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Review

Title:

Preference for dietary fat: from detection to disease

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Abbreviations: GIT, gastrointestinal tract; LCFAs, long-chain fatty acids; TBC, taste bud cell

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Abstract

Recent advances in the field of taste physiology have clarified the role of different basic taste modalities and their implications in health and disease and proposed emphatically that there might be a distinct cue for oro-sensory detection of dietary long-chain fatty acids (LCFAs). Hence, fat taste can be categorized as a taste modality. During mastication, LCFAs activate tongue lipid sensors like CD36 and GPR120 triggering identical signaling pathways as the basic taste qualities do; however, the physico-chemical perception of fat is not as distinct as sweet or bitter or other taste sensations. The question arises whether “fat taste” is a basic or “alimentary” taste. There is compelling evidence that fat-rich dietary intervention modulates fat taste perception where an increase or a decrease in lipid contents in the diet results, respectively, in downregulation or upregulation of fat taste sensitivity. Evidently, a decrease in oro-sensory detection of LCFAs leads to high fat intake and, consequently, to obesity. In this article, we discuss recent relevant advances made in the field of fat taste physiology with regard to dietary fat preference and lipid sensors that can be the target of anti-obesity strategies.

1- Introduction

The sense of taste plays a key role in food choice, either to like or dislike at the first contact with it. There are five taste qualities, i.e., bitter, salt, sour, sweet and umami [1]. It has been considered that sweet taste allows the detection of energetic high calorie and pleasant (hedonic) substances, whereas bitter taste perception leads to avoid or reject toxic or noxious substances. The salty taste governs the intake of Na⁺ and it is essential for maintaining body's water balance and blood circulation [2]. Umami taste allows the recognition of amino acids, particularly of glutamate [3]. The sour taste is an important sensory input to inform on the ingestion of acidic food sources [4].

Taste perception is brought about by specialized cells that are grouped in taste buds which, in turn, are assembled in papillae, distributed principally throughout the tongue epithelium. There are three principal gustatory papillae on the tongue: circumvallate, fungiform and foliate which are localized, respectively, on posterior, dorsal and lateral regions. The taste buds form a cauliflower like structure whose apical part, containing microvilli, is bathed with salivary/buccal secretions and is in direct contact with sapid agents. The tuned gustatory message is sent to the brain, particular to the nucleus tractus solitarius (NTS), via afferent VII and/or IX cranial nerves. The NTS, central relay for gustatory and visceral information, further sends gustatory information to different regions of the brain which, in turn, modulates eating behavior of the organism. A detailed account of the morphology of taste system and its communication with NTS can be seen be consulted elsewhere [5].

2. Fat taste: basic or alimentary?

The generalized definition of a basic taste modality should follow, at least, 4 criteria: 1) a taste receptor on the taste bud cells (TBCs), 2) its coupling to Ca²⁺ signaling, 3) transfer of the gustatory message from tongue to brain, and 4) activation of gut-brain-axis, responsible for anticipatory physiological mechanisms. According to these 4 criteria, fat taste might be considered as a basic taste as the mechanisms of fat taste transduction from tongue to brain (and to gut) follow the same pathways.

The chemical perception of a basic taste leads to a non-overlapping and “distinct” oro-sensory feeling as is the case of four basic taste modalities: sweet, sour, salt, and bitter. However,

there is no distinct taste perception when a fat stimulus (fatty acid) is placed on the tongue. Any perceptions that occur are generally at higher concentrations than required for taste and are linked with smell or irritation. There is recent controversy whether umami and fat should be considered a basic taste, and whether they should be classified in a separate category of “alimentary taste” [6]. As opposed to the basic tastes, alimentary does not have the salient perceptual function observed with sweet, sour, salt and bitter. Rather activation of a fat taste receptor in the oral cavity still results in signals being sent to the brain and gut for signal interpretation, and there is a lack of a clear perception [7].

The implications of alimentary taste are post-ingestive, for example, the decision to continue or to stop an eating episode are made after swallowing of the food. Lipid sensors identified in the oral cavity are also located on the epithelial surface of the gastrointestinal tract (GIT), as is also case of bitter and sweet taste receptors. Lipid sensors have the same function, i.e., to identify the various ingested chemicals but the action is specific to the GIT, with preparation for uptake and appropriate hormonal response to the nutrient [8]. The presence of fat in the GIT slows gastric emptying and inhibits appetite through the release of satiety inducing hormones like cholecystinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide Y (PYY), and inhibition of ghrelin. Thereby, alimentary tastes, like fat, have a key role in satiety and satiation as recognition of ingested fat is an essential step in developing fullness and minimizing energy intake. Dietary LCFAs-triggered taste sensation can be classified as an ‘alimentary’ taste, because eating of a fat-rich food influences the next food episode [7]. The link between fat taste sensitivity and satiety has been established, with participants who are classified as “hypersensitive” to fat taste and consume lesser fat-rich meal than individuals classified as “hyposensitive” to fat taste [9,10]. There is also significant cross sectional evidence of the link between fat taste sensitivity and energy/fat intake [11-13].

