

2005

CD36 may determine our desire for dietary fats

Nada A. Abumrad

Washington University School of Medicine in St. Louis

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Abumrad, Nada A., "CD36 may determine our desire for dietary fats." *The Journal of Clinical Investigation.*, 2965-2967. (2005).
https://digitalcommons.wustl.edu/open_access_pubs/1523

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.



- Elevated interleukin-6 expression in keloid fibroblasts. *J. Surg. Res.* **89**:74–77.
20. Choi, I., Kang, H.S., Yang, Y., and Pyun, K.H. 1994. IL-6 induces hepatic inflammation and collagen synthesis in vivo. *Clin. Exp. Immunol.* **95**:530–535.
21. Natsume, M., et al. 1999. Attenuated liver fibrosis and depressed serum albumin levels in carbon tetrachloride-treated IL-6-deficient mice. *J. Leukoc. Biol.* **66**:601–608.
22. Bansal, M.B., et al. 2005. Interleukin-6 protects hepatocytes from CCl₄-mediated necrosis and apoptosis in mice by reducing MMP-2 expression. *J. Hepatol.* **42**:548–556.
23. Bot, A. 1996. Immunoglobulin deficient mice generated by gene targeting as models for studying the immune response. *Int. Rev. Immunol.* **13**:327–340.
24. Bona, C.A. 2000. Anti-fibrillin autoantibodies in scleroderma and mixed connective tissue disease. In *Autoantigens and autoantibodies: diagnostic tools and clues to understanding autoimmunity: report on the 5th Dresden Symposium on Autoantibodies held in Dresden on October 18-21, 2000*. K. Conrad, R.-L. Humbel, and M. Meurer, editors. Pabst Science Publishers, Lengerich, Germany. 637–647.
25. Dubuisson, L., et al. 2001. Expression and cellular localization of fibrillin-1 in normal and pathological human liver. *J. Hepatol.* **34**:514–522.
26. Zhou, X., et al. 2005. Autoantibodies to fibrillin-1 activate normal human fibroblasts in culture through the TGF- β pathway to recapitulate the 'scleroderma phenotype'. *J. Immunol.* **175**:4555–4560.

CD36 may determine our desire for dietary fats

Nada A. Abumrad

Department of Medicine, Division of Nutritional Science, Washington University School of Medicine, St. Louis, Missouri, USA.

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). Dysfunction within 1 or more homeostatic mechanisms 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 supertasters. 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

has been recently accomplished in the identification of taste receptors for various sensations such as sweet, salty, and bitter (7), and this is beginning to contribute insight into the interaction between heredity and the environment in determining food preferences and intake patterns (8, 9).

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 inter-meal interval (11). Postingestive 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

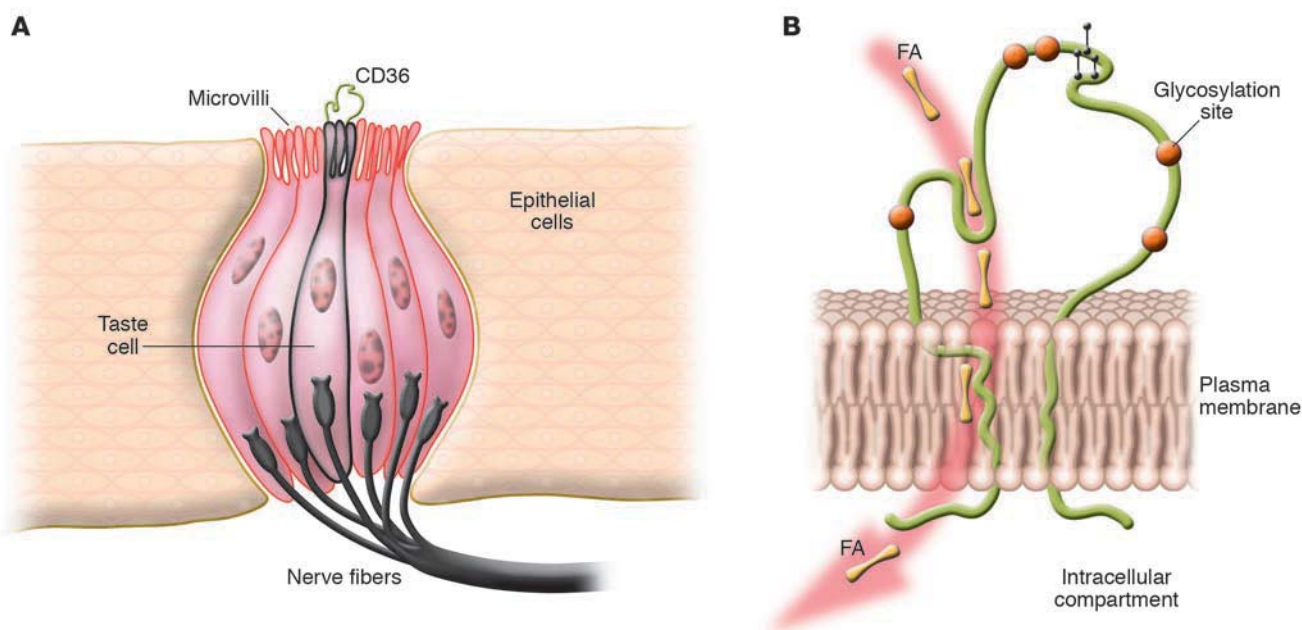
Nonstandard abbreviations used: FA, fatty acid; SR-BI, scavenger receptor type B, class I.

