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Oral fatty acid signaling and intestinal lipid processing: Support and supposition

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ABSTRACT

There is increasing recognition that specialized processes once thought to be relatively isolated to the oral cavity (e.g., taste) and intestine (e.g., nutrient absorption) are better characterized as common and continuous. This is exemplified by accumulating evidence linking oral detection of dietary fats to their intestinal processing. This review first summarizes this literature focusing on purported gustatory signaling by free fatty acid stimulation and enterocyte lipid storage and mobilization in humans. It then willfully speculates on the possible functions of this integrated system. It is proposed that it may aid absorption of fat soluble nutrients, enhance acute energy intake, sustain intestinal function during long inter-meal intervals, modulate appetite and/or detoxify ingested compounds including free fatty acids.

A number of recent, novel and converging observations have drawn attention to the links between oral fat detection, lipid metabolism and chronic disease risk. Among these are findings that: A) oral fat detection likely includes a gustatory component [1,2]; B) free fatty acids (FFA) are important signaling molecules with common receptors and/or transduction mechanisms on the tongue, in the GI tract and elsewhere in the body [3–13]; C) the gustatory contribution to oral fat detection uniquely influences aspects of lipid processing [14]; D) the gastrointestinal tract retains a substantive proportion of the lipid consumed at a meal until the next eating event [15–17]; E) this stored lipid is rapidly mobilized by oral fat exposure [15,16,18,19]; F) the release of this lipid leads to a rapid and prolonged elevation of post-prandial serum triacylglycerol (TAG) [14,16,19–25]; and G) elevated post-prandial TAG is an independent risk factor for cardiovascular disease [26–29]. Verification of each of these observations and their apparent links serves as a formidable research agenda alone, but each step is also currently spawning intriguing new questions with important health implications. It is unlikely that this purported system evolved to compromise health but rather presents some functional role. Following an expanded consideration of the evidence supporting the above statements, and to be consistent with the theme of this special issue, this paper will specifically explore, i.e., speculate upon, potential functions of intestinal lipid storage and its responsiveness to oral lipid signaling. Evidence from humans will be emphasized when possible as the suitability of rodent models remains to be established (e.g., there may be species differences in the types, concentrations and lingual distribution of FFA receptors, affective responses to FFA, intestinal lipid trafficking mechanisms and peripheral lipid metabolism).

1. Gustatory detection of FFA

Dietary fats are clearly detected when in the oral cavity by tactile [30] and retronasal olfactory cues [31]. If there is a gustatory component as well, FFA are the most likely effective stimuli. There is no known or proposed receptor for triglyceride, the predominant form of lipid in the diet, as its ligand. A number of rodent studies indicate that esterified fatty acids are not effective stimuli [32–36]. Psychophysical studies indicate that humans can detect FFA with chain lengths ranging from six to 18 carbons [23,24]. It is possible that the range is larger; testing has not probed beyond this range. FFA of a common chain length, but varying in the number of double bonds (i.e., C18:0 (stearic — saturated); C18:1 (oleic — mono-unsaturated); and C18:2 (linoleic — poly-unsaturated)) can also be detected [31]. The principal issue in documenting a taste component is isolating this cue from other properties. Visual cues are easily eliminated by testing under red light or with blindfolds, and olfactory cues can be blocked by the use of nose plugs. More problematic is the control for tactile properties. To date, a masking approach has been used where high concentrations of compounds that add viscosity (e.g., gum acacia) and lubricity (mineral oil) are added to the taste stimulus to mask any contribution the FFA stimulus may contribute to these sensations. Further, testing has been conducted after capsaicin desensitization to minimize irritancy cues. Correlations between presumed taste, olfactory and irritancy thresholds for FFA have not been significant,

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suggesting that they are transduced by different mechanisms. Similarly, presumed FFA taste thresholds have not correlated with measured thresholds for prototypical sweet, sour, salty and bitter stimuli [23,37] nor has the addition of FFA to prototypical taste stimuli enhanced sensitivity to them in humans [38], suggesting that FFA are also detected by mechanisms that differ from those for other taste qualities. In contrast, correlations between presumed taste thresholds for different FFA have been significant in some work [37], though not in other trials [23,31]. Still, the evidence is not definitive because the adequacy of measures to isolate the taste component has not been verified, and there are other uncontrolled properties of fats that may be detected (e.g., mouth coating and thermal sensation).

Using the same masking approach, humans have also demonstrated an ability to scale the intensity of FFA with increments of concentration [39,40]. Absolute ratings are inversely related to FFA chain length, though the slopes of the intensity functions did not differ markedly. With small variations, ratings were similar on different tongue regions, (i.e., tip (fungiform papillae), sides (foliate papillae) and back (circumvallate papillae)).

The inter-individual variability in FFA thresholds spans about 4 orders of magnitude [23,37] and some suggest that there are fatty acid tasters and non-tasters [37,41,42]. Data pertaining to a genetic basis for sensitivity to FFA is not available, but twin and family studies suggest a moderate contribution to fat preference. Several candidate genes have been identified [43].

It has also been posited that fatty acid beta-oxidation in taste bud cells signals the presence of fat in the oral cavity [44], though support for this is lacking.

Taken together, evidence indicates that humans can detect FFA in the oral cavity when non-gustatory cues are minimized. Definitive attribution to taste will have to await further mechanistic studies.

