Dysgeusia: Experimental evidence suggesting Neurological Impairment in Taste Perception among the Elderly and HIV-infected patients

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Abstract

Dysgeusia, characterized as an altered perception of taste to any one of the four major tastant qualities (sweet, salt, sour, and bitter), is frequently experienced after dental anesthesia and neuroma (middle ear) surgery. Many medications, ranging from anti-inflammatory drugs and protease inhibitors to antihypertensive drugs such as amiloride, have also been found to disrupt gustatory perception. Possible peripheral sites of damage are confined primarily to the two major gustatory nerves, the chorda tympani and the glossopharyngeal nerve. Studies addressing central nervous system impairment have focused mainly on the NST (nucleus of solitary tract), where taste input from these two cranial nerves converge, and the somatosensory cortex in the frontal lobe. Experiments involving cranial nerve blocks and crushes in laboratory animals have greatly enhanced our knowledge of the complex interactions between the chorda tympani and the glossopharyngeal nerves. This paper reviews literature concerning deficits in the peripheral gustatory system due to medications and injury.
Background information:

Dysgeusia is a general term that denotes alterations in taste perception that are manifested in either the peripheral nervous system (PNS) or the central nervous system (CNS). This disorder presents itself in many different forms. Some patients report a localized loss in the ability to detect various tastants (hypogeusia). Others experience a persistent intensification of specific tastant qualities, a condition referred to as taste phantoms. Patients frequently describe this form of altered taste perception as a metallic taste that continues in the absence of gustatory stimulation (Frank, 1992). A disproportionately large percentage of both the elderly population and HIV-infected patients have reported symptoms of dysgeusia. This has sparked much research with the main objective of uncovering neural mechanisms responsible for these taste disturbances.

Recent studies and experiments have shown that taste is exceedingly more complex than earlier research anticipated. The complexity of taste perception is attributed largely to the fact that the tongue is innervated by three cranial nerves, of which the glossopharyngeal nerve (GL) and the chorda tympani branch of the facial nerve (CT), have received the greatest attention in studies that have attempted to probe the possible taste mechanisms responsible for dysgeusia (Heald, 1997). Although dysgeusia, whether temporary or permanent, is frequently regarded as a “minor impairment” in comparison with the vast array of existing life-threatening diseases, it has been shown to affect patient compliance with a variety of medications and therapy treatments (Schiffman, 1999). Therefore, taste disruptions induced by, but not limited to, the aging process and specific medications, significantly inhibit recovery or prognosis of many fatal diseases. Although the vast majority of the American population will never
experience the adverse affects of dysgeusia, it is nevertheless an imperative subject that has the potential to improve the effectiveness of several existing treatment regimes.

Different factors, ranging from specific chemicals in psychotropic drugs, cardiovascular medications, and protease inhibitors to damage induced by dental anesthesia and nerve blocks, have been implicated experimentally as potential sources of taste disturbance (Heald, 1998). Experimental findings have addressed impairments in taste-specific neural circuitry that may be responsible for dysgeusia. Progress in this field has greatly enhanced our knowledge of the general interactions between gustatory nerves and general cortical and subcortical destinations of taste input. However, the functions of specific localized groups of gustatory neurons in both the CNS and PNS are largely subject to empirical scrutiny. A physiological cause to altered taste perception will allow doctors to recognize causes of taste interference and prescribe medications that have minimal adverse effects on the gustatory system.

**Experimental evidence of taste mechanisms involved in dysgeusia:**

Taste perception is highly specific to the particular quality of the tastant. Different groups of taste receptor cells are specialized to transduce sweet, salty, sour, and bitter taste stimuli. Furthermore, the transduction process is largely dependent on the tastant quality. Salty compounds directly open Na\(^+\) channels in an ionotropic manner. Sweet and bitter compounds, on the other hand, are transduced through a metabotropic process involving the activation of a second messenger and g-protein. Even though the transduction mechanism for each of these tastants is a highly localized and specialized process, the CT and GL nerves are the primary pathways for relaying taste input to the
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brain. Complex interactions between these two nerves allow for the development of compensatory mechanisms in the face of neural damage or injury to one of these nerves. The CT and GL exhibit mutual inhibition in the absence of neural damage. However, if one nerve is injured, the other nerve will increase its sensitivity through a neurological compensation referred to as release-of-inhibition.

The chorda tympani nerve innervates the anterior two-thirds of the tongue and has been a focal point in experiments designed to examine the effects of anesthesia, nerve blocks, and sectioning on taste detection. The chorda tympani is the primary gustatory nerve relaying specific tastant qualities such as bitter to the CNS. Early research in the field of taste detection centered on the finding that rats with lesions or other forms of neural damage to the CT exhibited a diminished response to several tastants in controlled experiments. One experiment in particular provided evidence that blocking the chorda tympani nerve between the tongue and the middle ear results in a persistent inability to exhibit normal licking behavior across a number of taste stimulants and concentrations (Hellekant, 1979). This experimental finding associated an intact chorda tympani nerve with the ability to relay proper neural signals to the CNS (specifically the NST and thalamic nuclei), where these signals are perceived as aversive or appetitive depending on their reinforcing qualities.

