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Review

Extra-oral bitter taste receptors: New targets against obesity?

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ABSTRACT

Taste perception on the tongue is essential to help us to identify nutritious or potential toxic food substances. Emerging evidence has demonstrated the expression and function of bitter taste receptors (TAS2Rs) in a wide range of extra-oral tissues. In particular, TAS2Rs in gastrointestinal enteroendocrine cells control the secretion of appetite regulating gut hormones and influence hunger and food intake. Furthermore, these effects may be reinforced by the presence of TAS2Rs on intestinal smooth muscle cells, adipocytes and the brain. This review summarises how activation of extra-oral TAS2Rs can influence appetite and body weight control and how obesity impacts the expression and function of TAS2Rs. Region-selective targeting of bitter taste receptors may be promising targets for the treatment of obesity.

1. Introduction

Taste or gustation is the sensation produced when chemicals present in ingested food, beverages or medications interact with taste receptors located on taste buds in the oral cavity. This sensation will distinguish between five basic tastes: bitter, sweet, umami, sour, salty and fat [1]. It is still a matter of debate whether fat can be considered as the sixth taste, independent from its textural and olfactory cues. Generally, bitter and sour tastes are innately aversive and function to warn against consuming toxic, spoiled or unripe foodstuff. In contrast, sweet, umami and fat tastes are perceived as appetitive and signal the presence of energy rich foods. Salty taste indicates the presence of sodium ions which are important for the body's electrolyte balance.

Taste buds, the peripheral organs of gustation, are mainly distributed in the tongue epithelium and contain three main subtypes of taste receptor cells (TRCs, for a review see [1]). Type II TRCs are chemosensory cells because of the expression of taste-related G protein-coupled receptors (GPCRs). Taste GPCRs are divided into the taste receptor type 1 family (TAS1Rs) for sweet and umami sensation [2,3], and the taste receptor type 2 family (TAS2Rs) for bitter stimuli detection [4]. Apart from their role in oral sensing, these receptors are ectopically expressed in a wide range of tissues to exert a variety of functions (for a review see [5]). For instance, the gastrointestinal (GI) tract is under constant exposure of ingested food stuff, drugs and bacterial products consisting of a vast variety of different molecules such as bitter tasting compounds. Chemosensory mechanisms in the gut are extremely important to determine whether a compound needs to be assimilated or expelled.

Several *in vivo* studies in both rodents and humans have reported that intragastric administration of bitter compounds decreased hunger scores and food intake [6–10] and reduced body weight in obese mice [9]. This review will discuss how activation of TAS2Rs can influence body weight, via four different mechanisms: release of gut hormones, regulation of gastrointestinal motility, brain activation, and adipocyte metabolism. The impact of obesity on the expression and function of TAS2Rs is summarized as well.

2. TAS2Rs

Different species have evolved with different subtypes of TAS2Rs: 3 subtypes in chickens, 25 in humans, 35 in mice and 51 in frogs [11]. In chickens, the low number, is partially compensated by the fact that these TAS2Rs are broadly tuned. A high number of TAS2Rs reflects the development of highly specialized receptors and may be related to the proportion of plants in the diet which often contain toxic bitter compounds [11].

Human TAS2Rs (hTAS2Rs) can be categorized into three groups: "generalists" which are broadly tuned and respond to several bitter agonists, "specialists" which can only be activated by few bitter compounds, and an "intermediate" group which represents the majority. For example, denatonium benzoate (DB) activates 8 different hTAS2Rs (hTAS2R4, -R8, -R10, -R13, -R39, -R43, -R46 and -R30 (formerly known as hTAS2R47)), and chloroquine activates 5 hTAS2Rs (hTAS2R3, -R7, -R10, -R14, -R39), of which 2 are in common with DB, while

