

# *Role of taste receptors in salty taste perception of minerals and amino acids and developments in salt reduction strategies: a review*

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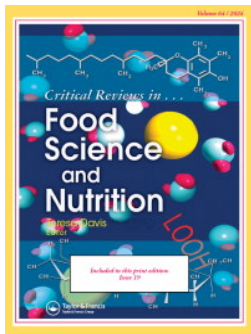
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## Role of taste receptors in salty taste perception of minerals and amino acids and developments in salt reduction strategies: A review

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### ABSTRACT

Salt (sodium chloride) plays a key role in maintaining the textural, microbiological, and sensorial aspects of the foods. However high dietary salt intake in the population has led to a series of health problems. Currently manufacturers are under pressure to reduce the sodium levels in foods without compromising the consumer experience. Because of the clean salty taste produced by sodium chloride, it has been challenging for the food industry to develop a suitable salt substitute. Studies have shown that different components within a food matrix can influence the perception of saltiness. This review aims to comprehend the potential synergistic effect of compounds such as minerals and amino acids on the perception of saltiness and covers the mechanism of perception where relevant to taste resulting from sodium ions and other metallic ions (such as K, Mg, Ca), as well as various amino acids and their derivatives. Finally, the review summarizes various salt reduction strategies explored by researchers, government organizations and food industry, including the potential use of plant-based extracts.

### KEYWORDS

Salt reduction; amino acids; minerals; saltiness perception; salt substitutes; sodium reduction

### Introduction

According to the Health Survey for England (2017), about 26.2% of England's population, aged 16 years or older, had hypertension in 2017 (Public Health England 2020a). Even though the treatment and diagnosis of high blood pressure has improved in some high-income countries, the overall global burden of hypertension is still high, especially in low- and middle-income countries (Zhou et al. 2021). In 1995, a report published by the Committee on Medical Aspects of Food and Nutrition Policy (COMA), highlighted the relationship between salt intake and increased blood pressure, and consequently the increased risk of cardiovascular disease (Hunty 1995). Rucker, Rudemiller, and Crowley (2018) highlighted that sodium accumulates in the bloodstream altering the blood cells (T cells and monocytes), thereby elevating blood pressure. Hence, there is global guidance on limiting salt intake; WHO suggests consumption is restricted to less than 5 g of salt (or 2 g of sodium) per day for an average adult. However, on average, adults consume about twice the amount of recommended salt, i.e., 9–12 g salt/day (World Health Organisation 2020). In the UK, approximately 67% of adults in England, and 70% in Scotland, consume more than 5 g salt/day (Purdy 2019). Therefore, Public Health England re-set salt reduction targets in 2020 for different food product categories such as meat products (e.g., bacon; maximum 2.59 g salt/100 g bacon), breads (maximum 1.01 g/100 g) and standard potato crisps (maximum 1.38 g/100 g) to help consumers monitor their sodium intake.

While achieving these salt levels on the labels or products is voluntary, a monitoring report is expected to take place in 2024 and 2025 (Public Health England 2020b).

Archaeological evidence suggests that the first human harvesting of salt happened in around 6000 BC at Lake Yuncheng in China and the first usage of salt in food was to preserve fish which is evidenced to around 2000 BC (Kurlansky 2002). Up to now, numerous studies have confirmed the essential role of sodium ( $\text{Na}^+$ ) in maintaining various functions of the body such as acid-base balance, functioning of cells, transmission of nerve impulses and maintenance of plasma volume (World Health Organisation 2020). Besides the importance of  $\text{Na}^+$  in human health, nutrition, and physiology, it has been a key ingredient in food manufacturing. Firstly, salt has been used as a preservative to extend the shelf life of food products since early times. Second, the salty taste is desirable in many products and can enhance other flavors in the food, and finally salt aids in the processing and handling of some products (Hutton 2002). However, due to the increased health concerns associated with high  $\text{Na}^+$  intake as mentioned above, policy makers have set up recommendations and guidelines for the food industry to reduce the levels of salt in food products. However, the role of salt is extremely diverse, and it can perform various functions in different food matrices. Its functions are inter-linked, which can make it challenging to reduce the amount of sodium chloride ( $\text{NaCl}$ ) in food products. Therefore, there remains

the need for on-going research on alternative salt reduction strategies as no single solutions are currently able to sufficiently reduce NaCl in all food systems. Substitutes often bring sensory defects in the final product, such as noticeable loss of salty taste, and or increased bitter or metallic taste (Vidal et al. 2020). NaCl also plays a key role in food processing, and reduction of salt can affect the textural and microbiological aspects of the product as well as their taste and flavor, which is often unacceptable to consumers.

This review aims to comprehend the role of different components known to contribute or enhance salty taste, such as alternative minerals and amino acids, and discuss the mechanisms by which they influence the perception of saltiness. It also considers specific molecules as well as alternative ingredients (such as plant-based substitutes) that may be present in a complex matrix. Hence, the review includes discussion of alternatives that may directly influence receptors (especially sodium channels) or may operate *via* a cross-modal effect (such as umami-salt taste interaction or odor-induced salt perception). This will expand our knowledge on the synergistic effect of these components and may pave the way for finding new substitutes to replace NaCl for the food industry.

## Mechanism for saltiness perception by minerals

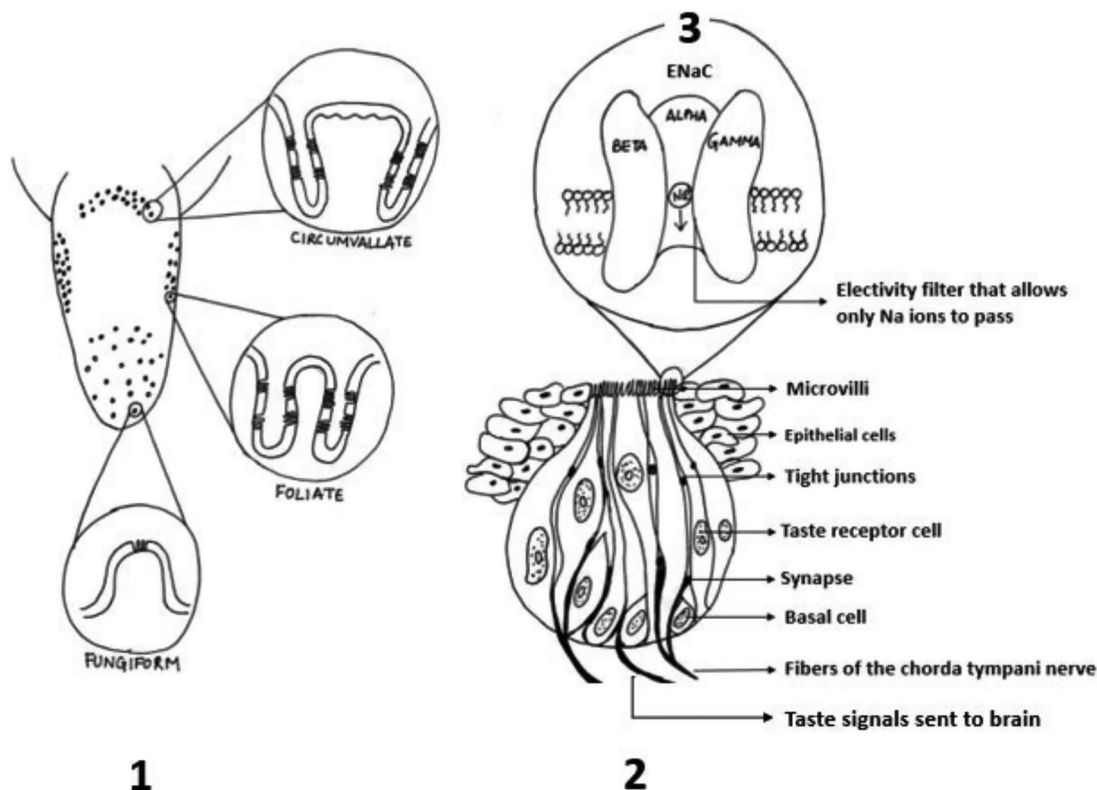
### Taste transduction of sodium ion

Saltiness is a distinctive sensory quality linked to  $\text{Na}^+$  containing compounds and this quality is unique to only sodium

and lithium. Other cations like potassium and calcium also exhibit salty taste, but it is not the dominant taste quality for these cations (Man 2007; van der Klaauw and Smith 1995). Salty taste transduction is a complex mechanism and is still under investigation. However, the two most widely studied pathways known to be involved in the perception of salty taste are amiloride sensitive (particularly the epithelial sodium channel, ENaC) and amiloride insensitive pathways.

