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T1R and T2R receptors: The modulation of incretin hormones and potential targets for the treatment of type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM), which is characterized by insulin and glucose dysregulation, is a major contributor to the development of cardiovascular disease, renal failure and premature death. Incretin hormones are released from the intestines upon nutrient ingestion and contribute to glucose homeostasis in part by promoting insulin secretion from the pancreas. Drugs that enhance the incretin response have emerged as effective treatments for T2DM. Several recent studies have revealed that incretin secretion from enteroendocrine cells in the intestines can be modulated by T1R and T2R receptors, proteins that have been demonstrated to function as taste receptors. This review focuses on the intriguing finding that taste receptors may be involved in modulating the incretin response, and considers T1Rs and T2Rs as potential targets for new hypoglycemic drugs.

Keywords

Bitter; enteroendocrine cell; glucagon-like peptide-1; glucose-dependent insulinotropic peptide; sweet; taste

Introduction

Diabetes mellitus is a major health concern, affecting more than 20 million individuals in the US [1]. This condition encompasses several related diseases characterized by insulin deficiency and/or insulin resistance, and results in dysregulated glucose homeostasis. Type 2 diabetes mellitus (T2DM), the most prevalent form, is a major risk factor for the development of cardiovascular and cerebrovascular diseases, various neuropathies, retinopathy, kidney disease, and premature death [1]. The prevalence and severity of the complications and comorbidities of T2DM makes the development of more effective

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treatment strategies a high priority for clinicians, researchers and the pharmaceutical industry.

Components of the incretin pathway have emerged as attractive targets for hypoglycemic drugs. The ‘incretin response’ refers to the release of insulinotropic hormones (called ‘incretins’) from the intestines in response to nutrient ingestion [2]. The incretin response is diminished in patients with T2DM [2–4]. Drugs that prolong endogenous incretin signaling or act as incretin mimics enhance insulin release from the pancreas and reduce blood glucose levels [2,3]. Recent studies from several research groups indicate that T1R- and T2R-type GPCRs, which function as sweet (T1R2+T1R3), umami (ie, the savory taste of glutamate; T1R1+T1R3) and bitter (various T2Rs) taste receptors in the gustatory system, are also involved in nutrient responses in the intestines [5,6]. For example, both classes of receptors are expressed on enteroendocrine cells in the intestines, where the receptors act to promote the secretion of incretins, cholecystokinin (CCK) and other peptides [5,6]. In this review, recent studies investigating both oral and intestinal chemosensing are discussed. Furthermore, the suitability of T1Rs or T2Rs as effective molecular targets for novel hypoglycemic drugs is considered.

The incretins

Ingested nutrients, particularly carbohydrates and fats, promote the release of incretins from the intestines. Several intestinally derived peptide hormones have been implicated in prandial insulin-stimulating effects, including glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide-1 (GLP-1) [7,8] and CCK [9,10]. In humans, the effect of oral glucose on insulin secretion appears to be primarily mediated by GIP and GLP-1, which are the only two hormones that fulfill the definition of incretins. The post-translational processing of GIP and GLP-1 from their pro-protein forms (pro-GIP and pro-glucagon, respectively) requires the pro-protein convertase isoform PC1/3 [2,11]. These two incretins are produced in distinct cell types in the intestines: GIP is secreted by K-cells, a group of intestinal enteroendocrine cells located primarily in the duodenum and jejunum, while GLP-1 is secreted from the enteroendocrine L-cells of the distal intestines [2,11]. GIP and GLP-1 are produced in various tissues besides the intestines, where the peptides may perform other functional roles [2]. For example, GLP-1 is also produced in a small number of taste cells in the gustatory epithelium [12,13], where the peptide appears to modulate sensitivity to sweet [12] and umami [14] taste stimuli through GLP-1 receptors that are located on adjacent afferent nerve fibers [12].