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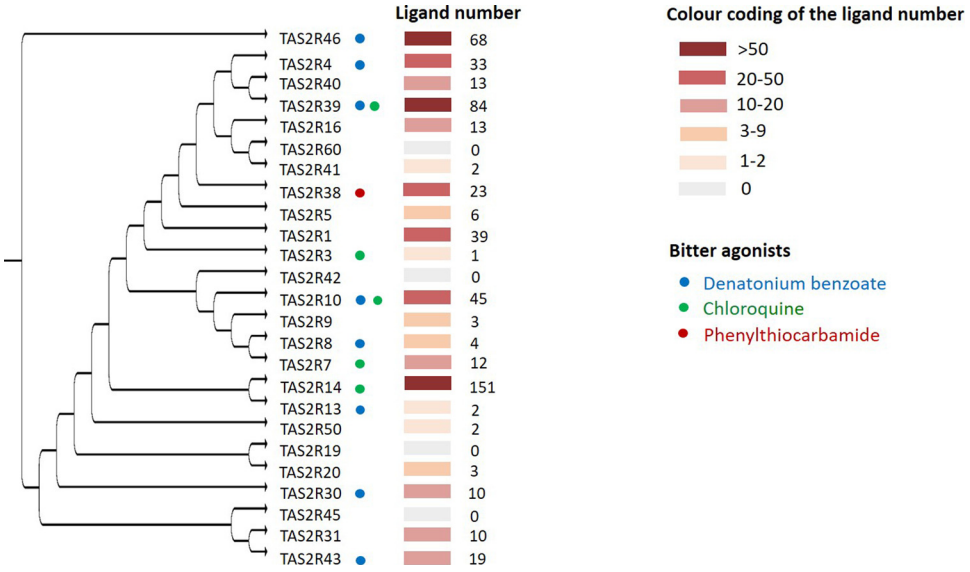

Fig. 1. Example of a selection of bitter agonists (denatonium benzoate, chloroquine, phenylthiocarbamide) that bind to subtypes of the human bitter taste receptor (hTAS2Rs) family and the number of known ligands for a receptor according to the bitter database "BitterDB" [75]. Bitter taste receptors are clustered according to their mRNA sequence identity. Dots represent the bitter agonist, and the rectangles represent the number of ligands that can bind to the respective hTAS2R subtype. TAS2R19: formerly known as TAS2R48, TAS2R20: formerly known as TAS2R49, TAS2R31: formerly known as TAS2R44.

phenylthiocarbamide (PTC) or propylthiouracil (PROP) only interact with hTAS2R38 [12] (Fig. 1). This wide and overlapping range of tuning explains why only a limited number of TAS2Rs have the ability to detect thousands of plant-derived bitter substances found in nature. Of note, the agonist selectivity of TAS2Rs differs between species [13].

Futhermore, more than 150 single nucleotide polymorphisms (SNPs) have been discovered in hTAS2R coding regions [14], which may drive profound differences in receptor functionality and bitterness perception among people. The best described SNPs are those in the hTAS2R38 gene, dividing it into two common haplotypes: the functional hTAS2R38 (containing proline (P), alanine (A), and valine (V) residues) and the non-functional hTA2R38 (containing alanine (A), valine (V), and isoleucine (I) residues) [15]. Homozygous PAV/PAV subjects are classified as "tasters" and experience PTC/PROP as very bitter, while AVI/AVI individuals are considered as "non-tasters" and virtually do not taste PTC/PROP [15].

Besides hTAS2R38, high levels of polymorphisms including SNPs and copy number variations have been found in other hTAS2R genes, for example in hTAS2R3, -R4, -R5 and -R16 [16,17]. For others, e.g. hTAS2R43 and -R45, even whole gene deletions have been reported [18]. The hTAS2R gene variants have been shown to influence bitterness sensation, liking and intake of alcoholic beverages, coffee and grapefruit juice in healthy adults [19,20], indicating a link between hTAS2R genetic variation and food preference.

3. Role of TAS2Rs in the release of gut hormones

Gut hormones, including the orexigenic peptides (ghrelin and motilin) and the anorexigenic peptides (glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and cholecystokinin (CCK)), play an essential role in the regulation of food intake and body weight.

3.1. Role of TAS2Rs in the release of orexigenic peptides (ghrelin and motilin)

3.1.1. Ghrelin secretion

Ghrelin, a 28 amino acid peptide mainly produced in gastric X/A-like cells in rats or P/D1 cells in humans [21,22], is the main peripheral orexigenic hormone. A variety of functions have been attributed to ghrelin, for instance, stimulating appetite and food intake [23,24], increasing body weight gain by preventing fat utilization [25], inhibiting glucose-induced insulin secretion [26] and stimulation of gastrointestinal motility [27].

The gustatory G proteins, α-gustducin and α-transducin, colocalize with the ghrelin cell in the mouse stomach [8]. In the ghrelinoma cell line MGN3-1, the monomeric flavanol, epicatechin gallate, targeting hTAS2R14 and hTAS2R39 stimulated ghrelin secretion via TAS2Rs and a PLC signaling pathway [28]. In mice, intragastric administration of a mixture of bitter agonists induced an acute release of ghrelin in an α-gustducin dependent manner. The effect was accompanied by a GHSR1a-dependent increase in food intake during the first 30 min but was followed by a prolonged decrease in food intake during the next 4 h [8]. Similarly, in rats, short-term treatment with bitter-sensing flavanols stimulated ghrelin secretion, while long-term treatment inhibited ghrelin secretion [28].

