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Influence of temperature on taste perception

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Abstract. Daily experience tells us that temperature has a strong influence on how we taste. Despite the longstanding interest of many specialists in this aspect of taste, we are only starting to understand the molecular mechanisms underlying the temperature dependence of different taste modalities. Recent research has led to the identification of some strong thermosensitive molecules in the taste transduction pathway. The cold activation of the epithelial Na^+ channel and the heat activation of the taste variant of the vanilloid receptor (TRPV1t) may underlie the temperature dependence of salt responses. Heat activation of the transient receptor potential channel TRPM5 explains the enhancement of sweet taste perception by warm temperatures. Current development of methods to study taste cell physiology will help to determine the contribution of other temperature-sensitive events in the taste transduction pathways. *Vice versa*, the analysis of the thermodynamic properties of these events may assist to unveil the nature of several taste processes.

Keywords. Taste receptor, gustatory nerve, ENaC, TRPV1, TRPM5, thermal taste.

Introduction

The influence of temperature on the perception of taste is part of our daily experience. Well-known examples are the extreme sweetness of melted ice cream and the bitterness of warm beer. To understand these phenomena we first need to know in detail how taste perception works. Interestingly, pioneers of taste research considered solving the opposite problem. They envisaged that by determining the temperature sensitivity of gustatory responses they could dissect whether taste perception was based on physicochemical or enzymatic processes [1, 2]. This idea might now seem far-fetched, but as we argue below, the study of the temperature dependence of events in taste transduction may greatly help to unravel the mechanisms of taste perception.

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The perception of five taste qualities, namely sweet, bitter, umami (savoury), sour and salty occurs through segregated pathways. Interaction of 'tasty' compounds with specialized receptors in the taste buds of the tongue and palate is transduced into an electrical excitation of taste receptor cells. This excitation is further transmitted to the brain, where the final representation of each taste modality takes place. The result is the trigger of appetitive or aversive behaviour, as well as preingestive physiological responses in the digestive tract.

What is the influence of temperature on our perception of taste?

The answer to this question is not straightforward. There are many conflicting data in the literature, which reflects both technical complications and the large variability among individuals [1–3]. Psychophysical studies in hu-

mans, which attempt to quantify the subjective taste experiences [4], have shown that the concentration threshold for the detection of salty, bitter, sweet and sour stimuli shows a U-shaped dependence with temperature, with the lowest thresholds between 20 and 30 °C [2, 5]. The temperature dependence of taste intensity varies for suprathreshold stimuli. In general, sweetness increases with heating and, notably, the influence of temperature decreases at higher concentration of the stimuli [6–8]. This suggests that temperature directly modulates the transduction of taste, as opposed to a summation of independent gustatory and thermal inputs. It is important to notice that the effects of temperature may not be generalized for a taste modality, but rather be restricted to specific compounds. For example, in contrast to other sweeteners, the sweetness of saccharin is not affected by temperature [8]. The bitterness of caffeine is decreased by cooling [9], whereas for quinine, the paradigm compound for bitter taste, it was reported that taste threshold increases with heating [10]. In addition, cool NaCl but not cool KCl can elicit rat chorda tympani nerve responses [11]. These are examples of how the thermal modulation of taste reflects the heterogeneity of the transduction mechanisms within taste modalities [9].

Notably, the effects of temperature on the perception of umami have only been studied at the level of taste nerve responses. It was reported [12] that the magnitude of canine chorda tympani nerve responses to monosodium glutamate (MSG), which is described as a salty-dependent component, peaked at 10–15 °C. However, the magnitude of the responses to the synergic mixture of MSG and guanosine 5′-monophosphate, which represent an umami-dependent component, showed a maximum at 30 °C. These observations may explain why ham appears to taste saltier at cold temperatures and more savoury at high temperatures.