Nerve transection studies are one source of research that seeks to determine the role of each component in dysgeusia. In general, experimenters have found that lateralized damage to the tongue’s surface significantly inhibits activity and receptivity of the ipsilateral CT nerve to taste input. Recent studies have tested the ability to detect and discriminate individual tastant qualities before and after unilateral cranial nerve
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transection. One study found that taste detection thresholds in subjects with a unilaterally sectioned chorda tympani nerve were more than twice as high on the sectioned side compared to the side of normal functioning (Kveton, 1994). In addition to this finding, taste recognition thresholds for all tested tastants were significantly higher on the side of the tongue ipsilateral to chorda tympani nerve sectioning (Grant, 1989). In an experiment designed to determine the effects of unilateral chorda tympani damage on gustation, localized taste testing confirmed these CT transection results. Localized taste deficits were reported ipsilateral to the damaged area (Goto, 1983).

Some studies, such as the two aforementioned experiments, involve sectioning the chorda tympani nerve only, while others have incorporated sectioning the glossopharyngeal nerve into their experimental methodology. Generally, findings have supported the idea that detection thresholds to a variety of tastants are significantly elevated after transectioning the chorda tympani nerve (Kopka, 2001). Therefore, tastants that are found to be reinforcing under normal conditions, such as sucrose solutions, are not as reinforcing after chorda tympani nerve sectioning (Tonosaki, 1993). In a similar fashion, tastant qualities generally regarded as aversive, such as quinine HCl, are not as aversive after the CT is severed.

However, many studies have provided evidence of a complex series of interactions between the CT and glossopharyngeal nerves, which may serve as a compensatory mechanism when one of these nerves is severely damaged. One study has corroborated the hypothesis that unilateral CT sectioning or application of topical anesthesia to a lateralized region of the CT has little effect on taste function, even though these procedures eliminate innervation to roughly one-half of the taste receptor cells on
the anterior tongue (Mattes, 1994). This study specifically found that these two experimentally-induced methods of unilateral gustatory neural injury did not lead to increased detection thresholds for any of the four major tastant qualities. Therefore, it was concluded that a neural mechanism exists between the CT and GL nerves in which taste can be preserved at normal detection levels in the presence of unilateral damage to one of these two cranial nerves. A recent study suggested that neither the glossopharyngeal nor the chorda tympani nerve is necessary for normal detection of bitter (aversive) tastants provided the other is intact (St. John, 1996). However, when both of these nerves are transected, the remaining input to the CNS is not sufficient to maintain normal detection performance (St. John, 1996). One intact nerve is sufficient to avoid changes in receptivity to incoming tastants. This redundancy in neural signaling is experienced when either the CT or GL is damaged or otherwise unable to relay input.

Several experiments have shown that sucrose detection and recognition is mediated primarily through the CT. One experiment examined the effects of bilateral sectioning in mice of the chorda tympani and glossopharyngeal nerves, together and separately, on sucrose detection thresholds. The results showed evidence of the chorda tympani’s role in stimulating the reinforcing qualities of sweet tastants. The mouse that was bilateral-sectioned only in the glossopharyngeal nerve demonstrated a similar preference to control mice for low concentration sucrose solutions over distilled water. Experimental mice that had bilaterally sectioned chorda tympani and glossopharyngeal nerves or bilaterally sectioned chorda tympani nerves decreased their number of licks to the low concentration sucrose solutions (Tonosaki, 1993). This emphasizes the CT’s role in maintaining normal detection performance and perception of sweet tastants. Another
experiment demonstrated that bilateral CT-sectioned rats decreased their oral responses to sucrose solutions compared to healthy controls (Grill, 1992). Taste reactivity tests, measured by degree of consumption and reinforcement ratings by subjects, revealed that significant decreases during sucrose ingestion were indicative of bilateral CT nerve transection.

Evidence also links the chorda tympani with receiving NaCl, citric acid, and QHCl gustatory input. In response to aversive tastants such as NaCl or quinine, experiments with laboratory animals have supported the possibility that detection thresholds for these tastants are significantly diminished after bilateral CT transection. This suggests that the chorda tympani is critical in the formation of conditioned taste aversions to many tastants, most importantly NaCl, citric acid, and quinine. One experiment with rats demonstrated a loss of sensitivity to NaCl after the CT was sectioned bilaterally. Rats in the experimental treatment group increased their licking behavior to NaCl compared to those rats in the control group (O’Keefe, 1994). This finding has been generalized to other salts as well. In a similar study of chorda tympani nerve transection in rats, it was found that a learned taste aversion to KCl was severely altered. Sham group rats formed an aversion to 0.1 m KCl after 1 trial, whereas the rats with chorda tympani nerve transection were unable to form this aversion after 1 trial. Furthermore, the rats in the experimental group did not suppress licking to 0.03 or 0.3 m KCl or any concentration of NaCl when compared to controls (St John, 1997). In a similar experiment, chorda tympani nerve transection significantly impaired the selectivity of NaCl by Fischer-344 rats, a laboratory strain that shows an increase in preference for NaCl in response to salt depletion (Breslin, 1995). Furthermore, chorda
tympani nerve blocks were found to reverse the NaCl aversion that these rats exhibit under normal conditions in the absence of salt depletion (Sollars, 1991).

Another study confirmed these experimental results for altered NaCl taste preference in hamsters. In this experiment of long-term salt preference, transection of the CT nerve induced a loss of discrimination between potassium and sodium salts (Barry, 1993). Hamsters in the experimental treatment no longer demonstrated a strong preference for KCl over NaCl. These findings indicated that preference ratios for KCl after CT nerve transection were almost identical to those for NaCl (Barry, 1993). Conclusions from this study implicate the chorda tympani’s crucial role in taste discrimination of NaCl and other salts. The CT nerve may be the primary peripheral mediator in initiating a strong and selective aversion to sodium solutions.

