Tasty and healthy TR(i)Ps

The human quest for culinary pungency

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For the majority of the developed world, the hunter–gathering lifestyle that served our predecessors for millennia is a distant memory. Yet, despite our increasingly sophisticated approach to food as top chefs compete for Michelin stars, our basic ability to taste chemical signatures and perceive flavour has not changed. In fact, in addition to sight, the ability to taste might have been one of our ancestors’ most important senses, and one under strong selective pressure. From the taste and texture of a food we are able to discern much about whether it will be healthy or harmful for us, and this probably meant the difference between life and death for our predecessors. Thus, our ability to taste is a function of survival and might explain much about the otherwise-strange things that humans find palatable today.

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This article, however, focuses not on taste per se, but on a related physiological phenomenon: chemesthesia. Chemesthetic sensations arise when chemical compounds activate receptors associated with other senses that mediate pain, touch, texture (mechanical) and thermal perception. These sensations do not fit into the traditional sense categories of taste and smell, but are often perceived as a burn-like irritation, stinging or tingling in the nose and mouth. Remarkably, we deliberately add compounds that trigger such sensations to our food, and even enjoy the pain-like sensation that they induce. The question is: why?

Various explanations, ranging from anthropology to psychology have been put forward to explain why this kind of pungency makes food more enjoyable and why humans appreciate the irritancy associated with spices. Indeed, although pungency increases the sensitivity of the oral cavity to stimulants, it actually diminishes the appreciation of taste and flavour, usurping the attention that our brain would normally give to these stimuli.

Gustatory signalling starts with the binding of chemical compounds (tastants) to taste receptors, which are present on different receptor cells in the taste buds of our tongue. Taste receptors and transduction components for five basic tastes have been identified: sweet, umami (loaned from the Japanese for ‘pleasant savoury taste’), bitter, salty and sour. Beyond these, taste is probably even more complex if we consider ‘fatty’, ‘kokumi’ (another Japanese word, translated as ‘mouthfulness’ or ‘heartiness’) and ‘metallic’ as additional qualities. In theory, by assessing food for these five qualities, we are able to consume a healthy and nutritious diet. Each type of taste corresponds to a vital constituent of food: sweetness indicates carbohydrates, ‘umaminess’ proteins and amino acids, and saltiness stems from important osmolytes, such as sodium chloride. A bitter taste warns us about the presence of harmful and toxic environmental compounds, while sourness tells us something about the freshness of food, allowing us to avoid rotten material.

In order to detect these tastants, humans have evolved three cell types that transmit signals to our gustatory nerve fibres (Fig 1). Taste cells are present not only on the tongue, but also throughout the mouth in solitary chemosensory cells and in the gut and the respiratory system. The taste cells on the tongue, throat and mouth synapse with afferent fibres that travel to our brain via three cranial nerves. Once they have reached the brain, taste information is further modulated by hormones and other endogenous factors. These peripheral modulations influence our preferences in terms of food intake and play important roles in regulating energy homeostasis. In addition, olfaction has a huge impact on flavour—the combination of all sensory signals about the food, which includes chemical taste signals. While the sensory systems in the palate can detect only five types of taste, it is our sense of smell, with its far greater detective range, that gives us a sensation of flavour when combined with our other senses.

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However, as mentioned, our focus here is on chemesthesia, rather than taste. Thus, it is worth noting that sensory fibres from the trigeminal nerve, which express TRP (transient receptor potential) V1, TRPA1, TRPM8, TRPV4 and TRPV3 channels, innervate the whole palate. Palatine keratinocytes also express TRPV3 channels that encode heat, cold and pain sensations. They probably also encode tingling signals and might function indirectly as mechanosensitive channels. These channels, and probably more, process additional information about the chemical nature of food and modulate the activity of the real ‘taste machinery’, sensing
the texture, temperature and fluidity of food and providing the ‘mouth-feeling’ during eating. Culinary pungency itself is coupled to the activation of TRPV1. Many food supplements interact with these palatine channels and provide chemesthetic information, and their flavour and use have been known for generations. The Greek historian Plutarch (ca. 45–120 BC), for example, wrote about the use of such supplements to marinate meat: “We mix oil, wine, honey, fish paste, vinegar, with Syrian and Arabian spices, as though we were really embalming a corpse for burial”. Indeed there was no shortage of pungent ingredients in the cuisine of our ancestors. Ancient humans were already familiar with the piquant taste of the three main classes of dietary activators of TRP-type channels: alkamides, isothiocyanates and terpene dialdehydes.

