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CD36 mRNA in the Gastrointestinal Tract Is Differentially Regulated by Dietary Fat Intake in Obesity-Prone and Obesity-Resistant Rats

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Abstract

Background—The gastrointestinal tract (GI) is important for detection and transport of consumed nutrients and has been implicated in susceptibility to diet-induced obesity in various rat strains.

Aims—The current studies investigated the regulation of CD36, a receptor which facilitates uptake of long-chain fatty acids, in the GI tract of obesity-prone Osborne–Mendel and obesity-resistant S5B rats fed a high-fat diet.

Methods—Osborne–Mendel and S5B rats consumed a high-fat diet (HFD, 55 % kcal from fat) or a low-fat diet (10 % kcal from fat) for either 3 or 14 days. CD36 messenger RNA (mRNA) levels were measured from circumvallate papillae of the tongue and from duodenal enterocytes.

Results—In Osborne–Mendel rats, consumption of HFD for 3 and 14 days led to an increase in CD36 mRNA on circumvallate papillae and in duodenal enterocytes. CD36 mRNA levels were positively correlated with body weight gain and kilocalories consumed at 3 days. In S5B rats, consumption of HFD for 3 days did not alter CD36 mRNA levels on circumvallate papillae or in the duodenum. Duodenal CD36 levels were elevated in S5B rats following 14 days of HFD consumption. CD36 mRNA levels in the duodenum were positively correlated with body weight gain and kilocalories consumed at 14 days.

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Conflict of interest None.

Conclusions—These data support the differential sensing of nutrients by two regions of the GI tract of obesity-prone and obesity-resistant rats consuming HFD and suggest a role for CD36 in the strain-specific susceptibility to obesity.

Keywords

Obesity-prone; Obesity-resistant; CD36; Taste bud; Duodenum; High-fat diet

Introduction

The role of the gastrointestinal tract (GI) in detection and absorption of nutrients is an increasingly important component for understanding the increase in the prevalence of obesity. There are numerous hormones and receptor systems produced in the GI tract which are affected by the intake of macronutrients. The release of hormones and the activation of these receptors alter the physiology of the GI tract (i.e., motility), are important modulators of nutrient detection and absorption, alter pancreatic function, and produce effects on the continued ingestion of nutrients (i.e., hunger, satiety). The combined action of cues in the mouth (taste) and gut controls what an individual consumes and may alter an individual's susceptibility to developing obesity. Investigation of the mechanisms by which the GI tract detects and responds to specific nutrients enhances our knowledge of this region and its role in obesity.

Evidence from animal models of diet-induced obesity suggests that there are differences in the response of the GI tract to the detection of dietary fat in obesity-prone and obesity-resistant strains. Obesity-prone Osborne–Mendel (OM) and obesity-resistant S5B/Pl (S5B) rats are animal models used to assess the mechanisms underlying food intake and obesity [1–8]. OM rats are susceptible to diet-induced obesity and gain more weight and adiposity when eating a high-fat diet (HFD) than S5B rats, which are resistant to diet-induced obesity.

Several aspects of the GI tract have been investigated in obesity-prone (OM) and obesity-resistant (S5B) rats. Using these animal models, Greenberg et al. [2] reported that duodenal infusions of Intralipid and sodium linoleate into sham-fed animals suppressed food intake more completely and for a longer period of time in S5B rats compared with OM rats, suggesting that the obesity-resistant S5B rats were more sensitive to the presence of dietary fat in the duodenum than the OM rats. A recent study examined the role of glucagon-like peptide-1 (GLP-1), a circulating hormone released from the GI tract in response to a meal, in OM and S5B rats. Peripheral administration of a GLP-1 agonist (Exendin 4) led to greater suppression of HFD intake in obesity-resistant S5B rats compared with obesity-prone OM rats, indicating increased sensitivity to Exendin 4 in S5B rats [8]. The response to fatty acids on taste receptors from the tongues of OM and S5B rats also differ and has been investigated using patch clamp techniques [9]. A dose analysis of the effects of linoleic acid on the potassium current of delayed rectifying potassium channels demonstrated greater suppression in OM rats, indicating suppression of the channel's ability to repolarize following an action potential, suggesting prolonged depolarization of the taste receptors. The data from these studies indicate that the GI tract plays a role in the response to fat and fatty

acids in these obesity-prone and obesity-resistant strains and supports a role for the GI tract in the susceptibility to obesity in these animals.

