

## Review

## Mechanism of fat taste perception: Association with diet and obesity

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## ABSTRACT

Energy homeostasis plays a significant role in food consumption and body weight regulation with fat intake being an area of particular interest due to its palatability and high energy density. Increasing evidence from humans and animal studies indicate the existence of a taste modality responsive to fat via its breakdown product fatty acids. These studies implicate multiple candidate receptors and ion channels for fatty acid taste detection, indicating a complex peripheral physiology that is currently not well understood. Additionally, a limited number of studies suggest a reduced ability to detect fatty acids is associated with obesity and a diet high in fat reduces an individual's ability to detect fatty acids. To support this, genetic variants within candidate fatty acid receptors are also associated with obesity reduced ability to detect fatty acids. Understanding oral peripheral fatty acid transduction mechanisms and the association with fat consumption may provide the basis of novel approaches to control development of obesity.

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## 1. Introduction

Obesity is a contributor to the major causes of global disease burden, including cardiovascular diseases, cancer and diabetes [1,2]. Both genet-

ic and environmental factors are implicated in obesity: family and twin studies estimate the genetic contribution between 45% to 75% [3] and genome wide association studies (GWAS) implicating loci like FTO and MCR4 [4]. Furthermore, a lack of physical activity and high caloric food consumption such as diets rich in fats and sugars are commonly accepted environmental factors associated with the development of obesity [5].

The sense of taste functions as a nutrient sensing system, and any irregularity may contribute to excess energy intake and obesity. This

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review explores the association between taste and obesity by examining the evidence for gustatory mechanisms of fatty acid chemoreception (fat taste) and how these mechanisms may be implicated in the reported associations between fat taste threshold, weight gain and obesity.

## 2. The taste system and gustatory anatomy

The function of the taste system in humans is to determine if the food is nutritious and safe to consume, as well as to prepare the digestive tract for the processing of the nutrients consumed [6]. The machinery of taste is located in the oral cavity, with the gustatory papillae housing groups of 50–100 taste receptor cells (TRCs) in structures called taste buds. The papillae are divided into three types according to the topographical representation on the tongue: fungiform, foliate and circumvallate papillae [7].

The TRCs are morphologically distinct with four different types of cells—classified as type I, II, III and the Basal (IV) cells with different functional significance [8]. Type I cells are glial-like cells [9] with many electron-dense granules in the apical cytoplasm [10]. Type II are spindle shaped cells, with large nuclei and short microvilli that protrude from the apical region [10]. Type II cells are associated with the taste of sweet, bitter and umami compounds [11]. Phospholipase C $\beta$ 2 (PLC $\beta$ 2), an essential second messenger during the transduction of these tastes, is a commonly used marker for type II cells [12,13]. Type III cells are slender shaped with large vesicles in the nuclear region and a single microvillus that protrudes into the taste pore [10]. They contain synapses with primary sensory terminals, express synapse-related proteins, and are often referred to as presynaptic cells [14]. The basal (type IV) cells appear to be immature or undifferentiated and their function is unknown.

After the excitation of the primary sensory afferent fibres by the TRCs [15], the gustatory signals are transmitted from the taste buds to the central nervous system (CNS) through cranial nerves [16], which forms the sense of taste and informs the acceptance or rejection of the food [17]. While the events triggered by a specific tastant within the taste cell have been established, the signal processing from the taste cell through nerve fibres to form a specific taste percept remains unclear.

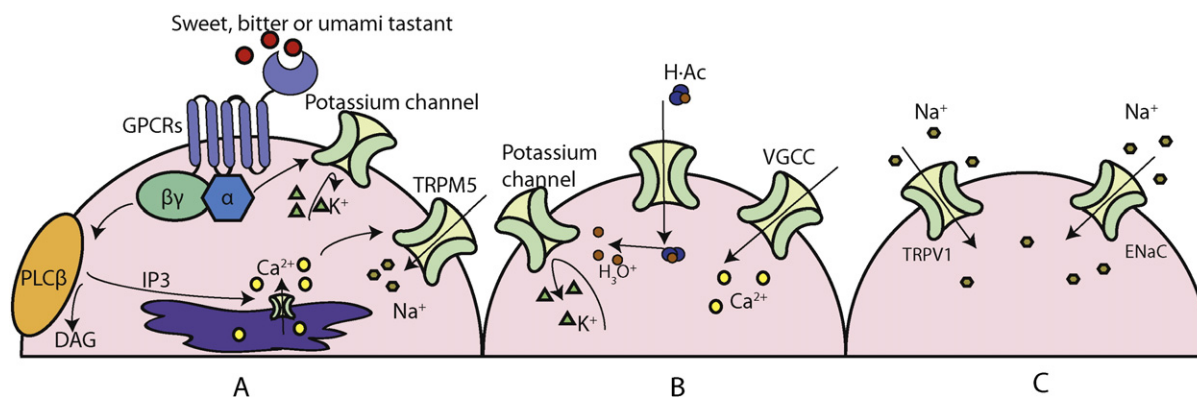
## 3. The five taste primaries

Taste is responsible for recognising and distinguishing key dietary components. It is believed to have evolved to help intake of essential and scarce nutrients, while preventing the consumption of toxic and indigestible substances [8,18]. The five taste primaries—sweet, bitter,

umami, sour and salty—enable humans to perceive desired nutrients at the appropriate levels as pleasant and many toxins at harmful levels as unpleasant [6].

