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Research Article

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Role and Mechanism of AQP1 in the Transformation of Chronic Pain

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Abstract

The mechanism of chronic pain transition is unclear. Some studies have revealed that aquaporin 1 (AQP1) is involved in chronic neuropathic pain, but its role in the mechanism of chronic pain transition has not been paid attention to. AQP1 is abundantly expressed in the small diameter, unmyelinated C fibers of dorsal root ganglion neurons, and co-located with nociceptant markers substance P and IB4. AQP1 is a new target for the treatment of pain. The signal transmission between macrophages and neurons promotes the sensitization of nociceptors. According to their polarization, they are divided into pro-inflammatory type (M1) and anti-inflammatory type (M2), and changing their ratio can regulate chronic neuropathic pain. Oxidative stress promotes chronic migraine. PI3K/Akt/HIF-1α pathway has adaptive changes to oxidative stress and chronic hypoxia microenvironment, and intersects with p38MAPK pathway through downstream miRNAs/AQP1. This review summarizes the role of AQP1 in M1/M2 ratio and endothelial barrier function, and discusses that oxidative stress caused by early impairment of endothelial barrier function may be an important cause of delayed AQP1 expression enhancement. Oxidative stress, M1/M2 change and miRNAs/AQP1 signal in the microenvironment may respectively be important mechanisms and potential intervention targets of chronic pain transformation.

Keywords:
chronic pain transformation; Oxidative stress; Endothelial barrier; miRNAs; AQP1; p38MAPK; PI3K; HIF-1α

Aquaporins (AQPs) are a class of conserved transmembrane proteins expressed in various organ systems. They are cellular channels for bidirectional diffusion of water and small molecular compounds such as urea, lactate, hydrogen peroxide, and carbon dioxide. Human contains 13 kinds of aquaporins (AQP0-AQP12), which are widely distributed in various tissues and are involved in the pathological process of various non-infectious diseases, including renal insufficiency, nervous system diseases, skin diseases, metabolic syndrome and so on [1-3].

AQP1 is abundantly expressed in the small diameter, unmyelinated C-fiber neurons of Dorsal root ganglion (DRG).

AQP1 is abundantly distributed in the cell body and the periphery of neurons, and is densely expressed in the unmyelinated axons, myelinated axons and synaptic terminals. The co-localization of AQP1 with nociceptic markers substance P and IB4 is the anatomical basis for AQP1 to regulate some types of nociceptive signals [4-8]. DRG axon growth is impaired in AQP1-deficient mice, and the expression of AQP1 increases after sciatic nerve compression injury. AQP1 promotes axonal extension through water transport, which is a potential target for neuronal regeneration [6-7, 9]. AQP1 is a non-selective cation channel gated by cyclic guanosine monophosphate (cGMP) [10-12]. cGMP inhibitors reduce allodynia after chronic DRG compression injury in rats by reducing AQP1 levels [7,13]. The water permeability of neurons of AQP1 (-/-) mice and the perception of hot and cold pain induced by bradykinin, prostaglandin E2 and capsaicin are significantly reduced, which is a new target for pain treatment [7-8].