The temperature dependence of the mammalian gustatory nerve responses, recorded as the integrated electrical responses of afferent nerves (chorda tympani and glossopharyngeal nerves), seems to recapitulate the main features observed in psychophysical assays in humans. The temperature dependence of the magnitude of the responses shows a bell shape with peak at 20–30 °C and the thermal effects become weaker at higher stimulus concentrations [1, 13]. This indicates that key temperature-dependent processes occur before transmission of the gustatory nerve response.

An intriguing key finding is that some taste fibres are also responsive to thermal stimuli, with sweet-sensitive fibres responding to heating and fibres responsive to HCl, quinine or NaCl being sensitive to cooling [1, 14, 15]. These observations may help in explaining the enhancement of sweet taste perception with heating and of salty and quinine taste with cooling. Moreover, they may underlie the phenomenon called thermal taste, whereby changes in temperature alone induce taste sensations in some humans. Warming produces sweetness and cooling produces saltiness and/or sourness in the anterior part of the tongue, whereas cooling produces bitterness and sourness in the back of the tongue [16].

Effects of burning and cooling agents

Burning and cooling agents like capsaicin (the pungent component of hot peppers) and menthol simulate thermal stimulation of the oral mucosa. Therefore, it is interesting to analyse their influence on taste perception. It is known that capsaicin suppresses human responses to sweet, bitter and umami but not sour and salty stimuli [17–20]. Another ‘hot’ compound, capsicum oleoresin, decreases the responses to acid, bitter and sweet compounds, whereas piperine has also an effect on responses to salt [21]. In contrast, the effects of cooling agents have received much less attention, although it has been reported that acute menthol application enhances feline gustatory nerve responses to several tastants. On the other hand, pre-incubation with menthol affects the neural responses to sucrose, inducing potentiation at low concentrations and inhibition at high concentrations, and inhibits the responses to NaCl, quinine, acetic acid and ethanol [22]. These complex interactions may cause, for example, the extreme distortion of the taste perception after chewing menthol-flavoured gum. Although the mechanisms underlying these observations remain obscure, it seems clear that these effects are not related to the modulatory action of capsaicin and menthol on thermosensation [23], but to their irritating effects through the stimulation of trigeminal nerve fibres carrying noxious information from the mouth [19, 22]. Of note, bitter compounds may also elicit oral irritation at high concentrations, thus influencing the overall taste sensation [20, 24]. Additionally, both capsaicin and menthol can elicit bitter responses on their own [19] and may therefore interact with the transduction pathways of other taste stimuli [22].

Temperature-sensitive steps in the taste transduction pathways

In principle, all processes involved in taste transduction are temperature dependent and one would need to determine the extent to which each step contributes to the overall temperature dependence of taste perception. However, it seems that neither the interaction of tastants with their receptors [6, 12], nor the process of transmitter release leading to the stimulation of the gustatory afferent fibres are major contributors for the thermal effects on taste perception [12]. As we discuss below, most evidence points to the thermal modulation of the signalling pathways

leading to the excitation of the taste receptor cells, and in particular, to the activity of ion channels that are involved in the reception and the transduction of taste stimuli.

Cold- and hot-activated salty channels

There is strong evidence indicating that the amiloride-sensitive epithelial Na^+ channel (ENaC) and a taste variant of the vanilloid receptor TRPV1t are salt receptors in the tongue, contributing the amiloride-sensitive and amiloride-insensitive components of the salty taste response, respectively [25]. Interestingly, cold activation of ENaC [26, 27] was proposed to underlie the enhancement of salty taste perception with cold temperatures [26] and, given that ENaC is constitutively open, it may also explain the induction of salty taste by cooling alone [16].

