Characteristics of Salt and Umami Taste

Molly McGinnis

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Abstract

This review aims to study the taste qualities of umami and salt and to establish a relationship between the two. The rat model is used as a means to assess these taste qualities. Behavioral studies including conditioned taste aversion experiments and discrimination studies provide the basis for what is known about the two tastes, salt and umami. In addition, nerve transections and electrophysiological studies allow for further knowledge into both the nerves associated with these tastes, as well as the CNS areas receiving input from these nerves.

Whereas salt has long been recognized as its own taste category, umami has just recently been deemed a unique tastant. Therefore, much more research is provided for salt tastes than for umami tastes.

Introduction

By sampling chemicals in the environment with the tongue, the sense of taste allows one to gain information about the world. The focus of the taste system lies in the ability to discriminate one stimulus from the other and also to compare the intensity of one stimulus to the next. The tongue is important in the study of the taste system, in which the taste buds serve as the physiological-anatomical unit of sensory reception (Palmer, 2005). A receptor, present within the taste buds, is responsible for interacting with the chemical signals, known as “tastants”. Yamamoto (2008) proposes two classes of taste receptor mechanisms: metabotropic (GTP protein related) receptor mediated pathway and ionotropic receptor mediated pathway. The T1R1/T1R3 heterodimeric receptor is for umami taste, T1R2/T1R3 heterodimeric receptor is for sweet taste, and T2Rs are for bitter taste. Ion channel couple receptors, on the other hand, are thought to
be involved in salt and sour tastes. A common pathway for the two includes an increase in intracellular Ca\(^{2+}\) and then neurotransmitter release (Spector & Travers, 2005; Chaudhari, Landin, & Roper, 2000; Palmer, 20005).

**Taste transduction**

Taste receptor cells located in the taste buds interact with tastants, such as NaCl, hydrochloric acid, sucrose, quinine and MSG. These tastants represent each of the five basic tastes, such as salty, sour, sweet, bitter and umami, respectively. Information from these cells is conveyed through the taste nerve fibers (NaCl-best, HCl-best, sucrose-best, quinine-best or umami-best fibers) to reach the relevant areas in the central nervous system. Branches of the facial nerve (chorda tympani and greater superficial petrosal), and the glossopharyngeal nerve, which synapse with receptor cells in the taste buds, convey taste messages to the first relay nucleus, the rostral part of the nucleus of the solitary tract (NST). The second relay nucleus for the taste inputs is the parabrachial nucleus (PBN) of the pons in the brain stem. The third relay station is the parvocellular part of the ventral posteromedial thalamic nucleus (VPM). This thalamic nucleus projects to the cortical gustatory area in the insular cortex. Taste information is further processed in terms of the emotional aspect in the limbic system of the brain with the participation of brain neuroactive substances. The outcome is finally conveyed to the hypothalamus, the feeding center in the lateral hypothalamic area and the satiety center in the ventromedial nucleus, for the regulation of feeding (Yamomoto, 2008).
There are different techniques for assessing the feeding patterns of rats during testing that allow for a means by which to assess their gustatory system. First of all, 2-bottle preference tests are a very simplistic test used to assess the hedonic properties of a taste substance (Wifall, Faes Taylor-Burds, Mitzelfelt, & Delay, 2007). Two bottles are presented with an equal volume of two different stimuli, and, based on the consumed volume of each bottle after testing, a preference ratio is calculated.

Detection threshold procedures are used for determining the absolute threshold for stimulus concentrations to be used in discrimination studies. A typical detection threshold model is an operant procedure in which one stimulus serves as the $S^+$ and another stimulus serves as the $S^-$. The animal receives reinforcement if it correctly identifies a solution. If the animal correctly identifies the positively reinforced tastant ($S^+$), water is delivered to the spout. If the animal fails to identify the tastant associated with shock ($S^-$), then it receives a shock through the spout on the tongue. Detection thresholds are typically defined as the concentration detected in 50% of the trials (Stapleton, Luellig, Roper, & Delay, 2002).

Conditioned taste aversion studies are helpful in determining if two substances have similar taste qualities because once the aversion is learned for one substance, the subject will also learn to avoid other substances with similar tastes (Taylor-Burds, Westburg, Wifall, & Delay, 2004). If two substances activate the same afferent processes (i.e. taste receptors) they are likely to produce the same tastes, but if they activate different afferent processes, the rat may detect differences between the tastes of the substances (Delay, Sewczak, Stapleton, & Roper, 2004). While CTA experiments can
reveal whether substances taste similar, they are not able to indicate the extent to which perceptual differences exist between two stimuli. Stimuli discrimination experiments are better for determining perceptual differences, because the subject associates a different response and response consequence with each stimulus (Stapleton, Luellig, Roper, & Delay, 2002).

