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PLENARY ABSTRACT

Drug related hyposalivation: a review of physiology and sites of drug action

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Oral health is dependent upon the film of saliva that forms on the soft and hard surfaces in the mouth. The presence of saliva on oral surfaces is dependent not only on the rate at which saliva is secreted by salivary glands but on the composition of salivas secreted. Xerostomia, the subjective perception of dry mouth, is a relatively prevalent condition that is frequently associated with the intake of prescribed drugs. The relationship between xerostomia and presence of saliva on oral surfaces and in turn the rate at which saliva is produced is not necessarily straight-forward. It is clear, however, that reduced secretion of saliva should lead to reduced presence of saliva on oral surfaces and therefore the perception of dry mouth.

Salivary glands provide a 'resting' or 'unstimulated' flow of saliva that coats and protects oral mucosal surfaces and then for short periods in which food is tasted and chewed a greatly increased flow of saliva is produced by overt reflex stimulation. Parotid saliva makes a much greater contribution to the latter whilst the mucin secreting salivary glands provide the predominant contribution to resting or unstimulated salivary secretion. The greater content of mucin in unstimulated whole mouth saliva (UWMS) is evident when handling saliva in the laboratory. Flow rate of UWMS is usually used to assess the presence of salivary gland hypofunction since it is simple to perform and determines the saliva volume delivered to the mouth for most of the day. A review of previous studies demonstates that UWMS flow can vary widely. Part of the variation can be accounted for by a decreased flow rate observed in older age groups (beginning at 50 yr old) and lower flow rates in women (Percival *et al*., 1994). The reduced flow appears to be due to decreased submandibular gland function but it is also apparent that stimulated salivary secretion is less affected by aging. Secretion from labial and buccal minor salivary glands is not reduced with age although there is an age-dependent reduction in flow from palatal glands (Shern et al., 1993). The variation in UWMS flow rates makes it difficult to select a cut-off value for the designation of salivary gland hypofunction but review of a number of studies indicates a figure of 0.1–0.2 ml/min. Previous studies suggest that dry mouth is perceived by an individual when UWMS is reduced by 50% (Dawes, 1987).

The saliva film on mucosal surfaces differs in volume (thickness) with the thickest films being present on the floor of the mouth and anterior tongue and the thinnest film present on the anterior hard palate (see Figure 1). A number of studies have demonstrated reduced thickness of the salivary film in subjects complaining of dry mouth associated with salivary gland hypofunction (see Figure 1). Measurement of mucosal wetness is a relatively straight-forward undertaking using standardized filter paper strips in combination with a micro-moisture meter (Periotron) and could be incorporated into the routine Oral Medicine Dry Mouth Clinic. Some subjects complaining of dry mouth but with normal UWMS flow rates have reduced mucosal wetness suggesting that a change in salivary composition might be impacting on saliva retention on mucosal surfaces (Osailan et al., 2010). Saliva is retained on surfaces due to its viscoelasticity and this in turn largely depends upon the presence of glycoproteins, particularly the high and low molecular weight mucins MUC5B and MUC7. If saliva is sampled from mucosal surfaces and its protein composition studied by Western blotting analysis and or periodic acid Schiff staining, secreted mucins are found to be prominent components (Pramanik *et al*., 2010). Since the main source (70%) of MUC5B in saliva is minor submucosal salivary glands it is likely that minor salivary glands play an important role in maintaining mucosal health. The subjective feeling of dryness may be linked with reduced minor salivary gland secretion (Eliasson *et al*., 2009; see Figure 1) and it may be that the reduced flow rate from these glands plays a major role in the reduced retention of saliva on mucosal surfaces. Lack of retention of saliva on oral surfaces leads to clinical signs that can be assessed and scored and used as an index for monitoring dry mouth severity. Studies by the authors have demonstrated that a 10 point clinical oral dryness score (CODS) is negatively correlated with measured mucosal wetness and UWMS flow rate. Others have demonstrated an association between mucosal status and salivary flow rates.