2. Fatty acid signaling

Fatty acids are critical components of cell signaling processes through multiple mechanisms [7]. As integral components of cellular lipid membranes, they modulate cellular uptake of signaling compounds by diffusion and through channels. Additionally, the nature of fatty acids in lipid rafts determines the efficacy for docking of signaling proteins [6,7]. Fatty acids are also precursors for hormones and substrates in signaling pathways [45]. Further, they are modulators of intracellular processes through effects on DNA transcription (e.g., ligands for PPARS) and posttranslational events via binding to signaling proteins. However, most important to the present topic, FFA are ligands for purported receptors in taste receptor cell membranes.

Identification of fatty acid receptors throughout the body [5,8,10] has prompted exploration of their presence on taste receptor cells, the end organs of the most proximal signaling system for nutrient-related compounds. The first FFA receptor to be proposed was the Kv1.5 delayed rectifying potassium channel based on electrophysiological evidence of rodent taste bud cell depolarization after long-chain polyunsaturated fatty acid application [32]. It has yet to be isolated from and shown to transduce a fatty acid signal in human taste receptor cells. CD36, the ubiquitous fatty acid scavenger of long-chain FFA, was proposed next as a putative FFA receptor [46]. It has recently been identified in human circumvallate and foliate taste bud cells [3]. CD36 knockout mice are insensitive to FFA compared to wild type mice, yet the knockouts remain sensitive to sweet and bitter stimuli [46,47]. Whether CD36 serves as a receptor or docking protein, has not been determined [48]. More recent evidence supports a role for several G-protein coupled receptors. GPR40 and GPR120 bind medium and long-chain FFA [36,49,50]. They have been localized to taste bud cells in rodents [4,51]. Compared to wild-type controls, GPR40 (FFA1) and GPR120 knockout mice are less sensitive to an array of FFA but respond equally to sweet, sour, bitter, salty and umami stimuli. GPR84 also binds medium-chain FFA and has recently been identified in taste bud cells on the posterior tongue of mice [52]. Its presence and function in human lingual tissue have not been determined. GPR41 and GPR43, now referred to as FFA3 and FFA2, bind short-chain FFA. Both are present in cells from circumvallate and foliate papillae of rodents [52,53] while FFA3 is also documented in taste bud cells in fungiform papillae. Collectively, if this array of receptors is present and functional in human taste receptor cells, they could account for the broad sensitivity to FFA reported in human psychophysical studies [23,54]. In addition, or alternatively, transduction may entail diffusion of FA across taste receptor cell membranes [1].

Complicating attribution of FFA detection in the oral cavity to taste is the difficulty in isolating taste and somatosensory sensations. Taste is a contact sense, so the two are highly confounded. This is exacerbated by recent evidence that all of the receptor proteins identified to date are also present on trigeminal neurons [52]. Claims that humans can detect FFA by taste are presently only based on controlling somatosensory cues through crude tactile masking and irritancy desensitization. However, the observed very low threshold concentrations are also more consistent with a taste effect.

A taste component for dietary fats in humans has long been discounted for the lack of plausible transduction mechanisms. Although none has been confirmed, supporting evidence is accumulating.

3. Oral fat detection and lipid processing

Oral detection of dietary fats and fatty acids may be assessed by psychophysical methods, as noted above, or through measurement of biomarkers of lipid metabolism, most commonly, a change of serum triacylglycerol concentration [14–16,18–25]. It is hypothesized that oral exposure to fat leads to afferent signals carried by gustatory nerves to the nucleus of the solitary tract followed by reflexive efferent vagus activity that alters intestinal lipid digestion and trafficking in the enterocyte as well as peripheral clearance mechanisms. Evidence that the response is neurally-mediated derives from observations that the elevation occurs with modified sham feeding alone [14–16,18–25,55,56]; it is coincident with pancreatic polypeptide release (an index of neural activation) [18,56]; pre-treatment with atropine, a parasympathetic antagonist, blocks the TAG rise [55]; and only 10 s of oral stimulation is required to elicit an increase [57]. In the absence of human data, findings from rodents [46] document that oral exposure to linoleic acid and linolenic acid enhances the protein content of pancreatic exocrine secretions needed for fat digestion. Further, this did not occur in CD36 null mice or when linoleic acid was applied to the soft palate (CD-36 negative sensory tissue). Elevations of pancreatic protein output were not observed after oral exposure to oleic (monounsaturated), stearic (saturated) or caprylic (medium chain) fatty acids.

Evidence of oral fat exposure effects on enterocyte lipid processing derive from recent work in rodents [58] and humans [15–17], suggesting that these cells retain substantive quantities of lipid between eating events and contribute to resting circulating TAG concentrations [17]. It is also intriguing that the initial peak of TAG occurs 15–30 min after oral stimulation, a time course consistent with de novo TAG synthesis [59]. Although it is premature to state that there is a causal effect, additional evidence supports such a claim. Stable isotope studies indicate that preformed chylomicrons that may have been present in the lymph continue to decline after oral stimulation and the fatty acid composition of chylomicrons sampled after oral stimulation differs from those present just before oral stimulation and 1 h after [16]. How oral fat exposure may influence enterocyte lipid trafficking is not known, but increasing understanding of regulatory processes such as activation of DGAT1 and DGAT2 for directing lipids toward storage or chylomicron synthesis [60] and PAT proteins that may regulate enzymatic access to stored cytosolic lipid droplets [61–63] is a target for future research. Effects on lipid clearance are also likely as the greatest discrepancy in serum TAG concentrations following oral exposure to full-fat and fat-free versions