**Oral Diseases (2008) 14**, 683–689. doi:10.1111/j.1601-0825.2008.01486.x

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## MEDICAL REVIEW

# The oral mucosa as a therapeutic target for xerostomia

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**Autoimmune disorders, medical interventions, and aging are all known to be associated with salivary gland hypofunction, which results in the uncomfortable feeling of dry mouth (xerostomia) and significantly diminished oral health. The current therapeutic regimen includes increasing oral hydration using over-the-counter oral comfort agents and the use of systemic cholinergic drugs to stimulate salivary output. However, these approaches produce very transient relief or are associated with uncomfortable side-effects. Thus, new treatments that provide long-lasting relief from discomfort and improve oral health with minimal side-effects would benefit the therapy of this disease. The processes that mediate fluid loss from the oral cavity, such as the absorption of fluid from the oral mucosa, represent novel therapeutic targets for xerostomia. Preventing fluid absorption from the oral cavity is predicted to improve oral hydration and alleviate the clinical symptoms and discomfort associated with dry mouth. Furthermore, therapeutic strategies that prevent fluid absorption should complement current approaches that increase salivary output. This review discusses the current understanding of oral fluid balance and how these processes may be manipulated to provide relief for those suffering from dry mouth.**
*Oral Diseases* (2008) **14**, 683–689

**Keywords:** xerostomia; dry mouth; buccal mucosa; epithelial sodium channel; ENaC; absorption

## Introduction

By lubricating and protecting all surfaces in the oral cavity, saliva is critical for oral function. Saliva hydrates and cleanses the mouth, protects teeth through its buffering and remineralizing properties, and provides anti-microbial activity. The importance of saliva for oral health is evident from the conditions arising from salivary gland hypofunction. Diminished secretions give rise to a spectrum of complications, including xerostomia (the subjective feeling of dry mouth), complaints of painful or burning oral mucosa, dental caries, oral candidiasis, bacterial sialadenitis, and ulcers of the oral mucosa (Talal, 1987; Atkinson and Fox, 1993). In addition, dry mouth significantly diminishes quality of life as activities including chewing, swallowing, taste, speech, and sleep are typically disrupted.

Chronic diseases, medical interventions, and aging are all known to be associated with salivary gland hypofunction. Autoimmune disorders such as Sjögren's syndrome represent one of the most common causes of dry mouth. Sjögren's syndrome is characterized by lymphocyte-mediated destruction of exocrine glands and internal organ involvement because of auto-antibody production or by a pre-existing connective tissue disorder (Vivino *et al*, 1999). Over time, progressive infiltration of salivary glands by immunologically active cells leads to diminished secretions, resulting in xerostomia and other oral complications (Talal, 1987). Medical interventions such as radiation therapy administered to individuals with head and neck cancers irreversibly damage salivary glands. Additionally, thousands of pharmaceutical agents are known to induce xerostomia as a side-effect. Salivary function is also reported to wane with aging. Although there is acinar cell atrophy with aging (Scott *et al*, 1987), in healthy, non-medicated elders there is no decrement in salivary output (Ship *et al*, 2002). This suggests that age-related salivary hypofunction is primarily the result of systemic disease or medications, more frequent in older persons than younger, and not the result of an intrinsic loss of function.

## Salivary output and dry mouth

Although decreases in salivary output underlie xerostomia and the clinical manifestations associated with dry mouth, defining what constitutes pathological hyposalivation has proven difficult. Data from several large studies have estimated the mean flow rate of unstimulated whole saliva in normal healthy individuals to be 0.3 ml $min^{-1}$ (Dawes, 1987). However, clinical observations indicate that salivary flow rates exhibit a broad inter-individual variation. In a study of 661 healthy subjects ranging in age from 5 to 95 years, the flow rates for unstimulated whole saliva ranged from 0.008 to 1.85 ml $min^{-1}$ (Becks and Wainwright, 1943). In another study of 629 individuals ranging in age from

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Received 3 July 2008; accepted 11 July 2008

15 to 74 years, stimulated whole saliva rates varied from 0.25 to 5.58 ml $min^{-1}$ (Heintze *et al*, 1983). The high degree of variability in salivary output hinders the clinician from determining whether an individual exhibits an abnormally low flow rate. Further complicating the establishment of useful clinical parameters for defining hyposalivation, not all individuals with 'low' salivary flow rates experience xerostomia and pathologies associated with dry mouth (Ship *et al*, 1991). Thus, it is often the case that patients are categorized as having dry mouth only on the basis of subjective symptoms.

