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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 tongue, 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 (Cvick, 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 arisotricholic 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 orphaned (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 G_{α} -gustducin (McLaughlin, McKinnon, & Margolskee, 1992), G_{α} -transducin (Ruiz-Avila et al., 1995), $G_{\alpha 14}$ (Tizzano et al., 2008), $G_{\beta 1}$ or $G_{\beta 3}$, and $G_{\gamma 13}$ (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 $G_{\beta 3}/G_{\gamma 13}$ heterodimer stimulates phospholipase $C\beta 2$, 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; Wolffe 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 (Morrone, 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

the nasal cavity (Sbarbati & Osculati, 2005). They express gustatory transmitting proteins such as α -gustducin (Hofer et al., 1996), α -transducin (Clavenzani et al., 2009), and TRPM5 (Bezencon et al., 2008). They are found in several regions of the gut, especially where food passes from the fundus to the corpus, and digestive processes are initiated (Eberle et al., 2013).

Similar to taste receptor cells of the tongue, brush cells possess a single apical tuft of rigid microvilli (Sbarbati & Osculati, 2005), and they were the first cells outside the oral cavity shown to express α -gustducin (Hofer et al., 1996). Since then, EEC types as well as solitary chemosensory cells have been shown to also express α -gustducin (Bezencon et al., 2007; Hofer & Drenckhahn, 1998; Jang et al., 2007; Wu et al., 2002).

Brush/tuft cells are a source of interleukin IL-25 which in turn causes rapid expansion of immune cells, and hence keys to the “weep and sweep” function that expels parasites and toxic content from the gut (Harris, 2016). Tuft cells possess the machinery for chemosensory taste receptors and there might be a crucial role for this chemosensation in promoting tuft cell expansion in response to parasite infection.

The EEC of the GI tract are placed together with other epithelial cells (Egerod et al., 2012; Sternini, Anselmi, & Rozengurt, 2008). In response to changes in the gastric and intestinal lumen composition, they secrete a variety of signalling molecules (Sternini, 2007; Sternini et al., 2008). Different types of EEC are the I cells of the duodenum and jejunum, producing CCK, and the L cells of the ileum and colon, either secreting GLP-1, or peptide YY (PYY). A subpopulation of EEC can express bitter taste receptors (Jeon, Zhu, Larson, & Osborne, 2008).

Together all EEC in the gut constitute the largest endocrine organ of the human body, even if they represent less than 1% of the epithelial population (Egerod et al., 2012). They can be divided into more than 20 different subtypes. They produce and secrete a variety of hormones, including gastrin (G cells), ghrelin (P or X/A cells), somatostatin (D cells), CCK (I cells), serotonin (enterochromaffin cells), glucose-dependent insulinotropic peptide (GIP) (K cells), GLP-1, and PYY (L cells). We now know that a subtype of EECs has the ability to coexpress several different peptides with related functionality. They can be differentiated into two groups according to their place in the epithelium: The ‘open-type cells’ have microvilli enabling direct sensation of the content in the lumen. This triggers release of hormones entering the blood stream and activation of extrinsic or intrinsic afferent nerves or other nearby target cells. The “closed-type cells” do not reach the epithelial surface, and can only be indirectly affected through signals of neural origin or via the blood stream. In this case the brush cells can be the primary sensors, and transfer information from the lumen to the ‘closed’ EECs (Hass, Schwarzenbacher, & Breer, 2007).

A number of peptide hormones with anorexigenic (GLP-1, PYY3–36, CCK) or orexigenic (ghrelin) effect are released from the gut mucosa, as a consequence of a fed or fasted state, and they play important roles in regulating food intake on a short-term basis (Diepvens, Haberer, & Westerterp-Plantenga, 2008; Havel, 2001). The macronutrient composition and energy content of a meal cause fluctuations in plasma levels of GLP-1, PYY, CCK (postprandial increase), and ghrelin (postprandial decrease) (Perry & Wang, 2012). Taste receptor (α -gustducin-positive) cells are co-localized with GLP-1 and PYY producing L cells, GIP-producing K cells, and with ghrelin-producing X/A cells of the stomach (Janssen & Depoortere, 2013; Pais, Gribble, & Reimann, 2016). Other elements of the chemosensory signalling transduction chain (including PLC β 2 and TRPM5) have been demonstrated in L cells and X/A cells.

