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AQUAPORINS: THE CANDIDATE TRANSPORTER FOR WATER REGULATION IN MAMMARY GLAND

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ABSTRACT

Milk production is a critical and complex process connected to different transport systems and mechanisms. The transfer of milk of compounds in lactating mammary epithelial cells is a process that involves several transporters, but it remains unclear how the water content in milk is regulated in lactating mammary gland. Aquaporins (AQP) are family of channel proteins that facilitates the movement of water and small molecules across the cell membrane. Aquaporins are widely expressed in the body particularly in tissues that are actively involved in fluid transport. Some studies suggests that several aquaporin proteins are present in mammary glands.

KEY WORDS : Aquaporins, Mammary gland, Water Transport

AQUAPORINS

Aquaporins (AQP) are family of channel proteins that facilitates the movement of water and small molecules across the cell membrane. First AQP was identified in erythrocyte by Dr. Peter Agre and he got Nobel prize in 2003.Till date thirteen AQPs are reported in mammals. Aquaporins are widely expressed in the body particularly in tissues that are actively involved in fluid transport. Aquaporins are essential, integral membrane proteins with different functions in animal bodies. These proteins have permeability features for water, some gases, and specific small neutral solutes. Therefore, they will allow these substances to pass through the biological membranes. These proteins are conserved in animals, plants, and bacteria. Each aquaporin molecule has a pore in the center, which would be differentially found in various tissues and cells. In mammals, about thirteen aquaporin isoforms have been identified in the cells, and different isoforms are more common in some tissues than in others. These proteins molecular mass ranges from 26 to 29 kDa, and the complete proteins will have six membrane-spanning α helices, with loops connecting them (**Fig.1**). structure, features, permeability, and selectivity of this protein molecules enable them to perform their functions appropriately and adequately. The functions of aquaporins are critical to cellular and tissue functions in the body. Mainly, these proteins are essential to transport mediators, and

they will play significant roles in pathological and physiological processes in the body. Some aquaporins will conduct only water; others will conduct water and some carbohydrates. They conduct water at the high rate of 109 molecules for every second, which is a rate almost equal to how water would diffuse freely. They are involved in water transport in the cells and will also move some solutes, making them have different functions in the plant and animal tissues. They assist in cell volume regulation, stress response, and absorption of uncharged ions. They are involved in neuro excitation, cell migration, transepithelial fluid transport, and brain edema. In mammals, aquaporins have been associated with fluid transport in different body parts, including the eyes, gastrointestinal areas, kidneys, lens, and lungs. Some will help in the secretion and transport of sweat in the skin, and others will help absorb digested food products in the digestive tract. These channel proteins could also facilitate the transport of some hormones.

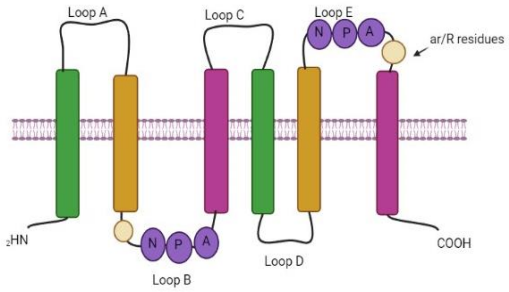

Fig. 1 Topology of aquaporin

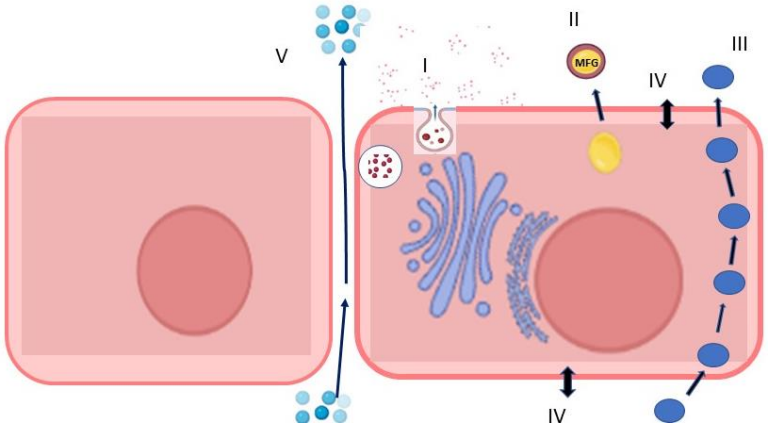

Fig. 2 Major routes of transportations in mammary epithelial cells. (I) Exocytosis (II) Reverse Pinocytosis,(III) Transcytosis, (IV) Apical Transport, (V) Paracellular transport

MAJOR ROUTES OF TRANSPORTATIONS IN MAMMARY GLAND

Till date there are five major routes of secretion across the mammary epithelium from blood side to the milk (**Fig.2**).

