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REVIEW ARTICLE

Popular Beverages Stimulate Oropharyngeal and Gut Receptors Eliciting Modulation of the Upper Digestive Processes

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ABSTRACT

This paper reports clinical studies on the effect of agonists of taste and chemethesis receptors in the oropharyngeal cavity and the gut. The peripheral nerve system plays a vital role in our selection or rejection of what we eat and drink. Although the degree to which it is hard-wired has not been determined, it is known that our food and drink choices change with age. Scientific studies on the impact of food and drink on the body have been concerned predominantly with nutritional factors and, more recently, impacts on cholesterol and blood sugar levels. On the other hand, the sensations we experience during eating and drinking have long been regarded, perhaps even dismissed, as purely hedonistic. The idea that foods and drinks may actually influence digestion is a novel one and is based on the discovery 20 years ago of taste buds, innervated by the vagi, in stomach and intestinal tissues. Studies indicate some of our most popular drinks modulate both postprandial hyperaemia and gastric emptying. It is proposed that the bitter taste experienced with some foods and drinks promotes increased blood flow to the splanchnic circulation and slows the flow of chyme to the small intestine. In cases of toxicity, these actions promote emesis whereas at non-toxic levels, bitter substances promote digestion by increasing postprandial hyperaemia and slowing gastric emptying. Additionally, chemethesis agonists can act on the oropharyngeal receptors resulting in a slower gastric emptying. These effects may lead to a learned behaviour and subsequent enjoyment of bitter tastants, rather than their rejection, amongst those with reduced digestive capacity. It provides a rationale for the popularity of certain bitter tasting aperitifs and digestive alcoholic beverages originating in southern Europe.

INTRODUCTION

This paper reviews studies that support the notion that the peripheral nerve system is involved in regulating the digestive processes. This perspective implies that activity in the enteric nerve system can be altered by food and drink choices. Studies with commonly consumed food items are presented demonstrating that the stimulation of oropharyngeal receptors influences gastro-intestinal hyperaemia and gastric emptying. It is proposed that the pleasure experienced from the ingestion of some foods and drinks - including wine, beer, coffee and bitter aperitifs - which modulate digestion may be a learned behaviour.

The novel idea that foods and drinks can influence digestion is based on the discovery 20 years ago of taste buds, innervated by the vagi, in stomach and intestinal tissues.[1] It supported by clinical studies on the effect of agonists of taste and chemethesis receptors in the oropharyngeal cavity and the gut. Some of our most popular drinks modulate both postprandial hyperaemia and gastric emptying. It is proposed that the bitter taste, at enjoyable levels, promotes increased blood flow to the splanchnic circulation and slows the flow of chyme to the small intestine. In excess, as in cases of toxicity, emesis is promoted.

In the oropharyngeal cavity two distinct perceptual systems coexist: taste and somato-sensory (chemesthesis). The taste system enables us to detect and differentiate between items that are: bitter, salty, sour, sweet or umami (savory). Chemesthesis is the global sensitivity of mucous membranes to a diverse range of chemicals and gives rise to perceptions of irritation, pungency, cooling, warmth or heat.[2]

Taste receptors are innervated by the VII (facial), IX (glossopharyngeal) and X (vagi) cranial nerves. The VII, IX and X afferent fibres synapse in the gustatory section of the rostral nucleus tractus solitarius – part of the medulla. Axons project to the parabrachial nucleus in the pons, onward to the ventral posterior nucleus and then to the gustatory cortex in the thalamus. Parallel axons project to the limbic forebrain areas associated with feeding and autonomic regulation. As well as signalling to the higher cortical taste centres, the VII, IX and X nerves also provide information used at the level of the nucleus tractus solitarius to stimulate the salivary glands and gaping (food rejection).[3] Additionally, numerous receptors for taste and chemesthesis have been located in stomach and small intestine tissues which are innervated by the vagi.[1]

