REVİEW

The Role of Aquaporins in Sinonasal Mucosa Physiopathology

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Abstract: The nose, an organ with crucial respiratory and olfactory functions, is the first organ to be exposed to external stimuli. As the first point of contact during inhalation, the sinonasal airway has various functions, including thermoregulation, humidification, removal of airborne particles and response to infectious agents. The sinonasal airway is exposed to many detrimental stimuli, some of which might be allergic. Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are the most prevalent diseases associated with the respiratory function of the nose. As typical pathological mechanisms, the pathogenesis of both diseases includes many common characteristics, such as edema and hypersecretion of the nasal mucosa. In this process, the roles of water channels, such as aquaporins (AQP), are vital. AQPs are water-specific membrane channel proteins that regulate cellular water homeostasis. Various AQPs are expressed in both nasal respiratory mucosa and olfactory mucosa. The human normal nasal respiratory epithelium contains AQP1, AQP2, AQP3, AQP4, AQP5, AQP7 and AQP11. The expression of AQPs is different in inflammatory diseases, such as AR or CRS than that in normal tissues. Nasal polyp tissue expressed abundant AQP1 than normal tissue, whereas AQP5 level was at lower levels in the sinonasal mucosa in AR and CRS with the polyp. The expression of AQPs in the olfactory epithelium differs from the expression in the respiratory epithelium. In this study, we investigated the relationship between AQPs and the sinonasal epithelium, which reveals a comprehensive overview of the physiopathological connections between allergic rhinitis, rhinosinusitis, and the olfactory system. This study can provide valuable insights into further investigation of AQPs as a potential therapeutic target.

Received : 01/05/2022
Received in revised form : 03/01/2022
Accepted : 03/30/2022
Available online : 06/21/2022

Keywords:

Aquaporins
Nasal Mucosa
Allergic Rhinitis
Chronic Rhinosinusitis
Physiopathology
Quality of Life

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http://dx.doi.org/10.47009/jamp.2022.4.2.16

Int J Acad Med Pharm,
2022; 4 (2); 72-77

INTRODUCTION

The sinonasal airway acts as a gateway between the external environment and the human body. As the first point of contact during inhalation, the sinonasal airway serves many roles, such as thermoregulation, humidification, removal of airborne particles, and response to infectious agents [1]. The sinonasal airway is exposed to a series of harmful stimuli, some of which might be allergic. It may lead to an immunoglobulin-mediated inflammatory response characterized by several symptoms, including runny nose, itching, sneezing and nasal congestion. This allergic response to inhaled stimuli is known as allergic rhinitis and is one of the most prevalent illnesses[2]. The nasal epithelium plays a key role in maintaining the water homeostasis of the airway. The nasal epithelium actively secretes most of the mucus and determines the electrolyte composition of nasal secretions. Nasal hypersecretion is one of the common characteristics of disorders, such as rhinitis and sinusitis [1,2]. This fluid layer, which determines the electrolyte composition of nasal secretions, covers the airway surface. The main role of this fluid is to protect the airway epithelium from inhaled hazardous substances. Hence, the nasal respiratory epithelium forms a crucial physiological defense barrier in the body[2,3]. Aquaporins (AQP), also termed water channels, are integral membrane proteins that belong to a large family of major proteins that form pores in biological membranes, facilitate the intercellular transport of water, and regulate water flow osmotically [4,5]. AQPs are generally known to be passive carriers of water. Some of these proteins mediate the transport of small solutes, including glycerol [6]. AQPs, which play a role in the transport of water to various cells, passively transport water across cell membranes and prevent the passage of ions and other solutes [4,6]. In addition to being critical for water homeostasis, AQPs also act as signaling factors in the physiological transport of molecules other than water, regulation of surface expression of other membrane proteins, regulation of cell adhesion, and cell volume [5,7,8].

This review aims to investigate the relationship between AQPs and the sinonasal epithelium, reveal a comprehensive overview of the physio pathological connections between allergic rhinitis, rhinosinusitis and the olfactory system.

