21. Nasuno, M., et al. 1999. Attenuated liver fibrosis of CD36 as a taste receptor for fatty acids provides insight into the molecular basis of our preference for fat (see the related article beginning on page 3177). As we gain more information regarding the function of this receptor, we may be able to devise better strategies to address the addictive potential of dietary fat.

CD36 may determine our desire for dietary fats

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There is a strong link between high fat intake and obesity. In addition to its high caloric density, dietary fat has a hyperphagic effect, in part as a result of its high palatability. The recent identification by Laugerette et al. of CD36 as a taste receptor for fatty acids provides insight into the molecular basis of our preference for fat (see the related article beginning on page 3177). As we gain more information regarding the function of this receptor, we may be able to devise better strategies to address the addictive potential of dietary fat.

The eighteenth-century French philosopher Charles De Montesquieu once commented, “Lunch kills half of Paris, supper the other half.” The potential of food consumption to lead to serious health complications is well known and has been extensively studied. The last decade has witnessed impressive progress related to some of the molecular mechanisms underlying the development of nutrition-related pathologies such as obesity, type 2 diabetes, and cardiovascular disease. Information on interorgan cross-talk, on various adipokines and myokines, and on proteins involved in controlling energy intake, storage, or expenditure has greatly enhanced our insight into how the body maintains homeostasis (1, 2). Dysfunctions of the sensory perception of a meal can occur as a result of complex interactions between genetic predisposition and today’s affluent lifestyle, often leading to serious health consequences. This has been highlighted by numerous studies of genetically altered animals and by the identification of polymorphisms in humans (3–5).

A potential new frontier in nutrition research is the examination of how the orosensory experience of food can impact food intake and processing as well as the development of long-term addictive patterns. In addition to food abundance, current enhancements in food palatability through high sugar or fat content further challenge our ability to control food intake and maintain body weight homeostasis. The sensory experience of food can be a primary reinforcer of intake. To what extent food perception is determined by genes versus the environment is a topic that has received limited attention. There is evidence that obesity may be associated with an abnormal brain response to the sensory perception of a meal. This abnormal response may even persist in post-obese individuals, creating a high risk of relapse (6). There is little doubt that as individuals, we greatly differ in our ability to experience food at the basic level of taste. According to the NIH, approximately 25% of Americans are nontasters, 50% are medium tasters, and 25% are supersensitivities. So what are the factors that contribute to determining our food perception, and how are they reflected in what we choose to eat and how much? These questions are important, since our food choices greatly impact body weight outcome in terms of how big and how fast. Impressive progress

Why do we like fat?

An exciting new development is the identification of a taste receptor for fat that specifically recognizes fatty acids (FAs), as reported in this issue of the JCI by Laugerette et al. (10). It seems a propos that the report is by a group of French researchers from the University of Bourgogne in Dijon, an area with a rich gastronomic tradition. Dietary fat is particularly addictive, and its excessive intake is strongly linked to obesity. Orosensory perception is thought to play an important role in the spontaneous preference for fat-rich food exhibited by humans and rodents. A hyperphagic effect of a diet with high fat content has been documented and is manifested in increased meal size and decreased intermeal interval (11). Postigestive effects of fat, which include feelings of contentment and satiety and possibly elevation in endogenous opiate levels, also promote long-term preference and positive reinforcement. These effects are not observed with equally palatable, but nondigestible, fat substitutes (12).

Existence of an orosensory receptor for FAs would necessitate a revision of currently held concepts related to food perception. Textbooks still state that taste buds recognize 5 basic sensations; sweet, sour, bitter, salty, and umami (L-amino acid). Evidence presented in several earlier publications strongly suggested that the

Nonstandard abbreviations used: FA, fatty acid; SR-BI, scavenger receptor type B, class I.
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The fat messenger

CD36, the protein identified as a taste receptor for fat, is an integral membrane glycoprotein and a member of a family of proteins expressed both at the cell surface and within lysosomes. The class B scavenger receptor family includes the high-density lipoprotein receptor scavenger receptor type B, class I (SR-BI; also known as CLA-1), which functions in selective cholesterol uptake from high-density lipoproteins. CD36 and SR-BI share a hairpin membrane topology (Figure 1) with 2 transmembrane domains and with both termini in the cytoplasm (3, 18).

