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Bitter tastants alter gastric-phase postprandial haemodynamics

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ABSTRACT

Ethnopharmacological relevance: Since Greco-Roman times bitter tastants have been used in Europe to treat digestive disorders, yet no pharmacological mechanism has been identified which can account for this practice. This study investigates whether the bitter tastants, gentian root (*Gentian lutea* L.) and wormwood herb (*Artemisia absinthium* L.), stimulate cephalic and/or gut receptors to alter postprandial haemodynamics during the gastric-phase of digestion.
Materials and methods: Normal participants ingested (1) 100 mL water plus capsules containing either cellulose (placebo-control) or 1000 mg of each tastant ($n=14$); or (2) 100 mL of water flavoured with 500 or 1500 mg of each tastant (a) gentian ($n=12$) and (b) wormwood ($n=12$). A single beat-to-beat cardiovascular recording was obtained for the entire session. Pre/post-ingestion contrasts with the control were analysed for (1) the encapsulated tastants, in the "10 to 15" minute post-ingestion period, and (2) the flavoured water in the "5 to 10" minute post-ingestion period.
Results: Water, the placebo-control, increased cardiac contraction force and blood pressure notwithstanding heart rate decreases. Encapsulated tastants did not further alter postprandial haemodynamics. In contrast gentian (500 and 1500 mg) and wormwood (1500 mg) flavoured water elicited increased peripheral vascular resistance and decreased cardiac output, primarily by reducing stroke volume rather than heart rate.
Conclusions: Drinking 100 mL water elicits a pressor effect during the gastric-phase of digestion due to increased cardiac contraction force. The addition of bitter tastants to water elicits an additional and parallel pressor effect due to increased peripheral vascular resistance; yet the extent of the post-prandial blood pressure increases are unchanged, presumably due to baroreflex buffering. The vascular response elicited by bitter tastants can be categorised as a sympathetically-mediated cephalic-phase response. A possible mechanism by which bitter tastants could positively influence digestion is altering gastric-phase postprandial haemodynamics and supporting postprandial hyperaemia.

1. Introduction

Prior to the modern era of medicine, fluid preparations derived from bitter tasting plants were regularly "given to promote appetite and thus to aid digestion" (Douthwaite, 1963). Today, the treatment of digestive disorders with bitter tastants continues in both traditional medicine systems of eastern and southern Asia (Chang-Liao et al., 2011; Williamson, 2002) and modern European phytotherapy (Knoss and Stolte, 2009b; Koch, 2009b; Schulz et al., 2004). However, despite their widespread usage, the pharmacological activity of bitter tastants has as yet to be either scientifically investigated (Laurence et al., 1997) or clinically studied (Heinrich et al., 2012).

1.1. Bitter tastant theories

Although the pharmacological mechanism by which bitter tastants impact digestion is unknown, pharmacologists have acknowledged that the mechanism is likely to be chemosensory. There are two principal and one less well known hypothesis:

(1) The **cephalic-response** model (i.e. responses originating from the head) proposes that with intake of bitter tastants "the appetite is sharpened because the gustatory nerves are stimulated; this reflexively leads to dilation of the gastric vessels and to an increase in the gastric and salivary secretions" (Hale White, 1892). This hypothesis drew support from Pavlov's

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research on the autonomic nerve system (Hale-White, 1920). A more modern account of this hypothesis is that "bitter stimuli pass primarily by way of the glossopharyngeal nerve to a special group of cells in the cerebral cortex. The taste is interpreted there as bitter, and causes stimuli to be forwarded through the vagus nerve to both the salivary gland and the stomach …. This stimulation of the digestive processes enhances the appetite" (Robbers and Tyler, 1999). The cephalic-response model is supported in the European Medical Agency's Assessment Report on gentian which states: "it is fact that the bitter constituents stimulate the gustatory nerves in the mouth and give rise to an increase in the secretion of gastric fluid and bile" (Knoss and Stolte, 2009a). Notably the modern view (Mills and Bone, 2000; Sandberg and Corrigan, 2001; van Wyk and Wink, 2004) focuses entirely on the vagal stimulation of gastric secretions and excludes the circulatory component that was suggested a century before by Hale White. Some pharmacologists have suggested that earlier work (Glatzel, 1968) indicates that "bitter principles act reflexively on the cardiovascular system causing a decrease of in heart rate and cardiac stroke volume" (Schulz et al., 2004). However, the statistical analysis upon which this concept is based has been shown to be faulty, and there is no evidence from cardiovascular research indicating that bitter tastants increase vagal tone (McMullen, 2013).

(2) The **local-response** model proposes that bitter tastants "act directly on the mucosa of the upper part of the gastrointestinal tract and especially on the bitter receptors of the tongue stimulating the release of saliva and gastric juices" (Heinrich et al., 2012). This hypothesis is supported by recent observations that bitter, sour, sweet and umami taste receptor cells are present in the stomach, duodenum, jejunum, ileum and colon of rats (Horn, 2008). Some proponents of the cephalic-response model accept that local stimulation augments cephalic-elicited vagal stimulation (Hale White, 1892; Knoss and Stolte, 2009a; Robbers and Tyler, 1999). In contrast, other proponents of the cephalic-response model maintain that there is insufficient evidence that local stimulation produces effects and that if bitter tastants are to be effective "they must be tasted" (Mills and Bone, 2000).