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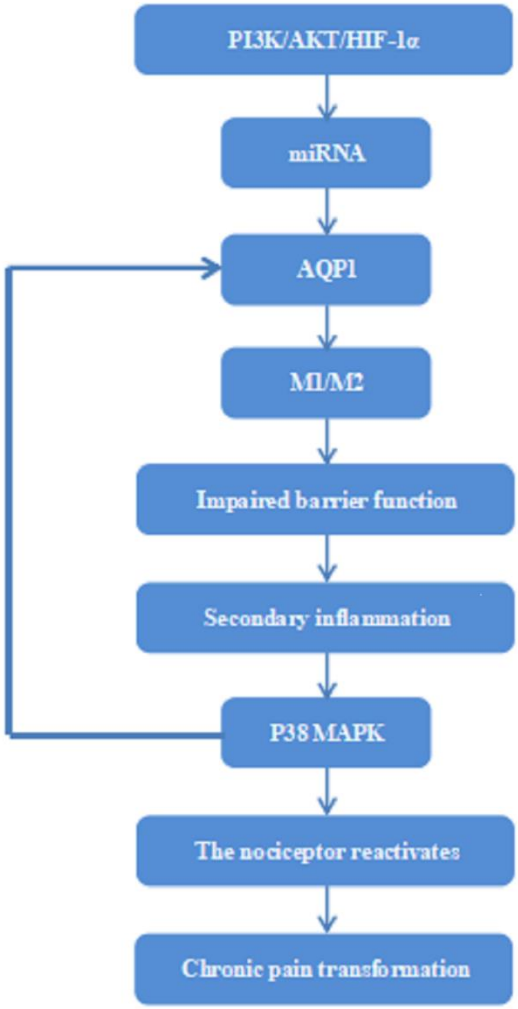
MiRNAs regulate the transcription of most human protein-coding genes, and their dysfunction is related to the pathological process of many diseases [14], regulate the pathological changes of nervous system diseases [15], and have a huge impact on the development of neuropathic pain [16-17]. Ischemia and hypoxia reduce the level of AQP1, which is regulated by miRNAs subunits miR-214 and miR-133a-3p.1 [18-19]. Mycobacterium leprae is an intracellular pathogen that relies on the glutathione antioxidant system to control oxygen free radicals (ROS) and the REDOX state of cells, thus changing the miRNA profile of leprosy patients, and promoting successful leprosy infection [20-22]. MiRNA participates in pathological processes such as skin dryness and loss of elasticity through AQP1 transcription loss in skin lesions, and is a new therapeutic target for leprosy pain [23], suggesting that oxidative stress microenvironment regulates AQP1 expression pattern, and miRNAs/AQP1 may be a potential mechanism for regulating chronic neuralgia signals.



P38 mitogen-activated protein kinase (p38 MAPK) pathway clears intracellular pathogens by affecting macrophage structure and function [24]. The transient inflammatory stimulation in the subacute phase after tissue incision is reactivated by p38 MAPK induced nociceptor, causing long-term nociceptive hypersensitivity and promoting the transformation of chronic pain, but the mechanism is unclear [25]. Pulmonary ischemia-reperfusion injury activates p38 MAPK to promote the increase of blood-air barrier permeability and macrophage infiltration by down-regulating the expression of AQP1, eNOS and VE-cadherin [26]. p38MAPK-AQP1 signal may be a new approach for targeted therapy of acute inflammatory injury [27]. These results suggest that secondary inflammation, oxidative stress and AQP1-mediated macrophage and endothelial barrier dysfunction are important regulatory mechanisms and effectors of p38 MAPK, respectively. Combined with the literature report that "miR-495 overexpression activates p38MAPK to promote mouse osteoblast proliferation and differentiation by inhibiting AQP1 [28]", it is suggested that mirRNA-p38MAPK-AQP1 pathway may be a potential mechanism to regulate chronic inflammatory pain signaling.

Long-term and frequent migraine attacks increase oxidative stress events in the brain and promote the chronicity of migraine. Moreover, anti-migraine drugs have antioxidant effects [29-30], suggesting that oxidative stress microenvironment plays an important role in the transformation of chronic pain. Phosphatidylinositol 3-

