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Herbs, Spices and Alcoholic Beverages May Elicit Cephalic Phase Responses, Involving Innate Reflexes, which Modulate Digestive Activity

McMullen MK*

Life Force Research, Sweden

***Corresponding author:**

Michael K McMullen,
Life Force Research, Sweden

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1. Abstract

Almost half of humanity suffers from digestive disorders so, it is not surprising that people have developed treatments with plants for these disorders. Today we have a wealth of information from all parts of the world and from many diverse cultures. What is common in this knowledge bank is the frequent occurrence of both bitter tasting and aromatic plants for digestive disorders. Bitter tasting plants are agonists of the TAS2R receptors and aromatic plants are agonists of several TRP somatosensory receptors. The prevailing view in physiology is oropharyngeal receptors act to regulate our food intake; to accept nutritionally rich substances, the sweet and umami tastes, and reject potentially toxic items, the bitter and sour tastes. In addition, we learn to consume and seek out the nutritionally rich substances and avoid potentially toxic items. Here is a discontinuity: traditional phytotherapy indicates the use of bitter tastants while physiology recommends avoidance. In addition, many popular vegetables taste bitter as do beer, coffee and tea. This paper proposes that both bitter tasting and aromatic plants elicit cephalic phase responses, involving innate reflexes, which modulate digestive activity. Furthermore, different bitter tasting plants produce characteristic responses that are not predictable from the single hedonic sensation of bitterness. Support for this proposal can be inferred from the available literature but goal-oriented research is required to substantiate or reject these concepts.

2. Introduction

Potential foods, both solid or fluid, entering the oropharyngeal cavity are assessed by three sensory systems (smell, taste and somatosensory) and five cranial nerves (I, VI, VII, IX and X). So, food intake is closely monitored by the central nerve system. The blending of food with saliva during mastication (chewing) releases additional compounds which adds to the sensory information.

• Smell receptors in the nasopharyngeal cavity sense odoriferous substances and signal to the cognitive centres via the I cranial nerves. There may be as many three separate olfactory systems in operation that have evolved at different periods with somewhere between 100 and 1000 different odorant receptors [1].

• Taste receptors in the oropharyngeal cavity sense bitter, salt, sour, sweet and umami (savory or meaty) and signal to the cognitive centres via the VII, IX and X cranial nerves [1].

• The somatosensory receptors in the nasopharyngeal and oropharyngeal cavities sense touch, pressure, position, movement, vibration, pain, temperature, pH and a wide range of both dietary and noxious compounds, referred to a as chemethesis. These receptors signal to the cognitive centres via the VI, IX and X cranial nerves [2].

3. Food Sensing

The primary purpose of the three sensory systems is to determine the suitability of a food; should it be ingested or not, i.e. a binary decision. Smell is important even before a food enters the gustatory cavity. If something smells unpleasant then it is likely to be avoided, similarly if a smell is associated with nausea because of a previous exposure, it is likely to be avoided. On the other hand, pleasant smells, learned and unlearned, can be a powerful stimulant to human emotions [1].

The different tastes indicate the usefulness of a food [3]. The pleasant tastes of sweet and umami are related to the presence of carbohydrates and protein respectively. Simple sugars taste sweet and indicate high energy nutritious food. Simple sugars are found in fruits and honey as well as being produced during mastication of complex carbohydrates. Simple sugars are also used extensively in the food industry. Glutamic acid (l-glutamate) and some ribonucleotides taste umami which has been variously described as savoury, brothy and meaty, it is also used extensively in the food industry. Glutamic acid, either as one of the amino acids of protein or in free form, constitutes up to 8–10% of amino acid content in the human diet, with an intake of about 10–20 g/day in adults [4], yet it is only available for tasting when protein is degraded. During mastication glutamic acid becomes available. It is also present in prepared foods such as broths and soups as well as fermentations of protein rich foods such as cured meats/seafood, cheese, soja sauce and seafood sauces. The existence of the umami taste was only documented in 1908 [5] and recognition of its existence has been slow until 2000 when the molecular structures of the oropharyngeal bitter, sweet and umami taste receptors were reported [6].