It should be noted, however, that in Na^+-replete humans the amiloride-sensitive component of the salty taste response to Na^+ accounts for only one fifth of the total response [25, 28]. This contrasts sharply with the observations in rodents, where the contribution of ENaC to salty taste transduction is much stronger [25, 29]. Notably, the amiloride sensitivity of salt-evoked lingual surface potentials seems to vary significantly among humans, suggestive of inter-individual differences in the contribution of ENaC to salt sensing [30]. Considering that ENaC expression in taste tissue and salty taste responses can be altered by dietary conditions through hormonal regulation [31], it would be interesting to test whether the amiloride-sensitive component of the response to NaCl is larger in Na^+-depleted human subjects and if this influences the cold stimulation of salty taste.

Interestingly, the gustatory nerve response to NaCl in rats and mice contains amiloride-sensitive components that are enhanced either by cold (LT, low-temperature component) or heat (HT, high-temperature component) [14, 32]. Notably, there is a differential expression of temperature-dependent and temperature-independent amiloride-sensitive components in several murine strains [32], which may echo the large inter-individual variability in the amiloride sensitivity of human responses to salt [30]. Later identification of LT and HT single chorda tympani fibres suggests the existence of amiloride-sensitive salt receptors with different temperature sensitivities [33]. It remains to be clarified whether these receptors represent different ENaC variants.

The complex behaviour of gustatory salt responses [1, 13] may result from the effects of temperature on the gating of ENaC and TRPV1t (Fig. 1a). Cooling may increase the salty response via LT amiloride-sensitive components that are most likely relying on ENaC (blue lines and arrow). On the other hand, heating may enhance the response via HT amiloride-sensitive components and/or the heat-activated TRPV1t channel (red lines and arrow). At low Na^+ concentrations, only the ENaC may contribute to the salty response (Na^+ influx) since, in contrast to TRPV1t, it is highly selective for Na^+. It would be interesting to determine whether the salty taste of non-Na^+ containing salts like KCl, $CaCl_2$ and NH_4Cl, which is independent of the ENaC (amiloride insensitive) [34], is enhanced at high temperatures, as might be expected if TRPV1t is involved.

Heat-activation of TRPM5: From voltage sensing to ice-cream taste

TRPM5 is a Ca^{2+}-activated Ca^{2+}-impermeable non-selective cation channel belonging to the transient recep-