The effects of both GIP and GLP-1 are mediated through specific GPCRs, each of which is broadly expressed throughout the body. The GIP receptor is expressed in diverse tissues including the pancreas (on both α-cells and β-cells), intestines, adipose tissue, the heart, the adrenal cortex, the pituitary and several regions of the brain [2,4]. GLP-1 receptors are also broadly expressed; the receptors have been identified in the gastrointestinal (GI) tract, pancreas, lungs, kidneys, in heart and vascular smooth muscle, and in regions of the CNS and peripheral nervous system that include cranial nerves, the hypothalamus and cortex [2,4]. As a result, both GIP and GLP-1 can have pleiotropic effects [11,15]. At least some of these effects may be mediated through a neuroendocrine pathway rather than by direct

endocrine action (see reference [16] for an example). GIP and GLP-1 are both rapidly degraded into inactive metabolites by the enzyme dipeptidyl peptidase-4 (DPP4) [11]; a short half-life (1 to 2 min; [2,17]) is consistent with a need for receptor targets, perhaps on afferent nerves, near the site of incretin production.

GIP and GLP-1 receptors are insulinotropic on pancreatic β-cells in conjunction with an ingested meal. However, both GIP and GLP-1 have other physiological effects, including the suppression of glucagon secretion, the slowing of gastric emptying, the promotion of β-cell proliferation and the inhibition of β-cell apoptosis [11]. Additionally, GLP-1, the more potent of the incretins, increases insulin biosynthesis, decreases appetite and food intake, and has beneficial effects on cardiac function [4,11,15]. The responses to GIP and GLP-1 are significantly curtailed in patients with T2DM, albeit in distinct ways [18,19]. Patients exhibit normal plasma levels of GIP, but an impaired response to the hormone; in contrast, the response to GLP-1 is normal, but the secretion of the hormone is impaired [4,20,21]. Given that the physiological action of GLP-1 is preserved in patients with T2DM, this peptide has become a prime target for therapeutic intervention in this disease.

Targeting the incretin pathway

Two classes of pharmaceuticals that target the incretin pathway are available for the treatment of T2DM [2,3]. Members of the first class, the incretin mimetics, act to supplement endogenous GLP-1. Both exenatide (a synthetic version of the peptide exendin-4 [22]) and liraglutide (a GLP-1 derivative [23]) are GLP-1 receptor agonists that are resistant to degradation by DPP4; related compounds are also being investigated [3]. Drugs of the second class, DPP4 inhibitors, elevate endogenous incretins by slowing their degradation, and thus prolonging their effects [3,24,25]. Several DPP4 inhibitors are available (eg, sitagliptin, vildagliptin and saxagliptin) or are in various stages of development (eg, alogliptin [Takeda Pharmaceutical Co Ltd]) [3]. While both classes of drugs have been effective, the compounds have limitations. For example, incretin mimetics must be administered by regular subcutaneous injection and can have significant side effects, including nausea. Limited case reports involving acute renal impairment [26] and severe pancreatitis [27] have also raised concerns regarding the safety of incretin mimetics in at least some patients. In contrast, while DPP4 inhibitors have few known side effects, these drugs are less selective in their actions (DPP4 has a diverse range of substrates) and are not as potent hypoglycemic agents as the incretin mimetics [3]. Therefore, there remains a need to explore alternative methods of modulating the incretin pathway for therapeutic effect.

Compounds that directly and specifically increase incretin secretion are not currently part of the treatment regimen for patients with T2DM. Until recently, the identity of receptors that could detect the presence of luminal nutrients, such as sugars, and transduce that signal into increased incretin secretion was unknown. Recently, however, receptors that were first discovered as key components of the gustatory system, the T1Rs and T2Rs, have also been implicated in the initial stages of the incretin response [5,6]. The role of these receptors in postprandial glucose responses is discussed in the sections following the introduction of T1Rs and T2Rs and the involvement of these receptors in taste transduction.