One part of the somatosensory receptor system shares the VII and IX nerves while a second somatosensory system is innervated by the V (trigeminal) cranial nerve which projects to the pons The chemesthesis system also exists outside the oral cavity. Massage therapists commonly use analgesic creams; some use hot creams, while others use cold creams. Many may find these practises contradictory but not the "peripheral neurologists" among you. For readers not familiar with "peripheral neurology", the receptors in the somato-chemosensory system are polymodal. Analgesic creams, both cold and hot, elicit messaging that overwhelms signalling from the pain receptors. Although these creams are at room temperature, they contain pungent and/or aromatic substances that create the sensation of temperature. Menthol is commonly used in cold creams and chilli in hot creams. Menthol stimulates neurons giving the sensation of approximately 18-24 degrees Celsius, while Cayenne gives the sensation of approximately 43-52 degrees Celsius.[2]

Both natural and synthetic substances, which produce responses in the taste sensory system are known as *tastants*. Perceptions of substances by the somatosensory are more difficult to describe, at least in English, and relate more to sensation. The term *flavour* is used to describe the total sensation experienced, when either single or multiple substances are present in the oropharyngeal cavity. Contributions from the olfactory and somatosensory systems, as well as the oropharyngeal taste receptors, are integrated in the anterior ventral insula.[4]

An ingested meal has physical characteristics: volume, weight, and temperature. To accommodate the ingested mixture your muscular stomach wall fills with blood to allow for an expansion of volume, as well as to hold the weight of the mixture and bring it to body temperature. This is the gastric phase of digestion, a process involving increased blood flow to the stomach, pancreas, and duodenum that is referred to as *gastric hyperaemia*. Once accommodation has been achieved (about 15 minutes after ingestion has ceased) the intestinal phase of digestion begins. This involves both *intestinal hyperaemia* and *gastric emptying*. Intestinal hyperaemia is required for all metabolic activities involved in digestion, including the removal of nutrients from the small intestine.[5]

Gastric emptying - largely regulated by cholecystokinin (CCK) - is the process whereby the pylorus valve opens to allow a tiny amount of the ingested mixture to enter the duodenum. The mixture, now referred to as *chyme*, is acted on by digestive secretions from the small intestine, gallbladder, and pancreas. The secretions are

matched to the macronutrients of the chyme by local sensors. The two governing processes of digestion are postprandial hyperaemia and gastric emptying. While gastric emptying can be measured non-invasively, currently hyperaemia can only be measured invasively.

Investigating the effects of agonists on the digestive system is challenging as there are no established investigative models, leaving unresolved any number of considerations such as:

- Should investigations focus on *in vitro* or *in vivo* studies?
- Should human investigations focus on young healthy participants or those with digestive problems?
- Where is an agonist active – oral cavity, stomach, small intestine?
- During which postprandial state is an effect elicited?
- Is the agonist active only in the presence of a meal?
- Does the type or size of a meal affect response to an agonist?

Chemesthesis and gastric emptying

Cinnamon contains essential oils that are agonists for the chemethesis receptors. Cinnamaldehyde (the main constituent of cinnamon oil) stimulates TRPA1.[2] In a relatively well-known study, the effect of 6 g cinnamon on the digestion of 300 g rice pudding (16 g carbohydrate, 4 g fat, 3 g protein) was investigated in a healthy group aged 20-38 years.[6] When compared to the control, the inclusion of cinnamon reduced gastric emptying and blood glucose levels in the intestinal phase. Satiety was not affected. Notably, median values of gastric emptying were similar for both the test and control groups, suggesting it was only a subgroup that responded to cinnamon. (Note: The dose of 6 g is large and subsequent research used lower doses.[7])

When data from follow up studies (Table1) is examined it becomes clear that dosage form plays a significant role. For example, when cinnamon is consumed in capsules there are no effects on the parameters studied.[8-10] However, when cinnamon is consumed as a powder, gastric emptying is reduced, as are the parameters (insulin levels and blood glucose) influenced by the slowing of gastric emptying.[6,7,11] The one study using capsules that reported an effect for encapsulated cinnamon used the same data for analysis twice[8] and did not follow serial measurement recommendations.[12] The findings suggest that the effect of cinnamon on gastric emptying is due to the oral chemesthetic stimulation.

