Published in final edited form as:
Adv Tech Stand Neurosurg. 2011 ; 36: 31–59. doi:10.1007/978-3-7091-0179-7_3.

Gustatory and reward brain circuits in the control of food intake

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Abstract

Gustation is a multisensory process allowing for the selection of nutrients and the rejection of irritating and/or toxic compounds. Since obesity is a highly prevalent condition that is critically dependent on food intake and energy expenditure, a deeper understanding of gustatory processing is an important objective in biomedical research. Recent findings have provided evidence that central gustatory processes are distributed across several cortical and sub-cortical brain areas. Furthermore, these gustatory sensory circuits are closely related to the circuits that process reward. Here, we present an overview of the activation and connectivity between central gustatory and reward areas. Moreover, and given the limitations in number and effectiveness of treatments currently available for overweight patients, we discuss the possibility of modulating neuronal activity in these circuits as an alternative in the treatment of obesity.

Keywords

Taste; postingestive; feeding; deep brain stimulation

Introduction

In most societies the prevalence of obesity has risen dramatically to reach epidemic proportions. In the United States alone, a staggering 30% of all adults are obese (Stein and Colditz 2004). Increase in adiposity leads to significant metabolic dysregulation, with important health and economic consequences (Stein and Colditz 2004). Increased availability of palatable and high-calorie food and reduced requirement for energy expenditure through physical activity are usually identified as the main culprits of this obesity epidemic (Keith, Redden et al. 2006). Nonetheless, the participation of genetic factors in the definition of individual susceptibility for the occurrence of obesity is also

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widely accepted and has been extensively described (O'Rahilly and Farooqi 2006). While such factors are commonly assumed to influence metabolic rate or the partitioning of excess calories into fat, current data suggests that a significant part of the genetic influence on human obesity has a direct impact on neural regulation of hunger, satiety and food intake (Friedman 2009). An important objective in neuroscience research is thus to further understand the central mechanisms of food reward and appetite regulation, which will predictably allow a deeper comprehension of eating disorders such as obesity.

Gustation and the gustatory system: definitions

Gustation has historically been defined as a synonym of taste. Recently, however, this term has been used to define a broader concept, which extends beyond taste (Simon, de Araujo et al. 2006). In this broader sense, gustation is considered as the multisensory process that allows for the selection of nutrients and rejection of irritating and/or toxic compounds (Simon, de Araujo et al. 2006).

Gustatory processing begins when a motivated animal searches for and detects a desired food, usually using visual and/or olfactory cues. Once a desired substance is found, the decision to pursue and maintain consumption usually involves active oral exploration. The unitary sensory perception resulting from taste, odour, texture and temperature of that stimulus, i.e., its' flavour, will be a central contributor in the decision of ingestion vs. rejection (Small and Prescott 2005). Gustatory decision making is also impacted by the organisms' internal state. The central nervous system (CNS) detects a multitude of neural and humoral signals from the periphery, reflecting several aspects of homeostatic balance such as gastrointestinal status, current energy needs and availability, and energy stores (Broberger 2005). The maintenance of energy homeostasis and stable body weight depends on the integration of these endogenous signals with sensory feedback, and the ability to respond adequately through modulation of both energy expenditure and food intake (Schwartz and Porte 2005). Finally, the memories of orosensory, olfactory and postingestive effects of previous encounters with a similar substance also influence food seeking and ingestion (Sclafani 2004), as do emotional, cognitive and social factors (Wilson 2002).

The multisensory properties of intra-oral and ingested stimuli are conveyed to the brain through specialized taste, somatosensory, olfactory and visceral sensory neurons that converge on several CNS centres. Thus, once beyond the periphery, single neurons responding to gustatory stimuli are often found to be broadly tuned to diverse combinations of chemosensory, somatosensory, olfactory and even visual information (Rolls and Baylis 1994). Furthermore, the CNS detects humoral signals that cross the blood-brain barrier and transmit information not only about the properties of ingested stimuli, but also about physiological states, such as satiety (Zheng and Berthoud 2008), providing additional modulatory influences for central gustatory neurons (Nakano, Oomura et al. 1986). Neurons with these multimodal response properties, distributed through several CNS areas, integrate sensory and homeostatic information, participating with neural circuits of affective, cognitive and motor processing to organize ingestive behaviour (Kelley, Baldo et al. 2005).

Orosensory gustatory input

The peripheral gustatory system extracts multisensory information from substances placed in the mouth, and conveys this information through multiple neural pathways to brainstem structures (Kawamura, Okamoto et al. 1968). Taste receptor cells (TRCs) are responsive to the type and quantity of chemicals dissolved in saliva and allow for the detection of at least five distinctive taste qualities: salt, sweet, bitter, sour (acidic) and umami (savoury taste of amino acids) (Spector and Travers 2005). Information about less water-soluble compounds, as well as food characteristics such as texture, viscosity and temperature, is primarily

transduced by specialized somatosensory neurons with endings distributed throughout the oral epithelium (Halata and Munger 1983).

In vertebrates, TRCs are found in specialized microscopic taste receptor organs – the taste buds. Mammalian taste buds are onion-shaped cell groups embedded at the surface of several intra-oral structures, mainly the palate and tongue, where they cluster into macroscopic structures named gustatory papillae. Each taste bud contains several distinct morphological cell types that can be distinguished by ultrastructural and immunohistochemical features (Murray 1971). Type I or dark cells have processes that envelop nerve fibres and other taste cells and, given their expression profile of neurotransmitter-related enzymes and transporters, are thought to have a support function (Bartel, Sullivan et al. 2006). However, a recent report demonstrated that type I cells have responses that depend on epithelial sodium channels (ENaCs – see below), suggesting a possible role in salt taste transduction (Vandenbeuch, Clapp et al. 2008). Type II (light or receptor cells) and type III (intermediate or presynaptic cells) are considered the main chemosensing TRCs. Type II receptor cells express G-protein-coupled receptors (GPCRs), phospholipase C β2 (PLCβ2) and transient receptor potential ion channel 5 (TRPM5). Different type II cell subtypes appear to respond exclusively to sweet, bitter or umami tastants (Tomchik, Berg et al. 2007). Given their ultrastructural and molecular characteristics, these cells do not seem to have conventional synapses and, rather, appear to release transmitters via pannexin or connexin hemichannels (Huang, Maruyama et al. 2007). Type III presynaptic cells have synaptic contacts with intragemmal nerve fibres and, accordingly, express synapse-related proteins such as SNAP-25 (synaptosomal-associated protein of 25kD) (Yang, Crowley et al. 2000). Since they have broadly tuned responses to tastants of multiple qualities, some authors propose that presynaptic cells may receive converging information from receptor cells, presumably via purinergic signaling (Tomchik, Berg et al. 2007). Finally, type IV or basal cells, in contrast to the remaining cell types, do not have an elongated shape. They are thought to have a proliferative role to support constant cell turnover in the taste bud (Murray 1971).