The other tastes indicate the possibility of toxicity but may be pleasant in small quantities. Many like salty snacks but the salt taste receptor prevents us from drinking sea water, which is poisonous. Many enjoy drinking carbonated drinking water, which is more acid than regular drinking water, yet the sour taste prevents us from ingesting spoiled food. The world's most popular drinks, beer, coffee, tea and wine, all taste bitter. We eat many bitter tasting vegetables; however, we reject excessively bitter tasting plants which are intensely unpleasant and are often poisonous.

The somatosensory system has two major types of sensory receptors the mechanoreceptors stimulated by touch and polymodal nocichemo receptors stimulated by temperature, pain, pH and a wide range of dietary and noxious compounds.

The mechanoreceptors give tactile information about the physical characteristics of food and position in the oropharyngeal cavity. This information is utilised for XI cranial nerve afferent signalling. This motor nerve steers chewing, saliva secretion, the movement of the tongue, swallowing and the production of speech [7]. The mechanoreceptors are sensitive to astringent substances, particularly the dietary polyphenols. The polyphenol group includes flavonoids, tannins and phenolic acids, all of which have ani-oxidant and anti-inflammatory effects. Polyphenols are the most common secondary metabolite in plants and are found in a wide variety of foods including berries, fruits, vegetables, cocoa, coffee, tea and wine. On the hand, polysaccharides in plants reduce the sensitivity the sensitivity of the mechanoreceptors and block the perception of the polyphenols. Polysaccharides used in the food industry include pectin, Arabic gum and xanthan gum [8].

The noici-chemo receptors register pain, temperature, pH and a wide range of both dietary and noxious compounds [9]. These compounds include:

- pungent substances - cayenne, pepper mustard and ginger
- aromatic oils - hops, peppermint, cinnamon and aniseed [10].

Some noci-chemo somatosensory receptors are stimulated by both particular temperatures and compounds found in foods, Table 1.

There are some agonists that stimulate receptors in both sensory systems. Carbonated water is both a sour taste and a TRPA8 agonist while the tannins in red wine are an agonist to the mechanoreceptors as well as the bitter receptor TAS2R4 [12]. Also some agonists of TRPA1 and TRPV1 influence the perception of bitter, sour, and salt agonists [13].

Table 1: TRP channels and their temperature sensitivity, with examples of agonists acting on each receptor and suggested functions of the receptor in the intact animal [11].

Receptor	Temperature Range	Dietary Agonists	Function
TRPV2	≥52º C	Cannabidiol	Extreme heat sensor
TRPV1	≥42º C	Capsaicin, ethanol, allicin*, eugenol, gingerols*, omega 3 fatty acids, piperine, vanilla	Noxious heat sensor
TRPV3	32 - 39º C	Camphor, carvacrol, thymol, eugenol	Warmth
TRPV4	27 - 34º C	Arachidonic acid??	Warmth, pain
TRPA8	25 - 34º C	Carbonated water, eucalyptol, menthol*	Cold perception
TRPA1	≤17º C	Cinnamaldehyde, allicin*, gingerols*, menthol*, allyl isothiocyanate, nicotine, gingerols*	Cold, mechanical and chemically induced nociception

* agonists for 2 TRP receptors.

4. Neural Transmission

The cranial nerves VI, VII, IX and X synapse in the medulla with secondary neurons carrying signals to the gustatory and somatosensory cortexes. The information is transferred by means of both labelled-line and across-fibre pathways.

The taste signalling nerves (VII, IX and X) use a labelled-line pathway ending in different cognitive regions of the gustatory cortex [1]. Consequently, we can discriminate between the different tastes and experience all five tastes: bitter, salt, sour, sweet and umami tastes, as distinct entities. While there is thought to be only one, or perhaps several, types of taste receptors for salt, sour, sweet and umami, there are 26 types of the bitter taste receptors referred to as TAS2R [14]. Transmission from the individual bitter receptors utilises across-fibre pathways as we experience only one cognitive sensation of bitter.