There is evidence that long-term encapsulated cinnamon administration does affect long-term blood sugar levels,[13,14] in ways which probably are unrelated to the chemethesis system. It would be interesting to test whether other TRPA1 agonists elicit the same responses as cinnamon.

Table 1. Gastric emptying and the agonist cinnamon.

Study – type and participant description	Meal (% marconutrients)	Test Substance + Form	Amount	T_{50}	T_{lag} or T_{peak}	GE time: (AUC)	Insulin Response	Plasma Glucose
Hlebowicz et. al. 2007,[6] controlled crossover, 14 normal young 6F + 8M	330 kcal, C58, L32, P10	Cinnamomum cassia; powder	6 g	-	-	↓ AUC 2h (<0.05)	-	↓ AUC 2h (<0.05)
Hlebowicz et. al. 2009,[7] controlled crossover, 15 normal young 6 F + 9M	330 kcal, C58, L32, P10	Cinnamomum cassia; powder	3 g 1 g	- -	- -	- -	↓ AUC 2h (<0.05) 0	0 0
Markey et. al. 2011[9] controlled crossover, 9 normal young 6F + 3M	632 kcal, C42, L46, P14	Cinnamomum zeylanicum; capsules	3g	0	0	0	-	0
Magistrelli and Chezem 2012,[11] young 24 F + 5 M; 15 normal, 14 obsese	Cereal, C 60 g, 470 mL water (≈ 240 kcal)	Cinnamomum zeylanicum; powder	6 g,	-	-	-	-	↓ AUC 2h (0.008)
Wickenberg et. al. 2012,[10] controlled crossover, impaired glucose tolerance 4 F + 6 M older	75 g oral glucose (≈ 300 kcal)	Cinnamomum zeylanicum; capsules	6g	-	-	-	0	0
Beejmohun et. al. 2014,[8] controlled crossover, 16 normal young to middle aged	≈ 200 kcal from 103 g white bread = C 50 g	Cinnamomum zeylanicum; 10:1 extract, capsules	1 g extract (10g powder)	-	-	-	0	↓ AUC 1h (<0.05) 0 AUC 2h (0.150) Peaks no difference

T_{50} = gastric emptying time for 50% of meal, T_{lag} = gastric emptying of 10% meal, T_{peak} = time to peak gastric emptying, GE = gastric emptying, AUC = area under the curve, F = female, M = male, C = carbohydrate, L = lipid/fat, P = protein, y = years old.

There are other dietary substances that also influence gastric emptying. Studies with alcoholic drinks indicate that ingestion of alcoholic beverages with meals slows down gastric emptying in healthy participants (Table2).[15-19] One study reported a decrease in gastric emptying when 20ml of snaps (also known as schnapps) comprising 40% ethanol was ingested 90 minutes after the meal was finished, with the impact on gastric emptying lasting at least 150 minutes.[17] At the time the snaps was ingested, the stomach was full of food whereas the mouth would have been empty. In the mouth, the snaps would have been in full contact with receptors as opposed to later when it was in the stomach mixed with food. The findings suggest that the effect of ethanol on gastric emptying is more likely due to the effect of alcohol on oropharyngeal receptors than on the stomach or intestinal receptors. The drinking of wine with meals has been recommended for the treatment of dumping syndrome,[20] to slow gastric emptying when it proceeds too quickly.

Table 2. Gastric emptying and the agonist alcohol.