Sweet and umami tastants are detected by the homodimeric or heterodimeric complexes composed of G protein coupled receptors (GPCRs)—T1R1, T1R2 and T1R3 [19]. Bitter taste is mediated by a family of GPCRs called T2Rs [20]. The T1Rs and T2Rs are located in the distinct population of type II taste receptor cells [21], with signal transduction involving a series of reactions (Fig. 1) triggered by the combination of the tastant with a specific receptor. Even though different sweeteners activate the same T1R heterodimers, natural and artificial sweeteners are reported to trigger different signalling pathways. The pathway for sugars is believed to start from the  $\beta\gamma$  subunits (G $\beta\gamma$ ) of the  $\alpha$ -gustducin, which involves the activation of PLC $\beta$ 2 and the production of IP3 [7]. On the contrary, artificial sweeteners activates the  $\alpha$  subunit of the  $\alpha$ -gustducin and initiates the reaction involving the cAMP [7]. Both pathways ultimately lead to the elevation of cytoplasmic calcium levels. The elevated calcium concentration and IP3 amounts lead to the opening of the transient receptor potential M5 (TRPM5) ion channel [22], and depolarization of the TRC (Fig. 1A). As a result, the neurotransmitter ATP is released into the extracellular space surrounding the activated receptor cell through the Panx1 hemichannel [23,24]. ATP then stimulates multiple targets: one is the gustatory afferent nerve fibres directly. The other is the adjacent presynaptic cells [25], which releases the transmitters including norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT) through synaptic exocytosis [26]. Sour and salt tastes are generally believed to be detected through ion channels (Fig. 1B). Sour taste is considered to be triggered by the intracellular proton concentration change [27] following the fully protonated acids permeating the cell membrane and releasing protons [28]. Several channels have been associated with sour taste, including PKD2L1 and PKD1L3 [29,30]. For salt taste, the principal stimulus ( $\text{Na}^+$ ) can permeate through the cation channels on the apical taste buds, leading to the depolarization of the receptor cells (Fig. 1C). The putative candidate is the epithelial-type sodium channel (ENaC) [31,32].

Signal transduction for the five primary tastes involves the release of the neurotransmitters 5-HT, NE and ATP, after TRC stimulation. Thus, the question comes to how the different taste qualities are transported and encoded by the brain. Whether a single nerve fibre conveys a specific taste quality or multiple tastes to the brain has been assessed in previous studies, with the emergence of two main stream theories [33]. Current evidence suggests some of the afferent fibres conservatively tuned to a single taste quality, but others broadly respond to multiple qualities [34,35].



**Fig. 1.** Proposed mechanisms by which five taste qualities are transmitted in taste cells adapted from [8]. (A) Sweet, bitter or umami stimuli bind to the GPCRs on Type II cells activating two parallel pathways. One is from the G $\beta\gamma$  subunit, which increases the secretion of  $\text{Ca}^{2+}$  through a phosphoinositide pathway and depolarises the generator potential of the cell. The other pathway begins from  $\alpha$  subset of the  $\alpha$ -gustducin (G $\alpha$ ), which leads to the transient change in cAMP and depolarises the cell by the blockage potassium channels. Both pathways lead to the release of ATP through Panx 1 hemichannel pores into the extracellular space. (B) Sour taste transduction occurs in Type III cells. Acids can travel through membrane of presynaptic cells and releases  $\text{H}^+$  (binds with  $\text{H}_2\text{O}$  to  $\text{H}_3\text{O}^+$ ) upon disassociation to acidify the cytosol and block the potassium channel as a result. Then the cytoplasmic  $\text{Ca}^{2+}$  concentration is increased through the  $\text{Ca}^{2+}$  influx from Voltage-gated calcium channels (VGCC) to release 5-HT and NE through synaptic vesicles. (C)  $\text{Na}^+$  can permeate through the ENaC or TRPV1 ion channels directly to cause the cell depolarisation.

#### 4. Measurement of taste function

Humans can detect the taste qualities from a vast range of chemical compounds, with large interindividual differences in sensitivity to those chemicals the norm. Sensory threshold is commonly used as a phenotypic indicator of the taste function (sensitivity). The absolute or detection threshold (DT) is the lowest level that a stimulus is perceivable [36,37]. This is the concentration when the person can detect there is something other than water in solution, but cannot identify a quality. If an individual has a high DT value for a stimulus in comparison to the distribution of DT values in the cohort then they have a low sensitivity or a compromised taste function to that stimulus. Increasing the concentration of the stimulus reveals the recognition threshold (RT). RT is termed as the minimum level that takes on the characteristic taste of the compound, i.e., sucrose, is sweet [38]. Besides the DT and RT measurements, suprathreshold (above the level to produce a perceptible effect) is considered to be an important indicator of taste function when considering food intake [37]. An important note is that no one measure of threshold is representative of taste function as a whole. For example, there was no relationship between detection threshold, recognition threshold and suprathreshold intensity to a range of stimuli in a cohort of university students [37], highlighting a limitation of single threshold measurements when assessing taste function of an individual. A more accurate assessment of taste function requires a multifaceted approach including multiple threshold measurements [37].