Immunofluoresence studies showed co-localization between hTAS2R10 and ghrelin in human fundic primary cultures [29]. The broadly tuned bitter agonist DB and chloroquine, as well as the hTAS2R10 specific agonist erythromycin A and the hTAS2R5 specific agonist 1,10-phenanthroline stimulated ghrelin release in these cultures [29]. The hTAS2R38 agonist PTC did not affect ghrelin release, which was in line with the absence of hTAS2R38 mRNA expression in the human fundus. In healthy females, intragastric administration of DB (1 μmol/kg body weight) or quinine (10 μmol/kg body weight) reduced hunger scores in the fasting state, delayed the return of hunger after a meal and tended to reduce caloric intake [6,7]. This was accompanied by a suppression of gastric motility and for quinine treatment with a decrease in ghrelin plasma levels [7,30]. It should be pointed out that bitter agonists stimulate ghrelin secretion *in vitro* but inhibit ghrelin secretion *in vivo* in humans. These findings suggest that *in vivo* the secretion of other circulating hormones or neural reflexes may mask the local stimulatory effect of bitter agonists on ghrelin secretion. Therefore, care should be taken to directly extrapolate findings from *in vitro* studies to clinical applications *in vivo*.

3.1.2. Motilin secretion

Motilin is a 22 amino acid peptide produced in the small intestine. The main function of motilin is to induce strong gastric contractions during the interdigestive phase to signal hunger [31,32]. It has been shown that intragastric administration of DB or quinine decreased plasma motilin levels in healthy volunteers [6,7,30], but no study has shown the expression of hTAS2Rs on motilin-producing cells.

3.2. Role of TAS2Rs in the release of anorexigenic peptides (CCK, GLP-1, PYY)

Taste signaling elements such as α-gustducin, PLCβ2 and transient receptor potential cation channel subfamily M member 5 are expressed

in GLP-1 producing L-cells in the human duodenum [33,34]. Furthermore, hTAS2R5 was shown to colocalize with L-cells in human duodenal sections [35] while hTAS2R38 was expressed in enteroendocrine cells (EECs) containing the anorexigenic peptides CCK, GLP-1 and PYY in the human colonic mucosa [36]. α-gustducin was also colocalized with mTas2r106 and GLP-1 in a mouse STC-1 cell line [37].

3.2.1. CCK secretion

CCK is secreted by I-cells in the small intestine in response to dietary fat and proteins. It induces the release of digestive enzymes and bile from the pancreas and gallbladder, respectively. CCK also acts as a satiety hormone that inhibits food intake and gastric emptying.

The bitter agonist DB stimulated CCK release in STC-1 cells via Ca^{2+} influx involving the opening of L-type voltage sensitive Ca^{2+} channels [38]. H.g.-12, a steroid glycoside purified from the bitter tasting Hoodia gordonii extract, increased CCK release in *ex vivo* rat duodenal segments [39]. The same effect was shown *in vitro* in the human EEC cell line HuTu-80 [39]. The effect was inhibited by compound 03A3, a putative hTAS2Rs antagonist acting on hTAS2R14, but no details on the molecular structure have been provided. Additionally, H.g.-12 selectively activated hTAS2R7 and hTAS2R14 in hTAS2Rs transfected human HEK 293 T cells [39]. In healthy volunteers (12 women, 8 men) administration of an acid-resistant capsule containing 18 mg of quinine hydrochloride, increased plasma CCK levels and lowered calorie intake of a buffet meal compared to placebo [40]. In contrast, Bitarafan et al. showed that slow intraduodenal administration of quinine at higher doses (37.5 mg – 225 mg quinine) to healthy men did not affect plasma CCK levels or energy intake [41]. Since women appear to be more sensitive to bitter taste than men [6], gender might be a factor that explains the contradictory responses to quinine beside the dose and mode of administration.

3.2.2. GLP-1 and PYY secretion

GLP-1 is secreted after a meal by L-cells to increase satiety and delay gastric emptying. It is an important incretin that decreases blood glucose levels by stimulating insulin release. GLP-1 mimetics are currently used for the treatment of obesity-related type 2 diabetes [42]. PYY is also released from L-cells in the distal gut in response to feeding to reduce appetite. It delays gastric emptying and induces the ileal brake to enhance nutrient uptake [43].