Study – type and participant description	**Meal (% marconutrients)**	**Test Substance + Form**	**Amount**	**T_{50}**	**T_{lag} or T_{peak}**	**GE time: (AUC)**
Franke et. al. 2004,[16] controlled crossover, 10 normal young	. - - - + 125 mL water + 125 mL water - -	Ethanol 4% Beer ≈ 4% ethanol Ethanol 10% Red wine ≈ 10% ethanol Ethanol 40% Whisky ≈ 40% ethanol 5.5% (w/v) glucose 11.4% (w/v) glucose	500 mL 500 mL 500 mL 500 mL 125 mL 125 mL 500 mL 500 mL	↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05)	- - - - - - - -	- - - - - - - -
Franke et. al. 2005,[15] controlled crossover, 8 normal young M for each meal	1) 270 kcal; C25g, L12g, P17g 2) 780 kcal; C55g, L38g, P46g 1) 270 kcal; C25g, L12g, P17g 2) 780 kcal; C55g, L38g, P46g 1) 270 kcal; C25g, L12g, P17g 2) 780 kcal; C55g, L38g, P46g 1) 270 kcal; C25g, L12g, P17g 2) 780 kcal; C55g, L38g, P46g 1) 270 kcal; C25g, L12g, P17g 2) 780 kcal; C55g, L38g, P46g 1) 270 kcal; C25g, L12g, P17g 2) 780 kcal; C55g, L38g, P46g	Ethanol 4% Beer ≈ 4% ethanol Ethanol 10% Red wine ≈ 10% ethanol 5.5% (w/v) glucose 11.4% (w/v) glucose	300 mL 300 mL 300 mL 300 mL	↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05)	0 0 0 0 0 0 0 0 ↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05)	- - - - - - - -
Heinrich et. al. 2010[17] controlled crossover; 20 young to older, 6F + 14M	780 kcal; C2g; L52g; P32g	Tea (control) White wine 13% Water (control) Snaps (40%)	300 mL 300 mL 20 mL 20 mL	- -	- -	↑ (<0.001) ↑ (<0.075)
Kasicka-Jonderko et. al. 2013,[18] controlled (an isotonic glucose solution) crossover 12 healthy young Beer 9F + 3M, Red wine 7F + 5M, Whisky 8F + 4M	355 kcal; C43g, L17g, P16g	Beer 4.7% Ethanol 4.7% Red wine 13.7% Ethanol 13.7% Whisky 43.5% Ethanol 43.5%	400 mL 200 mL 100 mL	↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01)	↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01)	- - - - - -
Kasicka-Jonderko et. al. 2014,[19] controlled (an isotonic glucose solution) crossover 24 young healthy non-drinkers (< 2 drinks per month)	355 kcal; C43g, L17g, P16g	Beer 4.7% Ethanol 4.7% Red wine 13.7% Ethanol 13.7% Whisky 43.5% Ethanol 43.5%	400 mL 200 mL 100 mL	- - - - - -	↑ (<0.01) 0 ↑ (<0.01) ↑ (<0.01) ↑ (<0.01) ↑ (<0.01)	- - - - - -

T_{50} = gastric emptying time for 50% of meal, T_{lag} = gastric emptying of 10% meal, T_{peak} = time to peak gastric emptying, GE = gastric emptying, AUC = area under the curve, F = female, M = male, C = carbohydrate, L = lipid/fat, P = protein, y = years old.

Bitter tastants and postprandial hyperaemia

Adequate postprandial hyperaemia is necessary for gastric emptying to function. Increases of blood flow in the postprandial splanchnic circulation require a systemic circulatory response to maintain adequate systemic circulation. Normally this response is an increase in heart rate.[21,22] When the response is insufficient, as in some elderly or diabetic populations, the systemic blood volume is inadequate resulting in problems ranging from nausea, dizziness, heart palpitations and fainting, through to stroke and heart attack.[23] Fear of these conditions amongst those prone to them can lead to nervousness when eating and even food avoidance. Two bitter herbs traditionally used to support digestion - wormwood (*Artemisia absinthium herba* Linn.) and gentian (*Gentiana lutea radix*, Linn.) - have been shown to increase vascular peripheral resistance in the small arteries and arterioles.[24] An increase in peripheral resistance supports the postprandial increase in the systemic circulation and decreases demands on the heart. The increase in peripheral resistance does not lead to hypertension, as increases in blood pressure are modulated by the baroreflex. This response is due to oropharyngeal stimulation, as capsules had no effect on peripheral resistance.

