

# **On The Innervation of Salivary Glands and Treatment of Dry Mouth**

## **-An Experimental and Clinical Study**

**Nina Khosravani**

Institute of Odontology, The Sahlgrenska Academy, University of Gothenburg, Box  
450, 405 30 Gothenburg, Sweden

### **Abstract**

Detailed knowledge of the innervation of the parotid gland is essential in basic studies on various neuroglandular phenomena as well as in various types of orofacial surgery. The innervation is more complex than usually depicted in Textbooks. Using the rat as experimental model, it was shown that not only the classical auriculo-temporal nerve but also the facial nerve contributed to the cholinergic innervation of the gland, and that facial nerve-mediated impulses, reflexly elicited, evoked secretion of saliva. In humans, aberrant regenerating parasympathetic nerve fibres of the facial nerve may, therefore, be a potential contributor to Frey's syndrome, characterized by sweating and redness over the parotid region. Little is known about the sensory innervation of salivary glands. A co-localization of the neuropeptides substance P and calcitonin gene-related peptide signals sensory nerve fibres in the salivary glands. Though the auriculo-temporal nerve trunk carries sensory fibres from the trigeminal ganglion, denervation experiments showed that those sensory substance P- and calcitonin gene-related fibres that innervate the gland use other routes. The comparison of a number of various types of glands in the ferret revealed large differences in the acetylcholine synthesis, the mucin-producing sublingual, zygomatic and molar glands showing a synthesizing capacity, expressed per gland weight, 3-4 times higher than that of the serous parotid gland and the sero-mucous submandibular gland, implying a high cholinergic tone in the mucin-producing glands. The acetylcholine formation was due to the specific action of choline acetyltransferase, and denervation experiments showed this enzyme to be confined to the nerves. Thus, no support for an extra-neuronal synthesis of acetylcholine by the activity of choline acetyltransferase was found. Dry mouth jeopardizes the oral health. A new approach to the treatment of dry mouth was tested in healthy subjects and in patients suffering from salivary gland hypofunction. The cholinesterase inhibitor physostigmine prevents the breakdown of acetylcholine released from cholinergic nerve endings: acetylcholine accumulates and either evokes an effector response or enhances it. Physostigmine was applied locally on the oral mucosa aiming at activating hundreds of underlying, submucosal minor glands (producing lubricating mucin), while at the same time minimising systemic cholinergic effects. A dose-finding showed that it was possible to obtain a long-lasting secretion of saliva in the two study groups concomitant with a long-lasting relief from oral dryness (as revealed by Visual Analogue Scale-scoring) in the group of dry mouth patients at a dose level, where side-effects were absent or in the form of mild gastro-intestinal discomfort. The local drug application, directed towards the minor salivary glands, seems promising and may develop into a therapeutic option in the treatment of dry mouth.

**Keywords:** Parotid gland, denervation, acetylcholine synthesis, otic ganglion, auriculo-temporal nerve, facial nerve, neuropeptides, salivary gland hypofunction, physostigmine.

**ISBN: 978-91-628-7939-6**

# On The Innervation of Salivary Glands and Treatment of Dry Mouth - An Experimental and Clinical Study

Akademisk avhandling  
som för avläggande av odontologie doktorsexamen vid Sahlgrenska Akademin vid  
Göteborgs Universitet kommer att offentligens försvaras i lokal Lyktan,  
Konferenscentrum Wallenberg, Medicinargatan 20 A, Göteborg,  
onsdagen den 9 december kl. 09:00

av  
Nina Khosravani

Fakultetsopponent: Docent Anders Thulin, Medicinsk Direktör,  
Skåne Regionen, Kristianstad/Lund

This thesis is based on the following papers:

- 1. Khosravani N, Sandberg M, Ekström J.** The otic ganglion in rats and its parotid connection: cholinergic pathways, reflex secretion and a secretory role for the facial nerve. *Exp Physiol* 2006; **91**:239-247. Erratum in: *Exp Physiol* 2006;**91**:481.
- 2. Khosravani N, Ekström J.** Facial nerve section induces transient changes in sensitivity to methacholine and in acetylcholine synthesis in the rat parotid gland. *Arch Oral Biol* 2006; **51**:736-739.
- 3. Khosravani N, Ekman R, Ekström J.** The peptidergic innervation of the rat parotid gland: effects of section of the auriculo-temporal nerve and/or of otic ganglionectomy. *Arch Oral Biol* 2008; **53**:238-242.
- 4. Khosravani N, Ekman R, Ekström J.** Acetylcholine synthesis, muscarinic receptor subtypes, neuropeptides and secretion of ferret salivary glands with special reference to the zygomatic gland. *Arch Oral Biol* 2007;**52**: 417-426.
- 5. Khosravani N, Ekström J, Birkhed D.** Intraoral stimulation of salivary secretion with the cholinesterase inhibitor physostigmine as a mouth spray: a pilot study in healthy volunteers. *Arch Oral Biol* 2007;**52**:1097-1101.
- 6. Khosravani N, Birkhed D, Ekström J.** The cholinesterase inhibitor physostigmine for the local treatment of dry mouth: a randomized study. *Eur J Oral Sci* 2009;**117**:209-217.



UNIVERSITY OF GOTHENBURG