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Etiological relationships of parotid saliva cyclic nucleotides in patients with taste and smell dysfunction

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ABSTRACT

Objective: We previously demonstrated that parotid saliva cAMP and cGMP were lower in patients with taste and smell dysfunction than in normal subjects. We subsequently demonstrated parotid saliva cAMP and cGMP were inversely correlated with smell loss degree such that as smell loss severity increased parotid saliva cAMP and cGMP decreased proportionately. To learn more about these relationships we studied parotid saliva cAMP and cGMP with respect to aetiology of sensory loss in these patients.

Design: Parotid saliva cAMP and cGMP in patients with smell loss (hyposmia) who participated in an open label fixed design controlled clinical trial with treatment with oral theophylline were evaluated with respect to their initial etiological diagnosis. Levels of cyclic nucleotides in each etiological category were compared to each other, to the entire patient group and to normal subjects.

Results: Mean cAMP and cGMP in all patients combined were below those in normals, as previously described. However, categorized by aetiology, there was a stratification of levels of both cyclic nucleotides; some levels were below the normal mean and some were at or above the normal mean.

Conclusions: Parotid saliva cyclic nucleotides characterised in hyposmic patients by aetiology indicate (1) there are differential alterations in these nucleotides related to aetiology of sensory dysfunction and (2) these moieties measured prior to treatment indicate which patient groups may benefit from treatment with phosphodiesterase (PDE) inhibitors which increase levels of these moieties and thereby correct their sensory dysfunction.

1. Introduction

There are many causes for loss of taste and smell. We have been interested in the biochemical changes responsible for these sensory changes. We, as others before us, have recognized that saliva, through its components, is a factor in maintaining taste function in humans. To understand this concept in more detail we defined the major proteins present in human parotid saliva.[1] We then established that loss of one of these salivary proteins, gustin or carbonic anhydrase VI [CAVI[2]], a zinc containing glycoprotein,[1,2] was responsible for loss of taste[3] and smell[4] in some of these patients. We also established that treatment with exogenous zinc improved taste and smell function in CAVI deficient patients.[4] However, many patients with taste and smell loss did not exhibit loss of CAVI and did not respond to exogenous zinc with improvement in their smell loss (hyposmia).[5]

We then investigated other aspects of the biochemistry of these sensory changes by further analysis of both saliva[6–10] and nasal mucus.[11–13] In doing so we recognized that the saliva cyclic nucleotides cAMP and cGMP play important roles in

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maintaining taste function.[14] We also recognized that these salivary moieties were also present in nasal mucus[15] and they also played a role in smell function.

To continue this investigation, we demonstrated that parotid saliva levels of both cAMP and cGMP were lower in patients with taste and smell dysfunction than in normal subjects.[14] We also demonstrated that parotid saliva levels of cAMP and cGMP were correlated with degree of hyposmia such that as smell loss severity increased parotid saliva levels of cAMP and cGMP decreased proportionately.[16] We also demonstrated in these patients by use of functional magnetic imaging of brain (fMRI) that after theophylline treatment there was increased brain activation in specific brain regions to olfactory stimulation whereas before theophylline treatment there was little or none.[17] We also demonstrated in an open label fixed design controlled clinical trial that treatment with an oral phosphodiesterase (PDE) inhibitor (theophylline) in patients with lower saliva levels of these cyclic nucleotides which increased these levels[18] corrected their hyposmia.[19] However, whilst 65% of these hyposmic patients increased their levels of both cAMP and cGMP after theophylline treatment, which improved their smell function, these cyclic nucleotides did not increase in the remainder of these patients and their hyposmia did not improve.[20] These results[20] as well as other studies[19] indicated that not all patients with lower than normal levels of saliva cyclic nucleotides respond to treatment with oral theophylline. These results were similar to previous findings in which salivary CAVI may be abnormal but exogenous zinc treatment was not useful in restoring their sensory function.[5]

To investigate these phenomena further we wished to understand more about the clinical parameters which were associated with initiation of these sensory changes in patients with taste and smell dysfunction in relationship to their salivary levels of cAMP and cGMP.