DB stimulated GLP-1 and PYY secretion in human enteroendocrine NCI-H716 cells, and the effect on GLP-1 release was abolished using siRNA knockdown of α-gustducin, hTAS2R4, hTAS2R43 and hTAS2R46 [44]. The hTAS2R5 specific agonist, 1,10-phenanthroline, also increased GLP-1 secretion in NCI-H716 cells [35]. The intracellular signaling pathway of both DB- and 1,10-phenanthroline-induced GLP-1 secretion involved a stimulation of PLC signaling and for DB also a reduction in intracellular cAMP levels which ultimately led to increased Ca^{2+} release [35,44]. Cucurbitacin B treatment of NCI-H716 cells stimulated GLP-1 secretion via activation of AMP-activated protein kinase, and the effect was mediated via α-gustducin and hTAS2R10 [45].

Gavage of DB to diabetic mice decreased blood glucose levels via stimulation of GLP-1 release [44] and oral gavage of cucurbitacin B increased plasma GLP-1 and insulin levels which alleviated hyperglycemia in diabetic mice [45]. Recently, Kok et al. [46] showed that acute intragastric treatment with the mTas2r108 agonist KDT501, a pure derivative isolated from hops isohumulone, stimulated GLP-1 release and enhanced glucose tolerance in diet-induced obese mice. Chronic treatment (28 days) with KDT501 resulted in body weight and fat mass loss, enhanced glucose tolerance and insulin sensitivity, and normalized plasma lipid levels. The effects were amplified in combination with a dipeptidyl peptidase 4 inhibitor [46]. Similar effects on glucose tolerance were observed with the mTas2r108 agonist, emetine [46]. In insulin-resistant prediabetic patients, KDT501 treatment (28 days) reduced inflammation and improved postmeal plasma triglyceride levels [47]. Mennella et al. [10] showed in a randomized cross-over trial, that a vanilla pudding enriched with microencapsulated bitter compounds (from *Gentiana lutea*) to mask the bitter taste, increased plasma GLP-1 levels. This was accompanied by a 22 % reduction of the 24 h energy intake. Recently, Bitarafan et al. [48] showed that intragastric administration of quinine decreased postprandial blood glucose levels and increased insulin and GLP-1 levels, but did not reduce energy intake, in healthy men.

4. Role of TAS2Rs in gastrointestinal motility

Gastrointestinal smooth muscle cells play an essential role in smooth muscle contractility, which is one of the main physiological functions of the gut. The bitter taste receptors *mTas2r108*, *-r135* and *-r137* but not *mTas2r118*, *-r138* are expressed in mouse gut smooth muscle tissue [49]. *hTAS2R3*, *-R4* and *-R10*, but not *hTAS2R38* mRNA expression were demonstrated in human gastric smooth muscle cells as well as α-gustducin and α-transducin [49].

Gastrointestinal motility plays an important role in the regulation of hunger signaling. The gastrointestinal tract responds to the different phases of food intake by inducing specific motility patterns [50]. During the ingestion of food, the proximal stomach relaxes to accommodate food. The process is called gastric accommodation and induces a satiating effect that will determine the meal size. Avau et al. [49] showed that intragastric administration of DB impaired fundic relaxation in response to nutrient infusion, decreased nutrient volume tolerance, and increased satiation scores during an oral nutrient drinking test in healthy volunteers.

In the next phase, food moves to the more distal part where it is further digested and grinded into small particles by strong contractions and emptied into the duodenum. A delay of gastric emptying will prolong the presence of food in the stomach and will induce early satiety and increase the interval between meals. Janssen et al. [8] showed that intragastric administration of PTC markedly delayed gastric emptying in mice, which correlated with a reduction in food intake. *In vitro* studies showed that bitter agonists had direct effects on contractility in mouse gastric smooth muscle strips [8,49]. Likewise, gavage of DB also resulted in a delay of gastric emptying in mice, which was blocked by the TAS2R antagonist probenecid [49]. Nevertheless, DB did not delay gastric emptying in healthy volunteers but increased satiety and delayed the return of hunger in between meals [6]. Intragastric or intraduodenal infusion of quinine did not affect gastric emptying or antropyloroduodenal motility in healthy men [41,48].

In the fasting state, gastrointestinal motility is characterized by the migrating motor complex. A specific motility pattern of strong contractions (phase 3) that starts in the stomach and migrates distally to clean the small intestine in between meals from food remnants, bacteria etc. It has been shown that gastric phase 3 contractions which are regulated by the gut hormone motilin, signal hunger in the fasted state in humans [32]. Intragastric administration of DB or quinine decreased interdigestive gastric motility and decreased hunger scores which was accompanied by a decrease in plasma motilin and/or ghrelin levels [6,7].

