

Mammalian Aquaporins

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Mammalian aquaporins (AQPs) are transmembrane channels expressed in a large variety of cells and tissues throughout the body. They are known as water channels, but they also facilitate the transport of small solutes, gasses, and monovalent cations. To date, 13 different AQPs, encoded by the genes *AQP0–AQP12*, have been identified in mammals, which regulate various important biological functions in kidney, brain, lung, digestive system, eye, and skin. Consequently, dysfunction of AQPs is involved in a wide variety of disorders. AQPs are also present in the heart, even with a specific distribution pattern in cardiomyocytes, but whether their presence is essential for proper (electro)physiological cardiac function has not intensively been studied. In a recent review published in *Int. J. Mol. Sci.* (<https://doi.org/10.3390/ijms20082039>) (<https://doi.org/10.3390/ijms20082039>), we summarize recent findings and highlight the involvement of AQPs in normal and pathological cardiac function. We conclude that AQPs are at least implicated in proper cardiac water homeostasis and energy balance as well as heart failure and arsenic cardiotoxicity. However, our review also demonstrates that many effects of cardiac AQPs, especially on excitation-contraction coupling processes, are virtually unexplored.

Keywords: Aquaporin ; water channel ; heart ; myocyte ; edema ; failure ; energy ; electrophysiology ; ion channels ; Ca²⁺ transient.

1. Introduction

Aquaporins (AQPs) constitute a major and diverse transmembrane channel family found in most living organisms ^{[1][2][3]}. They facilitate movement of water along osmotic gradients and were originally named water channels ^[4]. Water constitutes approximately 70% of organism mass ^[5], and therefore, AQPs—together with simple water diffusion across the hydrophobic bilayer—are important for many different (patho)physiological processes (for reviews, see ^{[6][7]}).

AQPs are relatively small membrane proteins that constitute a monomer containing six transmembrane spanning domains, intracellular C- and N-termini, and a central water pore ^{[5][8][9][10]}. In the plasma membrane, four monomers form a functional tetramer, with each monomer functioning independently. Although somewhat controversial, the central tetrameric pore of some AQPs has been proposed to conduct also small solutes, monovalent anions, heavy metal ions, and gasses, i.e., O₂ and CO₂. AQP channels are voltage independent and do not show gating properties. To date, 13 AQPs are known in mammals (*AQP0–12*, encoded by the genes *AQP0–AQP12*), and they are divided into three subfamilies based on their pore selectivity. Table 1 summarizes the subdivision of the mammalian AQPs and their non-controversial basic properties. In short, AQPs 0, 1, 2, 4, 5, 6, and 8 belong to the classical water selective AQPs. AQPs 3, 7, 9, and 10, also named aquaglyceroporins, are less water permeable, but they also pass small neutral solutes, such as glycerol and urea. AQPs 11 and 12, initially named AQPX1 and AQPX2, are classified to another AQP subfamily, named unorthodox aquaporins, the properties of which are less clear.

2. Mammalian AQPs Types

The mammalian AQPs are present in many cell types and organs, for example in kidney, brain, lung, digestive system, eye, and skin ^[7]. It is generally accepted that they have important (patho)physiological roles in, for example, water reabsorption in the kidney, water exchange across the blood–brain barrier, and growth and vascularity of tumors. We refer to several extensive reviews for their role in normal physiological processes as well as their pathophysiological function in the above-mentioned organs, cancer, and obesity ^{[11][12][13][14][15][16][17][18][19]}. AQPs are also found in the heart and cardiomyocytes ^{[20][21][22]}, but their role in normal heart function and cardiac disorders has not intensively been studied ^[23]. In a recent review ^[24], we first provide a brief overview of the presence of AQPs in the heart. Subsequently, we highlight their (patho)physiological role, which has primarily been studied using AQP knock-out transgenic mice. In our review, we conclude that AQPs are not only important for cardiac water homeostasis, but may also affect cardiac excitation-contraction coupling—either directly or indirectly via dysfunction of other organs—due to their permeability to glycerol,

arsenite, and other small, neutral solutes as well as to interactions with various ion channel proteins and connexins. However, as set-out in our review [24], despite the great progress in the determination of the characteristics and functions of AQP's in the heart, various effects of cardiac AQP's seem still unknown.

Table 1. Summary of mammalian AQP's and their basic properties.

HGNC Gene symbol	Synonym	Subfamily	Permeability
<i>AQP1</i>	<i>CHIP28</i>	water-specific channels	H ₂ O, CO ₂
<i>AQP2</i>	<i>WCH-CD</i>	water-specific channels	H ₂ O
<i>AQP3</i>	<i>GLIP</i>	aquaglyceroporins	H ₂ O, urea, glycerol, NH ₃ , arsenite
<i>AQP4</i>	<i>MIWC</i>	water-specific channels	H ₂ O
<i>AQP5</i>	–	water-specific channels	H ₂ O
<i>AQP6</i>	<i>AQP2L</i>	water-specific channels	H ₂ O, NH ₃ , anions
<i>AQP7</i>	<i>AQPap</i>	aquaglyceroporins	H ₂ O, urea, glycerol, NH ₃ , arsenite
<i>AQP8</i>	–	water-specific channels	H ₂ O, urea, NH ₃
<i>AQP9</i>	–	aquaglyceroporins	H ₂ O, urea, glycerol, NH ₃ , arsenite
<i>AQP10</i>	–	aquaglyceroporins	H ₂ O, urea, glycerol
<i>AQP11</i>	<i>AQPX1</i>	unorthodox aquaporins	H ₂ O
<i>AQP12A</i>	<i>AQP12; AQPX2</i>	unorthodox aquaporins	H ₂ O
<i>AQP12B</i>	<i>INSSA3</i>	unorthodox aquaporins	H ₂ O
<i>MIP</i>	<i>AQP0</i>	water-specific channels	H ₂ O

CHIP28 = channel-forming integral membrane protein of 28 kDa; WCH-CD = water channel- collecting duct; GLIP = glycerol intrinsic protein; MIWC = mercurial-insensitive water channel; AQP2L = AQP2-like; AQPap = aquaporin adipose; AQPX1 and AQPX2 = aquaporin-like channels of a new subfamily; INSSA3 = insulin synthesis associated 3; MIP = major intrinsic protein of lens fiber. Modified from [9][10][25][26].

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