Herbal bitters: their role in appetite regulation, blood glucose management, and obesity.
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Summary: Bitter herbs have a well-deserved reputation as digestive aids in most systems of traditional medicine, and in many systems of cuisine. The ability of bitters to support balanced secretion and motility, especially in the gastric phase of digestion, relies on a few important mechanisms that are mediated through taste receptors (T2R family) and involve neuronal, hormonal, and vascular effectors. New research is uncovering additional interesting facts about bitter tasting herbs: first, not all bitter flavors are alike, and a certain degree of variability exists in their effects and spheres of action. Second, additional mechanisms involving adipose tissue, inflammatory mediators, the microbiome, and hepatic glucose balance reinforce the idea that certain bitter herbs may be one of the best strategies for the management of blood sugar and lipid imbalances, the regulation of appetite, and the reversal of the metabolic syndrome.

Background: bitter taste receptors: traditional and modern understanding

The current understanding of our ability to sense taste transcends the classical notions that specific areas on the tongue correspond to specific flavors, or that taste perception is indeed localized to the tongue. Wolfgang Meyerhof studies molecular genetics at the German Institute of Human Nutrition and has provided extensive research into the structure, coding sequences, and function of bitter taste receptors (TAS2Rs, aka T2Rs, a family of G-protein coupled receptors). Some interesting points include the facts that T2Rs present numerous different isoforms, able to sense over 100 different bitter tastants and their combinations[1]; they relay information from the tongue to the nucleus tractus solitarius (medulla) and from there to the hypothalamus using proteins such as alpha-gustducin; and participate in parasympathetic activities such as increased oral and gastric secretions[2]. More recent research by Meyerhof and others indicates that, unlike most stimulus/receptor pairs in human physiology, the expression of T2Rs increases (to a point) the more stimulus is presented: that is, the more we taste bitter, the more we are able to experience its effects[3]. What we may, in fact, be noticing is that the human physiology *under*expresses T2Rs until an adequate amount of bitter stimulus is present, at which point a "normal" level of expression is achieved.

Perhaps more interestingly when we consider the inflammatory nature of chronic disease, especially the metabolic syndrome, emerging research is indicating that high levels of pro-inflammatory compounds also serve to *over*express T2Rs, leading to a highly aversive response to even small amounts of the bitter flavor[4]. Taste-sensitive cells throughout the body have highly tuned TNF receptors (tumor necrosis factor, a pro-inflammatory compound).
Reducing inflammatory load seems to reduce bitter taste receptor expression, which is of interest when we consider that the effects of phytochemicals associated with bitter taste often are anti-inflammatory.

The neuronal feedback elicited by T2R stimulation (via cranial nerves VII-fascial, IX-glossopharyngeal and X-vagus) helps control the cephalic and gastric phases of digestion, coordinating secretion and motility by increasing the former and decreasing the latter. This process has been extensively studied and is well-reviewed by Catia Sternini[5]. The net result is

improved molecular breakdown of macronutrients in the chyme that enters the intestinal phase of digestion, as well as slower delivery of those digested products. This underlies the traditional indications for digestive bitters: dyspepsia, indigestion and reflux, gas and bloating. But the slower delivery of metabolized carbohydrates to the small intestine also has a role to play in post-prandial (after-meal) glycemia.

It has been clear for some time that T2R stimulation modulates levels of hormones associated with appetite: ghrelin, a hunger hormone, increases at first. But reduced gastric motility leads to a feeling of fullness, and this, coupled with increased levels of hormones associated with satiety (fullness) such as peptide YY (PYY) and glucagon-like-protein 1 (GLP-1), leads to less caloric intake overall[6]. The modulation of these hormones was long thought to be connected to neuronal reflexes, but emerging research shows that the taste cells themselves function as enteroendocrine cells, are present throughout the GI tract, and secrete appreciable levels of their own hormones into the gastrointestinal circulation. Bitter-tasting substances can harness these enteroendocrine cells and contribute to local secretions that affect absorption, appetite, and the metabolism of fat and carbohydrates[7,8]. Thus, bitters may act directly as endocrine triggers, not requiring intervention by the central nervous system.

Another fascinating result of experimental research underscores yet another effect of herbal bitters. A recent review article by Julie Whitehouse and others[9], lends evidence to the hypothesis that certain bitters (particularly the more strongly-flavored, classic "eupeptic" herbs gentian and wormwood) increase blood flow to the GI tract. This post-prandial hyperemia is achieved, interestingly, via peripheral vasoconstriction and localized (mediated by enteroendocrine cells again) vasodilation. The overall shifting of circulatory volume can act as a negative cardiac chronotrope and inotrope (reducing frequency and strength of heart muscle contractions), and is most likely the reason (rather than increased tone along the vagus nerve) why this phenomenon has been observed after the consumption of bitters. Practically speaking, this suggests that herbal bitters should include at least one of these classic "eupeptics" for maximal effect - for not all bitter tastants elicit the same effects, and not all reduce ingestion of calories equally, as Lindsay Schier observed[10]. Additionally, Whitehouse notes that the vascular shift is almost instantaneous (within 5 minutes) after T2Rs in the tongue are stimulated by strong bitter flavors. This implies that one can take bitters before, during, or even after a meal and that the effects can still be beneficial (consuming them 10-15 minutes before eating is not necessary).