Notably, the observed changes in gastrointestinal motility *in vivo* are likely to represent an integrated result from the effect of activation of TAS2Rs on gut hormone secretion and on smooth muscle cells.

5. Role of TAS2Rs in the gut brain axis

TAS2Rs and their intracellular signaling molecules (α-gustducin, PLCβ2 and TRPM5) are expressed in multiple regions of the rodent brain, such as hypothalamus, brain stem and cortex [51–54]. Wolfle et al. [55] reported that hTAS2R16 was expressed in human brain tissue and the human neuroblastoma cell line SH-SY5Y.

The gut brain axis, a neurohumoral communication system between the gastrointestinal tract and the brain, plays an important role in the regulation of energy homeostasis. Indeed, brain imaging studies

revealed that intragastric administration of quinine in healthy volunteers increased brain activity in the hypothalamus and hedonic brain regions but decreased activity in the homeostatic medulla [30]. These differential brain responses covaried with a decrease in hormonal responses (motilin, ghrelin), decreased prospective food consumption scores and a reduction in hedonic food intake observed after quinine versus placebo. In addition, it cannot be excluded that quinine directly interacts with TAS2Rs present in various brain regions [51] since quinine can penetrate into the cerebrospinal fluid.

6. Role of TAS2Rs in adipose tissue

Avau et al. [9] showed the expression of α-gustducin and TAS2Rs in white adipose tissue and in murine 3T3-F442A pre-adipocytes, indicating a role for the taste signaling pathways in adipocyte metabolism. High-fat diet induced α-gustducin$^{-/-}$ mice show an obesity-resistant phenotype owing to an increased heat production. Treatment of 3T3-F442A cells with the bitter agonists DB or quinine inhibited the differentiation of pre-adipocytes into mature adipocytes, which resulted in a decrease in lipid accumulation. It was suggested that this may have contributed to the α-gustducin-dependent reduction in body weight of obese mice caused by daily gavage of DB or quinine during 4 weeks [9]. In contrast, Ning et al. [56] showed that quinine but no other bitter tasting compounds, promoted adipogenesis through mTas2r106 and the activation of extracellular signal-regulated kinase/ribosomal protein S6 signaling. The different outcome between these two studies could be due to different quinine concentrations or cell types that were used in the experiments. Momordica charantia (bitter melon) has been shown to reduce pre-adipocyte proliferation and lipid accumulation in mouse 3T3-L1 pre-adipocytes [57], to suppress lipogenesis and to stimulate lipolysis in human primary adipocytes [58]. Furthermore, bitter melon ameliorated high-fat diet-induced obesity and insulin resistance in rats [59]. It remains to be proven whether these effects are due to the bitter tasting cucurbitacins present in bitter melon.

Further studies are required to clarify whether and which TAS2Rs are involved in the effect of bitter agonists on adipocyte metabolism.

7. Expression and function of TAS2Rs in other extra-oral tissues

Except for the tissues mentioned above, TAS2Rs have been reported in many other tissues where they have different functions. For example, the activation of TAS2Rs in the airways induce innate immune responses and smooth muscle relaxation, and are therefore considered as new targets for the clinical treatment of respiratory inflammatory diseases and obstructive diseases [60]. The expression and function of bitter taste receptors in extra-oral tissues are summarized in Table 1.

8. Impact of obesity on the expression and function of TAS2Rs

In order to qualify bitter compounds as putative anti-obesity agents, it is important to know whether extra-oral TAS2Rs expression is altered by obesity and whether obese patients are still sensitive to bitter agonists. At least in human fungiform taste papillae, a recent RNA-seq study showed that the expression of type II taste-related genes, including α-gustducin and *hTAS2R31*, was reduced in obese subjects compared to the lean group [61]. This may result in the reduced sensitivity to bitter taste observed in obese subjects and may affect food choices [61–66].

In the stomach and duodenum, the mRNA expression of some *hTAS2Rs* was altered in a region-dependent manner in obese patients compared to lean controls [29]. There was no consensus for either an up- or downregulation of *hTAS2R* subtypes. In the colon, the protein expression of hTAS2R38 positive enteroendocrine cells was upregulated in overweight or obese subjects compared to normal weight subjects [36]. Moreover, the stimulatory effect of DB on ghrelin secretion was selectively blunted by obesity in the small intestine but not in the fundus [29]. These findings suggest that the route of administration of bitter compounds is important and may have an effect on the outcome of clinical studies in which modulation of gut hormone levels is requested.

9. Bottlenecks and perspectives of targeting gut TAS2Rs for therapeutic applications

Although studies showed emerging roles for targeting TAS2Rs against obesity, there are still some problems concerning their therapeutic applications.

