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Accumulating Evidence Supports a Taste Component for Free Fatty Acids in Humans

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Abstract

The requisite criteria for what constitutes a taste primary have not been established. Recent advances in understanding of the mechanisms and functions of taste have prompted suggestions for an expanded list of unique taste sensations, including fat, or more specifically, free fatty acids (FFA). A set of criteria are proposed here and the data related to FFA are reviewed on each point. It is concluded that the data are moderate to strong that there are: A) adaptive advantages to FFA detection in the oral cavity; B) adequate concentrations of FFA to serve as taste stimuli; C) multiple complimentary putative FFA receptors on taste cells; D) signals generated by FFA that are conveyed by gustatory nerves; E) sensations generated by FFA that can be detected and scaled by psychophysical methods in humans when non-gustatory cues are masked; and F) physiological responses to oral fat/FFA exposure. On no point is there strong evidence challenging these observations. The reviewed findings are suggestive, albeit not definitive, that there is a taste component for FFA.

Keywords

gustatory; taste transduction; human; taste primary; taste quality; fat perception; oral

The nature of the sense of taste continues to be a source of debate. The prevailing view holds that it is comprised of 4-5 primary qualities (i.e., sweet, salt, sour, bitter, ~glutamate). However, over the last two millennia perspectives have varied widely. Some argued that because of the lack of transitions between primaries (as is noted in color vision), taste is better described as a collection of different sensory systems or modalities [1, 2]. Others have emphasized the relatedness of stimuli and sensations and drawn the opposite conclusion [3]. Most recently, findings that stimuli conventionally viewed as taste compounds are ligands for receptors throughout the body has led to descriptions of taste occurring in non-traditional sites, e.g., intestine [4, 5] and respiratory tract [6, 7]. Additionally, there are reports of taste sensations following exposures to unconventional stimuli (e.g., heat [8]). These findings have introduced new dimensions to the discussion of what is taste.

Is taste defined by stimulus properties, transduction systems, neural pathways, and/or perception? If the transduction mechanism is the primary determinant, one can refer to gut

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taste or renal taste since the T1R2-T1R3 sweet receptor is present on L-cells of the intestine and the ENAC (salt) channel is present on renal cells. However, these mechanisms do not lead to conveyance of a signal by gustatory nerves to taste centers in the CNS, nor do they result in any perception of sweetness or saltiness. One could just as readily speak of skin sight because exposure of epithelial cells to electromagnetic radiation in the visible range evokes physiological responses (e.g., [9, 10]), but this has not led to the same extrapolations by vision researchers. At the same time, the adequacy of perception as the hallmark of taste is questionable, as subthreshold concentrations of taste compounds alter transduction processes and gustatory nerve activity [11, 12]. Rather, convention would hold that the senses are defined by a unique set of features including: A) the involvement of mechanisms to capture and transduce (i.e., convert the chemical signal to an electrical signal) specific stimuli; B) dedicated neural systems to convey and decode signals; and C) discrete sensations. The currently popular reference to taste in other body sites largely reflects the fact that early findings were made by chemosensory scientists working with taste compounds attempting to characterize the sense of taste by drawing on existing knowledge of other chemosensory detection systems in the body. If gut physiologists had sought insight by studying the oral cavity, different terminology may have emerged. Attribution of the transduction processes to one system or another will likely change as their functions are better characterized and various outstanding philosophical issues about the definition of taste are resolved.

The other body of science provoking a rethinking of the nature of the sense of taste concerns the number of qualities it mediates. Some argue the concept of primaries lacks a scientific basis and the constraints it imposes on thinking hampers research on the sense [13, 14]. The more widely accepted view is that there is a limited set of primaries [15]. The current controversy concerns the number. Evidence is amassing that supports several qualities proposed previously, but not widely accepted. Among these qualities are water taste [16] and fat taste [17, 18]. Newer proposed additions include calcium [19, 20], starch [21] and CO₂ [22] taste. Acceptance of these recent claims holds important implications as it raises the question of how many primaries can exist in a system before the functionality of the distinction loses relevance. The criteria for acceptance or rejection of taste primaries have not been clearly articulated, hampering resolution of the controversy. We propose the following minimal elements of a primary taste quality:

- A. provide some adaptive advantage;
- B. have a defined class of effective stimuli;
- C. have unique transduction mechanisms;
- D. initiate peripheral signals conveyed by gustatory nerves that is decoded in gustatory centers;
- E. be perceptible and unique; and
- F. evoke a functional physiological and/or behavioral response.