In studies with combinations of Chinese herbs administered as bitter tasting teas, symptoms due to gastroparesis (reduced gastric emptying) were lessened.[25-27] This symptom improvement was attributed to improved gastric emptying, possibly due to increased peripheral resistance and leading to an enhanced postprandial hyperaemia.

Humans have 25 different bitter receptors (TAS2Rs) and in nature there are estimated to be tens of thousands of bitter tasting substances. Not all bitter tastants stimulate the same bitter receptors. Bitter agonists have been tested *in vitro* with the 25 different bitter receptors.[28] Our knowledge base is largely limited to commercially available agonists and although some testing of traditional bitter herbal remedies has begun[29,30] there is still much to be discovered. Some agonists stimulate only one TAS2R, while others can stimulate as many as eight.[28] Regular coffee contains a range of bitter taste substances including caffeine, quinides (lactones) and mozambioside (a glycoside). Quinides, formed during roasting of the beans, are primarily responsible for roasted coffee's bitterness.[31] While it is known that caffeine stimulates five of the 25 TAS2Rs (7, 10, 14, 43, 46), it is not known which receptors are stimulated by the quinides.[28] Mozambioside is a glycoside found only in Arabica coffee. Unlike quinides, its content decreases as roasting increases.[32] TAS2R43 and TAS2R46 responded to mozambioside with much higher sensitivity than to caffeine, as it did for the related bitter substances bengalensol, cafestol and kahweol.[33]

Coffee and caffeine

Both regular coffee, and decaffeinated coffee with added caffeine, increase heart rate whereas decaffeinated does not.[34,35] In these studies the effect of regular coffee on heart rate lasted at least 30 minutes and may be based on vagal withdrawal rather than a generalised sympathetic activation, as the vascular system parameters were not affected. The fact that different bitter agonists elicit different cardiovascular changes indicates that neural transmission from the oropharyngeal cavity to the medulla is partly or completely label-lined.[36]

The ingestion of caffeine capsules stimulates caffeine TAS2R receptors in the stomach, but it is not known which of the TAS2Rs. Upon opening, caffeine capsules increase diastolic pressure, though the effect is short lived as caffeine is quickly absorbed.[34] This is notable because although caffeine in the mouth elicited prolonged increases in heart rate, caffeine in the stomach elicited short-lived increases in diastolic blood pressure. It is yet to be determined whether this is because different TAS2Rs are stimulated in different tissues or because the vagi signals arriving from the stomach at the medulla are treated differently from those arriving from the oropharyngeal cavity.

There are other complexities to grapple with, such as our understanding of the role of TAS2Rs in the stomach. The increase in diastolic pressure observed for caffeine capsules was not observed when either regular coffee or decaffeinated coffee with caffeine was ingested. This was not due to the dilution of caffeine as the amount of fluid ingested was the same, although the water drunk with the caffeine capsules was at room temperature but hot for the coffee drinks. It is unclear whether this is due to interactions at the receptor level in the stomach or at the medulla or higher structures.

Yet another complexity relates to the mechanism/s by which caffeine elicits increases in gastric acid. Caffeine capsules opening in the stomach elicit gastric acid secretion. However, when caffeine is administered orally the release of gastric acid is delayed, indicating a vagal intervention in the physiological processes of the stomach tissue.[37] It was suggested that this may be due to caffeine eliciting vagal withdrawal, as previously proposed when it was reported that the taste of caffeine increased heart rate without influencing vascular parameters.[35] It was also reported that blocking the

bitter taste of caffeine with homoeriodictyol, an inhibitor of caffeine's bitter taste, reduced gastric acid secretion.[37]