3.2. Expression of GPCR taste receptor genes

Many of the GPCR taste receptor genes are reported to be expressed in the GI tract, at least in the rat. They have also been shown to have transcripts as determined by RT-PCR (Wu et al., 2005), and recent research has shown that α -gustducin and α -transducin expression in the

gut is influenced by diet (De Giorgio et al., 2016). Additional molecules in the taste signalling cascade like PLC β 2 (Ogura et al., 1997; Rossler et al., 1998) and TRPM5 have also been localized in the GI tract (Perez et al., 2002). α -Gustducin has been shown to be colocalised with TRPM5 and more rarely with PLC β 2, but this differs in various cell subsets along the gut, from duodenum to colon (Bezencon et al., 2007). A special case are the short chain fatty acid receptors in colon (Canfora, Jocken, & Blaak, 2015), influencing glucose homeostasis as well as immune system activity (Correa-Oliveira, Fachi, Vieira, Sato, & Vinolo, 2016).

4. Cell lines for in vitro studies

Several research groups have used model cell lines that allow characterisation of homogenous cellular models for studying the mechanisms of taste sensing on a cellular level in the GI tract (Chen, Wu, Reeve, & Rozengurt, 2006; Dotson et al., 2008; Dyer et al., 2005; Jang et al., 2007; Le Neve, Foltz, Daniel, & Gouka, 2010; Margolskee et al., 2007; Rozengurt et al., 2006; Wu et al., 2002; Wu et al., 2005).

- Mouse EEC line STC-1
- GLUTag intestinal tumor
- Human NCI-H716 colorectal carcinomas
- Human HuTu-80 duodenal cancer
- Rat AR42J pancreatic tumor

By means of in vitro experiments with useful cell lines like these, the agonist function of various dietary components can be tested. If binding to taste receptors occurs, and this in turn induces production and secretion of peptide hormones like CCK or GLP-1, this is a strong indication of physiological function of these dietary components also in vivo.

5. Bitter taste receptors – signalling the presence of xenobiotics and toxic substances

Bitter taste is considered to be a warning signal for toxicity, enabling us to avoid consuming harmful substances (Mueller et al., 2005). In the large intestine of rats and humans, detection of bitter compounds via the luminal chemosensing initiates enhanced fluid secretion, and helps to flush out harmful compounds (Kaji et al., 2009; Vidyasagar, Rajendran, & Binder, 2004).

The finding of bitter taste receptors in extraoral tissues has led to the discovery of intriguing involvement in physiological and pathophysiological mechanisms, e.g. in respiratory tract infections, rhinosinuitis, alcohol dependence, various forms of cancers, cystic fibrosis (studies of TAS2R expressions in this context show promising future drug-target perspectives) (Shaik et al., 2016).

One example from the animal kingdom, is the gustatory receptors for coumarin in the fruit fly (*Drosophila melanogaster*), which can detect the toxic substance coumarin, and make the fly avoid feeding and laying eggs where this substance could be present (Poudel & Lee, 2016). These signalling pathways are channelled via the brain and affect the behaviour of the fly.

The function of TAS2Rs in non-gustatory tissues depend on the extraoral sites where they are found, eg the respiratory epithelia, gastrointestinal tissues, reproductive organs, and brain (Bachmanov & Beauchamp, 2007; Behrens & Meyerhof, 2011). In these organs TAS2Rs may not function as taste receptors, reacting only on xenobiotics, but they might also have endogenous agonists (An et al., 2012; Pulkkinen, Manson, Safholm, Adner, & Dahlen, 2012). One example is regulation of thyroid function (Clark et al., 2015). This can be an interesting aspect of the evolution of TAS2Rs. The elucidation of more receptor-ligand interactions of TAS2Rs is going on, including several quite specific synthetic and natural bitter receptor agonists. In combination with an ever growing number of reports on the

pharmacological effect of TAS2R stimulation, a more detailed picture of ligand interaction is emerging, which might be used for finding pharmaceutical targets (Abrol, Tan, Hui, Goddard, & Pandol, 2015; Di Pizio et al., 2016; Karaman et al., 2016).

Intra-gastric administration of a bitter mixture resulted in the release of the hunger hormone ghrelin (Avau et al., 2015). This caused a short-term increase in food intake, followed by a long-term decrease, correlating with a decrease in gastric emptying and modulation of gastrointestinal motility (Avau et al., 2015).

One effect of bitter compounds in the GI tract is to *delay gastric emptying*, shown in rodents (Glendinning et al., 2008) and in humans (Little, Gupta, Case, Thompson, & McLaughlin, 2009; Wicks, Wright, Rayment, & Spiller, 2005). It would make sense that toxic bitter compounds, passing the oral cavity, delay gastric emptying to reduce the rate of ingestion, especially for rodents lacking the vomiting reflex. After intra-gastric administration of denatonium benzoate, healthy human subjects showed an impaired fundic relaxation in response to nutrient infusion and increased feeling of satiety after nutrient challenge. This might indicate a role for intestinal TAS2Rs as targets to alter GI motility and to interfere with hunger signalling (Avau et al., 2015).