### The ENaC channel (an amiloride sensitive pathway)

The ENaC channel is a voltage-gated sodium ion ( $\text{Na}^+$ ) channel. When sodium chloride (NaCl) enters the taste bud, the  $\text{Na}^+$  interact with these ENaC receptors. This leads to depolarization, an increase in membrane potential inside the receptor cells which causes calcium ions to enter the taste receptor cells through specific voltage ion channels sensitive to calcium. This regulates the release of neurotransmitters and stimulates the sensory neurons, so that the signal travels to the cranial nerves and finally reaches the thalamus region of the brain. The thalamus sends these signals to the gustatory cortex which allows us to differentiate between the tastes, including salty taste (Figure 1) (Mattes 1997; Behrens and Meyerhof 2015; McCaughey and Scott 1998; McCaughey 2019). Besides  $\text{Na}^+$ , other monovalent cations like lithium ( $\text{Li}^+$ ) and cesium ( $\text{Cs}^+$ ), can permeate through the ENaC channels, however their permeability is less than  $\text{Na}^+$ , and these monovalent cations are usually not seen safe for human consumption (Bigiani 2016).



**Figure 1.** Depiction of tongue and taste buds in rats: (1) taste receptor cells within the papillae on the tongue and cross section of three types of papillae- circumvallate, foliate, fungiform. (2) Cross section of a taste bud with its components. (3) Cross section of ENaC channel present on the taste bud. Rats have 3 ENaC subunits, while in humans there is an additional ENaC- $\delta$  subunit present (adapted from McCaughey 2019; McCaughey and Scott 1998).

The ENaC is known to comprise of  $\alpha$ -,  $\beta$ - and  $\gamma$ - and  $\delta$  subunits. In humans it has been proposed that the ENaC- $\delta$  plays an important role in salty taste transduction (Coscoy et al. 1998). A recent review evaluating the role of ENaC in saltiness perception emphasized that the location of the subunits in the human taste system is also extremely important (Bigiani 2020). When the ENaC- $\delta$  is present at the apical membrane, then the transduction pathway is likely to be *via* the ENaC ion channels. Besides the location of the subunit, studies have reflected on the concentration of the subunits in the human taste system. Upon analysis it has been observed that among all the four subunits ( $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -), the concentration of  $\delta$ -ENaC in the taste system is extremely low (Stähler et al. 2008). There is still the uncertainty whether all four subunits, or a combination of the subunits, are synergistically playing a role in the  $\text{Na}^+$  transduction pathway.

However, the  $\text{Na}^+$  transduction can be hindered in the presence of a drug “amiloride,” which is a diuretic compound known to interfere with  $\text{Na}^+$  transduction, leading to lower perception of salty taste in mice and in humans. Schiffman, Lockhead, and Maes (1983), examined the psychophysical and neurophysiological effects of amiloride on humans and observed significant reduction of salty taste in both studies. Interestingly the suppression of salty taste was only noticed on  $\text{Na}^+$  as well as lithium salts and not on potassium or calcium salts. With increasing interest in taste transduction and the role of amiloride, several studies confirmed the suppression of salty taste in the presence of amiloride. It has been observed that amiloride is attracted toward the  $\text{Na}^+$  channels due to several factors, such as the transmembrane voltage, extracellular pH,  $\text{Na}^+$  concentration and charge of the amiloride compound (only the cationic form of amiloride can bind to the ion channels). Therefore, it has been concluded that amiloride is capable of blocking the ion channels through attraction; thereby reducing the affinity of  $\text{Na}^+$  to the channels and eventually leading to a reduced saltiness perception (Smith and Ossebaard 1995; Avenet and Lindemann 1988; Kellenberger and Schild 2002; Chandrashekar et al. 2010; Garty and Palmer 1997).

Conversely, Halpern and Darlington (1998) did not observe suppression of salty taste in the presence of amiloride at or below a certain concentration (i.e., 100  $\mu\text{M}$  NaCl). This was further investigated by other researchers and led to an understanding of the role of different ENaC subunits. Thereby researchers proposed that it could be the ENaC- $\delta$  that affects the sensitivity of receptor to amiloride, however, to what extent ENaC- $\delta$  modulates the perception of saltiness is unclear (Ji et al. 2006; Stähler et al. 2008).

#### Amiloride insensitive pathway

Amiloride related research has provided evidence that receptors other than ENaC can be involved in salt taste transduction. In 2004, Lyall and coworkers reported the involvement of an “amiloride-insensitive”  $\text{Na}^+$  taste receptor. One predominant receptor cell involved is called the vanilloid receptor-1 (TRPV-1), which is an ion channel (further detailed in TRPV-1 section). There are other amiloride

insensitive receptors involved in the taste perception, which is further discussed in the following sections. These amiloride-insensitive receptors are nonspecific to  $\text{Na}^+$  and have been shown to detect response from several mineral salts such as potassium, calcium, ammonium, and sodium salts (Lyall et al. 2004). However, more recent research has contradicted this and highlighted the importance of the anion. In mouse taste cells, Roebber, Roper, and Chaudhari (2019) concluded that the amiloride-insensitive salt taste response can be generated by chloride and not sodium or any other cation.

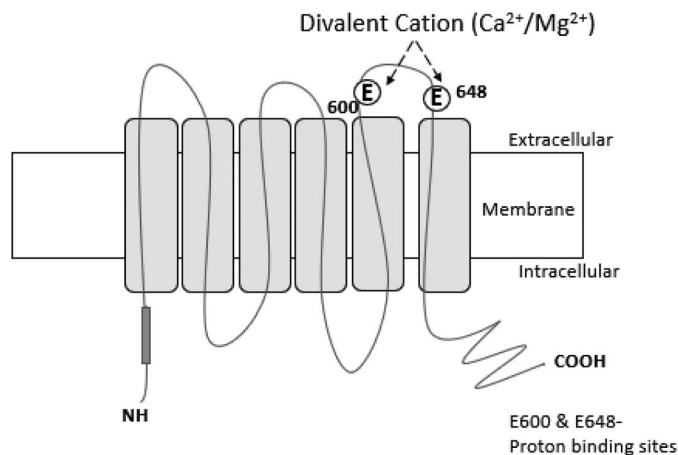
Overall, to summarize the salty taste transduction mechanism, in humans, there is more than one mechanism for the perception of salty taste from NaCl, it can occur *via* the amiloride sensitive pathway, particularly the ENaC channels, or *via* other channels (like TRPV-1) which are not specific to  $\text{Na}^+$  and are insensitive to amiloride. Indeed, both above mechanisms could be activated during detection of NaCl. Moreover, the complexity of human salty taste system is not limited to the mechanism of NaCl perception. It is hypothesized that other factors such as protein derived compounds (amino acids, peptides) and minerals (other than  $\text{Na}^+$ ) might also contribute to salty taste perception, which will be discussed in the sections below.