Amiloride, an epithelial sodium channel blocker, is a vital part of the studies conducted on the tastes of salt and umami. This competitive antagonist is able to block the Na\(^+\) channel, while appearing tasteless to rats. It is useful in umami studies because it blocks the Na\(^+\) component of MSG, allowing for the perception of the glutamate ion.

In addition, nerve transection is used to study the input from the different nerves in transferring the taste signal to the brain. The seventh cranial nerve, consisting of the chorda tympani nerve (CT) and the greater superficial nerve (GSP), and the ninth cranial nerve, the glossopharyngeal nerve (GL) are the nerves typically used for studying taste. Likewise, electrophysiological techniques are used to study the impact that a tastant has on a nerve or a CNS area.

**Introduction: Salt**

Amiloride is a competitive antagonist of the epithelial sodium-channel (ENaC) which has been shown to inhibit sodium responses in the 7\(^{th}\) cranial nerve of the rat (Geran & Spector, 2000a; Frank, 1999). The chorda tympani (CT) nerve is a branch of the seventh cranial nerve which innervates the anterior tongue (Blonde, Mircea, & Spector, 2006), and the greater superficial petrosal (GSP) nerve is a branch of the seventh cranial nerve which has been found to innervate taste buds in the soft palate. This ENaC blocker has been shown to inhibit activity in the CT and GSP in response to sodium salts.
Amiloride is useful in taste experiments because it appears to be tasteless to rats while selectively blocking the ENaC channel (Geran & Spector, 2000a and 2000b; Hill, Formaker, & White, 1990). Amiloride, as well as large anion salts, are useful tools in discerning the relative contributions of the transcellular and paracellular pathways, respectively, to taste guided behaviors (Geran & Spector, 2000b).

Two mechanisms for salt taste transduction by gustatory receptor cells have been proposed. One mechanism, known as the transcellular pathway, involves the entry of cations through amiloride-blockable ENaC’s (Geran and Spector, 2000a and 2000b). The paracellular pathway, the less clearly defined mechanism, appears to depend on electroneural diffusion of salt through the tight junctions between receptor cells to access a basolateral transduction mechanism. The two pathways differ in their relative selectivity for sodium. The transcellular pathway is selective for the sodium ion, whereas the paracellular pathway is less selective allowing other cations such as $K^+$ and $NH_4^+$, in addition to $Na^+$ to pass through (Ye, Heck, & DeSimone, 1994).

The paracellular pathway is thought to involve submucosal receptor sites unaffected by amiloride (Ye, Heck & DeSimone, 1994). This pathway is anion-dependent, and is much less cation selective (Geran & Spector, 2000a and 2000b; St. John & Smith, 1999). Taste responses evoked by non-sodium salts, such as KCl or $NH_4Cl$, are predominately insensitive to amiloride treatment, although there is evidence that amiloride reduces the response to KCl (St. John & Smith, 1999; Boughter, St. John, & Smith, 1999). These non-sodium salts, therefore, are thought to stimulate receptors predominately through this paracellular pathway.
Input from the amiloride sensitive and insensitive transduction mechanisms are segregated into fibers on the CT (Hettinger and Frank 1990; St. John & Smith, 1999). Because these two mechanisms are differentially sensitive to sodium and non-sodium salts and because their inputs remain segregated in the CNS, the activation of these two pathways could underlie the ability of rats to discriminate among salts on the basis of taste (St. John & Smith, 1999).

Based on what is known about the two different transduction pathways’ affinities for different salts, much can be learned about the pathways’ underlying processes using discrimination experiments and conditioned taste aversions to indicate both differences and similarities (respectively) to different salts. For example, rats trained on a NaCl versus KCl discrimination task respond to NaCl as if it were KCl when amiloride was added, indicating that NaCl tastes more like KCl to the rat when the transcellular pathway is blocked (Spector, Guagliardo, and St. John 1996). In addition, conditioned taste aversion experiments change the qualitative perceptual characteristics of NaCl, making it taste more like non-sodium salts by adding amiloride (Blonde, Garcea, & Spector, 2006). Results show that the rats treated with amiloride and given NaCl as the conditioned stimulus will generalize the aversion to KCl.