Microvillar processes from taste receptor cells extend towards the bud pore, on the mucosal surface, where contact with sapid chemical stimuli occurs. Taste receptors are transmembrane proteins found on these microvilli and are the basis for many of the chemosensory properties of TRCs. Upon detection of a specific stimulus, they will activate intracellular transduction cascades to initiate the process of gustatory neural signalling (Margolskee 2002). Proteins belonging to the GPCR superfamily have been established as receptors for sweet (T1R2/T1R3 receptors), umami (T1R1/T1R3 receptors), and bitter (T2R receptors) tastants (Zhao, Zhang et al. 2003; Mueller, Hoon et al. 2005). The predominant downstream signaling pathways for these receptors require PLCβ2 and TRPM5 (Zhang, Hoon et al. 2003). There is also evidence implicating gustducin, a G-protein almost exclusively expressed in TRCs, in bitter and sweet taste transduction (Wong, Gannon et al. 1996). Sour and salt taste qualities rely on a different set of receptors and signaling pathways (Zhang, Hoon et al. 2003). Recently, two TRP ion channels from the polycystic kidney disease-like family, co-expressed in a subset of TRCs that are necessary for sour taste transduction (Huang, Chen et al. 2006), were proposed to form a candidate sour receptor (Ishimaru, Inada et al. 2006). Alternate mechanisms for detection of sour tastants have been described, but it is unclear to what degree these putative pathways for sour taste are specific for different species and/or regions of the tongue (Huque, Cowart et al. 2009). For salt taste, at least two distinct mechanisms exist in rodents: an amiloride-sensitive epithelial sodium channel (ENaC), accounts for part of the responses to sodium and lithium ions (Heck, Mierson et al. 1984) while other, amiloride-insensitive mechanisms, serve as receptors for multiple ions including sodium, potassium, ammonium and calcium (DeSimone, Lyall et al. 2001). A variant of TRPV1, a transient receptor potential vanilloid

receptor, has been proposed as an amiloride-insensitive salt taste receptor (Lyall, Heck et al. 2004) but the perceptual relevance of this receptor mechanism is still controversial (Treesukosol, Lyall et al. 2007).

Perception of a given taste quality seems to reflect the activation of a specific population of TRCs rather than the properties of a specific interaction between a tastant and a taste receptor (such as the kinetics of taste receptor activation). In fact, taste receptors for sweet, bitter, umami and sour are present in largely segregated populations of taste cells that function as narrowly tuned sensors for each of these taste qualities (Zhang, Hoon et al. 2003; Huang, Chen et al. 2006). Additionally, the selective activation of a TRC population expressing a particular taste receptor is, in itself and irrespective of the actual receptor being activated, sufficient to generate approach or rejection behaviours that are specific for that taste quality (Zhao, Zhang et al. 2003; Mueller, Hoon et al. 2005). It is therefore clear that sweet, bitter, umami and sour taste pathways are segregated at the TRC level. However, this labelled-line model does not seem to be conserved in the CNS, where most authors suggest the occurrence of multisensory and distributed gustatory processing (Simon, de Araujo et al. 2006).

Adenosine triphosphate (ATP) signaling is necessary for transmission of taste information to the CNS. Tastant evoked ATP release activates $P2X_2/P2X_3$ ionotropic purinoreceptors on primary gustatory afferent nerve terminals (Finger, Danilova et al. 2005). Serotonin and norepinephrine are also released from taste buds upon chemosensory stimulation, but their functional role is not as clear as that of ATP (Heath, Melichar et al. 2006; Huang, Maruyama et al. 2008). Other transmitters, peptides and respective receptors, namely acetylcholine, glutamate, cholecystokinin (CCK), vasoactive intestinal peptide, substance P and leptin, have also been identified in taste cells. Many of these compounds are thought to modulate, in an autocrine or paracrine manner, the responses to tastants (Heath, Melichar et al. 2006; Huang, Maruyama et al. 2008).

The chorda tympani and greater superior petrosal branches of the facial (VII^{th}) nerve carry sensory axons of cells in the geniculate ganglion and innervate taste buds respectively in the anterior tongue and palate. Sensory axons of the glossopharyngeal (IX^{th}) nerve, with cell bodies in the petrosal ganglion, terminate in taste buds in the posterior tongue (lingual branch) and pharynx (pharyngeal branch). The nodose ganglion of the vagus (X^{th}) nerve contains primary taste neurons with axons that integrate the pharyngeal, superior laryngeal and internal laryngeal branches to innervate taste buds in the epiglottis, larynx and oesophagus (Miller 1995). Primary sensory neurons in these nerves transmit activity generated in TRCs centrally to the solitary tract nucleus (NTS) (Simon, de Araujo et al. 2006).

Peripheral neural taste pathways are functionally and anatomically very close to the somatosensory system, allowing chemical, thermal and tactile detection to act in concert to evaluate substances in the mouth. In fact, the glossopharyngeal and vagal nerves also carry somatosensory nerve fibres from the oral and upper digestive mucosa, as does the lingual branch of the trigeminal (V) cranial nerve (Matsumoto, Emori et al. 2001), allowing for the transduction of information relating to the temperature and texture of ingested stimuli (Halata and Munger 1983). Some intra-oral somatosensory nerve endings are activated by high concentrations of the same chemical stimuli that define some primary tastants, such as NaCl (Wang, Erickson et al. 1993), usually producing irritating sensations. Oral mucosa nerve endings may also have other chemosensing properties, as exemplified by the responses to capsaicin, found in chilli peppers and producing a burning sensation (Liu and Simon 1996), and to menthol, producing a cooling sensation (Chuang, Neuhausser et al. 2004), mediated by the thermo-sensitive TRPV1 and TRPM8 channels respectively.

Furthermore, dietary fats and oils, thought to be sensed mainly by their texture (Kadohisa, Verhagen et al. 2005) have recently been shown to activate chemosensory mechanisms, such as a fatty acid receptor/transporter, CD36, which is expressed in TRCs and modulates preference for long-chain fatty acid-enriched solutions (Laugerette, Passilly-Degrace et al. 2005). On the other hand, physical variables, such as temperature, can affect TRC taste transduction function, as exemplified by thermal modulation of sweet taste intensity (Talavera, Yasumatsu et al. 2005). Thus, it becomes clear that, already in the mouth, input to the gustatory system is inherently multisensory.

Postingestive sensory processes

Once a stimulus has been ingested it is not beyond detection by the CNS. In fact, there are multiple and complex humoral and neural postingestive mechanisms that signal not only the presence but also the character of intestinal content. Neural signals depend on the intrinsic and extrinsic enervation of the gastrointestinal tract (GIT). The latter is performed by the autonomic nervous system through both its divisions: parasympathetic (vagal and pelvic nerves) and sympathetic (splanchnic nerves) (Zheng and Berthoud 2008). These nerves, the vagus in particular, contain afferent neurons that transmit mechanical (i.e., touch, distension, contraction) and chemical sensory information from the GIT to the brain. The neural transmission of chemical information is thought to result from the detection of signaling peptides, such as CCK, produced by enteroendocrine epithelial cells with chemosensing properties (Cummings and Overduin 2007). These peptides also reach the circulation, acting on the brain as humoral signals, and are thus called ‘gut hormones.’ Absorbed nutrients (e.g., glucose) and feeding-related peptides produced in sites other than the gut (e.g., insulin), can also be humoral signals that modulate the activity of central gustatory circuits (Zheng and Berthoud 2008).

With a single exception, discussed below, all known sensory mechanisms originating in the gut are negative feedback signals that lead to decreases in food intake. They are called satiety or satiation signals (Cummings and Overduin 2007). Gastric content is detected by vagal afferent fibres in the mucosa, sensitive to touch, while other mechanosensory vagal afferents, in or between muscle layers, report intragastric volume (Wang and Powley 2000). While gastric satiation processes are predominantly mechanosensory, those originating from the intestine are essentially chemosensory or nutritive (Powley and Phillips 2004). Enteroendocrine cells in the gut lining detect chemical properties of intraluminal content and respond by releasing peptides through their basolateral membrane (Cummings and Overduin 2007). Chemosensing activity in enteroendocrine cells is thought to occur through mechanisms and transduction molecules similar to those used in taste, such as T1R3 receptors and gustducin, involved in both orosensory and intestinal responses to sugars (Margolskee, Dyer et al. 2007).