3. Tongue lipid sensors

In this article, we will employ the term lipid sensors for lipido-receptors like CD36 and GPR120 or other G-protein coupled receptors (GPCR) involved in fat taste perception. CD36, also known as FAT (fatty acid translocase) and discovered by the team of Nada Abumrad, has been largely studied for its implication in lipid metabolism [14]. CD36 is also known as scavenger receptor because it is expressed by a number of cells where it assures a number of diverse functions [15]. CD36 can be considered as the first lipido-receptor reported to be

involved in oro-sensory detection of dietary LCFAs [15, 16]. Beside CD36, LCFAs also bind to a number of GPCR. There appears a divergent expression profile of the candidate fat taste receptors in human beings compared to rodent models [17]. It has been concluded that GPR43 binds to short chain (C2:0–C6:0) saturated fatty acids, whereas GPR84 exhibits high affinity for medium chain (C8:0–C14:0) fatty acids [18]. GPR40 and GPR120 with their affinities, respectively, for short medium-chain and long-chain fatty acids [16, 17], are expressed in mice circumvallate papillae [20]; however, GPR40 is absent in human papillae. Gilbertson et al. [21] reported that fatty acids could inhibit the delayed rectifying K⁺ (DRK) channels in rat TBC and they suggested that DRK channels might represent a mechanism that could contribute to the chemosensory recognition of dietary fat. KCNA2 appears to be the most abundant DRK channel in human fungiform papillae, whereas KCNA5 serves as the major DRK channel expressed in rat tongue [17, 22]. The gene expression analysis indicated that the predominant subfamily of the DRK channels in human fungiform papillae was KCNA [23] opposed to KCNB or KCNC channels observed in rodent models [22]. By employing mRNA expression, western blots, immunoenzymatic staining for different fatty acid receptors, Liu et al. [22] have confirmed the expression of CD36, GPR120, GPR43, GPR84 and KCNA2 in human fungiform TBCs.

3.1. Lipid gustatory signal transduction

Taste buds are composed of elongated cells that can be divided into 4 categories: Type I glial-like cells, Type II cells express gustatory receptors for sweet, bitter and umami, Type III cells are neuron-like cells that release neurotransmitters (and also ATP) to send the gustatory message afferently, and type IV cells are basal cells that are responsible for the renewal of all taste bud cell lines as per requirement of the organism. The taste bud cells (TBCs) that express lipid sensors belong to type II cells [24].

As regards fat taste signal transduction, the reader is advised to consult our two previously published review articles [5, 17]. In this review, we will cut short this section and we will focus on principal events of membrane receptor activation leading to gustatory message transmission. We will only highlight the signaling mechanisms via CD36 and GPR120 which are well identified in fat taste perception. The dietary LCFAs, naturally present in foods and released during mastication by the action of lingual lipases, bind to lipid sensors (CD36 and GPR120). CD36 exhibits high affinity, whereas GPR120 is a low affinity receptor for LCFAs. Though CD36 is not directly coupled to a G-protein, its binding to LCFAs phosphorylates the

Src-protein tyrosine kinases which, in turn, recruit phospholipase-C, PLC [24]. The activated PLC catalyzes the hydrolysis of phosphatidyl-inositol-tris-phosphate (PIP₂) which gives rise to free inositol-tris-phosphate (IP₃) and diacylglycerol (DAG). The IP₃ by binding to its receptors on the endoplasmic reticulum (ER) triggers the release of free Ca²⁺ that contributes to massive increases in free intracellular Ca²⁺ concentrations, [Ca²⁺]_i, followed by Ca²⁺ efflux and then influx to refill intracellular pool, via opening of store-operated Ca²⁺ (SOC) channels like Orai1 and Orai1/3, according to capacitive model of Ca²⁺ homeostasis [25] (**Figure 1**). The depletion of ER Ca²⁺ pool also releases CIF (Ca²⁺ influx factor) and STIM1 (Stromal interaction molecule 1). The CIF controls the opening of SOC channels, whereas STIM1 senses the quantity of Ca²⁺, required to fill in ER pool [5, 26]. These novel findings remain to be confirmed in the perception of other taste modalities.