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: *J. Clin. Invest.* **115**:2965–2967 (2005). doi:10.1172/JCI26955.



commentaries

**Figure 1**

The taste bud and the predicted structure of the taste receptor for fat, CD36, expressed on the apical surface of taste cells. **(A)** Schematic structure of a taste bud, which contains 50–100 taste cells. One such taste cell is highlighted, showing CD36 expression on its apical surface. Following interaction of CD36 with FAs derived from hydrolysis of triglycerides by lingual lipase, a signal is transduced to nerve fibers, which leads to taste perception and release of bile acid, preparing the digestive system for fat absorption. **(B)** The predicted structure of membrane CD36, which is proposed to function as a taste receptor recognizing long-chain FAs (10). CD36 is heavily glycosylated (orange circles) and also N-myristoylated and palmitoylated at multiple sites adjacent to both the N and C termini (not shown). CD36 binds FAs with high affinity, presumably in its extracellular domain, and facilitates their transfer into the cell, a process that may involve interaction with other proteins. In taste bud cells, interaction of the FA with CD36 may be sufficient to initiate signaling events without internalization. Alternatively, internalization and generation of intracellular FA derivatives may be required for signal transduction.

list should be revised to include a receptor for fat. In particular, 2 reports in 1997 are worth noting, since they specifically implied involvement of FAs in gustation. Gilbertson et al. (13) reported that dietary fat may be sensed by taste cells via FA inhibition of the delayed rectifying K^+ channels. Fukuwatari et al. (14) documented apical expression of the membrane FA translocase CD36 in taste bud cells. However, the relevance of gustatory cues for FAs remained uncertain, since dietary fat is mostly present as triglycerides that have to be hydrolyzed by digestive lipases during absorption. Then in 2003, Kawai and Fushiki (15) asked whether the lipase present in the mouth (lingual lipase) functioned to release free FAs for interaction with taste receptors. They reported the significant observation that addition of a lipase inhibitor diminished the spontaneous preference of rodents for triglycerides but not that for free FAs.

The work of Laugerette et al. (10), which uses CD36-null mice, provides compelling evidence to implicate CD36 in oral fat perception and in trigger-

ing neural mechanisms that lead to bile secretion. The article nicely illustrates the physiological functions of taste receptors. Although the sensory experience of fat can lead to serious food addiction and health problems, its intended role is to guide appropriate food selection and also to enhance digestion. The role of neural input from taste receptors in the digestive process was probably first demonstrated in a study with subjects that failed to show absorption of vitamin A palmitate, which was published in the *JCI* in 1954 (16). The author of the study, Mendeloff, stated that, surprisingly, the thought or act of eating appeared to activate mechanisms that markedly increase fat absorption. His conclusion was based on the observation that sham feeding, which involved mastication of a palatable meal without swallowing any of it, was associated with an immediate increase in blood levels of vitamin A palmitate given 2 hours earlier (16). Subsequent studies have extended these observations and further demonstrated that orosensation contributes to enhancing fat absorption

and to a faster appearance of absorbed products in the blood (17).

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-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 diabetogenic effects of high-fat diets, but are more susceptible to those diets high in simple sugars like fructose (3, 18). CD36 deficiency also has a protective effect against atherosclerosis promoted by apoE deficiency, probably reflecting a blunting of the inflammatory response (3, 19). At the level of the small intestine, CD36 deficiency is associated with defects in the secretion of chylomicrons into the lymph and in their clearance from the blood (20).

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.

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 likely to mediate 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 orosensation.

Address correspondence to: Nada A. Abumrad, Department of Medicine, Division of Nutritional Science, Campus Box 8031, Washington University School of Medicine, St. Louis, Missouri 63110, USA. Phone: (314) 747-0348; Fax: (314) 444-3432; E-mail: nabumrad@wustl.edu.