CCK, glucagon-like peptide 1 (GLP-1), oxyntomudulin, peptide YY (PYY) and ghrelin are all examples of gut hormones that have been well established as regulators of food intake (Cummings and Overduin 2007). CCK is produced in the duodenal and jejunal mucosa, mainly in response to lipids and proteins, and acts hormonally or via the vagal nerve to reduce food intake (Smith, Jerome et al. 1981; Blevins, Stanley et al. 2000). GLP-1, oxyntomudulin and PYY are produced in the more distal segments of the small intestine and the colon, in response to lipids and carbohydrates and, to a lesser extent, proteins (Brubaker and Anini 2003). When administered systemically or directly into the CNS, these peptides act as satiation factors (Turton, O'Shea et al. 1996; Dakin, Gunn et al. 2001; Batterham, Cowley et al. 2002) and, again, their effects upon peripheral administration involve afferent activity in the vagus nerve (Abbott, Monteiro et al. 2005). Many other gut peptides have

been described but, at this time, the regulation of their secretion and their status as physiologic modulators of feeding is unclear (Berthoud 2008).

Ghrelin is the only gut hormone that has been described to act as a positive feed forward stimulus of ingestion (Tschop, Smiley et al. 2000). It is secreted from neuroendocrine cells in the gastric mucosa with a temporal pattern of release that is out of phase from all other known gut and pancreatic peptides. Peak circulating levels occur prior to meals and a rapid decrease is observed when nutrients are emptied into the duodenum (Cummings, Purnell et al. 2001). Other than ghrelin and palatable oral gustatory stimulation, other ingestion-stimulating mechanisms have been proposed to exist, but remain undefined (Sclafani 2004).

Gut peptides are not the only humoral factors that modulate food intake. Free fatty acids, amino acids and glucose, can also convey information about nutritional status to the CNS. In fact, in the first theories for control of energy balance, circulating levels of glucose (Mayer 1953) or of lipids (Kennedy 1953) were proposed as the signals of nutritional status. We now know that nutrients in the bloodstream can cross the blood-brain barrier (Lam, Schwartz et al. 2005) and act directly on the CNS. Oleic acid (a long-chain fatty acid) (Obici, Feng et al. 2002), the amino acid leucine (Cota, Proulx et al. 2006) and glucose (Booth 1968) are examples of nutrients shown to inhibit food intake when administered centrally. Direct CNS nutrient sensing is thought to occur through key intracellular energy sensors in CNS neurons, found predominantly in the hypothalamus, such as ATP-sensitive potassium channels (Obici, Feng et al. 2002), malonyl-coenzyme A (malonyl-CoA) (Loftus, Jaworsky et al. 2000), AMP-activated protein kinase (Minokoshi, Alquier et al. 2004), long-chain fatty acyl-CoAs (Lam, Pocai et al. 2005) and mTOR (a highly conserved serine-threonine kinase) (Cota, Proulx et al. 2006).

Circulating nutrients also activate chemosensors in the pancreas and liver, resulting in the release of hormonal satiation peptides and/or vagal afferent activation (Cummings and Overduin 2007). In response to caloric load or vagal efferent activity, the pancreas releases insulin, pancreatic polypeptide (PP) and amylin (Lutz, Geary et al. 1995; Schwartz, Woods et al. 2000; Katsuura, Asakawa et al. 2002). With the exception of PP, that acts peripherally (Banks, Kastin et al. 1995), these peptides have effects directly in the CNS to exert an anorectic effect (Lutz, Del Prete et al. 1995; Obici, Feng et al. 2002). Portal-hepatic vagal afferents are also sensitive to circulating metabolites such as glucose (Niijima 1969), amino acids (Tanaka, Inoue et al. 1990) and fatty acids (Orbach and Andrews 1973), and also to gut peptides such as GLP-1 (Mithieux, Misery et al. 2005). While the chemosensing mechanisms in the porto-hepatic system are still unclear (Langhans 1996), it is well established that the activity of this system is relevant for the regulation of food intake (Tordoff and Friedman 1986). Finally, glucose-sensing cells have also been described in the carotid body (Pardal and Lopez-Barneo 2002).

Central gustatory sensory pathways

Taste pathways in the CNS are intimately associated with general viscerosensory afferents from the cardiovascular, respiratory and, importantly, gastrointestinal systems (Lundy and Norgren 2004). This is the case for all central taste relays, namely the NTS, parabrachial nuclei (PbN) of the pons, parvicellular division of the ventral posterior nucleus of the thalamus (VPpc) and insular or gustatory cortex, through which gustatory taste and visceral projections ascend mostly ipsilaterally (Lundy and Norgren 2004). However, in contrast to what happens in rodents, the primate PbN are essentially visceral relays and the NTS projects taste afferents directly to the thalamus (Norgren 1984). Circulating metabolic signals can also modulate neural responses in relays of the gustatory system, such as the

NTS, and in areas that receive direct or indirect gustatory afferents such as the hypothalamic homeostatic centres and reward-related areas in the midbrain (Zheng and Berthoud 2008).

Taste-related information derived from all chemoresponsive cranial nerves, and visceral input, mainly from the vagus nerve, converge in the NTS. The rostral division of the nucleus (rNTS) receives mostly taste afferents while the caudal NTS (cNTS) is the main target for vagal visceral information (Altschuler, Bao et al. 1989). Trigeminal somatosensory inputs from oral branches of the fifth nerve also project to the rNTS (Torvik 1956). Thus, trigeminal stimulants with irritating effects can modulate taste responses in the rNTS (Simons, Boucher et al. 2003), as does afferent vagal activity, such as that produced by gastric distension (Glenn and Erickson 1976). The NTS has ascending projections to the PbN and local or descending projections to somatic and visceral premotor/motor areas (Norgren 1978). Local medullary connections with somatic motor or autonomic preganglionic nuclei, either directly or through interneurons in the parvicellular reticular formation, are substrates for reflexes involved in chewing (motor nuclei of the trigeminal and facial nerves), tongue movement (hypoglossal nucleus), salivation (superior and inferior salivatory nuclei), swallowing (nucleus ambiguus) and GI motility and secretion (dorsal motor nucleus of the vagal nerve) (Contreras, Gomez et al. 1980; Travers and Norgren 1983; Beckman and Whitehead 1991). Thus, circuits in the hindbrain are sufficient for decerebrate rats to display both acceptance and rejection behaviours to oral stimulation with tastants (Grill and Norgren 1978).

The parabrachial complex is a collection of nuclei located in the dorsolateral aspect of the pons. The PbN nuclei are physically divided into medial and lateral subdivisions by fibres of the superior cerebellar peduncle. In rodents, ascending neural pathways from the NTS synapse in the ipsilateral PbN (Norgren and Leonard 1971). The segregation of taste and visceral projections to the rat PbN is not as clear as in the NTS (Hermann, Kohlerman et al. 1983). Nevertheless, visceral afferent projections arising from the cNTS terminate primarily in nuclei of the lateral subdivision while taste responsive neurons are found mainly in the medial PbN (Karimnamazi, Travers et al. 2002). From the PbN, third order neurons ascend to form two gustatory projection systems: one projecting dorsally to the thalamus and another projecting ventrally to the forebrain (Norgren and Leonard 1973).

PbN projections to forebrain centres are mostly reciprocal. In fact, taste-responsive PbN neurons are modulated by electrical stimulation of forebrain sites (Di Lorenzo 1990; Li, Cho et al. 2005). The rNTS is also a target of descending forebrain projections from the insular and prefrontal cortices, central nucleus of the amygdala (CeA), lateral hypothalamus (LH), bed nucleus of the stria terminalis and substantia innominata (van der Kooy, Koda et al. 1984). These descending neural pathways are presumably involved in the modulation of taste activity by physiological and experiential factors (Li, Cho et al. 2005).

