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Challenges and achievements in the therapeutic modulation of aquaporin functionality

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ABSTRACT

Aquaporin (AQP) water and solute channels have basic physiological functions throughout the human body. AQP-facilitated water permeability across cell membranes is required for rapid reabsorption of water from pre-urine in the kidneys and for sustained near isosmolar water fluxes e.g. in the brain, eyes, inner ear, and lungs. Cellular water permeability is further connected to cell motility. AQPs of the aquaglyceroporin subfamily are necessary for lipid degradation in adipocytes and glycerol uptake into the liver, as well as for skin moistening. Modulation of AQP function is desirable in several pathophysiological situations, such as nephrogenic diabetes insipidus, Sjögren's syndrome, Menière's disease, heart failure, or tumors to name a few. Attempts to design or to find effective small molecule AQP inhibitors have yielded only a few hits. Challenges reside in the high copy number of AQP proteins in the cell membranes, and spatial restrictions in the protein structure. This review gives an overview on selected physiological and pathophysiological conditions in which modulation of AQP functions appears beneficial and discusses first achievements in the search of drug-like AQP inhibitors.

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1. Introduction

A survey of the currently used pharmacological agents and classification of their respective drug targets puts a figure on the large predominance of compounds that address receptor molecules (44% of all human drug targets; Rask-Andersen et al., 2011). Within the class of receptor drug targets almost half represent G-protein coupled receptors and one fifth are ligand-gated ion channel receptors, followed by tyrosine-kinase receptors. The next large target group contains various enzymes (29% of the drug targets) with a major focus on lipid mediator-producing oxidoreductases, such as the cyclooxygenases, COX, i.e. the targets of nonsteroidal anti-inflammatory drugs. The drug target class of transport and channel proteins ranks third (15% of all drug targets). Here, mainly ion channels of the heart and circular system are modulated in their function to treat arrhythmia and hypertension as well as neurotransmitter transporters of the brain for neurological disorders. The new anti-diabetic class of gliflozins, that inhibit the renal sodium-dependent glucose transporter, SGLT2, represents one of the very few cases in which high-level transport of a nutrient at millimolar concentrations is targeted.

This brief overview shows that the great majority of drugs interfere fairly directly with signal transduction, be it at the receptor, the small-molecule transmitter, or the action potential level. The advantages are obvious: the drugs compete with very low transmitter concentrations,

Abbreviations: AQP, aquaporin; NMO, neuromyelitis optica.

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which can be as low as in the femtomolar range, and the target proteins exhibit explicit binding sites, which allow for high-affinity interactions. Both are prerequisites for optimizing drug compounds towards low-dose application and specificity of action.

The situation of transmembrane water transport facilitated by one of the thirteen different human aquaporin channel proteins (AQP0–12) is vastly opposite in both, substrate concentration and affinity aspects. Water represents the most abundant molecule in the human body (about 60% of the total body mass) and its concentration in the body fluids is 55 M, i.e. 10,000 times higher than that of the most important energy carrier molecule glucose. With respect to substrate affinity, AQP proteins appear inconspicuous to passing water molecules by mimicking the hydrogen bond situation and binding energy of the aqueous bulk. Thus, the energy barrier for water permeation through the AQP channel following an osmotic gradient is hardly higher than diffusion in free solution. Structure-wise, AQPs are rigid proteins and exhibit little thermal fluctuations of the amino acid residues in the channel region in order to maintain a 20 Å long and very narrow channel pathway of only 2–4 Å in diameter open for water (orthodox AQPs; Murata et al., 2000) or small, uncharged solutes, mainly glycerol and chemically resembling compounds (aquaglyceroporins; Fu et al., 2000), posing major space limitations for putative inhibitor molecules. On top of that, AQPs tend to populate the cell membranes in large numbers, i.e. the membrane of a single erythrocyte contains about 200,000 AQP copies (Solomon et al., 1983; Denker et al., 1988).

Despite the challenges due to the AQP structure and protein abundance, it appears worthwhile to search for small molecule modulators due to the many and central roles AQPs play in physiology and pathophysiology. A recent review by Verkman et al. (2014) provides a comprehensive and excellent overview on AQP-related disorders and pharmacological intervention attempts. In this paper, we will focus – after going through physiology and AQP-related therapeutic possibilities – on options for compound screening, and the protein structural and chemical aspects of AQP modulator design.

