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Review

Taste receptors in the gut – A new target for health promoting properties in diet

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ABSTRACT

In this review we describe a new target for food functionality, the taste receptors in the gastrointestinal tract. These receptors are involved in an intricate signalling network for monitoring of taste and nutrient intake, homeostasis and energy metabolism, and they are also an early warning system for toxic substances in our diet. Especially the receptors for bitter taste provide a new possibility to activate a number of health related signalling pathways, already at low concentrations of the active substance, without requiring uptake into the body and transport via the circulation. When ligands bind to these receptors, signalling is induced either via peptide hormones into the circulation to other organs in the body, or via nerve fibers directly to the brain.

1. Introduction

The newly discovered presence of taste receptors outside the oral cavity, especially in the gastrointestinal (GI) tract, opens up new perspectives for explaining and exploring the bioactive and health related principles in our food. There might be effects already at low concentrations of bioactive compounds present in the GI tract, without the need of them being taken up through the gut mucosa and transported to their target tissues in the body.

Taste is the sense related to the nutritional qualities of our diet. We traditionally speak of five basic tastes: sweet, salt, umami, bitter, and sour. These are being sensed by taste-specific receptor cells (TRCs), which are clustered together in the so-called taste buds on the tongue (Chaudhari & Roper, 2010; Efeyan, Comb, & Sabatini, 2015; Meyerhof et al., 2010).

Sweet taste indicates the presence of carbohydrates, serving as an energy source.

Umami taste is associated with the presence of amino acids and protein-rich foods. Bitter taste is felt aversive, and is a warning against the consumption of poisonous substances in the food (Richter & Fidler, 2014).

Sour taste is related to the presence of acids that are present in eg spoiled foods and unripe fruits. Salty taste governs the intake of Na^+ and other salts, essential for maintaining the mineral and water balance of the body. High concentrations of sodium are also felt aversive (Oka, Butnaru, von Buchholtz, Ryba, & Zuker, 2013).

The taste of fat has earlier been believed to rely on textural, olfactory, and post-ingestive properties, but with the identification of lipid sensors on the tounge, fat can be defined as the sixth taste (Laugerette et al., 2005).

2. Taste receptors

Of the five basic tastes, sweet, umami and bitter tastes are sensed through activation of so-called G-protein-coupled receptors (GPCRs). Since the discovery, a vast number of GPCRs and their important physiological functions in the body have been described (Lefkowitz, 2013). They are divided into sub-families, associated with different intracellular signalling mechanisms, dependent on which transmembrane proteins they are associated with. The structure-based sequence alignment of the transmembrane domains of all human GPCRs and its phylogenetic and functional implications has been published (Cvicek, Goddard, & Abrol, 2016). There is a global database for GPCRs accessible via the Internet (http://gpcrdb.org/, see Munk et al., 2016 for a background and detailed description).

Sweet and umami tasting substances activate defined combinations (heterodimers) of the taste receptor type 1 (TAS1R) family: the combination TAS1R2-TAS1R3 senses sweet, whereas the combination TAS1R1-TAS1R3 detects umami (Hoon et al., 1999; Kitagawa, Kusakabe, Miura, Ninomiya, & Hino, 2001; Max et al., 2001; Montmayeur, Liberles, Matsunami, & Buck, 2001; Nelson et al., 2001; Sainz, Korley, Battey, & Sullivan, 2001).

Bitter-tasting substances activate receptors of the taste receptor type 2 (TAS2R) family, which in humans consists of 25 members (Adler

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et al., 2000; Behrens & Meyerhof, 2011; Chandrashekar et al., 2000; Matsunami, Montmayeur, & Buck, 2000). Structurally very different molecules can act as ligands for these taste receptors, including both naturally occurring plant metabolites and synthetic compounds. A wide range of activation thresholds has been reported (Meyerhof et al., 2010), for instance human TAS2R43 (hTAS2R43) is activated by aristocholic acid at a concentration as low as 1.3 nM, whereas hTAS2R1 is activated by sodium cyclamate at a concentration as high as 30 mM. However, for moderately toxic substances, e.g. some glycosides, the threshold is usually in the millimolar range. These differences can actually act as a cost-benefit strategy, as some substances like amygdalin can have a protective effect against malaria, and therefore a less sensitive variant of the amygdalin receptor (TAS2R16), prevail in African regions (Behrens & Meyerhof, 2013).

