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Review

Segmental and cellular expression of aquaporins in the male excurrent duct

Nicolas Da Silva, Christine Piétrement, Dennis Brown, Sylvie Breton *

Program in Membrane Biology-Nephrology Division, Massachusetts General Hospital, Department of Medicine, Harvard Medical School, Boston, MA 02114-2790, USA

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Abstract

The male reproductive tract and accessory glands comprise a complex but interrelated system of tissues that are composed of many distinct cell types, all of which contribute to the ability of spermatozoa to carry out their ultimate function of fertilizing an oocyte. Spermatozoa undergo their final steps of maturation as they pass through the male excurrent duct, which includes efferent ducts, the epididymis and the vas deferens. The composition of the luminal environment in these organs is tightly regulated. Major fluid reabsorption occurs in efferent ducts and in the epididymis, and leads to a significant increase in sperm concentration. In the distal epididymis and vas deferens, fluid secretion controls the final fluidity of the luminal content. Therefore, the process of water movement in the excurrent duct is a crucial step for the establishment of male fertility. Aquaporins contribute to transepithelial water transport in many tissues, including the kidney, the brain, the eye and the respiratory tract. The present article reviews our current knowledge regarding the distribution and function of aquaporins in the male excurrent duct.

Keywords: Water channel; Fluid reabsorption; Fluid secretion; Male fertility

Contents

1. Introduction

The establishment of functional sperm in the male reproductive tract is a complex process that includes the production of a large number of diluted spermatozoa by the testis, followed by several maturation steps that occur in the male excurrent duct. The excurrent duct of the male reproductive tract is composed of distinct tissues having specific functions. The efferent ducts connect the testis with the epididymis and are involved in major water reabsorption driven by the transepithelial movement of NaCl, which results in sperm concentration [1–5]. The epididymis is the site where spermatozoa acquire their ability to become motile and fertilize an egg, and is also involved in significant water reabsorption leading to a further increase in sperm concentration [6–11]. In

* Corresponding author. Massachusetts General Hospital, Program in Membrane Biology-Nephrology Division, CPZN 8150, 185 Cambridge Street, Boston, MA 02114-2790, USA. Tel.: +1 617 726 5785; fax: +1 617 643 3182.
E-mail address: sbreton@partners.org (S. Breton).

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the distal portion of the epididymis and the vas deferens, water secretion driven by CFTR-dependent chloride secretion was proposed to control the fluidity of the luminal content [12]. Thus, major water transport across the epithelium lining the male excurrent duct accompanies the maturation of spermatozoa.

Epithelial cells engage in transepithelial fluid movement by inserting different transporters into their plasma membrane. Among these numerous transporters, aquaporin water channels (AQPs) are now seen as major contributors to water transport across biological membranes. Whereas aquaporins in the male gamete and Sertoli cells of the testis are clearly important players in the establishment and regulation of male fertility (for review see [13]), the present mini-review article focuses on the expression and regulation of aquaporins in the male excurrent ducts and discusses their potential role in modulating male fertility.

2. The aquaporin family

During the last decade, the identification of the major intrinsic protein (MIP) superfamily has revolutionized our understanding of the basis of water transport across the plasma membrane. MIPs are transmembrane integral proteins, which form an aqueous channel through the lipid bilayer and, consequently, play a major role in the regulation of membrane water permeability. Living organisms exhibit more than 450 MIPs and among them, 13 vertebrate aquaporins (AQP0 to 12) have been identified to date [14]. However, sequence analysis indicates that AQP11 and AQP12 are only distantly related to the MIP family. Two subgroups of mammalian aquaporins have been defined on the basis of their permeability characteristics: the aquaporins (AQP0, 1, 2, 4, 5, 6 and 8) are highly selective for water, whereas the aquaglyceroporins are also permeated by glycerol (AQP3, 7, 10) or even larger solutes (AQP9), in addition to water. Aquaporins are widely expressed in fluid-conducting and secretory organs: at least seven distinct aquaporins are expressed in the kidney [15,16], five in the eye [17], four in the respiratory tract [18,19], and they are also found in salivary, sweat and lachrymal glands as well as other tissues (reviewed in [20]). Aquaporins are involved in many cellular and physiological processes, and mutations in aquaporin genes have been shown to trigger pathological conditions including nephrogenic diabetes insipidus (mutation of *Aqp2* [15,21–25]) and inherited cataract (mutation of *Aqp0* [26]). Hence, a considerable amount of work has been initiated during the last decade to elucidate the function of aquaporins in the male reproductive tract and, consequently, evaluate their potential to serve as biomedical targets for the control of male fertility (also reviewed in [13]).

