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Mini-review

Appetite control by the tongue-gut axis and evaluation of the role of CD36/SR-B2

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ABSTRACT

Understanding the mechanisms governing food intake is a public health issue given the dramatic rise of obesity over the world. The overconsumption of tasty energy-dense foods rich in lipids is considered to be one of the nutritional causes of this epidemic. Over the last decade, the identification of fatty acid receptors in strategic places in the body (*i.e.* oro-intestinal tract and brain) has provided a major progress in the deciphering of regulatory networks involved in the control of dietary intake. Among these lipid sensors, CD36/SR-B2 appears to play a significant role since this membrane protein, known to bind long-chain fatty acid with a high affinity, was specifically found both in enterocytes and in a subset of taste bud cells and entero-endocrine cells. After a short overview on CD36/SR-B2 structure, function and regulation, this mini-review proposes to analyze the key findings about the role of CD36/SR-B2 along of the tongue-gut axis in relation to appetite control. In addition, we discuss whether obesogenic diets might impair lipid sensing mediated by CD36/SR-B2 along this axis.

1. Introduction

The long evolution of human species in a context of food unpredictable food availability has produced complex biological adaptations optimizing the identification of caloric-rich foods and controlling the efficiency of their subsequent digestion, absorption and metabolic fate [1,2]. This selection pressure has generated specialized sensors able to detect caloric sources in foods and induce adapted behavioral and metabolic responses to variations in the availability of energy nutrients (carbohydrates, proteins, lipids) in order to limit nutritional deficiencies and defend body fat stores in an environment of food scarcity. Consistent with this paradigm, a set of sensors known to bind and be activated by fatty acids has been found along the oro-intestinal tract, over the last twenty years. Among these lipid receptors, identification of CD36/SR-B2 both in murine and human taste bud cells [3,4] and enterocytes [5,6] and in mouse entero-endocrine cells [7] may seem surprising at first glance. Indeed, CD36/SR-B2 is known to be a multifunctional protein expressed in various tissues and able to bind a broad range of native or modified hydrophobic ligands circulating both in external body fluids (saliva, alimentary bolus) and in blood [8–11]. Nevertheless, it has been shown that the disruption of CD36/SR-B2 gene in mice or genetic variants associated with CD36/SR-B2 protein depletion in humans disturb both oral fat detection [3] [12] and post-prandial lipoprotein metabolism [13]. Moreover, by controlling the intestinal secretion of appetite regulating peptides, as cholecystokinin (CCK), secretin, glucagon-like peptide-1 (GLP-1) [7] and endocannabinoids [14], CD36/SR-B2 might also play a role in the regulation of food intake. Altogether these observations raise a basic question: What is the influence of CD36/SR-B2 expressed along the tongue-gut axis on eating behavior? After a brief overview about the main CD36/SR-B2 characteristics, this mini-review will attempt to respond to this question.

2. Structure, functions and regulation of CD36/SR-B2

Determination of CD36/SR-B2 sequence predicts a hair-spin structure with a large extracellular domain anchored at the cell surface by two transmembrane domains [8,9]. This ecto-domain

Abbreviations: ApoAIV, apo-lipoprotein AIV; CCK, cholecystokinin; CM, chylomicron; DIO, diet-inducd obesity; GLP-1, glucagon-like peptide-1; LCFA, long-chain fatty acids; LPL, lipoprotein lipase; OEA, oleoylethanolamide; SNP, single nucleotide polymorphism; SR-B2, scavenger receptor B2; SSO, sulfosuccidimidyl oleate ester; TG, triglycerides.

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contains a hydrophobic pocket that binds negatively charged saturated and unsaturated long-chain fatty acids (LCFA; number of carbons ≥16) with an affinity in the nanomolar range [15]. By creating an electrostatic interaction with the carboxyl-group of LCFA, the positively charged Lys^{164} is required both for LCFA binding to CD36/SR-B2 and Ca^{2+} efflux from the endoplasmic reticulum [16], a crucial step in the CD36/SR-B2 signaling cascade. Interestingly, the sulfo-N-succinimidyl oleate ester (SSO), a pharmacological drug currently used to study CD36/SR-B2 response to fatty acid, irreversibly binds Lys^{164} [16]. Therefore, SSO is a versatile tool that can be used as agonist (short-term experiment mimicking LCFA action on CD36/SR-B2) or antagonist (long-term experiment preventing LCFA binding to CD36/SR-B2) to study LCFA binding to CD36/SR-B2. Whether CD36/SR-B2 binding affinity for LCFA differs in function of their saturation level, is not yet known. Nevertheless, a greater CD36/SR-B2 signaling response was found with unsaturated than with saturated LCFA [16]. Moreover, binding specificity for fatty acids appears to be highly selective since medium and short chains fatty acids are not ligands for CD36/SR-B2. Interestingly, the cytosolic Tyr^{463} and Cys^{464} located in the C-terminal tail of CD36/SR-B2 are able to interact with members of the Src-protein tyrosine kinases (Src-PTK) family, known to be involved in the cell signaling [17]. In brief, CD36/SR-B2 displays all the features required to transfer an exogenous LCFA signal into target cells.