The focus of other experiments has centered on the impairments in quinine detection following cranial nerve transection. These studies have generally supported the involvement of both the glossopharyngeal nerve and the chorda tympani nerve in quinine taste detection. Both of these nerves must be sectioned to cause a substantial reduction in responsiveness to quinine (St John, 1994). The results of this experiment were confirmed by a later study, which replicated the results that combined glossopharyngeal and chorda tympani nerve transection is necessary to increase QHCl detection thresholds in rats (St John, 1996). A similar experiment addressed how each of these nerves were involved in quinine taste aversion. After bilateral section of either the chorda tympani nerve or the glossopharyngeal nerve, the conditioned rejection response to quinine was significantly reduced. However, bilateral sectioning of the chorda tympani nerve caused an increased latency to the first lick and did not affect licking behavior thereafter (Travers, 1987). On
the other hand, bilateral sectioning of the glossopharyngeal nerve did not affect latency to the first lick, but severely altered subsequent licking behavior (Travers, 1987). These findings support the role of taste receptors on the anterior tongue, innervated by the chorda tympani, in initiating a rejection response to aversive tastants. However, gustatory receptors on the posterior tongue, innervated by the glossopharyngeal nerve, play an important role in sustaining the physiological rejection to these tastants. These separate neural pathways act in combination to produce and relay gustatory input, which converges in the CNS at the nerve termination fields in the NST (nucleus of solitary tract) of the brain stem (St John, 1996). Convergence of input in the NST is crucial to initiating and sustaining rejection responses to aversive stimuli, particularly QHCl.

Recovery of function in patients suffering from dysgeusia is largely determined by the degree of injury and the time of onset. Studies addressing the recovery ability of chorda tympani nerve function after injury are generally favorable. In one experiment with hamsters, the chorda tympani was crushed in the middle ear and the subsequent effects on taste were monitored for 16 weeks. By 4-8 weeks after injury, responses to taste stimuli in experimental rats were similar to control responses (Cain, 1996). Another study examined the loss and recovery of sodium-specific taste after bilateral sectioning of the chorda tympani nerve. In the first part of the experiment, bilateral damage to the CT nerve removed a previously learned conditioned taste aversion to 0.1 M NaCl (Barry, 1993). This provides evidence for the CT’s role in formation of taste aversion responses. After adequate time surpassed for recovery of CT nerve function (10 to 16 weeks), the hamsters were reconditioned three times to 0.1 M NaCl. The subjects demonstrated a renewed ability to relearn the conditioned taste aversion. Furthermore, by 16 weeks, the
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experimental and sham groups showed equally strong and specific aversions to 0.1 M NaCl (Barry, 1993). Regeneration of CT nerve fibers has been correlated with a high chance of complete recovery, resulting in detection and aversion thresholds similar to those measured before the injury.

While cranial nerve sections and crushes have supported the importance of an intact chorda tympani nerve (sometimes coupled with the glossopharyngeal nerve) in taste detection at localized regions of neural injury, anesthesia and neuroma studies have addressed the effects of neural blocks to whole-mouth taste detection. These studies have favored the existence of a compensatory mechanism in the presence of chorda tympani nerve anesthesia commonly referred to as the release-of-inhibition hypothesis (Lehman, 1995). Much of this research was initially triggered by the discovery that many patients with severe nerve damage exhibited normal patterns of taste detection in experiments that addressed overall gustatory perception. One early follow-up study assessing the effects of chorda tympani damage on taste perception revealed that 20% of patients with unilateral or bilateral damage to the CT nerve reported no overall deficits in taste (Bartoshuk, 1994). This study further showed that the other 80% reported primary symptoms that were indicative of dry mouth or metallic taste phantoms (Bartoshuk, 1994). In conclusion, CT nerve damage is generally not sufficient to initiate symptoms, such as increased detection and recognition thresholds, that are associated with whole-mouth hypogeusia or generalized taste loss (Bull, 1965).

The discovery of taste phantoms has been investigated in numerous experiments involving gustation. Taste phantoms occur when taste input is perceived and experienced in the absence of actual stimulation (Bartoshuk, 1994). In one neuroma study of
particular importance, taste intensities decreased in the CT region ipsilateral to the site of
tumor detection, as expected (Kveton, 1994). However, in this same study, an
unexpected increase in taste intensity occurred in posterior regions innervated by the
glossopharyngeal nerve (Kveton, 1994). An earlier study demonstrated this release-of-
inhibition hypothesis because patients receiving anesthesia to the chorda tympani nerve
reported no loss or deficits in perceived taste intensities. Rather, in the whole-mouth
method of taste perception, patients actually reported intensifications to some tastants
(particularly bitter and metallic) after anesthesia application (Ostrom, 1985). This
finding, which has been replicated in recent studies, revealed that neural mechanisms of
taste reflect a redundancy in the presence of localized damage, thereby enabling
unaffected regions of the tongue to compensate for the loss of taste perception in
damaged regions. Therefore, mutual inhibition between the CT and glossopharyngeal
nerves in the absence of neural damage provides one mechanism that supports the
interaction between these two nerves addressed earlier. Further evidence for the release-
of-inhibition hypothesis revealed that anesthesia of the chorda tympani not only produced
increased taste responses from glossopharyngeal (posterior) regions, but a significantly
greater increase in taste detection was observed in the CT region contralateral to the
anesthetic (Kveton, 1994). This study on unilateral chorda tympani nerve damage and
anesthesia supports similar observed effects in patients after surgery for acoustic
neuroma. (Kveton, 1994).