In the GI tract, there are various cellular proteins capable of detecting and transporting fatty acids across the cell membrane. One mechanism by which fatty acids are detected in the GI tract is the long-chain fatty acid receptor, CD36. CD36 is an integral membrane glycoprotein which has been identified in numerous tissues including taste buds, small intestine, muscle, heart, brain, liver, and adipose tissue [6, 10, 11]. A major function of CD36 is to facilitate uptake of long-chain fatty acids. In addition, CD36 is a receptor for several ligands, including thrombospondin 1, collagen, and Gram-negative bacteria [12, 13]. CD36 knockout mice exhibit decreased preference for fatty acids and HFD, decreased cephalic response to fatty acids, and decreased food intake, body weight, and body adiposity, and are protected from weight gain when eating a HFD [14–20]. In the mouth, CD36 has been proposed as the taste receptor for dietary fat and/or fatty acids and is primarily located on the circumvallate papillae of the tongue. As an extension of the mouth, the small intestine expresses many of the same receptors as found on the tongue [21–24]. CD36 is highly expressed in the small intestine and presents a proximal to distal gradient that would be consistent with its function in lipid transport. High-fat diets rich in long-chain fatty acids increase CD36 mRNA levels in the duodenum [25].

Quantitative differences in CD36 expression on the circumvallate papillae and duodenum may be fundamental for sensing of fat in the GI tract, and the current experiments tested the hypothesis that these differences are related to the susceptibility to diet-induced obesity in obesity-prone OM and obesity-resistant S5B rats. Basal expression of CD36 mRNA was evaluated in the circumvallate papillae of the tongue and the duodenal enterocytes of obesity-prone OM and obesity-resistant S5B rats. In experiment 2, the effect of HFD consumption on CD36 mRNA levels on the circumvallate papillae and in the duodenal enterocytes was evaluated in OM and S5B rats. Due to temporal changes in the adaptation to a HFD, two time points (3 versus 14 days) were assessed in this experiment.

Materials and Methods

Animals

The male obesity-prone Osborne–Mendel (OM) and obesity-resistant S5B/Pl (S5B) rats (8–9 weeks old) used in these studies were bred in the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-approved Pennington Biomedical Research Center vivarium. Rats were individually housed on a 12/12 h light/dark cycle (lights on at 0700) with food and water available ad libitum. All procedures were approved by the Pennington Biomedical Research Center Institutional Animal Care and Use Committee.

Experiment 1: Basal Levels of CD36 Receptor mRNA on the Circumvallate Papillae of the Tongue and in the Duodenum—OM ($n = 5$) and S5B ($n = 5$) rats were given ad libitum access to a standard laboratory chow prior to sacrifice. Average daily food intake was assessed over 3 days prior to sacrifice. For the circumvallate papillae of the tongue, the tongue was removed and cleaned, and the epithelial layer of the tongue

encompassing the circumvallate papillae was excised using a sterile scalpel blade. For the duodenum, a 2.5-cm section of the duodenum was removed and cleaned, and the duodenal enterocytes were excised by gentle scraping with a clean metal spatula. Samples were immediately frozen on dry ice and stored at −80 °C until further processing. Body weight was measured immediately prior to sacrifice.

Experiment 2: CD36 Receptor mRNA on the Circumvallate Papillae and in the Duodenum Following 3 or 14 Days Consumption of High-Fat or Low-Fat Diet— OM and S5B rats were given ad libitum access to one of two custom semisynthetic, pelleted rodent diets as previously described [26–28]. The high-fat diet (HFD) and low-fat diet (LFD) differed in their quantity of dietary fat (HFD: 55 % kilocalories from fat; LFD: 10 % kilocalories from fat). Rats consumed either the HFD or the LFD for 3 days (early response; n = 5/group) or 14 days (adaptive response; n = 10/group). Average daily food intake over 3 days was assessed for the 3-day group, and average daily food intake over the last 4 days of diet access in the 14-day group. Body weight was measured prior to dietary manipulation and at the time of sacrifice. Upon sacrifice, the epithelial layer of the tongue containing the circumvallate papillae and the duodenal enterocytes were collected as described in experiment 1. Excised tissue was immediately frozen on dry ice and stored at −80 °C until further processing.

