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Review

Cell signaling mechanisms of oro-gustatory detection of dietary fat: Advances and challenges

Timothy A. Gilbertson [a], Naim A. Khan [b,*]

[a] Department of Biology, Utah State University, 5305 Old Main Hill, Logan, UT 84322, USA
[b] INSERM U866, Université de Bourgogne/AgroSup, Dijon 2100, France

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ABSTRACT

CD36 and two G-protein coupled receptors (GPCR), *i.e.*, GPR120 and GPR40, have been implicated in the gustatory perception of dietary fats in rodents. These glycoproteins are coupled to increases in free intracellular Ca^{2+} concentrations, $[Ca^{2+}]i$, during their activation by dietary long-chain fatty acids (LCFA). The transient receptor potential type M5 (TRPM5) channel, activated by $[Ca^{2+}]i$, participates in downstream signaling in taste bud cells (TBC). The mice, knocked-out for expression of *CD36*, *GPR120*, *GPR40* or *TRPM5* have a reduced spontaneous preference for fat. The delayed rectifying K^+ (DRK) channels believed to lie downstream of these receptors are also important players in fat taste transduction. The trigeminal neurons by triggering increases in $[Ca^{2+}]i$ may influence the taste signal to afferent nerve fibers. Why are there so many taste receptor candidates for one taste modality? We discuss the recent advances on the role of CD36, GPR120, GPR40, TRPM5 and DRK channels, in signal transduction in TBC. We shed light on their cross-talk and delineate their roles in obesity as a better understanding of the molecular mechanisms behind their regulation could eventually lead to new strategies to fight against this condition.

Contents

* Corresponding author. Address: Physiologie de la Nutrition & Toxicologie, UMR U866 INSERM/Université de Bourgogne/AgroSup, 6 Boulevard Gabriel, F-21000 Dijon, France. Tel.: +33 3 80 39 63 12; fax: +33 3 80 39 63 30.
E-mail address: Naim.Khan@u-bourgogne.fr (N.A. Khan).

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1. Introduction

Due to increasing abundance of food, the Western diet is constituted of almost 40% fat, thus providing high daily caloric intake that greatly contributes to the prevalence of obesity and other diseases like type II diabetes, atherosclerosis and hypertension. Moreover, obese subjects have been shown to exhibit higher preference for dietary lipids as compared to lean subjects [1,2]. It has been well accepted that dietary fat modulates feeding behavior principally *via* its textural and olfactory properties. Beside these sensory properties, an additional gustatory component for the detection of long-chain fatty acids (LCFA) in rodents and humans has been proposed [3–13].

There are five basic taste modalities which comprise of sweet, sour, bitter, salty, and umami. Sweet taste allows the identification of energy-rich nutrients [14]. Salty taste ensures the proper dietary electrolyte balance, and sour and bitter warn against the ingestion of potentially toxic substances. Umami taste, associated with a savory sensation, allows the recognition of amino acids, particularly of glutamate [14,15]. The taste receptors cells (TRC) are specialized cells, responsible for the transmission of information of a tastant to the afferent nerve fibers, leading to the brain *via* connections between the gustatory nerves (chorda tympani and glossopharyngeal nerves) and the nucleus of solitary tract (NST) in the brain stem [16]. It has been generally accepted that TRC belong to type II cells, which detect sweet, bitter and umami tastes and share a common signal transduction pathway. The type I cells are glial-like whereas the type III cells are neuron-like, and all the three populations of cells are clustered in taste buds which are localized in the lingual gustatory papillae. There are three kinds of papillae: circumvallate papillae are found in the central region of the posterior tongue, foliate papillae are positioned in the lateral region whereas fungiform papillae are localized on the anterior part of the tongue. In this article, we will also use the term taste bud cells (TBC) where the nature of lingual gustatory cells is not well characterized.