Another reported mechanism is the elevated anion secretion within the large intestines of humans and rats, caused by bitter compounds, which indicates a mechanism to *flush out* potentially harmful content faster from the colon (Kaji et al., 2009).

Dotson et al. (2005) showed that the human receptor hTAS2R9 was associated with *altered glucose homeostasis*, which was caused by a direct effect on the secretion of the incretin hormone GLP-1.

Jeon et al., (2008) showed that a *low-cholesterol diet* could activate the expression of the bitter taste receptor in mouse Tas2r138 in STC-1 cells of enteroendocrine origin. This resulted in an elevated release of CCK, in presence of a suitable bitter agonist for the receptor.

In addition to the direct humoral effect of bitter compounds in the GI tract, part of the bitter sensing mechanisms seems also to be caused by the activation of the *vagal nerve fibers* (Wu et al., 2002; Wu et al., 2005). If a mixture of bitter compounds were administered intragastrically in mice, it led to an activation of brainstem neurons within the nucleus tractus solitarius (NTS), which is the first relay station of taste information within the brain (Hao et al., 2008; Hao et al., 2009). Vagal nerve fibers contain receptors for CCK and PYY and terminate close to enteroendocrine cells. Because bitter compounds stimulate the secretion of these peptide hormones, it would in turn activate the vagal nerve fibers. As reactivity to taste signals associated with taste aversion is not limited to the NTS, but also exists in other brain areas, bitter compounds present in the gut might elicit complex behavioural patterns (Hao et al., 2009). Further research on which of these behavioural responses that are mediated by the presence of bitter taste receptors in the GI tract is needed.

Taste receptors are reported to be present also in the liver (Yamamoto & Ishimaru, 2013), and the question is whether these receptors detect toxic compounds in the blood stream, influencing liver detoxification activity. Beside the dietary sources of bitter and toxic substances, the intestinal microbial flora might also be a source of compounds that activate the liver detoxification mechanism (Rasmussen, Balaguer, Ekstrand, Daujat-Chavanieu, & Gerbal-Chaloin, 2016).

TAS2Rs and taste signalling elements are also expressed in smooth muscle tissue along the mouse gut, and in human *gastric smooth muscle cells* (Avau et al., 2015). Bitter tastants induced region-dependent changes in contractility in mouse intestinal muscle.

Recently Avau et al., (2015) studied the influence of intra-gastric treatment of obese mice with the bitter agonist DB or quinine, and found a decrease in body weight gain associated with a decrease in food intake, maybe also by directly affecting *adipocyte metabolism*?

6. Dietary factors affecting metabolism via bitter taste receptors

Isohumulones from hops, used for beer brewing, exert a direct interaction with the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR) α and γ , maybe involving bitter signalling via bitter taste receptors (Yajima et al., 2004).

Berberine, the major bitter constituent of the Chinese herb Coptis root (*Rhizoma coptidis*), has been shown to influence secretion of GLP-1 via binding to the bitter taste receptor TAS2R38 (in this case expressed on human enteroendocrine NCI-H716 cells) (Yu et al., 2015) (Yu et al., 2015). The GLP-1 secretion was associated with good effects on hyperglycemia (Lu et al., 2009; Yu et al., 2010).

The steroid glycoside H.G.-12 extracted from the South African plant *Hoodia gordonii*, is well known to have an appetite-suppressant effect in both animals and humans, but the glycoside is unable to pass the blood-brain barrier. Now it has been shown to activate the human bitter taste receptor TAS2R14 of the EEC line HuTu-80. This activation initiates secretion of CCK (Le Neve et al., 2010), and might explain its appetite-regulating effect via the vagus nerve.

7. Bile acids – a special case of gut-liver interaction

Bile acids have traditionally been considered as “biological detergents” for emulsifying hydrophobic lipids and vitamins in the gut enabling their absorption from the diet. After the identification of the farnesoid X receptor (FXR) as an endogenous receptor for bile acids (Makishima et al., 1999; Parks et al., 1999), several nuclear receptors (eg SHP, HNF4 α , LRH-1) have been discovered to be important for bile acid homeostasis (S. Li, Ni, & Feng, 2015).