Reflex secretion by salivary glands is mediated by afferent nerves which synapse in medullary salivary nuclei, from whence secretomotor autonomic parasympathetic nerves emerge to supply the parenchyma and blood vessels of major and minor salivary glands. The principal parasympathetic neurotransmitter is acetylcholine but neuropeptides such as Substance P and purines activate secretory acinar cells and different intracellular signaling pathways. Sympathetic nerves supplying major salivary glands arise from centres in the upper thoracic segments of the spinal cord although it remains unclear precisely where in this region; activation of salivary acinar cells is principally through the release of noradrenaline. Signaling from autonomic nerves has a stimulatory effect on salivary secretion and there is no peripheral inhibition, for example due to sympathetically mediated stimuli. Any agent that interrupts the salivary reflex can potentially cause salivary gland hypofunction or dysfunction by interrupting vasodilatation and the supply of water and or the fluid and protein secretory mechanisms operating in acinar cells and ductal cells. Physiologically this is seen at times of anxiety when the inhibition of secretion is mediated by stimuli from inhibitory nerves synapsing with the salivary nuclei and arising from other centres including higher centres in the brain. Sympathetically mediated stimuli modify the extent of salivary protein secretion whilst fluid secretion is mainly dependent upon the parasympathetic innervations (see Proctor & Carpenter, 2007).

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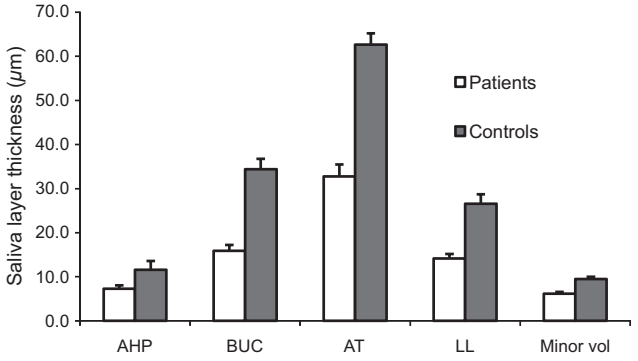

Figure 1 Comparison of calculated thickness of the saliva film on anterior hard palate (AHP), buccal (BUC), anterior tongue (AT) and lower labial (LL) mucosal surfaces of patients complaining of dry mouth and control subjects. Flow rate from labial minor salivary glands is also compared. Dry mouth patients included those with primary and secondary Sjögrens syndrome, drug induced dryness, sialadenitis nodal osteoarthritis and xerostomia (SNOX) syndrome. All surfaces and minor salivary flow rate (μl min^{-1}cm^{-2}) showed significant reductions in dry mouth patients.

The incidence of xerostomia is correlated with the number of drugs taken, regardless of whether these drugs have a known association with dry mouth (Nedefors, 1996). Many classes of drugs are associated with xerostomia/dry mouth including analgesics, anti-cholinergics and anti-spasmodics, anti-hypertensives, diuretics, anti-psychotics, psychotropics, anti-depressants, anti-Parkinson's, anti-histamines, appetite suppressants and anti-diarrhoeals emetics (Scully, 2003). However, relatively few drugs have been investigated for their effects on salivary gland function.

Drugs may cause hyposalivation by acting at central synapses or peripheral neuroeffector junctions. An example of the former is the central action of adrenergic agonists such as clonidine, tramadol and amphetamine which appear to exert a xerogenic effect by acting on central alpha-2 adrenoceptors (see Götrick *et al*., 2009). Peripheral inhibition of salivary secretion is seen with muscarinic receptor antagonists used in the treatment of overactive bladder which also interact with M3 muscarinic receptors which are major mediators of salivary fluid secretion. Tricyclic antidepressants have been shown to reduce salivary secretion through an anti-cholinergic action whilst alternative selective serotonin reuptake inhibitors appear to have a lesser effect. A recent study determined that xerogenic drugs broadly grouped as 'cardiovascular', 'tranquillizers', 'antidepressants', 'antihistamines' and 'gastrointestinal' reduced unstimulated and stimulated secretion from submandibular sublingual glands and had a lesser effect on parotid secretion (Wolff *et al*., 2008).

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