(3) Weiss hypothesised that bitter tastants also elicit **sympathetic stimulation.** Similarly to Hale White (1892) he proposed that "the appetite-inducing action of bitters is probably due to improved circulation in the abdominal organs" (Weiss, 1988). Furthermore he proposed that the general tonic action of bitter tastants was due to repeated stimulation of the sympathetic nervous system by bitter tastants.

A key reason for the lack of research on the mechanisms of bitter tastants is the lack of investigative tools for assessing digestive activity. While it is well accepted that cephalic-phase responses modulate the production of digestive secretions via the efferent branch of the vagus nerve (Zafra et al., 2006), techniques to measure digestive secretions are not routinely available for researchers (Furness, 2006).

1.2. Postprandial hyperaemia

The development of precise cardiac stroke volume measurement in the 1980s stimulated studies on the cardiovascular response to eating in dogs. The findings indicated that the cardiovascular system responded to the challenge of food intake in two distinct phases (Chou and Coatney, 1994). Similar phases have subsequently been reported for humans (Harthoorn and DransWeld, 2008; Someya et al., 2008). The first phase of digestion, the gastric-phase, begins with the intake of food and/or drink and continues for 10 to 20 min after intake has ceased. During this phase increases of celiac blood flow and velocity are accompanied by a decrease of celiac vascular resistance. Systemically these changes are accompanied by increases of heart rate, cardiac output and systemic blood pressure. During the second phase of digestion, the intestinal-phase, similar changes occur in the superior mesenteric arteries as occurred for celiac artery during the gastric-phase. Systemically, there are smaller heart rate increases, decreases in mean and diastolic blood pressure and reductions in skeletal muscle blood flow (Someya et al., 2008).

The increased splanchnic blood circulation during digestion is referred to as postprandial hyperaemia. Postprandial hyperaemia facilitates gastrointestinal motor and secretory activity as well as the absorption and removal of digested substances (Hall, 2011). Crucially, postprandial hyperaemia requires compensatory postprandial sympathetic activation, namely increased cardiac activity, to preserve systemic blood pressure levels (Sidery and Macdonald, 1994; van Baak, 2008). Inadequate postprandial hyperaemia is associated with digestive problems (Mensink et al., 2011) and systemically with postprandial hypotension (Brignole et al., 2001). Postprandial hypotension is an independent predictor of mortality and may trigger syncope, falls, strokes, transient ischaemic attacks, angina and myocardial infarctions (Luciano et al., 2010).

This study investigates whether bitter tastants stimulate cephalic and/or gut receptors to alter haemodynamics (i.e. cardiovascular activity) during the gastric-phase of digestion. *Gentiana lutea radix* L. Fam. Gentianaceae (gentian) and *Artemisia absinthium herba* L. Fam. Asteraceae (wormwood) were chosen for this study because both plants

1) are well-known for their bitter taste (Sweetman, 2002);
2) serve as standards in research on bitter tastants (Olivier and van Wyk, 2013);
3) are used in Mediterranean cultures to flavour alcoholic beverages, known as aperitifs, which are traditionally taken to stimulate the appetite (Bruneton, 1999) i.e. they are part of the "Mediterranean diet";
4) contain compounds known to stimulate multiple cephalic bitter taste receptor cells. Gentian contains the secoiridoid glycoside amarogentin, which stimulates the human taste receptors (*h*TAS2Rs) 1, 4, 39, 43, 46, 47 and 50, while wormwood contains the sesquiterpene absinthin, which stimulates the *h*TAS2Rs 10, 14, 46 and 47 and thujone, a compound found in the essential oil of wormwood, which stimulates *h*TAS2Rs 9 and 14 (Meyerhof et al., 2010). Gentian also contains numerous other secoiridoid glycosides which are known to taste bitter, as well as bitter carbohydrates (Knoss and Stolte, 2009a). Similarly, wormwood contains numerous compounds regarded as bitter tasting, particularly the sesquiterpenes (Koch, 2009a), although some of these sesquiterpenes appear to be *h*TAS2R46 partial agonists or antagonists (Brockhoff et al., 2011);
5) have similar bitterness indexes: gentian, 10,000 to 30,000 and wormwood, 10,000 to 25,000 (Wagner and Bladt, 2001).

2. Methods

This investigation was approved by the University of Westminster Ethics Committee (03/04–08) and conforms to the principles outlined by the Declaration of Helsinki. Written informed consent was obtained from the participants, who were volunteers recruited from the staff, students and associates of the University of Westminster, London. Hypertensive individuals (systolic pressure >140 mmHg or diastolic pressure >90 mmHg), smokers,

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