In fact, spices have been popular throughout human history and have had a significant impact on societies and economies. In ancient Rome, for example, exotic spices were used with such profligacy that one gets the idea that actual food was, for wealthy Romans, simply a vehicle for delivering spice. Indeed, both Roman and Medieval Europe were dependent on spices, socially and economically, just as Europe is nowadays dependent on oil (Turner, 2004). Pepper, for example, which was used extensively in Roman cuisine, was imported from India in exchange for metals and silver. In fact,
the importance of pepper cannot be overestimated. It was pepper, rather than a noble quest for discovery, that fuelled the ‘Age of Exploration’ and the passage from the medieval to the modern age. The goal of dominating the pepper trade was driven by the enormous amount of money that Europeans were willing to spend to activate their TRPV1 channels with piperine, the active ingredient of pepper. Thus, the discovery of America was merely a by-product of seeking a new and faster route to India. Indeed, from this perspective, one can understand why the Dutch exchanged New Amsterdam, now called New York, with the British for the tiny group of islands in the East Indies that produce nutmeg (Milton, 1999).

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India and the Far East are certainly where most spices grow, so it is not surprising that eastern cuisine is so spicy. Furthermore, the cuisine of the Far East has a particular note lacking in the other cuisines of the world, namely the sensation of ‘tingling’. Tingling is a curious and fascinating form of pungency, somewhat similar to the numbing sensation experienced by placing a battery on one’s tongue (the reader should note that we recommend curry as preferable to licking batteries). The archetypal tingling spice is Szechuan pepper, a popular ingredient of Chinese and Japanese cuisine, and also one of the very few spices present in the cuisine of Tibet. α-Sanshoool, the active ingredient of Szechuan pepper, interacts with many sensory end points and activates TRP channels and potassium channels. At the same time, it has a similar effect on sodium channels as does the neurotoxin tetrodotoxin, resulting in overall sensory confusion. Szechuan pepper is the only spice that rivals chilli peppers for its versatility of use and has interesting applications in cosmetics, where it is popular in lipsticks—to induce a numbing sensation that mimics the expansion of the lips—and for the temporary removal of superficial wrinkles (Artaria et al, 2011).

Although modern Europeans associate spices with India and the Far East, the most celebrated and expensive spice of the Greek–Roman world was silphion, which comes from the Mediterranean area. This gum-resin was obtained from a Ferula species of plant that grew around Cyrene, in today’s Libya. Weight for weight, silphion was more expensive than silver and gold. As such, it was a status symbol, associated with sexuality and purported to have both contraceptive and/or aphrodisiac properties. Sadly, silphion was driven to extinction through its consumption in the first century AD: the first documented example of the extinction of a plant by the agency of humans. Libyan silphion was eventually replaced by Persian silphion, nowadays known as asafoetida. This vile gum-resin has a faecal note that is largely lost during heating. It is especially popular in India, where it is used by Hindu sects that forbid their followers to eat vegetables that contain a sprout, such as garlic and onion. Because asafoetida is derived from a root and not a sprout, it represents a religiously correct garlic replacement (McGee, 2001).

...it was the French lawyer, politician and gastronome, Jean Anthelme Brillat-Savarin (1755–1826), who was probably the first in recent history to understand the value of culinary pungency and, incidentally, to use the phrase “you are what you eat” (Fig 2). His famous 1826 book called Physiologie du Gout, ou Meditations de Gastronomie Transcendante (still available) is witty, anecdotal and enjoyable, but might shock scientists with the statement that the discovery of a new dish does more for human happiness than the discovery of a new star. Nevertheless, Brillat-Savarin does offer us an intriguing insight into the pursuit of healthy eating: the pleasure of spicy food, the value of culinary pungency and their relation to health and the enjoyment of life in general.

Ancient humans were already familiar with the piquant taste of the three main classes of dietary activators of TRP-type channels

This idea of pleasure leads us to the first possible explanation of the human quest for pungency. As omnivores, early humans had a highly diversified diet, probably dependent on the season and the availability of various berries, nuts and animals. The advent of agriculture simplified our diet to include only a few plants that did little to stimulate the human palate. In a certain sense, agriculture separated entirely the nutritional and sensory elements of the human diet such that what was good for us no longer tasted so good. In this context, spices can be viewed as concentrated sources of flavour, and our quest for them as an attempt to satisfy a sensory system primed by the diversified and flavour-rich diet of our hunter–gatherer ancestors. Alternatively, and in psychological terms, hot cuisine might be the culinary equivalent of benign masochistic activities, similar to a parachute drop, a hot bath, a cold shower, or a horror movie. All of these activities are characterized by a constrained risk—that is, a risk typical of a life-threatening event but evoked in a safe setting—and the effect has been cogently named the ‘rollercoaster effect’. We enjoy it because it feels harmful, but we know it is safe.