Structure and function of aquaporins

Water is necessary for all molecular interactions, which are indispensable for the survival of living beings, and which are required for anabolic and catabolic reactions. Therefore, it is vital to regu-

late the transport of water, which is the primary component of living organisms [5]. AQPs, also known as water channels, are molecules with protein structures that pass through biological membranes. They assist in the rapid transport of water through membranes and are also crucial in regulating cell volume [4,5]. Although water passage is bilateral in diffusion, aquaporins allow unilateral passage controlled by the osmotic gradient [7]. Because its molecular weight defined in the erythrocyte membrane is 28-kDa, AQP was first termed CHIP28 (channel dependent integral protein-28) and later termed AQP1, as it is used today [9]. These proteins have a very specific molecular structure that resembles an hourglass and consists mainly of helices. They are found in cells of a great variety of species, including mammals, microorganisms, animals, and plants [4,7]. Recent studies have revealed that AQPs regulate other processes, such as cell migration, cell proliferation, and cell adhesion, in addition to the previously mentioned functions [5]. Hitherto, 13 aquaporin isoforms have been discovered in mammals, all involved in critical functions in various tissues [5,8].

Members of the AQP family are divided into three subgroups based on their permeability properties:

AQPs with water permeability: AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, AQP8.

AQPs that are permeable to both water and small molecules, such as urea and glycerol: AQP3, AQP7, AQP9, AQP10.

Hybrid AQPs: Those with permeability for water (AQP 11, AQP 12) and glycerol (AQP 11) [5,9].

Tissue-specific distributions of AQPs in the human body are summarized in Table 1. Many AQP isoforms (AQP1, 3, 4, 5,7, 8, 9, and 11) are found in the brain and nervous system, but AQP1 and AQP4 are found at relatively higher rates in the brain [8,10]. AQP1 is expressed in epithelial cells of the choroid plexus and plays a role in the formation of cerebrospinal fluid [11,12]. AQP1 is also present in primary sensory neurons and is suggested to play a role in pain perception [13]. Eight of the AQPs (AQP0, 1, 3, 4, 5, 7, 9, and 11) are found in the eye. These AQPs play many physiological roles, such as maintenance of the cornea and lens, wound healing, tear osmolarity, and maintenance of retinal homeostasis [14,15]. It has been reported that AQPs (AQP1, 2, 3, 4, 5, 6, 8, 10, and 11) found in the human ear are involved in immunological functions as well as in the regulation of neuronal signal transmission and cell movement [16].

In the skin, AQPs are distributed in the epidermis (AQP1, 3, 7, and 10), dermis (AQP1, 3, and 5), and hypodermis (AQP7) aid skin hydration, cell proliferation, immunity, and wound healing [8,17]. Kidney AQPs (AQP1, 2, 3, 4, 5, 6, 7, 8, and 11) play key roles in both short-term and long-term regulation of water balance [8,18]. AQP3 is expressed in the submucosal glands of the lung, while AQP4 and AQP5 are expressed in the airways and alveolar type I cells. AQP1, AQP3, and AQP9 are expressed in erythrocytes. AQP7, an aquaglyceroporin, is expressed in adipocytes, regulating glycerol transport through the cell[8].

Relationship between AQPs and nasal respiratory epithelium

The nasal cavity is divided into two parts, the respiratory segment and the olfactory segment. The respiratory segment makes up most of both nasal cavities and is covered by ciliated pseudostratified columnar epithelium, also called respiratory epithelium. This epithelium contains mucus-producing Goblet cells. The secretion of goblet cells is supported by mucus and serous glands in the connective tissue located under the epithelium called the lamina propria. The vessels in the lamina propria form thin-walled cavernous sinusoids, also called cavernous bodies [19,20]. Nasal epithelial cells play a crucial role in maintaining an even temperature by moistening and lightly lubricating the surface, thanks to water/ion channels like AQPs [20,21]. The expression of AQPs in the respiratory epithelium of the nasal cavity is summarized in Figure 1.

It has been revealed that the human nasal cavity has AQP1, AQP2, AQP3, AQP4, AQP5, AQP7 and AQP11 under respiratory physiological conditions [22].

Although the AQP1 protein is distributed in a variety of tissues in humans, it is especially remarkable in the kidneys. In addition to being a membrane channel that allows rapid water movement funneled by a transmembrane osmotic gradient, AQP1 also has a secondary function as a cyclic nucleotide-gated ion channel [20,23].