In addition to affecting the taste quality, amiloride also alters sensitivity to sodium. Dissolving NaCl into a 100 uM solution of amiloride significantly raises the detection threshold for this salt, strongly implying that the transcellular transduction pathway is necessary to maintain normal sodium detectability in the rat (Geran & Spector, 2000a as cited in Geran & Spector, 2000b).
Transduction

Research has sought to determine the relative contributions of the two different taste transduction pathways for NaCl taste. Geran and Spector (2000a) used a signal detection task in which rats were trained to press one lever in response to NaCl and another lever in response to water. In this task, brief access to water served as reinforcement, due to the fact that the rats are water deprived prior to testing. NaCl concentrations were systematically lowered to determine detection thresholds. The manipulation included the use of 100 uM amiloride as a solvent for all stimuli. They hypothesized that amiloride should significantly raise the NaCl detection threshold due to their belief that the transcellular pathway plays a more important role than the paracellular pathway for NaCl detection. That is, amiloride essentially blocked the input from the transcellular pathway, allowing for solitary transduction via the paracellular pathway. This allowed them to assess the sensitivity of the paracellular transduction pathway alone. A significant unit increase in threshold with amiloride suggests that the amiloride sensitive sodium transduction pathway is necessary for NaCl detection at low concentrations. Interestingly, the amiloride treatment created a threshold increase similar to that accomplished with CT nerve transection (Spector, Schwartz, & Grill, 1990 as cited in Geran and Spector, 2000a).

Rats could still detect the NaCl at higher concentrations. This may suggest that the amiloride-insensitive pathway is responding to the NaCl, or that residual sodium is undoing the job of amiloride. There is a possibility that the ENaC receptors that are blocked by amiloride are being activated at higher concentrations of NaCl, thereby allowing for the detection of sodium in the transcellular transduction pathway. As
previously mentioned, amiloride is a competitive antagonist acting on the same receptors as NaCl. Once bound with the receptors, amiloride prevents NaCl from binding, and in addition does not activate the NaCl receptor preventing transduction of the salt. However, at higher concentrations of the salt, NaCl molecules actively compete for the receptors and outnumber the amiloride molecules, therefore allowing for transduction.

This experiment shows that the transcellular pathway is necessary for normal NaCl detection in the rat. Results from this study fall short of determining whether the transcellular transduction pathway alone is responsible for the detection of NaCl. That is, it is unknown whether the contribution from the paracellular pathway was responsible as well for the normal detection of NaCl. Findings from this experiment set up the idea for Geran and Spector (2000b) by proposing that in order to rule out the contribution from both pathways, the latter needs to be blocked as well. By singling out one of the transduction pathways with the use of competitive antagonists, it allows for closer observance of the functioning of the other pathway.

Experimenters want to see that, if devoid of the influence from the paracellular transduction pathway, whether or not the transcellular pathway would be sufficient to detect the presence of NaCl. To determine this, the large anion salt sodium gluconate (NaGlu) was used to functionally block the paracellular pathway. Gluconate anions limit the passage of sodium through tight junctions between cells, thus preventing the stimulation of paracellular reception sites (Ye et al., 1994). Normal NaCl detection thresholds were determined via the operant discrimination task, and then again after the addition of amiloride. The same task was used for NaGlu in place of NaCl in the second part of the test. Results show that the NaCl and NaGlu thresholds did not differ. Blocking
the paracellular pathway by replacing Cl\(^-\) with Glu\(^-\) had almost no effect on detection threshold, suggesting that the paracellular pathway is not required for sodium detection under normal conditions. In conclusion, the transcellular pathway is said to be both necessary and sufficient for the transduction of sodium at low to mid-range concentrations. In addition, this suggests an alternate role for the paracellular pathway. As previously mentioned, the paracellular pathway is selective for the entry and discrimination of other salts, such as K\(^+\) and NH\(_4\)\(^+\), in addition to Na\(^+\) (Ye, Heck, & DeSimone, 1994).

**Peripheral Pathway: Neural Coding**

Lundy and Contreras (1999) used extracellular single-cell recording procedures to characterize the chemical sensitivity of the rat geniculate ganglion of the 7\(^{th}\) cranial nerve to varying concentrations of NaCl, KCl, and NH\(_4\)Cl. Using hierarchal cluster analysis as an initial recording of the responses of neurons to different taste stimuli indicated the presence of NaCl-specialist and NaCl-generalist neurons. The NaCl-specialist neurons are most likely the neurons that make up the transcellular pathway, whereas the NaCl-generalist neurons most likely make up the paracellular pathway. The NaCl-specialist neurons were highly responsive to NaCl in a dose-dependent manner yet were relatively unresponsive to equimolar concentrations of KCl and NH\(_4\)Cl. NaCl-generalists, on the other hand, were found to respond equally to the three salts. The latter group of neurons is the most likely path of transduction of NaCl when the ENaC channel is blocked with amiloride.