#### Taste perception of minerals other than sodium

Mineral salts of copper, zinc, iron, calcium and magnesium are some of the most common mineral salts known to contribute to taste quality (Riera et al. 2007; Ahern et al. 2005; Lim and Lawless 2005). It is widely accepted that they are transduced by amiloride insensitive, or nonselective cation channels known as the “transient receptor potential” (TRP) family consisting of receptors including Transient receptor potential melastatin-5 (TRPM5), as well as the transient receptor potential vanilloid-1 (TRPV-1) discussed below. Initially, these receptors were only known to be activated by potentially harmful stimuli like capsaicin, noxious heat and protons (Ishida et al. 2002). However, later studies revealed minerals such as calcium, magnesium, potassium, and sodium (or their salts) could provoke additional activation of sweet, bitter and umami receptors, thereby contributing to the transduction of other taste qualities, though the mechanism for the activation of the specific receptor cells (i.e., TRPV-1 and TRPM5) might vary (Ahern et al. 2005; Lyall et al. 2004; Riera et al. 2009).

#### TRPV-1

The TRPV-1 (Figure 2) are abundantly located around the fungiform papillae (Figure 1) (Ishida et al. 2002). In addition to the evidence of anion response discussed above, TRPV-1 consists of two proton binding sites (E600 and E648), and an influx of divalent cations (e.g.,  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ ) into the taste bud increases the extracellular membrane potential activating these two sites (Ahern et al. 2005). The interaction of the cations with E600 and E648 has been stated to be essential to fully activate the TRPV-1 receptor cells (Figure 2), eventually stimulating the sensory neurons



**Figure 2.** Transient receptor potential vanilloid-1 (TRPV1) [adapted from: Ahern et al. (2005), and Aroke et al. (2020)].

(Ahern et al. 2005). Once activated, the C terminal of the TRPV-1 interacts with the calcium sensor calmodium (CaM) which regulates the influx of the ions *via* the voltage gated  $\text{Ca}^{2+}$  channels and protects against the potential harmful effects of calcium overload (Aroke et al. 2020; Singh et al. 2018).

As mentioned in Amiloride Insensitive Pathway section, TRPV-1 is also known to be a major component of the amiloride insensitive pathway and can detect response from several mineral salts including  $\text{Na}^+$  salts, thereby contributing to the salt taste transduction (Smith et al. 2012; Lyall et al. 2004). This indicates that minerals other than  $\text{Na}^+$  can contribute to salty taste by the activation of the TRPV-1 receptors. Ahern et al. (2005) conducted a study by injecting different minerals salts including magnesium chloride ( $\text{MgCl}_2$ ) and calcium chloride ( $\text{CaCl}_2$ ) on mice with and without TRPV-1 receptors, and patch clamp recordings were carried out to measure if current was generated upon the activation of the sensory neurons *via* TRPV-1 channels. Results demonstrated that even though all  $\text{Na}^+$ ,  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  cations could activate the TRPV-1 channels, the charge and the cationic density played essential roles in the activation of the TRPV-1 channels. Cations with a higher charge, like  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  (divalent cations) activated the channels more efficiently and quickly than monovalent cations such as  $\text{Na}^+$  (Ahern et al. 2005). Other divalent salts of zinc, copper and iron can also bind to the TRPV-1 activation sites, but their salty taste perception is less dominant compared to calcium and magnesium-based salts, perhaps because the former might not completely dissociate (Riera et al. 2007).

### TRPM5

TRPM5 is another member of the transient receptor potential (TRP) family that functions as a nonspecific cation channel (Hofmann et al. 2003). When tastants containing monovalent cations like  $\text{K}^+$  and  $\text{Na}^+$  comes in contact with the taste buds, they can activate the TRPM5 receptor. There are three potential pathways; (i) as a response to increased calcium influx, (ii) responding in combination with G-protein receptors, or (iii) the coupling of TRPM5 with Inositol

1,4,5-trisphosphate receptor type III ( $\text{IP}_3\text{R3}$ ) and (or) indirectly by diacyl glycerol (DAG) (Pérez et al. 2002).

TRPM5 is extremely sensitive to calcium and even a minor change in the membrane potential or change in calcium influx can lead to the activation of this receptor (Hofmann et al. 2003; Prawitt et al. 2003). That means, even when ENaC is activated during the presence of  $\text{Na}^+$ , there could be a possibility of activation of TRPM5 along with ENaC as TRPM5 is a sensitive nonspecific cation channel. Interestingly, a study by Nomura et al. (2020) speculates that since both TRPM5 and ENaC share the similar calcium gated voltage channel facilitating the ATP neurotransmitter release, there could be a possibility of some sodium channels (ENaC) existing along with GPCRs or TRPs. Nonetheless, there is no evidence to verify this to date, and the current ENaC mechanism for salty taste perception (Na transduction) cannot be ignored, thus suggesting that it is independent of the activation of the TRPM5 (Zhang et al. 2003; Aroke et al. 2020). However, activation of TRPM5 has a direct association with the taste transduction of other taste qualities like sweet, bitter and umami (Talavera et al. 2008; Dutta Banik et al. 2018).

### G Protein receptors (GPCR)

Some divalent cations like copper, magnesium, iron and zinc are detected by a combination of TRPM5 and the T1R3G-protein receptor, and some salts at high concentrations have been shown to activate the T2R bitter receptors. The T1R3 is known to function as part of two heterodimers, T1R2-T1R3 for detecting sweet stimuli and T1R1-T1R3 for detecting umami stimuli. Interestingly, T1R3 is also known as the calcium tasting receptor, i.e., it is capable of detecting the taste of calcium based salts in the human taste system (Tordoff et al. 2012). The taste of calcium varies from salty to sour depending on the anion attached to it and leads to an undesirable chalky taste at high concentrations (Tordoff 1996). Besides activating TRPM5 and binding to T1R3, calcium also binds to the “calcium sensing receptor” (CaSR). Studies have shown that calcium can activate both T1R3 and CaSR receptors in the presence of magnesium (Tordoff et al. 2008). Additionally, CaSR is also activated by kokumi peptides (i.e., GSH,  $\gamma$ -Glu-Val-Gly and various  $\gamma$ -glutamyl peptides) upon which it imparts a distinct taste quality or sensation known as kokumi, i.e., the feeling of mouthfulness or thickness within flavor (Ohsu et al. 2010). These compounds do not substitute for salty taste, but the activation of CaSR by kokumi peptides in salt-reduced products might improve the overall perception/acceptance of the products.

Recently, a small-scale study by Wang et al. (2019) analyzed the activation of another G-protein coupled receptor, “TAS2R7” in the presence of divalent mineral ions and found that calcium, magnesium, zinc, copper, manganese and aluminum all activated the TAS2R7. Since the T2R receptor family is responsible for bitter taste transduction, therefore, activation of TAS2R7 by the divalent ions leads to the perception of bitter taste (Chandrashekar et al. 2000). However, interaction of TAS2R7 with the CaSR or T1R3 receptors is unclear. Furthermore, in the presence of larger

cationic molecules, such as salts of  $\text{Fe}^{3+}$  or ammonium chloride derivatives, the cations are not capable of binding to the receptor cells, and in these cases they are perceived by direct adsorption onto the apical membrane of the taste cells (Nakamura and Kurihara 1991). Subjects have reported quite a wide range of taste qualities resulting from magnesium and calcium salts, including bitter and salty with metallic and sour sensations, with bitterness being more dominant (Yang and Lawless 2005; Lim and Lawless 2005). Therefore, the involvement of the specific taste receptors like TRPM5 and T1R3, which are involved in the transduction of sweet, bitter and umami taste, may explain why the taste of some minerals can be confused between salty, bitter, sweet and umami, possibly depending on their concentration.