As already noted, CCK plays a major role in controlling the rate of gastric emptying. It stimulates the production of pancreatic enzymes and the release of bile. CCK also relaxes the Sphincter of Oddi allowing pancreatic juices and bile to enter the duodenum.[38] Drinking a cup of filtered regular coffee increases CCK 10 minutes after ingestion, i.e. during the gastric phase, and levels remain elevated for another 30 minutes.[39] This time frame is similar to increases in heart rate following the ingestion of both regular coffee and decaffeinated coffee with added caffeine.[35] As the increase in CCK occurs during the gastric phase, i.e. before the coffee has reached the duodenum from where CCK is secreted in response to chyme, it suggests that the increases in CCK are likely the result of oropharyngeal stimulation. Similarly, mental arousal increases have been reported in the period 10 to 30 minutes after drinking caffeinated coffee, but only at 10 minutes after drinking decaffeinated coffee.[40] The time line of responses elicited by decaffeinated coffee is similar to the time line of responses elicited by hot water.[41] The magnitude of increases in plasma CCK after drinking regular coffee is similar to the increase experienced following a light meal.[42] Decaffeinated coffee also elevated CCK, but only 30 minutes post-ingestion, indicating that bitter substances other than caffeine are eliciting responses when present in the gut.

The effect of coffee on gastric emptying is controversial (Table 3).[43-46] Although a recent review concluded that coffee does not affect gastric emptying[47] one study may have been incorrectly evaluated, on the basis of the original authors having referred to the "control condition" as "baseline". The authors stated "we conclude that coffee accelerates liquid-phase gastric emptying in the majority of patients with non-ulcer dyspepsia".[45] The study was robust, having 95 participants in a controlled crossover design and contrasts with other studies, with only 10-15 participants, that report no effect of coffee on gastric emptying.[44,46,48] Yet another study, using 10 young males, reported that coffee increased gastric emptying.[43] Further support for the concept that coffee increases CCK is the observation that coffee increases gallbladder secretions,[39] one of the actions of CCK.

Table 3. Gastric emptying and the agonists coffee and caffeine.

Study – type and participant description	Meal (% marconutrients)	Test Substance + Form	Amount	T_{50}	T_{lag} or T_{peak}	GE time: (AUC)	Plasma Glucose
Akimoto et. al. 2009,[43] controlled crossover, 10 normal young M	200 kcal, 200 mL liquid meal (milk)	Black coffee	190 mL	↓(<0.05)	↓(<0.05)	-	-
Boekema et. al. 2000,[44] controlled crossover, 12 healthy	400 kcal, liquid meal	Instant coffee 180 mg caffeine	280 mL 15 g	0	0	-	-
Lien et. al. 1995,[45] controlled crossover, 95 non-ulcer dyspepsia	100 kcal, 500 mL 5% glucose solution	Instant coffee	4 g	-	↓ (<0.01)	-	-
Schubert et. al. 2014,[46] controlled crossover, 12 normal young to middle aged 9F + 3M	400 kcal, C 48 g, L17 g, P 15 g	Decaffeinated coffee,	225 mL	0	0	0	0
		Caffeine capsule (4mg/kg)	262 ± 33 mg	0	0	0	0
		Decaffeinated coffee + Caffeine capsule	225 mL + 262 ± 33 mg	0	0	0	0

T_{50} = gastric emptying time for 50% of meal, T_{lag} = gastric emptying of 10% meal, T_{peak} = time to peak gastric emptying, GE = gastric emptying, AUC = area under the curve, F = female, M = male, C = carbohydrate L = lipid/fat, P = protein, y = years old.

This presents us with a physiological discrepancy: elevated CCK would be expected to reduce gastric emptying, yet evidence suggests that coffee either increases or does not affect gastric emptying. It appears that plasma CCK elicited by oropharyngeal receptors does not impact stomach activity in the same manner as paracrine CCK produced in the duodenum.