The somatosensory signalling nerves (VI, IX and X) also utilise both labelled-line and across-fibre pathway signalling. It is likely, but not proven that transmission from the mechanoreceptors, which are not primarily hedonistic, is labelled-line to facilitate motor activity in the XI cranial nerve. On the other hand, the polymodal noci-chemo receptors use across-fibre pathways which is the reason why some room temperature foods can taste hot or cold, and why chemical agonists can have analgesic properties by blocking pain signals. Stimulation from one type of ligand can override the stimulation from another type of ligand [15]. The somatosensory system also covers the skin and in Eastern Asia aromatic oils, such as Tiger Balm, are applied externally to treat headaches and other pains, with the chemesthesis signalling overriding the pain signalling.

5. Cephalic Phase Responses

As well as acting to accept/reject and experience pleasant/unpleasant sensations, the taste of a food elicits digestive responses [1]. Researchers have investigated the responses elicited by the thought, smell, sight, and taste of food, referred to as cephalic phase responses (CPR). This paper will limit discussion to clinical studies and CPRs elicited once foods have entered the oropharyngeal cavity.

Digestive disorders afflict 40% of the human population [16] and plants are used worldwide in the treatment of digestive disorders, particularly bitter tasting plants and aromatic plants [17-21]. It has been suggested that the oral perception of plants played a key role in the development of phytotherapy [22].

5.1. Saliva

Saliva in the gustatory cavity is involved with lubrication and mastication as well as the digestion of carbohydrates and fats. The ingestion of food and chewing increase the flow of saliva that occurs with a meal. Signals from both the taste and somatosensory receptors elicit increases in saliva flow via the XI cranial nerve. Saliva flow is increased by tastants in the following order: sour > umami > salt > sweet > bitter [5]. Perhaps coffee is an exception because it tastes bitter and is a well-known stimulant of saliva [23]. Numerous chemosensory agonists are sialagogic: capsaicin (TRVP1), piperine (TRVP1), nonivamide (TRVP1), menthol (TRVP1 and TRPA8), carbonated water (TRPA8), cinnamaldehyde (TRPA1) [24].

5.2. Postprandial Hyperaemia

Chewing also elicits gastric hyperaemia, an increased flow of blood in the celiac artery [25, 26]. Gastric hyperaemia is necessary to accommodate the ingested food in the stomach, to sterilise the food and to start the digestion of food. In the initial phase, the gastric phase, the stomach wall

1. expands to hold the food volume,

2. hardens to resist the weight of the food,

3. has increased blood flow to bring food temperature to body temperature (by diffusion), in addition, gastric hyperaemia is essential for

4. stomach movements,

5. production and secretion of gastric juices, and

6. the removal of cellular wastes.

The gastric phase begins when food enters the stomach and continues for about 15 minutes after the cessation of eating. When gastric emptying commences, the intestinal phase starts. In this phase gastric hyperaemia is required for

1. enzyme and bicarbonate production,

2. secretion of digestive juices,

3. absorption and removal of digested particles,

4. peristaltic activity, and

5. the removal of cellular wastes.

Gastric hyperaemia increases the circulatory volume without markedly increasing the blood volume. To avoid a decrease in blood pressure heart rate increases [27]. An inadequate cardiac response leads to postprandial hypotension with the risk of syncope, falls, stroke and angina, as well as mortality [28]. Postprandial hypotension is common in geriatric patients, and an important but under-recognized cause of syncope. Other populations at risk include those with diabetes, Parkinsons disease and autonomic failure [29]. Additionally, because food intake is partially regulated by learned behaviour [1] those with a predisposition to postprandial hypotension can engage in food avoidance strategies, such as undereating, missing meals, or complaining about the quality of the food.