Chorda tympani nerve transection does not have to occur in regions of the mouth
to experience these taste alterations. Frequently the chorda tympani nerve is injured or
sacrificed during middle ear surgery (acoustic neuroma) because this nerve runs
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immediately below the tympanic membrane in its neural path to the NST. A study involving patients who underwent this type of surgery revealed that trauma to the chorda tympani produced significant symptoms of dysgeusia. The majority of these patients recovered normal taste ability, indicating the chorda tympani’s remarkable ability to regenerate and restore lost gustation perception. However, when the chorda tympani was sacrificed and few, if any, neural fibers were left in its tract, there was a 31% increased incidence of permanent dysgeusia, which frequently led to the onset of taste phantoms (Yeo, 1997). These findings support the idea that gustation is affected by neural damage of the chorda tympani in widespread regions of the PNS, particularly in the middle ear.

While most of the ramifications of the release-of-inhibition hypothesis are experienced in the periphery, this concept of mutual cranial nerve inhibition has most of its origins in the CNS. The CNS neural basis for taste intensifications has been a main focus of recent research on taste. The chorda tympani nerve normally inhibits taste receptor detection in the glossopharyngeal nerve. It has been established that input via the chorda tympani inhibits the units in the NST that receive input from both the chorda tympani and glossopharyngeal nerves (Dinkins, 1999). However, in the presence of chorda tympani anesthesia, this inhibition is released and glossopharyngeal nerve responses are intensified. Similarly, when the chorda tympani nerve is damaged (either cut, sectioned, or blocked), normal inhibition of the glossopharyngeal nerve is removed. This may reflect a neurological process that serves to preserve overall taste perception by lowering detection thresholds in one region of the tongue (of interest, the glossopharyngeal nerve) in order to minimize the adverse effects of taste loss in the damaged area (of interest, chorda tympani) (Catalanotto, 1991).
One experiment performed on rats suggests that unilateral chorda tympani nerve anesthesia facilitates disinhibition in the rat NST to a variety of tastants. This study found that during anesthesia, rats displayed increased taste responsiveness at several individual sites on the side of the tongue contralateral to the anesthesia (Dinkins, 1998). In two experiments, which both applied a unilateral lingual nerve block through topical anesthesia on the anterior tongue, results confirmed taste impairment as expressed through a complete taste loss ipsilateral to the region of anesthesia injection. Furthermore, as predicted, there was an increased perceived intensity of most stimuli in the posterior circumvillate papillae regions innervated by the glossopharyngeal nerve (Lehman, 1995). This increase in posterior taste intensity was not sufficient to elevate thresholds of most tastants to normal detection levels. However, some bitter tastants, particularly QHCl, were overly compensated in posterior regions during anesthesia, causing patients to report an increase in perceived intensity of these taste qualities during whole-mouth taste tests (Lehman, 1995). Two follow-up experiments, one using dental anesthesia through lingual nerve blocks, and the other using anesthesia in the ear canal, reported similar findings for this increased whole-mouth taste detection for bitter (Lehman, 1995). This increase in whole-mouth detection thresholds for bitter probably reflects an evolutionary safeguard to avoid potentially fatal toxins because these chemicals often possess a bitter taste.

Many studies that have explored the presence of taste phantoms have supported the release-of-inhibition hypothesis. An experiment that examined the effects of bilateral anesthesia to the chorda tympani supported the ipsilateral loss of taste reported in prior experiments. However, it also reported that 8 out of 17 total subjects experienced
anesthesia-induced taste phantoms (Yanagisawa, 1998). In this experiment, anesthesia was administered bilaterally (one at a time) through a needle into the posterior ear canal wall. Spontaneous phantoms were reported prior to anesthesia of the second ear canal wall and localized to a region contralateral to the anesthesia (Lehman, 1995). These regions of taste phantoms were further confirmed by unilateral anesthesia application after the initial experiment was complete. This suggests that taste phantoms are also a direct product of release-of-inhibition in the CNS because unilateral anesthesia of the chorda tympani releases inhibition normally exerted on the contralateral posterior tongue, even in the absence of gustatory stimulation. Taste phantoms included qualities perceived as salty, sweet, sour, and, most frequently, bitter and metallic (Lehman, 1995).

These phantoms have not been reported by subjects in bilateral anesthesia studies. Experiments involving anesthesia application to CT regions on both sides of the tongue have extended the adverse effects of unilateral anesthesia to the second side of the tongue. Intensifications in posterior regions for QHCl were not adequate to compensate for lost perception in the palate and more anterior regions. All four tastants underwent significant increases in whole-mouth taste detection thresholds, presumably because the release-of-inhibition compensatory mechanism was notably less effective, perhaps nonexistent, in the face of bilateral chorda tympani nerve anesthesia (Lehman, 1995).