Real-Time Polymerase Chain Reaction (PCR)

RNA was isolated from the circumvallate papillae and the duodenal enterocytes using Tri-Reagent (Molecular Research Ctr, Cincinnati, OH USA) and RNeasy Minikit procedures (Qiagen, Valencia, CA USA) and based on previous experiments [27, 29]. Briefly, enterocytes were homogenized in Tri-Reagent using a motorized tissue homogenizer, chloroform was added to the lysate, and the mixture was centrifuged (12,000×g) in phase lock tubes to separate RNA. Ethanol (70 %) was added to the upper aqueous phase, applied to column, and filtered by centrifugation (8,000×g). Following multiple washes, the samples were subjected to an elution step using RNAase-free water. Reverse transcription (RT) was conducted using the High-Capacity cDNA Reverse Transcriptase Kit (Applied Biosystems, Foster City, CA, USA). For RT, 2.0 μg RNA from each sample was added to random primers (10×), dNTP (25×), MultiScribe Reverse Transcriptase (50U/μl), and RT buffer (10×) and incubated in a thermal cycler (PTC-100; MJ Research, Inc., Watertown, MA, USA) for 10 min at 27 °C, then for 120 min at 37 °C. Primers were designed using Primer Express (Applied Biosystems, Foster City, CA, USA). The following primers were used for CD36: 5′-GAGGTCCTTACACATACAGAGTTCGTT-3′ and 5′-ACAGACAGTGAAGGCTCAAAGATG-3′ and cyclophilin: 5′-CCCACCGTGTTCGACAT-3′ and 5′-CTGTCTTTGGAACTTTGTCTGC-3′. For real-time PCR, SYBR Green 2× Master Mix (Applied Biosystems), forward and reverse primers (10 μM), and RT product (10 ng) were added to 384-well plates. The cycling parameters consisted of an initial 2 min incubation at 50 °C, followed by 10 min at 95 °C, then 15 s at 95 °C, and a 1 min annealing/extension step at 60 °C (40 cycles). The levels of CD36 receptor mRNA were based on a standard curve and normalized to cyclophilin levels and are shown in arbitrary units (a.u.) (ABI Prism 7900 Sequence Detection System, Applied Biosystems).

Statistical Analyses

In experiment 1, two-tailed, between-subjects *t* tests were used to compare average daily food intake and CD36 receptor mRNA levels between OM and S5B rats fed a standard chow diet. In experiment 2, a between-subjects analysis of variance (ANOVA) (strain × diet) was conducted to assess differences in average daily food intake (kcal), body weight change, CD36 mRNA levels in the circumvallate papillae, and duodenal CD36 receptor mRNA levels for each time point (3 and 14 days). Bonferroni post hoc tests were used to assess differences between individual groups. Correlation analyses were performed to determine the relationship between CD36 mRNA levels in the duodenum and tongue with body weight change and food intake. A significance level of $p < .05$ was used for all tests.

Results

Experiment 1: Basal Levels of CD36 Receptor mRNA on the Circumvallate Papillae of the Tongue and in the Duodenum

Obesity-prone OM rats consuming a standard chow diet consumed more chow than the obesity-resistant S5B rats ($t = 2.41$, $p < .05$, data not shown). Basal CD36 mRNA levels on the circumvallate papillae did not differ between OM and S5B rats (Fig. 1a). Basal CD36 receptor mRNA levels in the duodenal enterocytes were elevated in S5B rats compared with OM rats fed a chow diet ($t = 2.27$, $p < .05$; Fig. 1b).

Experiment 2: CD36 Receptor mRNA on the Circumvallate Papillae and in the Duodenum Following 3 or 14 Days Consumption of High-Fat or Low-Fat Diet

OM and S5B rats consumed either HFD or LFD for 3 or 14 days. A significant diet × strain interaction was detected for body weight gain following 3 days ($F = 27.66$, $p < .05$) and following 14 days ($F = 20.28$, $p < .05$). As expected, consumption of the HFD increased body weight in S5B and OM rats, compared with rats consuming the LFD. Additionally, OM rats consuming the HFD gained more weight than S5B rats eating the HFD (Fig. 2a). A significant diet × strain interaction was detected for average daily food intake of HFD and LFD following 3 days ($F = 24.45$, $p < .05$) and 14 days ($F = 17.36$, $p < .05$). Overall, the rats consumed more HFD than LFD, and OM rats consumed more HFD than the S5B rats (Fig. 2b).

CD36 mRNA levels on the circumvallate papillae and in the duodenum were assessed following 3 or 14 days of HFD or LFD consumption. CD36 mRNA levels on the circumvallate papillae were significantly altered by diet following 3 days of HFD consumption ($F = 5.08$, $p < .05$) and 14 days of HFD consumption ($F = 4.41$, $p < .05$). In OM rats, consumption of the HFD for 3 days increased expression of CD36 mRNA, compared with OM rats fed the LFD or S5B rats fed the HFD or LFD. Consumption of the HFD for 14 days increased CD36 mRNA levels on the circumvallate papillae of OM rats. Following 3 days of LFD intake, S5B rats exhibited a short-lived increase in CD36 mRNA on the circumvallate papillae compared with OM rats (Fig. 3a).