- Chen, H.C., and Farese, R.V., Jr. 2002. Fatty acids, triglycerides, and glucose metabolism: recent insights from knockout mice. *Curr. Opin. Clin. Nutr. Metab. Care*. **5**:359–363.
- Matsuzawa, Y. 2005. Adipocytokines and metabolic syndrome. *Semin. Vasc. Med.* **5**:34–39.
- Febbraio, M., et al. 2002. The impact of overexpression and deficiency of fatty acid translocase (FAT)/CD36. *Mol. Cell. Biochem.* **239**:193–197.
- Ma, X., et al. 2004. A common haplotype at the CD36 locus is associated with high free fatty acid levels and increased cardiovascular risk in Caucasians.

- Hum. Mol. Genet. **13**:2197–2205.
- Perusse, L., et al. 2005. The human obesity gene map: the 2004 update. *Obes. Res.* **13**:381–490.
- Delparigi, A., Chen, K., Salbe, A.D., Reiman, E.M., and Tataranni, P.A. 2005. Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. *Neuroimage*. **24**:436–443.
- Lindemann, B. 2001. Receptors and transduction in taste. *Nature*. **413**:219–225.
- Kim, U.K., and Drayna, D. 2005. Genetics of individual differences in bitter taste perception: lessons from the PTC gene. *Clin. Genet.* **67**:275–280.
- Mennella, J.A., Pepino, M.Y., and Reed, D.R. 2005. Genetic and environmental determinants of bitter perception and sweet preferences. *Pediatrics*. **115**:e216–e222.
- Laugerette, F., et al. 2005. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. *J. Clin. Invest.* **115**:3177–3184. doi:10.1172/JCI25299.
- Warwick, Z.S. 2003. Dietary fat dose dependently increases spontaneous caloric intake in rat. *Obes. Res.* **11**:859–864.
- Suzuki, A., Yamane, T., Imaizumi, M., and Fushiki, T. 2003. Integration of orosensory and post-ingestive stimuli for the control of excessive fat intake in mice. *Nutrition*. **19**:36–40.
- Gilbertson, T.A., Fontenot, D.T., Liu, L., Zhang, H., and Monroe, W.T. 1997. Fatty acid modulation of K⁺ channels in taste receptor cells: gustatory cues for dietary fat. *Am. J. Physiol.* **272**:C1203–C1210.
- Fukuwatari, T., et al. 1997. Expression of the putative membrane fatty acid transporter (FAT) in taste buds of the circumvallate papillae in rats. *FEBS Lett.* **414**:461–464.
- Kawai, T., and Fushiki, T. 2003. Importance of lipolysis in oral cavity for orosensory detection of fat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **285**:R447–R454.
- Mendeloff, A.I. 1954. The effects of eating and of sham feeding upon the absorption of vitamin A palmitate in man. *J. Clin. Invest.* **33**:1015–1021.
- Mattes, R.D. 2002. Oral fat exposure increases the first phase triacylglycerol concentration due to release of stored lipid in humans. *J. Nutr.* **132**:3656–3662.
- Hajri, T., and Abumrad, N.A. 2002. Fatty acid transport across membranes: relevance to nutrition and metabolic pathology. *Annu. Rev. Nutr.* **22**:383–415.
- Abumrad, N.A., el-Maghrabi, M.R., Amri, E.Z., Lopez, E., and Grimaldi, P.A. 1993. Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36. *J. Biol. Chem.* **268**:17665–17668.
- Drover, V.A., et al. 2005. CD36 deficiency impairs intestinal lipid secretion and clearance of chylomicrons from the blood. *J. Clin. Invest.* **115**:1290–1297. doi:10.1172/JCI200521514.
- Luiken, J.J., Coort, S.L., Koonen, D.P., Bonen, A., and Glatz, J.F. 2004. Signalling components involved in contraction-inducible substrate uptake into cardiac myocytes. *Proc. Nutr. Soc.* **63**:251–258.
- Bastie, C.C., et al. 2005. FoxO1 stimulates fatty acid uptake and oxidation in muscle cells through CD36-dependent and -independent mechanisms. *J. Biol. Chem.* **280**:14222–14229.
- Huang, M.M., Bolen, J.B., Barnwell, J.W., Shattil, S.J., and Brugge, J.S. 1991. Membrane glycoprotein IV (CD36) is physically associated with the Fyn, Lyn, and Yes protein-tyrosine kinases in human platelets. *Proc. Natl. Acad. Sci. U. S. A.* **88**:7844–7848.
- Zhu, W., and Smart, E.J. 2005. Myristic acid stimulates endothelial nitric-oxide synthase in a CD36- and an AMP kinase-dependent manner. *J. Biol. Chem.* **280**:29543–29550.