

Lipid intrinsic lipid-mediated membrane permeability to most



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Lipid bilayer in cell separates the intracellular and extracellular cytoplasmic matrix, maintaining the structural integrity of the cell. It plays a vital role in exchange of substances between the cells and its environment, providing energy for the physiological processes.

The major component of living organisms including all vertebrates, invertebrates, unicellular organisms and plants is water. Water freely diffuses the lipid membrane only at a limited rate. Movement of these water molecules across the membranes is essential for life. It was presumed that transport of water molecules is via simple diffusion through the lipid bilayer until the discovery of aquaporins. Earlier in 1970's prediction towards the presence of water channel in cell membranes were described.

It was Peter Agre and colleagues who named water channel as aquaporins (AQPs)(1) (Preston et al., 1992). Aquaporins exist as different isoforms till date there are 13 isoforms (AQP0-12) identified in mammals. Aquaporins are family of membrane intrinsic proteins, forming pores facilitating massive transport of water across the membranes. AQPs based on the sequence analysis has been classified under three subtypes classical, aquaglyceroporins and orthodox aquaporins (2-4) (Agre and Kozono, 2003; Zardoya, 2005; Nozaki et al., 2008). Classical AQPs 1, 2, 4, 5, 6&8 are selective water channels and restricts the entry of small organic and inorganic molecules.

Aquaglyceroporins 3, 7, 9 & 10 are non-selective channels permeable to water, urea, glycerol and small non-electrolytes. Unorthodox aquaporins

11&12 are being investigated. In addition, AQPs also facilitate transport of gases like carbon dioxide (5-7) (Nakhoul et al.

, 1998; Cooper and Boron, 1998; Uehlein et al., 2003), nitric oxide (8) (Herrera and Garvin, 2007), and ammonia (9-11) (Holm et al., 2005; Musa-Aziz et al., 2009; Gruswitz et al., 2010). Gases are small enough to pass through aquaporins captivating evidence is lacking for physiologically relevant gas transport, partly because the intrinsic lipid-mediated membrane permeability to most gases is high (12-14) (Yang et al., 2006; Missner et al., 2008; Madeira et al.

, 2016). Aquaporins biological functions are mostly attributed to facilitated water and/or glycerol transport as evident from current studies. Structure of Aquaporins Aquaporins are simple proteins concerning the structure and functions compared to ion channels. Several mammalian AQPs have been determined using X-ray structures each with ~30-kDa monomer, spanning six helical domains with cytoplasmic oriented amino and carboxy termini, including NPA sequences in their short helical segments forming a distinct water pore. In addition to the effect of NPA motifs, reentrant loops also help to maintain the configuration of the bipolar water file, the two-helices generate two electrostatic dipoles which point toward the center of the channel, forcing water dipoles to orient in the opposite direction. Under their influence, water molecules tend to point their oxygens toward the center of the channel. The movement of water occurs as a single file through the pore via electrostatic and steric factors (15, 16) (Hub et al.

, 2008; Khalali-Araghi et al., 2013). AQP1, AQP2, AQP4, AQP5 and AQP8 primarily functions as bidirectional water-selective transporters. It is well established that heavy metals can directly interact with AQPs thereby affecting their activity. Studies have shown that heavy metals are found to have inhibitory effect on aquaporins, especially mercury (17) (Hasegawa et al., 1994). Copper and nickel involving amino acids in loop C and E mediates AQP inhibition (18, 19) (Zelenina et al., 2003, 2004).

Further silver and gold does have inhibitory effect on AQPs (20)(Niemi et al. and Tyerman, 2002). The new insights into the regulation and functions of AQPs in reproduction are revealed in recent years. This review extensively discusses the distribution of AQPs in male reproductive tissues and their functions, mainly focuses on the recent advances in our understanding of the physiological and pathophysiological roles of AQPs in male reproductive systems. Functions of Aquaporins in Male Reproductive System Fluid secretion and reabsorption are of central importance in male reproductive (MR) physiology (21) (Calamita, 2001).

Water movement across the male reproductive tract plays a pivotal role in maintaining the luminal environment for spermatogenesis and also in increasing the concentration of sperm. The water channel, aquaporins is found to play an important role in reproductive system facilitating transepithelial fluid secretion in exocrine glands and other secretory epithelia (22) (Tradtrantip et al., 2009). Multiple aquaporins are found to be expressed in the male reproductive system and few have been reported to be tissue specific and further regulated by steroid hormones. In regard, to

human male reproductive system there are only few reports on aquaporins (23, 24) (Zaniboni and Bakst, 2004; Zaniboni et al.

, 2004). Moreover, the specific expression pattern of AQPs suggests transport of water is locally modulated. Alteration in the expression, function and/or regulation of AQPs lead to disorders of male reproductive system. AQPs aids in transcellular transport, maintaining water homeostasis and also is strongly associated with male reproductive system.