kinase (PI3K)/protein kinase B (Akt)/hypoxia-inducible factor 1α(HIF-1α) pathway is involved in various biological processes such as oxidative stress and glycolysis [31-33], and activation of PI3K/Akt can reduce AQP1 levels [34]. HIF-1α regulates key functions including cell migration, ROS production, pH [35] and is a major cause of intervertebral disc degenerative pain [36-37]. The level of AQP1 in DRG of rats with intervertebral disc degeneration pain increased significantly within 14 days [38], and the level of AQP1 at the site of spinal cord injury continued to increase for 11 months, and the delayed enhanced expression pattern was not related to local hypertonicity. Melatonin, an antioxidant, inhibits mechanical hyperalgesia in rats by reducing the level of AQP1[39]. Low expression of AQP1 in the early stage of ischemia reperfusion promotes high microvascular permeability and high expression of HIF-1α, and chronic hypoxia leads to high expression of AQP1 in the 7-14 days after injury [40]. These results suggest that oxidative stress microenvironment leads to delayed enhancement of AQP1 expression in subacute and chronic phase after injury, which induces nociceptor reactivation and long-term nociceptive hypersensitivity. PI3K/Akt/HIF-1α may promote chronic inflammatory pain transformation through AQP1.

Loss of AQP1 leads to intercellular connectivity disorders, paracellular leakage, edema and macrophage infiltration in peripheral areas, neuroinflammation, and pain disorders [41-42]. Endothelial permeability was significantly increased in neuron-rich areas 7 days after nerve compression injury, but no further increase was observed 7 days later, but macrophage migration and nerve sensitivity were increased [43]. Endothelial barrier dysfunction leads to secondary damage such as inflammation induced by impaired peripheral blood supply [44], which further worsens the primary lesion [45]. These results suggest that early impairment of endothelial barrier function induces secondary inflammatory reactions such as oxidative stress and chronic hypoxia in damaged tissues in subacute and chronic stages after injury, which may be an important mechanism for the delayed enhancement of AQP1 expression, and may also be an important mechanism for the reactivation of nociceptors induced by activation of p38MAPK.

Signaling between macrophages and neurons promotes axonal sprouting and nociceptor sensitization [46-47]. According to their polarized state, macrophages can be divided into resting state (M0), proinflammatory type (M1) and anti-inflammatory type (M2). M1 produces proinflammatory cytokines, which promote sensitization of nociception, and M2 produces anti-inflammatory cytokines, which play multiple roles in the induction and resolution of inflammation. M2 releases a large number of opioid peptides including enkephalin and β-endorphin to control pain [48], and changing the M1/M2 ratio can alleviate chronic neuralgia in mice [49]. Xanthine oxidorereductase promotes oxidative stress and M1 polarization of sciatic nerve [50], and targeting the mitochondrial antioxidant peptide SS-31 inhibits M1 polarization and proinflammatory cytokine release by reducing ROS production in macrophages [51], suggesting that oxidative stress regulates M2/M1. Activation of PI3K/AKT promotes M1 polarization and induces inflammation [52-53]. HIF-1α regulates immune metabolism and REDOX homeostasis of macrophages [54-55]. AQP1 relies on PI3K to promote M1 migration and M2/M1 change [56]. The activation of PI3K in AQP1siRNA mouse macrophages leads to the decrease of M2 [57], suggesting that there were positive and negative feedback effects between AQP1 and PI3K. PI3K/Akt/HIF-1α/AQP1 regulates immune metabolism of macrophages and M2/M1 ratio. Combined with the literature reports that "HIF-1α/miRNAs is a new regulatory mechanism for pathological processes such as myocardial fibrosis and asthma [58-60]", it is suggested that PI3K/Akt/HIF-1α/miRNAs/AQP1 pathway may be a potential mechanism for regulating chronic inflammatory pain.

This article reviews the role of AQP1 in the change of M2/M1 ratio and endothelial barrier function, and discusses that the early damage of endothelial barrier leads to oxidative stress and dynamic changes of M2/M1 in the microenvironment, inducing delayed AQP1 expression enhancement, which may be an important mechanism for the transition of chronic pain. Since miRNAs/AQP1 is a crossing point between PI3K/Akt/HIF-1α pathway and p38MAPK pathway, it is speculated that miRNAs /AQP1 may be a potential intervention target for the transformation of chronic pain.

Data Availability Statement:*No new data:* Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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