The release-of-inhibition hypothesis emphasizes the importance of intact cortical areas (NST and thalamus), where ipsilateral input from the three gustatory nerves converge. However, other areas of taste research, including studies of middle ear surgery and dental anesthesia, have demonstrated the functional relevance of taste receptor cells and peripheral gustatory neural circuitry in taste detection and perception. Several
studies have implicated dental anesthesia procedures, specifically by inferior alveolar nerve blocks, as sources of fungiform papillae degeneration and dysgeusia. Two patients addressed in one study of topical dental anesthesia through this nerve block reported a temporary inability to perceive bitter and a persistent burning sensation on the ipsilateral side of the dental molar extraction procedure (Hotta, 2002). Bitter taste perception was intensified on the contralateral side, supporting the release-of-inhibition hypothesis and the role of the CNS to compensate for injured regions of the tongue. However, similar to acoustic neuroma procedures, dental procedures have been found to severely alter taste perception in the PNS. The likely cause of these taste alterations is that the needle with anesthesia injured the chorda tympani nerve at the injection site, thereby damaging taste receptors in this region of the tongue and causing long-term atrophy of the fungiform papillae in the anesthesized region (Hotta, 2002). An earlier experiment suggested this possibility when unilateral CT nerve-sectioning in rats led to rapid degeneration of ipsilateral fungiform papillae (Inoue, 1978). These studies indicate the importance of peripheral gustatory nerves and taste receptor cells for facilitating normal taste transduction. Experimental observations have also concluded that when the CT nerve is severed on one side of the tongue, the ability to perceive bitter disappears on the ipsilateral side until damaged fungiform papillae are able to regenerate (Matsuyama, 1986). Therefore, the chorda tympani nerve is specialized not only in its ability to relay “salty” sensory input, but also in relaying bitter sensory input to the CNS. This suggests that an inability to perceive bitter tastants may be indicative of CT nerve damage in the periphery.
Whether damage to the fungiform papillae is temporary or permanent depends, not only on the extent of damage, but more importantly on when the damage occurs in development. One experiment with rats found that bilateral CT nerve transection at 10 days of age led to both a significant loss of taste buds and a permanent loss in numbers of fungiform papillae (Sollars, 2000). Effects of this magnitude are not observed when the CT is sectioned in adult rats. The chorda tympani nerve is a critical factor in ensuring proper growth and maturation of fungiform papillae during a particularly sensitive period of development. After this development is complete, the ability of papillae to regenerate is greatly enhanced and CT denervation is likely to produce only temporary adverse effects on normal fungiform morphology.

There is further evidence that CT transection in neonates leads to permanent alterations in adult preference for specific taste stimuli. In one study, findings indicated that neonatal CT transection produced a significant change in rats’ preference for ammonium chloride. Ammonium chloride, which is generally not preferred by rats under normal conditions, displayed a significant increase in preference among experimental rats (Sollars, 1996). Failure for the chorda tympani to regenerate after this sensitive period of development and subsequent permanent loss of fungiform papillae are likely contributors to this change in taste preference.

Many scientific studies and experiments have shown the complex interactions, both in the periphery and central regions, between tastant qualities, gustatory perception, and taste preference. The glossopharyngeal and chorda tympani nerves appear to play crucial roles in specific detection avoidance behaviors. Results that have been replicated in several experiments have inicated that these two cranial nerves compensate for one
another in the presence of localized damage, anesthesia, or nerve blocks. This interaction takes the form of mutual inhibition under normal conditions in the absence of damage to neural regions of the mouth. However, release of this inhibition serves as a compensatory mechanism in the face of gustatory injury to one nerve or the other. Taste phantoms have been reported in the absence of gustatory stimulation and occur when one nerve becomes hypersensitive and over-compensates for the other one during periods of impairment. The exact neurological cause of these phantoms remains unknown. From an evolutionary perspective, this redundancy demonstrates the vital importance of taste for survival.

**Applying neural mechanisms to altered taste perception in the Elderly and HIV-infected patients:**

Dysgeusia is a common side-effect of many medications, particularly those involved in sustaining normal cardiovascular and immunological function. Past experiments have shown that many of these medications, as well as psychotropic drugs and protease inhibitors, are strongly correlated with dysgeusia (Schiffman, 1994). As a result, the elderly and HIV-infected patients are particularly vulnerable to these adverse symptoms. One recent study addressed the long-term effects of 6 anti-inflammatory drugs and 13 antimicrobial drugs on taste (Schiffman, 2000). These medications serve a variety of functions, from treating chemotherapy to boosting the body’s own immunological defense mechanisms against invading organisms. Eight of the 13 antimicrobials are used for HIV-related infections or infectious disorders most frequently experienced in elderly patients. Experimental subjects were comprised of young, healthy
subjects, HIV-infected (but currently unmedicated) subjects, and elderly subjects, who were also refrained from medication use at the time of the experiment. Subject medications were avoided during the course of the experiment to avoid potentially confounding interactions with the drugs of interest. Each of the 19 medications was administered to the subjects through topical application on the apical tongue surface (Schiffman, 2000). The forced choice ascending method was utilized either with paper tongues or directly through application on the anterior tongue. All medication tests were perceived by subjects as having a bitter and metallic taste. Results revealed that elderly subjects exhibited significantly higher detection thresholds compared to young subjects for diflofenac sodium, ethambutol, and tetracycline, all of which are used to treat infections (such as pneumonia) in the elderly (Schiffman, 2000).