To explore the physiological relationship between basal salivary flow and the sensation of dry mouth, Dawes (1987) conducted a series of investigations in normal healthy volunteers. A total of 23 volunteers participated and gave samples for the determination of salivary flow rates over a 6-h period. In five separate sessions, all subjects received a single treatment with placebo, 1 mg of atropine sulfate, or three different dosages of an experimental anti-cholinergic agent to induce mouth dryness pharmacologically. During each session, the subjects recorded the time of onset to any symptoms, including those of dry mouth. Nineteen of the 23 subjects reported symptoms of dry mouth following administration of atropine and the highest dose of the anti-cholinergic agent. Despite a difference in the mean time of onset of dry mouth symptoms between the two treatment groups (1 h for the atropine group; 2 h and 40 min for the anti-cholinergic group), the times of onset corresponded to the time when the salivary flow rates decreased from 40% to 50% of the value recorded after administration of the placebo. Wolff and Kleinberg confirmed the finding that mouth dryness was observed when an individual's baseline salivary output fell by ~50% (Wolff and Kleinberg, 1999). These results suggest that despite wide inter-individual variation in salivary flow rates within the population of volunteers, the onset of symptoms of dry mouth occurred when the unstimulated salivary flow rate decreased to approximately one-half of the baseline value.

The mechanisms by which decreases in salivary output are interpreted as the sensation of dry mouth are not well understood. Saliva forms a thin film that coats the oral cavity, which based on the calculated surface area of the mouth and the residual volume of saliva, was estimated to range from 72 to 100 $\mu$m in thickness, assuming that the volume was evenly distributed (Collins and Dawes, 1987). However, the actual thickness of the salivary film varies depending upon factors such as proximity to salivary glands, absorptive properties of the epithelium, susceptibility to evaporation, and influence of gravity. Furthermore, the regional differences in salivary thickness are predicted to give rise to areas of the oral cavity that are more sensitive to desiccation (DiSabato-Mordarski and Kleinberg, 1996a,b; Wolff and Kleinberg, 1998, 1999; Dawes, 2004). Using a paper strip absorption technique, Kleinberg *et al* found that the posterior surface of the dorsum of the tongue had the highest film thickness (70 $\mu$m) and the lips and hard palate had the lowest film thickness (10 $\mu$m) (DiSabato-Mordarski and Kleinberg, 1996a; Wolff and Kleinberg, 1998). Additionally, Wolff and Kleinberg observed that individuals with dry mouth exhibited a lower average salivary fluid thickness (27.8 $\mu$m *vs* 41.8 $\mu$m) and that fluid films on the lips and hard palate, that are covered in the smallest volume per surface area, were decreased to $< 10$ $\mu$m (Wolff and Kleinberg, 1998). These data lead to the proposal that regions most sensitive to drying, such as the hard palate, are critical to the development of xerostomia. Importantly, these observations highlight that factors besides hyposalivation contribute to the sensation of dry mouth.

## The contribution of fluid clearance to dry mouth

The 'steady state' volume covering the oral mucosa reflects the salivary gland output balanced by fluid clearance (Figure 1). Although a few studies have explored the importance of fluid clearance in individuals with dry mouth, it has been suggested that fluid loss contributes to the etiology of this disease (Dawes, 2004). Furthermore, as discussed below, the prevention of oral fluid loss may be a viable therapeutic target for treating dry mouth, which theoretically would work synergistically with oral comfort agents and systemic agents that increase salivary output.