#### 5. Mechanisms of fat taste

“Fat” is the term used to refer to naturally occurring triglycerides and fats are an essential component of normal food intake of humans. Dietary fatty acid deficiency leads to impaired vision, growth retardation, skin lesions and reduced learning ability among others [39]. Nevertheless, overconsumption of fat has negative health impacts and increases the risk of morbidities, such as obesity [40,41], diabetes [42] and cancer [43,44].

Many physical and chemical attributes have been reported to contribute to the rewarding effect of fatty foods, such as texture, olfaction [45] and oral irritation [46]. Furthermore, mounting evidence suggests the existence of a chemosensory component for fat taste when the other sensory attributes, like textural cues and oral irritation, are masked [47–49]. It is likely that the chemical information would combine with the textural signals to form the full sensory perception of fat. But for the sense of taste to have a fat component, the tastant must be soluble in saliva, and triglycerides (the predominant form of dietary fat) are generally insoluble in saliva. Fat should be similar to the other macronutrients carbohydrate or protein, where the breakdown products namely sugar and amino acids respectively are the taste stimuli. Studies in rodents suggest that free fatty acids (FFAs) are liberated from the glycerol backbone of triglycerides in the oral cavity by the reaction of lingual lipase [50–52] and lingual lipase activity has also been demonstrated in humans, albeit much lower activity than rodents [48,53,54].

Measurement of fat taste in humans is complex as some researchers believe fatty acids do not elicit perceptual taste qualities such as sweet, umami, bitter, salty and sour tastes. Rather, fat taste appears to only define a detection threshold [48,55], although this is controversial [56].

There are commonly three types of FFAs: saturated (e.g., stearic and lauric acid), monounsaturated (e.g., oleic acid) and polyunsaturated (e.g., linoleic acid) fatty acids [57]. The weak correlation between different FFA thresholds [48,58] suggests one of two hypotheses: the presence of multiple transduction pathways utilising different receptors as seen in the bitter taste modality that involves a diverse family of taste receptors (T2Rs) [59], or may reflect varying affinities for the different fatty acids to the same receptor as seen in the sweet taste modality with differences in sweetness between equimolar concentrations of sucrose and glucose [60].

Previous studies suggest the chemoreception pathway starts with the fatty acids triggering the receptor or ion channel, which activates a complex signalling cascade including increased cytoplasmic calcium level leading to the depolarization of the receptor cell. As this reaction also involves the production of IP3 [61], the transduction system resembles that of the sweet, bitter and umami (Fig. 2). Several receptors and ion channels have been identified that show responsiveness to FFA stimuli (summarised in Table 1) based on its saturation degree and chain length:

##### 5.1. CD36 receptor

CD36 is a plausible candidate as the gustatory lipid sensor, which is also known as the fatty acid transporter. The CD36 amino acid sequence exists as a transmembrane glycoprotein with an extracellular pocket structure between the cytoplasmic amino and carboxyl terminal tails [62], allowing the transduction of external signal into the cell [63]. It has a nanomolar-range affinity [64] to a range of lipid-based ligands, such as lipoprotein, apoptotic cells, and LCFAs [65]. CD36 has been detected in human foliate and circumvallate papillae [66]. Furthermore, CD36 gene inactivation abolishes the preference for long chain fatty acids (LCFAs) in rats [67] without affecting the sensitivity to sweet or bitter taste [67].

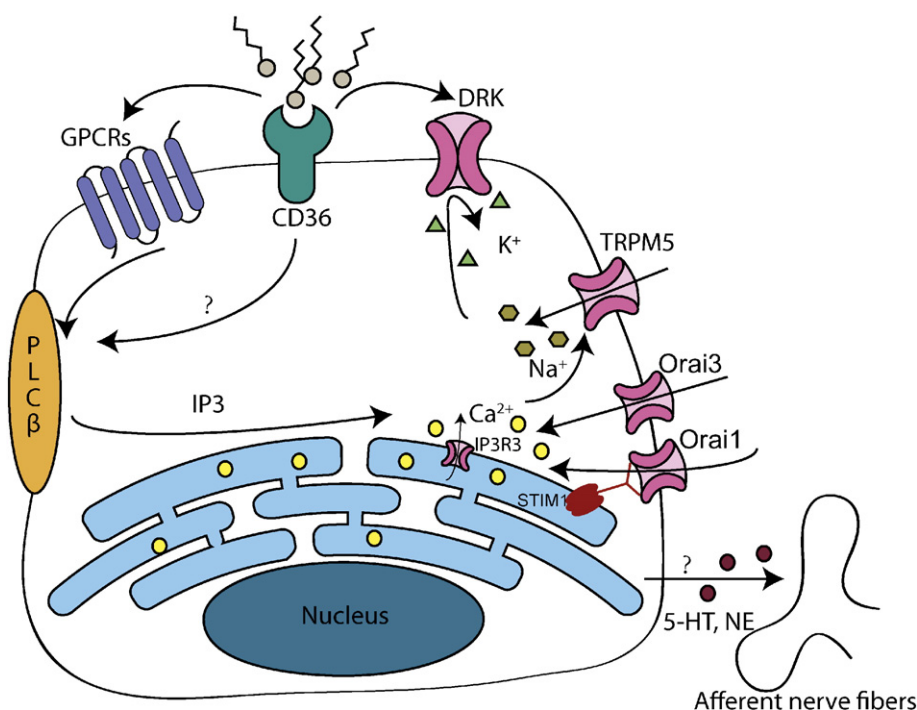
In recent years, the single nucleotide polymorphism (SNP) rs1761667 of CD36 has received much attention, with the A and G alleles linked with lower and higher sensitivity to fatty acid detection, respectively [53,68–70]. Another CD36 SNP (rs1527483) was also associated with oral fat perception in African American populations [71]. These studies indicate the fatty acid specific role for CD36.