Bitter tasting herbs have a long history as agents to treat dyspepsia [30]. Gentian (Gentiana lutea) contains bitter secoiridoids, including amarogentin an agonist to 7 TAS2Rs (1, 4, 39, 43, 46, 47, 50), while wormwood contains bitter sesquiterpene lactones, including absinthin an agonist to 4 TAS2Rs (10, 14, 46, 47) [31]. When fluid extracts of gentian and wormwood (Artemsia absinthium) were administered to healthy adults, at physiological doses (the equivalent of 1000mg dried plant) and without food, they elicited increases in arterial compliance immediately after ingestion. In contrast encap-

suled equivalents did not elicit this effect [32]. These increases in arterial compliance act to increase blood pressure but any increases of blood pressure above the set-point are blunted by the baroreflex. Thus, these tastants act to increase low blood pressure and prevent hypotension without the risk of hypertension, while at the same time reducing the cardiac workload. The reduction in cardiac workload may be of benefit for those with heart problems as well as those engaging in physical activity after meals.

Coffee (Coffea arabica) has many positive effects on digestion [23] including CPRs. Coffee contains caffeine which is an agonist to 5 TAS2Rs (7, 10, 14, 43 and 46) and a group of diterpene glycosides including mozambioside, bengalensol, cafestol and kahweol which are agonists to 2 TAS2Rs (43 and 46) [33] . Caffeine and regular coffee, but not decaffeinated coffee, have an immediate effect on heart rate. A cup of coffee containing 130 mg caffeine has been reported to elicit an increase of heart rate, about three beats per minute, for at least thirty minutes. This effect is purported to be due to vagal withdrawal rather than sympathetic activation [34, 35]. The increase in heart rate acts to support postprandial hyperaemia but whether caffeine and coffee have the same effect at a meal has yet to be investigated.

By comparing the CPRs and the TAS2Rs involved it appears that the stimulation of TAS2R47 elicits an increase of arterial compliance and the stimulation of TAS2R7 elicits an increase of heart rate. Other agonists of TAS2R47 include andrographolid, cascarillin, picrotoxinin, quassin and artemorin [31]. The first four are found in the well-known bitter tasting plants Andrographis paniculate [18], Croton eleuteria [30], Picrorhiza kurroa [20] and Quassia amara [30] respectively. Artemorin is a bitter sesquiterpene lactone, similar to absinthin, and widely distributed in the bitter tasting Artemisia species. Other agonists of TAS2R2 include papaverine, quinine and possibly strychnine [31]. Quinine is found in the Chincona species. It is used to flavour alcoholic beverages bitter and for the treatments of malaria and leg cramps [36]. It remains to be established whether these other plants elicit the same CPRs as those previously reported for gentian, wormwood and caffeine.

5.3. Slowing Gastric Emptying

Gastric emptying delivers partly digested food (chyme) from the stomach into the duodenum. The chyme is mixed with digestive juices from the pancreas, gallbladder and small intestine and the rate of emptying is hormonally governed. Dumping syndrome, rapid gastric emptying, occurs when food moves too quickly from the stomach to the duodenum. Symptoms occurring within the first hour are referred to as early dumping syndrome and include: gastrointestinal symptoms (abdominal pain, bloating, borborygmi, nausea and diarrhoea) and vasomotor symptoms (flushing, palpitations, perspiration, tachycardia, hypotension, fatigue, desire to lie down and, rarely, syncope). Late dumping syndrome occurs one to three hours after food intake and are primarily manifestations of hypoglycaemia due to an incretin-driven hyperinsulinaemic response after carbohydrate ingestion. Hypoglycaemia-related symptoms are attributable to neuroglycopenia (which is indicated by fatigue, weakness, confusion, hunger and syncope) and to vagal and sympathetic activation (indicated by perspiration, palpitations, tremor and irritability). The more severe symptoms often occur as a side effect of surgical intervention [37].