Bile acids are therefore no longer considered as simple molecules facilitating fat digestion, but as agents with real therapeutic value in treating complex autoimmune and metabolic liver diseases (Hegade, Speight, Etherington, & Jones, 2016). Bile acids and their receptors, such as FXR, transmembrane G protein-coupled receptor 5 (the so-called Takeda G protein coupled receptors 5, TGR5) and PPAR, have been identified as novel targets for drug development. FXR was shown to be a key factor in the downregulation of CYP7A1 mRNA in response to high availability of bile acids in the gut (Sinal et al., 2000), a mechanism involving the induction of the small heterodimer partner (SHP), inhibiting CYP7A1 (Kir, Zhang, Gerard, Kliewer, & Mangelsdorf, 2012). There is also a feedback mechanism, where high bile acid load in the ileum acts via FXR transcription of fibroblast growth factor 19 (FGF19 in humans, FGF15 in rodents), which travels in the blood stream and binds to its hepatocyte FGF receptor 4 (FGFR4), initiating a SHP-independent downregulation of CYP7A1, resulting in reduced bile acid synthesis (Jones, 2012; Kir et al., 2012). There are reports on control of liver growth in mice with humanized livers, where the FXR-FGF19 gut-liver axis works as a “hepatostat” (Naugler et al., 2015).

This is a key example of GPCR receptor signalling and its effect on metabolism, considering the presence of TGR5 in many tissues (Hodge & Nunez, 2016). TGR5 was identified as the first cell surface receptor for bile acids (Kawamata et al., 2003; Maruyama et al., 2002) and it functions by increasing cAMP, resulting in diverse downstream actions in a tissue-specific manner (Hannah, 2014). TGR5 is not expressed in the hepatocytes, but found in the cholangiocytes as well as in a variety of other cell types, such as brown adipose tissue, brain, gall bladder epithelium, intestines, spleen, endothelial cells, Kupffer cells and CD14+ cells (Kawamata et al., 2003; Keitel, Donner, Winandy, Kubitz, & Haussinger, 2008; Maruyama et al., 2002). Although many bile acids are capable of activating TGR5, the most potent natural ligands are taurine-conjugated secondary bile acids, such as tauro-lithocholate (Keitel et al., 2008). It has been shown that bile acid-induced TGR5 activity plays a major role in glucose homeostasis, increased energy expenditure, oxygen consumption and gallbladder filling (Katsuma, Hirasawa, & Tsujimoto, 2005; T. Li et al., 2011; Thomas et al., 2009; Watanabe et al., 2006; Watanabe et al., 2004). In addition,

TGR5 activation prevents hepatic steatosis and improves insulin sensitivity, and protects biliary epithelium against the detergent effects of bile acids. More recently, bile acid-mediated TGR5 activation has also been ascribed an anti-inflammatory role by reducing nuclear factor κ B (NF κ B) translocation (T. Li et al., 2011). Accumulating clinical and experimental evidence shows an association between disrupted bile acid homeostasis, gut-liver signalling via bile acid receptors, and various liver disease conditions. This is a rapidly expanding area of research, with important implications for identifying nutritional effects as well as pharmaceutical targets.

8. Conclusions

Traditionally, health effects of bioactive components in the diet have been explained by uptake and distribution of these compounds in circulation and in the body, or effects on the microbial flora in the gut. Now, the discovery and increasing knowledge of the presence of taste receptors in the intestinal tract, opens up a new avenue for how components in the food can affect both metabolic homeostasis and dietary behaviour. For instance, bitter taste receptors, which are designed to react towards minute amounts of possibly toxic substances, makes it interesting to search for new bioactive principles in our diet.

For *food research* it means that we should include these receptor mechanisms and their signalling pathways in our in vitro and animal model experiments. When an effect is found in in vivo animal experiments or human intervention studies, and cannot be verified via in vitro cell culture studies, signalling pathways from intestinal taste receptors, which can only be studied in whole organisms is a plausible explanation. This opens up a plethora of new possibilities, and also offer explanations to effects of dietary components, that has so far eluded us because of the instability of the substances.

This can also be a part of the explanation of the so-called *hormesis* effect, that anti-nutritional factors can have beneficial effects at low concentrations.

For *product development* and creation of new health promoting foods, we could now design and finetune health effects from our diet via the presence of bioactive compounds in the food, which do not have to rely on the uptake, degradation or stability during transport and circulation to the relevant organs in the body, but can affect homeostasis and specific physiological mechanisms via signalling from “a distance”, from the gut, via secretion of peptide hormones or nerve signals directly to the brain centres responsible for our metabolic control, or to other parts of the body.

The *sensory design* of our food products and whole meals will be important not only for the gastronomic aspect and organoleptic preferences, but will certainly in the future become a central part of improving their health promoting function.

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