### Taste perception of anions

Besides the activation of the taste receptor and the concentration of cation, studies show that anions also contribute to taste perception. In an early study, Murphy, Cardello, and Brand (1981) concluded that salts of chloride, bromide and iodide exhibited unique taste properties, and noted that NaCl, NaBr, NaI did not all have the same taste. Their study also concludes that, even though it is not always a determining factor, the size and weight of the cation and anion can

influence the perceived taste. Organic salts can lead to difference in perception; for example, organic salts of sodium and lithium exhibit slight saltiness but majorly sour taste (van der Klaauw and Smith 1995). Zinc also demonstrates both salty and bitter taste, and the resulting taste quality is affected by the anion attached to zinc. For example, “zinc iodide” exhibits sourness and astringency, whereas “zinc chloride” exhibits strong salty taste and further increasing the concentration increased the perception of the particular taste qualities (Keast 2003). Similarly, the chloride salts of calcium and magnesium also exhibit salty as well as bitter taste, depending on their concentration (van der Klaauw and Smith 1995; Lawless et al. 2003; Tordoff 1996). A recent study conducted both in human and mice identified a voltage dependent chloride specific channel which could be involved in salty taste perception, known as the transmembrane channel-like 4 (TMC4), which is amiloride insensitive (as discussed above). The function of the TMC4 channels showed similar properties in both mouse and humans (Kasahara et al. 2022) (Table 1).

In summary, taste perception mechanisms for minerals other than  $\text{Na}^+$  are quite complex as there is not one single receptor involved. It is quite likely that we perceive the taste of minerals *via* different receptors, however, whether these receptors are activated all at the same time or within discrete combinations is not yet clear. The multiple receptors

**Table 1.** Key receptors activated by minerals and amino acid and the taste qualities elicited by them.

Receptor family	Receptor	Stimuli	Taste qualities	References
Ion Channels	ENaC	Sodium salt	<b>Salty</b> taste, intensity dependent on the anion	Bigiani (2020); Mattes (1997); Behrens and Meyerhof (2015); McCaughey (2019); McCaughey and Scott (1998) Stähler et al. (2008)
Transient Receptor Potential (TRP) (Ion Channel)	TRPV-1 TRPV1 (and/or) TRPA1 (i.e., TRP ankyrin 1)	Harmful stimuli like capsaicin, protons, and noxious heat, Cations (Ca, Mg, K, Zn, Cu, Fe) Herbs and spices (TRPV1 agonists, e.g., capsaicin and resiniferatoxin, N-geranyl cyclopropyl carboxamide)	<b>Salty</b> , Sweet, Bitter, Umami <b>Salty</b> , Sweet, Bitter, Umami	Ahern et al. (2005); Lyall et al. (2004); Riera et al. (2009); Ishida et al. (2002) Rhyu, Kim, and Lyall (2021)
	TRPM5	Cations, particularly of mineral salts (extremely sensitive to calcium)	Sweet, Bitter, Umami	Talavera et al. (2008); Dutta Banik et al. (2018); Hofmann et al. (2003).
G Protein coupled receptors (GPCR)	Heterodimer T1R3/T1R2*	Sugar and sugar alcohols	Sweet	Li et al. (2002); Nelson et al. (2001)
	T1R3	Amino acid (MSG) + nucleotides	Umami <b>Salty/Sour/Chalky</b>	Tordoff et al. (2012); Tordoff (1996)
	T1R1+	Amino acid (MSG) + nucleotides	Umami	Nelson et al. (2002)
	TAS2R7	Divalent cations (calcium, magnesium, zinc, copper, manganese, aluminum)	Bitter	Wang et al. (2019)
	CaSR	Calcium ions Tripeptide glutathione (Glu-Cys-Gly)	<b>Salty/Sour/Chalky</b> Kokumi/Umami/Salty/Sweet (Majorly kokumi taste, however, might mildly elicit the other mentioned taste qualities)	Tordoff et al. (2008) Ahmad and Dalziel (2020); Ohsu et al. (2010)
	mGluR4 mGluR1 Family C, subtype 6A (hGPRC6A) (h=human)	Glutamate L-amino acid	Umami Umami^ (^known so far)	Chaudhari, Landin, and Roper (2000) Pallante et al. (2021); Jørgensen and Bräuner-Osborne (2020)
Transmembrane channel like 4 (TMC4)	mTMC4, hTMC4 (m=mouse, h=human)	Chloride anion	Salty	Kasahara et al. (2022)

\*T1R3+T1R2 works as a heterodimer sweet receptor|+T1R1+T1R3work as a heterodimer umami taste receptor.

involved may partly explain why we may be unable to associate a unique taste quality to each mineral. Depending on the ion, minerals are either perceived as bitter, salty, sweet, umami or sour. However, bitter and salty are the most dominant taste qualities associated with mineral salts.

## The role of free amino acids and peptides in taste transduction and interaction with salty taste

### *Taste perception of free amino acids and peptides*

The contribution of amino acids to taste was first noticed by Ikeda in 1908 who termed another taste quality known as “umami” besides the four-basic tastes, i.e., sweet, salty, sour, and bitter. The major stimulus responsible for umami taste is the amino acid “glutamic acid or glutamate” (Ikeda 2002). Likewise, several studies have confirmed that most amino acids contribute to at least one of the five basic tastes. For example, L-lysine is perceived as salty-bitter-sweet, L-arginine is known to have a flat (i.e., virtually indistinguishable) bitter taste, whereas L-glycine, L-alanine, L-threonine are perceived as sweet (Schiffman, Sennewald, and Gagnon 1981; Delompré et al. 2019; Schmidt, Olsen, and Mouritsen 2020). Additionally, L-lysine, L-glutamic acid and L-aspartic acid were found to exhibit salty taste along with sweet/bitter/umami tastes in unstimulated saliva (Feron 2019). Kawai et al. (2012) proposed that all amino acids exhibit at least one of the basic tastes, and there is a strong possibility that the taste of amino acids can be perceived as a combination of the five basic tastes. However, since the number of subjects ( $n=8$ ) in the above-mentioned study was substantially low, this theory could not be validated.

Many food products contain naturally occurring free amino acids, such as mushroom, vegetables, milk products, etc. (Sun et al. 2017; Górska-Warsewicz et al. 2018; Ito, Ueno, and Kikuzaki 2017). Usually, the savory taste of amino acids, resulting predominantly from L-glutamic acid and L-aspartic acid is categorized as “umami taste” and it has been observed, in certain foods, to increase the perception of saltiness (Kawai et al. 2012; Delompré et al. 2019), but can be argued as in certain foods the presence of L-glutamic acid doesn't lead to the perception of umami taste. Additionally, individual sensitivity can also lead to the association between umami and salty taste, (Hartley, Liem, and Keast 2019). Other amino acids might also play a role in mediating the salty taste (and/or other tastes) of foods, for example arginine and histidine have been used as flavor enhancers to enhance the salty taste of low  $\text{Na}^+$  meat products (da Silva et al. 2020). Processes such as fermentation, ripening and extraction, can break peptide bonds to release various free amino acids which subsequently can contribute to taste and lead to the improvement and enhancement of flavor of many food products; like sake, soy sauce, cheese, etc. (Ikeda 2002; Kirimura et al. 1969).

Besides the taste contribution of free amino acids, short peptides have also shown some contribution in taste perception, including salty taste enhancement. A recent study using both enzymatic hydrolysis and thermal reactions to prepare Maillard products from pea proteins, reported smaller

peptides were quickly degraded into low molecular weight peptides (<1kDa), which were not salty on their own but played a role in salty and umami taste enhancement when added in a 0.5% NaCl solution. Furthermore, the study showed that only the Maillard reaction products [low molecular weight pea peptides (LPP) such as LPP-Glu] derived from hexoses (such as glucose) led to an increase in saltiness (by 8.03%), but saltiness enhancement was not observed with Maillard products derived from pentoses. This is related to the slower rate of Maillard reaction from hexoses compared to pentoses. Indeed the study suggests greater the degree of Maillard reaction the weaker the impact of the peptides or Maillard reaction products on saltiness or umami enhancement. (Yan et al. 2021). While this study mentions the low molecular weight compounds that could be generated it does not specify any further details of these products. Other researchers have also identified some specific umami, kokumi and salt enhancing peptides in soy sauce (Jünger et al. 2022), salt enhancing arginyl dipeptides in fermented fish sauce (Schindler et al. 2011) and some specific umami peptides with salt enhancing effects have also been identified in a variety of mushrooms (Wang et al. 2024). It is still unclear if the saltiness of peptides is perceived due to the activation of a specific receptor, or it is a result of activation of umami taste receptors leading to the perception of umami and subsequently enhancement of salty taste. As per a recent review by Le et al. (2022), there is a strong possibility that peptides can activate one or more amino acid taste receptors in order to lead to saltiness perception.