Our team has recently added another component, i.e., the MAP kinase cascade (MEK1/2-ERK1/2-ETS1), to fat signal transduction in human and mouse TBCs [27]. The MAP kinase cascade, was not coupled to c-ras or c-raf as is the case of most of the mammalian cells rather it was activated by Ca²⁺ signaling via opening of the calcium-homeostasis modulator-1 (CALHM1) channel. It is noteworthy that in neuronal cells, the MAP kinase (MAPK) is also activated by an increase in [Ca²⁺]_i which, by binding to calmodulin (CaM) makes an enzyme-complex, called Ca²⁺/CaM/Kinase, upstream to MEK [28]. The MAPK cascade seems indispensable for the transmission of the gustatory message of LCFAs as the inhibition of lingual MAPK by siRNA or MEK inhibitor resulted in the increase in detection thresholds for a dietary LCFA in mice and human participants [27]. Furthermore, the ERK1 knockout mice developed more severe obesity than wild-type animals [29]. These observations demonstrate that a defect in fat taste signaling contributes to decreased oro-sensory detection of lipids and, consequently, to obesity.

We do not know whether the opening of CALHM1 channels is also linked to the activation of purinergic receptors, and consequently to the release of a neurotransmitter as is the case of sweet taste perception [30]. Nonetheless, the activation of TBCs by dietary LCFAs has been shown to release serotonin, responsible for the transmission of the gustatory information to the NTS via afferent chorda tympani and glossopharyngeal nerves [24]. Recently, electrophysiological experiments have shown that F-waves are generated by binding of LCFAs to lingual GPR120 to transfer fat gustatory signal afferently via chorda tympani nerve

[31]. How the LCFAs-generated F-waves interact with other signal transducers remains to be studied in future.

3.2. CD36 and GPR120 play complementary roles

The multiple receptor-processes responsive to fatty acids on taste cells implies a sophisticated system that underpins fat taste perception. A cross-talk model which combines multiple receptors and ion channels has been previously proposed [17, 32]. The cross-talk between CD36 and GPR120 during fat taste perception has been explained where CD36 and GPR120 seem to play a “hide and seek” game to regulate fat eating behavior. Martin et al. [33] observed that CD36 and GPR120 mRNA expression follows opposite trends in murine TBCs during food intake: the former was downregulated whereas the latter was upregulated during fat rich food intake in mice. By further exploring the localization of lipid sensors in lipid rafts and cytosolic fractions in TBCs, LCFAs downregulated CD36 and upregulated GPR120 in membrane lipid rafts of mouse and human TBCs [34].

We propose that the role of CD36 may be to mediate short-term response to dietary fat, as it is downregulated throughout an eating event, then upregulated to pre-meal situation following a prolonged fast; whereas GPR120 is involved in the regulation of long-term response to dietary fat between meals with greater gradual change in expression over longer periods of time (**Figure 2**). These observations have been recently reproduced in human subjects wherein the participants in two groups were advised to take a low- or high-fat diet for eight weeks [35]. After the dietary intervention, there were significant negative associations between GPR120 mRNA expression in fungiform papillae and fat intake. Hence, the GPR120 mRNA expression was upregulated after an eight-week of low-fat dieting in these volunteers. More studies by other investigators are required to confirm these plausible observations.

3.3. Autocrine/paracrine regulation of fat taste

A number of recent studies have clearly demonstrated that TBCs also release CCK, PYY, NPY and express their corresponding cognate receptors [36]. The *in situ* secretion and autocrine or paracrine action might modulate taste perception and, consequently, impact GIT function and metabolic homeostasis [36]. Most of the studies on lingual neuroendocrinology of taste have dealt with sweet taste, and what follows is the little we know of these peptides in fat taste perception.

Galanin can be synthesized by TBCs, and mice that exhibited high expression of galanin had increased intake of fat-rich diets [37]. Conversely, mice that were deficient for galanin had reduced preferences for fatty diets [38]. These results strongly support the implication of galanin in the regulation of fat consumption, possibly by modulating the lipid sensor signaling (via CD36 and/or GPR120) in type II TBCs. Another GPCR cannabinoid receptor 1 (CB1) is expressed in type II TBCs, where it functions to enhance perception of fat taste in the mouse [39].

PYY (1-36) and GLP-1, generally secreted from L-cells in the gut, are also synthesized in TBCs. PYY^{-/-} mice exhibited reduced preferences for fat [40]. Shin et al. [41] identified GLP-1 receptor (GLP-1r) in gustatory nerves. A LCFA triggered GLP-1 secretion via GPR120 in both intestinal secretin tumor cells-1 (STC-1) and in mice TBCs. Leptin also exerts anorectic effects. The leptin receptor is expressed on type II cells and its activation hyperpolarizes TBCs to sweet stimuli and suppresses sweet taste perception [42,43]. Low salivary leptin concentrations were associated with low sweet taste sensitivity in children [44]. However, nothing is known regarding fat taste perception and taste bud leptin regulation. CCK was found to be co-expressed on type II cells, and CCK-A and -B receptors were identified in both TBC and gustatory neurons, and administration of a CCK agonist blocked the bitter taste responses [45].