Over the past years, however, the anthropological and psychological theories about our craving for spices have been increasingly questioned by research suggesting that evolution might have programmed us to like spices simply because they are good for our health. The classic rationale for the use of pungent spices is that they sanitize food due to their antibacterial activity—as Plutarch intimated. Spices such as pepper and cinnamon were certainly used to preserve food, especially from animal sources, but the historical decline of the use of spices in European cuisine was not accompanied by any significant improvement in food preservation, suggesting this had not been their original use. An alternative reason—and one that ties in with the use of natural remedies through the ages—is that spices were known to provide health benefits. In our modern age of molecular techniques, we now have strong preclinical evidence for the health-promoting properties of several constituents of spices (Aggarwal, 2011a,b).

From an evolutionary point of view, food choice requires a vital decision to ‘take it or leave it’. For our hunter–gatherer ancestors, this decision might well have been one of life or death. Accepting or rejecting a food is a complex process. Acceptance of food depends not only on taste, but also on olfactory, tactile and visual signals, as well as memories of previous, similar experiences and social expectations. Food palatability and hedonic value therefore play central roles in nutrient intake. As a result,
Ancestral humans who liked spicy food—and therefore gained from its health benefits—might well have had longer, healthier lives and more offspring. Their children, in turn, would have become acquainted with the use of certain spices, spreading the habitual tolerance to offensive gustatory sensations throughout early human society.

In this modern age of molecular biology, spice compounds have proven extraordinarily complex to study because they are pleiotropic agents with both direct, receptor-mediated, and indirect, gene-transcription-mediated effects. Curcumin, the principle phytochemical from turmeric (Fig 3), exemplifies these difficulties. Curcumin has more than 100 distinct molecular targets, affects the transcription of thousands of genes, and has a promiscuous pharmacophore that combines Michael-acceptor, metal-chelating and antioxidant properties. Despite evidence from more than 3,000 preclinical investigations, curcumin has never emerged from the quagmire of the health food market to become a mainstream drug. Its promiscuous binding behaviour makes it impossible to explore the chemical space around its pharmacophore, since analogues would have to be assayed against multiple molecular end points, substantially transcending the ‘magic bullet’ principle that permeates modern drug discovery. Furthermore, nature seems to have produced a well-honed mechanism for preventing curcumin from reaching our blood, as the compound shows dismally low oral absorption, at least in a pharmaceutical matrix (Cuomo et al., 2001).

Nevertheless, ethnobotanist James Duke, creator of an important database on phytochemicals at the US Department of Agriculture, advocates accompanying any pharmaceutical with selected spices; a suggestion already followed by thousands of cancer patients who take turmeric in addition to their mainstream treatment (Duke, 2010).

Duke argues that humans developed the ability to selectively use the phytochemicals in the plants they consumed and that, in this sense, spices are treasure troves.
Given the lack of success with the multitalented curcumin, it is not surprising that capsaicin, a TRPV1 ligand devoid of significant affinity for any other biological target, is the only dietary TRP ligand that has reached the status of a mainstream drug. Capsaicin, along with other pungent spices such as piperazine, chilli and rutaecarpine—an alkaloid found in certain herbs including the Chinese herb Wu-Chu-Yu—seem to have extensive health benefits in relation to problems associated with being overweight.

Obesity has become a serious problem in the developed world and is associated with diabetes, hypertension, heart failure, immune deficiency and late-life dementia.

Interestingly, these spices exert hypotensive effects or protective effects against cardiac or gastrointestinal injury (Peng & Li, 2010). The extensive ingestion of natural capsaicin agonist or chilli, for example, has been shown to decrease dyspeptic and gastrointestinal reflux disease (GERD) symptoms. The typical Asian diet, which includes rice and a range of hot spices, might therefore lower cardiometabolic risks and the prevalence of hypertension. The method of action appears to be that TRPV1 activation by dietary capsaicin enhances endothelium-dependent relaxation, an effect that is based on a TRPV1-mediated increase in nitric oxide production and that might represent a promising new therapeutic intervention for hypertension (Sessa, 2010; Yang et al, 2010).

Dietary capsaicin can also reduce obesity-induced inflammation and metabolic disorders such as insulin resistance and hepatic steatosis (Kang et al, 2010): pass the chilli peppers, please.