In primates, including humans, rNTS projection fibres have not been shown to terminate in the PbN and synapse directly in the VPpc (Beckstead, Morse et al. 1980). Thus, input to the primate PbN is essentially viscerosensory, the bulk of the projections from PbN are directed towards the ventral forebrain (Pritchard, Hamilton et al. 2000) and the VPpc receives most of its gustatory input directly from the NTS (Norgren 1984). In rodents, the dorsal thalamocortical pathway, originating mainly in the medial PbN, synapses in the VPpc of the thalamus and terminates in the insula. The VPpc is the dorsal thalamic relay for orosensory and visceral information. PbN efferents to this thalamic nucleus are bilateral with an ipsilateral predominance (Fulwiler and Saper 1984). In fact, while the receptive field for parabrachial gustatory neurons is ipsilateral (Hayama, Ito et al. 1987), they can be antidromically driven from the thalamus on either side (Ogawa, Hayama et al. 1984). However, viscerosensory projections to the thalamus from the external medial parabrachial

subnucleus are mainly contralateral (Cechetto and Saper 1987). VPpc neurons respond to combinations of chemosensory and/or somatosensory oral stimulation (Nomura and Ogawa 1985) with a medial to lateral arrangement described for taste, thermal and tactile responses (Kosar, Grill et al. 1986), and also for taste, GI and cardiovascular/respiratory responses (Cechetto and Saper 1987). Neurons in the VPpc projects to the insular cortex and also to the amygdala (Ottersen and Ben-Ari 1979).

The primary taste cortex in macaques is defined as the area receiving afferents from the VPpc, extending posteriorly ~4mm from its anterior limit at the junction of the orbitofrontal and opercular cortices (Scott and Plata-Salaman 1999). Functional neuroimaging studies have shown that, in the human brain, homologous gustatory cortical areas, in the insula and frontal operculum, respond to unimodal taste stimuli (Small, Zald et al. 1999). The rodent insula is a cortical region ventral to the oral region of the somatosensory cortex and dorsal to the rhinal sulcus. According to the presence or absence of a granule cell layer, the insular cortex is divided into two histologically distinct subdivisions: the granular and agranular insular cortices. In the dorsal segment of the agranular cortex, adjacent to the granular area, there are scattered granule cells that define a thin strip of dysgranular cortex (Lundy and Norgren 2004). It has been noted that insular somatosensory and visceral responses occur in the more dorsal granular insula, whereas taste responses occur ventrally, in the dysgranular area, that is thus proposed to be the primary gustatory cortex (GC) (Cechetto and Saper 1987; Lundy and Norgren 2004). This stringent definition of the GC as a distinct functional unit, anatomically separated from the more dorsal granular viscerosensory and somatosensory cortex, is challenged by the fact that single neurons in the insula can respond to multiple sensory modalities, namely taste, somatosensory, visceral and nociceptive stimuli (Hanamori, Kunitake et al. 1998). Also, upon stimulation of the entire oral cavity, taste responsive neurons are found not only in the dysgranular but also the granular and, to a lesser extent, the agranular insular cortex (Ogawa, Ito et al. 1990). Recent work with optical imaging of the rat insular cortex upon stimulation of the tongue with multiple tastants has equally described responses that include but are not restricted to the dysgranular insula (Accolla, Bathellier et al. 2007).

The different insular regions projects back to their respective thalamic sensory relays and to other cortical areas (Shi and Cassell 1998). The orbitofrontal cortex (OFC), sometimes defined as a secondary taste cortical area (Rolls, Yaxley et al. 1990), receives converging projections from the GC and primary olfactory cortex, proposed as relevant for the perception of flavor (Small and Prescott 2005).

Amygdala and brain reward pathways

The ventral forebrain gustatory projection system includes projections to several structures in the limbic forebrain, such as the hypothalamus (Zaborszky, Beinfeld et al. 1984), amygdala, substantia innominata and bed nucleus of the stria terminalis (Fulwiler and Saper 1984). The amygdala and the hypothalamus receive other ascending and descending projections from gustatory sensory relays and have important roles in the integration of gustatory input. In the amygdala, the central (CeA) and basolateral (BLA) nuclei are the main sites receiving gustatory projections from the NTS (Ricardo and Koh 1978), PbN (Fulwiler and Saper 1984; Karimnamazi and Travers 1998), VPpc (Ottersen and Ben-Ari 1979) and insula (Ottersen 1982). The CeA projects back to the NTS and PbN (Krettek and Price 1978) while the BLA has projections to the insula (Krettek and Price 1977). The two amygdalar areas are also interconnected (Ottersen 1982).

The amygdala is reciprocally connected with areas of the midbrain dopaminergic reward system. The latter arises from ventral tegmental area (VTA) dopamine producing neurons

that project to the nucleus accumbens (NAcc) and participate in the processing of food reward (Wise 2006). The amygdala is connected both with the VTA (Phillipson 1979) and the NAcc (Kirouac and Ganguly 1995) through the CeA and the BLA. The NAcc also receives afferents directly from other gustatory-related centres, namely the NTS (Ricardo and Koh 1978), insula (Brog, Salyapongse et al. 1993) and LH (Baldo, Daniel et al. 2003). Additionally, circulating pancreatic and gut hormones such as insulin (Figlewicz 2003), PYY (Batterham, ffytche et al. 2007) and ghrelin (Abizaid, Liu et al. 2006) have been shown to directly modulate the activity of midbrain dopamine neurons. The NAcc seems to be a central interface in the integration of sensory, emotional and cognitive controls of food intake (Kelley, Baldo et al. 2005). Single accumbens neurons receive convergent inputs from the hippocampus, BLA and prefrontal cortex (French and Totterdell 2002; French and Totterdell 2003), and dopamine regulates the effect of these afferents on NAcc neurons (Goto and Grace 2005). NAcc projections to the LH, either direct or through the ventral pallidum, are thought to be its' major effector pathway in the control of feeding behaviours (Stratford and Kelley 1999).

Food reward, however, is not a unitary concept, and its different conceptual components have been ascribed to different neural substrates. The dissociation between motivational ("wanting" or incentive salience) and hedonic ("liking" or affective salience) components of food reward is one that has been extensively explored (Berridge 2009). While incentive and affective salience often occur simultaneously and are modulated by neurons found in the same brain areas, such as the NAcc and ventral pallidum, they are behaviourally and neurally distinguishable. "Wanting" reflects the value of a rewarding stimulus in terms of its capacity to elicit an action to obtain that stimulus, and is thought to depend highly on mesolimbic dopamine neurotransmission. "Liking," on the other hand, is the actual pleasurable sensation obtained upon contact with that stimulus, which is often quantified according to stereotypical orofacial responses that can be observed during consumption (Berridge 1996). While activation of opioid receptors in the NAcc is a potent stimulant of food intake, this effect is specific for palatable foods (Woolley, Lee et al. 2006). Furthermore, opioidergic stimulation of a small subsection of the NAcc ("hedonic hotspot") can specifically modulate orofacial "liking" responses in rats, suggesting a central role for endogenous opioid neurotransmission as a substrate for affective salience (Berridge 2009).

Hypothalamus, brainstem and energy homeostasis

Other than the amygdala, the hypothalamus is the main target of the ventral forebrain gustatory projections system. The NTS projects directly to the median preoptic, paraventricular (PVH), dorsomedial (DMH) and lateral (LH) hypothalamic nuclei (Ricardo and Koh 1978), while the PbN nuclei project to the median preoptic, PVH, LH, and ventromedial hypothalamus (VMH) (Fulwiler and Saper 1984; Zaborszky, Beinfeld et al. 1984). Furthermore, descending projections from the agranular insular cortex target the LH (Yasui, Breder et al. 1991). Lesion studies have established the importance of the hypothalamus for the control of feeding, weight and energy homeostasis. Destruction of the VMH, DMH or PVH induces hyperphagia and obesity (Hetherington and Ranson 1940; Brobeck, Tepperman et al. 1943) while LH lesions induces hypophagia (Anand and Brobeck 1951). These findings led to the dual centre model for appetite regulation, with the 'satiety centre' based in the VMH and the 'hunger centre' in the LH (Stellar 1954).

