Kadohisa *Flavour* (2015) 4:37
DOI 10.1186/s13411-015-0047-8

Flavour

REVIEW Open Access

Beyond flavour to the gut and back

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Abstract

This paper describes how food is sensed in both the mouth where it produces food reward and pleasantness that guides food intake and is sensed in the gut where it produces satiety and conditioned effects including learned appetite and learned satiety for the food eaten. Taste and other receptors present in both the mouth and gut are involved in these effects. The signals about the presence of food in the mouth and gut are transferred by separate pathways to the brain where the satiety signals from the gut reduce the reward value and subjective pleasantness of taste and other oral sensory signals including food texture. Food flavour preferences can be associatively conditioned by pairing with food in the gut in brain regions such as the orbitofrontal cortex and amygdala. Current issues considered in this paper are how gut sensing of food influences hormone release including cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1); how the sensing of different nutrients in the gut may influence unconditioned satiety and conditioned preference and satiety; and how cognition may modulate the pleasantness of food and thus the control of food intake.

Keywords: Food intake, Taste, Oral signal, Visceral signal, Reward, Satiety

Review

Background

Food provides us with nutrition, energy, and reward with its subjective correlate of pleasure, and then satiety. Signals elicited by food in the mouth produce reward and pleasantness, while those in the gut produce satiety, but can also lead to a conditioned (learned) preference and/or a conditioned satiety for the orally sensed flavour. This paper reviews the taste and other sensing mechanisms in the mouth and the gut and shows how they contribute to these reward, satiety, and conditioned effects mediated by signals produced when food reaches the gut. Understanding these signals and their interactions in the brain provides an important foundation for understanding the control of food intake and its disorders in which hunger, satiety, and food reward signals may be altered.

Taste and other receptors for food in the mouth and gastrointestinal tract

Taste sensation is an important contributor to the reward value and delicious sensation produced by food in the mouth. In addition to taste, other oral sensory processes including oral texture contribute to the reward value of food flavour, as do olfactory, visual, and cognitive effects. At least five classes of oral taste receptor or sensors (T1R2 + T1R3 for sweet, sodium channel ENaC for salt, T2Rs for bitter, and PKD2L1-expressing TRC for sour, and T1R1 + T1R3 for umami) [1–6] sense food and transmit signals to the brain, with the rostral part of the nucleus of the solitary tract (NTS), the first synapse in the central nervous system. When taste reaches the brain, it, together with olfactory and visual inputs, can change the physiological state including the production of saliva and secretion of hormones [7–9]. These cephalic phase responses elicited by the sight, smell, and taste of food before ingestion are primarily mediated through the parasympathetic system to change physiological states and secretion of hormones such as insulin, ghrelin, and pancreatic polypeptide (PP) [7–9]. A palatable stimulus elicits greater cephalic PP release than a non-palatable stimulus [10], and cephalic PP release depends on the macronutrient [9]. It has been suggested that psychological and/or cognitive attitudes towards food can influence individual cephalic phase responses [10]. Recently, it has been reported that taste cells in the mouth express different types of peptides such as glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and peptide YY (PYY) [11–13]. In rodents, these peptides

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may influence salt and sour sensitivity [14, 15]. In addition to taste, other oral sensing transmits information about food viscosity, fat texture, and temperature, as shown by the responses of neurons in the primary and secondary taste cortical areas [16–18].