Fluid is cleared from the oral cavity by several modes including swallowing, the absorption of water (and salt) across the mucosal surface, and evaporation as a consequence of mouth breathing and speaking. Models for salivary clearance suggest that the volume of saliva in the mouth oscillates between a maximum volume that triggers the swallowing response and a residual volume that remains immediately after swallowing. In a study of 40 healthy individuals, Lagerlof and Dawes determined that the average volume of saliva in the mouth was

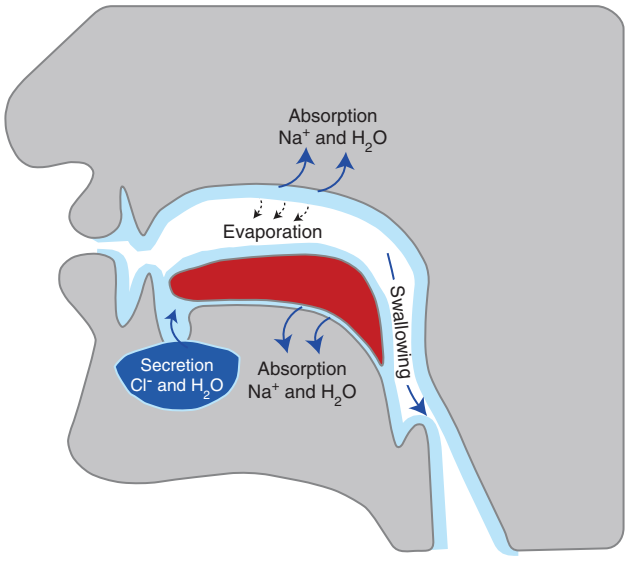


**Figure 1** Model of oral fluid balance. The 'steady state' volume of fluid in the oral cavity reflects fluid secretion by the salivary glands balanced by fluid loss. Fluid is lost through swallowing, absorption across the mucosal epithelium, and evaporation that occurs during speaking and mouth breathing

1.07 ml, which decreased to 0.77 ml on average after swallowing (Lagerlof and Dawes, 1984). A second study found that for the individuals who experience xerostomia in the mean residual volume after swallowing was reduced by an additional 29% (Dawes and Odlum, 2004). Dawes speculated that for individuals with low salivary flow rates, a constant residual salivary volume could be maintained by decreasing the frequency of swallowing, thereby alleviating xerostomia (Dawes, 2004). However, the prevalence of xerostomia, reported to be >10% of the population worldwide (Ben-Aryeh *et al*, 1984, 1985; Handelman *et al*, 1989; Osterberg *et al*, 1992; Turner and Ship, 2007), suggests that 'training' swallowing frequency is difficult/impossible to achieve; and that other factors, such as absorption, significantly contribute to the development of dry mouth . Dawes further suggested that xerostomia could potentially be avoided if the rates of fluid absorption and evaporation were less than the rate of salivary output (Dawes, 2004). Thus, for individuals with low salivary output, the symptoms of dry mouth could conceptually be alleviated by decreasing absorption or evaporation.

Evaporative loss of salivary fluid occurs primarily as a result of mouth breathing and speaking. Furthermore, evaporative loss is thought to be a particularly significant factor in drying oral regions, such as the hard palate that are (1) covered in the thinnest salivary films and (2) in the direct flow path of inspired air (Wolff and Kleinberg, 1998; Dawes, 2004). However, minimizing evaporative loss is difficult to conceptualize beyond minimizing mouth breathing and speaking, and use of humidifiers. Decreasing absorptive loss, on the other hand, may present a reasonable mechanism for improving mouth dryness. Unlike other epithelial tissues of the lungs, GI tract, and kidneys where absorptive processes are well understood, relatively few studies have examined the mechanisms that underlie fluid absorption from the oral mucosa. However, the available data suggest that the 'hydration' status of the oral surfaces, in part, reflect the active transport of electrolytes and the passive transport of water in response to the generated osmotic gradient. The remainder of this review will focus on the cellular mechanisms that mediate oral fluid absorption and how this process could be manipulated to improve mouth dryness.