### *Amino acid taste receptors*

Studies confirm the most probable mechanism for the perception of L-glutamic acid and L-aspartic acid to be *via* the G protein coupled receptors, i.e., the T1R1+T1R3 heterodimer and mGluR (Chaudhari, Landin, and Roper 2000). However, the mechanism for perception of other amino acids, such as lysine, is less clear. One possibility is that the receptors for the transduction of L-glutamic acid and L-aspartic acid amino acids, might also be responsible for the perception of lysine or any other amino acids (Wang et al. 2022). However, Smith (2015) highlighted that the activation of T1R1+T1R3 may not be necessary for the perception of all L-amino acids, thereby suggesting the possibility of the activation of other taste receptors. Stähler et al. (2008) proposed other receptors to be involved in taste perception of amino acids. They reported that amino acids like L-lysine and L-arginine might lead to the activation of ENaC subunits, as they noticed an increased  $\text{Na}^+$  membrane current in oocytes for  $\alpha\beta\gamma$ - and  $\delta\beta\gamma$ -ENaC units, which is usually observed in the presence of  $\text{Na}^+$ . This might explain the salty taste associated with L-lysine, however further research is needed to verify this in association with the human taste system. It is interesting to note that there was no effect observed for L-glutamine upon interaction with the ENaC subunits in the above study, which further supports the most likely mechanism that glutamine perception is by the G-protein coupled receptors.

Furthermore, another G-protein coupled receptor in humans known as family C, subtype 6A (hGPCR6A) has gained some attention in its ability to transduce the perception of amino acids, such as L-arginine and L-lysine. Genetically, the hGPCR6A has similarities with two other human taste receptors, i.e., 34% with CaSR [G Protein Receptors (GPCR) section] and 28% with T1R1 (Wellendorph et al. 2005). Recently, Jørgensen and Bräuner-Osborne (2020) summarized the pharmacology and physiological function of hGPCR6A and Pallante et al. (2021) highlights the role of hGPCR6A in the umami taste perception. However, there is still not enough understanding about the activation and mechanism of this specific receptor in the taste system, and if there is association with any other taste quality including salty taste.

### **G-protein receptors**

As discussed earlier in G Protein Receptors (GPCR) section, the G-protein receptor heterodimer between T1R1 and T1R3 and is responsible for umami taste, comprising  $\alpha$ ,  $\beta$ - and  $\gamma$ -subunits which activates upon interaction with amino acids or nucleotide (Behrens and Meyerhof 2015). The activated  $\alpha$ -subunit triggers signal transduction, elevating calcium influx and the opening of the “non-selective cation channel” TRPM5, which is crucial for umami taste perception (Zhang et al. 2003; Behrens and Meyerhof 2015; Li et al. 2002).

Furthermore, it is also proposed T1R3 may also form homodimers, binding to amino acids. (Nelson et al. 2001; Smith 2015; Zhao et al. 2003). A recent study by Banik et al. (2020) identifies a “broadly responsive (BR)” type 3 cell with a transduction mechanism similar to T1R1/T1R3, influencing the perception of umami, bitter and sweet taste. However, it is yet fully understood if other L-amino acids can activate these cells and further if they are involved in the salty perception, or if the activation of these receptors leading umami is what leads to perception of enhanced salty taste.

### **Metabotropic glutamate receptors (mGluR)**

Metabotropic glutamate receptors (mGluR1-8) are receptors known to be activated by L-glutamate and/or a mix of glutamate and inosine 5'-monophosphate (IMP) (Chaudhari, Landin, and Roper 2000; Pal Choudhuri, Delay, and Delay 2015). These receptors are known to be found within the circumvallate and foliate papillae of the posterior tongue. Activation of these receptor cells, similar to T1R1/T1R3, leads to the formation of IP<sub>3</sub> which can boost calcium influx and thereby signaling the brain (Masu et al. 1991). Additionally, the signals can be further amplified in the presence of calcium homeostasis modulator 1 (CALHM1), a voltage channel, helping facilitate the release of ATP in the taste buds (Lazutkaite et al. 2017; Taruno et al. 2013; Ma et al. 2018).

San Gabriel et al. (2009) points out the possibility that mGluR may only be activated within specific concentration ranges of L-glutamate, i.e., when present in  $\mu\text{mol/L}$ . However, when the glutamate concentration is not enough to activate the mGluR, research suggests the synergetic

involvement of both T1R1+T1R3 and mGluR in the perception of amino acid (glutamate), thus confirming their significance in taste perception (Yasumatsu et al. 2015; Lazutkaite et al. 2017; Vandenbeuch and Kinnamon 2016). The current knowledge, only supports the activation of mGluR by glutamate, however, Pal Choudhuri, Delay, and Delay (2015) puts forward a very fascinating possibility that the mGluR receptors (such as mGluR4, Table 1) might form a complex with each other or with one of the T1Rs, which might act as a receptor for other L-amino acids, generating taste response. However, there is no such evidence to date.

In summary, amino acid derived umami perception is the result of the synergistic effect of T1R1+T1R3 as well as mGluR taste receptor cells. Additionally, as mentioned previously, TRPM5 is sensitive to calcium, therefore, the release of calcium during the activation of T1R1, T1R3 and mGluR receptors, can also lead to the activation of TRPM5. The umami taste can arise from multiple sources including amino acids (i.e., L-glutamic acid, L-aspartic acid), peptides and nucleotides (i.e., IMP, GMP), and thus multiple binding sites are involved on these receptors. The current understanding suggests that umami taste derived from amino acids, which sometimes has been shown to lead to an increased perception of salty taste, is perceived either *via* the umami taste receptor pathway (mGluR) or the G-protein receptors (GPCRs) or can be a synergistic effect of the two (Wu et al. 2021). However, as previously stated, several studies have highlighted the possibility of amino acids other than glutamic acid and aspartic acid contributing to other basic tastes, suggesting the activation of other taste receptors which needs further investigation.

## **Current salt reduction strategies**

### **Actions by government, restaurants and manufacturers**

Consumer awareness is one of the key pillars in the WHO for action on salt reduction (WHO European Salt Action Network 2013). Besides setting up salt reduction targets, the governing bodies are making more efforts to educate consumers about the importance of reducing their consumption of salt. This is being carried out *via* campaigns in newspapers, television, radio, social media, press releases, etc. These campaigns include educating consumers about food labels, for example using color coded front of pack labeling on all products and dedicating national salt awareness days or weeks (WHO European Salt Action Network 2013). Annually, several countries around the world participate in “World Salt Awareness Week,” with a different theme each year, to educate consumers on the profound consequences of consuming too much salt (World Action on Salt 2021). Additionally, other non-governmental organizations, food manufacturers and retailers’ partner with the government to raise public awareness. However, education alone is not enough, caterers and food manufacturers have a key role in bringing awareness into action.

Consumers consider dining out as one of the challenges in limiting their salt intake, as such meals contribute to a significant amount of dietary  $\text{Na}^+$  intake. Except in Finland and the United States of America, implementing salt reduction guidelines is a voluntary action. The most common salt reduction strategies at restaurants include “menu labeling,” i.e., highlighting foods containing high  $\text{Na}^+$  (or salt). Additionally, some countries use symbols or have special campaigns highlighting foods with less salt, sugar and fat on their menus. Some countries with mandatory guidelines for salt reduction recommend reformulating products to ensure products are below maximum  $\text{Na}^+$  limits. Besides the guidelines, educating chefs on the effects of high salt in food and providing them with training on various low salt dishes are also carried out (Ding et al. 2020).