3. Aquaporins in efferent ducts

The efferent ducts (ductuli efferentes) are a series of tubules that extend from the rete testis to the initial segments of the epididymis. The ducts are lined with a columnar epithelium composed of two cell types: ciliated and non-ciliated cells [27]. Sperm moving through the efferent ducts are not mobile and are propelled downstream by the cilia of ciliated cells [27]. Efferent ducts are remnants of the mesonephric kidney (mesonephros) and are, therefore, closely related to renal proximal tubules in appearance and in many aspects of their function [28]. After further development of the kidney, some mesonephric tubules persist to become the efferent ducts. Interestingly, the mesonephros is also the source of hematopoietic stem cells [29]. An abundant secretion of fluid accompanies the production of spermatozoa in the testis [30]. Major fluid reabsorption (between 50 and 90% of the fluid is reabsorbed) occurs subsequently in the efferent ducts and this results in a 25-fold increase in sperm concentration [1–4,31]. In this respect, the efferent ducts resemble renal proximal tubules, which absorb up to 80% of the glomerular ultrafiltrate [2,15]. Indeed, absorptive epithelial cells in the efferent ducts have a well-developed apical brush-border membrane and are connected by gap junctions, as are proximal tubule epithelial cells. The considerable amount of data published on kidney reabsorption yielded some clues for the study of fluid reabsorption in the efferent ducts. The water channel CHIP28, which is expressed in the apical and basolateral membranes of kidney proximal tubule epithelial cells, is also present in the apical and basolateral membranes of non-ciliated cells of the rat efferent ducts [32] (Figs. 1 and 7(1)). The presence of AQP1 in non-ciliated cells of efferent ducts was confirmed in a subsequent report [33], but the cilia of the adjacent ciliated cells were also reported to be positive for AQP1.

CHIP28 (later renamed aquaporin 1—AQP1) was the first member of the aquaporin family to be cloned and characterized in model systems. Expression of AQP1 in Xenopus oocytes [34], and incorporation of purified protein into phospholipid vesicles [35,36] demonstrated that AQP1 functions as a selective water channel. CHIP28/AQP1 has been shown to be a major contributor to the constitutive plasma membrane water permeability of erythrocytes, renal proximal tubules and descending limbs of Henle, all tissues which, like efferent ducts, derive from the mesonephros.

Since the identification of AQP1 in the efferent ducts, the role of aquaporins in male fertility has been widely investigated. Impairment of solute and fluid reabsorption in efferent ducts could lead to the establishment of an abnormal luminal environment and, subsequently, to a decrease or loss of fertility [37–39]. Fluid reabsorption in the efferent ducts is controlled by androgens [40] and, more surprisingly, by the “female” sex steroid estrogens [41]. Androgens are converted into estrogens by cytochrome P450 aromatase, which is expressed in Leydig cells of the adult testis and, more importantly, in germ cells and spermatozoa [42]. In addition, epithelial cells of the efferent ducts express both androgen and estrogen receptors [43,44]. The characterization of male αERKO mice, lacking the estrogen receptor (ER) α, has revealed that the structure of the apical surface of the efferent duct epithelium is altered, triggering an impairment of fluid reabsorption, the subsequent accumulation of fluid in the lumen, and finally a loss of fertility [37]. A similar pattern has been described in rats treated with the anti-estrogen ICI 182,780 [38]. The mechanisms of fluid reabsorption in the

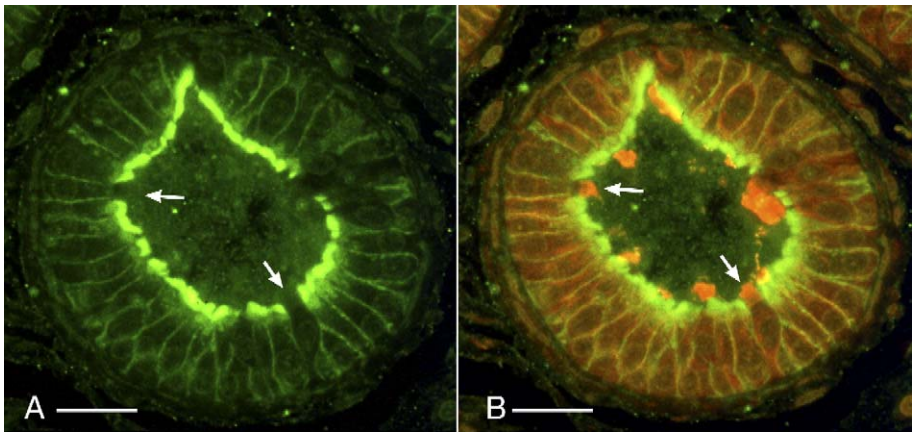

Fig. 1. Localization of AQP1 in rat efferent ducts. (A) AQP1 (green) is located in the basolateral and apical membrane of most epithelial cells. A few cells are negative for AQP1 (arrows). (B) Double-labeling for tubulin (red) showing that cells negative for AQP1 are the ciliated cells (arrows). A brighter staining for AQP1 was detected in the apical brush border membrane compared to the basolateral membrane of non-ciliated cells. Scale bars = 25 μm. Reprinted from the cover figure of the European Journal of Cell Biology, Vol 62 related to [32], with permission from Elsevier.

