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Aquaporin 2: From its discovery to molecular structure and medical implications

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ABSTRACT

This review describes the discovery of rat aquaporin 2 AQP2 as a vasopressin-regulated water channel, and subsequent isolation of human AQP2. Regarding the structure and function of AQP2, further structural analysis is necessary to understand the basic properties of individual channel function, for examples, such as possible regulation by gating. The critical importance of AQP2 in the urine concentrating ability is demonstrated by a human disease, nephrogenic diabetes insipidus (NDI), and by gene targeting of AQP2 in mice. AQP2 is regulated by many mechanisms from gene transcription to final protein degradation, and vasopressin-stimulated recycling of AQP2 is important for accumulation of AQP2 at the apical membrane. In AQP2-affected NDI, comparison of genotype (types of mutations and mutated residues) and phenotype (clinical characteristics) provides better understanding of both clinical entity of the disease and molecular mechanisms regulating AQP2. Finally, it has become increasingly clear that AQP2 is greatly involved in many human abnormal water balance disorders that await new therapies and clinical markers.

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1. Introduction

Aquaporin-2 (AQP2) is a vasopressin-regulated water channel which determines water permeability of kidney collecting duct. In terrestrial animals including humans, preventing water loss is mandatory for survival in dry circumstances on land. To minimize water loss through urine, urine should be highly concentrated; a typical example is that a desert rodent concentrates urine as high as 5000 mOsm/Kg H_2O. Consequently, the mechanisms of urine concentration had attracted researchers' interest and many studies have been performed. Smith and coworkers proposed that vasopressin reduces urine flow by increasing the permeability of the distal nephron to water, thereby stimulating water reabsorption from the lumen to the interstitium, resulting in enhanced urine concentration (Smith, 1951). In the 1960s, based on studies on amphibian skin and toad urinary bladder (model tissues of kidney distal nephrons), the concept of vasopressin-regulated water channels became widely accepted (Orloff and Handler, 1967). Subsequent studies using freeze-fracture electron microscopy indicated the presence of intramembrane particles (presumably water channel proteins) in the apical membrane of the toad urinary bladder and showed that these particles aggregate in response to vasopressin (Chevalier et al., 1974; Kachadorian et al., 1975). Furthermore, these clusters of particles traffic between plasma membrane and cytoplasmic vesicles upon administration/withdrawal of vasopressin, and the shuttle hypothesis was proposed (Finkelstein, 1986; Handler, 1988). Thus, the time to isolate the molecule for vasopressin-regulated water channels was near.

2. Discovery of AQP2, the vasopressin regulated water channel

To identify water channel molecules, biochemical studies such as labeling outer portion of membrane proteins with specific reagents (Benga et al., 1986; Harris et al., 1988) and a cloning strategy with oocyte heterologous expression system (Zhang et al., 1991) were employed. However, true molecular identification did not occur until serendipitous discovery of a water channel molecule of red blood cells by Agre and coworkers (Preston et al., 1992). During the studies of membrane proteins in red blood cells, they recognized the presence of large amount of a 28-kDa protein of unknown function. Purification and partial amino acid sequencing led to the isolation of a cDNA for an integral membrane protein of 28 kDa, which was named CHIP28 (channel-like integral protein of 28 kDa) (Preston and Agre, 1991). The appearance of water permeability in oocytes injected with in vitro-transcribed mRNA of CHIP28 was the moment when molecular identification of a water channel occured (Preston et al., 1992).

Based on this cloning and the fact that CHIP28 is not present in the kidney collecting duct (Denker et al., 1988), we began a search for homologs of CHIP28 using a PCR-based cloning strategy applied to kidney medulla mRNA. The study successfully resulted in isolation of a full-length cDNA and subsequent functional assay in oocytes within 5 months, confirmation of its immunohistochemical localization with newly generated antibodies in another 4 months, and final publication within 1 year in February 1993 (Fig. 1) (Fushimi et al., 1993). This newly identified water channel is 42% identical in amino acid sequence to CHIP28, exclusively localized in the apical and subapical regions of kidney collecting ducts, and was named WCH-CD (water channel of collecting duct). Later, a new systematic name, aquaporin 2 (AQP2) (GenBank ID: D13906) was assigned to this kidney collecting duct water channel and the name AQP1 was assigned to CHIP28 (Agre et al., 1993). Interestingly, at the same time, two other clones were isolated in our laboratory; one is a water channel expressed in the basolateral membrane of collecting duct and is called AQP3 (Ishibashi et al., 1994), and the other is a chloride channel expressed in the thin ascending limb of Henle and is named ClC-K1 (Uchida et al., 1993). Both were later shown to be critically involved in urine concentration (Matsumura et al., 1999; Ma et al., 2000). Thus, the kidney medulla was like a treasure island for cloning of molecules that contribute to urine concentration. It was fortune that we first isolated AQP2 instead of AQP3.

At the time that AQP2 was cloned, demonstration that AQP2 is actually regulated by vasopressin was lacking. Subsequent studies by many researchers including us demonstrated this. Upon vasopressin stimulation, trafficking of AQP2 to the apical membrane from intracellular storage vesicles was demonstrated with immunoelectron microscopy (Yamamoto et al., 1995a; Nielsen et al., 1995; Sabolić et al., 1995). More importantly, accumulation of AQP2 labeling in intramembranous particles was demonstrated in freeze fracture replicas of AQP2-experssing LLC-PK1 cells (Sun et al., 2002). Such a particle structure is thought to represent vasopressin-regulated water channel molecules in toad urinary bladder and rodent kidney collecting duct. Thus, AQP2 has been shown to be a vasopressin-regulated water channel.

3. Human AQP2

Future clinical implications and applications required cloning of human AQP2. Soon after the cloning of rat AQP2 cDNA as described above, we began the isolation of a human homolog of AQP2. The isolated cDNA encodes a 271-amino acids protein with 91% identity to rat AQP2 that is localized to human collecting duct cells (Sasaki et al., 1994). The human gene encoding

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