##### 5.2. GPCRs

Given that bitter, sweet and umami tastes utilise GPCRs, such as T1R and T2R, it is reasonable to speculate that GPCRs may also play a role in fatty acid detection. The two receptors, **GPR40 and GPR120 may be candidate FA receptors as in vitro calcium mobilisation assay indicate they respond to medium-chain and long chain fatty acids [72,73]. GPR40 and GPR120 gene knockout studies in mice show a diminished preference for some FA such as linoleic acid and oleic acid [74].**

**GPR120 has been found in gustatory tissue of mice and expressed mainly in type II taste receptors cells of foliate, circumvallate and fungiform papillae [74]. Within the oral cavity, GPR120 acts as a receptor for medium to long chain fatty acids, which mediates the transduction of signal from the taste cell to the CNS via afferent taste nerves [74].** Expression analysis shows that GPR120 mRNA is present in human circumvallate, fungiform papillae and non-gustatory epithelia [75]. GPR40 is predominantly expressed in type I cells in foliate and fungiform taste buds of mice [74]. GPR40 expands the types of effective fat stimuli as it binds with shorter medium-chain fatty acids as well as LCFAs [76]. GPR40 is reported to be absent in human lingual epithelium, suggesting it may not be involved in fatty acid taste detection in humans [75]. However, the study did not analyse the expression level of GPR40 in the foliate papillae or other gustatory tissues. Therefore, the role of GPR40 in human fat taste cannot be excluded absolutely.

Other candidate GPCRs respond exclusively to short or medium chain fatty acids, such as GPR41 and GPR43 to short chain [77] and GPR84 to medium chain fatty acids [78]. A previous study analysed the role of GPR41 and GPR43 in human GI tract where they detect short chain fatty acids produced from carbohydrate digestion by the endogenous bacterial flora [79]. Although no human data is available to date, GPR41, GPR43 and GPR84 have been detected in rodent gustatory papillae [80]. If expressed in human gustatory tissue, they may also play a role in fatty acid taste detection.



**Fig. 2.** Proposed FFA induced signal transduction in human taste bud cells. FFAs bind to the fatty acid translocase CD36, which directly or indirectly (transfer through GPCRs and DRK channels) leads to the release of the  $\text{Ca}^{2+}$  from the endoplasmic reticulum (ER) or blocking of the efflux of  $\text{K}^{+}$ . After the  $\text{Ca}^{2+}$  releasing from the ER, the  $\text{Ca}^{2+}$  sensor stromal interaction molecule 1 (STIM1) located on the ER membrane moves toward the store operated calcium (SOC) channels on the cell membrane (such as Orai1 and Orai3) to form complexes. The complexes induce the  $\text{Ca}^{2+}$  influx through the SOC channels and lead to the rise of the cytoplasm  $\text{Ca}^{2+}$  concentration. The resulted depolarization of the cell induces the release of the neurotransmitters such as NA and 5-HT onto the afferent nerve. The mark of interrogation (?) shows the complicated issues in the pathway.

### 5.3. DRK channels

Delayed Rectifying  $\text{K}^{+}$  (DRK) channels were firstly reported to be associated in the fat taste perception in rats. **The DRK channels are embedded within the apical membrane of lingual taste cells, which allows the flow of  $\text{K}^{+}$  into the extracellular space. However, cis-polyunsaturated fatty acids (PUFAs) block the channels, directly or indirectly, leading to the depolarization of the cell for signal transduction [81]. Fatty acid sensitive DRK channels have been found in fungiform and the posterior part of the tongue in mice [80] and kv1.5 is the major channel found in rat fungiform taste buds. Gilbertson et al. linked fatty acid taste sensitivity with DRK channel expression levels in animal models [82]. The expression of DRK channels in human taste buds has not yet been established.**

### 5.4. Cross-talk between receptors and ion-channels

Limited evidence indicates that taste receptors and ion channels may coordinate to regulate the signal transduction cascade for fatty acid detection, rather than functioning independently [83,84]. That is,

LCFAs may bind to CD36, followed by the communication with GPCR (most likely GPR120) and thus trigger intracellular signal transduction. The co-expression of CD36 with GPR120 in single taste cells provided the basis for this model [85]. This model is supported by the higher affinity of CD36 for FFAs compared to GPR120 (i.e. CD36 functions as a FA catcher that passes the FA to GPR120 that has lower affinity) [86,87]. LCFAs may also block the DRK channels via CD36 translocation or directly in order to maintain the cell activation (Fig. 2).

However, a recent study indicated the independent role of CD36 and GPR120 through the selective knockdown of either CD36 or GPR120 in human fungiform taste bud cells [85]. It suggested CD36 as the primary receptor while GPR120 only functioned under high FA level. The increase of intracellular calcium concentration in either CD36 or GPR120 knockout cells after being induced by FA [85] indicated the signal transduction pathway for fatty acids is not limited to the cross-talk reaction between CD36 and GPR120.

