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Review

Water channel proteins in the peripheral nervous system in health and disease

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ABSTRACT

The expression and function of aquaporins (AQPs) in the peripheral nervous system is a relatively under-investigated subject. Since the original description of AQP1 mRNA expression in the trigeminal ganglion in 2004, there has been significant progress in describing the expression, regulation and function of AQPs in the peripheral nervous system. Three out of the 13 mammalian AQPs (AQP1, AQP2 and AQP4) have been localized to neurons or glial cells in trigeminal ganglia, periodontal Ruffini endings, dorsal root ganglia and the enteric nervous system. Functional studies using knockout mice have suggested the involvement of AQP1 in peripheral pain perception. This review discusses current progress in this field and the possible involvement of AQPs in peripheral neuropathies.

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1. Introduction

The aquaporins (AQPs) are a family of water-transporting proteins expressed in specific cell types of various mammalian organs. AQPs not only have important roles in fluid transport in many epithelial and endothelial tissues, but also participate in the regulation of important cellular functions including cell proliferation and migration, apoptosis, phagocytosis and neuronal signal transduction (Verkman, 2012; Benga, 2009; Carbrey and Agre, 2009). Studies of the expression and function of AQPs in the central nervous system have been a major focus in the AQP field. Studies from many laboratories have shown the expression of several AQPs including AQP1, AQP3, AQP4, AQP5, AQP8 and AQP9, in the brain and spinal cord (reviewed in Tait et al., 2008). Functional studies using transgenic knockout mice revealed the involvement of AQP1 in cerebral spinal fluid (CSF) secretion (Oshio et al., 2005) and pain sensation (Oshio et al., 2005; Shields et al., 2007; Zhang and Verkman, 2010; Xu et al., 2010); and AQP4 in brain edema (Manley et al., 2000; Papadopoulos et al., 2004), neuronal signal transduction (Li and Verkman, 2001; Binder et al., 2006; Lu et al., 2008), neurogenesis (Kong et al., 2008), glial scar formation (Saadoun et al., 2005), neuroinflammation (Li et al., 2011) and pain perception (Wu et al., 2008; Bao et al., 2010; Chen et al., 2010).

Whereas there are extensive data on AQP expression and function in the central nervous system, the distribution and functional significance of AQPs in the peripheral nervous system are relatively under-investigated. Since the first description of AQP1 mRNA expression in the trigeminal ganglion in 2004 by Matsumoto et al. by DNA microarray analysis and *in situ* hybridization (Matsumoto et al., 2004), significant progress has been made in the cellular localization, regulation and function of AQPs in the peripheral nervous system. To date, three out of the 13 mammalian AQPs (AQP1, AQP2 and AQP4) have been localized to neurons or glial cells in trigeminal ganglia, periodontal Ruffini endings, dorsal root ganglia and the enteric nervous system. Functional characterization in transgenic knockout mice indicated the involvement of AQP1 in peripheral pain perception. This review discusses progress on studies of expression and function of AQPs in the peripheral nervous system, and possible involvement of AQPs in diseases associated with peripheral neuropathies.

2. Aquaporins in cranial sensory nerve

2.1. Expression of AQP1 in cranial sensory ganglia

The first evidence of AQP expression in the peripheral nervous system was reported by Matsumoto et al. (2004) in a study to identify candidate genes involved in somatosensory functions of cranial sensory ganglia. Expression of AQP1 mRNA was found in neurons of somatosensation-related ganglia by DNA microarray analysis. *In situ* hybridization showed expression of AQP1 mRNA in neurons in trigeminal and petrosal ganglia, and to a lesser extent in nodose ganglia. AQP1 expression was restricted to small- and medium-sized neurons with a diameter under 30 μm. The study suggested the involvement of AQP1 in somatosensation in cranial structures such as the face, oral cavity and pharynx.

2.2. Expression of AQP1 in the mechanoreceptive periodontal Ruffini endings

The Ruffini endings are the primary mechanoreceptors in the periodontal ligament, which are categorized as low-threshold, slowly adapting, type II mechanoreceptors (Maeda et al., 1999). Nandasena et al. (2007) reported the immunolocalization of AQP1 in the periodontal Ruffini endings of the rat incisors. Immunostaining showed AQP1 protein in axon terminals of periodontal Ruffini endings and their associated terminal Schwann cells. Double staining with AQP1 and a neuronal marker, PGP9.5, or a glial marker, S-100 protein, confirmed AQP1 localization in nerve endings and surrounding Schwann cells (as illustrated in Fig. 1, lower left panel). They reported AQP1 expression in 16% of trigeminal neurons and in a subset of satellite cells that surrounded AQP1-positive or -negative neurons. Quantitative analysis on size distribution of AQP1-positive trigeminal neurons indicated that majority of the AQP1-positive neurons (67%) were 400–1000 μm^2 (average at 671 μm^2), indicating that they belong to medium-sized neurons that mediate mechanotransduction. This is the first report that localized an AQP protein to the axon terminals of mechanoreceptors. The findings suggest that AQP1 is involved in the maintenance of the osmotic balance necessary for the mechanotransduction process in the periodontal Ruffini endings. In addition, based on prior studies suggesting a high potential for neuroplasticity of the Ruffini endings and the involvement of AQP1 in cell migration, it was proposed that AQP1 might facilitate the continual remodeling of the periodontal Ruffini endings against occlusal force. Further investigation using AQP1 knockout mouse model will provide direct evidence for the functional significance of AQP1 expression in the periodontal Ruffini endings.

2.3. Expression and regulation of AQP2 in trigeminal ganglia

AQP2 expression in peripheral nervous system was first reported by Mobasheri et al. (2005) in a study on AQP distribution in human tissue microarrays. Although abundant AQP2 mRNA was detected in peripheral nerve bundles, no information about protein localization was reported. In 2009, Borsani et al. described AQP2 expression and regulation in trigeminal ganglia in a murine inflammation model. They analyzed the expression of AQP2 protein in the trigeminal ganglia in a mouse model of perioral acute inflammatory pain induced by formalin (Borsani et al., 2009). Under baseline conditions, the AQP2 immunostaining was seen mainly in the cytoplasm of neurons in trigeminal ganglia, with stronger labeling in med-

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