Furthermore, due to the increased consumer demand for clean label and minimally processed foods, food researchers and manufacturers have been exploring the use of non-thermal processing to extend the product shelf life by restricting the microbial growth, thereby, reducing the use of salt in the products. These technologies use very minimum heat, thus safeguarding the sensorial and nutritional properties while confirming the microbial safety of the food (Morris, Brody, and Wicker 2007). Non-thermal methods like “high pressure processing (HPP),” “ultrasound” and “pulse electric fields” have shown some positive results in extending the shelf life of food products, mainly meat products even in the presence of low salt (Parniakov et al. 2020; Inguglia et al. 2017). O’Flynn et al. (2014) found that high pressure processed “low salt” sausages did not have a negative impact on the sensorial and textural properties of the sausages. Additionally, there was no negative impact on the pH and water holding capacity as well, which was not the case in “low salt” sausages without high pressure treatment. However, the application of these novel technologies is quite restricted to certain food products, potentially due to the high equipment cost and low production yield.

### Available salt substitutes and their application

As noted earlier, salt has multiple properties in food products and there are different alternatives available that can partially impart some of these properties, however it remains extremely challenging to substitute NaCl with one specific ingredient. Table 2 summarizes several combinations of salt substitutes which have been explored by the food industry so far. For example, the use of mineral salts (such as KCl,  $\text{CaCl}_2$  and  $\text{MgCl}_2$ ) which can activate the TRPV-1 receptor leading to the perception of salty taste or the use of amino acids (such as glutamic acid, arginine and histidine) which can activate the umami taste receptors like T1R1/T1R3 or mGluR leading to umami taste in sodium reduced products, subsequently leading to enhanced perception of saltiness. The interaction of different salt substitutes with taste receptors leading to enhanced salty taste perception is further discussed in more detail in Discussion section.

## Discussion

Table 1 summarizes the key receptor cells which, when activated by minerals, amino acids other compounds, either directly contribute to salty taste or indirectly enhances the perception of saltiness in food products. Additionally, it is interesting to note that many of these receptors are not specific to single amino acids or minerals, they can be activated by wide range of stimuli. For example, TRPV-1 can be activated by both noxious heat stimuli contributing to bitter taste and by minerals like Na, K, Ca, contributing to salty taste. In the case of amino acids, one receptor is common for both sweet and umami taste, i.e., T1R3. Additionally, T1R3 (Tordoff et al. 2012; Tordoff 1996) and another G protein receptor, i.e., TAS2R7 (Wang et al. 2019) are also activated by minerals which have some salty taste like K, Ca, Mg and thus their activation can lead to enhanced salty taste perception. On the other hand, these minerals can also activate two or more of these taste receptors which might lead to the perception of one or more taste qualities. Thus, from our current knowledge we would expect these receptors, along with ENaC, could be activated when salt substitutes such as KCl,  $\text{MgCl}_2$ ,  $\text{CaCl}_2$  are used in  $\text{Na}^+$  reduced products like cheese (Grummer et al. 2012; Horita et al. 2011) or meat products (Vidal et al. 2020).

There are some receptors which are not linked to salty taste, but their activation is necessary for the detection of other tastes involved with minerals, including umami, bitter and sweet taste, for example TRPM5. TRPM5 is identified as a key receptor in the transduction mechanism for both mineral salts as well as amino acids as its activation has been observed to be associated with the release of ATP, which is known to activate the sensory neurons, as discussed previously. There is a possibility of activation of the TRPM5 receptors along with the activation of the known mineral (TRPV-1) and amino acid (T1R1+T1R3) receptors in cases where amino acids and mineral salts are present in the same food products. For instance, the study by da Silva et al. (2020) used a combination of mineral salts (KCl) and amino acids (arginine and histidine) and Guo et al. (2020) used a combination of NaCl and lysine. Therefore, the activation of both mineral and amino acid taste receptors, along with ENaC receptors are expected, in the presence of NaCl. However, it is still unclear if these receptors can be activated simultaneously, or if the saltiness is only perceived by the activation of one dominant receptor.

Furthermore, even though umami taste can be recognized as a different taste quality, it can play a key role in enhancing the saltiness perception of the food products. As we can see from Table 1, umami taste receptors including the heterodimer T1R1/T1R3, as well as TRPV-1 and CaSR, are activated by various stimuli, including mineral ions and umami tasting compounds like amino acids. Even though there are specific receptors for individual minerals (like sodium) and amino acids (like glutamate), there may be some overlap between the activation of some receptors (like CaSR) by calcium ions, as well as peptides eliciting salty/umami/kokumi taste (Table 1). Could this overlap be the reason why umami taste is associated with enhanced salty taste, or could it be

**Table 2.** Available salt substitutes and their applications.

Author and year	Food matrix	Substitute	Sensory method	Results
<b>Mineral salts, amino acid and their derivatives</b>				
Nakagawa et al. (2014)	Aqueous solutions	Mixture of NaCl (335 mM) + KCl (335 mM) + Sodium aspartate (1.7 mM)	Discrimination test (Binomial comparison method) to evaluate saltiness; untrained panel ( $n = 10$ )	Sodium aspartate enhanced the salty taste of solution containing both NaCl & KCl. Sodium aspartate reduced the bitterness of KCl. The study proposed that the ionic channels perceiving Na & K undergoes changes when both the ions are present in the same system, which is further changed in the presence of sodium aspartate, leading to an increase in the perception of saltiness.
Vidal et al. (2020)	Low sodium salted meat	NaCl, KCl, (control 1: 100% NaCl and control 2: 25% NaCl + 75% KCl) & $\text{CaCl}_2$ . Seven treatments with 75% NaCl replacement by KCl + different flavor enhancers (Lysine, Taurine, Arginine, Inosinate + Guanylate, yeast extract, i.e., Bionis YE MXE NS, and Bionis SFE 201, Purac Arome NA4)	Overall acceptance and overall difference test; untrained panel ( $n = 120$ ).	Lysine and yeast extracts (Bionis YE MXE NS) led to the best results in reducing sensorial defects (predominantly bitterness) caused by KCl / $\text{CaCl}_2$
Dos Santos Alves et al. (2017)	Low-fat Bologna-type sausages	KCl + amino acid (lysine) + flavor enhancers (50% IMP + 50% GMP), liquid smoke, other spices and herbs like black pepper coriander, garlic	Liking (9-point hedonic scale) and attribute rating (color, aroma, flavor, texture); untrained panel ( $n = 100$ )	50% replacement of NaCl with KCl – no negative impact on the technological, physiochemical, and microbiological properties. Sensorial defects suppressed after the addition of lysine and/or liquid smoke.
Campagnol et al. (2011)	Fermented cooked sausages	KCl + amino acids (lysine, taurine), flavor enhancers 5'-ribonucleotide disodium inosinate and disodium guanylate (50% IMP + 50% GMP)	Liking (9-point hedonic scale) and attribute rating (color, aroma, taste and texture); untrained panel ( $n = 60$ ).	50% replacement of NaCl with KCl to avoid manufacturing defects. Addition of amino acids and flavor enhancers compensated the sensory defects.
Mitchell, Brunton, and Wilkinson (2011)	Frozen ready meal (chilli con carne),	5 different combinations used: KCl, KCl + Lysine, KCl + autolyzed yeast, whole cell yeast, nucleotide yeast extract	Paired comparison & preference test (30 trained panelists), discrimination test (triangle test) (20 trained panelists), ranking test (15 trained panelists)	40% NaCl reduction achieved by gradual salt reduction in recipe. 60% NaCl reduction achieved by substituting NaCl with nucleotide yeast extract.
(Rocha et al. 2020)	Aqueous solutions	Flavor enhancer [disodium inosinate (IMP), monosodium glutamate (MSG), disodium guanylate (GMP), monosodium glutamate (MAG)]	Temporal profile analysis (T1 and TDS); Trained panel ( $n = 15$ )	MAG & MSG enhanced salty taste in sodium reduced solutions more effectively than IMP and GMP. These flavor enhancers elicited both salty and umami taste. Intensity of umami taste was majorly affected by the concentration of flavor enhancers.
Guo et al. (2020)	Reconstructed Ham	35.8% Na reduction + 0.2 to 0.8% Lysine	Liking (9-point hedonic scales) (mouthfeel, appearance, taste and global acceptance); trained panel ( $n = 13$ ).	0.8% Lysine improved the water holding capacity, textural and sensory acceptance of low salt reconstructed ham. No significant increase in the perception of saltiness. i.e., addition of lysine increased the acceptance of the low salt foods but did not increase the saltiness perception.
da Silva et al. (2020)	Low-fat and low-sodium bologna-type sausages	KCl + Arginine & histidine (as flavor enhancers)	Liking (9-point hedonic scales) (color, aroma, flavor, texture, overall acceptance); untrained panel ( $n = 100$ )	Reduction of 60% NaCl by KCl, but KCl caused textural, sensorial defects and emulsion instability. Addition of arginine and histidine reduced these defects.
Grunmer et al. (2012)	Cheddar cheese	KCl, $\text{MgCl}_2$ , or $\text{CaCl}_2$	Descriptive Analysis; trained panel ( $n = 9$ )	$\text{CaCl}_2$ and $\text{MgCl}_2$ substitution resulted in detectable off notes like bitter, metallic, earthy, and soapy flavors. Cheddar cheese manufactured with KCl in combination with NaCl resulted in closest to the NaCl control cheese.
Horita et al. (2011)	Reduced-fat mortadella	$\text{CaCl}_2$ , $\text{MgCl}_2$ , KCl	Liking (9-point hedonic scale); untrained panel ( $n = 112$ )	Different combinations of these salts were used in addition to NaCl. Best sensory attributes were observed with 50% NaCl + 25% KCl + 25% $\text{CaCl}_2$ .
<b>Herbs and Spices</b>				
Ghawi, Rowland, and Methven (2014)	Tomato soup	<b>Basil modification</b> - basil, black pepper, celery and garlic <b>Cumin &amp; coriander</b> - cumin, coriander, ground celery seed and garlic <b>Oregano modification</b> -oregano, bay leaves, garlic, celery, and black pepper.	Profiling (trained panel; $n = 10$ ), Unstructured line-scale scoring of liking (overall liking, liking of appearance, flavor, texture, and aftertaste) & JAR (just-about-right flavor intensity), untrained panel ( $n = 148$ )	Direct incorporation of herbs and spices into a salt reduced tomato soups decreased consumer liking in comparison to the full salt soup. However, liking of the herb and spice reduced salt soups increased significantly over repeated tasting days (exposure) whereas liking for the reduced salt soups without herbs and spices did not. 53% reduction in salt achieved with enhanced perception of saltiness on using blend of herbs and spices (especially, the oregano blend).