efferent ducts are not completely elucidated, but a growing number of transporters have been identified in epithelial cells of this segment. These transporters include the Na^+/K^+-ATPase, SLC9A3 (Na^+/H^+ exchanger 3, previously known as NHE3), CFTR (cystic fibrosis transmembrane regulator) and three members of the aquaporin family: AQP1, 9 and 10 [1,32,33,45–50]. While AQP1 is abundantly expressed in the efferent duct epithelium, the morphology of the ducts and the fertility of AQP1 null males are not affected, contrary to αER and NHE3 knock out males [39]. Thus, whereas SLC9A3 (NHE3) seems to be a major contributor to fluid reabsorption in efferent ducts, the work on AQP1 knockout mice also suggests that other members of the aquaporin family might compensate for the lack of functional AQP1. In agreement with this hypothesis, AQP9 has been identified in the apical membrane of non-ciliated cells of the efferent ducts [33,46]. However, because AQP9 immunostaining is restricted to the apical membrane of these cells (Figs. 2 and 7(1)), it would compensate only partially for the absence of AQP1 in the AQP1 knockout mice to preserve their fertility. Recent data show that sperm concentration and motility are decreased in αERKO mice [51]. The authors suggest that this effect could be the consequence of a decrease of AQP1 and AQP9 expression in the efferent ducts. In addition, AQP10 was identified in the apical membrane of non-ciliated cells of the efferent ducts but, as for AQP9, not in the basolateral membrane [45]. AQP10 immunostaining is also present in ciliated cells. Together, these data indicate that non-ciliated epithelial cells of the efferent ducts express at least three members of the aquaporin family. The co-expression of several aquaporins in the same cell type, or even in the same membrane domain of a given cell type, has been reported in several epithelia actively involved in water transport, including the kidney collecting duct. This apparent redundancy suggests that aquaporins, in addition to facilitating the rapid movement of water across the epithelium, could also be involved in other functions. In this respect, it is interesting to note that AQP9 and AQP10 are neutral solute channels, in addition to being water channels. In particular, they allow the passage of glycerol, which has been

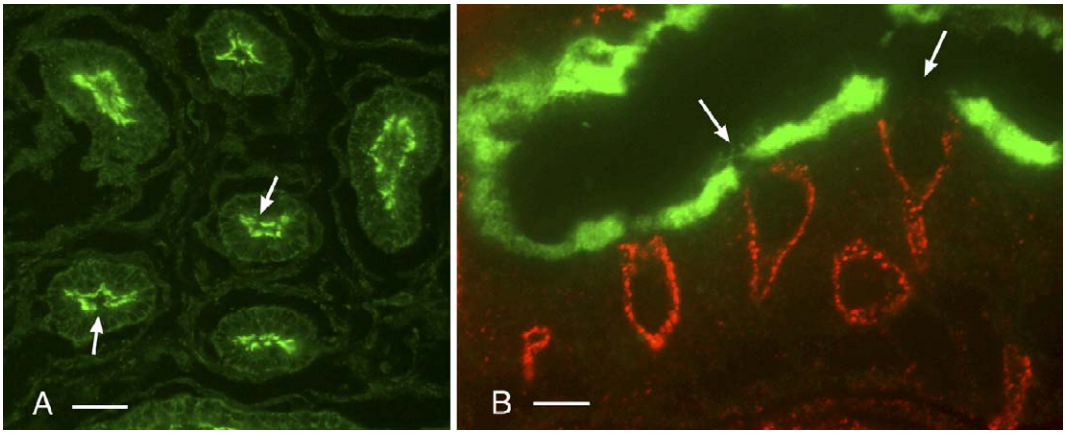

Fig. 2. Localization of AQP9 in rat efferent ducts. (A) A bright AQP9 (green) apical brush border membrane staining is seen in most epithelial cells. A few cells are negative for AQP9 (arrows). (B) Double-labeling for the anion exchanger, AE2, showing that ciliated cells, which express this protein in their basolateral membrane are negative for AQP9 (arrows). No staining for AQP9 is detected in the basolateral membrane of non-ciliated cells. Scale bars = 50 μm (A); 10 μm (B).

proposed to serve as metabolic substrate for sperm [52]. Spermatozoa express AQP7 [53], another aquaglyceroporin, and therefore have the capacity to transport glycerol.