Taste transduction

The human gustatory system detects stimuli that elicit five perceptual qualities: sweet, bitter, umami, sour and salty, with distinct receptors expressed on specialized sensory cells that are located within the oral cavity [28,29]. Sweet-tasting molecules, such as sugars and artificial sweeteners, are recognized by a heterodimeric GPCR composed of two T1R subunits, T1R2 and T1R3 (Figure 1A) [29–32]. The deletion of the genes encoding these two subunits in mice abolishes taste responses to all sweet substances [33]. The T1R3 subunit paired with another T1R protein, T1R1, functions as the umami receptor [29,32,34]. Bitter-tasting molecules are recognized by a distinct family of GPCRs, the T2Rs [29,35,36] (Figure 1A). Humans express approximately 25 different T2Rs, which vary in their breadth of stimulus tuning: some respond to only a few compounds, while others are relatively promiscuous [37]. Many of the molecules used by taste cells to transduce sweet, bitter and umami-tasting stimuli have been identified [38], including the G-protein subunit α-gustducin [39,40], the effector enzyme phospholipase C β_2 (PLCβ_2) [41], the inositol 1,4,5-trisphosphate (IP_3) receptor type 3 (IP_3R3) [42,43], and the Ca^{2+}-activated cation channel transient receptor potential M5 (TRPM5) [41,44] (Figure 1B). The molecular mechanisms underlying salty and sour tastes have not been fully resolved, although the epithelial sodium channel ENaC is a major factor in salt taste in rodents [29].

T1Rs and T2Rs outside the gustatory system

Although the T1Rs and T2Rs expressed on taste cells of the oral cavity clearly function as taste receptors, these same proteins likely also serve as chemoreceptors throughout the body (Figure 2). For example, T1R2, T1R3 and α-gustducin are expressed in pancreatic islets in mice and in the MIN6 pancreatic β-cell line, in which the receptors may contribute to sweetener-dependent insulin secretion [45]. T1R3 expression has also been reported in the brush cells of the intrahepatic bile duct and pancreatic duct, in which the receptors have been suggested to be involved in monitoring secretions from these organs [46]. T1Rs may function as glucosensors in the hypothalamus and other brain regions [47], while α-gustducin-positive/T2R-positive cells in the anterior nasal cavity [48,49] and respiratory tract [50] may act to sense and promote the expulsion of inhaled toxins.

Of particular interest for this review is the observation that T1Rs and T2Rs, as well as associated taste transduction proteins, are expressed in cells of the GI tract [5,51–61]. Phenotypic similarities between taste and chemosensing cells in the intestines were first suggested with the observation that the brush cells of the GI tract express the taste-related G-protein subunit α-gustducin [51]. Subsequently, human and rodent enteroendocrine K- and L-cells and several cell lines (eg, the murine STC-1 and GLUTag lines, as well as the human NCI-H716 line) were shown to express α-gustducin [54,55,60,61], as well as other components of the taste transduction pathway, including PLCβ_2 [54], TRPM5 [54], T1Rs [54,55] and numerous T2Rs [52,58–60]. Considering the established role of these proteins in chemosensory transduction, the expression of T1Rs and T2Rs (particularly the components of the sugar-sensitive sweet taste receptor, T1R2+T1R3) in enteroendocrine cells suggested that these receptors may also function as luminal nutrient sensors in the GI tract. Several recent studies, discussed in the next section, provide important support for this hypothesis.

T1Rs, T2Rs and incretin secretion

The glucose-dependent secretion of incretins from enteroendocrine cells in the intestines is well established [2,11]. A landmark study by Jang *et al* provided strong evidence that the T1R2+T1R3 receptor and α-gustducin mediate this response [54]. α-Gustducin knockout mice exhibited no GLP-1 secretion and altered GIP secretion compared with their wild-type littermates in response to a gavaged glucose load. In these same experiments, the glucose-dependent increase in plasma insulin was delayed and plasma glucose levels were elevated in knockout mice (ie, insulin secretion in response to the GLP-1 receptor agonist exendin-4 or to ip glucose was normal). In response to stimulation with natural or artificial sweeteners, GLP-1 secretion from the human enteroendocrine cell line NCI-H716 was dependent on both α-gustducin and T1R3: GLP-1 levels were reduced after the siRNA-mediated knockdown of α-gustducin or the inhibition of the sweet taste receptor by lactisole, an inverse agonist that binds to an allosteric site on human T1R3 [62,63]. A contemporaneous paper [55], which reported that the sweetener-dependent secretion of GLP-1 and GIP from GLUTag cells is abolished in the presence of the mouse T1R2+T1R3 inhibitor gurmarin, provided important confirmation of these results.