More recently, the VMH has been determined to be the main brain region mediating the effects of leptin (Dhillon, Zigman et al. 2006) - a protein produced and secreted in white adipose tissue that is one of the most important homeostatic mediators of hypophagia (Zhang, Proenca et al. 1994). Subsets of LH neurons, on the other hand, contain either orexin (also known as hypocretin) or melanin concentrating hormone (MCH) (Elias, Saper

et al. 1998) and both of these peptides are potent stimulators of food intake (Qu, Ludwig et al. 1996; Sakurai, Amemiya et al. 1998). The two hypothalamic centres are connected reciprocally to the arcuate nucleus of the hypothalamus (ARC), that is thought to be the master central regulator of energy balance and food intake (Zaborszky and Makara 1979; Horvath, Diano et al. 1999). Separate subsets of GABAergic ARC neurons have opposed effects on feeding behaviour. Pro-opiomelanocortin (POMC) is a precursor to α- and β-melanocyte stimulating hormones (MSH), two melanocortins that, when released from anorexigenic neurons, act to reduce food intake and body weight while increasing energy expenditure (Biebermann, Castaneda et al. 2006). Orexigenic ARC neurons express neuropeptide Y (NPY) which stimulates feeding and reduces energy expenditure (Baskin, Breininger et al. 1999). The same neurons also express agouti gene-related transcript, an antagonist of melanocortin receptors that inhibits the anorectic effects of α-MSH (Ollmann, Wilson et al. 1997). The ARC is located just above the median eminence, where the blood-brain barrier comprises fenestrated capillaries allowing access to humoral signals that do not reach most other brain areas (Gao and Horvath 2007). Neurons in the ARC are sensitive to glucose (Wang, Liu et al. 2004) and possibly also to intermediates of fatty acid metabolism (Loftus, Jaworsky et al. 2000). Additionally, they express receptors and respond to a variety of other metabolic factors including insulin, leptin and ghrelin (Willesen, Kristensen et al. 1999; Spanswick, Smith et al. 2000; Cowley, Smart et al. 2001).

The area postrema (AP), lying immediately dorsal to the NTS, is also a circumventricular organ, that lies outside the blood-brain barrier (Broadwell and Brightman 1976). Some NTS neurons have dendrites in this zone (Herbert, Moga et al. 1990) and AP neurons project to the reticular formation and the PbN in a manner very similar to that of NTS neurons (Shapiro and Miselis 1985; Herbert, Moga et al. 1990). AP neurons express receptors for, and in some cases have been shown to respond to, amylin (Rowland, Crews et al. 1997), CCK (Moran, Robinson et al. 1986), GLP-1 (Rowland, Crews et al. 1997) and insulin (Werther, Hogg et al. 1987). The AP participates, with the NTS and the dorsal motor nucleus of the vagus, in the control of food intake by the caudal brainstem. In fact, the caudal hindbrain contains glucose-sensitive neurons that are involved in ingestive and sympathoadrenal responses to glucopenia (Ritter, Slusser et al. 1981) and also neurons that express receptors for, and coordinate ingestive responses to, both leptin (Grill, Schwartz et al. 2002) and ghrelin (Faulconbridge, Cummings et al. 2003). Thus, even when the brainstem is isolated from all forebrain connections, rats exhibit not only acceptance and rejection behaviours to oral stimulation with tastants (Grill and Norgren 1978), but also basic satiety-related behaviours (Grill and Norgren 1978). However, these animals are unable to increase meal size in response to food deprivation, suggesting that the forebrain is needed to respond adequately to a long-term homeostatic challenge (Grill and Kaplan 2001).

Novel opportunities in the management of obesity?

In the introduction to our description of the gustatory system, the dramatic increase in the prevalence of obesity was referred to as the underlying motivation for the study of the central mechanisms of food reward and appetite regulation. In fact, obesity is not without consequence. Excess weight has been linked to the development of cardiovascular and cerebrovascular disease, hypertension, type 2 diabetes, dyslipidemia, a variety of cancers, gallstones, osteoarthritis, sleep apnea, asthma, cataracts, benign prostatic hypertrophy and depression, among other disorders (Stein and Colditz 2004). In fact, obesity is second only to smoking as a leading cause of both preventable mortality and health-related economic burdens. While the health consequences of obesity are important and potentially life-threatening, they are also reversible: even modest reductions in weight lead to improvement in health outcomes such as blood pressure, glucose tolerance and lipid profile (Stein and Colditz 2004).

Treating and preventing obesity are thus important objectives in healthcare. However, the treatment options available currently have important limitations. Counselling for dietary modifications, exercise and pharmacologic therapy are the more conservative approaches. Weight loss can be achieved initially but only a small proportion of excess weight is lost and, even so, the maintenance of these losses depends, in most cases, on sustained pharmacologic therapy (Bray and Wilson 2008). In fact, there is extensive evidence that any deviation from a theorized weight "set-point," thought to be based in the hypothalamus, will activate feedback signals, such as leptin and ghrelin, leading to behavioural and metabolic responses that resist and minimize the original weight change (Keesey and Powley 2008).

Bariatric surgery is the only effective long-term alternative for the treatment of morbid obesity. In 2005, 140,000 such interventions are estimated to have been performed in the U.S., and reported success rates are high, with up to 80% average excess body weight loss (Nguyen and Wilson 2007). Furthermore, laparoscopic alternatives, with very low perioperative mortality rates (below 1%), have become available for many bariatric procedures. Nevertheless, bariatric surgery is not devoid of adverse consequences and is not an option for many patients. Superobese individuals, for example, have higher surgical risks (Buchwald, Estok et al. 2007), potentially leading to limitations in access to abdominal surgery for those patients that need it most (Gottig, Daskalakis et al. 2009). Moreover, there are important late complications after bariatric surgery, such as metabolic imbalances and nutritional deficiencies (Bult, van Dalen et al. 2008), and late postoperative mortality rates are thought to be grossly underestimated (Buchwald, Estok et al. 2007). In summary, while the effectiveness of bariatric surgery remains unchallenged, it is clear that new alternatives are needed for weight management, especially for extremely obese patients.

The CNS seems to be an important therapeutic target in obesity management. Most of the pharmacological alternatives for obesity treatment act, at least partially, through effects in the brain (Bray and Greenway 2007), and modulation of gut hormones constituting the 'gut-brain axis' is thought to be responsible for some of the long-lasting effects of bariatric surgery (Ashrafian and le Roux 2009). The possibility of manipulating food intake and weight by lesions of the hypothalamus was demonstrated in early studies, done in rats, leading to the dual centre model with the VMH as the 'satiety centre' (Hetherington and Ranson 1940; Brobeck, Tepperman et al. 1943) and the LH as the 'hunger centre' (Anand and Brobeck 1951). LH lesions have also been performed in a small group of obese patients with significant, albeit temporary, effects in reducing food intake and promoting weight loss (Quaade, Vaernet et al. 1974).The use of electrical stimulation to modify neuronal activity in discrete brain areas has revolutionized functional neurosurgery, with widespread use in the treatment of movement disorders, namely Parkinson's disease (Benabid, Chabardes et al. 2009). The use of deep brain stimulation (DBS) has also been attempted for several psychiatric disorders, namely Tourette's syndrome, obsessive-compulsive disorder and major depression, with promising results (Larson 2008). The consideration of neuropsychiatric factors underlying the pathophysiology of obesity (Volkow and O'Brien 2007) has thus led some to propose the use of DBS in hypothalamic or ventral striatal regions for the treatment of obesity (Halpern, Wolf et al. 2008). The feasibility of such an approach is suggested by research in animals, demonstrating inhibition of food consumption (Hoebel and Teitelbaum 1962), or prevention of weight gain (Sani, Jobe et al. 2007) by hypothalamic stimulation in rodents. Furthermore, a case of bilateral ventral hypothalamic DBS for treatment of morbid obesity has been reported in the literature, with moderate weight loss and few side effects (Hamani, McAndrews et al. 2008). While there is still very little information for or against the use of this technique in the treatment of obesity, the possibility of conducting DBS surgery under local anaesthesia (Benabid, Chabardes et al. 2009) may prove to be an advantage for those patients where abdominal surgery poses a significant risk.