9.1. Which TAS2Rs are promising targets?

Not one but 25 subtypes of TAS2Rs exist in humans. Some bitter compounds can activate several hTAS2Rs, while some are more specific. Broadly tuned hTAS2Rs, e.g. hTAS2R10, hTAS2R14 and hTAS2R46, each recognize about one-third of the bitter substances for which their activation pattern of TAS2R is known [12]. Their combined response pattern facilitates detection of about 50 % of the bitter substances. Bitter agonists that target these hTAS2Rs may amplify the response but may also have a broad spectrum of action because hTAS2R10, hTAS2R14 and hTAS2R46 are widely expressed in the body. From this point of view, more specific bitter agonists could be a better option. In a study of Behrens et al. [67], 26 bitter substances extracted from medical herbs were screened for the activaton of the 25 hTAS2Rs using functional Ca^{2+} mobilization assays. The majority activated TAS2R14 and TAS2R46 suggesting that these receptors are probably involved in the physiological activities of Chinese herbal medicines.

Importantly, even a single hTAS2R can be expressed in different types of cells and thus induce distinct functions. Using specific bitter agonists, Wang et al. [29] showed that hTAS2R5 and hTAS2R10 may participate in the regulation of ghrelin secretion. Previously, hTAS2R5, hTAS2R4, hTAS2R43, hTAS2R46 and hTAS2R1 have been shown to regulate GLP-1 secretion in human L-cells [35,45]. Therefore, these hTAS2Rs may represent promising targets for the treatment of obesity through modulating gut hormone secretion. Nevertheless, further *in vivo* studies in humans are required.

Notably, the number and agonist selectivity of TAS2Rs differ between humans and rodents, which contain 25 and 35 subtypes, respectively [13,68]. Therefore, studies in rodents cannot be extrapolated to studies in humans.

Thus, extensive screening studies are required with bitter agonists in several physiological systems and species to determine which TAS2R should be targeted for a certain application.

9.2. Route of administration

TAS2Rs are expressed almost all over the body, therefore region-specific targeting is important to avoid unwanted side effects. To avoid causing aversion by the activation of TAS2Rs on the tongue, capsules with bitter compounds could be used that allow controlled release in the gut region of interest. In this way, the mode of action is limited to the gastrointestinal tract. For other organs (e.g. adipocytes), uptake of the bitter compound in the bloodstream might be a prerequisite.

9.3. Effective concentrations of TAS2R agonists

Chemical structures of bitter compounds are highly diverse as well as their effective concentrations to activate TAS2Rs, which are ranging from nanomolar to millimolar in an *in vitro* heterologous expression model [12]. For instance, DB showed an effective concentration range from 30 nM (for the activation of hTAS2R47) to 1 mM (for the activation of hTAS2R8), while quinine activates all its 9 hTAS2Rs in the same concentration range (10 μM) [12]. In human intervention studies

Table 1
Overview of studies investigating the expression and function of bitter taste receptors in extra-oral tissues.

