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Chemical Reception of Fats in the Oral Cavity and the Mechanism of Addiction to Dietary Fat

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Introduction

Fatty foods, such as cream cakes, butter cookies and fried potatoes, give us some sort of satisfaction. When we eat fatty foods, we perceive them to be tender and juicy because the melted fat spreads throughout the oral cavity. It is thought that the oral sensation constitutes the palatability of fat. Today, various kinds of fat substitutes that have a similar texture to real fat have been developed, such as those used in soft-serve ice cream and low-calorie mayonnaise. Most of these substitutes are made from polysaccharides and reduce the calorie count without any marked change in taste. The tastes of fat substitutes, however, are not palatable in themselves. By retaining just a little real fat in food, the 'body' or 'thickness' of that food can be maintained. Therefore, the palatability of fat cannot be explained completely by its texture. On the other hand, some researchers maintain that odor is important in the palatability of fat. However, even anosmic rodents show a strong preference for fat (Takeda *et al.*, 2001; Fukuwatari *et al.*, 2003). In terms of the gustatory cues for fat, recent evidence suggests that dietary fat, especially free fatty acids, may be perceived chemically in taste-bud cells.

Recognition of dietary fat in the oral cavity

Ever since Pavlov first reported that chemical and physical stimuli in the oral cavity and esophagus reflexively trigger an immediate transitory elevation of digestive juice secretion in the digestive tract, many reports have discussed the cephalic phase of pancreatic enzyme secretion in response to taste stimuli (Sarles *et al.*, 1968; Preshaw *et al.*, 1966; Ohara *et al.*, 1988). The cephalic response is limited to palatable taste stimuli (Ohara *et al.*, 1988). A similar transitory elevation in insulin secretion occurs in response to the sweetness of a stimulus in the oral cavity. Learned taste aversion to sweetness resulted in the loss of the cephalic insulin release in response to sweetness. The test subjects were rats in which the esophagus was tied off at the stomach and cut at the oral cavity, creating an orifice called a 'natural fistula' at the base of the throat. After the rats had recovered from the surgical procedure, administration of sucrose into the oral cavity produced a transitory elevation in pancreatic enzyme secretion. The same amount of oleic, linoleic, linolenic or arachidonic acid, typical fat constituents of foodstuffs, produced similar elevations. There was no secretory response to caprylic acid, a fatty acid with a short carbon chain, or to oleic, linoleic or linolenic acids when their carboxyl groups were methylated. Corn oil produced this response, trilinolein did not (Hiraoka *et al.*, 2003).

Detection of fat in behavioral experiments: a choice of two bottles

The results described above closely match those reported from behavioral experiments into short-term selectivity when rats were offered a choice of two bottles. Rats chose the three (oleic, linoleic and linolenic) long-chain fatty acids and corn oil in preference to vehicle solution, but did not choose triolein, trilinolein or caprylic acid, or the same three fatty acids with methylated carboxyl groups (Tsuruta *et al.*, 1999). Together, these results suggest that stimulation by fatty acids in the oral cavity may provide the chemical information underlying such selective behavior and that the relevant chemical information includes at least fatty-acid chain length and the presence or absence of carboxyl groups. Both taste cells and enteroendocrine cells are categorized as paraneurons (Fujita, 1991). These cells are said to receive chemical stimuli in the apical parts of the cells, and then to transmit the information by releasing neurotransmitters at their bases. Paraneuronal cells are considered morphomechanisms for the release of granules. Therefore, similar mechanisms may be responsible for the recognition of fatty acids in taste cells and small-intestinal cells. Interestingly, the behavioral findings regarding the rats' preference for fats are quite similar to those on the recognition of fats by small-intestinal cells (Shintani *et al.*, 1995).

Fatty-acid-binding protein in the tongue

Circumstantial evidence has begun to accumulate that may explain the mechanism underlying the reception of fatty acids. Gilbertson *et al.* (1997) have clearly demonstrated, using a patch clamp technique, that long-chain unsaturated fatty acids impede delayed-rectifying potassium polarization in tongue taste-bud cells. Moreover, Fukuwatari *et al.* (1997) reported that immunoreactivity for the membrane-bound long-chain fatty-acid transporter was specifically localized to the apical parts of taste-bud cells, possibly gustatory cells, in the circumvallate papillae. Using immunohistochemistry and PCR, they identified CD36 in circumvallate taste tissue, which is consistent with a gustatory cue for fatty acids in the oral cavity. The strongest labeling was in the apical membranes of taste cells, where potential interactions with fatty acids are likely to occur. Together, these results support the theory that the tongue's receptors show little affinity for triglycerides, the energy storage form of fats, but show instead an affinity for fatty acids, the more metabolically active form of fats. This recognition of fatty acids instead of the triglycerides that generally constitute the bulk of fats in foodstuffs comes as a surprise. Circumvallate papillae taste-bud cells are immersed in lingual lipase secreted from von Ebener's glands and significant amounts of triglycerides are lipolyzed immediately in the oral cavity (Kawai and Fushiki, 2003).

Fatty-acid transporter (FAT/CD36) as a sensor

CD36 was first isolated and purified from adipocytes as a fatty-acid-binding protein with a molecular weight of 88 kDa, combined with *N*-sulfosuccinimidyl fatty acid and 4,4′-diisothiocyano-stilbene-2,2′-disulfonic acid (DIDS). These chemicals suppress the fatty-acid transport rate in adipocytes (Abumrad *et al.*, 1993). CD36 is thought to have a major extracellular moiety and two transmembrane regions. Because it differs in structure from most membrane carriers, which have many transmembrane regions, it is considered to act as a receptor for long-chain fatty acids rather than as a transporter. The

fact that CD36 has a region at its C-terminal end that interacts with Src kinase suggests that it has a role in the signal tranduction process initiated by its binding with fatty acids (Huang *et al.*, 1991). CD36 is also expressed in macrophages and plays a receptor role for oxidized low-density lipoproteins (LDL). Recently, CD36-null mice have been engineered and reveal that the CD36 signal cascade mediates the inflammatory effects of β-amyloid (Moore *et al.*, 2002). Short-term two-bottle choice tests to minimize post-ingestive effects demonstrated that CD36-null mice show no preference for fatty acids (unpublished data). Neural recordings of the glossopharyngeal nerve indicated that wild-type mice had a small but significant response to fatty acids when the fatty acid was applied to their posterior tongues, whereas the CD36-null mice displayed no chemical response (unpublished data). These findings suggest that CD36 works as a taste sensor for dietary fat and that the signal is conveyed to the brain via the glossopharyngeal nerve.

Preference for digestible and indigestible fat in mice

Mice showed a strong preference for corn oil and fatty acids over a test fluid containing no oil in a two-bottle choice test and voluntary intake of oil in rewarded (reinforcement) conditioning of place preference (CPP) (Imaizumi *et al.*, 2000), which has been used to evaluate the reward effects of addictive drugs (Schechter and Calcagnetti, 1998). Stimulation of the oral cavity by corn oil has positive reinforcing effects and the stimulation is at least partly mediated via the opioidergic system through the opioid μ and δ receptors, and the dopaminergic system through the D1 receptors (Imaizumi *et al.*, 2000; Sawano *et al.*, 2000). However, artificially synthesized oil, low in calories because it is not digestible by lipase, had no reward effect (Suzuki *et al.*, 2003), even though mice still preferred the indigestible fat over the control in a two-bottle choice test. This suggests that, if given a choice, mice prefer even indigestible fats, although they may not be susceptible to addiction without the guarantee of calories.

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