This finding suggests three possible reasons for the correlation between age and increases in taste detection threshold. First, age in itself, may be a source of dysgeusia despite adequately good health. The aging process may contribute to taste bud and papillae degeneration and, likewise, the decreased ability to regenerate taste receptor cells. Second, long-term medication-use in elderly people may interact with the chorda tympani or peripheral taste transduction mechanisms, thereby leading to a reduction in taste perception and a decreased ability to perceive tastant qualities. Lastly, interactions between the chorda tympani and glossopharyngeal nerves in the NST may demonstrate a decreased level of interaction with one another over time or with persistent use of anti-inflammatory medications. In other words, release-of-inhibition normally projecting to the glossopharyngeal nerve receptor cells in the face of chorda tympani nerve damage may be diminished by age or use of these medications.
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An earlier study provides evidence for this deficit in neural compensation between the glossopharyngeal and CT nerves. Elderly subjects, particularly those on medications associated with metallic or bitter taste qualities, showed an increase in detection threshold of a variety of tastants (Frank, 1992). Furthermore, in the experiment addressing anti-inflammatory and antimicrobial medications, elderly subjects used more descriptive adjectives such as “burning” or “spicy” to describe these bitter medications (Schiffman, 2000). This may reflect cognitive problems in describing tastes or underlying dysgeusia. A potential conflict with this experiment is presented by the fact that the methodology and analysis of results did not discriminate unmedicated from medicated elderly subjects.

In this same experiment, taste thresholds among HIV-infected subjects did not differ statistically when compared with the young, healthy control group (Schiffman, 2000). However, HIV subjects rated pentamidine and trimethoprim as more bitter at suprathreshold concentrations. This reflects a possible link between HIV status, use of related medications, and altered taste perception. The fact that HIV subjects were unmedicated indicates this increased sensitivity to bitter, metallic medications may be triggered by the disease itself. Perhaps through the early progression of HIV, the chorda tympani degenerates and demonstrates a diminished ability to inhibit the glossopharyngeal nerve. This could lead to an increase in taste perception because the release-of-inhibition hypothesis has shown that the GL nerve is particularly specialized in its ability to relay bitter sensory input to the CNS (Matsuyama, 1986). Furthermore, HIV medications may also be a source of dysgeusia because the unmedicated HIV patients in Schiffman’s experiment reported similar detection thresholds as healthy young subjects.
Virtually all of the HIV patients in ‘real world’ case studies were on medications when they initially reported taste alterations (Mattes, 2002). A probable link between these medications and taste disturbances should not be overlooked. Once again, a conflict is presented because the medication history of HIV-infected subjects is usually not recorded and taken into account when results are interpreted (Mattes, 2002). It can only be suggested that medications associated with treatment of HIV are correlated with changes in taste perception. Furthermore, Schiffman’s experiment did not address which ones, specifically, have the potential to cause these disruptions.

According to current research, taste and smell are generally well preserved with age (Mattes, 2002). Anatomical evidence for this has been provided by experiments in which the chorda tympani was sectioned unilaterally in older patients. Results showed that this had minimal effects on taste bud distribution and function (Miller, 1991). However, the gradual onset of taste disturbances may disguise these malfunctions (Madeira, 1989). In earlier studies, a progressive decline in taste sensitivity was strongly correlated with advancing age (Schiffman, 1991). Studies of taste thresholds in the elderly suggest that these increase for sucrose, NaCl, HCl, and QHCl, which are representative of all four major taste qualities (Schiffman, 1997). Experiments involving repeated testing of healthy elderly subjects show that a marked reduction in sensitivity to all taste qualities occurs in nearly everyone (Stevens, 1995).

Evidence of taste losses in the elderly correlates dysgeusia with adverse health effects. A dietary supplementation trial with elderly individuals reported a decline in intensity ratings and a higher preferred sucrose concentration in foods by these subjects compared to younger controls (de Jong, 1996). An older study found that patients
experiencing taste distortions tolerate high fat foods better than low fat foods (Henkin, 1989). A preference for sugar and high fat foods can lead to adverse health conditions, demonstrated by the fact that patients in both of these studies had higher cholesterol levels than controls of similar age. Atrophy of the fungiform papillae may be responsible for this diminished perception of sweet and fat tastants. Losses in taste perception of salt have also been shown in older individuals (Schiffman, 1991). This can make it especially difficult for patients with high blood pressure to adhere to a low-sodium diet. Furthermore, use of amiloride, a common chemical in the treatment of hypertension, has been found to result in metallic dysgeusia (Frank, 1992). This is probably initiated by loss of inhibition of the glossopharyngeal nerve caused by a decreased capacity for the chorda tympani to carry bitter neural input to the brain stem (NST). Amiloride has also been found to raise NaCl taste detection thresholds in rats (Kopka, 2001). This is attributed to its ability to block ion channels in taste receptor cells, thereby altering transduction of ionic tastes from normal threshold levels (Kopka, 2001).

Many of these age-related taste losses are caused by a slower rate in turnover of taste cells (Schiffman, 1997). The aging process decreases the ability of taste receptor cells to regenerate as older cells undergo apoptosis. Olfactory dysfunction may also be associated with taste loss and a lower preference for foods with bitter or sour qualities (Duffy, 1995). Therefore, impairments in the sense of smell may contribute to decreased ingestion of vital nutrients found in vegetables (bitter) or many citrus fruits (sour).

Taste impairments in HIV-infected patients are of vital importance because they contribute to HIV associated wasting, a term that addresses the gradual degeneration of life-sustaining functions such as respiration. One study suggested that, in addition to the
antimicrobial drugs already discussed, amphotericin B, ampicillin, metronidazole, and tetrapentamidine can cause a loss or distortion of taste (Schiffman, 1991). A more recent study found that glutamic acid detection thresholds were significantly elevated in HIV patients compared to controls (Graham, 1995). The taste identification task in this experiment also revealed a significant difference between experimental (HIV, medicated) subjects and controls (Graham, 1995). In this portion of the study, the experimenter named a particular taste quality and the subject determined which of the two stimuli of a pair had that taste. Experimental subjects had significantly fewer correct identifications. Both of these findings indicate that a diminished ability to correctly perceive tastants is correlated with the HIV virus and associated medications.