Today ligands have been described for most of the human TAS2Rs (Meyerhof et al., 2010; Thalmann, Behrens, & Meyerhof, 2013). In mice, the situation is less clear, with only a few of the mouse TAS2Rs (mTAS2Rs) effectively deorphaned (Chandrashekar et al., 2000). The taste receptor cells for bitter taste constitute a distinct subpopulation of chemosensory cells characterized by the expression of TAS2R genes, and they are well differentiated from receptor cells devoted to the detection of other taste stimuli (Hoon et al., 1999). Each receptor cell for bitter taste expresses multiple bitter taste receptors (Behrens, Foerster, Staehler, Raguse, & Meyerhof, 2007).

The signal transduction of GPCR taste receptors has been described in detail (Margolskee, 2002). Binding of a ligand to the receptor causes a conformational change, giving rise to the activation of an associated G protein by exchanging its bound GDP for a GTP. The activated taste receptor proteins interact with a heterotrimeric G protein complex consisting of subunits such as Gα-gustducin (McLaughlin, McKinnon, & Margolskee, 1992), Gα-transducin (Ruiz-Avila et al., 1995), Gα14 (Tizzano et al., 2008), Gβ1 or Gβ3, and Gγ13 (L. Huang et al., 1999; Rossler, Kroner, Freitag, Noe, & Breer, 1998). The α subunit of the G-protein, together with the bound GTP, can then dissociate from the β and γ subunits to further affect intracellular signalling proteins or target functional proteins directly depending on the α subunit type ($G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q/11}$, $G_{\alpha 12/13}$). GPCRs coupled to $G_{\alpha s}$ or $G_{\alpha i/o}$ could either activate or inactivate adenylate cyclase and thereby increase or decrease the content of cAMP, which in its turn affects the activation of AMP-activated protein kinase (AMPK) (the exact targets of cAMP have not been identified) (Kinnamon, 2012).

Upon activation of a taste receptor the complex dissociates and the Gβ3/Gγ13 heterodimer stimulates phospholipase Cβ2, resulting in the formation of the second messengers diacylglycerol (DAG) and IP_3 (Dotson, Roper, & Spector, 2005; Ogura, Mackay-Sim, & Kinnamon, 1997; Rossler et al., 1998; Zhang et al., 2003), leading to increased intracellular calcium and depolarisation (Hutchinson, Summers, & Bengtsson, 2008).

α-Gustducin is unique to gustatory tissues, and closely related to α-transducin. Bitter taste receptors are only found in cells positive for α-gustducin expression.

The complex mechanism of signal transduction within taste buds and the transmission to the brain is currently a matter of intense research. Activation of the IP_3-receptor within the endoplasmic reticulum membrane (Clapp, Stone, Margolskee, & Kinnamon, 2001) causes an increase in intracellular calcium ion level, followed by the opening of a transient receptor potential channel, TRPM5, located in the plasma membrane (Damak et al., 2006; Talavera et al., 2005). This causes the production of ATP, the transmitter substance of type II taste receptor cells (Y. J. Huang et al., 2007; Romanov et al., 2007) which can have several functions. Firstly, it stimulates afferent nerve fibers terminating within the taste bud (Finger et al., 2003). Secondly, ATP activates type III taste receptor cells resulting in the secretion of the neurotransmitter serotonin (Y. J. Huang et al., 2007) and norepinephrine (Dvoryanchikov, Tomchik, & Chaudhari, 2007). Thirdly, ATP acts in an auto- and paracrine fashion also on type II taste receptor cells (Behrens & Meyerhof, 2013; Y. A. Huang, Dando, & Roper, 2009).