When food enters the gastrointestinal (GI) tract, it activates a wide range of gut receptors, which stimulate locally the release of peptides such as CCK, PYY, ghrelin, and GLP-1 from endocrine cells [12, 19–24], which play a crucial role in the regulation of food intake [25–30]. Sugar or sweetener delivered into the GI tract acts through sodium-glucose transporters (SGLTs) to stimulate the release of GLP-1 [12, 31, 32]. In contrast, glucose transporter type2 (GLUT2) is not involved in the release of GLP-1 [12, 33, 34]. Activation of T2R bitter receptors in the GI tract can lead to the release of CCK or PYY, which can influence vagal afferents [19, 35, 36]. However, the role of gut taste receptors in releasing hormones is controversial. An artificial non-caloric sweetener, sucralose, does not induce the release of GLP-1 by affecting L cells in rats [37] and humans in vivo [38, 39], but it does induce the release of GLP-1 from mouse enteroendocrine cells in vitro [40]. Gut receptors for other nutrients such as amino acids and fatty acids have been identified. For example, GPRC6A and CaSR are receptors for amino acids and FFARs for free fatty acids including FFA2 (GRP43) and FFA3(GRP41) which are receptors for short-chain fatty acids (SCFAs) produced by the gut microbiome [12, 41–43]. These receptors are involved in the secretion of peptide hormones such as GLP-1, CCK, and PYY with contribution to energy metabolism [12, 41–43]. Thus, taste receptors in the gut will not alone be responsible for peptide hormone release and other receptors for amino acids and fatty acids, and transporters such as SGLTs are also involved in peptide hormone release. These peptide hormones may act both peripherally and centrally to influence processes in the gut and in the brain. Vagal afferents which project to the caudal part of the NTS convey information about some nutrients in the GI tract [44].

Intragastric administration of different taste solutions modulates blood-oxygen-level-dependent (BOLD) signals in different areas of the rat brain; for example, glucose modulates BOLD signals in the anterior cingulate cortex (ACC), insular cortex (IC), the ventral tegmental area (VTA), the substantia nigra (SN), and the amygdala, and umami modulates BOLD signals in the NTS, hypothalamus, and the amygdala [45, 46]. However, saccharin administration did not modulate BOLD signals in the VTA, SN, or amygdala in the same way as glucose [47].

Importantly, although taste receptors in the gut are implicated in peptide hormone release, they are not involved in taste sensation. The fact that patients who take a meal through a nasogastric or gastrostomy tube state that they do not taste and do not enjoy the food [48] provides evidence that gut taste receptors are not involved in taste sensation.

In summary, taste receptors in the mouth and GI tract have different roles in food intake (Fig. 1). Taste receptors in the mouth primarily mediate taste sensations which reflect properties of tastants, such as their intensity and reward value and pleasantness. Oral taste receptors are necessary for the full rewarding effects of sweet taste in that sucrose consumption is reduced in the T1R3 knockout mice [49]. Taste receptors and other receptors including chemoreceptors in the gut contribute to activating the endocrine system to release peptide hormones and also carry signals via vagal afferents to the brain. Understanding these gut food sensing mechanisms better may lead to better treatments for metabolic disease such as diabetes mellitus as well as disorders in food intake control.

Pathways of oral and visceral information

Neural pathways

Taste receptors in the mouth connect via the facial (cranial nerve VII), glossopharyngeal (cranial nerve IX), and vagus (cranial nerve X) nerves to the central nervous system (CNS). In parallel, other food properties such as temperature and texture are conveyed to the CNS via the trigeminal nerve (cranial nerve V). The vagus also innervates the GI tract. The NTS in the medulla is the first central relay for the primary sensory

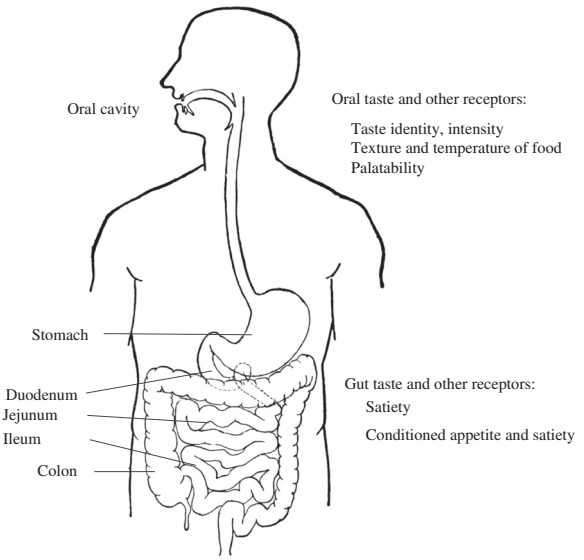

Fig. 1 Taste receptors in the mouth and gastrointestinal tract. Taste receptors in the mouth primarily mediate taste sensations which reflect the intensity and palatability of the taste. Taste receptors in the gut contribute to unconditioned (unlearned) satiety, to conditioned satiety, and to conditioned appetite effects, by neural pathways from the gut to the brain and by activating hormones

