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Invited critical review

Aquaporins, anti-aquaporin-4 autoantibodies and neuromyelitis optica

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ABSTRACT

The classification, distribution and functions of the different molecules of aquaporins (AQPs), including aquaporins, aquaglyceroporins and superaquaporins are reviewed together with their potential diagnostic and therapeutic uses. We analyzed the pathogenic importance of anti-AQP4 autoantibodies in neuromyelitis optica and related syndromes, as well as their diagnostic and predictive potential, prognosis, and monitoring of the disease. Finally, the analytical methods and current recommendations for testing anti-AQP4 autoantibodies in clinical practice are described.

Contents

1. Introduction

The diffusion of water across biological membranes has long been known. It occurs across all lipid bilayers and is a slow and low-capacity bidirectional process. However, many physiological processes require rapid movement of water. More than 30 years ago, it was considered that in certain specialized epithelia (renal tubules, red cells, secretory glands) there should be an additional system for the rapid movement of large masses of water. This system would possess high capacity for water and be specific, not allowing the passage of other substances, such as hydronium ions (H_3O^+). Water would move according to the saline osmotic gradient and the system could be modified or inhibited by various substances. The evidence pointed to the notion that it might be a membrane channel for water.

2. Membrane channels for water

In 1988, in studies addressing Rh cell antigens, a 28 kDa protein shared by red cells from different species that participated in the

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movement of water across biological membranes was found unexpectedly [1]. Later, coding DNA was isolated and a membrane polypeptide with several transmembrane domains with repeated amino acid sequences in the amino and carboxyl ends were identified. Its structure suggested that it might be part of a channel and that it could correspond to a component of water channels. Likewise, it was observed that this protein had homologous molecules in bacteria (*E. coli*), plants, and other mammalian cells [2]. Later, the name aquaporin was used for this membrane channel for water [3]. In 2003, Peter Agree was awarded Nobel Prize in Chemistry for the discovery of aquaporins (AQPs).

3. The aquaporin family of proteins

Aquaporin-1 (AQP1) was the first aquaporin described in humans. Currently, for aquaporins at least 13 physiological sequences have been described (Table 1), which can be divided into two broad groups. On one hand, there are the channels that transport water exclusively, and on the other there are the aquaglyceroporins, which transport water and glycerol. A third group of aquaporins called super-AQP, with less homology with the above, has been proposed.

3.1. Type I aquaporins

Using specific antibodies, it was observed that AQP1 is expressed in the nephron proximal tubules and not in the collecting duct (which could perhaps express another AQP). It was located in the apical membrane, in the basal membrane and in the intercellular borders, and it was involved in water movement across the cell, in favour of a concentration gradient between the apical and basal ends [4]. Later, it was demonstrated that AQP1 is also expressed in the basal and luminal membranes of the capillary endothelium [5]. AQP1 also participates in the secretion of fluid by the choroid plexus where CSF is produced, and seems to be involved in the regulation of intracranial pressure [6].

The AQP1 gene is located on the short arm of chromosome 7 (7p14) [7]. AQP1-null individuals have a limited capacity to concentrate water when subjected to functional testing of renal concentration; however, AQP1-null individuals are infrequent [8].

In the plasma membrane, AQP1 is located as a homotetramer, with each subunit containing an individually functional water pore [9]. In the centre of the four monomers lies a fifth pore, composed mainly of hydrophobic amino acids, which might provide a path for non-polar molecules such as gas molecules. Early studies of aquaporin-1 pointed to an "hourglass" model in which repeated sequences were responsible for forming the pore [10]. The crystal structure revealed that pore conformation enabled the electrostatic repulsion of protonated water (H_3O^+) [11] (Fig. 1).

Recent evidence has indicated that AQP1 is also involved in gas transport through cellular membranes. Thus, AQP1 transports CO_2, NO, and NH_3 across plasma membranes and AQP1-dependent CO_2 and NO transport appears to play an important role in mammalian physiology. A channel-dependent transport of gaseous molecules could match the tightly controlled intracellular environment and the rapid paracrine actions of gaseous molecules better and offers a means of controlling directional release [12]. Otto et al. have found that AQP1 tetramers exhibit higher rates of CO_2 transport than monomers [13], consistent with the concept that CO_2 crosses AQP1 via the central pore of the aquaporin tetramer. Also, NO molecules appear to cross the highly hydrophobic central pore formed by the AQP1 tetramer. Whether additional gas paths are created in between tetramers or not remains to be answered.