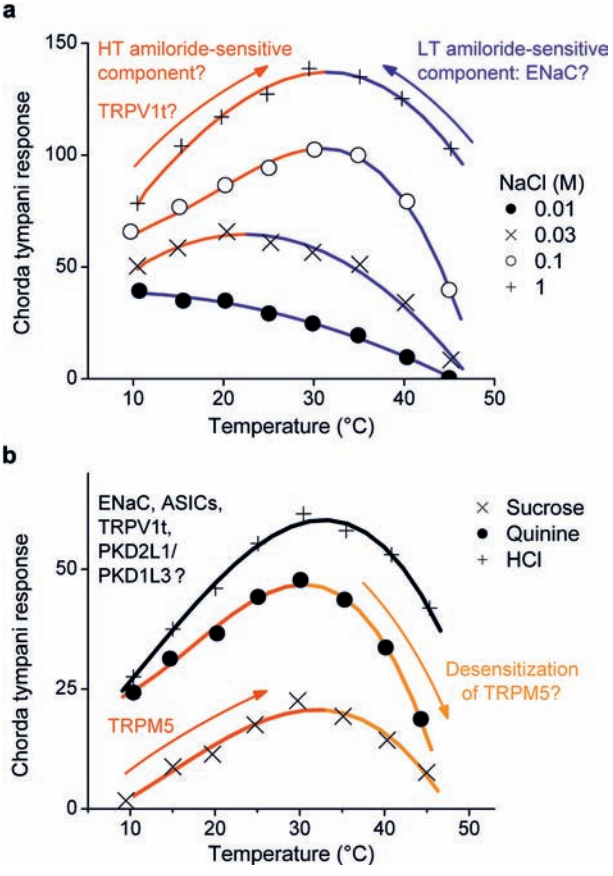

Figure 1. Tentative role of several ion channels in the thermal modulation of gustatory nerve responses. (*a*) Magnitude of phasic rat chorda tympani nerve responses to NaCl as a function of temperature. Cooling may increase the salty response via ENaC (blue lines and arrow), whereas heating may enhance the response via TRPV1t (red lines and arrow) (HT, high-temperature component; LT, low-temperature component). (*b*) Temperature dependence of the magnitude of phasic rat chorda tympani nerve responses to sucrose (0.5 M), quinine (0.02 M) and HCl (0.01 N). Heat activation of TRPM5 may explain why responses to sucrose and quinine are increased by warming from 10 °C (red lines and arrow), whereas desensitisation may cause that responses decrease at temperatures higher than 30–35 °C (orange lines and arrow). The nature of the biphasic response to HCl is still elusive, but it could result from the temperature dependence of ENaC, ASICs and PKD2L1/PKD1L3 channels. The data are adapted from Yamashita and Sato [13]. (With permission John Wiley & Sons, Inc.).

tor potential (TRP) superfamily of ion channels [35–37]. TRPM5 is expressed in the basolateral membrane of some taste receptor cells [37] and is involved in the transduction of sweet, bitter and umami tastes [38, 39]. It has been proposed that activation of TRPM5 by the increase in intracellular Ca^{2+} concentration that follows taste receptor stimulation induces a depolarisation of the taste receptor cells, which in turn leads to the transmission of the excitation to gustatory afferent fibres [36]. It was recently found that the activation of TRPM5 in the HEK-293 cell heterologous expression system is extremely sensitive to temperature [40]. In the presence of high intracellular Ca^{2+}, inward TRPM5 current was negligible at 14 °C, but it increased dramatically by warming up to 35 °C. Heat activation of TRPM5 is due to a shift of the voltage dependence of activation to more negative potentials, similar to that for TRPV1. Thus, TRPM5 follows the same principle of temperature modulation that applies to some thermosensitive TRP channels [23, 41]. Notably, chorda tympani nerve responses to sweet compounds were highly dependent on temperature for wild-type mice, whereas the residual gustatory responses in *Trpm5* knockout mice did not change with temperature [40]. It was concluded that the thermal sensitivity of sweet taste perception results from the strong temperature dependence of TRPM5 activation (Fig. 1b). We may also speculate that heat-activation of TRPM5 mediates the thermal stimulation of sweet taste. It remains to be investigated if the combination of high temperatures and basal level of intracellular Ca^{2+} is sufficient to activate TRPM5 and trigger the sweet sensation.

Interestingly, we have observed that TRPM5 currents decay at temperatures above 35–40 °C (Talavera and Nilius, unpublished observations). Although at this point we are unaware of the mechanism behind this observation, it is intriguing to speculate that it may explain the decrease of sweet taste responses at high temperatures (Fig. 1b) [1, 13].

The challenges

When revising the literature on the influence of temperature on taste perception, there is a surprising lack of new reports. As a result, many aspects remain unknown or controversial. This contrasts sharply with the potential applications in health care and food industry [42, 43]. For example, we are not aware of any study on how temperature affects the human perception of umami taste or the recently described fat taste modality [44, 45]. Likewise, the roles of putative sour receptors such as ENaC, ASIC, TRPV1 and the recently identified sour sensor channel PKD2L1/PKD1L3 [46–48] on the thermal modulation of sour taste (Fig. 1b) remain to be clarified.

We are also far from understanding all the details of how the transduction of taste occurs. For example, it is only recently that we started to learn about the mechanisms through which they communicate with afferent gustatory fibres in the taste buds [49] and that technology allows studying the physiology of taste receptor cells in detail [50]. These important technical advances will help to further investigate the influence of temperature on the diverse aspects of cell signalling, native ion channel function (*e.g.* TRPM5, PKD2L1/PKD1L3), exocytosis and nerve impulse generation. In the mean time, we should keep in mind the idea of using the thermodynamic characterization of biological processes when trying to unveil the mysteries of taste perception.

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