Neural stimulation outside of the brain might also prove to be a valid alternative for obese patients. Several experimental treatments, such as gastric electrical stimulation (Hasler 2009) and intra-abdominal vagal blocking therapy (Camilleri, Toouli et al. 2008) are currently being pursued with this purpose. It is critical to validate these approaches to weight control and accurately understand the mechanisms by which they act.

Conclusions

Gustatory, homeostatic and reward circuits in the mammalian brain are part of a complex and distributed neural system that coordinates feeding and other aspects of energy homeostasis. Therapeutic or experimental manipulation of neuronal activity in this system can reduce food consumption and promote weight control, in some cases with dramatic and/or long-lasting effects. Furthermore, with an ever-growing arsenal of neurobiological approaches to understanding brain function, knowledge on the physiology and pathophysiology of feeding behaviour, especially as it relates to hyperphagia and obesity, is already substantial. There are, however, still many unanswered questions. Treatments for obesity that reduce food intake are thought to modulate CNS activity mostly indirectly, through mechanisms that are still poorly understood but presumed to involve changes in neural and/or humoral input to the brain. On the other hand, experimental interventions that directly modify anatomical and/or functional properties of the brain and result in weight loss are yet to be applied clinically. In years to come, new approaches for the management of obesity are critically necessary. Research on the central neural mechanisms of gustation could contribute significantly towards uncovering novel avenues for the treatment of obesity and even related metabolic disorders such as diabetes.

Acknowledgments

We thank Susan Halkiotis for assistance in reviewing our original manuscript. This work was supported by Grant Number R01DC001065 to Sidney Simon from the National Institute on Deafness and Other Communication Disorders (NIDCD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIDCD or the National Institutes of Health.

Abbreviations

AMP	Adenosine monophophate
AP	Area postrema
ARC	Arcuate nucleus of the hypothalamus
ATP	Adenosine triphosphate
BLA	Basolateral amygdale
CCK	Cholecystokinin
CeA	Central nucleus of the amygdala
CNS	Central nervous system
cNTS	Caudal division of the solitary tract nucleus
CoA	Coenzyme A
DBS	Deep brain stimulation
DMH	Dorsomedial nucleus of the hypothalamus
ENaC	Epithelial sodium channel

GABA	Gamma-aminobutyric acid
GC	Gustatory cortex
GIT	Gastrointestinal tract
GLP-1	Glucagon-like peptide 1
GPCR	G-protein coupled receptors
IC	Insular cortex
LH	Lateral hypothalamus
MCH	Melanin concentrating hormone
MSH	Melanocyte stimulating hormone
NAcc	Nucleus accumbens
NPY	Neuropeptide Y
NTS	Solitary tract nucleus
OFC	Orbitofrontal cortex
PbN	Parabrachial nuclei
PLCβ2	Phospholipase C β-2
POMC	Pro-opiomelanocortin
PP	Pancreatic polypeptide
PVH	Paraventricular nucleus of the hypothalamus
PYY	Peptide YY
rNTS	Rostral division of the solitary tract nucleus
SNAP-25	Synaptosomal-associated protein of 25kD
TRC	Taste receptor cell
TRP	Transient receptor potential ion channel
VMH	Ventromedial nucleus of the hypothalamus
VPpc	Parvicellular division of the ventral posterior nucleus of the thalamus
VTA	Ventral tegmental area

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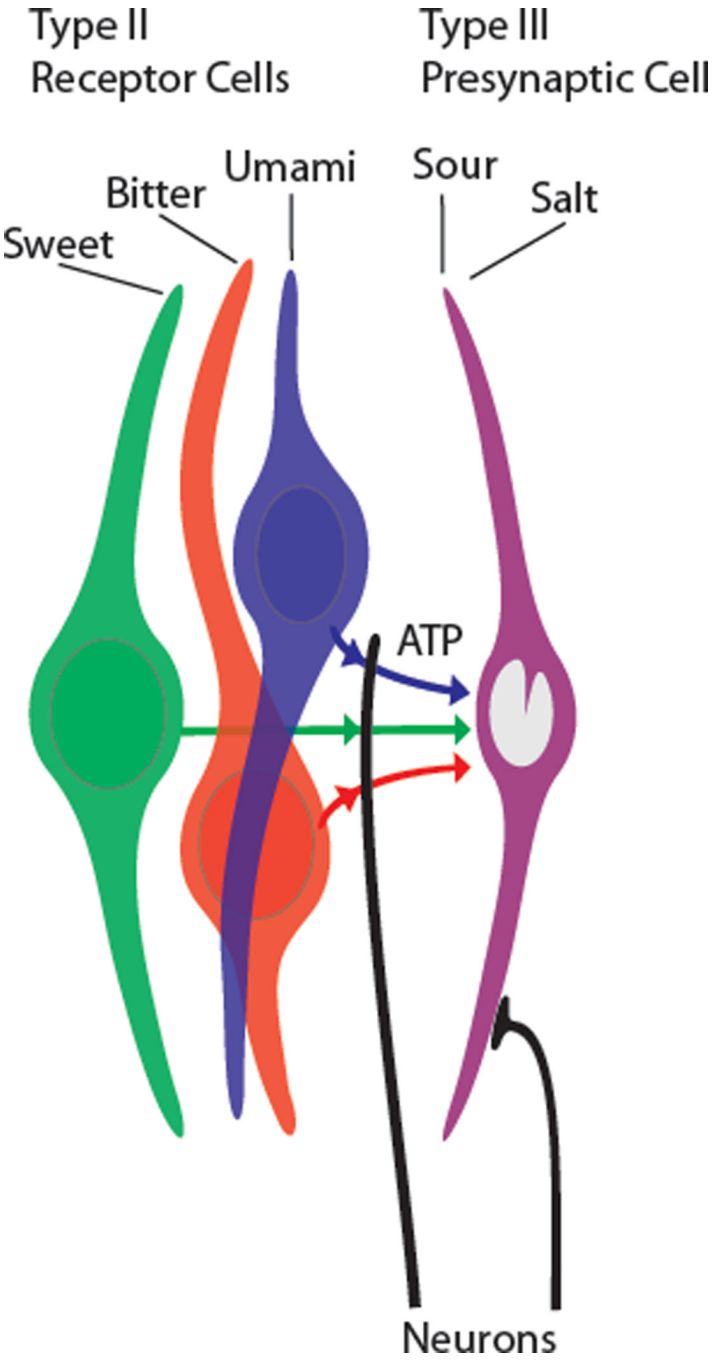

Fig. 1. Peripheral Taste Mechanisms

Tastants activate two classes of taste bud cells: Type II or receptor cells and Type III or presynaptic cells. Different subclasses of receptor cells (green, red, and blue cells), express T1R2/T1R3, T2R or T1R1/T1R3 G-protein-coupled taste receptors and are activated respectively by sweet, bitter or umami compounds. Downstream signaling pathways in these cells require phospholipase C β2 and transient receptor potential ion channel M5 (TRPM5). When activated, receptor cells release adenosine triphosphate (ATP), which is then thought to act upon intragemmal taste nerve fibers (black fibres) and/or presynaptic cells. Presypnaptic cells (purple cell) express synapse-related proteins such as synaptosomal-associated protein of 25kD and form conventional synapses with intragemmal processes of

peripheral taste neurons. In contrast with receptor cells, presynaptic cells are broadly tuned to tastants of multiple qualities – currently, they are thought to be activated directly by sour stimuli, through a different set of receptors and signaling pathways than those used by receptor cells, and indirectly by sweet, bitter and umami compounds, through ATP released from receptor cells. Serotonin (5-HT) is also released from taste buds upon chemosensory stimulation, presumably in synapses between receptor cells and taste neurons. Several taste bud cell types, including receptor cells and type I cells, have been proposed to transduce salt stimuli, but there is still no consensus (see text; adapted from Tomchik, Berg et al. 2007, used with permission).