Beside anorectic peptides, the TBC also express orexigenic peptides, for instance, ghrelin and its receptor GHS-R in the mouse [46]. We have observed that human and mouse TBCs express ghrelin and its putative receptor, GSH-R1a (unpublished observations). Nonetheless, there is a long way to better understand the implication of these peptides (which are anorectic and orexigen) in the regulation and transmission of fat taste signal to the afferent nerves. How will they amplify or curtail the fat taste tuning?

4. Fat taste activates tongue-brain-gut axis

As far as the activation of different brain areas are concerned, most of the studies have been conducted by employing fMRI technique. Eldeghaidy et al. [47] observed that fat activated cortex insula, frontal operculum and secondary somatosensory cortex, anterior cingulate cortex, and amygdala in human volunteers. In another study again on humans, the same team reported that a high-fat food inhibited the activation of amygdala if the subjects had a

previous experience with fatty food [48]. Recently, Frank-Podlech et al. [49] performed a study on healthy volunteers, by employing fMRI, on the functional connectivity (FC) in different brain areas before and after a high- vs. a low-fat food on two different days. They observed that oral fat sensitivity was positively correlated with FC between homeostatic regions and limbic areas in the high-fat condition, suggesting that neuronal network patterns might be a possible moderator of the association of oral fat sensitivity and eating behavior.

However, in these studies, the investigators have used either fat emulsions or a diet with added fat. Therefore, the question arises whether brain activation is due to the texture or fatty acids or triglycerides present in food. This question has been addressed by our team. Hence, we have applied a LCFA on the tongue of the conscious mice (without swallow) and assessed the neuronal firing [50]. The LCFA induced neuronal activation of the NST, parabrachial nucleus, and ventroposterior medialis parvocellularis (VPMPC) of the thalamus, the brain areas known to be activated by gustatory signals. LCFA also triggered c-Fos expression in the central amygdala and ventral tegmental area (VTA) involved in food reward in conjunction with emotional traits. Interestingly, we noticed high expression of BDNF, Zif-268, and Glut-1 mRNA in the arcuate nucleus and hippocampus, where neuronal activation leads to memory formation. Our study demonstrates that lipid taste perception might directly trigger the activation of canonical gustatory and reward pathways (**Figure 3**). Since VTA, amygdala and other hedonic brain areas are activated by dietary fat, it is tempting to suggest that these regions might be involved in fatty-food addiction as is the case of sugar addiction [51]. Indeed, Han et al [52] have proposed that sweet or high-fat food odors activate the identical brain areas related to food reward processing in healthy volunteers.

The brain communicates with gut via vagus nerve (VN) that innervates NTS in the brainstem, and GIT and other parts of the body. In response to palatable food, the VN regulates gut physiology by inducing the release of a number satiety hormones like CCK and PYY [53]. We have shown that oral administration of a LCFA triggered the release of pancreaticobiliary secretions via *tongue-brain-gut* axis, probably involving VN [54, 55]. In the similar protocol, a novel GPR120 agonist [56], TUG891 modulated fat preference. This is an interesting finding that TUG891, a non-caloric fat sensor agonist, exerts its anti-obesity action via *tongue-brain-gut* axis [55].

5. Fat taste interactions

5.1. Oral microbiota

It is now well demonstrated that gut microbiota plays a key role in the pathogenesis of obesity [57]. The transplantation of gut microbiota from obese individuals to lean subjects and *vice versa* can trigger or decrease obesity. Generally, obesity in animals (diet- or genetically-induced obesity in *ob/ob* mice) and humans, is marked with high number of Firmicutes and low number of Bacteroidetes bacteria in the gut [58]. As regards the changes in oral microbiota in obesity, Goodson et al. [59] studied the bacterial diversity and abundances in the salivary secretions of overweight and healthy participants and reported that oral *Selenomonas* could be the biomarkers for excess adiposity.

In several reports on the association of obesity with oral microbiota, the investigators have employed 6-*n*-propylthiuracil (PROP) as the phenotypic marker of genetic variation in taste sensitivity [60]. Indeed, PROP is not only used to ascertain bitter taste but also is considered as a candidate for the detection of chemosensory component of taste detection (see the next section). Shetty and Hegde [61] demonstrated that decreased PROP perception was associated with high population of *mutans streptococci* in the saliva. Solemdal et al. [62] have studied the correlation between sour taste and oral microbiota and further suggested that decreased sour taste was associated with high *lactobacilli* in the oral ecosystem. Mameli et al. [63] have recently performed a cross-sectional study in obese participants and assessed the role of oral microbiota in taste perception. These investigators reported that obese subjects had not only lesser PROP taste sensitivity and lingual fungiform papillae density but also had higher oral Proteobacteria than healthy normal weight participants. Besnard et al. [64] tested the hypothesis whether an impaired fat taste sensitivity in obesity might be linked to a change in the gustatory papillae microbial and salivary environment. The composition of microbiota and saliva surrounding the circumvallate papillae was analyzed in combination with the orosensory lipid detection threshold in normal weight and obese adults. These investigators observed that microbial architecture was similar to what was known in feces, but with an increased frequency of Proteobacteria in obese subjects. This is a new emerging field, much work is to be done to shed light on the interaction between fat taste perception, oral inflammation/microbiota and obesity (see the conclusions & perspectives).