4. Aquaporins in the epididymis

The epididymis is located downstream of the efferent ducts. It is a highly coiled tubule segmented into morphologically distinct regions: caput, corpus and cauda epididymidis. Epithelial cells lining this long tubule create the appropriate microenvironment for spermatozoa as they mature in this organ [6,7,9]. Spermatozoa acquire the ability to become motile and to fertilize an oocyte, and are stored in a quiescent state in the epididymis [6–11]. Caput, corpus and cauda epididymidis are further segmented into intraregional segments, harboring a distinct microenvironment within each segment. Ten segments are anatomically distinguished in the mouse epididymis, and a recent study shows that these 10 segments constitute 6 entities [54]. Each entity displays a distinctive pattern of individual gene and gene family expression, indicating that these units play complementary but distinct and highly regulated roles in the maturation, transport and storage of sperm. The epididymal epithelium contains several cell types, including principal, apical, narrow, clear, and basal cells [55]. In the adult, principal cells transport and secrete actively small organic molecules and proteins, and absorb fluid and particles [6,9,11,55], and narrow and clear cells are involved in luminal acidification (reviewed in [56]). A marked increase in sperm concentration during their transit toward distal regions, as well as the establishment of a hypertonic luminal fluid, indicate that considerable fluid reabsorption occurs in the epididymis [4,31,40,57–59]. So far, 6 members of the aquaporin family have been reported in principal cells and basal cells of the epididymis. In contrast, expression of most members of the aquaporin family has not been reported in clear cells.

AQP1 is absent from the epididymal epithelial cells but is expressed in adjacent smooth muscle and endothelial cells of vascular channels [32,33]. AQP1 was also detected in endothelial cells of the efferent ducts and may be involved in the removal of water from these tissues following its reabsorption by epithelial cells. AQP9 is expressed in all regions of the epididymis [33,46,60] and is clearly the predominant aquaporin in this tissue. In the initial segments, AQP9 staining is concentrated at the apical pole of principal cells, which are characterized by the presence of long apical stereocilia (Figs. 3A and 7(2)). The rare narrow V-ATPase-rich cells present in this segment are unstained [46], as well as the basolateral membrane of all cell types. By immunofluorescence, AQP9 remains abundant in the apical membrane of principal cells of caput, corpus and cauda epididymidis and is absent from V-ATPase-labeled clear cells (Figs. 3B, 4 and 7(3–4)). Whereas AQP9 expression in principal cells has been observed by several laboratories [33,46,60], expression in clear cells was also reported by Badran and Hermo using immunoperoxidase staining [33]. Whether this apparent discrepancy is attributed to different fixation protocols, different primary antibodies or different immuno-detection procedures still remains to be elucidated, and additional data will be required to determine whether or not clear cells express AQP9.

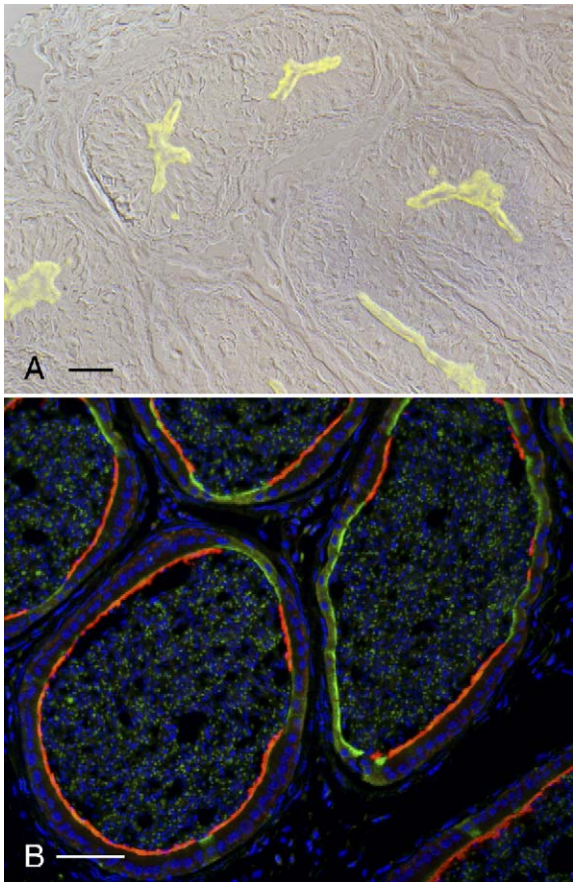

Fig. 3. Localization of AQP9 in mouse and rat epididymis. (A) Differential interference contrast image of initial segments of rat epididymis superimposed with immunofluorescence labeling for AQP9 (yellow-green). AQP9 is located in the long apical stereocilia of principal cells. (B) Mouse proximal cauda epididymidis showing apical AQP9 labeling in principal cells (red). Clear cells, identified by their positive staining (green) for the V-ATPase (B2 subunit, ATP6V1B2), are not stained for AQP9. In contrast to rat, mouse cauda epididymidis contains rows of adjacent clear cells. Spermatozoa also show positive labeling for ATP6V1B2. Nuclei are stained with DAPI (blue). No basolateral staining for AQP9 is detected. Scale bars 25 μm (A); 50 μm (B).

The epididymis at birth is a largely undifferentiated system of tubules, and the complex organization seen in adult animals is incompletely characterized. Cell-specific differentiation occurs prior to sexual maturity in rodents, and both androgens and estrogens influence the differentiation pattern of various cell types from the epididymis. Androgens and estrogens regulate AQP9 expression in efferent ducts [33,61], but only androgens modulate AQP9 expression in the epididymis [33,61,62]. Moreover, CFTR (cystic fibrosis transmembrane regulator), which is expressed in the apical membrane of principal cells of the rat epididymis [63], has a potentiating effect on AQP9-mediated water reabsorption when expressed in Xenopus oocytes, suggesting that this chloride channel could also be involved in epididymal water transport [64].