nerves [50]. Nerves V, VII, and IX which convey taste largely terminate in the rostral lateral segment of NTS, while vagal afferents (X) are much more concentrated in the caudal medial segment of the NTS [50]. After this, there are differences between primates and rodents. In the primate, the projections from the rostral, gustatory region of the NTS bypass the parabrachial nucleus (PBN) on their way to the thalamic gustatory relay in the caudal half of the parvicellular division of the ventroposteromedial nucleus (VPMpc). Then, gustatory information in the VPMpc is transferred to the granular IC [51, 52] which projects to the lateral and basal nuclei of the amygdala [53] and the orbitofrontal cortex (OFC) where visual and olfactory modalities converge with taste and oral texture [51, 52, 54–56]. In the rodent, the taste part of the NTS projects to the PBN [57] which projects to the VPMpc, the central nucleus of the amygdala (CEA), and to the hypothalamus [58, 59] (Fig. 2), and the PBN has reciprocal connections from the CEA and hypothalamus [60, 61].

With respect to visceral afferent pathways (Fig. 3), the visceral region in the caudal part of the NTS projects to the PBN. The PBN projects to the rostral half of the VPMpc (the non-taste part), the CEA, the lateral hypothalamic nuclei, the VTA, and to the SN in macaques [52, 57, 62, 63]. The visceral part of VPMpc projects to the agranular insula which is located just posterior to the OFC [64, 65] and the insula projects to the ventral striatum (VS) [66]. The VTA and SN project to the VS, which also receives inputs from the OFC and ACC [67–70], which is part of a reward circuit [69] that could drive the motivation for eating.

Humoral pathway

Individual gut peptide hormonal signals which influence the regulation of food intake are transferred to the CNS in different ways: some peptide hormones such as CCK, PP, PYY, oxyntomodulin (OXM), and GLP-1 may act via effects mediated peripherally transmitted through the vagus, some like leptin are transferred via the bloodstream, and others like ghrelin transfers information via both neural and humoral pathways [71–76]. Peptide hormone signals via the bloodstream reach the arcuate nucleus (ARC) of the hypothalamus [71, 72, 74, 75, 77, 78].

Cortical and subcortical areas involved in processing of information from the mouth and gut

Insular cortex

A taste region of the granular anterior IC receives oral information from the VPMpc [51, 52] and is therefore by definition primary taste cortex. Insular taste cortex neurons discriminate not only between taste stimuli [55, 79–82] but also between other sensory modalities such as texture and temperature, which in some cases are combined with taste responsiveness by some single neurons [18]. The activity of primate IC neurons is not modulated by satiety [80, 83], and the same applies to primate NTS neurons [84]. In contrast, in rodents, satiety influences taste processing even in the NTS [85], making the system very different from that of primates, and implying that reward value or hedonics is