5.2. Bitter taste and olfaction

The oro-sensory perception of a taste modality may be largely influenced by mechanoreceptors, nociceptors and retro-nasal olfactory epithelium. Why do some people

perceive fat as bitter or scratchy? Fat taste perception has two components: textural and chemosensory. We have proposed that textural perception might be relayed by bitter taste signaling via T2R38, whereas the chemosensory perception would involve the activation of CD36. This cross-talk will involve an interaction, probably via the activation of TRMP5 channels, downstream to lingual lipid sensors at the level of second messenger cascade [65].

Barbarossa et al. [66] have suggested that olfactory stimulation might play a critical role in the perception of “bitter taste” of LCFAs. These authors conducted a study on human participants wherein the presence of oleic acid in milk shakes triggered bitterness and the use of nose-clips suppressed bitter perception. They further performed genetic variability studies on olfactory binding protein (OBPIIa) and proposed that the subjects who were homozygous for A-allele for single nucleotide polymorphism (rs2590498) in the OBPIIa gene were able to perceive bitterness of oleic acid, whereas those with homozygous for G-allele or heterozygous failed to detect bitterness of LCFA.

Kindleysides et al. [67] reported that taste perception and olfactory detection for LCFA were positively correlated. Oleic acid taste hypersensitive women had significantly increased *n*-butanol olfactory sensitivity. It is noteworthy that an association between poor odor identification and fat discrimination has been reported in subjects who were given a HFD [68]. Other studies have reported that obesity (particularly morbid obesity) is associated with reduced olfactory perception? and sleeve gastrectomy improved olfactory perception in obese subjects [69]. The experiments on mice maintained on a HFD demonstrated that dietary fat might trigger a dysfunctioning of olfactory sensory neurons [70].

It is possible that dietary fatty acids, being hydrophobic in nature, may require OPBII to be transported to the saliva to bind to lipid sensors. Malik et al. [71] have recently characterized functional olfactory receptors, OR51E1, OR5P3, OR5A1, and OR2W1, in cultured mouse and human fungiform TBCs. In Ca^{2+} imaging experiments, the TBC were found to express olfactory receptors as they responded to some odorants like acetophenone and eugenol which are respective ligands for M71 and mOR-EG odorant receptors. Since these receptors are coupled to adenylate cyclase, the pharmacologic inhibition of adenylate cyclase activity blunted the responses of these odorant agonists in these TBCs. These interesting observations suggest that there might be a key role for OBP in fat taste perception. Kim and Carlson [72] have proposed that the olfactory and taste receptors both exhibit overlapping similarities in

sequence and expression pattern. Durzyński et al. [73] have found olfactory-like receptor cDNAs were present in human tongue cDNA libraries. In the brain, the taste and olfactory cortex is between amygdala and orbito-frontal cortex, the cross roads of gustatory perception. All of these observations make a *triangular story* of gustatory perception of dietary lipids as *fat-bitter-olfaction*. Is there any triangular communication among CD36/GPR120, T2R38 and OBPII in taste bud cells? This point should be studied in future.

6. Dietary intervention impacts fat taste

Dietary fat modulates fat taste sensitivity: increasing fat intake causes decreasing fat taste sensitivity, viz., an increase in fat taste thresholds. Multiple cross-sectional studies have shown negative associations between fat intake and fat taste sensitivity [74, 75], meaning individuals who consume high levels of dietary fat were found to have reduced taste sensitivity to fat. Intervention studies have conclusively demonstrated that modifications to long-term dietary fat intake mediate a change in fat taste sensitivity. A 4-week dietary fat cross-over intervention study reported increased fat taste sensitivity after low-fat intake [76] and decreased fat taste sensitivity after high-fat intake. A 6-week randomized dietary intervention, involving a low fat diet (25% fat) or portion control diet (33% fat), was completed in overweight/obese participants [77]. Both diets resulted in a decrease in fat taste thresholds. An 8-week dietary fat intake intervention using twins was run by the same research group with one twin within a pair randomly allocated to an 8-week low-fat (<20% energy fat) or high-fat (>35% energy fat) diet [78]. The twin design has significant advantages as the genetic component to fat taste phenotype can be assessed by comparing monozygotic (MZ) and dizygotic (DZ) twin pairs under the assumption that MZ pairs share 100% of their genes and DZ pairs share, on average, 50% of their genes. Results supported the earlier dietary intervention that a low-fat diet increased fat taste sensitivity [78]. The evidence from dietary interventions is conclusive, dietary fat does influence fat taste sensitivity with an increase in dietary fat resulting in an attenuation of fat taste sensitivity.