T1Rs and T2Rs are expressed in distinct subpopulations of taste cells, consistent with their roles in the detection of diverse stimuli that elicit discrete sensory perceptions (ie, sweet, umami or bitter taste). In contrast, enteroendocrine cells in the intestines express both T1Rs and T2Rs, which raises the question of whether T2R activation, similar to T1R activation, promotes incretin secretion. Studies in mouse and human enteroendocrine L-cell lines suggest that it does. Bitter-tasting compounds that can activate specific T2Rs *in vitro* promoted the elevation of intracellular Ca^{2+} [64] and the α-gustducin-dependent secretion of GLP-1 [58,59] from these cells. Thus, T1Rs and T2Rs appear to function in parallel to stimulate incretin secretion in L-cells.

These two studies of α-gustducin-dependent secretion of GLP-1 by T2Rs [58,59] also provided support for the physiological relevance of T2Rs in the intestines. Dotson *et al* demonstrated that a loss-of-function variant of T2R9 (ie, TAS2R9) was associated with glucose dysregulation and an increased incidence of T2DM in humans, indicating a role for T2Rs in the incretin response and the modulation of glucose homeostasis [58]. This finding is consistent with the observation that the hydrosylates of many dietary proteins have a bitter taste and would likely activate T2Rs in the intestines [65]. Jeon *et al* observed an upregulation of T2R138 expression in mice that were fed a low-fat diet, which would likely contain an excess of plant materials and thus could be higher in natural toxins [59]. Together, these results suggest that the activation of T2R can indicate the presence of both ‘positive’ (ie, nutritive) and ‘negative’ (ie, toxic) compounds in the intestinal lumen. Such observations may not be surprising in light of the diverse physiological effects of GLP-1, including the promotion of insulin secretion and the slowing of gastric emptying. Nonetheless, both T1Rs and T2Rs appear to be potential targets for modulating incretin secretion.

The promise and limitations of T1Rs and T2Rs as targets for new hypoglycemic drugs

Compared with insulin treatment, GLP-1 and its analogs improve glycemic control, decrease weight, and stabilize or improve pancreatic cell function and proliferation [2,11]. Controlling GLP-1 and synergistic CCK secretion from enteroendocrine L- and K-cells, respectively, by targeting T1Rs and T2Rs in patients with T2DM may represent a major advance in the treatment of the disease. However, whether T1R and T2R receptors are favorable candidates for the pharmacological control of glucose-regulated GI peptide hormone secretion must be addressed.

First, some potential limitations should be considered. A primary concern regarding any drug target is specificity of action. Both T1Rs and T2Rs are widely expressed (Figure 2), and the physiological roles for these receptors in several tissues have previously been discussed. Even within the intestines, these receptors are likely to have regulatory functions that are independent of incretin secretion; for example, T1Rs impact glucose sensing and assimilation by regulating the enterocyte expression of the glucose transporters SGLT1 and GLUT2 [55,56,66]. T1Rs may also have effects on glucose production through the promotion of CCK secretion from enteroendocrine K-cells [9,59]. In each of these cases, however, the effects on glucose homeostasis may be synergistic with the incretin effect. Furthermore, the oral delivery of medications to the GI tract could prevent systemic actions; however, medicines would require proper encapsulation to prevent actions on gustatory receptors.

A second issue is whether T1R- or T2R-mediated incretin secretion is physiologically relevant; for example, artificial sweeteners can promote the release of GLP-1 from human or mouse enteroendocrine L-cell lines [54,55] or insulin secretion from a mouse pancreatic β-cell line [45]. However, artificial sweeteners appear to have little to no effect on GLP-1 release or glucose homeostasis *in vivo* [67–69] (though see reference [66], which suggests artificial sweeteners could influence glucose absorption in enterocytes). This apparent contradiction has yet to be resolved, but may indicate the existence of T1R-independent regulators of incretin secretion that are specific to glucose and other metabolically relevant sugars. Furthermore, effective incretin secretion could require the concomitant activation of other receptors on the same enteroendocrine cells. Finally, different genetic or pharmacological manipulations of the incretin pathway do not phenocopy, given that the genetic deletion of various molecules related to the production or reception of GLP-1 (e.g., proglucagon, PC1/3 and the GLP-1 receptor) in mice yields somewhat different phenotypes [70–73], although these discrepancies may reflect strain effects or differences in testing procedures. The best example that not all incretin pathway manipulations are equal is the comparison of GLP-1 mimetics and DPP4 inhibitors, which exhibit somewhat different actions and efficacies [2,3]. Invoking known and unknown ‘compensatory mechanisms’ appears to be a simplistic explanation for these differences, but may in fact be the true explanation.