This review will consider the evidence on “fat taste” related to each of these points.

It may be noted that the evidence is not unequivocal for any of the accepted primaries at this time, so these criteria may be neither necessary nor sufficient. Drawing on several recent scholarly reviews [15, 23-25], Table 1 summarizes the author’s interpretation of evidence on the proposed criteria for the current primaries and fat. A critical review of the evidence related to each cell of the table is beyond the scope of the present review, but to highlight a few weaknesses, the array of effective sweet and bitter stimuli is vast, not clearly defined and, not uncommonly, overlapping (e.g., saccharin is sweet and bitter). With respect to

responses, sweetness may be associated with carbohydrate intake and metabolism, but it is neither required [26], nor an adequate (aspartame studies) stimulus to evoke an insulin response. The actual transduction mechanisms for salt and sour in humans are not fully characterized and there is no clear lexicon to describe the sensations elicited by glutamate. Thus, the standard for evidence required to establish a primary is uncertain and unevenly applied.

Finally, aside from a heuristic interest, the question may be asked, is it important to determine whether there is a taste for fat?. One response is that if a taste component is uniquely influencing physiological processes with health implications, then there are clinical, public health and commercial prospects for health promotion and disease management. We suggest that this is the case for fat taste. We now compile the evidence to-date related to each of the proposed primary criteria.

A. Provide some adaptive advantage

Teleological arguments have been made to support the function of each of the currently accepted primary taste qualities. Given that it is not possible to determine the veracity of each claim, all are speculative and conflicting hypotheses can be made. For example, bitterness is rejected by neonates [27] and often avoided by adults, a response that might have reduced toxin exposure. However, some of the most nutrient dense (i.e., nutrient/kJ) foods (e.g., cruciferous vegetables) have marked bitter notes and their exclusion from the diet based on taste could compromise nutritional status [28]. Similarly, sourness is often rejected and could have reduced exposure to dangerously acidic substances, but it is also associated with foods rich in vitamin C and nutritious fermented products. Exclusion of sour foods would increase the risk of scurvy, especially if bitter cruciferous vegetables were also avoided. In both of these cases, it is clear that in humans, whatever warning signal these taste qualities present, they may be overridden as bitter and sour foods (e.g., coffee, wine, oranges, lemons) are widely consumed and enjoyed. In part, this stems from learned associations between ingestion of such foods and positive health outcomes. This has also recently been documented for sweetness where ingestion of a nutritive sweetener remained elevated in sweet taste-blind rats whereas this was not the case for a non-nutritive sweetener that provided no energy [29]. Nevertheless, common experience would support a role for taste qualities in food choice.

The contribution of fat detection to ingestive behavior is complex. At one level, a preference for fat would be predicted as selected fatty acids are essential (i.e., cannot be endogenously synthesized) and they are the most energy dense substrate. The palatable qualities ascribed to fat largely stem from the textural properties they impart such as creaminess, smoothness and thickness. These attributes are properties of triacylglycerols (TAG), the principle (about 95%) form of fat in food (as well as our bodies). Food lipids may also carry desirable fat soluble flavor compounds, but this is not a direct effect of fat itself. Although the evidence is unclear about whether fat is inherently palatable based on fetal [30] and neonatal [31-33] responses to varying fat exposures, the sensations produced by TAG become desired food properties. Emphasizing the importance of sensory perception, the preferred concentration reflects the level of exposure more than a particular absolute concentration [34, 35].