Alcoholic beverages have been shown to reduce to reduce gastric emptying in several studies. Pure ethanol in concentrations of 4%, 10% and 40% (v/v) were reported to inhibit gastric emptying as did beer (500ml), red wine (200ml) and whisky (125ml) both in the presence and the absence of food [38, 39]. A similar study reported that beer (400ml), red wine (200ml) and whisky (100ml) as well as the ethanol equivalents of wine and whisky, but not beer, inhibited gastric emptying [40]. A small dose of a traditional Japanese plum liqueur (50ml, 14% ethanol) was also reported to inhibit gastric emptying [41].

White wine, consumed with the meal, reduced gastric emptying compared to tea following the consumption of a cheese fondue. An additional alcoholic beverage, 20 mL of cherry schnapps (40% ethanol) was served 90 minutes postprandially. The schnapps impacted on the gastric emptying rate of the tea group almost immediately but did affect the wine group. The delayed gastric emptying, elicited by the snaps, continued till the end of the session, circa another 150 minutes. This finding indicates that ingestion of an alcoholic beverage, even a long time after a meal, can still affect gastric emptying. Regarding the mechanism of activity, the authors suggested that the schnapps was stimulating receptors on the stomach wall [42]. To the contrary, I suggest that the effect of the schnapps is more likely a CPR because the mouth is empty whereas the stomach contained food, which would likely restrict alcohol's access to the receptors in the stomach wall. Therefore, I propose that alcoholic beverages stimulate oropharyngeal TRPV1 receptors eliciting vagal signalling that slows gastric emptying.

It has been reported that following a Nissen fundoplication, a patient experienced postprandial abdominal pain, bloating, nausea, vomiting and diarrhea, symptoms associated with dumping syndrome. At one-hour gastric emptying was 71%. Following the consumption of 240ml red wine before and during meals symptoms were resolved and gastric emptying was normalised to 23% [43, 44].

There are several commonly consumed types of cinnamon, but all contain the TRPA1 agonist cinnamaldehyde. A group of 14 young healthy adults received a high carbohydrate meal with or without 6g of powdered Cinnamomum cassia mixed in the food. In the cinnamon group gastric emptying was delayed and postprandial plasma glucose levels reduced. However, it is possible that only a subgroup of the participants was affected by the presence of cinnamon as the median gastric emptying rate was not greatly altered.

• Cinnamon group: median 34.5% (range: -29% to 74%; q1 7%, q3 52%).

• Placebo group: median 37.0% (range: 15 to 87%; q1 28.8%, q3 54%) [45].

In a follow-up study with 3g and 1.5g Cinnamomum cassia, the larger dose reduced postprandial serum insulin but gastric emptying was not affected by either dose [46]. Mixed in a high carbohydrate meal 6 g of powered Cinnamomum zeylanicum reduced postprandial plasma glucose levels, unfortunately gastric emptying was not measured [47]. In a glucose tolerance test, a 100ml infusion made with 6g Cinnamomum burmannii reduced postprandial plasma glucose levels in healthy volunteers [48]. In contrast, a similar infusion did not reduce postprandial plasma glucose in a group of type 2 diabetes [49].

When 3g of encapsulated Cinnamomum cassia was ingested with a high fat meal gastric emptying was not affected [50], nor did the intake of 6g encapsulated Cinnamomum zeylanicum affect glycaemic parameters [51]. Similarly, the ingestion of 1 g encapsulated concentrate (10:1) did not alter glycaemic parameters [52].

All three types of cinnamon contain a high level of the essential oil cinnamaldehyde [17] which stimulates TRPA1 as well as high levels of polyphenols [52] which stimulate the mechanoreceptors. Notably, polyphenols have been reported to have hypoglycemic activity [53]. While many plants contain high levels of polyphenols, cinnamaldehyde is specific for the Cinnamomum spp. The above findings suggest that cinnamaldehyde stimulates oropharyngeal TRPA1 receptors eliciting vagal signalling that slow gastric emptying, but possibly only in some individuals

6. Enhancing Gastric Emptying

Gastroparesis is a disorder due impaired gastric emptying and characterized by nausea, vomiting, early satiation, postprandial fullness, bloating, belching and upper abdominal pain. It occurs in functional dyspepsia [54], diabetics, neurodegenerative disorders such as Parkinson disease, myopathies, neoplastic syndromes and after gastrointestinal surgery [55].