I. **Exocytosis/ Golgi route:** Exocytotic secretion is a form of bulk transport of molecules from cells to the out side. In mammary epithelial cells casein, whey protein, lactose, calcium and citrates are secreted in to the milk space by exocytosis.

II. **Reverse pinocytosis/ Milk fat route: M**ilk fat is secreted by formation of cytoplasmic lipid droplets that move to the apical membrane to be secreted as membrane bound milk fat globule (MFG). Products that utilize the Golgi route must first synthesized within the cell and then packaged into secretory vesicles within the Golgi apparatus. Once these materials are packaged, vesicles bud from the stacks of Golgi membranes, travel to the apical membrane where they fuse with the membrane and release their contents. Lipid soluble hormones, milk fat globules are extruded from the apex of secretory cells by reverse pinocytosis

III. **Transcytosis:** Immunoglobulins during the colostrum formation, transferrin and hormones like prolactin are transported through the transcytosis process.

IV. **Apical transport/ Membrane route:** This route used for the direct movement of monovalent ions, water and glucose across the apical and basal membranes of the cell.

V. **Paracellular transport**: The paracellular pathway enables the direct movement of substances between the interstitial and milk spaces. This process is open and active in pregnancy and will ensure the transfer of large molecules. Usually, in entirely lactating glands, this system is close, offering an obstacle between the interstitial and milk spaces. In particular, this barrier could open up again in cases of involution or mastitis.

AQUAPORINS IN MAMMARY GLAND

Mammary glands are essential in producing and transporting milk intended for consumption by the young ones.In mammary gland the epithelial cells present in alveoli and ducts are in direct contact with milk. Alveolar mammary epithelial cells synthesize and secretes multiple milk components with abundant water to the lumen.Therefore, transport mechanisms are critical in these organs to ensure that different components are transported in the production and release of milk. Current understanding is that water is secreted across mammary epithelium in transcellular manner in response to an osmotic gradient produced largely by the lactose content of milk. Numerous pathways are involved in milk secretion and transport. Major pathways are associated with the transport system in the mammary glands, such as transmembrane

ion secretion, exocytosis, and extra-alveolar protein transcytosis, are among processes that could be associated with transport of different elements,but it remains unclear how the water content in milk is regulated in lactating mammary gland. Aquaporins are one of the transport molecules highlighted to be essential in the transport aspects of milk. In particular, studies have found AQP1 and AQP3 present in the water channels in human, bovine, mouse, and rat mammary glands. Other AQP4, AQP5, and AQP7 have also been identified in various areas in the mammary glands. Therefore, it is undeniable they have particular roles in this organ. Several aquaporins work together to produce milk in the mammary glands, and they may be helpful in various lactation stages.

Table 1. Summary of studies illustrating the AQPs in mammary gland

Animal species	AQP analysed	Location	Method adopted	References
Rat	AQP1	Endothelial cells of capillaries & venules.	IHC, WB, RT-PCR	Matsuzaki *et al.*, 2005.
	AQP3	Alveolar epithelium and duct system.		
Bovine	AQP1	Capillary endothelia in the cistern, teat & adipose tissue. Myoepithelial cells underlying cistern & teat duct.	IHC	Mobasheri A *et al.*, 2011.
	AQP3	Selected epithelial cells in teat acini and cistern.		
	AQP4	Diffuse immunopositivity in teat, cistern and acini. Very low positivity in teat smooth muscle bundle.		
	AQP5	Prominent immunopositivity in acini and small cistern duct.		
	AQP7	Present in adipocytes, smooth muscle bundle, teat, teat duct and secretory acini.		
	AQP9	Only detected in leukocytes with in the mammary gland.		
	AQP1	Expanding alveoli during pregnancy and in early lactation secretory epithelium and blood vessel.	IHC, RT-PCR, WB	

Rat	AQP3 AQP5	Secretory alveoli during lactation. Apical membrane of alveoli during lactation.		Nazemi S *et al.*, 2014.
Mouse	AQP3 AQP5	Basolateral membrane of alveolar MECs (late pregnancy and lactation). Apical membrane of ductal MECs.	IHC, WB, IMS	Kaihoko Y *et al*., 2020.

Abbreviations. IHC – Immunohistochemistry, WB- Western Blotting, RT-PCR- Real time PCR, IMS- Immuno fluorescence staining, MECs- Mammary epithelial cells

CONCLUSION

AQPs expression in mammary gland has been suggested to function in milk dilution to maintain an isotonic solution.Transport mechanisms are critical in the mammary glands and help ensure milk secretion and successful lactation. Various transport pathways are essential in milk secretion and other physiological functions in the mammary glands.Aquaporins play critical roles in water and solute transport in the body. More research is necessary to help fully understand the role of aquaporins in mammary glands.

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