In addition to AQP9, recent studies reported the expression of AQP3, AQP5, and AQP8 in a subpopulation of epithelial cells in the epididymis. However, conflicting results were

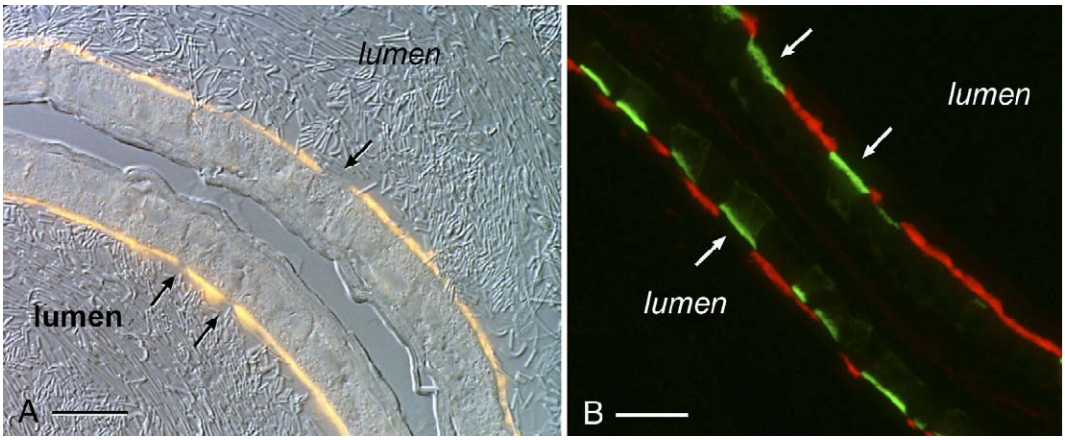

Fig. 4. Localization of AQP9 in the rat cauda epididymidis. (A) Differential interference contrast image of the rat distal cauda epididymidis superimposed with immunofluorescence labeling for AQP9 (orange). AQP9 is present in the apical membrane of a sub-population of epithelial cells, while a few cells are negative (arrow). Abundant sperm, negative for AQP9, are detected in the lumen of the tubules. (B) Double-labeling for AQP9 (red) and the E subunit of the V-ATPase (ATP6V1E2, green) shows that principal cells (negative for the V-ATPase) express AQP9 in their apical membrane, and that clear cells (positive for the V-ATPase) are negative for AQP9 (arrows). No basolateral staining for AQP9 is detected. Scale bars = 30 μm.

obtained for AQP3 and AQP8. AQP3 was detected by immunocytochemistry in basal cells from all regions of the rat epididymis [45]. However, data from our laboratory showed the absence of AQP3 mRNA from epididymal epithelial cells isolated by laser capture microdissection and the absence of immunofluorescence staining in epididymis sections [65]. In addition, while AQP8 mRNA and protein were not detected in epididymal epithelial cells [33,65,66] another study showed the presence of AQP8 protein in basal cells [67].

The selective water channel AQP5 is co-expressed with AQP9 in the apical membrane of a subpopulation of principal cells in corpus and cauda epididymidis (Figs. 5 and 7(4)) [65]. The potential role of AQP5 in epididymal water reabsorption remains to be elucidated. AQP2, which is abundantly expressed in the distal vas deferens of adult rats (see below), has also been reported in the rat epididymis, with a complex pattern of spatial and temporal expression [65]. AQP2 mRNA was detected at birth and increases markedly during postnatal development, with a maximum expression level observed after 4 weeks. The corresponding protein is transiently expressed in cauda epididymidis during postnatal development and, while the mRNA remains detectable during adulthood, AQP2 protein is not immunologically detected in the adult epididymis. This temporal variation in AQP2 might indicate an important role for this aquaporin during post-natal development.

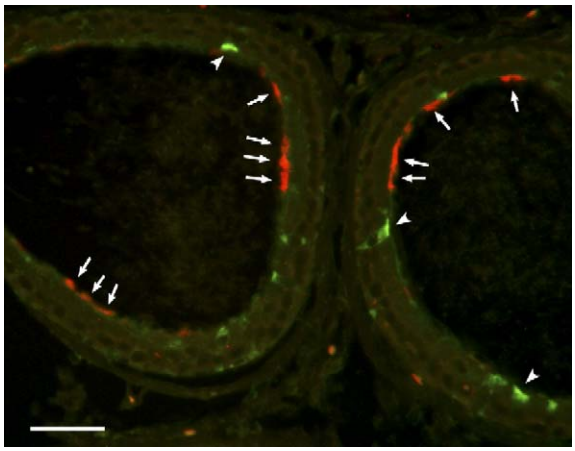

Fig. 5. Localization of AQP5 in the rat cauda epididymidis. AQP5 (red; arrows) is located in the apical membrane of a sub-population of epithelial cells. These cells are negative for the V-ATPase expressed in clear cells (green; arrowheads), and are therefore identified as principal cells. Scale bar = 30 μm.