Even with these caveats, T1Rs and T2Rs remain strong candidate targets for the development of new hypoglycemic drugs. As described previously, the roles of the receptors

in incretin secretion and the modulation of glucose homeostasis are supported by an increasing number of *in vitro*, *in vivo* and genetic studies. Moreover, both T1Rs and T2Rs are members of the GPCR superfamily [29], a well-studied group of proteins that are often effective drug targets and that are also amenable to high-throughput screening (eg, see references [37,58]). Numerous positive and negative allosteric modulators, including many natural and artificial sweeteners and the sweet taste inhibitor lactisole, have been identified for the sweet taste receptor [30], suggesting that drugs could be targeted to numerous sites on either T1R2 or T1R3. These interactions can be measured using multiple assays, which could facilitate the characterization and validation of lead compounds (eg, see references [74,75]). In contrast, the large number of T2Rs expressed in the intestines, each with different ligand specificities [37], offers diverse targets that may allow for selectivity and specificity. Furthermore, many common pharmaceuticals have a bitter taste and activate T2Rs (eg, see references [36,37,58]). Therefore, exploring whether any known bitter-tasting drugs have positive effects on glucose homeostasis would be of interest. No drug discovery activities involving T1Rs and/or T2Rs for the potential treatment of T2DM appear to be underway. However, at least one company, Senomyx Inc, has an active program using the high-throughput screening of T1Rs and T2Rs to identify novel taste compounds, including flavor enhancers and bitter blockers (e.g., see references [76–80]). A similar strategy could be used in the context of the incretin pathway and T2DM.

Conclusion

The incretin pathway has proven to be an excellent source of targets for useful hypoglycemic drugs. Incretin mimetics and DPP4 inhibitors have been valuable additions to previous treatment regimens for patients with T2DM. However, such drugs have limitations; for example, incretin mimetics must be administered by regular subcutaneous injection and can have side effects, including nausea, while DPP4 inhibitors are less selective in their actions and are not as potent hypoglycemic agents as incretin mimetics [3]. Recent discoveries demonstrating that T1Rs and T2Rs can regulate the secretion of incretins and other glucose-regulating GI peptide hormones suggest new opportunities to understand incretin physiology and synergies, and the possibility of therapeutically modulating the incretin response. Recent findings also raise the possibility that ingested pharmaceuticals (many of which have a bitter taste) could affect the incretin response (eg, see reference [58]). The potential for T1Rs to influence glucose absorption by regulating glucose transporters affords another therapeutic approach for drug targeting. Although research is in the early stages, the future is highly promising for identifying new targets for the potential treatment of T2DM.