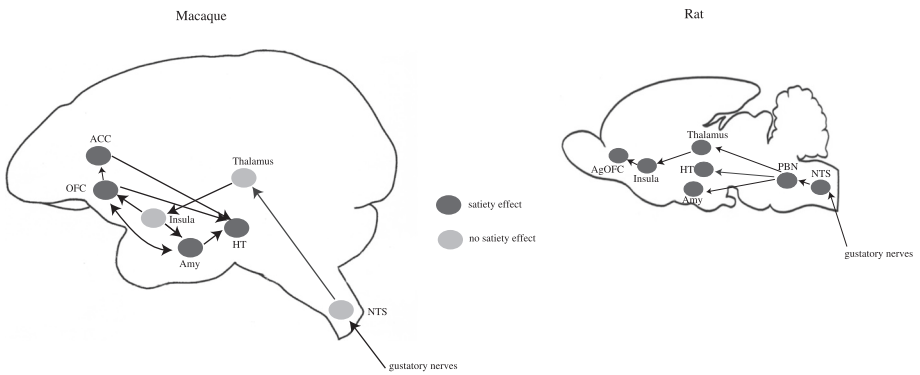

Fig. 2 Taste pathways in the macaque and rat. In the macaque, gustatory information reaches the nucleus of the solitary tract (*NTS*), which projects directly to the taste thalamus (parvicellular division of the ventroposteromedial nucleus, VPMpc) which then projects to the taste cortex in the anterior insula (*Insula*). The insular taste cortex then projects to the orbitofrontal cortex (*OFC*) and amygdala (*Amy*). The *OFC* projects taste information to the anterior cingulate cortex (*ACC*). The *OFC*, *ACC*, and *Amy* project to the hypothalamus (*HT*). In macaques, feeding to normal self-induced satiety does not decrease the responses of taste neurons in the *NTS* or taste insula (and by inference not VPMpc). In the rat, in contrast, the *NTS* projects to a pontine taste area, the parabrachial nucleus (*PBN*). The *PBN* then has projections directly to a number of subcortical structures, including the *HT* and *Amy*, thus bypassing thalamo-cortical processing. The *PBN* in the rat then projects to the taste thalamus (VPMpc), which projects to the rat taste insula. The taste insula in the rat then projects to an agranular orbitofrontal cortex (*AgOFC*), which probably corresponds to the most posterior part of the primate *OFC*, which is agranular. (In primates, most of the *OFC* is granular cortex, and the rat may have no equivalent to this [210, 211] Fig. 2.1, see also 87 Fig. 1.1). In the rat, satiety signals such as gastric distension and satiety-related hormones decrease neuronal responses in the *NTS* (see text) and by inference therefore in the other brain areas with taste-related responses, as indicated in the figure. Adapted from ref. [89]

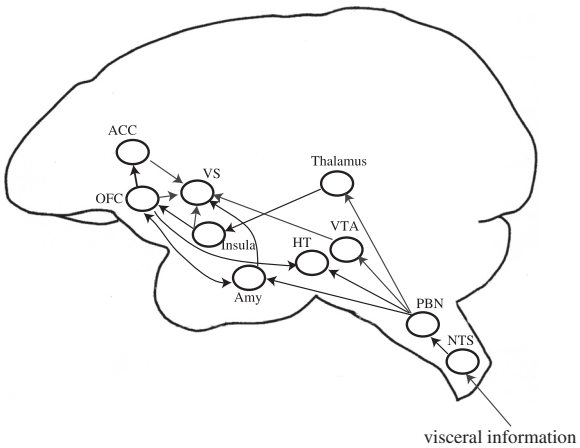

Fig. 3 Visceral information pathways in the macaque. Visceral afferent information reaches the caudal part of the nucleus of the solitary tract (*NTS*), which projects to the parabrachial nucleus in the pons (*PBN*). The *PBN* projects to the *Thalamus* (the visceral not taste part of VPMpc, amygdala (*Amy*), hypothalamus (*HT*), and the ventral tegmental area (*VTA*). Visceral information from the *Thalamus* reaches the visceral part of the *Insula*, which in turn projects to the orbitofrontal cortex (*OFC*). The visceral information from the *VTA*, *Amy*, *Insula*, and *OFC* reaches the ventral striatum (*VS*). Taste information (not shown in the figure) reaches the taste insula, which projects to the *OFC*. In the *OFC*, both oral and visceral information is integrated, in that the responses of *OFC* taste neurons are decreased to zero by feeding to satiety, which reduces visceral and hormonal satiety signals. As a result of this integration in the *OFC*, the reward value of taste is represented in the *OFC*. The *OFC* projects to the *Amy*, *HT*, and the *VS*. In the *ACC*, actions are linked associatively with outcomes such as taste to implement actions to obtain goals such as rewards

not clearly separate from sensory processing in rodents [86–89] (Fig. 2). In rodents, the IC is involved in the learning of conditioned taste aversions (CTAs) [90–94].

There also appears to be a visceral representation in the agranular area of the IC, in the ventral part of the anterior IC [65], and the agranular insula projects to the VS [66]. Stimulation of the anterior IC elicits autonomic responses and modulation of vascular and respiratory states [95]. Thus, signals from the mouth and gut are processed separately within the primate IC.