Lundy, Pittman, and Contreras (1997) conducted electrophysiological studies in the CT nerve and found that the Na\(^+\)/H\(^+\) exchanger antagonist, 5-(N,N-dimethyl)-
amiloride (DMA), suppressed NH$_4$Cl responses. This indicates that these Na$^+$/H$^+$
exchangers may be involved in NH$_4$Cl taste transduction in rats.

Peripheral Pathway: Nerve transection

The two non-sodium salts, ammonium chloride (NH$_4$Cl) and potassium chloride (KCl), share a common taste quality as well as an amiloride-insensitive route of transduction. A very limited amount of research supports the effects of amiloride on non-sodium salts. Geran, Garcea, and Spector (2002) want to determine if rats can discriminate between these two salts, and if so, whether it is due to amiloride or gustatory nerve transection.

Results show that 100 uM amiloride impaired the ability of rats to detect between NaCl and NH$_4$Cl, but not KCl and NH$_4$Cl, as was hypothesized. However, both groups showed significant impairments after transection of the CT and GSP branches of the facial nerve. These results suggest that rats can discriminate between NH$_4$Cl and KCl, and that this discrimination does not rely on an amiloride-sensitive mechanism but does rely on CT and GSP nerves.

In addition, these findings support the hypothesis that the facial nerve is important for salt taste recognition and discrimination. It has been found that transection of the Glossopharyngeal (GL) nerve (which innervates taste buds in the posterior tongue) does not affect any of the discriminations thus far (St. John et al. 1998). The GL is not sensitive to amiloride, suggesting that sodium transduction here occurs via the paracellular pathway (Formaker Hill, 1991). This is consistent with findings from (Brand, Teeter, & Silver, 1985; DeSimone & Ferrell, 1985; Heck, Mierson, & DeSimone, 1984; Ninomiya & Funakoshi, 1988; Schiffman, Lockhead, & Maes, 1983; Sollars & Hill, 1998).
as cited in Geran and Spector, 2002b) in which amiloride has been shown to inhibit activity in the CT and GSP nerves in response to sodium salts, suggesting that sodium transduction in these nerves occurs primarily by way of the transcellular pathway.

In Geran et al. (2002), combined transection of GSP and CT was shown to drop NaCl versus NH₄Cl and KCl versus NH₄Cl discrimination task performance to chance levels. Blonde, Garcea, and Spector (2006), however, aimed to determine the effect of GL transection, or combined CT and GSP on NaCl detection thresholds. Their hypothesis is that combined transection of the CT and GSP would shift the NaCl detection threshold more than that reported for transection of the CT alone, and that transecting the GL nerve would not affect sensitivity. That is, they hypothesized that input from the seventh cranial nerve, not the ninth, is crucial for detection and discrimination of salts.

To test their hypothesis, surgery was performed to transect the following nerves: (7x) = CT and GSP; (9x) = GL; and the remaining rats were given sham surgery. Before surgery, rats were given a task in which they were to discriminate between water and 0.2 M NaCl to determine the detection threshold for NaCl. After nerves were transected, rats were again tested to establish the impact of the surgery on their sodium detection threshold.

After surgery, histology reports verified that 7x rats had very few, if any, taste buds in the anterior tongue and palate ducts whereas 9x and sham surgery rats had many. These results showed that the nerves were successfully cut and that no significant regeneration occurred. Testing the rats after surgery and comparing results to pre-surgery rats, performance rates show that the 9x transection had little effect on the ability of rats
to detect NaCl. However, 7x transection detection threshold levels were raised from ~1.7 mM to about 500 mM NaCl, a very significant increase in threshold.

9x rats detected NaCl as well as sham rats. This is consistent with results from a previous study which show that GL transection has no effect on suprathreshold intensity discrimination between NaCl concentrations (Colbert, Garcea, and Spector, 2004). In contrast, there was a marked decrease in the sensitivity of 7x rats. Transection of the CT nerve alone increases NaCl detection threshold by 1-2 orders magnitude (Kopka and Spector, 2001). The observed 2.5log10 unit increase in threshold after 7x surgery indicated that combined transection of CT and GSP compromised sensitivity more than CT transection alone. Their results show that input of the GSP did contribute to the ability of the rat to detect NaCl; however, the extent to which GSP contributes to NaCl detection remains to be tested. The current surgical approach for transecting the GSP nerve alone requires potential damage to the CT nerve, making it difficult to determine whether the surgical effects are due to GSP transection, or damage to the CT nerve.

In conclusion, the seventh but not the ninth cranial nerve is necessary for normal NaCl detection threshold in the rat despite the fact that the latter nerve innervates twice as many taste buds. A complete understanding of the role of input from the GL nerve in taste function awaits further testing.