The reduction in fat taste sensitivity presumably relates to expression of candidate fat taste receptors. Papillae were removed at baseline and week 8 to investigate changes in fat taste receptor expression after the 8-week dietary fat intervention. Fat taste receptor mRNA expressions for CD36, GPR43, GPR120, GPR84 and KNCA2 were measured. Expression of GPR120 significantly increased (38%) in the low-fat group [35]. The change in GPR120

between baseline and week 8 was associated with change in fat intake and change in fat taste thresholds. This indicates that GPR120 is the dominant receptor involved with long term change in dietary fat [35]. Besides, Sclafani et al. [79] have also shown that CD36 is not involved in the regulation of post-oral physiological events during a meal. A cross sectional analysis at baseline revealed the expression level of CD36 had a positive association with total fat, saturated fat intake and the energy from saturated fat proportion in 24 hours [23]. It is possible that CD36 may mediate short-term response to dietary fat (within meal/day) with pre-meal high expression, while GPR120 might be involved in the regulation of long-term response to dietary fat with gradual changes in expression over time.

7. Fat taste sensitivity is decreased in obesity

There are more than 1.9 billion adults, 18 years and older, who are overweight on the globe. Of these, over 650 million are clinically obese [80]. Though there are several factors like genetic trait or socio-economic environment that are responsible for its incidence, high dietary fat intake that exceeds more than 40% daily ingested calories, in most of the advanced countries, remains a factor. Besides, the repeated exposure to palatable food increases hedonic pleasure, leading to obesity [81].

To study the pathogenesis of obesity, several models of high-fat diets (HFD) have been used. The diet-induced obesity has been associated with low lingual detection capacity of LCFA in mice, and this is due to altered Ca^{2+} signaling events in TBCs [34]. Another study showed that HFD fed mice developed obesity with low number of taste buds and low expression of CD36 in fungiform papillae [82, 83]. A study was conducted on wild gerbils, *Psamomys obesus*, which live in the desert and never drink water, but once kept in the laboratory, develop obesity. The obese gerbils also exhibited a preference for LCFA and an alteration in CD36-mediated Ca^{2+} signaling without any change in CD36 protein expression [84]. This kind of observations suggest that it is not necessary that there should be a change in lipid sensors at protein level rather a change in Ca^{2+} signaling/tuning could impact eating behavior. Such experiments on TBC Ca^{2+} signaling in humans will be difficult, but not impossible. Notwithstanding, if such experiments could be performed, they will shed light on relationship between fat detection thresholds, CD36 (or GPR120)-mediated Ca^{2+} signaling and eating behavior.

In most of the clinical studies conducted on Algerian obese children [85] and teenagers [86], Afro-American adults [87], Tunisian obese adults [88, 89], Czech obese adults [90] and Australian obese and non-obese participants [91], there was a positive correlation between obesity and fat detection thresholds; the higher was the body weight index (BMI), the higher was the oro-sensory detection threshold in these subjects. An interesting study has been conducted on obese mothers and their obese children to assess fat preferences in relation with their body weight [92]. The fat preferences in mothers was found to correlate with the overweight and/or obesity of their children. Beside all of these positive observations, Tucker et al. [93], in a meta-analysis, could not observe such association. In this meta-analysis, the studies included had employed different LCFAs like palmitic acid or linoleic or oleic acid to evaluate the detection thresholds. When we assessed Ca^{2+} signaling of these different fatty acids, we observed that they did not trigger identical responses in human and mouse TBC (personal communication, unpublished results). So, it is impossible to compare the oro-sensory detection capacity while employing fatty acids of different lengths and unsaturation. Besides, different methods of assessing threshold can have an influence on results.

8-Tongue taste signaling: the target of anti-obesity strategy

Many humans have trouble limiting dietary fat. The management of obesity costs a lot for governmental or private organizations all over the world. The products like inulin, maltodextrin and plant fibres that mimic “fat-like” texture are not very successful as they do not trigger “fat-like taste” [94]. Moreover, their prolonged use may cause a number of gastrointestinal complications. Since physiological mechanisms of fat taste perception are evident and increased thresholds for LCFAs detection are critically involved in obesity, it would be tempting to target lingual lipid sensors (CD36 and GPR120 or others) by non-caloric high affinity agents. Such kind of pharmacological agents would trigger “fat-like” taste more intense than natural dietary fat and induce satiation. Indeed, obese subjects, exhibit not only low oro-sensory detection capacity for dietary fat but also fat-diet associated satiation [95]. Hence, these agents would be “positive fat taste modulators” in analogy to sweeteners. We have previously used grifolic acid, a chemical agent purified from non-edible mushrooms, that acts as GPR120 agonist; however, its anti-obesity actions are awaited (34). Nonetheless, our hypothesis is supported by the observations wherein we have employed a novel non-caloric GPR120 agonist, TUG891 which exerts anti-obesity action in mice and activates tongue-brain-gut signaling [55].