### 5.5. Signal transmit from the cell to the brain

After cell depolarisation, neurotransmitters such as 5-HT and NE are secreted toward the afferent gustatory nerve fibres (specifically VIIth

**Table 1**  
Characteristics of candidate receptors and ion channels associated with FFAs chemoreception.

	Family type	Binding ligands	Function	Expression in human TBC
CD36	Scavenger receptor	LCFA	FA transporter, Downstream calcium signalling upon stimulation	Type II? <sup>a</sup>
GPR120	GPCR	MCFA, LCFA	Downstream calcium signalling upon stimulation	Type II
GPR40	GPCR	MCFA, LCFA	Downstream calcium signalling upon stimulation	Absent
GPR41	GPCR	SCFA	Downstream calcium signalling upon stimulation	— <sup>b</sup>
GPR43	GPCR	SCFA	Downstream calcium signalling upon stimulation	—
GPR84	GPCR	MCFA	Downstream calcium signalling upon stimulation	—
DRK	Potassium channel	PUFA	$\text{K}^{+}$ efflux blocked upon stimulation	—

<sup>a</sup> The mark of interrogation (?) represents undefined type of taste cell.

<sup>b</sup> No human data is available for this receptor/ion channel in TBC.



and IXth cranial nerves) [88], which relay the signal to the nucleus of solitary tract (NST), and then to the brain stem and digestive tract [49,61,88]. Compared to sweet, bitter and umami tastants, the neurotransmitters released in response to FFA stimulation are from the receptor cell itself [61], without the need for cell to cell communication with the adjacent presynaptic cell. Indeed, some of the PLC $\beta$ 2 positive cells also express 5-HT [10], which suggests that there might be a subset of type II taste cells. While the communication mechanism between these type II cells with the nervous system remains unknown, it has been speculated that the subsurface cisternae of smooth endoplasmic reticulum of the type II cell is involved [10].

## 6. Genetic variants in receptors associated with fat taste

Genetic variants in receptors may influence inter-individual differences in sensory perception which may affect dietary preferences, intake and health outcomes [89,90].

Table 2 summarises the research identifying candidate receptor variants with fatty acid perception and/or obesity. The CD36 receptor is the most studied to date, with the other candidate receptors having few (GPR120 and GPR40) or no publications (GPR41 and DRK channels). There is significant evidence of a link between variants within CD36 and fatty acid taste sensitivity, specifically the A allele of rs1761667 is associated with impaired oral fatty acid perception or in one study investigating increased intake of fat [71]. Given the A allele of rs1761667 is very common within the population, having a minor allele frequency (MAF) of 0.4 (i.e. equal to 40% of alleles within a population), suggests that this association with fatty acid detection maybe of clinical significance. The A allele of this SNP is also associated with the decreased expression of CD36 [91,92], suggesting reduced fatty acid taste detection may be mediated by lower CD36 present on the TRC. However, this is yet to be confirmed. While there appears to be a strong link between CD36 variants and fatty acid perception, there is conflicting evidence of an association of CD36 variants with obesity. Specifically, there is conflicting findings if an association is observed or no association is identified (Table 2).

Genome wide association studies (GWAS) catalogue hosted by the National Human Genome Research Institute (NHGRI) and the European Bioinformatics Institute (EMBL-EBI) [94] was searched to identify any association of candidate fatty acid receptors with obesity or similar conditions. Analysis of the GWAS catalogue identified the association of two DRK channels with obesity, specifically variants rs6063399 in KCNB1 ( $p = 8 \times 10^{-6}$ ) and rs7311660 in KCNC2 ( $p = 4 \times 10^{-6}$ ) [95]. Further analysis of the GWAS literature failed to identify further associations of candidate fatty acid receptors with obesity. In particular the most comprehensive and largest of these studies (GWAS meta-analysis), incorporating 322,154 individuals of European descent, did not find an association of candidate genes CD36, GPCR or DRK channels with obesity [4]. It should be noted that the lack of the association between the candidate gene variants and fatty acid perception or obesity does not negate the role the receptors play in fatty acid detection, as the variant measured may not be disease causing variant, or the correct phenotype may have not been measured (i.e. associations with obesity assessed, rather than FA detection).

## 7. Dietary influence on fat taste

The taste sensitivity to fatty acid exhibits a certain amount of plasticity. Consumption of a low-fat diet (<20% fat) decreases C18:1 (oleic acid) taste thresholds while high-fat diet (>45% fat) significantly increases C18:1 taste thresholds among lean subjects with no change in sensitivity among obese individuals [96,97]. The lack of threshold plasticity in the obese is hypothesised to be due to a habitual high-fat diet compared to lean. Also, the presence of fatty acids in the small intestine slows gastric emptying and suppresses appetite through the release of the hormones cholecystokinin (CCK), glucagon-like peptide-

1 (GLP-1) and peptide Y (PYY), and inhibition of ghrelin release [98]. The response to dietary fat in the GI tract is found to be attenuated following a high-fat diet [99,100]. Given the homologous expression of the taste receptors throughout the alimentary canal, a genetic mechanism/s may play an important role in this association, although this remains to be confirmed.