In contrast to the positive effects of TAG to food flavor and expected promotion of consumption, free fatty acids (FFA) might be expected to elicit antithetical effects. FFA are typically present in foods in small quantities and derive from hydrolysis of triglycerides. They are more susceptible to oxidation than when esterified [36]. Oxidation is promoted by exposure to oxygen, light, and heat and results in a host of compounds with adverse biological effects. Oxidized fats from the diet are cytotoxic and genotoxic and are linked to

increased risk of atherosclerosis and selected cancers among other disorders [36, 37]. Thus, it would be prudent to avoid rancid fats. The odor and taste of FFA provide a sensitive signal for the presence of oxidized fat [36], so could deter consumption of unwholesome foods, just as is hypothesized for bitterness. The effectiveness of this warning system is attested to by the considerable resources devoted to maintaining FFA concentrations below detection levels in foods by the food industry. Of course, there are also examples of foods (i.e., strong cheeses [38]) that are actually preferred because of a learned liking for the properties contributed by purposefully elevated FFA concentrations.

Taken together, the form and concentration of fats in foods can have orexigenic or anorexigenic effects. The former is primarily attributable to TAG, but as described below, this is not likely taste-mediated. The aversive sensations from rancid fats stem largely from FFA and are the more likely taste signal. Importantly, FFA are consumed in preference to vehicle by rodents [39-41], but are rejected by humans raising questions about the suitability of rodents as models for studies of hedonic responses to fats. We estimate the strength of evidence related to an adaptive advantage for fat taste detection to be strong, at least as strong as for other primary taste qualities.

B. Have a defined class of effective stimuli

One obstacle to acceptance of fat as a taste quality has been identification of an effective stimulus. TAG is the predominant form of fat in the food supply and energy storage form in the body, but the metabolically active form, especially for signaling is FFA (e.g., [42-45]). Attesting to the importance of each of these forms is the remarkable inefficiency in fat processing. Most (short and medium-chain TAG are exceptions) dietary TAG must be hydrolyzed in the intestinal lumen to FFA and monoacylglycerol to be absorbed into the enterocyte. Once inside the cell, they are re-esterified to TAG and either stored as cytosolic lipid droplets or packaged into chylomicrons for transport into the lymph and subsequently to the circulation [46]. When needed, the lipid stored as droplets in the cytosol is again hydrolyzed so it may enter the endoplasmic reticulum for packaging into chylomicrons. Then, for peripheral tissues to absorb fat from the circulation, lipoprotein lipase again hydrolyzes the TAG in circulating lipoprotein particles and the cell then takes up the FFA and monoacylglycerol where it may yet again be re-synthesized into TAG. Thus, throughout the body, processing of TAG entails its disassociation and it may be hypothesized to hold as well in the oral cavity at the taste receptor cell surface. This is supported by multiple studies in rodents documenting that application of FFA to taste receptor cells leads to depolarization [11] and oral exposure in vivo promotes pancreatic enzyme secretion [47, 48] whereas esterified fats are not effective. Rats also prefer solutions of FFA over vehicle or TAG [39-41]. The issue has not been systematically studied in humans.

If FFA are the effective taste stimulus, the question of their origin arises. As noted above, most dietary fat is in the form of TAG. Unlike rats, who have ample concentrations of lingual lipase to hydrolyze TAG in the oral cavity and generate adequate signal concentrations [41], evidence of functional concentrations of lingual lipase in humans is equivocal. Earlier studies raised questions about the capacity of humans to hydrolyze TAG orally [49, 50], but more recent evidence suggests this may be possible [51]. However, the necessity of lingual lipase may be moot if food provides adequate FFA concentrations. All other taste compounds are of food rather than endogenous origin. FFA are naturally present in high fat foods. They may be generated during oral processing through lipases present in the food (plants contain lipases so they can access this energy source). Hydrolysis may also occur via microbial degradation of fats. Recent studies have begun to explore these sources. Measurement of FFA concentrations in the saliva of humans who masticated high fat foods under controlled conditions either in the presence or absence of a lipase inhibitor reveal

comparable micromolar concentrations under the two conditions [52]. This both documents the presence of FFA in human saliva under physiological conditions and indicates lipase is not required for their liberation. The concentrations were generally in the 30-50uM range. Studies with isolated taste receptor cells from rodents suggest concentrations of only 1-20uM are required to depolarize taste receptor cells [53]. It is not known whether concentrations in this range are effective for humans, but if so, sufficient signal is present just from food sources.

In summary, FFA are the likely signaling molecules for oral fat taste detection in humans. They are present in foods at detectable concentrations based on rodent models. These structures are not known to be effective stimuli for other primary taste receptors. The strength of evidence related to the existence of a unique class of stimuli for fat taste is estimated to be moderate-strong.