Orbitofrontal cortex

The OFC receives gustatory information from the IC, and the posterior OFC has been recognised as an area which processes visceral and also olfactory and visual information about foods [16, 17, 55, 65, 96–104]. The OFC projects to the ACC, hypothalamus, amygdala, and VS [56, 64, 67–70, 103]. In addition, the OFC plays an important role in the reward value and the related subjective pleasantness of oral stimuli. First, OFC neurons discriminate between different visual stimuli which are associated with different rewards (such as foods) or punishers (such as the taste of salt) [100, 105–108]. Second, the responses of OFC neurons to taste, olfactory, and visual stimuli produced by food are decreased to zero after the reward value of the food has been decreased by feeding the food to satiety [109, 110]. Third, the activity of OFC neurons reflects the reward value of visual and olfactory stimuli, for the neuronal responses reverse when the association of the visual and olfactory stimuli with taste reward or punishment reverses [100, 111]. That is, the OFC updates stimulus value rapidly when it changes [87, 88]. Stimulation of the posterior OFC elicits vascular and respiratory responses [95, 112, 113].

Anterior cingulate cortex

Areas 24, 25, and 32 of the ACC (in the rat the infralimbic cortex and prelimbic area are counterparts of areas 25 and 32) receive inputs from the OFC [64, 114]. Areas 24, 25, and 32 project to the VS [70], and areas 25 and 32 project to the hypothalamus [103, 115, 116]. Neurons of areas 25 and 32 or the infralimbic cortex encode taste stimuli [117, 118] and in rodents show more sustained responses to palatable taste stimuli compared to IC neurons [118]. Neuronal activity in areas 25 and 32 is modulated by internal information such as thirst [119] and in area 24 is related to reward-related actions [120, 121]. There is preliminary evidence that the responses of ACC neurons to taste stimuli are influenced by feeding to satiety [117]. In addition, stimulation of the ACC produces vascular and respiratory responses [122, 123]. Primate lesion studies suggest that the ACC is a site of action-outcome learning, where the outcome is a reward such as taste [124].

Amygdala

The CEA receives visceral information directly from the PBN [52, 57, 62, 63, 125, 126] and gustatory information from the posterior OFC [56, 127] while the lateral nucleus of the amygdala (BLA) receives gustatory information from the IC [128, 129]. There are some connections between the CEA and BLA [130]. The CEA and BLA project to the VS [131]. Amygdala neurons are broadly tuned across taste and other oral sensory stimuli compared to the OFC and IC neurons [132, 133]. The amygdala is involved in associative learning, with the BLA involved in the formation of Pavlovian incentives involving the association of a conditioned stimulus (CS) with the specific sensory features of the unconditioned stimulus (US). By contrast, the CEA is involved in preparatory conditioning—that is, in the association of a CS with the general affective properties of the US [134, 135]. Taking account of information processed from the mouth and GI tract, the BLA may reflect signals elicited by food in the mouth while the CEA may reflect those in the GI tract. The responses of neurons of the CEA and BLA in rats to conditioned taste stimuli are influenced by the

conditioning [136]. Amygdala neurons of primates discriminate visual stimuli associated with a positive (sweet taste) or negative (air puff or tail pinch) outcome [137, 138], but do not reverse their firing rapidly when the reward contingency changes [139], and are thus unlike OFC neurons. In addition, the amygdala is involved in the evaluation of food reward during the period of selective satiation in that the devaluation is impaired by inactivating the BLA before the selective satiation, but not after satiation [140]. The responses to taste of some CEA neurons in primates showed relatively small decreases, on average by 58 %, during satiety [141].