Animal studies show that CD36 expression on the lingual tissue of rats was reduced following the consumption of 8 weeks of high fat diet [101]. The down-regulation of the CD36 in the circumvallate papillae (CVP) of mice has also been identified in response to the lingual deposition of oil [102]. As this reaction is triggered immediately after the oil being deposited directly onto the tongue, it excludes the post-oral influences on the regulation [102]. Intriguingly, the mRNA level of GPR120 and  $\alpha$ -gustducin seem to be insensitive to the quantity of fat during the studied period [102]. The dramatic drop of CD36 protein level while mRNA levels remain stable one hour after consuming a high fat meal indicates a possible post-transcriptional origin of the CD36 regulation [102], which has been recently linked to the ubiquitination of CD36 protein [103]. In humans, 20-min exposure to FA did not change of total protein levels of either CD36 or GPR120 [85]. The treatment however decreased the proportion of CD36 protein in the raft fractions (cholesterol or sphingolipid enriched domains) of the taste bud cell membrane, while GPR120 levels increased simultaneously [85]. The localisation of CD36 to the rafts was suggested to be linked with the ability of membrane FA uptake (include the interaction between taste receptors with FA and the downstream signal transduction for cells) [104].

## 8. Fat taste and weight status

Human and animal studies both identify an association between oral fatty acid sensitivity with fat consumption and body weight regulation [82,105]. Animals that exhibit oral hyposensitivity to fatty acids are more likely to consume excess fats and rapidly gain weight, conversely, animals that are hypersensitive consume less dietary fat, and avoid weight gain [82]. A similar relationship has been reported in humans, with individuals hypersensitive to fatty acid consuming less fat (21 g/day difference in average) and having lower BMI, compared to hyposensitive individuals. These findings suggest a role for fat taste in diet and weight regulation [48,106].

Fatty acid detection has also been linked with responses in GI tract, which suggests a coordinated detection system throughout the alimentary canal to dietary fatty acids (Fig. 3) [100]. Upon the stimulation with MCFA and LCFA in the enteroendocrine cells of the GI tract, GPR120 expressed on the membrane triggers a signal cascade which releases hormones such as GLP-1 and CCK [107]. The other receptors expressed along the intestinal lumen such as GPR41 and GPR43 respond to the SCFA produced by the bacterial fermentation of fibre and release hormones such as GLP-1 and PYY [108]. These hormones serve as critical signals in regulating the gastric emptying and postprandial satiety response during energy homeostasis [109,110]. Obese individuals are reported to have a compromised chemoreception response to fatty acids in the upper GI tract, compared to lean individuals [96,111]. Newman et al. suggests that reduced fatty acid detection at both the oral cavity and GI tract contribute to the impaired satiety response, resulting in excess nutrient consumption and obesity [112]. This impaired satiety hypothesis is supported by a recent study that identified excess energy consumption in individuals hyposensitive to fatty acid following a high-fat breakfast, compared to hypersensitive individuals [113].

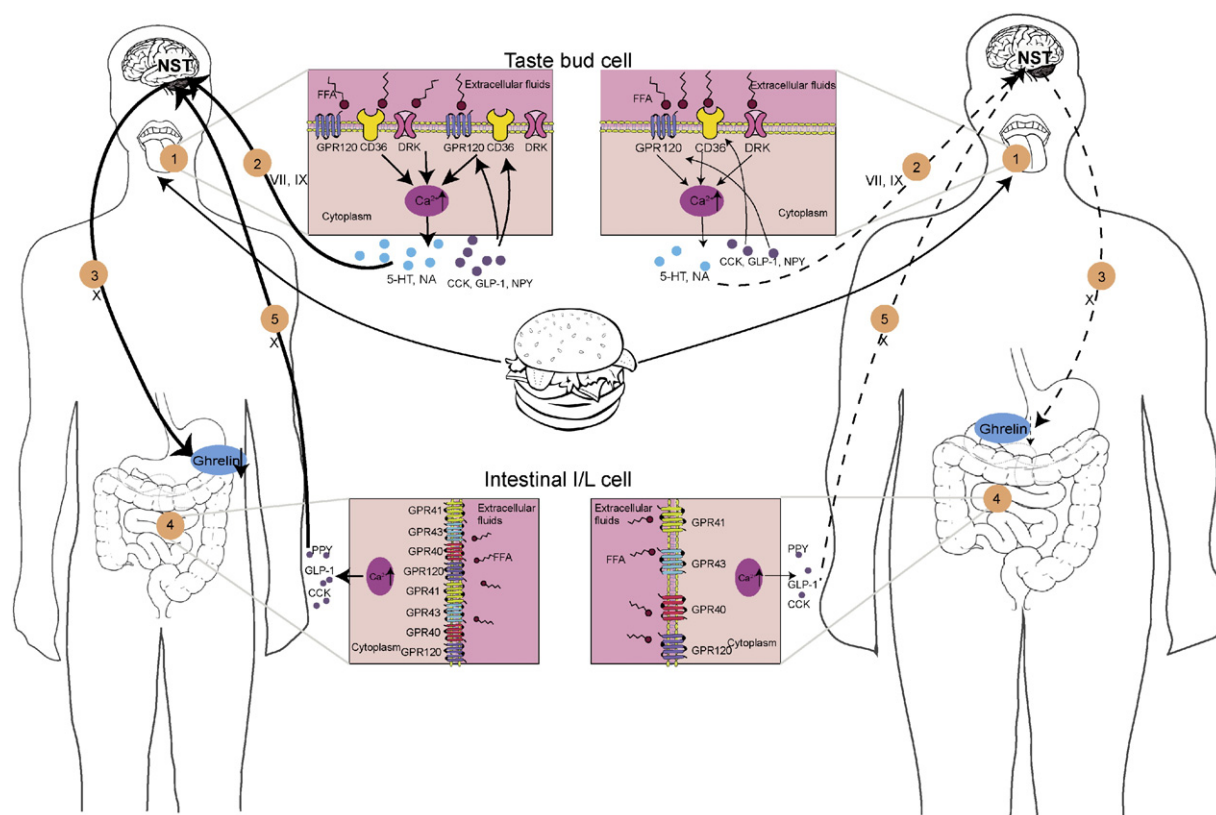
In summary, these studies highlight a relationship between fat taste and obesity, through the overconsumption of fatty food (Fig. 3). As shown with dash lines in Fig. 3, obese people have impaired chemoreception response to dietary fat in both the oral cavity and GI tract, which leads to the decreased chemoreception as well as attenuated