C) Have unique transduction mechanisms

Receptors for FFA are ubiquitous throughout the body [54-57]. They are present in numerous forms and each has an affinity for a limited subset of FFA which exert multiple and varied effects based on their degree of saturation and chain length. Recognition of these receptors and growing evidence of congruence of receptors in the oral cavity and GI tract has prompted exploration of FFA receptors in lingual tissue. A number of candidate receptors have now been isolated from papillae in rodents and one (CD36) in humans (Table 2). An early candidate was the family of delayed rectifying potassium channels (DRK). Electrophysiological studies on isolated rodent taste receptor cells from fungiform papillae revealed that application of uM concentrations of cis-polyunsaturated fatty acids resulted in depolarization [53]. Recordings from cells derived from foliate and circumvallate papillae indicated responsiveness to monounsaturated fatty acids as well as palmitic acid, a 16-carbon saturated fatty acid. While a number of DRKs have been identified in taste receptor cells, the predominant form is KCN5 (Kv1.5). Because this channel is instrumental in repolarizing cells, its blockage by a FFA could either be the primary mechanism for FFA detection or it could augment responses to other taste qualities by delaying repolarization after their activation of the cell. Evidence for the latter is mixed in rodents [11, 58, 59] and humans [60, 61]. The former mechanism requires that a proportion of these channels be open in the resting state so that their blockage would result in depolarization. Evidence for this is uncertain. Taken together the evidence is clear that selected FFA can block DRK resulting in taste receptor cell depolarization, but whether the FFA is the effective stimulus or enhances responses to other taste compounds requires additional study.

CD36 is present in the apical side of cells from circumvallate, foliate and, to a lesser extent, fungiform papillae in mice and rats [48, 62]. It has also recently been confirmed in human taste bud cells extracted from circumvallate and foliate papillae [63]. It is co-localized with alpha-gustducin in some cells and when activated promotes and increase in intracellular free calcium concentration, consistent with activation of intracellular signaling systems [64]. It is not present in non-gustatory oral tissue (palate) and CD36 knockout mice lose the ability to detect FFA [48] while sweet and bitter sensitivity remain intact. Knockouts also fail to express a preference for fats [21] and do not exhibit pancreaticobiliary responses to oral fat exposure as observed in wild-type animals [48]. Whether CD36 serves as a FFA transporter, binding site or docking site that delivers FFA to other receptors with subsequent taste receptor cell depolarization is not presently resolved [48].

GPCR120 is expressed in intestine, adipocytes and the apical portion of type I and II cells from taste buds [59, 65, 66]. Application of long-chain saturated and unsaturated fatty acids prompts a rise in free intracellular calcium in a dose dependent manner [67]. This was not

observed with esterified fatty acids. Effective concentrations are in the μM range as determined by GLP-1 [67] and CCK [68] secretion from STC-1 cells. GPCR120 knockout mice exhibited a lower preference for mM concentrations of linoleic acid in 48 hour 2 bottle preference tests and tended to prefer oleic acid less, but this was not statistically significant [59]. They did not show a preference for either fatty acid in a 5 second licking trial. No differences were noted for other primary taste qualities indicating the deletion selectively affected fat perception.

FFA₁R/GPCR40 is expressed in many tissues including intestine, liver, pancreatic alpha and beta cells, brain and skeletal muscle [69, 70] and type I and II cells from taste buds [59, 66]. It is not present in non-gustatory oral epithelium [66]. FFA application results in a rise of free intracellular calcium [71], but esterified fats are not effective [72]. Effective stimuli include medium to long chain saturated FFA and long chain mono and poly unsaturated FFA. The EC₅₀ concentrations are in the range of 1-150 μM [69, 70]. Among the effective saturated fats, potency is inversely related to chain length. For unsaturated fatty acids, the potency was directly related to the number of double bonds in one trial [69] but not in another [70]. FFA₁R knockout mice exhibited lower preference of mM concentrations of linoleic and oleic fatty acid solutions. They did not show a preference for either fatty acid in a 5 second licking trial. No differences were noted for other primary taste qualities indicating the deletion selectively affected fat perception.