## Water flux across the oral mucosa

The passive absorption of water in the oral cavity is mediated by (1) the osmotic gradient between saliva and plasma and (2) epithelial ion transport. The osmolality of saliva has been reported to vary from hypotonic (50–70 mOsM) with respect to plasma for unstimulated saliva to nearly isotonic for stimulated salivary flow. The hypotonicity of saliva reflects the ability of the salivary duct to remove salt, but not water, from the isotonic primary sections formed in the salivary gland acinus.

It is predicted that increases in the saliva/plasma osmolarity gradient will favor passive fluid absorption across the buccal mucosa. However, if absorption is indeed a relevant mechanism for fluid loss from the mouth, then the oral epithelium must be permeable to water. Numerous physiological studies have examined the water permeability of the oral mucosa by measuring the movement of tritiated water across the epithelium in the absence of an osmotic gradient. For example, Lesch *et al* (1989) calculated the water permeability constants ($K_p$) for regions of the human oral mucosa which were derived from the buccal mucosa ($K_p = 8.22 \times 10^{-7}$ cm s$^{-1}$), lateral border of the tongue ($K_p = 1.59 \times 10^{-7}$ cm s$^{-1}$), and the floor of the mouth ($K_p = 1.74 \times 10^{-6}$ cm s$^{-1}$). Additional studies examining water permeability across oral surfaces reported higher permeability coefficients of $\sim 8.0 \times 10^{-6}$ cm min$^{-1}$ for ventral tongue and $6.67 \times 10^{-6}$ cm s$^{-1}$ for primary cultures of buccal mucosa (Healy *et al*, 2000; Howie *et al*, 2001; Selvaratnam *et al*, 2001). Differences in experimental approaches limit the direct comparison of water permeability between the oral mucosa and other epithelial tissues. However, it is clear that the oral surfaces are substantially less permeable to water than the most permeable epithelial tissues, such as those of the thick descending limb of Henle or the alveolar surface, but are more permeable (by 10- to 100-fold in direct comparisons) than epithelial tissues such as skin (Selvaratnam *et al*, 2001). Furthermore, on the basis of water permeability coefficients for the ventral tongue epithelium (Healy *et al*, 2000), the estimated surface area of human oral mucosa (Collins and Dawes, 1987), and the osmolarity differential between whole unstimulated saliva *vs* plasma (assuming that the osmolality of saliva is equivalent to 0.15% saline *vs* 0.9% for plasma), Dawes (2004) estimated that the maximum rate of fluid absorption from the oral mucosa to be 0.19 ml min$^{-1}$. While this value is only an estimation that relies on multiple uncertainties, it suggests that absorption is a significant mode by which fluid is lost from the oral cavity. Taken together, these studies strongly support a role for fluid absorption across the oral mucosa as a significant means of salivary fluid clearance.

To further explore the water transport properties of buccal mucosa, Brennan *et al* (2007) conducted a pilot study to measure transepithelial water movement across the oral mucosa in healthy volunteers without complaints of oral dryness or oral mucosal pathology. A modified Carlson-Crittenden collector was used to hold approximately 0.3 ml of a hypotonic (0.45%) or isotonic (0.9%) saline solution, containing a known concentration of lactoferrin (1.0 mg ml$^{-1}$), as a volume marker, in contact with the buccal mucosa. The inner chamber of the collector, holding the test solution, was kept isolated from the rest of the oral cavity by an outer vacuum chamber. After 30 min, the fluid was drained from the inner chamber into a collection tube, and the concentration of the lactoferrin was measured. The change in the concentration of lactoferrin indicated the net movement of fluid across the buccal mucosa. An increased concentration of lactoferrin over time would be consistent with absorption of water in response to the osmotic gradient across the buccal mucosa. Conversely, a decrease in the concentration of lactoferrin over time

would be consistent with a net movement of water onto the buccal surface. A statistically significant increase in lactoferrin concentrations (mg $ml^{-1}$) in hypotonic saline ($P < 0.0004$), but not isotonic saline ($P < 0.34$), was observed between baseline and at 30 min (Figure 2). These results provide *in vivo* evidence that the buccal epithelium is permeable to water.