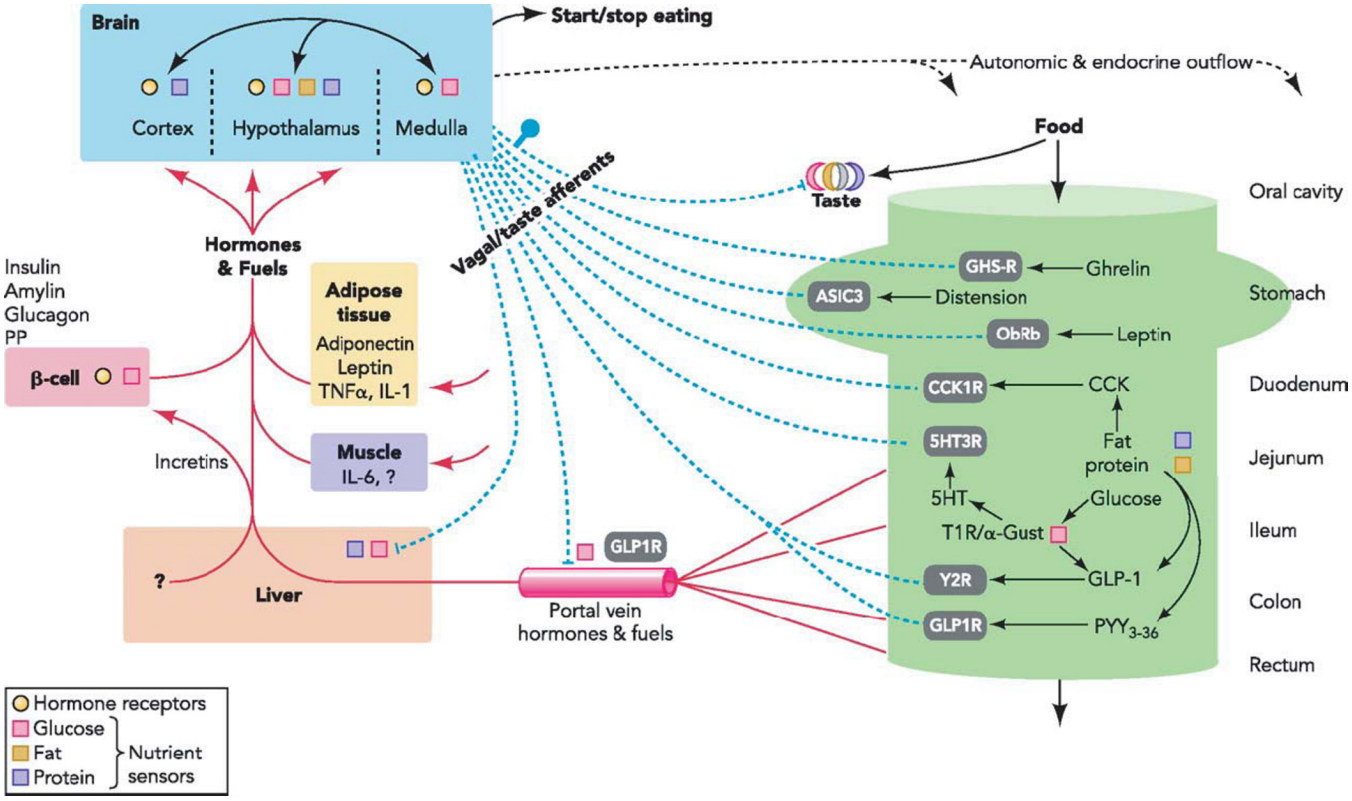

Fig. 2. Gut Nutrient Signaling Pathways

Ingested nutrients elicit mechanosensory and chemosensory responses in the gut, as represented in green on the right. Postingestive responses depend mainly on the production of gut hormones, such as CCK and GLP-1, that signal nutrient presence and quality by activating vagal afferents (blue, dashed lines) and/or entering blood circulation via the portal vein (red, solid lines). Absorbed nutrients (glucose and other 'fuels') and feeding-related peptides produced in sites other than the gut (liver, muscle, adipose tissue and pancreas, on the bottom left), are two other categories of gustatory humoral signals. The postingestive sensory information thus generated, modulates the activity of central neural circuits at several levels of the brain, represented on the top left (from Zheng and Berthoud 2008, used with permission).