In investigations with caffeine/coffee and the peripheral nerve system it is important to dose at safe levels as coffee elicits increases in CCK, which at high levels is regarded as a "panicogenic agent".[49,50] Single caffeine doses above 250 mg

may produce caffeine intoxication (caffeinism) with symptoms including nervousness, restlessness and facial flushing,[51] while single doses of 400 mg or more may produce anxiety.[52]

A potential confounding element in coffee/caffeine studies is that elevated CCK can occur when intestinal parasites are present. In cases of intestinal infection, such as Giardia lamblia, it has been reported that CCK levels are elevated both pre (~2x) and postprandial (~4x). These high levels of CCK may be responsible for the reported symptoms of nausea and abdominal discomfort following meals, in addition to being part of a defensive reaction against intestinal parasite infection (elevated CCK levels decrease bacterial translocation and increase IgA secretion).[42]

Bitter tastants and gastric emptying

The classical view is that the capacity to detect bitter taste evolved primarily to signal the presence of toxins and warn against their consumption.[53] This view does not withstand scrutiny, at least for humankind, because the world's most widely consumed drinks - beer, coffee, tea, and wine - all taste bitter, as do many popular vegetables including globe artichoke, lettuce, and okra. Rather, the response to bitters is related to the type of bitter or the intensity of the experience with high intakes producing nausea.[54] Bitter tastants at levels commonly consumed in our foods and drinks are hedonistically pleasing.

In the oropharyngeal cavity, the role of taste receptors is to accept or reject the ingestion of food. However, in the gut, the role of TAS2Rs is associated with allowing digestion of ingested food to proceed or stopping digestion and ejecting the food already ingested (emesis). Emesis, like the digestive process, requires increased levels of blood flow to the muscular walls of the stomach. Increased gastric emptying allows toxins into the small intestine more quickly, whereas decreased gastric emptying retains toxins in the stomach for a longer period, thereby allowing either for a slower digestion or promoting the emesis process – both of which can be considered defensive. It is suggested that bitter tastants in limited amounts improve digestion, because they support hyperaemia, but in large amounts they create a much greater hyperaemia, the consequence of which is to provide the blood flow required for emesis.

In the few clinical studies into the effect of bitter tastants on gastric emptying,[53] the common model measures acute change following intragastric or intraduodenal delivery. The following bitters (Table 4) did not affect gastric opening when administered in the gut: denatonium,[55] naringin[56] and quinine hydrochloride.[56-58] In contrast, when the bitter tastant, quinine sulphate, was orally administered (sham feeding) it slowed gastric emptying when compared to the control (strawberry taste).[59] More recently, when 600 mg quinine hydrochloride was administered to either the stomach or the duodenum, both modes of administration reduced both gastric emptying and plasma glucose while increasing plasma insulin.[60] When administered in the stomach, the agonist came in contact with both stomach and duodenal receptors, whereas when administered in the duodenum it had contact only with the duodenal receptors. This finding suggests bitter tastants elicit changes in the gastric emptying in the duodenum rather than the stomach. This is consistent with the finding that bitter receptors occur in greater density in the duodenum than the stomach.[1] In the only long-term study (12 weeks) with bitter herbs and Parkinson's patients suffering from gastroparesis, gastric emptying time decreased.[27] This is likely due to improved postprandial hyperaemia rather than CCK modulation. That the opposite effect occurs in pathologies demonstrates a conundrum for researchers: whether to test the healthy or test the pathological?

Table 4. Gastric emptying and bitter tasting agonists.

Study – type and participant description	Meal (% marconutrients)	Test Substance + Form	Amount	T_{50}	T_{lag} or T_{peak}	GE time: (AUC)	Insulin Response	Plasma Glucose
Wicks et. al. 2005,[59] controlled crossover; 16 normal young F	400 mL, soup at 47°C, osmolality 204 mosm/kg	Quinine sulphate Oral – sham feeding	10 mg	↑ (<0.05)	-	-	-	-
Little et. al. 2009,[56] controlled crossover 12 healthy, age 19–60 y, blended F&M	500 mL water 500 mL water	Naringin, IG Quinine hydrochloride, IG	1 mM 0.198 mM	- -	- -	0 0	- -	- -