Another alternative approach would be to target the cross-talk between lipid sensors and other lingual sensors. Recently, our laboratory has identified Takeda-G-protein-receptor-5 (TGR5) on human and mouse TBCs [96, 97]. The activation of TGR5 by bile acids or by a selective agonist has been shown to regulate glucose metabolism/energy homeostasis and to decrease obesity [98]. In search of plant derived “fat taste modifiers”, we purified Zizyphin ($C_{51}H_{80}O_{18}$), a triterpenoid from *Zizyphus lotus* L, known for anti-obesity effects in Arabic pharmacopeia. Zizyphin was found to bind to lingual TGR5 and to alter LCFA-induced Ca^{2+} signaling in mice TBCs. Interestingly, Zizyphin improved glucose tolerance, dyslipidaemia and fatty liver disease in obese mice [99]. Oleanolic acid, a triterpenoid present in olive oil from wild trees, was found to exert anti-obesity effects and to improve obesity-associated glucose tolerance, insulin level, plasma lipopolysaccharide (LPS), and hepatic cholesterol and triglyceride concentrations in mice [99]. This triterpenoid exerted these favorable effects by influencing, in part, CD36 mRNA expression in TBCs and gustatory lipid perception.

9. Conclusions and perspectives

The second messenger cascade, coupled to lingual lipid sensors like CD36 and GPR120 has been well explored. However, there still remains some gaps. During receptor activation, the PLC-catalysed hydrolysis of PIP_2 gives rise to IP_3 and diacylglycerol (DAG); the former triggers an increase in free Ca^{2+} , but the role of DAG in fat taste signal transduction is not known. Do taste bud cells also express other Ca^{2+} channels that can be activated by endogenous DAG? DAG is known to open transient receptor potential Ca^{2+} (TRPC) channels of TRPC3/6/7 family. Do taste bud cells express such Ca^{2+} channels?

By the point of view of oro-sensory perception/physico-chemical properties, a dietary fatty acid is not as distinguishable as sugar or salt or bitter. Dietary fatty acids can be perceived as “bitter” or “scratchy”, etc. by healthy volunteers, depending on their previous experience or eating habits, and there no consensus on “fat taste”, with any taste quality likely unrecognizable. Hence, oro-sensory perception of dietary fat can be classified as an alimentary taste. At the same time, it is also logical to stress that fat taste should be considered as a basic taste since its signaling mechanisms meet the criteria that allow to define sweet or bitter. It is mentionworthy that recent studies are also advocating for “calcium”, “magnesium” and “kokumi” taste [100-103].

It would be an exciting approach to synthesize/to obtain the “fat taste modifiers” as agonists and assess their anti-obesity properties in future. Such approaches will consist of synthesizing of new chemical agonists of lipid sensors (CD36 and GPR120) or the use of “adjuvant” or “carrier” like arginine (Arg) that may potentiate fat taste signal. Theoretically, the higher is the taste signal, the higher will be the release of satiation-inducing hormones from the GI tract in obese subjects. Melis et al. [103] have assessed the role of L-Arg supplementation on oral perception of oleic acid (OA) in human participants. Addition of L-Arg increased the OA perceived intensity in these subjects as this amino acid via hydrogen bond produced oleate-ArgH⁺ adducts. It would be interesting in future to explore how OBPII influences fat taste perception in animal models and human participants and whether CD36 SNP also influences odor perception?

In obese subjects, gut microbiota is composed of Gram-negative bacteria. However, the oral cavity contains Gram-positive bacteria (59). Do the buccal bacteria participate to local or peripheral low-grade inflammation in obesity? Nothing is known whether altered bacterial population in the mouth induce buccal epithelium permeability by rupturing the interpapillary tight junctions as is the case in the intestine of obese animals.

The studies on the lingual neuroendocrinology of fat taste perception should be stressed in future as the gustatory perception of dietary LCFAs will not only be solely a centrally regulated phenomenon rather taste bud-secreted peptides may amplify or decrease the gustatory signal in conjunction with lipid sensors (CD36 and GPR120), before being sent to brain afferently. High or low intensity tuning of lingual signal may impact the activation of gustatory cortex including other brain areas. Therefore, an understanding of the autocrine/paracrine signaling of oro-sensory detection of dietary lipids is mandatory to better define the strategies to target lingual lipid sensors. There is still a long way to go to explore the fat taste signal transduction mechanisms and their physiological relevant regulation in health and disease.