**CNS: NST recordings**

It is hypothesized that behavioral studies which show that amiloride impairs a rat’s ability to discriminate NaCl from KCl may do so by making both salts taste more like KCl. St. John and Smith (1999) conducted electrophysiological studies to determine the underlying cause of the inability of rats to discriminate NaCl from KCl when
amiloride is added to the solutions. They recorded responses to NaCl and KCl in the nucleus of the solitary tract (NST) to determine the central neural representation of the taste of these salts after blocking the amiloride sensitive or insensitive pathway.

Without the addition of amiloride, St. John and Smith found that NaCl and KCl were represented by distinct patterns of activity in the NST. Amiloride, in a concentration dependent manner, however, changed the pattern for NaCl to one more characteristic of KCl, primarily by reducing activity in neurons responding best to NaCl. In addition, St. John and Smith modeled the neural response patterns that would occur if they had the appropriate agent to block the amiloride-insensitive pathway.

The present study suggests that activity in both the amiloride sensitive and insensitive pathways contributes to the behavioral discrimination between NaCl and KCl and that the amiloride-sensitive activity alone is not sufficient to impart a unique signal for the taste of sodium salts. This is contrary to behavioral data from Geran and Spector (2000b) which shows that the transcellular pathway is sufficient for NaCl detection.

Smith, Liu, and Vogt (1996) recorded responses in the NST to NaCl, Na-gluconate, and KCl. For the two sodium salts, the ENaC channel (represented in the NST) was found to respond greater than for the potassium salt. NaCl had the greatest response in the NST, indicating the largest response of the ENaC channel. Amiloride adaptation showed very little response in the NST, indicating that it is tasteless and inhibits the Na\(^+\) response of the ENaC channel. As the size of the anion increased, the effect of amiloride became greater. For example, gluconate, a larger anion than Cl\(^-\), showed greater suppression of the ENaC channel in the NST.
Boughter, St, John, and Smith (1999) found that the N-best neurons (NaCl-specialists) respond best to NaCl, but also show a small response to KCl. Amiloride was shown to completely and reversibly block the response to NaCl in these cells in the NST. Amiloride was shown to have an effect on these cells responding to KCl. Boughter et al. (1999) likewise demonstrated the H-best neurons’ (NaCl generalists) response to NaCl and KCl and the effect of amiloride. Cells were found to respond equally to NaCl and KCl. In addition, responses to these two stimuli were not blocked by amiloride. As previously mentioned, these H-best cells (i.e. NaCl generalists) most likely contribute to the cells in the paracellular pathway.

**Introduction: Umami**

Monosodium glutamate (MSG) is a naturally occurring amino acid used in Asian foods to enhance flavor (Maga, 1983 as cited in Stapleton, Roper, and Delay, 2002). It is also a natural component in many foods rich in protein (including meat, cheese, and vegetables). Therefore, it is important for animals to be able to distinguish this flavor because it marks the presence of dietary protein. Glutamate is said to possess a taste distinct from sweet, sour, salty and bitter. Researchers call this unique taste “umami” (Yamaguchi as cited in Stapleton, Roper, and Delay, 2002). MSG is the prototypical umami substance (Delay, Sewczak, Stapleton, and Roper, 2004). Umami is also a taste quality of the two 5’-ribonucleotide monophosphates, IMP (disodium 5’inosinate) and GMP (guanosine monophosphate) as well as some other L-amino acids (Wifall, Faes, Taylor-Burds, Mitzelfelt, Delay, 2007; Yamomoto et al. 1991). Experiments aimed at determining certain qualities of the umami taste often use these pharmaceutical glutamate agonists to gain information about transduction processes.
Amiloride

In addition to amiloride’s use in experiments performed on salt taste, it is a vital tool in umami studies as well. Amiloride is able to block sodium channels, and by doing so is able to reduce the intensity of the Na⁺ component of MSG (Stapleton et al., 2002). The taste elicited by the glutamate ion is more salient in the presence of amiloride and therefore plays a more important role in the discrimination experiments (Delay et al., 2004). In addition, amiloride is undetectable to rats <100 uM and can therefore be used as a solvent in many taste discrimination behavioral tests (Stapleton et al., 2002). Amiloride raises the detection threshold for Na⁺ from 5 to 45 mM in rats (Geran and Spector, 2000 as cited in Delay et al., 2004). However, it is found that it does not significantly alter the detection threshold of many of the umami substances used in behavioral experiments (Stapleton, Luellig, Roper, and Delay, 2002).

In addition to amiloride, experimenters facilitate the use of another research tool, Gymnema sylvestre (GS), a sucrose antagonist. Yamamoto et al. (1991) demonstrate that MSG and sucrose are found to have similar taste qualities. This is due to the fact that on top of eliciting a salty taste component, MSG elicits a sweet taste component. Therefore, the GS antagonist is typically used in electrophysiological studies to block the sweet response in MSG, allowing for a nerve recording devoid of the sweet component of this substance.