In the duodenum, a significant main effect of diet on CD36 mRNA levels was detected following 3 days of HFD ($F = 8.44$, $p < .05$) and following 14 days of HFD consumption (*F*

= 20.51, $p < .05$). Consumption of HFD for 3 days increased duodenal expression of CD36 mRNA in OM rats, but not S5B rats. Consumption of HFD for 14 days increased duodenal CD36 mRNA expression in both S5B and OM rats. S5B rats consuming the LFD expressed higher levels of CD36 mRNA than OM rats consuming the LFD (Fig. 3b).

A correlational analysis was conducted to determine the relationship between CD36 mRNA expression in the duodenum and on the circumvallate papillae with body weight gain and kilocalories consumed in S5B and OM rats (Table 1). Following 3 days of HFD or LFD intake in OM rats, CD36 mRNA levels in the duodenum were positivity correlated with body weight change ($r = .71$, $p < .05$) and kilocalories consumed ($r = .90$, $p < .05$). In addition, CD36 mRNA levels on the circumvallate papillae were positively correlated with body weight gain ($r = .80$, $p < .05$) and kilocalories consumed ($r = .75$, $p < .05$). Following 14 days consumption of the HFD or LFD, CD36 mRNA in the GI tract was not correlated with either body weight gain or kilocalories consumed in OM rats. In the S5B rats, CD36 mRNA levels in the duodenum were positively correlated with body weight gain ($r = .67$, $p < .05$) and kilocalories consumed ($r = .46$, $p < .05$) following 14 days access to HFD or LFD.

Discussion

There are a number of molecular candidates for the detection and transport of fat/fatty acids in the GI tract, and the mechanisms by which fatty acids are detected in the GI tract are of great interest to understanding obesity. One potential mechanism is the long-chain fatty acid receptor, CD36, which is expressed on the tongue and in the small intestine. The purpose of the current experiments was to examine both strain- and diet-induced differences in the expression of CD36 in the GI tract of obesity-prone and obesity-resistant rats. Two time points (early response and adaptive response) were selected for analyses due to strain differences in the overconsumption of HFD at these time points. Our previous studies have shown a significant increase in HFD intake in S5B for 3 days following introduction to the HFD and for 14 days in the OM rats. It was hypothesized that the susceptibility to obesity would be related to the expression of CD36 on the tongue and in the duodenum.

Previous reports have suggested that the obesity-prone OM and obesity-resistant S5B rats differ neurochemically, behaviorally, and physiologically in their response to consumption of dietary fat [1, 3, 4, 8, 29–39]. Several studies have impacted the focus of the current experiments and led to the investigation of differences in the GI tract of these rats. Greenberg et al. [2] reported that duodenal infusions of Intralipid and sodium linoleate produced greater suppression of food intake in obesity-resistant S5B rats than in obesity-prone OM rats. These data suggested that there were strain differences in the detection of fatty acids in the gut. Gilbertson et al. [9, 40] reported strain differences in the response to the application of fatty acids on the taste receptors of OM and S5B rats using patch clamp techniques. Their data suggested that, at the level of the tongue, S5B rats were more sensitive to the effects of fatty acids than OM rats and that OM rats had fewer fatty acid-sensitive delayed rectifying potassium channels expressed on the tongue than S5B rats. Recently, we provided evidence that the response to the satiety hormone, GLP-1, was decreased in OM rats, again suggesting that S5B rats were more responsive to signals from

the GI tract. This increased sensitivity may ultimately decrease their susceptibility to obesity [8].

On the circumvallate papillae, CD36 has been proposed as a fat taste receptor [17, 19, 20, 41–49]. These reports have provided compelling evidence for the detection of dietary fat by CD36 on the tongue. As the first step in the GI tract, CD36 on the tongue has the potential to affect both positive and negative feedback responses to dietary fat, thereby increasing or decreasing the intake of dietary fat, in addition to altering the sensitivity to the “taste” of dietary fat. The relative differences in expression of CD36 on the tongue in response to short-term exposure to a HFD versus the adaptation to the consumption of HFD may provide insight into the ways by which these two rat strains alter their intake patterns of HFD.