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•• of outstanding interest

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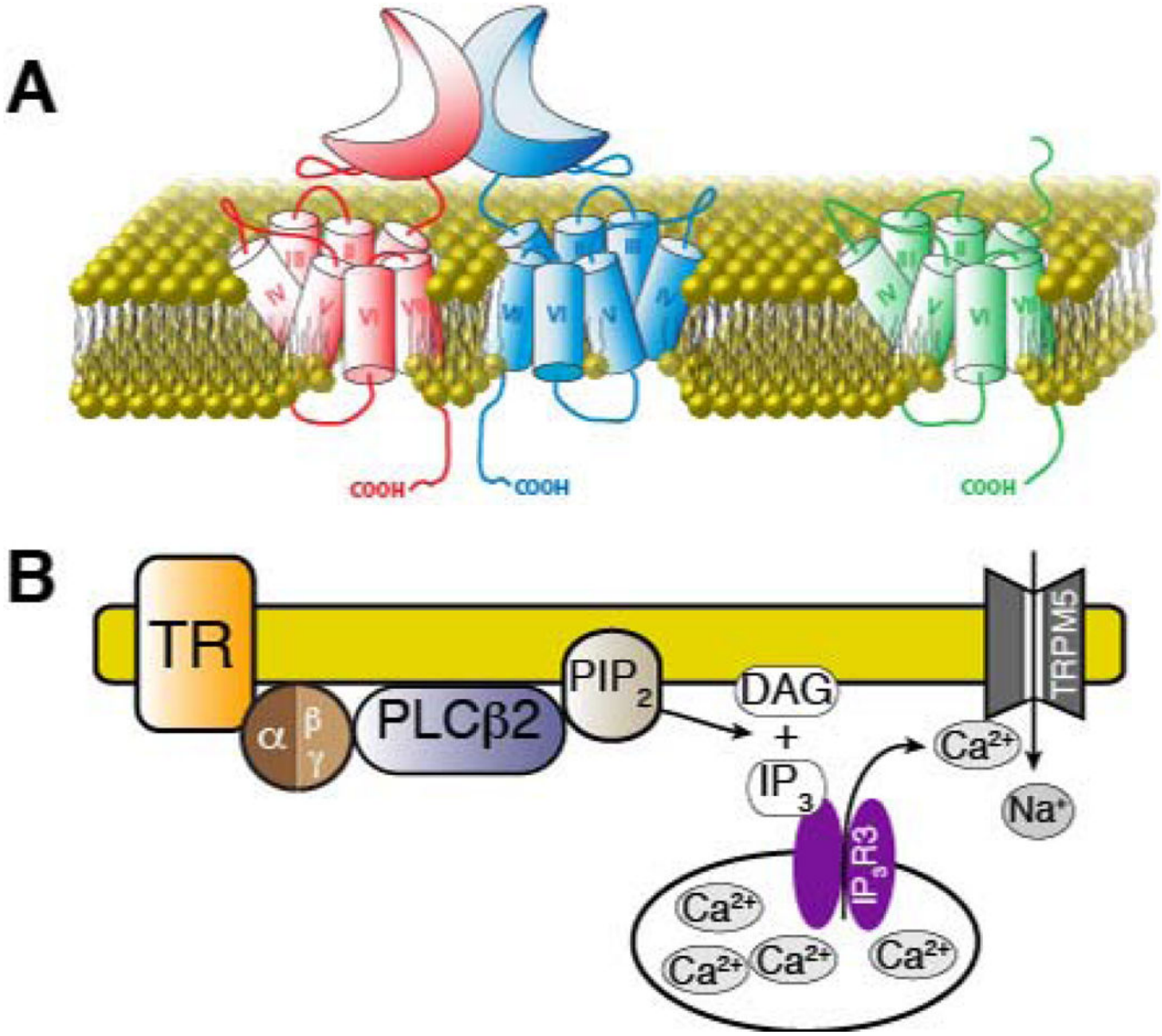

Figure 1. Taste transduction

(Legend) (**A**) T1Rs (left; shown in red and blue) and T2Rs (right; shown in green) function as taste receptors (**TR**s) for sweet (T1R2+T1R3), umami (T1R1+T1R3) and bitter (T2R) tasting stimuli. T1R2 and T1R3 contain many allosteric binding sites for sweeteners and sweet taste inhibitors [29,63,81–83], although sugars such as glucose and sucrose bind to the clamshell domains at the amino end of each subunit [74]. (**B**) The current model for the transduction of sweet, umami and bitter stimuli in the gustatory system is shown. When a tastant binds to a T1R or T2R receptor it activates a G protein-coupled signaling cascade that leads to the production of the second messenger IP_3, the release of Ca^{2+} from intracellular stores, the opening of Ca^{2+}-gated TRPM5 cation channels, and depolarization of the taste cell. The subunits of the heterotrimeric G-protein are represented by α, β and γ.