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Figure Legends

Figure 1: Lipid gustatory signaling in a type II TBC. Dietary long-chain fatty acids (LCFAs), released as a result of the hydrolysis by lingual lipases, will bind to lipid sensors (CD36 and GPR120). Their binding to high affinity CD36 will induce the phosphorylation of src-PTK that will activate PLC which, after the hydrolysis of PIP₂, gives rise to IP₃ and DAG. The IP₃, by binding to endoplasmic reticulum (ER), will release free Ca²⁺, followed by Ca²⁺ efflux. According to capacitative model of Ca²⁺ homeostasis, this mechanism will be followed by Ca²⁺ influx via the opening of SOC channels like Orai1 and Orai1/3 channels, orchestrated by STIM1 and CIF. CALMH1 channels also leak Ca²⁺ that is involved in CaM activation which will probably control the phosphorylation of MAP kinases. The mark of interrogation (?) shows the unresolved points. For the sake of simplification, the figure only shows the CD36-activated mechanisms; however, GPR120 also induce an increase in Ca²⁺ in the similar manner. The numbers in the circles show the sequences of the events, triggered by CD36.

Abbreviations: CaM, calmodulin; CIF, Ca²⁺ influx factor; DAG, diacylglycerol; IP₃, inositol-tris-phosphate; PIP₂, phosphatidyl-inositol-bisphosphate; PLC, phospholipase C; PTK, protein tyrosine kinase; STIM1, stromal interaction protein-1

Figure 2: The cross-talk between CD36 and GPR120. After the release of LCFAs in the mouth cavity, they first bind to high affinity CD36 lipid sensor whose levels are very high under fasting or pre-meal conditions, and then immediately CD36 is downregulated, followed by upregulation of GPR120 that is involved in post-oral regulation of fat eating behavior.

GPR120 is also involved in long-term regulation of fat-rich food under diet-changing (from high-fat to low-fat and vice versa) conditions. Both the lipid sensors are coupled to Ca^{2+} signaling, one of earliest gustatory key signal, that assures the transfer of taste message from tongue to brain. The numbers in the circles show the sequences of the events, triggered by CD36 and then followed by GPR120.

Figure 3: Activation of different brain areas by dietary LCFAs. The lipid lingual gustatory message is transmitted to brain by chorda tympani (VII) and glossopharyngeal (IX) nerves via NTS, the relay of peripheral and central regulatory pathways connecting the physiologic regulation of food behavior with gastro-intestinal tract (GIT). The results shown here are derived from the experiments conducted on mice (ref. 50), but for the simplification, we have tried to transpose them on human brain circuits. Arrows show the circuits activated in response to tongue gustatory lipid message. The numbers in the circles show the sequences of the neuronal pathways in different areas, but the interconnections may be delayed or accelerated as per emotional situation of the organism. The repeated numbers indicate that an information can be transmitted simultaneously from one area to another area in the brain, for instance, NTS communicates with PBN and VTA. Similarly, HIPP and PBN may communicate, respectively, with VTA, and ARC and VPMPC. VPMPC, VTA and HIPP will send the information, respectively, to AIC, nucleus accumbens and median frontal cortex.

Abbreviations: AIC, angular insular cortex; Arc, arcuate nucleus; amygdala; HIPP, hippocampus; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; VPMPC, ventroposterior medialis parvocellularis; VTA, ventral tegmental area.

Figure 2

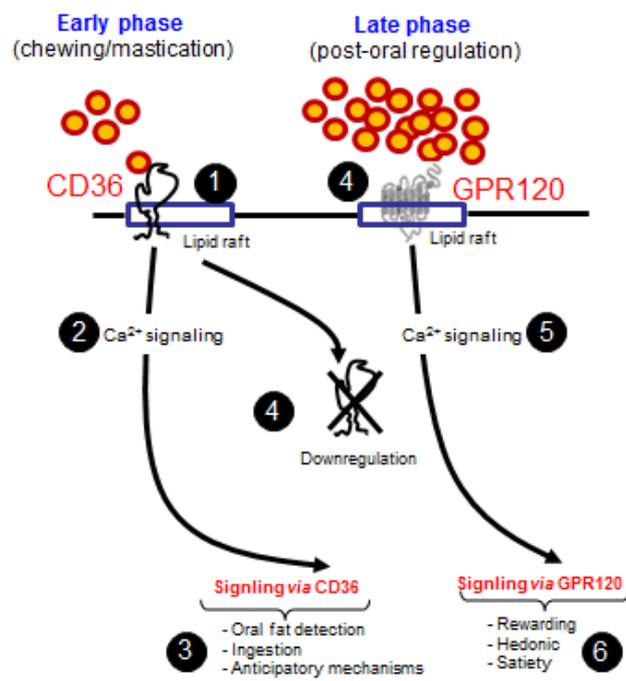


Figure 3