(Continued)

Table 2. Continued.

Author and year	Food matrix	Substitute	Sensory method	Results
Mitchell et al. (2013)	Chilled Ready meals: chicken supreme (a chicken and mushroom dish in a cream and wine sauce), a cottage pie (a savory minced beef dish topped with potato), and a chunky vegetable soup	<b>Oregano, sage, rosemary, garlic, pimento, and clove. Lactoferrin whey proteins</b>	Liking (9-point hedonic scale); untrained panel (n=60)	Addition of these herbs lead to increased acceptability of salt reduced meals as they act as natural flavor enhancers. Off notes associated with whey proteins was not observed, there was increased consumer likeability. Can be used as a natural flavor enhancer.
Lopes et al. (2014)	Margarine	10 treatments with 1.5g/100g spice mixture (A or B) and varied sodium content (0%, 25%, 50%, 75%, 100%) <b>Mixture A:</b> green onion, garlic, marjoram, thyme. <b>Mixture B:</b> lemon, oregano, basil, thyme (All spices in dehydrated form)	Liking Test (9-point hedonic scale); untrained panel (n=62)	Addition of spice mix (A or B) increased the overall purchase intent, taste and flavor of margarine. Spice mix addition showed promising results with up to 50 (~75% sodium reduction) Additionally, the spice mix (both A and B) also significantly increased the antioxidant activity of margarine Less salt was added in soups with herb blends and overall liking was increased, especially in fresh soups, the overall liking was not very significant for canned soups. But high levels of herbs reduced the overall acceptance of the soups.
Wang, Lee, and Lee (2014)	Fresh chicken noodle soup, retorted canned chicken noodle soup, fresh tomato soup, canned tomato soup	Oregano, basil, marjoram, thyme, bay leaf, carrot, celery, onion	Overall liking (9-point hedonic scale); untrained panel (n <sub>1</sub> =95; n <sub>2</sub> =101)	
<b>Plant extracts</b> Lee (2011)	Plant aqueous extract	Magnolia, kukoshi, mushroom, mint, sea tangle, Salicornia (saltwort), ginger, yam, green onion, radish, onion, garlic, nappa cabbage	Intensity scale rating (0 to 15) of taste attributes; trained panel (n=8)	Salicornia (saltwort), sea tangle, kukoshi were the three extracts scored high for umami and salty taste by the panel and was further selected for analysis. The sodium content of these plant extracts was 57% of that of NaCl (on dry weight basis). Salicornia substitution was effective in natural fermentation with desirable pH and acidity and no undesirable bacterial activity was observed. Conversely, it led to decrease in the population of fungi and coliforms to below detectable limits and had improved antioxidant capacity. Overall had a positive impact on the microbial and physical aspects of the fermented cabbage.
Pires-Cabral, Pires-Cabral, and Quintas (2021)	Fermentation of white cabbage	Salicornia ramosissima; three fermentation trials; A (Control)- 80g cabbage + 2.4g NaCl (~1.15% Na) B (with Salicornia):- 80g cabbage + 24g Salicornia (~0.34% Na) C(salt + Salicornia)- 80g cabbage + 0.4 g NaCl + 24 g Salicornia (~0.49%Na)	No sensory	
<b>Others</b> Smith, Metzger, and Drake (2016)	Cream of broccoli soup	Whey permeates from cheddar, mozzarella, cottage cheese, milk and de-lactosed (DLC) permeates (with a salt and no salt control)	Descriptive Analysis; trained panel (n=8)	Cottage cheese and de-lactosed (DLC) permeate was the saltiest. Cottage cheese has high lactic acid and lower lactose concentration. DLC had high mineral and organic acid content. However, they elicited other flavors (cardboard flavor, sour taste) in the soup, which was unacceptable by the consumers. Cuttlefish bone saltiest among other shells. At same level of saltiness, its Na content was 73% of that of NaCl. Cuttlefish bone also had higher mineral (K, Mg, Ca, Zn, P) and amino acid (e.g., Lys, His, Arg) content as compared to other shells. Note: This study also included some marine plants (Seaweed, kelp, semen cassiae, inula flower, sama leaf), however, they were not selected by the panelists during the screening process.
Zhang et al. (2014)	Aqueous extracts of seafood shells	Cuttle fish bone, clamshell, oyster shell, arabia cowry shell	Degree of difference test; semi trained panel (n=20)	Red wine pomace seasoning reduced microbial growth, produced patties with higher K, Ca, fiber and phenol levels, enabled salt reduction without affecting the shelf life. Potential to be used as a flavor enhancer in salt reduced products while maintaining shelf life.
García-Lomillo et al. (2017)	Beef patties	Red wine pomace seasoning (2% w/w) added to control patties containing 2%, 1.5% and 1% (w/w salt/base-meat mass)	No sensory analysis	50% sodium reduction achieved in biscuits and other snacks and 25% reduction in savory dishes. No information available on the physical or sensory properties of the products.
Desmond (2006)	Biscuits, snacks and savory dishes	Mycoscent (product derived from Mycoprotein)	Not available	