Furthermore, Graham’s experiment demonstrated a link between malnourishment in HIV patients and progression of the disease. Experimental subjects who were classified as malnourished (determined by serum levels in the body) showed larger deficits in taste detection, taste memory tasks, and taste identification tasks compared to those subjects in earlier stages of the disease (Graham, 1995). Progression of the HIV virus is probably associated not only with peripheral neural and taste receptor atrophy, but also a degeneration of CNS neurons in the prefrontal cortex, where sensory input is received and processed. Medications may increase the magnitude of these taste losses and subsequent malnourishment by distorting saliva secretion (PNS response) or penetrating the blood-brain barrier and affecting CNS information processing in the NST (Graham, 1995).

Another more recent study replicated the experimental observation that glutamic acid detection thresholds were increased in HIV patients compared to controls (Heald,
Pentamidine, which is commonly administered in HIV patients to fight off pneumonia, was perceived by many HIV subjects to have a persistent metallic taste that lingered for long periods of time (days) after it was removed (Heald, 1998). Control subjects did not report perception of this taste. This suggests the existence of taste phantoms in some HIV subjects on pentamidine, implicating that release-of-inhibition occurs in the NST of these individuals even without gustatory stimulation. Furthermore, this experiment concluded that the number of medications that HIV subjects were currently taking was an accurate predictor of taste complaints (Heald, 1998). A patient on more medications had an increased likelihood of reporting taste disturbances and showing signs of taste receptor atrophy compared to a patient on fewer medications.

Experiments have also shown that a disproportionately high number of taste complaints are reported by HIV patients on protease inhibitors (Heald, 1998). Protease inhibitors are necessary in most drug regimens and combination therapies used to treat HIV infection (Schiffman, 1999). Clinical evaluations have revealed their significant therapeutic value in decreasing maladies and nausea induced by both progression of the disease and other medications. Despite these benefits, protease inhibitors have been reported to have a metallic taste and cause long-term taste abnormalities (Schiffman, 1999). This has a severe negative impact on patient compliance and, subsequently, the quality of life of HIV patients. Taste distortions from these medications are likely to occur in the CNS because they interfere with natural inhibitory mechanisms between the chorda tympani and glossopharyngeal nerves. Unlike amiloride and other medications that directly manipulate ion channels in taste cell membranes, protease inhibitors are likely to alter second messenger systems in taste receptor cells because they decrease the
effectiveness of protease to break down cellular proteins (Schiffman, 1999). It is unlikely that these medications act directly on sodium and potassium channels, as seen with the ionotropic effects of amelioride in correcting hypertension in the elderly. Results of this experiment show that three of the four protease inhibitor medications (ritonavir, indinavir, and saquinavir) were rated by HIV-positive subjects as more intense, bitter, and sour than by controls (Schiffman, 1999). These findings are similar to other experimental findings of effects of antimicrobial and anti-inflammatory medications on taste.

Although protease inhibitors produce similar effects on perceived tastant quality and intensity (particularly for bitter) compared with other medications, the neural mechanisms involved are likely to be different. Rather than directly contributing to degeneration of the chorda tympani nerve, it is more probable that protease inhibitors cause taste cell atrophy by decreasing metabolic and sensory input transduction activity within individual taste cells (Stone, 1998). A further implication of experimental findings involving protease inhibitors suggests that these drugs affect the nucleus accumbens and opiate system in cortical regions to diminish reinforcing qualities of appetitive tastants (sweet) and increase the aversive qualities of negative tastants (bitter, sour). In one experiment, it was found that HIV patients reported increased taste intensities for citric acid and QHCl after the administration of many different protease inhibitors and a corresponding decrease in intensity ratings to sucrose (Melvin, 1997).

In summary, medications prescribed to the elderly and HIV patients have been experimentally shown to alter taste perception in numerous ways. They may have effects on the PNS by causing receptor cell or cranial nerve degeneration. They may also be
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secreted in the saliva at high enough concentrations to alter normal taste sensation and transmission mechanisms (Heald, 1997). Furthermore, the simple possibility that many of these medications produce a unique taste, thereby interfering with other taste qualities, should not be overlooked. Many medications (such as protease inhibitors) that are of adequately small size and lipid soluble demonstrate the ability to cross the blood-brain barrier (Heald, 1997). These chemicals may act in the NST or cortical regions such as the primary somatosensory cortex to negatively impact characteristics of peripheral taste cells such as membrane permeability and rate of regeneration (turnover). Lastly, chemicals in these medications may cause generalized damage to gustatory cranial nerves, inhibiting the ability of these nerves to transmit impulses to the brain.

In Conclusion:

Current treatment strategies for dysgeusia are limited because neurological mechanisms to correct or reverse cranial nerve damage have not been developed. Recovery is therefore restricted to the natural healing process and physical regeneration of neural fibers in the periphery and gustatory tract. Recovery is often slow and incomplete in elderly individuals and HIV patients (Mattes, 2002). However, chances of rapid and complete recovery from dysgeusia are high in young and healthy controls. Based on these findings, specific chemicals that initiate this regeneration can be isolated in future laboratory experiments. Synthetic forms of these chemicals can be developed and administered to elderly people and HIV-infected patients to restore normal gustatory detection thresholds. Furthermore, knowledge of the composition of these chemicals may enable medications to be developed that bypass the gustatory system altogether.
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Until these chemicals have been pinpointed, bitter medications in powdered or granulated form should be placed in tasteless capsules to avoid interactions with the papilla or associated nerves.