GPCR84 has been identified in rodent foliate and circumvallate taste cells [53] as well as a variety of other tissues, most notably, lung, bone marrow, leukocytes, placenta and fetal thymus in humans. It binds medium chain fatty acids with an EC₅₀ in the range of 5-100 μM [73]. FFA with chain lengths of 10-12 carbons are the most potent ligands. Binding results in an increase of intracellular free calcium.

FFA₃R/GPCR41 is highly expressed in adipose tissue [74], though this has not been consistently reported [75]. It is also present on a wide array of other cell types including spleen, skeletal muscle and heart and taste cells from the posterior tongue. Ligand binding results in an increase in intracellular free calcium ions [74, 76]. The EC₅₀ for FFA with chain lengths of 2-4 carbons is in the range of 10 μM to 8 mM. Effective ligands are short chain FFA and they activate cells in a dose response manner [74]. Binding does not follow chain length. Pentanoate is the most effective ligand [74].

FFA₂R/GPCR43 is highly expressed in polymorphonuclear cells and may mediate the effects of short chain fatty acids on immune function in the GI tract [77]. It is also present on a wide array of other cell types including intestine, spleen, skeletal muscle and heart as well as taste cells from the anterior and posterior tongue. The EC₅₀ for FFA with chain lengths of 2-4 carbons is in the range of 50-250 μM [74, 76] and no relationship is noted between FFA chain length and potency. Acetate is the strongest agonist.

Another potential mechanism for FFA detection entails their diffusion across the taste receptor cell membrane and activation of intracellular signaling systems. This mechanism has been documented for lipophilic sweet and bitter compounds [78-80]. FFAs are amphipathic so may traverse cell membranes. Passive flip-flop and saturable, protein-mediated absorption have been described in mammalian cells [81-83], but not studies in taste receptor cells. At physiological concentrations, over 90% of long-chain FFA uptake is protein mediated [84], but diffusion still occurs and at concentrations that saturate transport systems, diffusion will dominate with rates determined by FFA diffusion coefficients [85]. Diffusion coefficients are generally directly related to chain length [86]. Diffusion would be of particular importance for shorter chain FFA as transporters preferentially carry FFA with chain lengths greater than 8 [87, 88]. FFA may diffuse across cell membranes in

milliseconds when FFA concentrations are high [89]. Higher concentrations of disassociated FFA may be present in the oral cavity as compared to the circulation where they are largely bound to albumin [90].

In summary, the importance of FFA as signaling molecules is firmly established. There are an array of mechanisms by which this occurs throughout the body. Four have been proposed for taste receptor cells and one has been confirmed in humans. These include blocking rectifying potassium channels, interactions with CD36, binding to a range of G-protein coupled receptors and diffusion. The mechanisms have all been localized to taste cells and the effective concentrations are likely to occur in the oral cavity during food ingestion. Importantly, with the exception of diffusion, no other single mechanism can account for the evidence on human sensitivity to various FFA [28, 91]. This sensitivity to a range of FFA suggests the presence and function of most or all of the mechanisms described to date. The strength of evidence supporting FFA transduction mechanisms in humans is estimated as moderate-strong. An important caveat is that all of these mechanisms have also been localized to trigeminal neurons [53], thus hampering definitive attribution of FFA by these mechanisms to taste.

D) Initiate peripheral signals conveyed by gustatory nerves and be decoded in gustatory centers

The chorda tympani nerve conveys signals from taste cells in buds in fungiform and foliate papillae and the glossopharyngeal nerve innervates taste cells from the foliate and circumvallate papillae. Whole nerve recordings in mice exposed to selected FFA (oleic, linoleic, linolenic) revealed activity in both nerves with stronger activation of the glossopharyngeal [59]. The signal was weakened below wild-type animals in GPCR40 and GPCR120 knockout animals. Importantly, nerve activity varied for FFA that differentially bind to these two receptors. For example, activity to lauric acid was diminished in GPCR40 knockouts, but not in GPCR120 knockouts and lauric is a ligand for GPCR40, but not GPCR120. Further, chorda tympani responses were diminished to a greater degree in GPCR120 knockouts than GPCR40 knockouts which is consistent with the greater expression of GPCR120 in fungiform papillae. No responses were recorded to mineral oil indicating the activity was not due to tactile stimulation. Comparable evidence has been published in CD36 knockout and wild-type mice [92]. Gustatory nerve activity has also been documented with FFA blockage of DRK and a lack of activity following oral stimulation with esterified fatty acids [93].