It has been reported that AQP1 is distributed in various parts of the nasal cavity respiratory epithelium. In a study conducted on rats, it was reported that it was abundant in the venules in the capillaries under the nasopharyngeal epithelium, in the capillaries of the nasal conchas , and the venous sinuses, whereas it was not detected in the surface epithelium of the nasopharynx and nasal conchas [22]. Another study showed that AQP1 is expressed in endothelial cells of blood vessels and surrounding connective tissue cells in olfactory and respiratory mucosa [24]. Meanwhile, in studies on humans, it has been shown that it is localized in fibroblasts on the inferior turbinate tissue,

Table 1 Tissue-specific distributions of AQPs in the human body

GROUP	AQUAPORIN	TISSUES WHERE IT IS FOUND
Classical aquaporins	0	Lens
	1	Renal tubules and capillaries, choroid plexus, ciliary epithelium, corneal endothelium, pain-processing C fibers, vascular endothelial tumor vessels, and erythrocytes
	2	Renal collecting duct
	4	Astrocytes, retinal Muller cells, lacrimal gland, salivary duct, inner ear, olfactory epithelium, gastric parietal cells, airways, renal collecting duct, placenta, muscle, intestinal epithelium, and glioblastomas
	5	Corneal epithelium, sweat glands, lacrimal glands, salivary glands, airway submucosal glands, alveolar type I cells, and epidermis
	6	Intercalated intracellular vesicles in the renal collecting duct
	8	İntestinal epithelium
Aquaglyceroporins	3	Renal collecting duct, epidermis, conjunctiva, corneal epithelium, immune cells, intestinal epithelium, and erythrocytes
	7	Fat cells, renal proximal tubule, testis, and myocardium
	9	Hepatocytes, erythrocytes, and possibly certain brain cells
	10	Intestinal enterochromaffin cells
Hybrid aquaporins	11	Liver, testis, and intracellular membranes in the renal proximal tubule
	12	Exocrine pancreas

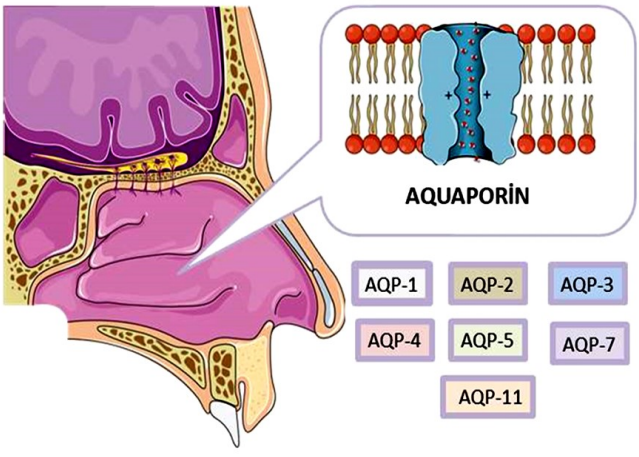

Figure 1. Expression of AQPs in normal nasal cavity respiratory epitheli-

especially in the subepithelial area and endothelial cells of blood vessels and the vascular and connective tissue of normal human sinonasal mucosa [25,26]. Collectively, these observations suggest that AQP1 might be involved in water transfer through the blood vessel wall.

AQP2 is found in structures called collecting ducts in the kidney, where it plays a key role in maintaining the body's water balance [27]. In a study conducted on lower turbinate tissue from humans, AQP2 was localized in the cytoplasm of epithelial cells and acinar cells[25]. However, to our knowledge, no other studies have been reported to support these findings, so it is considered that AQP2 has limited distribution to the renal collecting duct, and its significance in nasal cavity respiratory function is relatively weak than other AQPs.

AQP3 are protein channels that can mediate the passage of glycerol, urea, and other small solutes in addition to water molecules. AQP3 is a water channel protein that allows rapid and selective water transport through the membrane of the human respiratory epithelium in response to osmotic gradients [22]. AQP3 is also found in the skin, lungs, cornea, esophagus, colon, stomach, liver, intervertebral discs and sperm [20,25]. Studies have revealed that AQP3 is abundant in the basal cells of the trachea and nasopharyngeal epithelium and basolateral membranes of the surface epithelial cells of the nasal conchas [22,24,31]. AQP3 expression has been shown in immunohistochemically studies on human inferior turbinate tissue and normal sinonasal mucosa [25,26].