Hypothalamus

The hypothalamus receives neural inputs from different areas such as the PBN, amygdala, and the prefrontal cortex including the anterior IC, caudal OFC, and the ACC [52, 57, 63, 103, 115, 116, 126], and gut peptide hormone signals via a humoral pathway [71, 72, 74, 75, 77, 78]. The hypothalamus projects to the OFC [56, 142–144]. The hypothalamic nuclei, including the ARC where neural and humoral signals communicate, the lateral hypothalamic area, ventromedial hypothalamic nucleus, and the paraventricular nucleus are key regions for food intake control ([72, 74, 75, 77, 78]. The ARC contains agouti-related peptide-expressing neurons and pro-opiomelanocortin neurons which have positive and negative effects on feeding behaviour, respectively [74, 75, 145–147]. The ARC communicates with the paraventricular nucleus, lateral hypothalamic area, and ventromedial hypothalamic nucleus [72, 74, 75, 77, 78, 146, 147]. It is noted that rat hypothalamic neurons which express SGLTs respond to changes in glucose concentration [31, 148]. In addition, the responses of lateral hypothalamic area neurons to a taste stimulus and to the sight of food decrease to zero when the food is fed to satiety [149, 150] in a similar way to that of OFC neurons which may provide the relevant taste and visual inputs to the hypothalamus. Thus, the hypothalamus reflects the integration of sensory inputs produced by food with unconditioned and probably conditioned satiety signals of neural and humoral origins.

In summary, oral and visceral signals are transferred to the cortices via the thalamus in the primate. The IC is involved in the discrimination of oral sensory stimuli. In rodents, the IC may contribute to conditioned taste aversion. The OFC integrates individual sensory modalities of food (taste, olfactory, visual, oral texture, and temperature) to provide a multimodal representation of food and represents it in terms of its reward value. The ACC is implicated in action-outcome learning, that is, of which actions are associated with reward. The OFC and ACC project to the VS which also receives visceral- and emotion-related information from the agranular insula and amygdala, respectively, which takes part in a reward circuit. The amygdala and hypothalamus receive visceral inputs from the PBN directly as well as sensory inputs from these cortical areas. The OFC and amygdala are involved in learning associations of visual and olfactory stimuli with taste and will act together to influence feeding behaviour based on reward value [88, 151, 152]. The hypothalamus receives gut peptide hormonal signals and integrates these with neural information from the mouth and GI tract. Thus, in the primate, food-related signals from the mouth and gut are processed differently in separate areas and are integrated in the OFC and hypothalamus which are part of a reward circuit which drives goal-directed behaviours including food intake.

Human imaging studies including cognitive effects on food reward and GI function

Human imaging studies have shown taste-related activity in the IC, OFC, and in the ACC [153, 154]. Activations in a ventral part of the IC are related to autonomic signals [155] and the region may even overlap partly with the taste-responsive areas.

OFC BOLD signals represent the reward value and subjective pleasantness of taste as shown for example by taste devaluation by feeding to satiety [156–159] and are modulated by gut peptides, PYY, and ghrelin [160, 161]. The fact that the OFC and ACC show strong effects of cognitive labels and selective attention instruction that influence the palatability of taste and flavour indicates that the OFC and ACC are involved in the processes by which cognitive information modulates the pleasantness of flavour [162, 163]. In addition, the ACC plays a role in action-outcome learning [155, 164–167] to allow actions to be learned to obtain rewards. Thus, the orbitofrontal cortex and cingulate cortex contribute to control feeding behaviour by representing reward value including the effects of cognition and attention on reward value.

With respect to cognitive effect on GI function, it has been found, for example, that cognitive manipulation can modulate gut response such as gastric emptying [168] and affect subsequent food intake [169, 170]. Further investigation of how cognition affects food reward and GI function will be useful in developing our understanding of the control of food intake.

Interactions between oral and visceral sensory signals

Oral signals of taste, texture, and temperature, and retronasally sensed olfactory effects, implement the hedonic reward value of food, with subjective pleasantness correlated with activations in the OFC and ACC. Animals including humans work to obtain small quantities of these oral signals. Food placed directly into the gut or provided intravenously does not produce immediate unconditioned reward with small quantities [171, 172], though conditioning to food placed in the gut can be

acquired in what is a form of learned appetite [173], sometimes referred to as appetition [174]. When ingested food reaches the GI tract, it produces satiety by producing gastric distension (as shown by the absence of satiety in sham feeding when food drains from a gastric or duodenal cannula [175, 176]), and the gastric distension only occurs if food enters the duodenum where it activates gut receptors so causing closing of the pyloric sphincter. If the distension is reduced at the end of a meal, then feeding resumes very quickly in non-human primates [176]. This is probably an unconditioned satiety effect produced by gastric distension. In addition to unconditioned effects of food in the gut, there are also conditioned effects whereby the post-ingestive consequences of a flavour can influence the reward value of the flavour later, as described below.