In fact, it is the TRPV1 channel itself—and therefore agonists and antagonists of it—that is increasingly recognized as having a vital and multifaceted role in health. A first example is its increasingly obvious link to factors affecting obesity. Research has shown that the TRPV1 channel influences metabolism and visceral fat. Mice lacking TRPV1 exhibit only subtle alterations in body temperature, or in their responses to...
thermal challenges, but are hypometabolic—have lower oxygen consumption—and hypervasoconstricted—have lower tail skin temperature. In other words, they have a distinct thermoregulatory phenotype that is coupled with a predisposition to age-associated obesity and includes hypometabolism (Garami et al, 2011). Previous research has also shown that TRPV1 agonists prevent adipogenesis in pre-adipocytes. Thus, oral administration of capsaicin for 120 days prevented obesity in male wild-type mice, but not in TRPV1-knockout mice under a high fat diet. Spicy TRPV1 activators are therefore novel players in adipogenesis and obesity (Zhang et al, 2007; Gioffi, 2007).

A second example of the health function of TRPs is related to the avoidance of high concentrations of salt. The taste of salt triggers two divergent behavioural responses: concentrated saline solutions elicit aversion, whereas low concentrations of sodium chloride are considered enjoyable and tasty. The ‘attractive’ salt pathway is probably mediated via the epithelial sodium channel (ENaC), but the aversive pathway, which functions as a non-selective detector for a wide range of salts, might be coupled with TRPV1 or its variant TRPV1 (Chandrashekar et al, 2010). In this case, TRPs give us the unpleasant feeling of a badly over-salted meal. TRPV1 is also involved in detecting the bitter taste typical of high concentrations of Ca\(^{2+}\) and Mg\(^{2+}\), and sensations such as salty, metallic, astringent and sour. TRPV1 is thus involved in the avoidance of high salt concentrations, rather than in tasting salt per se.

Given the potential health benefits of influencing TRPV1 activity, the search for novel TRPV1 agonists has begun. Essential oils from rose, thyme geraniol, palmarosa and tolu balsam contain constituents that activate TRPV1. These include citronellol, the main constituent of rose oil, and geraniol, the main constituent of thyme geraniol and palmarosa oils (Ohkawara et al, 2010). But what if you do not like spicy foods? How are you to activate your TRPV1 channels?

Non-pungent TRPV1 agonists represent attractive dietary ingredients to support weight loss, given the effect of capsaicin on wild-type mice consuming high-fat diets. Fortunately, the pungent properties of TRPV1 agonists and their activating potency are substantially unrelated. The pungency of TRPV1 agonists is critically dependent on lipophilicity: highly lipophilic agonists are less pungent because they cause slow TRPV1 activation, delaying or even suppressing its ability to trigger action potentials in sensory neurons (Ursu et al, 2010). Nevertheless, all other TRPV1-related effects are maintained (Chu et al, 2009), including those on thermogenesis. These considerations underlie the development of capsinoids, a group of non-pungent ester isosteres of capsaicinoids, as slimming agents. These compounds were discovered in the late 1990s in a sweet pepper cultivar (CH-19 Sweet) from Thailand (Kobata et al, 1998, 1999) and later found in high concentrations in the Japanese cultivar Himo. The production of these compounds is associated with specific mutations in the putative aminotransferase gene (p-AMT) responsible for the reductive amination of vanillin, the key step in the biosynthesis of capsaicin in pepper fruits. In the absence of a functioning aminotransferase, vanillic alcohol, and not vanillamine, is produced, and this alcohol is eventually acylated to capsinoids in a striking example of biosynthetic tinkingering (Tanaka et al, 2010; Lang et al, 2009). In the cultivar CH-19 Sweet, a nonsense mutation prevents the translation of the gene (Lang et al, 2009), while in Himo, a single-nucleotide substitution results in a loss of function (Tanaka et al, 2010).

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The capsinoids are best represented by capsiate, the ester isostere of capsaicin. Capsiate is less pungent than capsaicin and is available as a dietary supplement in the USA and Japan for promoting weight loss in combination with diet and exercise. A study on the slimming properties of capsiate in humans found an interesting association between changes in abdominal adiposity and TRPV1 polymorphism (Snitker et al, 2009). Thus, the most pronounced slimming effects induced by capsiate were observed in individuals carrying a Val585Ile mutation in TRPV1 (Val/ Val and Val/Ile variants), while hardly any effect was associated with the Ile/Ile variant. Remarkably, sequence variation around residue 585 of TRPV1 has been associated with insensitivity to capsaicin pungency in birds and rabbits (Jordt & Julius, 2002). Genotypic analysis is therefore vital to identify the best candidates for capsinoid use as a polymorphism in TRPV1 could underlie negative results on thermogenesis as reported in some studies on capsiate (Galgani et al, 2010).