AQP4 is the most common AQP in the brain, spinal cord and optic nerve. It is expressed at the highest level in astrocytic foot processes. In the brain, it is involved in the production and absorption of CSF, water transport between the blood-brain barrier and the physiopathology of brain edema [28].AQP4 is also expressed in epithelial cells of many organs in the human body, such as the kidney, intestine, salivary glands, sensory organs and skeletal muscles [28]. Studies have revealed the presence of abundant AQP4 in the basolateral regions of acinar cells and columnar cells in the nasal mucosal epithelium and the basolateral membranes of columnar cells of the nasopharyngeal epithelium [20,22,26].

AQP5 takes part in the formation of saliva, tears and pulmonary secretions. AQP5 facilitates the secretion of fluid in the submucosal glands indicating that the lumen membrane of serous epithelial cells is the rate-limiting barrier against water movement [20,22,30]. In studies on the distribution of AQP5 to nasal tissues, it has been reported that it is expressed in abundance in the apical plasma membrane of the intraepithelial glands of the nasal conchas, on the apical surface of the nasal respiratory epithelium, and in the apical membrane of subepithelial glandular cells in the nasopharynx [20,22,24,26].

AQP7 is abundantly expressed in both white and brown adipose tissue [32]. It has been shown that in nasal tissue, normal human sinonasal mucosa, AQPs are localized in the surface and cytoplasm of glandular epithelial cells [26]. However, no studies have clearly reported the role of AQP7 in nasal tissue. In general, AQP7 may be involved in the movement of water and other molecules (glycerol, urea, and other small solutes) between subepithelial connective tissues and epithelial cells [33].

AQP11 is a relatively recently discovered member of the AQP family, and not much is known about its function yet. AQP11 is expressed in the nasal mucosa in humans and mice. However, to our knowledge, its specific functions in the nasal respiratory epithelium have not yet been studied [34,26].

In addition to showing the abundant expression of AQPs in the respiratory epithelium of the nasal cavity, it has also been shown that these proteins participate in normal physiological processes, such as humidification of inhaled air, but may contribute to the pathogenesis of nasal congestion and rhinorrhea [20].

Aquaporins and Allergic Rhinitis

Allergic rhinitis (AR) is a type of inflammation of the nasal mucosa that occurs when the immune system overreacts to airborne allergens. AR arises from type I hypersensitivity reactions associated with immunoglobulin E mediating allergic responses. AR affects approximately 10-30% of adults and 40% of children, and its prevalence tends to increase [35,36]. Hence, it is considered an important chronic respiratory disease due to its high prevalence and negative effects on quality of life. Various mechanisms of sinonasal epithelial barrier disruption include antigen proteolytic activity, tight junction disruption mediated by inflammatory cytokines, or exacerbation by environmental stimuli [2,20]. By stimulating allergy and inflammation, elevated IgE acts on mast cells to induce histamine release, which plays a crucial role in AR. Histamine also plays an important role in the secretory response of the submucosal glands in the nose. Besides, histamine causes vasodilation, tissue edema and sneezing [37]. Another characteristic feature of AR is glandular hypersecretion. Many studies have clearly revealed that AQPs play a key role in maintaining fluid balance in airways, such as the nasal cavity. Thus, AQPs have also been associated with dysregulated water metabolism in AR [20]. The AQP best studied in the context of AR is AQP5, a sub-member of the classical aquaporins family. AQP5, a transmembrane water channel protein, has a crucial role in water transport on the apical surface of the alveolar epithelium, the upper airways, and the submucosal epithelium of the nasopharynx [37]. It has been revealed that AQP5 is closely associated with serious glands and upper airway pathologies [2]. Most likely, AQP5 is the primary water channel in the human nasal mucosa, where it functions as a key tight junction protein in maintaining mucosal water homeostasis. It is a key molecular player in fluid secretion and a rate-limiting barrier to secretion observed during allergic inflammation [20,30,38]. Recent studies have shown that AQP5 performs this task in the mucosa using the cAMP Protein Kinase A pathway and that it is possible to halt it at various stages. For example, it has been shown that the cAMP-PKA/CREB pathway plays a role in regulating AQP5 expression in the nasal epithelium of rats [39]. NF-κB plays a significant role in the regulation of AR cytokine networks. In a study conducted with the AR model, it was revealed that AQP5 expression decreased in the AR group than in the control group, and this decrease was suppressed by NF-kB inhibitor treatment [40]. In another AR cell culture study by Chang et al., it was reported that the NF-kB pathway suppressed AQP5 expression [41]. Histamine, which induces hypersecretion in the nasal mucosa, is one of the most considerable contributors to the pathophysiology of AR. In another study on human nasal epithelial cells, it was demonstrated that histamine reduces the expression of AQP5 [1]. Chlorpheniramine has the ability to reverse the impacts of histamine. Antihistamines, such as chlorpheniramine, are among the most commonly prescribed medications for AR. Chang et al. showed that a significant dose-dependent increase occurred in the expression of membranous AQP5 in cells in the presence of chlorpheniramine [41]. Cholinergic stimulation plays an important role in inflammatory airway diseases. It was revealed that methacholine, a parasympathomimetic drug, disrupted airway surface fluid homeostasis and this effect was due to a decrease in AQP5 level after methacholine-induced activation of the NF-kB pathway, while dexamethasone reversed this effect by decreasing [42]. Many studies have shown that IL-13 is the central regulator of disorders, such as asthma, and some studies have argued that IL-13 blockade prevents allergen-induced airway inflammation [20,43]. Skowron-Zwarg et al. found that IL-13 did not affect AQP3 or AQP4 expression but removed AQP5 expression. They suggested that IL-13 can mediate AQP5 inhibition by activating TNF-α [20,44].