The data from Brennan *et al* can be further used to calculate the water transport rate across the buccal mucosa and to derive the permeability coefficient for this tissue. Based on the estimated surface area of the buccal mucosa in the Carlson-Crittenden collector chamber and the change in lactoferrin concentration in 0.45% saline, the average rate of water absorption from the buccal surface was calculated, under these conditions, to be $3.17 \pm 0.54$ $\mu l\ min^{-1}\ cm^{-2}$. Based on a total surface area of the oral cavity calculated to be 178 $cm^2$ (Collins and Dawes, 1987), it is estimated that the total oral cavity fluid absorption would be $\sim$564 $\mu l\ min^{-1}$. Furthermore, the permeability coefficient ($K_p$) can be derived from the experimentally determined rate of water transport (0.0313 mol $min^{-1}$) divided by the estimated mucosal surface area (178 $cm^2$) and the difference in water molarities between plasma and the mucosal fluid at 37°C (0.0667 mol $l^{-1}$ for 0.45% *vs* 0.9%). Using these assumptions, $K_p$ is calculated to be $4.39 \pm 0.75 \times 10^{-5}$ cm $s^{-1}$, which is >6-fold higher than has been calculated by others for the buccal mucosa (Lesch *et al*, 1989; Healy *et al*, 2000; Selvaratnam *et al*, 2001). It should be emphasized that all of the permeability calculations mentioned rely on assumptions, including that a $K_p$ value is representative of all oral mucosa. However, taken together, these studies by multiple labs utilizing different experimental approaches clearly demonstrate that the oral mucosa is permeable to water. While few studies have examined the expression of aquaporin water channels in the oral mucosa, aquaporins 3, 4, and 5 have been localized by immunohistochemistry to the epithelial cells of the lips, mouth, and tongue, providing the molecular basis for oral water permeability (Matsuzaki *et al*, 1999; Felszeghy *et al*, 2004).

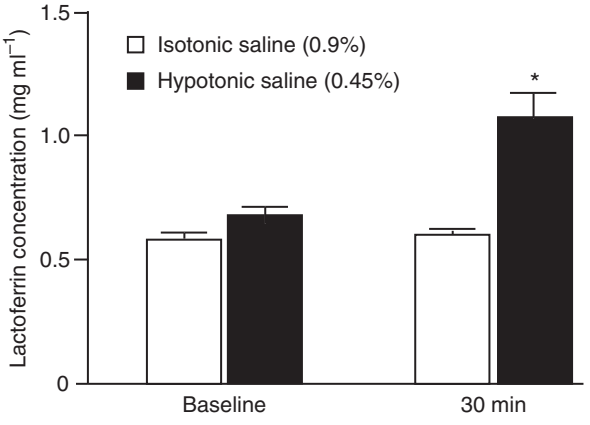


**Figure 2** Water transport across the buccal epithelium. The data reported by Brennan *et al* (2007) demonstrate that the buccal epithelium is permeable to water. Using lactoferrin as a volume marker, change in the volume of a hypotonic (0.45% NaCl) or isotonic (0.9%) saline solution applied to the buccal mucosa for 30 min was measured in healthy individuals. The concentration of lactoferrin is significantly increased after 30 min, indicating that the buccal mucosa is permeable to water as fluid was absorbed across the osmotic gradient. $n = 19$ for 0.45% saline and $n = 10$ for 0.9% saline. Error bars are s.e.m. and $*P < 0.0004$

## Ion transport properties of the oral mucosa

The active transport of electrolytes represents another mechanism capable of accelerating fluid absorption from the oral cavity. In an attempt to measure the ion transport properties of the buccal epithelium, Kaaber performed a series of studies examining electrolyte uptake from the mucosal surface onto filter paper, which was subsequently analyzed for sodium and potassium content using a flame photometer (Kaaber, 1974). Kaaber did not observe electrolyte transport in this assay; which led to a prevailing concept that ion transport in the buccal mucosa occurred via passive diffusion (Kaaber, 1974; Mackenzie and Binnie, 1983; Siegal, 1984). However, additional studies have not confirmed this finding, and indeed, they have provided strong evidence that the oral mucosa does indeed actively transport salts similar to other stratified squamous epithelial tissues such as esophagus and cornea.