3. Extraoral taste receptors

The first evidence for *extra-oral taste signalling* was reported by Höfer et al. in 1996 (Hofer, Puschel, & Drenckhahn, 1996), who described the presence of α-gustducin in "taste receptorlike cells" or brush cells in the gut. After that, the existence of taste signalling pathways have been reported in a variety of other tissues (Behrens & Meyerhof, 2011; Bezencon, le Coutre, & Damak, 2007; Dotson et al., 2008; Dyer, Salmon, Zibrik, & Shirazi-Beechey, 2005; Fehr et al., 2007; Finger et al., 2003). Most research concerning the TAS1R-family has been focused on the enteroendocrine cells in the gut (Depoortere, 2014), but functional TAS1Rs have also been reported in the pancreas (Kyriazis, Soundarapandian, & Tyrberg, 2012; Nakagawa et al., 2009), the brain (Ren, Zhou, Terwilliger, Newton, & de Araujo, 2009), adipose tissue (Masubuchi et al., 2013), the airways (Lee & Cohen, 2014), the testis (Mosinger et al., 2013), muscle tissue (Kokabu et al., 2015), and liver (Taniguchi, 2004). TAS2Rs have been found in the gut, the airways, the brain, the heart, in vascular endothelium, the thyroid, the kidney, the testis, the immune system, the thymus, in bone marrow, breast epithelium and skin keratinocytes (Roura et al., 2016; Wolfle et al., 2016).

A good model for studying the embryonic and postnatal development of taste receptor expression in the GI tract is in the growing chicken (Cheled-Shoval, Druyan, & Uni, 2015).

There are several physiological roles proposed for taste receptor signalling in the gut. These include the modification of digestive processes, such as the speed of gastric emptying (Avau et al., 2015; Glendinning, Yiin, Ackroff, & Sclafani, 2008), or metabolic adjustments like the regulation of blood glucose levels (Jang et al., 2007). These mechanisms may also involve local paracrine, humoral, and neuronal transmission events (Hao et al., 2009; Hao, Sternini, & Raybould, 2008; Jang et al., 2007; Margolskee et al., 2007).

3.1. Cell types in the GI tract expressing taste receptors

The taste receptor molecules are found in some identified cell types, most probably involved in nutrient sensing:

- Brush cells/solitary cells
- Solitary chemosensory cells
- Enteroendocrine cells (EEC)

However, which cell types are involved in taste reception is species dependent (Morroni, Cangiotti, & Cinti, 2007).

The first time it was reported that the GI tract also could have sensory properties was when Bayliss and Starling (1902) discovered the first gut hormone: secretin. Later, it was found that the gut responds to a large array of signals in the lumen, including nutrients and non-nutrient chemicals. The molecular sensing by GI cells plays an important role in the control of many functions during digestion, it initiates hormonal and neural responses as well as changes in mucosal ion transport that regulate motility, appetite, insulin secretion, etc. Sensing the composition in the lumen is also critical for appropriate physiological response, like mucus secretion or emesis, towards ingested harmful compounds. It is crucial that chemosensory cells have direct access to the luminal content. This is not the case for the vagus nerve sensory afferents in the lamina propria, which never enter the epithelial layer, and thus must get information of lumen content indirectly via signals released from cells such as enterocytes, brush cells, and EECs.

Intestinal sensory cells have been demonstrated to affect the secretion of the peptides cholecystokinin (CCK) and glucagon like peptide (GLP-1) (Kaji, Karaki, Fukami, Terasaki, & Kuwahara, 2009; Wu, Chen, & Rozengurt, 2005), while gavage of bitter tastants induced CCK-dependent hindbrain activation.

Brush cells are a subgroup of *solitary chemosensory cells*, also found in