Receptors

To date, two major families of G-protein coupled receptors have been identified as taste receptors. Members of the T1R family bind with sugars and amino acids whereas members of the T2R family bind with compounds that are perceived as bitter. In addition,
a splice variant of the mGluR4 receptor has been identified in TBC’s, and it has been suggested to bind with L-glutamate and the mGluR4 agonist L-AP4. The T1R family of taste receptors consists of three members: T1R1, T1R2, and T1R3 (Spector and Travers, 2005). These proteins combine to form heterodimers that serve as the functional receptors in the TBC’s.

The T1R1/T1R3 receptor appears to be more generally tuned and is activated by all the common L-amino acids (X.D. Li et al., 2002, as cited in Spector and Travers, 2005). This activation is enhanced by the presence of 5′-purine nucleotides such as IMP.

Electrophysiological and behavioral experiments show that knockout mice lacking T1R1 or T1R3 became unresponsive to prototypical L-amino acid stimuli. These results suggest that the presence of both T1R1 and T1R3 is necessary for normal responsiveness to L-amino acids to be maintained (Zhao et al. 2003 as cited in Spector and Travers, 2005).

A splice variant of the mGluR4 receptor which is likewise found in the brain has been identified in rat TBC’s. Using reverse transcriptase (RT)-PCR, Chaudhari et al. (1996) have identified a G-protein-coupled metabotropic receptor, mGluR4. Findings from this research show that mGluR4 is associated with taste buds within the lingual epithelium of rats. mRNA for this G-protein coupled receptor is not found in the surrounding “non-taste” epithelium. Behavioral findings from this experiment show that pharmacological activation of the mGluR4 receptor mimics the taste perception of MSG. Based on these findings, they conclude that mGluR4 may be a chemosensory receptor in taste buds that is involved in transducing the taste of MSG. Researchers proposed that the taste-mGluR4 was the primary receptor binding with L-glutamate, giving rise to the taste
sensation of umami. CTA’s of MSG with the addition of amiloride generalized to L-AP4 but not to N-methyl-D-aspartate (NMDA). However, because L-AP4 in addition appears to activate the T1R1/T1R3 receptor, at least in the presence of IMP (Nelson et al. 2002 as cited in Spector and Travers, 2005), conclusions cannot be made about mGluR4’s contribution to glutamate taste.

At this point, it cannot be concluded whether the T1R1/T1R3 receptors or the mGluR4 receptors are sufficient alone for the transduction of umami tastes. Therefore, to date it is suggested that both receptor types are necessary for the detection of the different umami tastants (Spector and Travers, 2005).

Transduction

To test the hypothesis that mGluR4 is a chemosensory receptor for MSG, Chaundhari et al. (1996) conducted a CTA experiment. They hypothesize that if mGluR4 is a primary taste receptor, then its activation by either glutamate or an appropriate agonist should elicit similar taste perceptions. MSG, AMPA, KA, NMDA, and L-AP4, known agonists for the subsets of iGluR4’s and mGluR’s, were used to determine a conditioned taste aversion. In addition, amiloride was used in all solutions to eliminate the Na\(^+\) component of MSG.

Chaundhari et al. (1996) found no aversions to AMPA or NMDA, implying that they do not activate the same taste receptor for glutamate and only a small aversion to KA at high concentrations. However, researchers found a strong aversion to L-AP4, a known agonist for mGluR4. Their data suggest that activation of mGluR4 by L-AP4 mimics the natural activation of a taste receptor by MSG.
Previous work suggests that NMDA or an NMDA-like ionotropic glutamate receptor may be responsible for detecting glutamate taste (Brand et al 1991 as cited in Delay et al., 2004). Delay et al. (2004) conducted discrimination studies to determine if the glutamate agonists, NMDA, ASP (aspartic acid, an amino acid), and L-AP4 (a ligand for mGluR4) share similar perceptual taste qualities as MSG. By determining similarities between these tastes, a similarity between afferent mechanisms can likewise be determined.

Results show that there were found to be marked differences between the tastes of NMDA and MSG but there are similarities between the tastes of ASP and MSG and L-AP4 and MSG. Rats readily discriminated between NMDA and MSG with or without amiloride. This indicates salient features not shared by the two and likewise a difference in receptors. NMDA may not by itself impart umami taste, but when paired with others it may.

In addition, these results are consistent with Chaudhari et al. (1996) in that MSG was found to share similar afferent mechanisms with L-AP4, including detection by the mGluR4 receptor. Results from Delay et al. (2004) indicate that ASP may likewise share this mGluR4 receptor.