First, multiple groups have provided evidence that cations are actively transported across the buccal epithelium. For example, in experiments utilizing canine tissue *in vitro*, Kawamura and Takata (1960) found that both sodium and potassium ions were transported across the oral mucosa in processes that resembled active transport, rather than the free diffusion of ions. Aoyama further found that $^{24}Na$ is unidirectionally transported *in vivo* in rabbit buccal mucosa from the mucosal surface to the serosal compartment (Aoyama, 1968).

Second, the buccal mucosa from human, dog, rabbit, and hamster generates a transmural electrical potential difference (PD), a hallmark of an epithelial tissue actively transporting electrolytes (Orlando *et al*, 1988; Hosoya *et al*, 1993). The development of a transepithelial PD requires the net transport of one or more ions against an electrochemical gradient, which, by definition, requires energy. Studies by Orlando *et al* and Hosoya *et al* confirmed that the buccal mucosa is a highly electrically resistant tissue (reported resistance values ranging from 997 to 1562 $\Omega\ cm^{-2}$ across species) capable of maintaining a large PD (reported PD values ranging from $-18.1 \pm 1$ to $-39 \pm 2$ mV across species) (Orlando *et al*, 1988; Hosoya *et al*, 1993). Orlando *et al* further characterized the electrolyte transport processes in the buccal epithelium by recording short-circuit currents ($I_{sc}$) and identified the ions that predominantly generated the $I_{sc}$. These studies indicated that the magnitude of the observed $I_{sc}$ reflected the rate of active sodium absorption ($\sim$68% of the $I_{sc}$) and that sodium enters the cell via the apical membrane through the amiloride-sensitive epithelial sodium channel (ENaC) and exits the cell via the activity of an oaubain-inhibited

sodium potassium ATPase (Orlando *et al*, 1988). These electrophysiological findings indicated that the buccal mucosa resembles other squamous epithelia by its ability to transport sodium transepithelially. Although the relative contribution of ion transport to fluid absorption has not been formally studied, it is likely that the buccal mucosa regulates the absorption of water through a mechanism coupled to the active absorption of sodium and passive absorption of chloride as the counter-ion. The absorption of salt osmotically draws water from the buccal surfaces and, therefore, is predicted to govern, in part, the hydration status of the surface of the buccal mucosa. The sensitivity of this sodium transport process to inhibition by amiloride suggests that sodium absorption by buccal ENaC is rate limiting.

## Therapeutic strategies for improving mucosal hydration

Ideally, an agent used to treat dry mouth would provide a long-lasting increase in mucosal hydration, requiring a minimal number of daily applications with minimal side-effects. This profile is particularly important for improving sleeping patterns for individuals with dry mouth, who are frequently awakened as a result of this condition. The primary therapeutic options currently available for dry mouth increase oral fluid, a strategy that targets only half of the fluid balance equation. As discussed below, preserving oral fluids via the inhibition of absorptive processes is predicted to work synergistically with current therapeutic agents and should promote an increased duration of the therapeutic benefit.

The current therapeutic options for dry mouth include both topical and systemic agents. Over-the-counter saliva replacements, mouthwashes, rinses, sprays, gums, and lozenges add fluid to the oral cavity and stimulate salivary flow though gustatory and masticatory reflexes. Furthermore, many of the over-the-counter products act as hyperosmolar agents with respect to plasma and, thus, are predicted to draw fluid onto the mucosal surfaces. Systemic agents include parasympathomimetic drugs that stimulate the secretion of fluid and protein from salivary glands (Fox, 2004). By acting on basolateral gland acinar muscarinic and adrenergic receptors, the cholinergic drugs activate the second messenger signaling pathways via elevated intracellular calcium or cyclic-AMP in acinar cells, thereby increasing gland secretion. One such approved agent, Pilocarpine, has been evaluated in multiple clinical studies where it has been shown to improve the symptoms of dry mouth and salivary output significantly in individuals with primary Sjögren's syndrome and postradiation salivary gland hypofunction (Fox *et al*, 1991; Johnson *et al*, 1993; LeVeque *et al*, 1993; Vivino *et al*, 1999; Horiot *et al*, 2000). A second agent, Cevimeline has also been shown in clinical studies to improve the symptoms of dry mouth significantly in Sjögren's syndrome patients (Petrone *et al*, 2002). Cevimeline has been reported to act more slowly than Pilocarpine, but provides a longer duration of action (Fox, 2004).

