cells and whole brains will identify the extent of this functional interaction and its physiological relevance.

Conclusion and Perspectives

Recent findings have evidenced the presence the interaction of AQP4 with vasopressin involved in neuronal maintenance and neuropretection against AD. There is a general agreement that

AQP4 at the plasma membrane, can induce preservation against Aβ toxicity and, furthermore, this water channel has been shown to influence vasopressin function. And the neuroprotective effects of AQP4 regulation against AD could also be regulated by vasopressin. Besides pituicyte, more efforts should be directed toward clarifying this phenomenon in other kinds of astocytes in certain cognitive-related functional brain regions. It is clinically important to further explore the pivotal role of the physiological relevance between AQP4 and vasopressin in the regulation of distinct cellular responses directed to neuropretection against AD, and further the precise mechanisms of the neuroprotection effect of AQP4 and vasopressin against AD.

Conflict Of Interest

The authors declare no competing financial interests.

Acknowledgement

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