2. Selected physiological roles of aquaporins and options for modulation

Besides water and glycerol, AQPs facilitate permeation, dependent on the isoform, of various other physiological molecules across cell membranes: ammonia, carbon dioxide, urea, hydrogen peroxide, and methylglyoxal (Wu & Beitz, 2007). Potential physiological roles of AQPs are, thus, in waste metabolite elimination (ammonia, urea, methylglyoxal), cellular gas exchange (carbon dioxide), and oxidative stress relief and/or signal molecule transport (hydrogen peroxide). Such AQP functions, if physiologically relevant, have not been attributed to diseases, yet. Hence, in the following, we will summarize data on the more classical roles of AQPs that are mainly related to water and glycerol transmembrane transport and in which pharmacological modulation is considered beneficial.

Lipid bilayers are permeable for water; yet, due to the lipophilic membrane core, osmotic diffusion rates are low and considerable activation energy (>10 kcal mol^{-1}) is required. In the presence of AQP water channels, transmembrane water permeability increases by one to two orders of magnitude and the energetic cost is lowered to that of breaking two to three hydrogen bonds (<5 kcal mol^{-1}; Preston et al., 1992). Two situations call for AQP facilitated transmembrane water transport (Fig. 1): a) rapid, high-volume transport (kidneys), and b) sustained water transport at small, near-isosmotic gradients (slow fluid exchange, secretory glands, cell motility). Transmembrane transport of glycerol along a chemical gradient is relevant in skin moistening and in the Cori cycle, i.e. glycerol release from adipocytes during lipolysis and uptake of glycerol by the liver for gluconeogenesis. We will discuss water transport in the kidneys and the inner ear in one section because in both cases regulation is via vasopressin; thereafter, we address the situation in the eye and surrounding secretory tissues together with water secreting salivary glands.

2.1. Kidneys and inner ear

The water transport capacity of the kidneys is unparalleled in the human body. It is driven by a steep osmotic gradient due to the active transport of salt reaching concentrations up to four times higher than in normal tissue. More than 150 l of blood is filtered by the nephrons per day, equaling 100 ml min^{-1} or 1.7 ml s^{-1}. This way, hydrophilic, potentially toxic substances, such as waste metabolites and xenobiotics, are cleared from the body. At the same time, the kidneys regulate the water, salt, and pH homeostasis of the organism. To maintain the water-balance, about 99% of the filtered pre-urine water is being reabsorbed. The proximal tubule and the descending thin limb of the Henle loop continuously take up the major volume, whereas the remaining, ~20% of the kidney filtrate is used to adjust homeostasis via the action of the hormone vasopressin that acts on the water permeability of the collecting duct endothelia.

The discovery of the AQPs eventually provided the molecular basis for the highly water permeable kidney sections. In total, eight AQPs have been localized in different segments of the nephron.

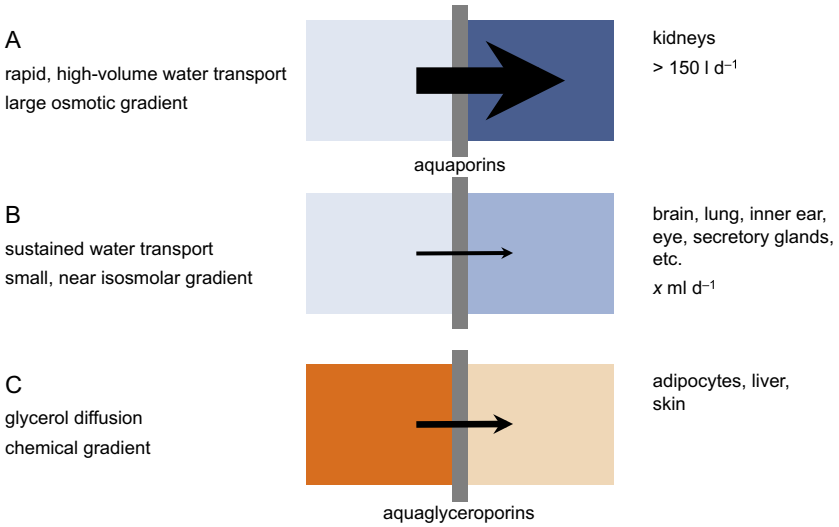

Fig. 1. Physiological situations that require AQP water or glycerol facilitation across cell membranes.