In humans, L-alanine is another non-essential amino acid found in many of the same foods as MSG that elicits a sweet sensation. Taylor-Burds, Westburg, Witfall, and Delay (2004) demonstrated that MSG and L-alanine have similar taste qualities based on evidence from CTA and discrimination behavioral studies.

The T1R family of receptors form heterodimers that appear to be selective for certain taste stimuli, including sweet sensations. The T1R1/T1R3 receptor has been found
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to be selective for L-amino acids, including L-glutamate and L-alanine. Taylor-Burds et al. (2004) hypothesize that if L-alanine and MSG share taste characteristics (as indicated by CTA and discrimination experiments) then they are said to activate the same receptors. In addition, this experiment was carried out with the addition of amiloride to all solutions to control for the Na⁺ component of MSG, allowing for more comparable taste qualities of the two amino acids.

Based on the strong generalization of CTA between MSG and L-alanine and the difficulty in discriminating between the amino acids when the Na⁺ component of MSG was controlled for show that these two amino acids activate a common receptor. These results point to the T1R1/T1R3 heterodimer versus the mGluR4 receptor as the taste receptor site since T1R1/T1R3 is selective for L-amino acids.

Ionosine monophosphate (IMP) and guanosine monophosphate (GMP) elicit an umami taste in humans and synergistically increase the intensity of the umami taste of MSG. CTA’s in rats show that the nucleotides and MSG elicit similar tastes, but recent physiological evidence suggests that these nucleotides and MSG may not activate the same population of taste receptors and therefore may not elicit identical taste qualities (Wifall et al. 2007).

Wifall et al. (2007) found that the thresholds for IMP and GMP did not significantly differ. In addition, amiloride did not change the thresholds for either. In addition, with the 2-bottle preference test, the addition of amiloride did not appear to alter preferences for either nucleotide, suggesting that these preferences were most likely related to the non-sodium component elicited by these nucleotides.

Based on CTA’s and discrimination studies conducted by Wifall et al. (2007), IMP
and GMP were found to be very similar to one another. MSG and the nucleotides were found to have similar taste qualities, however, rats could discriminate between them. This shows that these nucleotides do not elicit taste sensations identical to MSG.

Wifall et al. (2007) conclude that because IMP and GMP elicit perceptually identical taste qualities, they most likely activate the same population of taste receptors. This is not the same with MSG in that rats could discriminate between this tastant and the nucleotides. Wifall et al. (2007) propose that MSG and the nucleotides may activate a common set of taste receptors; however, it is also likely that they activate other sets of receptors as well. Therefore, it is concluded that although these nucleotides elicit an umami sensation, they are not identical to the taste of MSG.

**Peripheral Pathway**

Yamamoto et al. (1991) found that MSG and IMP individually may be different from the mixtures of these two components in terms of transduction mechanisms. For example, electrophysiological responses on the CT nerve show that with Gymnema sylvestre extract, responses to a mixture of the two were strongly suppressed. However, when the components were tested individually, the extract only weakly suppressed them. In addition, a CTA study was carried out in which umami substances were dissolved in amiloride and compared with four basic stimuli. Findings suggest that MSG elicits a sweet sensation because those with a learned aversion to MSG generalized the aversion to sucrose. In addition, Yamamoto et al. (1996) found that MSG could not be discriminated from NaCl when the chemicals were dissolved in water. However, as to be expected, they could be discriminated when dissolved in amiloride solution, in which the
Na\(^+\) component was controlled for. Results from this study which find similarities between MSG and both sucrose and NaCl indicate a common pathway for transduction.

Stapleton et al. (2002) suggest that in addition to activating glutamate receptors, MSG may also interact with afferent mechanisms signaling sucrose taste based on information gained from CTA experiments. In addition to amiloride, equimolar concentrations of Na\(^+\) were added to all solutions to control for the Na\(^+\) component in MSG by adding it to sucrose as well.

In the absence of amiloride, rats could distinguish between MSG and sucrose down to 10 mM solutions. However, they could correctly identify solutions only above 50 mM in the presence of amiloride, equimolar NaCl, or both. These results suggest that gustatory stimulation by MSG and sucrose interact somewhere in taste transduction, either at the receptors or with afferent mechanisms. The addition of NaCl to sucrose impaired the ability of rats to distinguish this mixture from MSG. The separate results from these experiments imply that the ability of rats to discriminate MSG from sucrose in solutions above 10 mM is facilitated by the presence of sodium ions in MSG.