CD36/SR-B2 is a cell surface receptor highly conserved throughout the animal kingdom since it was found from the sponge [18] to human [19] suggesting an involvement in basic functions. This ancestral protein, which belongs to the scavenger receptor family and now also termed SR-B2 [20], was first identified in various hematopoietic cells and tissues characterized by sustained lipid metabolism in mammals. As a result of its, broad binding specificity, CD36/SR-B2 participates in multiple biological processes. For instance, CD36/SR-B2 is known to modify the platelet aggregation by binding to thrombospondin and collagen, facilitate the phagocytosis of apoptotic cells by macrophages, increase the cyto-adhesion of erythrocytes infected with *Plasmodium falciparum,* participate in the uptake of LCFA by cardiomyocytes and adipocytes and in that of oxidized-LDL by macrophages (for a review, see Ref. [8]). An additional emerging function for CD36/SR-B2 is a role as lipid sensor [9,21]. Indeed, CD36/SR-B2 identification in cells directly in contact with the external environment allows the binding of exogenous lipid ligands including LCFA in oral cavity [3] and in olfactory mucosa [22] or microbial diglycerides in the intestinal lumen [23] suggesting its implication both in sensory detection of dietary lipids and in innate immunity in the context of TLR signaling pathways [24].

A set of post-translational modifications may rapidly modulate CD36/SR-B2 functions [9]. Indeed, the N- and C-cytosolic tails contain Cys residues of which acylation, especially palmitoylation, contributes to the recruitment of CD36/SR-B2 in the lipid rafts, known to act as signaling platforms promoting transient protein associations. Because palmitoylation is reversible, Cys acylation/deacylation is likely involved in a rapid regulation of CD36/SR-B2-mediated functions [25]. Moreover, poly-ubiquitination of Lys found in the C-terminal tail facilitates the sorting of CD36/SR-B2 to the plasma membrane and its subsequent degradation by the proteasome pathway [26,27]. Conversely, mono-ubiquitination by the E3 ubiquitin ligase Parkin stabilizes CD36/SR-B2 in the membrane [28]. Interestingly, insulin and LFCA seem to play a significant role in the CD36/SR-B2 trafficking to and from the membrane by promoting membrane localization and desorption, respectively [26,29]. For example, a rapid down-regulation of CD36/SR-B2 protein levels occurs both in circumvallate gustatory papillae and intestinal mucosa in presence of LCFA, limiting the CD36/SR-B2 sensing to early phase of ingestion and absorption [27,30]. Finally, presence of consensus phosphorylation sites in the CD36/SR-B2 ecto-domain provides an additive functional control. For example, dephosphorylation of CD36/SR-B2 by the intestinal alkaline phosphatase (IAP) optimizes LCFA transport in mouse-isolated enterocytes [31].

Paradoxically, in spite of a large spectrum of functions, CD36/SR-B2 usually displays a specific role in a given cell type, for instance cell adhesion in platelets, fatty acids uptake in myocytes or lipid sensing in taste bud cells and enterocytes. Variety of binding sites and post-translational modifications of CD36/SR-B2 combined with a specific cellular context (genotype and microenvironment) might explain this functional cell specificity.

3. Oral CD36/SR-B2 and appetite control

Regulation of food intake is a complex phenomenon, which results from integration by the brain of early orosensory (cognitive) cues and delayed post-prandial (metabolic) signals (Fig. 1). During the prandial period, the sense of taste plays a major role in the decision to consume or avoid foods. This selective eating behavior takes place through two successive steps: the oral detection of tastants by gustatory papillae and central perception of taste signals by the cortico-mesolimbic system (termed “emotional brain” in Fig. 1-1) [32]. Oral chemoreception is carried out by specific sensors located at the apical side of taste buds (Fig. 1-1). Five basic tastes are classically depicted: bitter, salty, sour, sweet and umami (savory). Nevertheless, over the last decade the existence of a gustatory determinant to explain the orosensory detection of dietary lipids was supported by a growing number of studies (for recent reviews, see Refs. [33,34]. Although, dietary fat is mostly composed of triglycerides (TG), LCFA are more efficiently detected than TG in the oral cavity during behavioral tests minimizing the textural, olfactory and post-ingestive cues in the mouse [35], rat [36] and human [37]. Role of CD36/SR-B2 as a gustatory lipid sensor is supported by the tight relationships between the efficiency of oral LCFA detection and CD36/SR-B2 expression level. Indeed, CD36/SR-B2 gene invalidation in the mouse [3] or targeted siRNA gene silencing of lingual CD36/SR-B2 in the rat [38] render animals unable to properly detect LCFA during behavioral tests. Similarly, the common single nucleotide polymorphism rs1761667 in the CD36/SR-B2 gene, known to be associated with a reduction of CD36/SR-B2 expression [39], attenuates the orosensory sensitivity for LCFA in humans [12]. Interestingly, an association between oral fat perception and food choice was found both in rodents and humans. In rats subjected to a brief-access licking test (10 s), known to minimize post-ingestive influences, the sensitivity of oral fat detection appears to be inversely correlated to preferential consumption of fatty foods (two-choice diets) [40], animals poorly sensitive consuming preferentially lipid-rich foods, probably to reach the expected hedonic gratification. In humans, low fat tasters consume more carbohydrates and lipids than high fat tasters [41]. Moreover, subjects identified as low-tasters, by reason of a deleterious mutation in the CD36/SR-B2 gene (rs 1761667 polymorphism), display more liking of added fats and oils [42], consistent with these subjects needed higher fat levels for gratification.

Oral CD36/SR-B2 is also implicated in the digestive anticipation. In a fasting mouse, a brief oral fat stimulation triggers a rapid rise in digestive secretions (*i.e.* pancreato-biliary juice) in a CD36/SR-B2-dependent manner [3]. This cephalic reflex loop prepares the small intestine to lipid arrival facilitating subsequent digestion and absorption (Fig. 1-2). This tongue-gut axis is also responsible for the prandial activation of intestinal endocannabinoid pathway. In rats subjected to a sham feeding protocol, oral exposure to an unsaturated LCFA triggers in the proximal intestine an accumulation of