If gustatory nerves are involved in oral fat detection, their transaction should disrupt responses on various behavioral assays. Interpretation of nerve cut experiments is complicated by the fact that the procedure may alter other processes linked to detection such as salivation to carry stimuli and bring them into contact with lipase to hydrolyze TAG as well as survival of taste receptor cells [94-96]. In addition, the chorda tympani and glossopharyngeal are mixed nerves conveying taste and somatosensory signals, so attribution of effects to one system is problematic. Nevertheless, nerve transaction studies provide useful insights. Gustatory nerve cuts in rodents reduce the preference for fats observed in two-bottle choice tests as well as aversion conditioning [92, 96-98]. Responses do show fat specificity. Nerve cut effects on aversion conditioning do not generalize to other taste qualities [99], but do generalize across fatty acids (e.g., linoleic and oleic acids). Recent work indicates that glossopharyngeal nerve cuts robustly diminish licking responses to corn oil, but have limited impact on glucose licking [96]. Nerve cuts also reduced pancreatic exocrine secretions following oral fat exposure [92] consistent with disruption of a FFA signaling system. The effect was stronger for concurrent transaction of the chorda

tympani and glossopharyngeal nerves than either alone consistent with a contribution from each [92].

Preliminary evidence suggests signals generated by oral fat exposure are detected centrally. Recent work in mice shows FOS-like immunostaining in the gustatory nuclei in the nucleus of the solitary tract, the first synaptic relay site for taste in the brain [92]. This response was markedly weaker with a somatosensory control indicating it was not solely attributable to tactile cues. Moreover, the response was not observed in CD36-null mice. Human neural imaging studies also indicate oral stimulation with fat results in activation patterns that differ from responses based on somatosensory stimulation [100].

Taken together, these data are consistent with oral fat, and more specifically, FFA signals being transmitted from the periphery to the brain via gustatory nerves. The data show sensory stimulus specificity and consistency with current understanding of FFA transduction mechanisms. No data challenge an interpretation of current knowledge as supportive, but due to the potential confounds associated with these types of studies and extremely limited data from humans, the strength of evidence is viewed as moderate.

E) Be perceptible and unique

There are two principle obstacles to confirming that FFA impart an identifiable sensation that cannot be attributed to some combination of cues from other primary taste qualities or mixture of cues from multiple sensory systems. One is that dietary fats can be detected by their contributions to the appearance, sound (e.g., crispiness), odor and somatosensory properties (e.g., viscosity, lubricity, heat transfer, mouth coating) of foods, so isolating the taste component is challenging. Second, unlike the case for sweet, salty, sour and bitter tastes, there is no clear lexicon for the sensation FFA elicit. Fat taste is more like glutamate taste in this regard. While this has not prevented adoption of glutamate taste as a primary by many, it does complicate confirmation of fat's detection and independence from the other taste qualities.

Several lines of study have provided evidence suggestive of a taste component. In humans, elimination of visual and olfactory cues is easily accomplished by testing individuals wearing blindfolds or under red-light and blocking orthonasal and retronasal olfaction with noseclip [51, 101, 102]. Auditory cues are considered inconsequential with stimuli composed of dilute solutions. The most problematic potential confound is with texture and this has been addressed in humans by masking. That is, stimuli are prepared including concentrations of compounds that impart the textural cues expected of FFA at concentrations that would overwhelm the FFA contribution to these sensations. So, discrimination between samples with and without FFA would presumably be based on taste alone. Additionally, irritancy cues can be mitigated through capsaicin desensitization of judges prior to sensory testing. When all of these controls are implemented, humans can still detect a signal in threshold tests [51, 101, 102] and can monotonically scale perceived fat content with gradations of physical concentration [51, 102, 103]. Still, the evidence is not conclusive because the adequacy of the controls has not been established. Additional support for a unique taste component is provided by findings that taste, olfactory and irritancy thresholds obtained in the same individuals are not significantly correlated [91] while there is evidence [51] albeit mixed [104], on the reliability of sensitivity across FFA. Further, "taste" thresholds for linoleic acid are lower than retronasal thresholds indicating the latter is not the basis of discrimination, though values did not differ for orthonasal thresholds [91]. Irritancy thresholds do not appear to contribute to detection at low concentrations [101].