**Table 2**

Genetic variants of candidate fat taste receptors associated with obesity and related conditions.

Gene/Variant	MAF	Study	Sample info	Phenotype	Finding
<b>CD36</b>					
rs1761667 G > A	0.4	Pepino et al., 2012 [53] Keller et al., 2012 [71] Melis et al., 2015 [70] Mrizak et al., 2015 [68] Sayed et al., 2015 [69] Solakivi et al., 2015 [114] Daoudi et al., 2015 [115] Bayoumy et al., 2012 [116]	21 population (obese) 317 African-American 64 Caucasian 203 Tunisian women (obese) 116 Algerian children 736 Finnish adults 165 Algerian teenagers 100 Egyptian adults	FA sensitivity FA sensitivity FA sensitivity FA sensitivity FA sensitivity, obesity BMI Obesity MetS	A allele associated with reduced sensitivity to fatty acid ( $p = 0.03$ ) A allele associated with increased creaminess and preference for added fats ( $p < 0.01$ ) AA genotype associated with lower sensitivity to oleic acid ( $p < 0.033$ ) AA genotype associated with attenuated oral detection threshold ( $p < 0.050$ ) A allele associated with obesity ( $p = 0.036$ ) and reduced FA taste sensitivity ( $p < 0.001$ ) AA genotype is associated with lower BMI ( $p \leq 0.010$ ) AA and AG associated with obesity ( $p = 0.008$ and $0.002$ respectively) G allele and GG/GA genotype associated with MetS, wider WC, dyslipidemia ( $p < 0.001$ )
rs3211867 C > A	0.2	Bokor et al., 2010 [117] Choquet et al., 2011 [118] Łuczynski et al., 2014 [119]	646 European adolescents 3509 French and German 1119 Polish children (T1D)	Obesity Obesity BMI	AA/CA associated with obesity ( $p = 0.003$ ) No association No association
rs3211883 A > T	0.4	Bokor et al., 2010 [117] Choquet et al., 2011 [118] Łuczynski et al., 2014 [119] Henri et al., 2011 [120]	646 European adolescents 3509 French and German 1119 Polish children 1790 white European	Obesity Obesity BMI BMI	TT/AT associated with obesity ( $p = 0.007$ ) No association No association TT genotype associated with larger BMI and waist circumference ( $p \leq 0.004$ )
rs1527483 C > T	0.1	Bokor et al., 2010 [117] Choquet et al., 2011 [118] Keller et al., 2012 [71] Łuczynski et al., 2014 [119] Melis et al., 2015 [70]	646 European adolescents 3509 French and German 317 African-American 1119 Polish children 64 Caucasian	Obesity Obesity FA sensitivity BMI FA sensitivity	TT/CT associated with obesity ( $p = 0.003$ ) No association T associated with increased perceived ratings of fat content & decreased BMI ( $p < 0.05$ ) No association No association
rs3211908 C > T	0.1	Bokor et al., 2010 [117] Choquet et al., 2011 [118] Henri et al., 2011 [120]	646 European adolescents 3509 French and German 1790 European	Obesity Obesity BMI	TT/CT associated with obesity ( $p = 0.0005$ ) No association CC associated with larger BMI and waist circumference ( $p \leq 0.004$ )
rs2103134 A > T	0.4	Choquet et al., 2011 [118]	3509 French and German	Obesity	No association
rs9784998 C > T	0.2	Henri et al., 2011 [120]	1790 European	BMI	CC associated with larger BMI and waist circumference ( $p \leq 0.004$ )
rs3211956 T > G	0.1	Henri et al., 2011 [120]	1790 European	BMI	TT associated with larger BMI and waist circumference ( $p \leq 0.0043$ )
rs3840546 Del16	0.1	Keller et al., 2012 [71]	317 African-American	BMI	DD deletions associated with higher BMI ( $p < 0.001$ )
rs2232169 A > C	0.4	Corpeleijn et al., 2010 [121]	722 European (obese)	Fat oxidation rate	A is related to the reduced fat oxidation rate ( $p = 0.02$ )
rs1527479 T > C	0.3	Corpeleijn et al., 2006 [122]	675 Dutch	T2D	TT genotype associated with T2D ( $p = 0.005$ ) and larger BMI
<b>GPR120</b>					
rs116454156 G > A	0.0	Ichimura et al., 2012 [123]	14,596 European	Obesity	A allele associated with obesity ( $p < 0.001$ ), through reduced LCFA signal transduction
rs1414929 A > T,	0.3	Waguri et al., 2013 [124]	1585 Japanese	BMI	No associations were found between the three SNPs and the BMI. Haplotype (T–T–T)
rs12219199 C > T,	0.2				associated with BMI in females with high dietary fat intake ( $p = 0.037$ ), haplotype
rs2065875 C > T	0.1				(T–C–C) associated with BMI in males with high or low dietary fat intake in males ( $p < 0.050$ )
<b>GPR40</b>					
rs1573611 G > A	0.3	Walker et al., 2011 [93]	720 population	BMI & body composition	C allele was associated with higher BMI ( $p = 0.009$ ) and body fat ( $p = 0.002$ )
rs2301151 G > A	0.1	Walker et al., 2011 [93]	720 population	BMI & body composition	No association with BMI, G allele associated with higher body fat ( $p = 0.030$ ), higher total cholesterol ( $p = 0.010$ ) and lower plasma non-esterified fatty acids ( $p = 0.040$ )
rs16970264 G > A	0.1	Walker et al., 2011 [93]	720 population	BMI & body composition	No association with BMI, A allele associated with lower LDL&HDL cholesterol ( $p < 0.050$ )