Sensory-specific satiety is the state in which a food becomes less rewarding after it has been eaten to satiety, but other foods may remain rewarding [87, 177, 178]. This phenomenon is implemented in the OFC [110], which receives not only sensory but also visceral information [55, 65, 97–99, 102, 103]. Further integration of all these signals may occur in the hypothalamus which receives projections from the OFC and PBN.

CTAs which involve associative learning between oral and visceral stimuli have been shown with rats [179–185]. For example, a novel taste solution (CS) followed by aversive malaise (US) will not be ingested afterward although the taste solution was rewarding before the conditioning. The acquisition of this conditioning depends on the IC in rats, but changes then occur in the NTS (which will influence activity in all rodent taste areas), and the CTA thereafter no longer requires the presence of the IC [93, 94]. CTAs have rarely been studied with non-human primates. Conditioned taste preferences (CTPs) depend on visceral signals, involving calories and nutrients that are components of the unconditioned stimulus [173, 184–186]. The conditioning can be fast, apparently influencing preference for a flavour stimulus such as cherry vs grape within 15 min [174, 187]. The post-oral effect apparently does not require T1R2 + T1R3 sweet taste receptors in the gut in that flavour preference was still conditioned to intragastric infusion of sucrose in T1R3 knockout mice [188]. A humoral pathway is involved in post-oral glucose conditioning since visceral deafferentiation does not impair glucose-conditioned flavour preferences [189]. In addition, humoral signals generated by intestinal SGLT1 and SGLT3, and to a lesser degree, GLUT2, may mediate post-oral sugar appetition in mice [190]. It has been suggested that sugar metabolism is not essential for the post-oral intake-stimulating and preference-conditioning actions of sugars in mice [190–193]. Interestingly, non-deprived and sated animals can still acquire strong conditioned taste preferences [194].

The energy value of food can produce conditioned appetite or preference for a food and can also produce conditioned satiety [173]. Most of the above studies have been on conditioned *preference* produced by food in the GI tract. It will be of interest in future research to analyse in addition how post-ingestive signals can produce conditioned *satiety* for the flavour with which they are paired. It would be of interest to develop our understanding of conditioned satiety, for this may be relevant to food intake control and its disorders. There is some evidence on this in humans below.

Sensory-specific satiety and associative learning in humans

Interestingly, there is no significant difference between sensory-specific satiety following high- and low- caloric sweetened food [195]. The OFC BOLD signal produced by the flavour of food is decreased in a sensory-specific satiety way by the food eaten to satiety, and this reduction of the BOLD signal in the OFC is correlated with the reduction of subjective pleasantness of the food eaten to satiety [159, 196]. The BOLD signals in the OFC and amygdala produced by visual stimuli associated with food are reduced after that food is fed to satiety [197].

CTAs have been described in humans [183, 198], in which the subjects describe feeling nausea after taking some food or drink and then decreased ingestion of the substances. In laboratory studies, subjects who have been exposed to unfamiliar flavoured food or drink (the conditioned stimulus) and are then rotated to cause motion sickness (the unconditioned stimulus) show less ingestion of the flavoured food or drink afterwards [199, 200]. CTPs are likely to be acquired depending on physiological state, such as a deficit in a particular nutrient, e.g., protein [201], or in energy [202]. Young children show preferences for high-caloric flavour after experiences of unfamiliar-flavoured foods with low- and high-energy density suggesting that they learn post-ingestive consequences of caloric density [203, 204]. Interestingly, umami flavour (monosodium glutamate) reduces hunger and enhances satiety [205, 206], which suggests that umami may produce conditioned satiety and act as a potential regulator of food intake. Thus, both learned appetite and learned satiety can result from an association between the flavour of a food and its post-ingestive consequences [173, 207] where the integrated information about that food will be transferred into a reward circuit to drive feeding behaviour.