Researchers point out that salient characteristics are used to tell stimuli apart. Amiloride is used to block the salient characteristics. Yet, as researchers point out, it is interesting that amiloride did not raise the detection threshold for MSG based on the fact that there is a Na\(^+\) component. Stapleton et al. (2002) suggest that this indicates that the sodium taste is not necessary for the detection of this compound. It did not raise the threshold for sucrose either, however, this was expected. They suggest that rats may be detecting the anion, glutamate, at threshold concentrations. However, sodium ions appear
to contribute to the perception or taste quality of MSG. This research likewise raises the question of whether the glutamate anion and sucrose activate similar receptors.

**Nerve Transection**

The chorda tympani (CT), glossopharyngeal (GL), and greater superficial petrosal (GSP) nerves are the three major nerves that innervate the tongue. The CT nerve detects sodium salts and sugars, the GL nerve detects quinine and acids, and the GSP nerve detects sugars but also salts moderately (Ogawa, 1972 as cited in Sako, Harada, and Yamomoto, 2000). Sako et al. (2000) were interested in determining which nerve was responsible for transmitting umami taste in rats. Based on an electrophysiological study conducted by Sako et al. (2000), the CT and GSP were found to be more responsive to MSG and IMP than was the GL nerve. In addition, a behavioral CTA experiment in which all three nerves were transected showed that rats with combined transection of the CT and GSP nerve did not acquire a taste aversion to umami tastants. This information taken together shows that umami transduction occurs mostly by way of the CT and GSP nerve.

Results from Yamomoto et al. (1991) indicate that the umami substances may bind sweet receptors. Based on this finding, one would expect their responses in the GSP to be larger than those in the CT because the GSP responds to sugars more robustly than the CT does (Sako et al., 2000). However, this was not shown to be the case in the current experiment. CTA results from Sato et al. (2000) do, however, show that rats with intact nerves cannot discriminate between umami substances and sweet-tasting substances (such as sucrose and l-alanine).
Although mGluR4 was found in the circumvallate papillae innervated by the GL (Chudhari, Yang, Lamp, Delay, Cartford, Than, and Roper, 1996 as cited in Sako et al., 2000), it does not indicate the importance of the GL for mediating umami taste among the three nerves. A recent pharmacological study (Sako and Yamamoto, 1999 as cited in Sako et al., 2000) showed a possibility that umami substances bind not only to mGluR4 but also to the sweeter-binding macromolecule, and this could also explain the larger responses to umami substances in the CT and GSP than in the GL.

**Discussion**

The rat is able to provide a good model for the study of tastes. Manipulations can be made on the taste system, whether it be the addition of amiloride or the transection of a nerve, allowing for the assessment of a taste. In addition, electrophysiological studies conducted on the rat allow one to gain information into the neural representation of the taste stimuli: salt and umami.

Based on both behavioral and electrophysiological data conducted on salt taste, it can be concluded that there are different transduction pathways needed for the detection of salts. That is, the transcellular pathway and paracellular pathway of transduction together are responsible for the detection of salts such as NaCl (under normal conditions), KCl, and NH₄Cl, and NaGlu. These pathways are represented in the CT and NST as the N-best or H-best pathways, respectively. Whereas the transcellular pathway is more responsive to the Na⁺ ion, the paracellular pathway is responsive to K⁺ and NH₄⁺, in addition to Na⁺ (Ye, Heck, & DeSimone, 1994).

A certain connection can be made between the electrophysiological data and the behavioral data collected on salt taste, including St. John and Smith’s (1999)
electrophysiological data and Geran and Spector’s (2002b) behavioral data. Geran and Spector (2002b) conclude that the transcellular pathway is sufficient for NaCl detection; whereas St. John and Smith (1999) conclude that the behavioral discrimination between NaCl and KCl in the amiloride-sensitive pathway alone is not sufficient to impart a unique signal for the taste of sodium salts. Based on these results, one can conclude that the transcellular pathway alone is sufficient for the detection of NaCl under normal conditions; however, when another salt is present (i.e. KCl), input from the paracellular pathway is needed in order to discriminate between the two salts.

Whereas most salt taste research focuses on input from either the transcellular or paracellular transduction pathway, umami research aims at providing more information about the receptors and taste nerves involved.

Although not much is known yet about umami, a relatively new tastant, current research provides information about the receptors and nerves involved. Whether or not the mGluR4 receptor is sufficient for the detection of umami tastants is up for speculation. However, as it stands both the mGluR4 and T1R1/T1R3 receptors are required for the detection of the different umami tastants (Spector and Travers, 2005). Electrophysiological studies have been conducted on the nerves involved with the taste of umami, including the CT, the GSP, and the GL (Geran et al., 2002). However, to date there are no articles present which discuss the activation of the NST in regards to umami taste.
References