Tissue	Cell type		Model	Function
Stomach	EECs_ P/D1 cell	in vitro	Mouse MGN3-1 cell [28]	Stimulate ghrelin secretion
			Human primary fundic cell [29]	
		in vivo	Mouse [8]	
			Human [7,30]	Inhibit ghrelin secretion
	Parietal cell	in vitro	Human HGT-1 cell [78,79]	Stimulate gastric acid secretion
		in vivo	Human [78]	
	SMC	in vitro	Mouse SM strip [49]	Regulate SM contractility
			Human SMC [49]	Induce functional Ca^{2+} responses
		in vivo	Human [6,7,48,49]	Attenuate fundic relaxation and interdigestive motility, no effect on gastric emtptying
Intestine	EECs_ P/D1 cell	in vitro	Human small intestinal segment [29]	Stimulate ghrelin secretion
	EECs_I-cell	in vitro	Mouse STC-1 cell [38]	Stimulate CCK secretion
			Human HuTu-80 cell [39]	
			Rat duodenal segments [39]	
		in vivo	Human [40,41]	Contradictory effects on CCK
	EECs_L-cell	in vitro	Human NCl-H716 cell [35,44]	Stimulate GLP-1 and PYY secretion
		in vivo	Mouse [45,46]	Stimulate GLP-1 secretion
			Human [10,48]	
	Tuft cell	in vitro	Mouse small intestinal section [80]	Stimulate IL-25 release
	Paneth cell	in vitro	Mouse ileum tissue [81]	Unknown
	Goblet cell	in vitro	Mouse colonic tissue [82]	Unknown
Nasal cavity	Ciliated cell	in vitro	Mouse sinonasal cultures [83,84]	Increase NO production and ciliary beating
			Human sinonasal cultures [83,85,86,87]	
	SCCs	in vitro	Mouse nasal SCCs [88,89,90]	Increase acetylcholine release and activate trigeminal nerves
			Human nasal SCCs [91,92]	Stimulate β-defensin secretion
Trachea, bronchus	Ciliated cell	in vitro	Human tracheal and bronchial tissue [93]	Promote ciliary beating
	SCCs	in vitro	Mouse isolated tracheal SCCs [94], and tracheal tissue [95]	Decrease respiratory rate via cholinergic transmission
		in vivo	Mouse [94]	
	SMC	in vitro	Human ASM cell [96,97]	Cause relaxation of isolated ASM
		in vivo	Mouse [96,97,98]	Relax bronchial smooth muscle
Brain	Neuronal cell	in vitro	Human SH-SY5Y cell [55]	Promote neuronal differentiation
Heart	Myocardial cell	in vivo	Mouse [99]	Elicit negative inotropic effects
Kidney	Renal corpuscle and tubule	in vitro	Mouse renal tissue [100]	Maintain the structure of the glomerulus and renal tubules
Urinary bladder	Detrusor SMC	in vitro	Mouse detrusor SM strip [101]	Relax the detrusor SM
			Human detrusor SM strip [101]	
		in vivo	Mouse [101]	Inhibit bladder activity
	Brush cell	in vivo	Rat [102], mouse [103]	Increase acetylcholine release and trigger bladder reflexes
Testis	Sperm cell	in vivo	Mouse [104]	Spermatogenesis
Thyroid	Thyrocyte	in vitro	Human Nthy-Ori 3-1 thyrocyte [105]	Decease TSH-induced Ca^{2+} release
			Human and mouse thyroid tissue [105]	
Adipose tissue	White adipocyte	in vitro	Mouse 3T3-F442A [9] and 3T3-L1 [57] pre-adipocyte, and mouse white adipose tissue [9]	Inhibit pre-adipocyte proliferation and differentiation, and lipid accumulation
		in vitro	Human primary adipocytes [58]	Inhibit lipogenesis and stimulate lipolysis
Skin	Keratinocytes	in vitro	Human HaCaT cells and primary keratinocyte [106]	May play a role in keratinocyte differentiation
	Epidermis and dermis	in vitro	Human skin tissue [107]	Unknown
Bone	MSC	in vitro	Human primary MSC [108]	Increase Ca^{2+} activity
Blood vessel	Vascular SMC	in vitro	Mouse and guinea-pig aorta [109]	Relax the vascular SM
			Human pulmonary arteries [109]	
			Human and rat aortic SMC [108]	Increase Ca^{2+} activity
		in vivo	Rat [108]	Decrease blood pressure
Immune cell	Leukocyte	in vitro	Human neutrophils [110,111]	Function as a receptor for AHL-12
			Human lymphocyte [111,112]	Inhibit TNF-α secretion
			Human leukocyte [113]	Inhibit LPS-induced cytokine release
	Mast cell	in vitro	Human mast cell [114]	Inhibit IgE-induced histamine and prostaglandin D2 release

EECs: enteroendocrine cells; SM: smooth muscle; SMC: smooth muscle cell; ASM: airway smooth muscle; SCCs: solitary chemosensory cells; TSH: thyroid-stimulating hormone; MSC: mesenchymal stromal cell; AHL-12: N-(3-Oxododecanoyl)-L-Homoserine Lactone; TNF-α: Tumor necrosis factor alpha; LPS: lipopolysaccharides.

physiological effects were observed after an intragastric infusion of 1 μmol/kg DB [6,49] while for quinine higher (10 − 25 μmol/kg) doses were used. Thus, there are no general suggestions on effective concentrations of bitter compounds, these need to be determined for each compound.

9.4. Importance of TAS2R polymorphisms and gender

A large number of single nucleotide polymorphisms have been discovered in TAS2Rs, which may result in different effects among individuals. In a cohort of 1319 subjects, Ortega et al. [69] showed an increased frequency of obesity in the PTC/PROP "non-tasting" cohort. In another study, lean woman that were PTC/PROP "nontasters" consumed more energy from a buffet meal compared to those that are highly sensitive to PROP-taste [70]. hTAS2R5 also contains gene variants [16,71], and it would be essential to investigate whether they affect the function of hTAS2R5 in the regulation of ghrelin and GLP-1 release [29,35]. For hTAS2R43 there is even a deletion polymorphism, thus the receptor is not expressed in about 33 % of the world population [18].