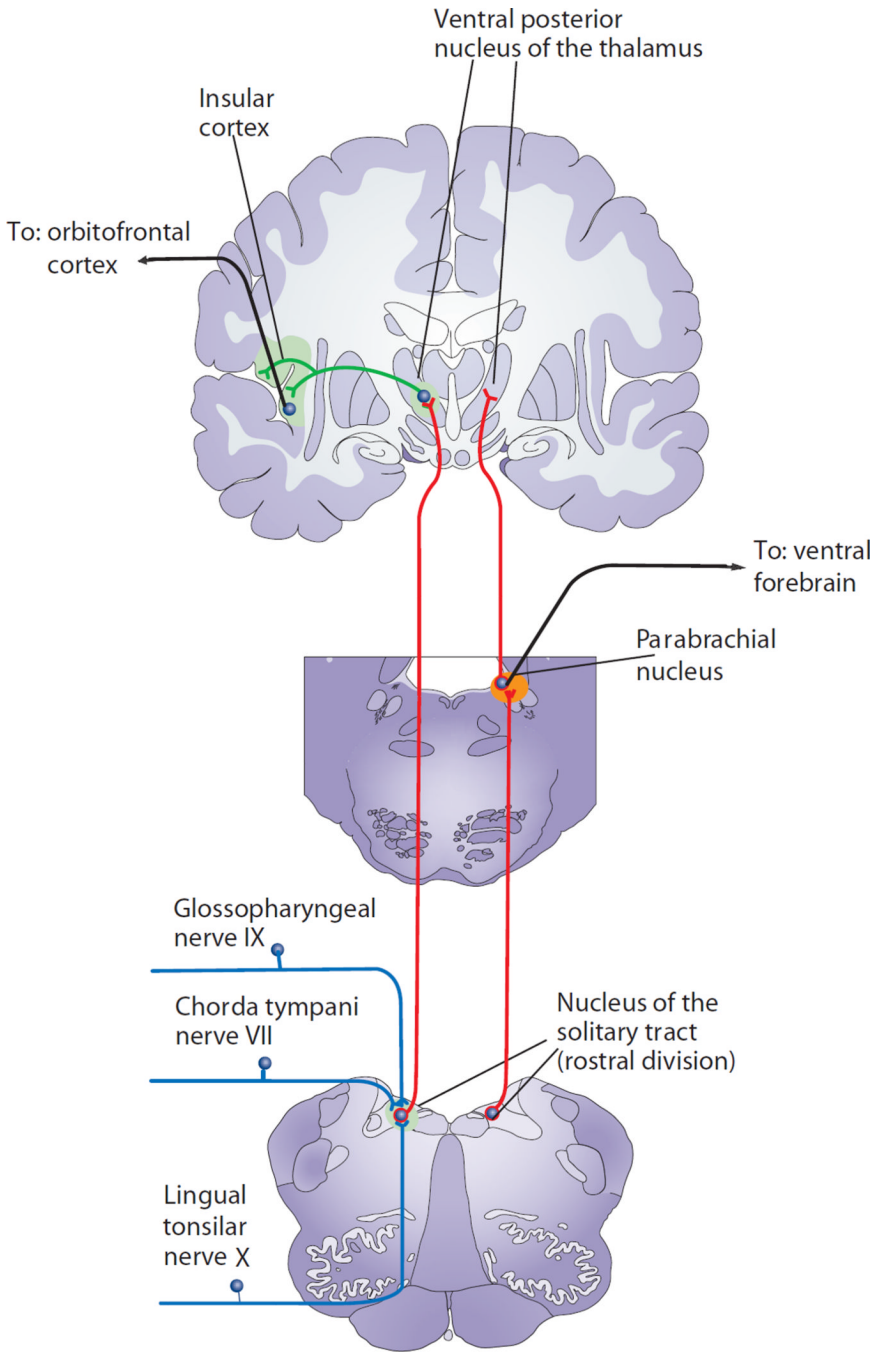

Fig. 3. Anatomy of the main central gustatory pathways

Taste-specific information is conveyed by cranial nerves VII, IX and X (blue lines) to the rostral division of the solitary tract nucleus (rNTS) in the medulla. In primates, fibres (red lines) from second-order taste neurons in the rNTS project ipsilaterally to the parvicellular division of the ventral posterior nucleus of the thalamus (VPpc). Thalamic efferents (green lines) then project to the insula, defining the primary gustatory cortex which, in turn, projects (black lines) to the orbitofrontal cortex, sometimes defined as a secondary cortical taste area. The parabrachial nuclei (PbN) of the pons are shown in orange. In rodents these are a relay for taste afferents from the rNTS. In both primates and rodents, the PbN also receive second order visceral sensory fibres from the caudal division of the solitary tract

nucleus (cNTS), transmitted mainly through the vagus nerve (not shown). The PbN has a dorsal thalamocortical projection to the VPMpc and also a ventral projection that terminates in amygdalar and hypothalamic nuclei, among others (adapted from Simon, de Araujo et al. 2006, used with permission).

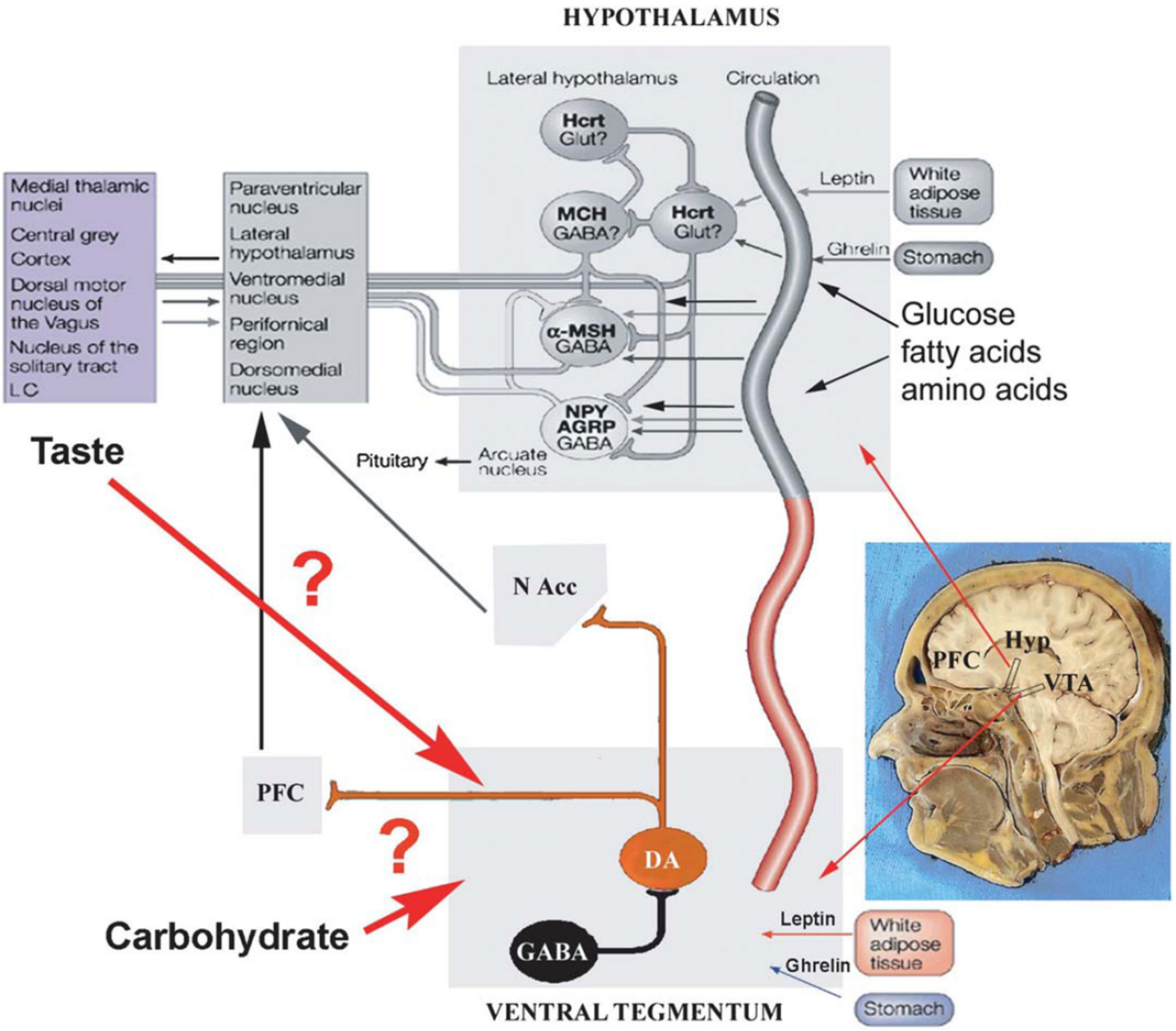

Fig. 4. Hedonic and homeostatic regulation of feeding

Current literature considers the hypothalamus as the main centre for feeding regulation. Lateral hypothalamus neurons that produce orexin (also known as hypocretin - Hcrt) and melanin concentrating hormone (MCH) are potent stimulators of food intake. Neurons in the arcuate nucleus of the hypothalamus synthesize melanocyte stimulating hormone (MSH) or neuropeptide Y (NPY) that have opposed effects in the control of food intake and energy expenditure. The hypothalamic nuclei are traditionally considered homeostatic centre for feeding regulation since they respond to peripheral metabolic hormones and fuels (such as leptin and ghrelin) that are critical for energy homeostasis (Gao and Horvath 2007). The mesencephalic dopamine system, on the other hand, responds robustly to a diverse array of rewarding stimuli, including food, and plays a critical role in the behavioural responses to these stimuli (Wise 2006). Orosensory responses to palatable food are sufficient for the occurrence of dopamine (DA) responses in the mesolimbic system (Hajnal, Smith et al. 2004), which have generally been considered as a system for ‘hedonic’ regulation of food intake. However, some of the peripheral hormones that modulate the behavioural

components of energy homeostasis also impact the activity in this system (see text). Furthermore, in a recent publication, de Araujo and Oliveira-Maia et al (de Araujo, Oliveira-Maia et al. 2008) have shown, using ‘taste-blind’ mice (Zhang, Hoon et al. 2003), that the caloric value of sucrose, in the absence of taste transduction, is also sufficient to activate the midbrain reward circuitry. While the physiological details of the signaling mechanisms involved remain to be described, it seems reasonable to suggest that the distinction between hedonic and homeostatic regulation of feeding is redundant. GABA, gamma-aminobutyric acid; Glut, glutamate; Hyp, hypothalamus, NAcc, nucleus accumbens; PFC, prefrontal cortex, VTA, ventral tegmental area (from Andrews and Horvath 2008, used with permission from Elsevier).