The primary sensory cue from low concentrations of FFA is olfactory (for TAG it is tactile). Thus, psychophysical studies conducted for product development and shelf life stability

have purposefully drawn on odor detection and characterization. Little work has been undertaken on the taste qualities of FFA. Very weak concentrations of short chain fatty acids have been described as sour [105], but stimulus purity was not confirmed in this work, contributions of other sensory systems were not adequately controlled and it is not clear that these terms were not used to characterized the hedonic impression of the samples. Thresholds for linoleic acid do not correlate with thresholds for prototypical sweet, salty, sour and bitter compounds [51, 102] suggesting an independence of fat perception from other taste primaries.

To circumvent problems with lexicon, evidence obtained on animal models can be extrapolated to humans and non-directional sensory tests (i.e., procedures that only require discrimination, but not identification of the quality upon which the judgment is made) can be used with humans. The animal literature shows rodents can discriminate weak concentrations of FFA from vehicle and TAG [39] even with masking [106] or olfactory ablation [40] and do so in short-term trials and in esophagostomized animals [47, 48] to minimize metabolic feed-back cues [107-110]. As noted above, putative fatty acid receptor knockout animals also exhibit a loss or diminished ability to detect FFA. Additionally, conditioned aversion trials demonstrate that aversions generalize between butter, margarine and lard, all potential sources of FFA, but not to petroleum jelly, a tactile control [111]. Generalization has also been reported between linoleic and oleic fatty acids [99] and in compound stimulus mixtures of fat with sucrose or mineral oil, aversions generalized to the fat component rather than the sweet taste or tactile cue [109]. Additional relevant human evidence derives from studies demonstrating the presumed taste of fat leads to a more robust post-prandial rise of serum TAG (a biomarker for oral fat detection) than sensory-matched, non-fat stimuli [26, 112, 113], stimuli with fat replacers that mimic the tactile properties contributed by fat [114] or olfactory stimulation alone [115].

This body of evidence is consistent with a view that FFA can be discriminated in the oral cavity when non-gustatory cues are minimized or eliminated. However, the adequacy of these controls to isolate a taste component is not known and the quality of the sensation contributed by FFA remains uncharacterized. Consequently, the strength of evidence is regarded as moderate. A potential contributor to the lack of clarity on this issue is the failure to control for the marked inter-individual variability for fat detection. Fatty acid thresholds vary over several orders of magnitude [51, 104]. Some have suggested there are fat tasters and non-tasters [51, 60, 116], but these positions are based on testing procedures that used arbitrary criteria for dichotomizing responses rather than empirical evidence of bimodality in a population distribution. Evidence on whether FFA thresholds vary with BMI is mixed [117, 118].

F) Evoke a functional physiological and/or behavioral response

Evidence for an oral exposure effect on lipid metabolism dates back over half a century. The early work demonstrated that oral stimulation via modified sham feeding of mixed nutrient foods led to an abrupt rise of serum Vitamin A, a marker of circulating TAG since it is a fat-soluble vitamin [119]. Later work with rats [120] indicated that fat was the most effective oral stimulus. Subsequent studies in humans by multiple groups [26, 102, 112, 114, 115, 121-126] have confirmed an oral exposure effect on postprandial lipemia and have begun to better characterize relevant features of the stimulus and consumer. The response 1) may occur with non-specific stimulation, but is most robust to food fats [26, 112, 113, 127]; 2) requires only a single, brief (i.e., 10 second) period of stimulation [113]; 3) requires a minimal amount of lipid (between 10-30g) available for absorption from the gut to be measurable [128]; 4) may be augmented by lower stimulus palatability [128]; 5) may entail both rapid mobilization of lipid stored in enterocytes [26] and delayed clearance at the

periphery [128]; and 6) is greater in individuals of higher BMI [118]. Human and animal studies also document effects of oral stimulation on digestive processes including secretion of gastric acid and lipase [129] gastric emptying [130, 131], as well as secretion of pancreatic enzymes [47, 48] and gut hormones [131].