AQPs and Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a common upper respiratory tract disease that occurs due to dysregulation of the inflammatory response, generally due to microbial infection in the nasal cavity and sinus. CRS has been divided into two: CRS with nasal polyps, which tends to Th2 cytokine polarization and CRS without nasal polyps, which is mostly associated with a Th1-type response [3,20]. Histologically, nasal polyps are characterized by sparse fibrous cell edematous fluid, few mucus glands without innervation, squamous metaplasia of the surface epithelium, proliferation of stromal and epithelial elements, and thickening of the basal membrane [45]. It has been put forward that such immunological and histological differences are associated with

differential expression of mucosal water membrane permeability proteins, such as AQPs [20]. In a study comparing nasal polyp tissue and normal tissue, it was revealed that AQP1 is abundantly expressed in polyp tissue fibroblasts, especially in the subepithelial area, in the periphery of seromucous glands and endothelial cells of venules. It has been suggested that AQP1, which is higher in polyp tissue than normal tissue, is among the mechanisms contributing to tissue edema [46]. In a study comparing AQP5 expressions in normal control, CRS without nasal polyps and CRS with nasal polyps, it was observed that the epithelial expression of AQP5 was lower in CRS tissues with nasal polyps than in the other two groups. Thus, the authors have argued that the mucosal epithelial barrier is compromised in the context of CRS disease, notably CRS with nasal polyps and that loss of AQP5, which can act as a tight junction protein, plays a role in the occurrence of mucosal edema and the pathophysiology of nasal polyp formation [3]. In a similar study reporting a decrease in AQP5 in tissues from patients who had CRS with nasal polyps, it was concluded that loss of AQP5 results in edema and polyp formation due to disruption of tight junction regulation of cell volume and failure to maintain epithelial water homeostasis, and the production of dark secretions, which are typical features of CRS with nasal polyps [47]. AQP5 expression levels in the control, CRS and dexamethasone treatment groups were compared in a study conducted in rats in which an experimental CRS model was established. Compared with the other two groups, AQP5 expression significantly increased in the dexamethasone-treated group. The findings showed that the infectious agent *Staphylococcus aureus*, which was used in the study to create a CRS model, decreased AQP5 expression by destroying the ciliary epithelium and glandular tissue where AQP5 is primarily localized in the CRS group. It was reported that this tissue destruction was suppressed by dexamethasone and resulted in increased AQP5 expression [48]. These findings suggest that treating patients with polyps may require strategies that target the epithelium and possibly modulate AQP5.

AQPs and Olfactory Epithelium

The olfactory mucosa is a yellowish mucous membrane located in the upper region of the nasal cavity. The olfactory epithelium is made up of olfactory sensory cells, support cells and basal cells. The ends of their dendrites emerge on the epithelial surface and their axons extend to the olfactory bulb in the central nervous system. Mucus protects the olfactory epithelium and allows odors to dissolve so that they can be perceived by olfactory receptor neurons [19,20].