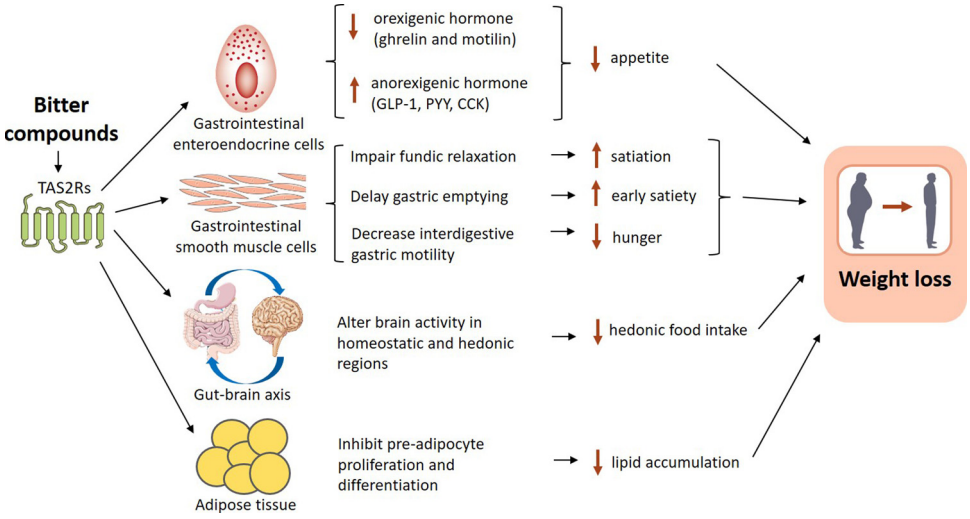

Fig. 2. Overview of the mechanisms that mediate bitter compounds-induced body weight loss.

Additionally, women appear to be more sensitive to PTC than men [72]. In women but not in men, intragastric administration of DB reduced gastric motility and hunger scores [6]. These data indicate that the potency of bitter compounds-induced responses might differ between males and females.

In general, not all patients may benefit from treatment with bitter agonists.

9.5. Interaction with sweet taste receptors

Sweet taste receptors interact with hTAS2Rs to inhibit the effect of a bitter agonist on ghrelin secretion in the human gut [29]. This finding may limit the anti-obesity effect of bitter compounds in diabetic patients, who usually have higher blood glucose levels. Sweet taste receptor antagonists might be a useful adjunct in augmenting ghrelin release in these patients. Nevertheless, the mRNA expression of sweet taste receptor subunits *hTAS1R3* in the small intestine was down-regulated in obese patients [29]. Young et al. [73] showed that the mRNA expression of *hTAS1R2* and *hTAS1R3* was negatively correlated with blood glucose levels in type 2 diabetic patients. This may result in less glucose sensing and abolish the inhibitory effect of sweet taste receptor activation on the function of TAS2Rs. In addition, the mRNA expression of glucose transporters SGLT1 and GLUT2 was significantly increased in the small intestine of obese patients [29,74], which may enhance glucose absorption and predispose obese patients to develop type 2 diabetes. However, an interaction between these glucose transporters and bitter taste receptors has not been studied.

9.6. Drug-like effects of bitter agonists

In the online available “BitterDB” database [75], the information of the binding profile of about 1000 bitter compounds to TAS2Rs in different species has been collected. Almost 10 % of them are approved medicinal drugs and it has been suggested that extra-oral TAS2Rs may be mediators of “off-target” drug effects [76]. For instance, one of the most potent agonists for the broadly tuned hTAS2R14 is flufenamic acid which is also an anti-inflammatory and analgesic drug. Thus ligand- and structure-based computer-aided drug design is necessary to improve binding and selectivity of bitter agonists [77].

Solving these problems would help us to study the function of extra-oral TAS2Rs and design favourable bitter drugs for the treatment of diseases.

10. Conclusions

Bitter compounds can support body weight control via several mechanisms involving TAS2Rs expressed at different sites of the body (Fig. 2). In order to tackle the obesity epidemic, these findings also reinforce the importance of retaining bitter tasting compounds in some food ingredients instead of banning them with the reasoning of making food more palatable. These studies also provide a rationale for the health promoting effects observed with bitter herbs used in traditional Chinese medicine. Nevertheless, only a few of the 25 expressed hTAS2Rs might be relevant targets to treat obesity and due to the broad expression of these receptors at several sites in the human body, specific targeting might be a necessity to exclude side effects.

Declaration of Competing Interest

The authors declare no conflicts of interest

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