In order to understand more about these patients we analysed levels of their parotid saliva cAMP and cGMP at their initial clinical evaluation to determine what role, if any, aetiology of sensory dysfunction might have on their projected treatment with PDE inhibitors. Indeed, if levels of salivary cAMP and cGMP were lower than normal, then treatment with PDE inhibitors could be of some value. However, if levels of salivary cAMP and cGMP were not below normal than treatment with PDE inhibitors may not be indicated.

2. Methods

All studies were performed at The Taste and Smell Clinic, Washington, DC between February 2001 and November 2007 and constitute studies on consecutive normal subjects and patients. Studies were approved by the Institutional Review Board of the Georgetown University Medical Centre.

Parotid saliva was collected from 66 normal subjects, aged 18–75 y [50 ± 5 y (mean ± SEM)]. Normal subjects were 40 men, aged 23–73 y (51 ± 7 y) and 26 women, aged 19–69 (49 ± 4 y) who were well and healthy, without any acute or chronic disease and not taking any medication. Taste and smell function was reported to be within normal limits by each subject by responses to specific questioning related to present and past sensory function.

Parotid saliva was also collected from 266 patients, aged 8–83 y (54 ± 2 y) with taste and smell dysfunction. Patients were all those with taste and smell dysfunction of any aetiology who presented to The Taste and Smell Clinic in Washington, DC for evaluation and treatment of their taste and/or smell dysfunction during this time period. These patients were 88 men, aged 9–83 y (56 ± 2 y) and 113 women, aged 12–79 y (55 ± 1 y). No patient was taking treatment related to their sensory function at the time of this study.

Aetiology of taste and/or smell dysfunction was determined in each patient based upon clinical data obtained at their initial visit to The Clinic. Patients were categorized into clinical etiologies as previously described (vi) and are shown in Table 1. Patients with loss of taste (hypogeusia) and oropyrosis did not always complain subjectively of smell loss but objectively demonstrated hyposmia as measured by olfactometry [v.i. 13,18,22,31] for one or more odorants.

Whilst all patients except those with hypogeusia and oropyrosis reported a subjective loss of smell function all exhibited a measurable loss of smell function. This was determined by olfactometry. Measurements of olfactory function were made by use of a standard, three stimuli, forced choice staircase psychophysiological sniff technique in a fixed, controlled design.[13,18,22,31] In this manner, detection thresholds (DTs), recognition thresholds (RTs), estimates of magnitude estimation (MEs) and hedonics [(Hs), estimates of odour pleasantness, unpleasantness or neutrality] were determined in each patient by use of four odorants [pyridine (a dead-fish-like odour), nitrobenzene (a bitter-almond odour), thiophene (a gasoline-like odour) and amyl acetate (a banana-like odour)]. Loss of smell function was defined by increased DTs and/or RTs and/or decreased MEs for one or more odorants and abnormal Hs (e.g., amyl acetate, usually considered pleasant was considered unpleasant). These techniques and results of these tests were documented both in a double-blind controlled clinical trial[5] and in an open label clinical trial of treatment of these patients with the PDE inhibitor theophylline.[19]

Loss of smell function was classified by degree of smell loss into three major types.[16,18,31,32] Type I hyposmia describes patients with the most severe degree of hyposmia with RTs = 0, MEs = 0, Hs = 0. Type II hyposmia describes patients with an intermediate degree of hyposmia with DTs and RTs > 0 but <normal and MEs > 0 but <normal; Hs may vary dependent upon MEs. Type III hyposmia reflects the least degree of hyposmia with DTs and RTs within normal limits but MEs > 0 but <normal; Hs vary dependent upon presence or absence of olfactory distortions.[19]

Most patients reported a subjective loss of taste. However, it was common for patients to state that they had impaired ''taste'' but were actually complaining of flavour loss (related more to smell function loss than a diminution in ability to taste per se; i.e., inability to taste salt, sweet, sour or bitter tastants.[6,24] Thus, they incorrectly considered their loss of flavour to be a loss of taste. However, all patients exhibited a measurable loss of taste function. Taste function was measured by gustometry in a manner similar to smell function, by use of a standardized three stimuli, forced choice,