The presence of AQP1, AQP3, AQP4 and AQP5 was determined in a study in which immunohistochemical and immunoblot analyses of the olfactory mucosa of normal rats were conducted. AQP1 expression in olfactory mucosa was found in endothelial cells of blood vessels and surrounding connective tissue cells. On the other hand, AQP1 was not detected in olfactory sensory cells in the olfactory epithelium. AQP3 was abundantly localized to supporting cells and basal cells, whereas AQP4 expression was limited to basal cells. In Bowman's gland, AQP5 was localized to the apical membranes of secreting acinar cells, while expression of AQP3 and AQP4 was detected in the basolateral membrane. A similar localization pattern was detected in the duct cells of Bowman's gland. Drawing on these findings, it has been suggested that there is a different localization pattern for AQPs in the olfactory epithelium and that AQP3, AQP4 and AQP5 in the Bowman gland may play a key role in establishing and maintaining secretory processes that generate a favorable microenvironment for olfactory perception on the apical surface of olfactory dendrites [20,34]. In animal experiments, the findings showed that AQP1, AQP3 and AQP4 were expressed in the olfactory mucosa. It has been suggested that AQP4 has a function in olfaction by showing that AQP4 is strongly expressed in the glomerulus, the synaptic unit of the olfactory bulb. Consistent with this finding, a study with AQP4-knockout mice found a reduced sense of smell [49,50,51].

The other chemosensory epithelium with olfactory function in the nasal cavity mucosa is the vomeronasal sensory epithelium. It is anatomically and physiologically distinct from the olfactory system and is a part of the nasal chemosensory system, considered a chemosensory organ for pheromones [20,52]. In a study investigating the expression of AQPs in the vomeronasal sensory epithelium, it has been revealed that AQP1 is localized in blood vessels and is especially abundant in the cavernous tissues of the non-sensory mucosa. AQP5 was detected in the apical membrane of gland acinar cells. AQP3 was detected in basal cells of the non-sensory epithelium. Meanwhile, AQP4 was higher in sensory cells of the sensory epithelium. The findings have shown that AQP4 is specifically localized in the nerve fiber bundles originating from neuronal sensory cells, in the plasma membrane of each axon, and in the lateral membranes of dendrites [52]. In a study on mice, it has been shown that AQP2, AQP3, AQP4 and AQP5 are expressed at different periods in the olfactory epithelium and vomeronasal sensory epithelium during the embryonic and postnatal periods, depending on the developmental stage. Based on the varying distribution of AQPs by developmental stage, it has been argued that this may be one reason why the olfactory epithelium and vomeronasal sensory epithelium display distinct characteristics as they grow [53]. The glia surrounding the olfactory covers or encloses large groups of olfactory receptor neurons along their course towards the olfactory nerve and glomerular layers of the lamina propria and olfactory bulb. AQP1 was expressed in glial cells surrounding the main olfactory bulb but not from olfactory receptor neurons, astrocytes and periglomerular cells. Hence, AQP1 expression is a feature that distinguishes the glial cells surrounding the olfactory system from other central nervous system cell types [54].

Conclusion

Expression of AQPs in the sinonasal respiratory epithelium and olfactory epithelium suggested that these proteins may contribute to the pathogenesis of nasal congestion, rhinorrhea, AR and CRS, as well as playing a role in normal physiological processes, such as humidification of inhaled air and olfactory functions. The expression of AQPs is different in inflammatory diseases, such as AR or CRS than that in normal tissues. Under physiological conditions, the expression of AQPs in the olfactory epithelium differs from that in the respiratory epithelium. In our study, by investigating the relationship between AQPs and sinonasal epithelium, the physiopathological connections between allergic rhinitis, rhinosinusitis, and the olfactory system were revealed through a comprehensive perspective. More comprehensive clinical and experimental findings are needed to fully elucidate the role of aquaporins in the pathophysiology of the sinonasal mucosa. Investigating the regulation and functional roles of AQPs will provide novel insights into the diagnosis and prognosis of diseases and facilitate the development of potential therapeutics for diseases and olfactory epithelium, such as the treatment of AR and CRS.

Conflict of interest

Authors declare that they have no financial interests or personal conflicts that may affect the study in this article.

Financial disclosure

The authors declared that this study has received no financial support.

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