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Clearly, further research is necessary before capsinoids are touted as the modern version of the Pill of Epimenides—the magic slimming ingredient inspired by the Greek philosopher who was rumoured not to have eaten for 50 years and then wrote a book entitled The Happiness of Fasting (Watanabe et al, 2011).

TRPV1 is not the only TRP channel to have potential health effects. Pungent spices often contain ingredients that activate another member of the TRP cation family, TRPA1. Almost everyone will have experienced the pungent and irritating taste of mustard. Its active component is allyl isothiocyanate (AITC), one of the most efficient activators of TRPA1. This channel is present in the sensory nerves of the mouth cavity and the palate, where activation of these channels modulates taste. Many cultures favour the addition of garlic to many meals. The active ingredient in raw garlic is allicin, which also activates TRPA1. Allicin is electrophilic and raw garlic has been shown to protect against the development of right ventricle hypertrophy, reduce right ventricular pressure in pulmonary diseases, and act as an antihypertensive. Boiled or aged garlic, which lack allicin, have no effect.

TRPA1 is a major target of many electrophilic molecules, which have wide-ranging biological effects including influencing the expression of cytoprotective proteins involved in the elimination of harmful oxidative stress. Indeed, low doses of the principal curcuminoid of the popular Indian spice turmeric, Curcuma longa, have been shown to increase the expression of genes encoding cytoprotective proteins, including antioxidant enzymes, protein chaperones, growth factors and mitochondrial proteins (Mattson, 2008). Sensing the presence of beneficial electrophiles in our food probably involves the activation of mainly TRPA1 channels in the
sensory fibres of our mouth, palate and tongue. Such electrophiles are present in cruciferous vegetables such as broccoli, cauliflower, watercress, Brussels sprouts, Japanese radish, black mustard, papaya and wasabi. They all cause special taste sensations that can be exploited by good chefs.

Other plants used widely in Asian cuisine also activate TRPA1. One is *Perilla frutescens*, which has interesting taste and somatosensory properties. Leaves from the plant are used as foods and its seeds are used to make edible oil or to flavour soup in Korea. It is also used in traditional Chinese medicine for inducing diaphoresis, dispelling heat, strengthening stomach contractions and improving digestion. Perillaldehyde and perillaketone are among the components of the aromatic extracts from *P. frutescens* that activate TRPA1 and are responsible for the chemesthetic properties of this plant (Bassoli et al, 2009).

...Roman and Medieval Europe were dependent on spices, both socially and economically, just as Europe is nowadays dependent on oil.

A new TRPA1 activator that has been used for a long time in Indonesian cuisine is aceotxychavicol acetate (ACA), the main pungent component in galangal (Narukawa et al, 2010). Galangal (blue ginger) is a rhizome of plants of the genus *Alpinia*, with many traditional medicinal and culinary uses. It stimulates the appetite, promotes blood circulation, including in the brain, and is psychoactive. However, large quantities have been reported to induce mild visual hallucinations.

Finally, it is worth considering the beneficial roles attributed to olive oil, especially to high-quality virgin olive oil. Oleocanthal is the major anti-inflammatory phenolic in extra-virgin olive oil. It causes oral pungecy and is psychoactive. However, large quantities have been reported to induce mild visual hallucinations.

In the context of healthier, longer lives, another TRP channel might also play an important role. Our ability to taste is not limited to the mouth, but also extends to the gut. The signalling cascade that allows us to taste sweet and bitter is dependent on TRPM5. This TRP channel is expressed in some gastric cells, where the activation of bitter taste receptors, and subsequently TRPM5, stimulates ghrelin secretion. Ghrelin is a hunger hormone with proagastinogenic effects. The modulation of endogenous ghrelin levels by bitter tastants—the famous German ‘Magenbitter’, bitter-tasting aperitifs or digestives—provide novel therapeutic applications for the treatment of weight and gastrointestinal motility disorders (Janssen et al, 2011). Indeed, bitter herbs and the liqueurs prepared from them were a mainstay of European pharmacopoeias, and some bitter compounds have now been found to activate both TRPA1 and bitter receptors, potentially providing a full range of beneficial gastrointestinal and anti-inflammatory effects.

In conclusion, spicy food not only tastes better than ‘plain’ food in which the five classical tastes dominate, but also often has beneficial health effects. Here we have explored how these health effects might have contributed to the development of the human taste for spicy food; a preference that social tastes and our penchant for thrilling experiences have cemented and elaborated. But the importance of spicy food does not end at the rise and fall of empires or the prevention of cancer, it also defines us as an advanced species. Unlike our animal relatives, humans have been able to move beyond eating simply for survival to eating for pleasure, for social and familial connectedness and for longer, healthier lives.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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