One treatment strategy of particular interest has been found to increase the appeal of nutritional foods and alleviate nutritional deficiencies in the elderly. Flavor enhancement, which increases the concentration of odor and taste compounds, has initiated a greater preference for nutritious foods in elderly people (Schiffman, 1993). It is believed to stimulate the underactive opiate system in the CNS present in many elderly individuals. Stimulating this system increases the pleasurable and reinforcing qualities of food stimuli. Also, flavor enhanced foods are easier to detect by the cranial nerves involved in taste and the NST. Therefore, the reinforcing qualities of these foods are more noticeable compared to foods that do not show flavor amplification. A recent study reported a significant effect of flavor amplification on corn and yogurt food preference in the elderly (Griep, 2000). Further evidence for the positive impact of food enhancement was provided by a long-term (16 weeks) trial of hospitalized senior citizens. This study concluded that energy intake declined less in a group served a flavor-enhanced meal daily than an age-matched control group (Mathey, 2001). This treatment strategy can also be extended to HIV patients, as long as they exhibit only a decreased or altered taste perception (dysgeusia) and not a generalized loss of taste (ageusia) (Heald, 1997).

Unfortunately, amplifying the natural tastes of food has been, to date, the only way to alleviate malnourishment with considerable success (Heald, 1998).

Several confounding variables in experiments involving HIV-infected subjects and elderly individuals limit the degree to which a causal relationship between
medications and taste disturbance can be inferred. Most experimenters addressing
dysgeusia in these segments of the population require subjects to abstain from taking any
medications other than those of interest throughout the duration of the experiment.
Furthermore, protocol usually requires control subjects to be medication-free for at least
two weeks to one month prior to the start of the experiment. Experimental subjects
typically terminate all medication regimens that are not incorporated in the study for a
similar timeframe before the experiment begins. This eliminates the likelihood that
administration and short-term exposure to these medications will interfere with the
neurological effects of drugs directly manipulated in the experiment. However, residual
effects of many drugs can last months after the last administration. Therefore, it may be
tempting to correlate significant findings with medications under investigation when, in
fact, the potential of other drugs in the subjects’ past to interfere with taste perception still
exists.

Furthermore, some experimenters fail to record medication histories of subjects in
their pre-experimental data. This information is crucial when applying results to the
general population. The long-term physiological and neurological effects of medications
taken in the past should never be overlooked. For example, penicillamine, one of the
most common medications to treat arthritis, induces long-term increased thresholds for
the detection and recognition of all four major tastant qualities in many individuals
(Mattes, 2002). If a disproportionately large percentage of elderly subjects who have
taken this medication for years are recruited to participate in an experiment addressing
the effects of captopril (antihypertensive medication) on taste, confounding is likely to
occur. Adverse health conditions should also be addressed before a causal relationship is
suggested between a specific medication and altered taste perception. Most elderly
people have experienced numerous ailments and sicknesses throughout their lives,
particularly in old age. Several studies have concluded that a severe viral infection of the
upper respiratory tract may result in a general hypogeusia that lasts for many years
(Mattes, 2002). There has also been some correlation observed between severe head
trauma in elderly individuals and an inability to perceive bitter substances in the normal
range of concentrations (Frank, 1992).

Medication history is also significant in studies of HIV-infected subjects. Many
protease inhibitors have similar effects on taste detection thresholds. For example,
indinavir, saquinavir, and nelfinavir have the potential to decrease sensitivity to quinine
HCl (Schiffman, 1999). Experimenters wishing to test the specific effects of any one of
these medications on taste should aim for two primary goals when recruiting subjects.
The first goal is to recruit as many HIV-infected experimental subjects as possible who
have taken only the medication that will be manipulated in the experiment. Previous
long-term exposure to any of these other protease inhibitors or antimicrobial/ anti-
inflammotry medications increases the possibility of a third variable confounding the
results. If this objective is exceedingly difficult to fulfill, the experimenter should
minimize the number of subjects with conflicting medication histories and select them
based on duration of exposure and last time of administration of these medications. The
second goal is to recruit HIV-subjects who are either in early onset stages or display
relatively few adverse symptoms. If time and money permit, medical examinations of all
HIV-infected subjects in questionable health should be performed prior to the experiment
to ensure adequate health and immune system functioning among all participants. This
objective centers on the ability to differentiate between medication interactions and direct physiological effects related to the progression of the disease. Several effects of the HIV-virus itself contribute to diminished and altered taste perception. HIV patients often have sinusitis, which decreases the sense of smell by blocking nasal passages (Heald, 1997). This adverse effect could invariably affect taste because gustation and olfaction neural circuitry are highly interconnected. Furthermore HIV-associated inflammation of the amygdala, hippocampus, and frontal and temporal cortex may also affect taste and smell perception (Heald, 1997).

At the present, the only certain way to avoid medication-induced taste dysgeusia is to abstain from the anti-inflammatory, antimicrobial, cardiovascular (amiloride), and protease inhibitor medications that have been shown to cause taste disturbances. Flavor enhancement largely compensates for dysgeusia-related nutrition loss. However, a better understanding of the neural gustatory and cortical mechanisms involved on a molecular level may promote development of medications that can avoid these adverse symptoms entirely. Continued experimentation involving localized gustatory nerve anesthesia, nerve blocks, and nerve transection in laboratory animals provide promising hope for future findings.
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