In the proximal tubule of mammals, AQP1 may play an important role in acid/base balance by facilitating CO_2 influx and therefore HCO_3^- reabsorption. AQP1 could play an important role in regulating arterial pH during metabolic acidosis, possibly by acting as a CO_2 transporter in the proximal tubule [14,15]. AQP1 carries NO across cell membranes by facilitated transport, which is three times faster than free diffusion. The studies of Herrera et al. have confirmed that endothelium-dependent relaxation requires AQP1-dependent transport of NO across cell membranes [16,17]. Thus, transport of NO by AQP1 is of physiological relevance because it mediates NO-dependent vasorelaxation. Also, the ability of aquaporins to transport NO may permit tight control of intracellular NO concentrations in target cells and directional release from cells where it is produced [12]. Moreover, AQP-1 is also involved in tumour angiogenesis, tumour cell proliferation and migration [18].

AQP2 is similar to AQP1, but it is expressed in renal collecting tubules. AQP2 forms a water channel regulated by vasopressin. It is expressed in the apical membrane of collecting tubules and it is also observed in intracellular vesicles. Its expression in the apical membrane is dependent on environmental conditions [19,20].

The main water channel in the brain is AQP4 (Fig. 2). This aquaporin is expressed in the endings of astrocytes surrounding blood vessels and, therefore, at the border of the blood–brain barrier. Similarly, it is located in the limiting glia (in the subarachnoid cerebrospinal fluid-brain interface) and in the ependyma (ventricular cerebrospinal fluid-brain interfaces). Through its expression in these interfaces it regulates water movement inside and outside the brain [21–23]. AQP4-deficient mice do not manifest significant baseline water balance abnormalities in the central nervous system (CNS), but show, under the appropriate stress, impairment in the brain and spinal cord [24]. Experiments in mice null for AQP4 or with alpha-syntropin, which down-regulates AQP4, have shown that AQP4 facilitates oedema formation in diseases that produce cytotoxic oedema (cell swelling), including cerebral ischemia,

Table 1
Classification of aquaporins.

Aquaporins (type I)	Aquaglyceroporins (type 2)	Superaquaporins (type 3)
AQP0	AQP3	AQP11
AQP1	AQP6	AQP12
AQP2	AQP7	
AQP4	AQP9	
AQP5	AQP10	
AQP8		

A short sequence of hydrophobic amino acids (NPA boxes) which form the pore and six transmembrane domains are common for all types of aquaporins. Type-2 AQPs have an aspartic residue that expands the pore and permit molecules with a higher molecular weight than H_2O, such as glycerol, to pass through. Type 3 AQPs do not have the aspartic residue in the pore but they have a characteristic cysteine residue near the pore and the pore amino acid sequence is less preserved.

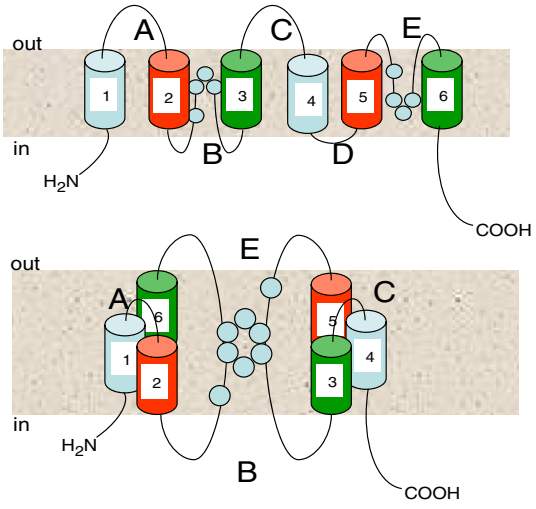

Fig. 1. Aquaporin-1 structure. Fragments of the AQP1 included within the membrane and in the interior and exterior of the cell. As can be seen, two repeats in tandem next to the amino and carboxyl ends are responsible for the shape of the pore for the passage of H_2O.