5. Aquaporins in the vas deferens

The vas deferens (ductus deferens) conducts sperm from the epididymis to the urethra through the ejaculatory duct. Epithelial cells lining the lumen of vas deferens maintain the environment in which sperm continue their maturation and are stored. The vas deferens can be divided into three regions (proximal, middle, distal), each region exhibiting diverse functional activities and, therefore, diverse patterns of gene and protein expression. The epithelium of the vas deferens contains, like the epididymal epithelium, principal cells and clear cells [68]. Similarly to efferent ducts, the vas deferens is a remnant of the mesonephric kidney. AQP1, the predominant water channel of the renal proximal tubule and efferent ducts, was also detected in the most distal portion of the vas deferens (also called ampulla) [32]. However, AQP1 is absent from the proximal and middle vas deferens. The distribution of AQP2 is heterogeneous along the vas deferens. In the adult rat, AQP2 is not detected in the proximal portion but its expression increases progressively in the middle portion, and finally all epithelial cells of the distal vas deferens contain AQP2 (Figs. 6 and 7(5–7)) [69,70]. AQP2 was originally identified in the renal collecting ducts [71]. When kidneys are stimulated by vasopressin, a modification of the trafficking process results in the accumulation of AQP2 on the plasma membrane of principal cell leading to a dramatic increase of transepithelial water reabsorption [15,24,72]. In the vas deferens, AQP2 is present constitutively in the apical plasma membrane of

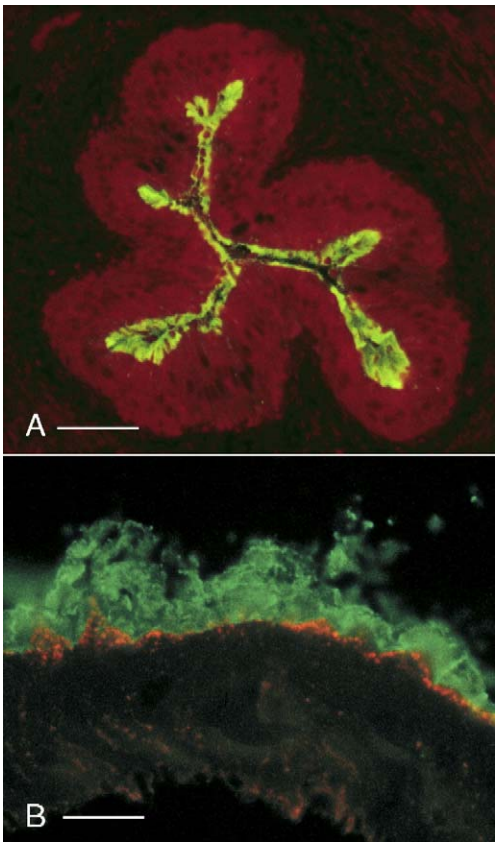

Fig. 6. Localization of AQP2 in the distal vas deferens. (A) Immunofluorescence AQP2 staining of a cross-section of the distal portion of rat vas deferens. An intense apical staining (yellow) is seen with no intracellular vesicular staining. The red background is a counterstain (Evans' blue) allowing visualization of the epithelial cells. (B) Longitudinal section of rat vas deferens incubated in vitro with Texas Red-dextran and double-stained for AQP2. Many sub-apical vesicles contain Texas Red-dextran (red), indicating active endocytosis. However, AQP2 staining (green) is restricted to the apical plasma membrane and extensive stereocilia of principal cells and no AQP2 staining is seen in the labeled endosomes. Scale bars = 50 μm (A); 10 μm (B). Reprinted from [70] with permission from Am J Physiol Cell Physiol.

principal cells and, in contrast to renal AQP2, is not regulated by vasopressin (this observation is corroborated by the absence of detectable levels of vasopressin receptors in epithelial cells of the vas deferens) [70]. As mentioned above, the regional distribution of AQP2 markedly varies during postnatal development of the rat epididymis. During the 4 first weeks following birth, AQP2 is transiently expressed in the proximal vas deferens, as well as in the cauda epididymidis. At weeks 3 and 4, an intense AQP2 staining is detected in the lumen of the vas deferens, in addition to the epithelial staining [65]. Thus, during the first weeks of postnatal development, AQP2 seems to follow a sequential pattern of expression, with an early expression in the distal epididymis and the proximal vas deferens, followed by a possible shedding of the protein into the lumen and a distal expression in the ampulla, which persists during adulthood.

In addition to AQP1 and AQP2, AQP9 is present in the rat vas deferens, where it is detected throughout the entire length of the duct [46]. AQP9 is abundantly expressed in the apical membrane of principal cells, and is co-expressed with AQP1 and AQP2 in the ampulla. Thus, three aquaporins have been identified so far in the vas deferens; these three water channels are present in the same membrane domain of epithelial cells from the most distal region, suggesting that the composition of the luminal environment in which spermatozoa terminate their maturation and are stored involves a complex regulation of transepithelial water and solute transport.