Taken together with animal studies, preferences and aversions to food can be conditioned by food in the GI tract where the OFC and amygdala can play an important role in associative learning between oral and gut information with the hypothalamus involved in the integration of humoral and neural signals such as hunger and satiety. To help control feeding behaviour better,

it is crucial to understand the mechanisms that produce signals for nutrient deficits and/or physiologically required energy, and those that produce satiety signals, and how these are integrated in the brain and combined with cognitive signals in which the OFC and ACC are involved. This is likely to lead to advances in the treatment of eating disorders such as anorexia nervosa where it has been reported that the bottom-up processing is decreased while the top-down cognitive processing is increased [208, 209].

Conclusions

Food is sensed twice, first in the mouth and then in the gut. The signals are transferred separately to the central nervous system through different pathways and interact in areas such as the orbitofrontal cortex and hypothalamus in primates to produce reward signals that influence food intake and that are reflected in the subjective pleasantness of taste, flavour, and food. The rewarding effect of food produced by food in the mouth is decreased by feeding to satiety and can also be influenced by learning by signals in the gut that lead to conditioned appetite and satiety for the flavour of the food. The amygdala and orbitofrontal cortex are involved in reward evaluations and conditioned preference and aversion. The effects of cognition and attention on taste and flavour are evident in the orbitofrontal cortex and anterior cingulate cortex.

The signals that originate in the mouth are a major contributor to the reward value of food, which can lead to a decision to eat that food. Signals that originate in the gut are involved in the termination of a meal, that is, in satiety. Gut signals which are transferred via neural and humoral pathways can provide information about the metabolic and nutritional content of the food that can lead, over time, to learned appetite and satiety for the flavour of a food and influence reward value of foods. The extent to which these gut signals mediate nutrient-specific effects on food intake is an important subject for future research. In addition, one key area for investigation is how the hunger and satiety signals represented in the hypothalamus modulate taste, olfactory, and flavour signals to produce a food reward signal that drives eating. Little is known for example about how these hunger and satiety signals project to reward-related areas such as the orbitofrontal cortex. Understanding further the dual sensing of food in the mouth and gut, and cognitive signals, is important for a better understanding of the control of food intake and potentially of its disorders and metabolic disorders. Identifying the neural processing of sensory signals produced by chemical components of food may lead to promising treatments for metabolic disorders, and understanding top-down cognitive processes may contribute to improve treatment for eating disorders.

Abbreviations

ACC: anterior cingulate cortex, ARC: arcuate nucleus, BLA: basolateral nucleus of the amygdala, BOLD: blood-oxygen-level-dependent, CEA: central nucleus of the amygdala, CKK: cholecystokinin, CNS: central nervous system, CS; conditioned stimulus, CTA: conditioned taste aversion, CTP: conditioned taste preference, GI: gastrointestinal, GLP-1: glucagon-like peptide-1, GLUT2: glucose transporter type2, IC: insular cortex, NTS: nucleus of the solitary tract, OFC: orbitofrontal cortex, PBN: parabrachial nucleus, PP: pancreatic peptide, PYY: peptide YY, SGLT: sodium-glucose transporter, US: unconditioned stimulus, VPMpc: parvicellular division of the ventroposteromedial nucleus, VS: ventral striatum.

In addition, a short glossary of some of the terms used follows:

Pleasure is a subjective sensation. *Pleasantness* describes how much pleasure is produced by a stimulus. A *reward* is a stimulus for which an instrumental action will be performed. *Delicious sensation* is a sensation produced by a delicious flavour, and implies the Japanese word umami which translates as delicious. *Reward value* is an operationally measure by how hard an animal will work to obtain a reward, and by the preference for that reward compared to other rewards. *Subjective pleasantness* refers to the subjectively reported pleasantness of a stimulus.

Competing interests
The author declares that there is no conflict of interest.

Acknowledgements
This work was supported by MRC intramural programme MC-A060-5PQ10.

Received: 24 September 2015 Accepted: 15 December 2015
Published online: 29 December 2015

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