CD36 was identified as a facilitator of FA uptake by binding sulfosuccinimidyl oleate, a reactive oleic acid derivative and inhibitor of FA transport. The protein purified from rat adipose tissue was initially called FA translocase (FAT) and later identified to be the rat homolog of CD36 (19). Expression of CD36 favors tissues with a high activity in FA flux or utilization. CD36 promotes the assimilation of dietary triglycerides to facilitate fat absorption and to a faster appearance of absorbed products in the blood (17).
CD36-null mice have impaired FA uptake by muscle and adipose tissues and rely on glucose metabolism for energy, which is reflected by fasting hypoglycemia (3, 18). The mice exhibit poor performance in exercise tests, with compromised endurance and recovery. The deficiency also alters the metabolic response to dietary nutrients. The mice have enhanced insulin sensitivity on a chow diet and are partially protected from the diabeticogenic effects of high-fat diets, but are more susceptible to those diets high in simple sugars like fructose (3, 18). CD36 deficiency also has an impact on the secretion of adipokines such as leptin and adiponectin, which play an important role in organ cross-talk and in the regulation of energy expenditure from lipids. In turn, adipokines may accomplish some of their effects on lipid metabolism via regulating CD36 levels. We also observed that CD36 function in FA uptake impacts expression and activity of PPARs, nuclear transcription factors that regulate genes of lipid metabolism (including CD36) in a tissue-specific fashion. In the small intestine, FA uptake via CD36 seems coupled to efficient chylomicron secretion into the lymph (20). In muscle it is coupled to FA oxidation.

Acute regulation of CD36 expression by relocalization is observed under situations where energy from lipids is needed. In muscle, contraction triggers CD36 translocation to the membrane, which supplies oxidative energy to the working muscle (21). Translocation also occurs with fasting, triggered by activation of the forkhead transcription factor FOXO1 (22). This enhances FA uptake and oxidation as glucose availability is diminished and spares it for glucose-dependent tissues. It will be interesting to determine whether translocation of CD36 also occurs in taste receptor cells in response to FAs and whether it contributes to signal transduction.

Decoding the message
How CD36 accomplishes its function in FA uptake or sensing is currently unknown, and so are the mechanisms that may alter its role in transducing neural signals for bile acid secretion. In many cells, CD36 has been shown to be associated with Src-like tyrosine kinases (23). Binding to CD36 may alter its dimerization state, leading to activation of Src kinases and to the initiation of signaling events. FA binding to CD36 has also been shown to activate NO synthase (24), and NO production has been implicated in the function of some taste receptors (7). For example, one could speculate that FAs alter the localization or dimerization state of CD36. Since CD36 is associated with membrane integrins, it is possible that such changes may result in membrane alterations that would perturb activity of neighboring K+ channels.

The identification of CD36 as a taste receptor for fat (10) is likely to have clinical relevance. As more is learned about the specificity and mechanism of this receptor’s function, it may be possible to devise strategies to treat some forms of obesity. As suggested by many studies, taste dysfunctions—whether inherited or acquired—may be responsible for abnormalities in food intake, leading to obesity. These dysfunctions may not be reversed by weight loss, predisposing individuals to a relapse. It is not unreasonable to suggest that polymorphisms in the CD36 gene (4) or environmentally induced changes in its expression levels or function may be responsible for some of the dysfunctions in fat osensation.

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Analogies can be made between the roles of CD36 in the taste bud and at the level of the whole organism. In both settings, FA interaction with CD36 contributes to transducing signals that alter lipid utilization downstream. For example, our recent unpublished observations indicate that CD36-FA sensing in adipocytes has an impact on the secretion of adipokines such as leptin and adiponectin, which play an important role in organ cross-talk and in the regulation of energy expenditure from lipids. In turn, adipokines may accomplish some of their effects on lipid metabolism via regulating CD36 levels. We also observed that CD36 function in FA uptake impacts expression and activity of PPARs, nuclear transcription factors that regulate genes of lipid metabolism (including CD36) in a tissue-specific fashion. In the small intestine, FA uptake via CD36 seems coupled to efficient chylomicron secretion into the lymph (20). In muscle it is coupled to FA oxidation.

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