that the umami taste and salty taste are cognitively associated to savory/salty taste? While this is still inconclusive, there are evidence (Table 2) of the role of umami compounds in enhancing the perception of saltiness. Besides, it is also proposed that amino acids such as lysine can also work as a flavor enhancer to mask the bitter after-taste arising from potassium chloride. Studies highlighted in Table 2 have explored the incorporation of umami taste compounds including amino acids (lysine, taurine, arginine, glutamic acid) and nucleotides (IMP and GMP) as flavor enhancers to mask the negative sensorial aspects arising by KCl (i.e., bitter, astringent and metallic taste) whilst maintaining the comparable saltiness of control samples (Campagnol et al. 2011; Rocha et al. 2020). Additionally, a very recent review highlights the promising aspect of using basic amino acids (like lysine, arginine, histidine) in low NaCl meat and fish products with sensory enhancement; indicating that amino acids can support salt reduction by being more than a taste enhancer (Zhang et al. 2022). However, these studies do not examine the effect of the salt substitutes at a receptor level, which is also highlighted by Zhang et al. (2022); therefore, it is not clear if the perceived saltiness/other taste attribute is due to the addition of lysine, flavor enhancer or herbs and spices. Considering flavor enhancers in Na<sup>+</sup> reduced products, a recent “salt-flip” theory was explored in food products available on the market, which involved switching to a Na<sup>+</sup> salt with less Na<sup>+</sup> than NaCl. In this case, MSG contains 12.2g Na<sup>+</sup>/100g whereas NaCl contains 39.34g Na<sup>+</sup>/100g, no undesirable flavors were observed and was accepted by the consumers (Halim et al. 2020). Since MSG is a Na<sup>+</sup> salt of the glutamic acid, it will activate the umami taste receptors, i.e., T1R1+T1R3, thereby leading to umami taste perception instead of salty taste (Halim et al. 2020). Although successful salt reduction using MSG was achieved with consumers’ acceptance; the acceptance was based on the “flavorful” and “savory” taste quality, rather than specifically on “salty”. The study did further confirm that MSG can be used as a flavor enhancer in salt reduced products. However, the consumers are hesitant in using MSG based products due to its negative reputation of causing harmful health effects. Thus, using MSG alone as a substitute to NaCl has not achieved success.

To cater for the aspect of consumer perception, an ingredient report by Mintel (2017) highlights the presence of glutamic acid and its salts in various ingredients like yeast extract, soy extract, hydrolyzed vegetable protein and protein extracts, which can enhance saltiness perception. Consumers are more than likely to perceive these ingredients as more natural than MSG. Strong evidence has shown (Table 2) the possibility of using ingredients like the yeast extracts and hydrolyzed vegetable protein for developing salt reduced products (Table 2). Mitchell, Brunton, and Wilkinson (2011) used different forms of yeast extracts (autolyzed yeast, whole yeast cell, nucleotide yeast extract) and achieved 60% salt reduction with nucleotide yeast extracts, without having any undesirable impact on the sensorial properties of frozen ready meals. Protein extracts and hydrolates (in essence free amino acids or peptides) do not possess strong salty taste, but they can enhance the taste of NaCl and reduce the total

amount of salt used. An interesting product in this category is a mycoprotein derivative, Mycoscent® (by-product from Quorn™), which is a natural flavor enhancer containing glutamic acid and nucleotides (Parniakov et al. 2020; Methven 2012). Industrial by-products from the wine industry have also been explored (Taladrí et al. 2020) as a potential option for salt reduction.

Studies have also explored the addition of herbs and spices as flavor enhancers in salt reduced products (Table 2). A review by Rhyu, Kim, and Lyall (2021) suggests that the chemical components of herbs and spices activate the TRP channels such as TRPV-1 and TRPA-1 (Transient Receptor Potential ankyrin member 1), which might lead to an increase in the intracellular calcium concentration, thereby activating the TRPV-1 leading to stimulation of the sensory neurons (TRPV-1 section). As previously discussed, TRPV-1 is activated by several stimuli (like capsaicin and minerals), and is associated with salty, sweet, bitter and umami taste qualities. Therefore, a salt substitute mixture containing herbs and spices along with Na<sup>+</sup> or other minerals, will activate TRPV-1 which might have an impact on the stimulation of ENaC. However, the relationship between the activation of TRPV-1 and TRPA-1 in the salt substitute mixture was not explained in the paper.

What remains unclear is where combination of salt substitutes or enhancers are present together in a food product, what receptors are being activated to determine the overall salty taste of the products? For example, to reduce NaCl by 50% in a low fat sausage, Dos Santos Alves et al. (2017) successfully used a combination of KCl, amino acid (lysine), flavor enhancers (50% IMP + 50% GMP), liquid smoke, other spices and herbs (black pepper, coriander and garlic) to reduce 50% NaCl. The lysine was assumed to mask the bitterness of KCl. The current understanding of taste receptors indicates that all the ingredients would activate a combination of different receptors leading to salty and umami taste. For instance, herbs and spices are broadly known to activate TRPA-1 (Table 1), the umami taste of amino acids and some nucleotides are perceived by the activation of the heterodimer T1R1+T1R3 and maybe the homodimer of T1R1 or T1R3 and hGPCR6A and it is known that NaCl can be perceived as slightly sweet in very low concentration (due to the activation of T1R2+T1R3) and sour at very high concentration (McCaughy 2019). It is tempting to assume that other minerals salts and amino acids might behave the same way, but to different extents. Even through the understanding of the salty taste perception has evolved greatly in past decades, there are still a lot of uncertainties needing for further investigation. Therefore we can neither ignore the possibility that all these receptors can be activated at the same time, leading to overall salty taste, nor the possibility of dominating receptors for overall saltiness perception. Conversely, another interesting possibility which needs in depth exploration is at the neurological level than the receptor level, i.e., the involvement of a common calcium gated voltage channel involved in the release of neurotransmitter ATP in the perception of the different taste qualities *via* different receptor cells such as GPCRs, TRPM5 and ENaC.

## Conclusion

This paper summarizes the taste receptors involved in the perception of saltiness, highlighting the necessity to understand the activation of such receptors in developing optimum salt substitute strategies. Using herb and spice blends has been one of the most widely accepted strategies to reduce salt in various food products, but mainly used for flavor enhancement in low Na<sup>+</sup> products. Other than imparting taste, salt plays many roles in forming the final product quality including textural and microbial stability. Therefore, depending on the food matrix, studies have explored using a combination of mineral salts with herb and spice blends to retain textural properties and avoid microbial deterioration.

However, with the increasing demand for using clean label and sustainably sourced ingredients, further studies are needed to gain a better understanding of the potential use of plant extracts or other industrial by-products. Additionally, since plants from the *Salicornia* species naturally grow around marshy land and have the potential to grow on infertile land not necessarily requiring fresh water, they may offer a solution to utilize land not used for other forms of agriculture. These underutilized plants may prove to be an asset to the food and beverage industry as sources of novel ingredients. Further, converting industrial by-products into food and flavorings ingredients is a smart technique to reduce food waste. Considering the composition of the plant extracts and by-products highlighted, we hypothesize that they will activate Na<sup>+</sup>, mineral and amino acid taste transduction pathways. So far there are only a limited number of studies exploring the use of plants and industrial by-products as salt replacers, and most research is limited to the investigation of sensorial attributes and elicitation of salty taste, rather than the fundamental mechanisms for their taste perception. With the complexity involved in the perception of taste, it will be beneficial to have a greater understanding of the mechanisms responsible for saltiness perception of such ingredients to enable product optimization and improved consumer acceptance. Therefore, there is a need to understand the synergistic effect of the different components, particularly minerals and amino acids on the salty taste perception derived from natural salt-alternatives.

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