This broad array of responses raises the question of what purpose(s) they serve. At this point, only speculative suggestions are possible and have recently been described [118]. They include, but are not limited to, facilitating packaging and secretion of fat soluble nutrients from enterocytes into the lymph and ultimately general circulation, modulation of appetite and energy intake, maintenance of intestinal function during long inter-meal intervals and/or detoxification of ingested cytotoxic compounds, including FFA.

The evidence related to effects of oral fat signaling on lipid metabolism is very strong. Whether it stems from FFA activation of the taste system remains to be determined. There is evidence from animal models supporting such specificity for aspects of the phenomenon such as pancreatic exocrine secretions [47, 48]. Combined, these data provide moderate-strong evidence for a functional role for oral fat detection.

Summary

Evidence outlined here supports each of the stipulated criteria for a taste primary. However, in no case is it definitive. At present, this seems to be due primarily to gaps in understanding rather than conflicting findings. As knowledge accrues, the question can be revisited, but more importantly, continued efforts to characterize the mechanisms and functions of oral fat detection are warranted to better inform health care policy and practice for fat-related chronic disorders such as cardiovascular disease, diabetes and obesity.

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Research Highlights

There is accumulating evidence supporting a taste component for free fatty acids in humans. This review summarizes findings on proposed criteria for establishing a taste quality as basic or primary. It concludes there is:

- strong evidence for an ecological advantage to oral fat detection;
- moderate to strong evidence that the effective taste stimuli are free fatty acids;
- moderate to strong evidence that there are multiple transduction mechanisms on taste cells that collectively bind the array free fatty acids present in foods and that signals generated by oral fat exposure are conveyed centrally by gustatory nerves;
- moderate evidence that humans can detect and scale the intensity of free fatty acids in the oral cavity based on taste cues; and
- moderate to strong evidence that oral fat detection by taste cues elicits physiological responses related to lipid metabolism.

Summary of evidence for each commonly accepted taste primary and fat from animal models or humans related to the proposed criteria for establishing them as a primary. (Y = strong or compelling evidence; ? = questionable evidence).

Table 1

Criteria	Taste Primaries and Fat					
	Sweet	Salt	Sour	Bitter	Glutamate	Fat
Provides an advantage	Y	Y	Y	Y	Y	Y
Unique class of stimuli	?	Y	Y	?	Y	Y
Unique transduction mechanism	Y	?	?	Y	Y	?
Signal carried by a gustatory nerve	Y	Y	Y	Y	Y	Y
Perceptible, unique sensation	Y	Y	Y	Y	?	?
Evokes a physiological response	?	Y	Y	?	?	Y

Table 2

Fatty acid transduction mechanisms. Purported receptors include: Delayed rectifying potassium channels (DRK); Coefficient of Differentiation (CD36); G-protein coupled receptors (GPCR). Fatty acid ligands include: saturated fatty acids (SFA); monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), unsaturated fatty acids (UFA); short chain fatty acids ($C < 6$), medium chain fatty acids ($6 < C < 14$); long chain fatty acids ($C > 14$).

Receptor/Mechanism	Site (Papillae)	Effective Stimuli	Exemplary References
DRK	Fungiform	cis-long-chain PUFA,	[53]
	Circumvallate Foliate	cis-long-chain PUFA, C18:1, C16:0	
CD36	Circumvallate Foliate Fungiform	Long-chain FA (SFA, MUFA, PUFA)	[48]
FFA ₁ R/GPCR 40	Circumvallate Foliate Fungiform (low)	C6:0 – C23:0 C10:1 - C18:1 C18:2 – C22:6	[59, 69, 70, 72]
GPCR 120	Circumvallate Foliate Fungiform	SFA – C:14-C:18, UFA-C:16-C:22	[59, 66, 67]
GPCR84	Circumvallate Foliate	C:9-C:14	[53, 73]
FFA ₃ R/GPCR 41	Circumvallate Foliate	C:1-C:5	[53, 74]
FFA ₂ R/GPCR43	Circumvallate Foliate Fungiform	C:1-C:5, but C:2-C:4 are more effective	[53, 77]
Diffusion	Presumed All	All	[81]