6. Aquaporins and male fertility

Epithelial cells from the male excurrent duct express at least seven members of the aquaporin family. Most of the testicular fluid is reabsorbed in efferent ducts, whereas the epididymis and vas deferens establish and maintain the appropriate environment in which spermatozoa mature and are stored. The three main aquaporins in the excurrent duct are AQP1 in efferent ducts and distal vas deferens, AQP9 in efferent ducts, epididymis and vas deferens, and AQP2 in the distal vas deferens. Some of these aquaporins are co-expressed in the same membrane domain of a given cell type. AQP1 and AQP9 are present in the apical membrane of non-ciliated cells from efferent ducts, but AQP1 is also present in the basolateral membrane and is, to date, the only basolateral aquaporin reported in the male excurrent duct. No basolateral aquaporin has yet been identified in the epididymis and in the proximal and middle vas deferens. AQP2 and AQP9 are present in the apical membrane of principal cells in the ampulla of the vas deferens, in addition to apical and basolateral AQP1. A similar "redundancy" of AQP expression has been observed in membranes of other cell types, including basolateral membrane of principal cells of the inner medullary kidney collecting duct, which express AQP2, AQP3 and AQP4. AQP4 is, like AQP1 and AQP2, a selective water channel, whereas AQP3 is, like AQP9, an aquaglyceroporin. Each epithelial system may, therefore, require a specific combination of aquaporins and aquaglyceroporins. The generation of new animal models, including double-knockout mice, would undoubtedly help us to further elucidate the relative contribution of individual aquaporins to overall transepithelial transport.

Aquaporin expression and function can be regulated at multiple levels. AQP2 mRNA expression is increased in the kidney and vas deferens following dehydration, however the corresponding protein is increased only in the kidney [70]. In fact, other major differences have been described between the kidney and vas deferens with respect to AQP2 regulation. Unlike kidney collecting duct AQP2, which is accumulated in the apical membrane of principal cells after the binding of vasopressin to its receptor, vas deferens AQP2 is constitutively expressed in the apical membrane of principal cells. In addition, the glycosylation status of AQP2 is different in the vas deferens and kidney, which could play a role in the intracellular targeting and/or the stability of the protein [70]. Therefore, AQP2 expression is likely to be controlled by tissue-specific transcriptional, posttranscriptional and posttranslational mechanisms, which remain to be elucidated. AQP9 is also a constitutive apical membrane protein in the male excurrent duct; microtubule disruption by colchicine does not affect AQP9