Clinical implications: Appetite, glycemia, lipidemia, hypertension and the metabolic syndrome

It appears that our ability to detect and respond to bitter tastants such as those found in bitter herbs is variable, and connected to the internal and external environment. This is the first step in realizing their therapeutic potential: as we age, the expression of T2Rs decreases naturally, and sometimes (in the absence of any bitter stimulus) appears to decrease beyond "normal" expression. This "normal" level can, however, be restored by applying regular bitter taste stimuli. The "bitter deficiency syndrome" hypothesized by James Green in The Male Herbal (J. Green, 2007) has indeed been documented. Women[11] and children[12] have much lower levels of obesity when they perceive higher levels of bitterness. Additionally, individuals with high bitter

sensitivity have improved blood glucose control, as extensively investigated by Cedrick Dotson at the University of Florida[13].

The intersection between bitters and inflammation is of particular interest, as is the potential for a post-prandial GI hyperemia (and a resultant reduced load on the heart and arterial system). First, a strong aversive response to bitterness by an individual who has little experience with the flavor may be indicative of a high background level of pro-inflammatory compounds such as TNF. As the aversion decreases, one could expect that the cholagogue, GI anti-inflammatory, hepatic "cooling" effect might be contributing to reduced inflammation (an interesting balance point between increased expression through T2R stimulation and decreased expression via reduced TNF). Second, reduced inflammation plus reduced cardiovascular load and stress are essential components to any therapy designed to address the metabolic syndrome - and through a wide range of mechanisms, bitters appear to do just that. The connection between the bitter flavor and the heart in some traditional healing systems is of note here, as well. Kimberly Palatini's research, mentioned above, suggests that bitters modulate immune responses in the GI tract and in the physiology overall - while balancing and regulating every aspect of carbohydrate absorption and metabolism, increasing glucose tolerance and insulin sensitivity. Of course, improved insulin sensitivity is a direct consequence of reducing high levels of pro-inflammatory compounds: TNF, as well as series-2 prostaglandins, have all been linked to insulin resistance.

Regulation of appetite, leading to the epidemiologic results observed (lower obesity rates), occurs by a variety of mechanisms. The first is related to motility: through cranial nerve feedback, bitters delay gastric emptying leading to a more rapid sensation of fullness. But just as importantly, wide-ranging effects on satiety, appetite, and carbohydrate metabolism, storage and processing are mediated through enteroendocrine cells - which turn out to be sophisticated "tastebuds" with chemoreceptors on the luminal side and the ability to secrete hormones on the basolateral side. T2Rs are found on P/D cells in the stomach, which secrete hormones involved in fat metabolism and insulin sensitivity (increasing both); on I cells in the duodenum which reduce food intake and stimulate CCK; and on the all-important L cells in the small and large intestines, which secrete PYY (satiety) and GLP-1 (insulin sensitivity)[14]. The recent research and potential of bitter tastants in regulating appetite, obesity and the metabolic syndrome are well-reviewed by Sarah Calvo and Josephine Egan in Nature Reviews[15].

And while bitters have important effects on preventing (and perhaps treating) insulin resistance and diabetes, as we have seen from the mechanisms above, I have also seen them correct episodes of transient, non-emergent hypoglycemia on many occasions. Since hypoglycemia in a non-insulin-dependent patient may actually be evidence of disregulated glucose homeostasis and metabolism (a consequence of insulin over-secretion earlier), this does not come as a surprise. Another mechanism whereby bitters correct transient hypoglycemia may involve "tricking" the hypothalamus into believing food is being consumed. This effect may seem like a simple novelty, but it becomes very clinically relevant when you consider the intense sugar cravings experienced during these episodes. If we had a tool to trick the hypothalamus into believing the craving had been satisfied, our patients could make more rational judgements for nutrition (nuts or other sources of fat and protein). Bitters can provide just such a tool.

T2R receptors, and enteroendocrine G-protein-coupled receptors in general, are receiving sustained attention as potential targets for reversing insulin resistance. Exciting research is coming out of Cedrick Dotson's office (mentioned above), who is stimulating T2R receptors with bitter tastants and comparing the insulin-sensitizing effects to the opposite effects found by stimulating sweet taste receptors (T1Rs)[16].

Finally, many bitters (especially the more "nutritive" bitters, such as dandelion, chicory, elecampane, angelica and burdock) possess appreciable quantities of pre-biotic starches and can deliver these important nutrients when consumed at clinically relevant doses. Oligosaccharides such as inulin can have useful regulatory effects on bowel function, and over time contribute to lower blood glucose, lower lipid levels, and better satiety[17]. This may be in part due to mechanical effects (such as an osmotic laxative effect), but may also be due to changes in enteroendocrine cell hormone production associated with a shift in microbial populations. A fascinating study by Patrice Cani hinted at just this type of effect in a small (n=10) group[18]. As Steven Abrams noted, this effect is best observed with long-term, habitual use: prebiotics, when combined with calcium (see dandelion root), reduce body mass index better than a placebo control (n=96, one year)[19].

Conclusion: The digestive-enhancing effects of bitters are well documented, but may be just the beginning of what these traditional preparations have to offer. When consumed in a formula that includes both "eupeptic", strong bitters such as gentian and wormwood, and "nutritive" bitters rich in pre-biotic starches, and taken habitually in material doses, they exert clinically relevant effects on the metabolic syndrome. Appetite, carbohydrate and lipid metabolism all are regulated. Inflammation and cardiovascular load are reduced. Bitters accomplish this through a variety of mechanisms, including neuronal, endocrine, immunologic, and vascular. They most likely need not be consumed too far ahead of a meal, but at any point before, during, or after, and at relatively high doses for the most substantial effects. Given the resurgence of interest in these traditional preparations from those well-versed in the beverage alcohol and cocktail world, we as herbalists may have at our disposal a powerful, flavorful tool for addressing obesity and the metabolic syndrome - one our patients can relate to, and easily incorporate into their lives as a daily habit.

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