MAF—Minor allele frequency, FA—fatty acid, T1D—Type 1 diabetes, T2D—Type 2 diabetes, BMI—body mass index, MetS—metabolic syndrome, WC—waist circumference, Del16—16 base pair deletion, LDL—low density lipoprotein, HDL—high density lipoprotein.



**Fig. 3.** Proposed mechanisms of the systemic energy regulation via fat taste receptors. (1) FFAs are naturally present in foods and also released from dietary fat by lingual lipase. In the oral cavity, the fat receptors such as CD36, GPR120 located on the taste bud cells respond to the FFAs and lead to the rise in intracellular  $\text{Ca}^{2+}$  and the release of neural transmitters such as 5-HT and NA and GI hormones such as CCK, GLP-1 and neuropeptide Y (NPY). The hormones can regulate the functions of the fat receptors. (2) The taste cell afferent nerve fibres VII and IX transmit the taste information to the nucleus of solitary tract (NST) of the brain. (3) The NST integrates the signals and induces the reflex to early digestive secretion. As a result, the food intake stimulating hormone—ghrelin is inhibited. (4) The FFAs combine with the fat receptors GPR120, GPR41 and GPR43 on the enteroendocrine cells of the intestine and releases satiety hormones (CCK, GLP-1 and PYY). The signal transduction involves the elevation of  $\text{Ca}^{2+}$ . (5) The vagus nerve (nerve fibre X) conveys the satiety information to the NST. The dash lines represent the compromised responses in the obese individuals. The obese individuals have less receptors expressed in the taste bud cells and intestinal cells than the lean, which perform compromised fat sensing system in both oral cavity and GI tract, thus attenuate the oral signals conveyed to the brain and delay the satiety response, which result in the excess food intake.

satiety signals. These responses altogether result in the overconsumption of fat and which aggravates the obesity situation.

## 9. Conclusion and summary

This review provides a summary of the taste mechanisms for fatty acids, and the associative evidence linking fat taste with diet and obesity. Knowledge gained from mechanisms underpinning the five basic primaries helps provide support for understanding the taste modality response to fat.

Similar to the genetic research in other tastes, candidate gene approaches can be applied to identify the receptors for fat taste. CD36 and GPR120 have attracted the most interest in recent years, while less is known about other candidate receptors. Although high affinity to free fatty acids is the basic requirement to qualify as a candidate, their expression and localisation on human taste tissues remain largely unclear. Also, the cell type (type I–IV) for candidate fat taste receptors has not been identified. The co-expression of the CD36 and GPR120 with PLC32 (cell marker for type II taste cell) implies fat taste receptors may be expressed on type II taste cells [85]. However, the release of 5-HT and NA in response to FFAs indicates added complexity. The co-expression also provides basis for the “cross-talk” model for the signal transduction, but whether this model truly exists warrants further confirmatory studies.

The taste sensitivity to some types of fatty acid has been linked with the predisposition of overweight or obesity in both animals [82] and

humans [48], with the exact mechanism(s) unknown. However, the current evidence suggests both a genetic and environmental (i.e. diet) basis for the relationship between fat taste sensitivity and obesity. A growing number of studies link SNPs of candidate fat taste receptors with either oral sensitivity to fatty acids, or obesity. However, there is a lack of studies that associated both phenotypes (obesity and FA sensitivity) with SNPs in candidate FA receptors. From several independent studies aforementioned, the SNP rs1761667 of CD36 was linked with fatty acid detection, potentially through altered CD36 expression. Further studies in larger sample sizes will be required to confirm associations, ideally assessing both FA sensitivity and obesity phenotypes.

Humans also seem to have an adaptive taste system, where the oral gustatory detection of fatty acids exhibits reduced sensitivity upon prolonged exposure to a high-fat diet. The cellular level of this adaptation has not been studied in humans. A better understanding of the fat taste mechanism and its association with food consumption may lead to altered nutritional advice lowering the burden of obesity. The genetic regulation of some of the genes identified and in vitro studies provide a potential breakthrough point for understanding human fatty acid taste detection.

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