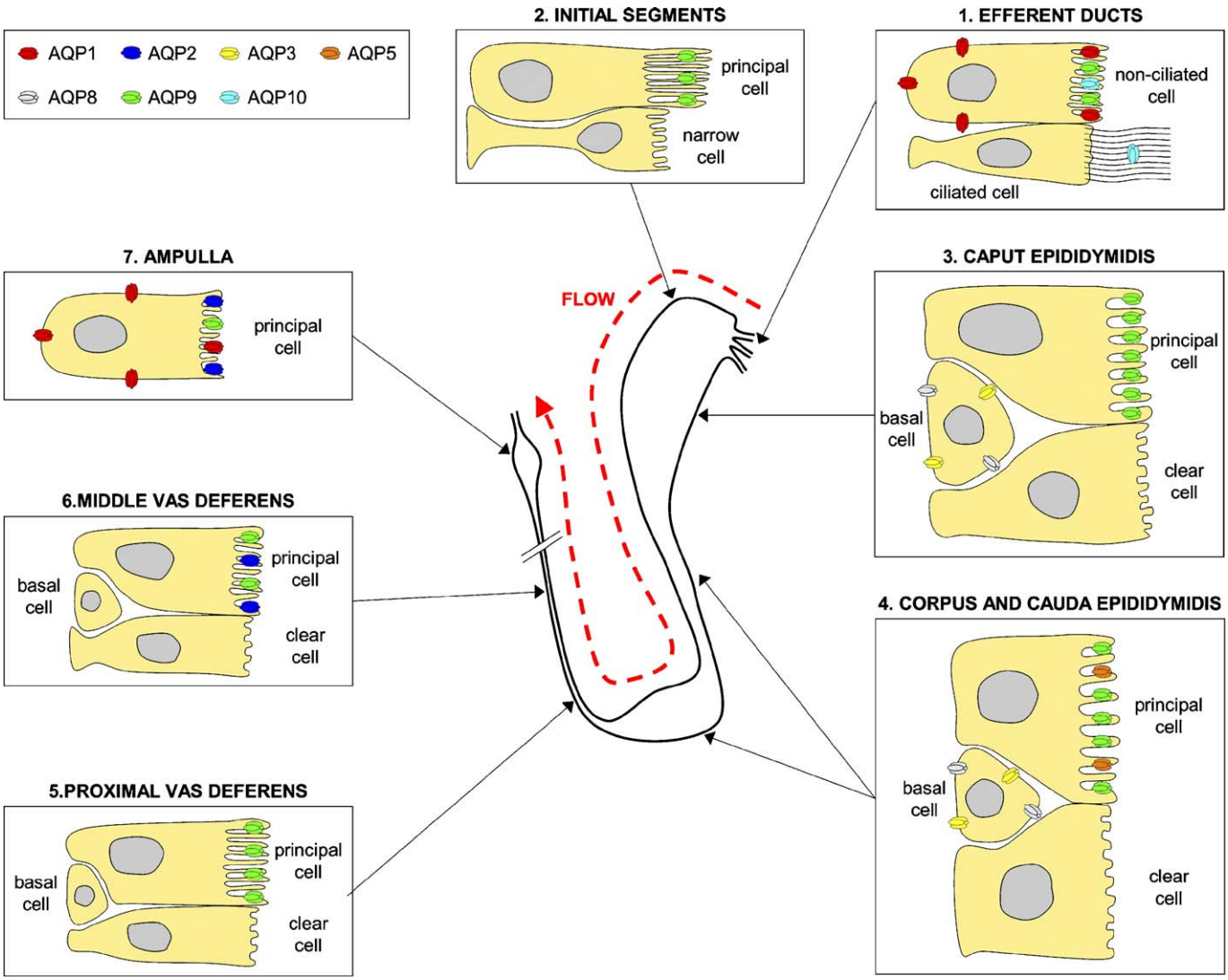

Fig. 7. Schematic view of aquaporin distribution in the adult male excurrent duct. AQP1 is present in the apical and basolateral membranes of epithelial cells of efferent ducts (1) and the ampulla (7), which is the most distal portion of the vas deferens. AQP2 is constitutively expressed in the ampulla (7) and the middle vas deferens (6), but is restricted to the apical membrane. AQP3 and AQP8 have been identified in basal cells of the epididymis (3, 4). Non-ciliated cells of efferent ducts (1) and all principal cells of the epididymis (2, 3, 4) and vas deferens (5, 6, 7), contain AQP9 in their apical membrane. In addition, AQP5 is present in a subpopulation of principal cells of the epididymis (4), and AQP10 has been reported in efferent ducts (1).

distribution in the rat epididymis, indicating that this channel is not actively recycling from the cell surface to intracellular vesicles [46]. In contrast, AQP9 has been localized on intracellular structures in prostatic epithelial cells [46]. Thus, aquaporins contain signals that can be interpreted in a cell-type specific fashion and will target the proteins towards different membrane domains and control their recycling rate. The regulation of aquaporins may also be controlled by direct interactions with other proteins. AQP4 contains a PDZ (PSD-95, Discs large, ZO-1) domain, which binds to syntrophin [73]. This interaction controls the polarized targeting of AQP4 to a large protein complex that is involved in the establishment of the blood–brain barrier. The luminal content of the male reproductive tract is also immunologically protected by the establishment of a blood–tissue barrier but, to date, aquaporins have not been implicated in this mechanism. In addition, AQP9 contains a “SVIM” motif in its carboxyl terminus, suggesting that it could interact with PDZ proteins. The chloride channel CFTR potentiates the AQP9-dependent water permeability in Xenopus oocytes [64], suggesting that the regulation of aquaporin-mediated water permeability may be regulated by interaction with other proteins. While major water reabsorption in the proximal regions of the epididymis is responsible for significant sperm concentration, in the distal regions water secretion driven by CFTR-dependent chloride transport has been described [12]. Both reabsorption and secretion are thought to exert a fine control over the net movement of water across the epithelium of the cauda epididymidis and vas deferens. Thus, the control of water transport by CFTR in these organs, either via chloride secretion or direct modulation of AQP9 activity, might be a key step in regulating the fluidity of the luminal environment.

7. Conclusion

Over the past few years, aquaporins have become the subject of considerable interest in the field of male fertility. The importance of water movement across the epithelium lining the excurrent duct is exemplified by animal models that are infertile or sub-fertile because of impaired reabsorption of the seminiferous fluid. In addition, bi-directional transepithelial water movement is thought to play a critical role in controlling the final fluidity of the luminal content of the distal epididymis and the vas deferens. So far several aquaporins have been described mainly in non-ciliated and principal cells of the excurrent duct. Interestingly, in the epididymis and the proximal and middle vas deferens no basolateral aquaporin has been identified to date and the identity of the aquaporin or water exit pathway that may participate in water transport across the basolateral membrane remains unknown. Recent data have clarified the spatial and temporal distribution of aquaporin mRNA and protein in the excurrent ducts [65]. This now provides a solid framework for future studies on the physiological and pathophysiological contributions of aquaporins to male reproductive function. Furthermore, the identification of these targets may allow the development of novel compounds aimed at modulating male fertility.

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