DAG Diacylglycerol, **IP_3** inositol 1,4,5-bisphosphate, **IP_3R3** IP_3 receptor type 3, **PIP_2** phosphoinositol 4,5-bisphosphate, **PLCβ2** phospholipase C β2, **TRPM5** transient receptor potential channel M5

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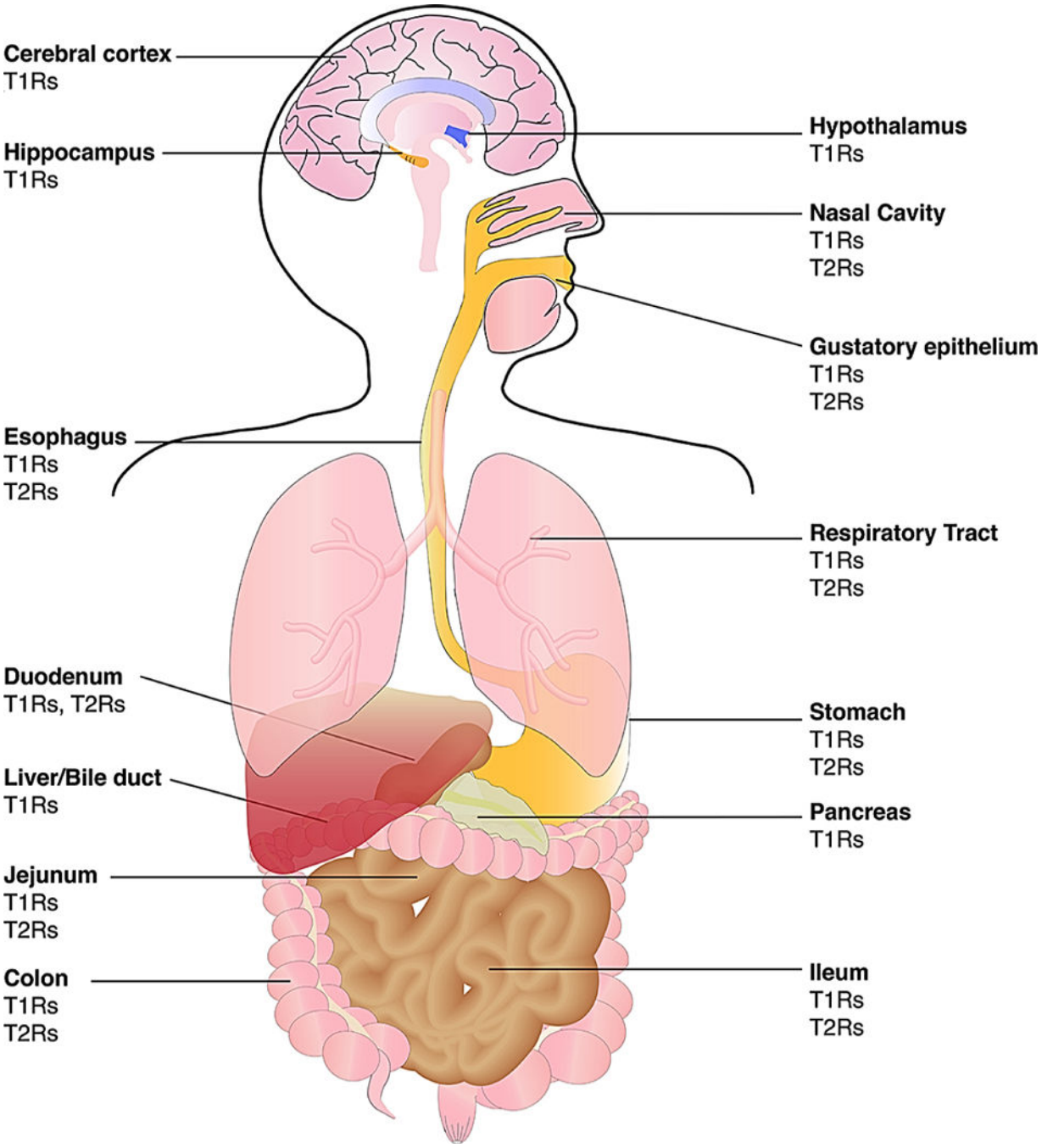

Figure 2. The expression of T1Rs and T2Rs in numerous tissues

(Legend) The expression patterns shown represent findings from studies conducted in humans and/or rodents [45–48,50,52–59].

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