2. Oral fat detection

2.1. Animal studies

Studies of oral fat preference have been conducted in mice or rats where two-bottle preference tests were performed. In most of the experiments, the control solutions contained either xanthan gum or paraffin oil in order to mimic the textural properties of dietary fatty acids. Takeda et al. [4] have shown that mice exhibited the spontaneous preference for corn oil and an anosmic condition did not influence the gustatory perception of lipids. In a test where the animals were given a 5-min access to an oily solution, rats exhibited a preference for solution containing oleic acid [5]. In rats and mice with an esophageal ligation, deposition of LCFA onto the tongue led to a rapid and sustained rise in flux and protein contents of pancreatobiliary secretions [17]. Bilateral sectioning of the glossopharyngeal and chorda tympani nerves that innervate gustatory papillae diminished the preference for a solution of linoleic acid in mice [18].

The question is whether we taste fatty acids or triglycerides since the predominant components of dietary lipids from vegetable and animal sources are the latters [19]. Rats subjected to a two-bottle preference test display a lower appetence for triglycerides than for LCFA [8]. It has been proposed that fatty acids released from triglycerides by lingual lipases would account for the gustatory activity. Indeed, lingual lipase activity in the oral cavity of rodents is sufficient to hydrolyze triglycerides even during short exposure times. In the presence of orlistat, a potent lipase inhibitor, the preference for triglyceride was significantly decreased, whereas the preference for free LCFA was not affected [20]. Lingual lipase activity is especially high in the vicinity of taste buds, since it is locally secreted in the cleft of papillae by Von Ebner glands. Further, it should be noted that fat containing foods contain significant amounts of free fatty acids [21] often well in excess of the concentrations required to activate TBC in cell based assays [22]. Indeed, the studies in rodents clearly demonstrate that these are LCFA that trigger sense of fat taste, neither triglycerides nor esterified fatty acids are effective stimuli [23].

2.2. Human studies

Most of the psychophysical studies on human fat taste perception have been conducted by Richard Mattes and colleagues [9–11,24–26]. Humans have the ability to scale the intensity of fatty acids while we increase their concentrations in tasting solutions [11,24]. These experiments were conducted in a situation where textural and visual cues were eliminated [9], and humans could detect LCFA with chain lengths ranging from 6 to 18 carbons [10]. Absolute ratings were inversely related to fatty acid chain length, though the slopes of the intensity functions did not differ markedly. With small variations, ratings in fatty acid testing were identical on different tongue regions, *i.e.*, fungiform papillae, foliate papillae and circumvallate papillae. The inter-individual variability in the thresholds for LCFA spans about 4 orders of magnitude and some investigators suggest that there are fatty acid "tasters" and "non-tasters" [12,13]. It is also noteworthy that human can "learn" to taste fat and some of them learn more quickly or slowly than others, thus contributing to the variability between-subjects and between-studies [26]. Therefore, it is advisable that there might be, at least, more than two rounds of LCFA detection tests in humans.

As regards the secretion of lingual lipases in humans, no detailed information is available; however, the concentrations of free LCFA in human saliva, in normal circumstances, may rise to 9 μM in the buccal cavity [27]. The concentrations of LCFA rise as high as 60 μM in the saliva in the volunteers when asked to chew for 1 min, at the rate of 1 bite/s, fixed amounts of high fat-foods, containing almonds, coconut, walnuts, almond butter, and olive oil [28]. These observations suggest that during a normal eating situation, the dietary fatty acids would be readily released and interact with lingual lipido-receptors.

In this article, we have chosen to focus on the cellular and molecular underpinnings involved in fat taste transduction rather than elaborating in-depth on the perceptual attributes of the lipid gustatory cues in animals and humans. The reader is directed to a recent series of reviews on advances of fat taste perception [3,25,26,28,29]. Taken together, evidence indicates that humans and rodents can detect LCFA in the oral cavity; and this ability is maintained when non-gustatory cues are minimized. Validation of fat taste as one of the basic primary tastes like salty, sour, bitter, sweet, and umami will have to await further mechanistic studies [26].