Doi et. al. 2014[27]– 22 pre/post; Parkinson's patients 9 F + 11 M	200 kcal, 200 mL liquid meal	RKT – bitter tastant, powder	15, g/day 12 weeks	-	↓(<0.05)	-	-	-
Andreozzi et. al. 2015[57] controlled crossover Healthy, 4F, 4M	480cal, 100 mL water C53, L31, P19	Quinine hydrochloride acid-resistant capsule	18 mg	-	-	0	-	-
Deloose et. al. 2017,[55] controlled crossover 6F, age: 31 ± 6 y; BMI: 23 2	2 pancakes (500 kcal)	Denatonium benzoate, IG	1 mmol DB/kg body weight,	-	-	0	-	-
Bitarafan et. al. 2020,[58] controlled crossover a) Healthy 15M age 26 ± 2 y b) Healthy 12M age 26 ± 2 y	a) mixed-nutrient drink 500 kcal, C74, L15, P18 25 b) buffet meal	Quinine hydrochloride, IG Quinine hydrochloride, IG	275 mg 600 mg 275 mg 600 mg	- - - -	- - - -	0 0 0 0	↑ (<0.05) ↑ (<0.05) ↑ (<0.05) ↑ (<0.05)	↓(<0.05) ↓(<0.05) ↓(<0.05) ↓(<0.05)
Rose et. al. 2021,[60] controlled crossover Healthy 14M age		Quinine hydrochloride, ID and IG	ID 600 mg IG 600 mg	- -	- -	↓ (<0.01) ↓ (<0.01)	↑ (<0.05) ↑ (<0.05)	↓ (<0.01) ↓ (<0.01)

T_{50} = gastric emptying time for 50% of meal, T_{lag} = gastric emptying of 10% meal, T_{peak} = time to peak gastric emptying, GE= gastric emptying, AUC = area under the curve, F = female, M = male, C = carbohydrate, L = lipid/fat, P = protein, ID = intraduodenal, IG = intragastric, y = years old.

Several clinical studies have reported increases in CCK plasma levels following the intake of encapsulated bitter tastants. In a crossover design, quinine hydrochloride delivered in intra-duodenal release capsule form elicited increases in CCK compared to control.[57] Also, in another crossover design, a hops concentrate designed to open either in the stomach or duodenum elicited increases in CCK compared to a control.[61] Other studies with intraduodenal infusions of bitter tastants reported no change in CCK. [58,62]

CONCLUSION

There is sufficient evidence that some substances can stimulate receptors in the oropharyngeal cavity, influencing the digestive processes of postprandial hyperaemia and gastric emptying. Thus, in addition to possessing hedonistic qualities, some foods and drinks elicit physiological effects, via the peripheral nerve system, which modulate the enteric nerve system. Similar receptors in the gut modulate postprandial hyperaemia and gastric emptying, as well as preparing the stomach muscles for emesis. Although these actions promote emesis at toxic levels, at non-toxic levels bitter substances promote digestion by increasing postprandial hyperaemia and slowing gastric emptying. Chemethesis agonists can also act on oropharyngeal receptors resulting in a slower gastric emptying, but whether they influence postprandial hyperaemia is unknown.

In southern Europe there is widespread use of aperitif and digestive alcoholic drinks, based on bitter and aromatic herbs, to support digestion. This suggests that the intake of bitter and aromatic substances to improve digestion may be a learned behaviour, at least among those with poor digestion. To date, clinical research in this area is limited and sometimes focussed on isolated substances. But there is scope for much broader investigations into areas such as substance interactions for example, following ingestion of the classic after-dinner drink the *Irish coffee* containing coffee, Irish whisky, sugar and cream.

This paper has focused on clinical trials related to postprandial hyperaemia and gastric emptying. There is a further body of literature which is beyond the scope of this article e.g., research concerning caffeine,[47] alcohol[20] and bitter tastants,[63] which the reader may find of interest.

Conflict of interest

The author has no conflicts of interest to declare.

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