While the therapeutic strategies described effectively increase oral hydration, their limitations are several-fold. Over-the-counter moisture replacements, such as artificial saliva and mouthwashes provide only a transient duration of action, requiring frequent application. Although cholinergic agents increase secretion from acinar cells, the therapeutic effect of these drugs is limited by the amount of functional salivary gland tissue remaining. Additionally, cholinergic drugs are associated with a number of uncomfortable side-effects including sweating, flushing, nausea and increased urinary frequency. Thus, there is a need for novel therapeutic agents that can provide longer relief from the symptoms associated with dry mouth with fewer side-effects.

As noted above, the oral mucosa is predicted to be an absorptive epithelium, with salt and water transport properties mechanistically similar to other epithelia. While no therapeutic agents are currently available for improving oral hydration via decreasing absorptive loss, this general strategy has been developed to treat numerous indications in other epithelia. For example, in the lungs, diseases such as cystic fibrosis (CF) result in the dehydration of the mucosal surface, resulting in mucous accumulation, airway obstruction, and persistent infection. The CF phenotype reflects an imbalance in epithelial ion transport with the loss of chloride secretion through the CF transmembrane conductance regulator and the hyper-absorption of $Na^+$ through ENaC (Matsui *et al*, 1998; Tarran *et al*, 2001; Mall *et al*, 2004). As such, therapeutic strategies presently being developed for the treatment of CF include (1) ENaC channel blockers that decrease $Na^+$ and fluid absorption, (2) $Cl^-$ channel activators that promote $Cl^-$ and water secretion, and (3) hyperosmotic agents that draw fluid onto the mucosal surface (Boucher, 2007; Tarran *et al*, 2007; Thelin and Boucher, 2007). Additionally, similar approaches have been developed or are presently being investigated for the treatment of other conditions resulting from mucosal dehydration, including dry eye and chronic constipation (Tauber *et al*, 2004; Lang, 2008).

Recent data suggest that the ion transport processes of the oral epithelium could be similarly targeted to decrease fluid absorption, thereby increasing oral hydration. Singh *et al* (2008) have presented their preliminary findings of a phase I clinical study which evaluated the safety and efficacy of a novel ENaC blocker, PS552-02, for dry mouth associated with primary Sjögren's syndrome. PS552-02 is approximately 100-fold more potent than amiloride and its ENaC-blocking activity is prolonged (Hirsh *et al*, 2008). In the Sjögren's study, PS552-02 was associated with significant improvement in mouth and tongue dryness, as well as improvements in the ability to speak, eat, and sleep. Importantly, the largest improvements in these parameters over the vehicle control were observed 12-h after dosing, suggesting a long duration of therapeutic benefit. Additional studies will be required to further validate this approach. However, this preliminary study suggests that blocking $Na^+$ absorption could be a useful means for improving oral hydration.

## Summary

A growing body of evidence suggests that fluid absorption is a relevant factor governing the hydration status of the oral cavity and that targeting the underlying ion transport processes may be of therapeutic benefit. Importantly, approaches that prevent fluid loss from the mouth should be fully synergistic with therapeutic agents that increase gland secretion, such as systemic secretogogues, as well as, to alternative approaches aimed at preserving/increasing salivary gland capacity using anti-inflammatory agents or gene therapy. By targeting multiple aspects of fluid balance (secretion and absorption), a combination therapy should significantly improve oral hydration, which is predicted to alleviate many of the clinical manifestations of dry mouth. While future studies are needed to test this strategy, combination therapies will probably offer the most significant benefit for those suffering from dry mouth.

### Author contributions

Thelin WR and Boucher RC wrote the manuscript. Brennan MT, Lockhart PB, Fox PC, Singh ML and Papas AS provided data and assisted with the drafting and review of the manuscript.

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