Increased gastric emptying, has been reported to be elicited by peppermint oil derived from Mentha piperita [56]. Although peppermint oil contains menthol which is both a TRPA1 and TRPA8 agonist, it also possesses Ca2+ antagonistic properties which may be causing relaxation of the gastrointestinal GI smooth muscles [57]. So, the mechanism producing increased gastric emptying is unclear. Gingerols, found in ginger (Zingiber officinalis) are both TRPA1 and TRPV1 agonists. The intake of 1.2g encapsulated ginger also increased gastric emptying [58] as did a combination of ginger and globe artichoke (Cynara scolymus) [59]. Thus, it appears that the presence of essential oils in the stomach can increase gastric emptying.

Clinical trials using bitter herbs have been conducted with Parkison patients and diabetics, groups that suffer from gastroparesis i.e. delayed gastric emptying. Parkinson patients with mild gastrointestinal symptoms including appetite loss, nausea, vomiting, postprandial abdominal or epigastric pain, and bloating were administered a bitter herbal combination (Rikkunshito) for 3 months. At the end of the trial gastric emptying times were reduced ($p=0.03$) [60]. A review of 52 studies with 5472 patients concluded that this combination reduced dyspepsia symptoms and improved the rate of gastric emptying rate [61]. In a review of 10 studies concluded that, in diabetics suffering from gastroparesis, the bitter combination Xiangshaliujunzi Decoction could restore the gastric emptying rate and improve symptoms [62]. The positive effect of bitter tastants in gastroparesis likely stems from increased postprandial hyperaemia.

7. Discussion

There are indications that herbs, spices and alcoholic beverages may elicit CPRs which modulate the digestive processes. The studies presented demonstrate that some bitter agonists produce CPRs involving increases of both peripheral resistance and heart rate. The increase in peripheral resistance results from an increase in sympathetic signalling whereas the increase in heart rate can be attributed to vagal withdrawal. These cardiovascular responses could support postprandial hyperaemia both in the gastric and intestinal phases of digestion, thus supporting gastric accommodation and gastric emptying. The results from gastroparesis studies supports this concept however, the studies were not been designed to separate CPR from gastrointestinal responses. Although it may be inferred that agonists supporting postprandial hyperaemia improve gastric accommodation it has not been demonstrated.

The studies indicate that cinnamon and alcoholic beverages likely produce CPRs that slow gastric emptying presumably via vagal withdrawal. This conclusion is inferred by comparing various studies as none were designed to separate CPR from gastrointestinal responses. There is lack of information regarding peppermint oil but as it produces the same result as ginger capsules it appears to be acting in the gut rather than producing a CPR.

The groundbreaking advances in oropharyngeal receptor cell physiology over the last 20 years have established a functional basis which enables neural pathways to be mapped. Some CPRs are likely generated in the nucleus of the tractus solitarius of the medulla where the neurons of VI, VII, IX and X cranial nerves terminate near the efferent vagal nerves. While the 26 individual bitter afferents are completely or partially labelled-line, there is insufficient evidence to determine the transmission mode of the somatosensory system. This information would aid in determining the most appropriate application of agonists, including food.

Additionally, the findings indicate that some foods may be contradicted in various medical conditions. When reduced gastric emptying is suspected cinnamon and alcoholic beverages may be contraindicated

8. Conclusion

The concept that specific foods produce specific CPRs that modulate the digestive processes is novel in physiology. The above reports support the concept, but more target-orientated studies are necessary

to accept or reject or refine it. Yet, the concept is not new, the use of bitter and aromatic plants, both as drinks and in meals, to treat digestive problems is universal and ancient. Similarly, alcoholic beverages are consumed with meals because they are enjoyable – the learned behaviour that combines different foods for a positive hedonic eating experience.

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