In the current experiments, the data indicate that, though there are no basal differences in the expression of CD36 mRNA on the circumvallate papillae of obesity-prone OM and obesity-resistant S5B rats, the consumption of the HFD produced significant strain effects on CD36 expression. CD36 mRNA levels on the circumvallate papillae were increased by consumption of the HFD in the OM rats only. OM rats consumed significantly more HFD than S5B rats at both time points, suggesting that this hyperphagia was associated with an increase in CD36. In the obesity-prone OM rats, CD36 mRNA levels were positively correlated with body weight gain and kilocalories consumed following 3 days access to HFD or LFD, but not at the 14-day time point. These data suggest that CD36 mRNA expression on the tongue plays a role in the early response to HFD intake in the obesity-prone rats, likely due to an increase in the rewarding aspects of the HFD. This relationship appears to be short-lived and is strain-specific.

The data reported in experiment 2 differ from a previous report which suggested that HFD intake led to a decrease in the expression of CD36 mRNA on the circumvallate papillae of rats [49]. These differences are likely due to a variety of factors, most importantly the use of different rat strains. In the current experiment, a possible explanation for the increase in CD36 mRNA levels found in the OM rats consuming the HFD is that these receptors are part of a positive feedback response to the HFD, which is specific to this strain and may signal an increase in the rewarding effects of HFD. Additionally, though CD36 mRNA levels were increased in this study, CD36 protein levels were not evaluated in the current studies and may not be increased to the same extent as the mRNA levels in the OM rats. Further studies are needed to explore this possibility. A study conducted by Gilbertson et al. [40] reported that, though the expression of delayed rectifying potassium receptors was elevated in OM rats, these rats had fewer fatty acid-sensitive receptors compared with S5B rats. Therefore, it is possible that gene expression and protein levels of CD36 do not correlate. More studies are needed to determine the role of CD36 on the tongue of OM and S5B rats.

Duodenal expression of CD36 was also investigated as the duodenum plays a role in fat detection and absorption in the GI tract. Interestingly, S5B rats expressed higher basal levels of duodenal CD36 mRNA than OM rats. This potentially reflects an increased sensitivity to the presence of dietary fat/fatty acids in S5B rats, as suggested by Greenberg et al. [2].

Though CD36 is involved in fat absorption, which may lead to weight gain, duodenal levels of CD36 in S5B rats likely play a role as a molecular sensor linking fat ingestion with satiety to initiate a release in satiety hormones [50–52]. In experiment 2, duodenal CD36 expression was increased by 3 days access to HFD in the OM rats, but not in the S5B rats. This demonstrates the rapid response to the HFD in the OM rats and the apparent resistance to the HFD in the S5B rats, with respect to changes in CD36 levels. After 14 days of HFD intake, duodenal CD36 mRNA levels were increased in the OM and S5B rats. Consumption of a HFD rich in long-chain fatty acids has been shown to increase CD36 mRNA levels in the duodenum [25]; therefore, the increase in duodenal CD36 mRNA levels following 14 days of consumption of HFD as the sole source of food was expected. More studies are needed to fully understand the role of CD36 in the duodenum of OM and S5B rats. Correlational analyses suggest that CD36 mRNA levels are positively correlated with body weight gain and kilocalories consumed following 3 days access to HFD or LFD in OM rats, but not S5B rats. These relationships are not detected once the OM rats have become adapted to the HFD or LFD; however, a positive relationship is detected between body weight gain and kilocalories consumed and CD36 mRNA expression in S5B rats following 14 days.

There are various cellular proteins which are capable of detecting and transporting fatty acids across the cell membrane. The current experiments examined the mRNA expression of CD36, which has been linked to detection and transport of long-chain fatty acids in the brain, muscle, tongue, and intestines. Overall, these experiments suggest that differential expression of CD36 following consumption of HFD in obesity-prone OM and obesity-resistant S5B rats contributes to the differential sensing of nutrients by two regions of the GI tract in these rat strains. There are apparent alterations in the topographical expression of CD36 suggesting a difference in the response to HFD on the tongue and in the duodenum. The increase in CD36 expression on the tongues of the OM rats suggests an increase in positive feedback or the rewarding aspects of the HFD through taste-sensitive pathways and supports previous reports with CD36 KO mice on fat preference and intake [14–20]. Alterations in the duodenum are representative of the postingestive effects of the HFD in our study. Prolonged consumption of the HFD increased the expression of CD36 in the S5B and OM rats, which may influence the detection of fatty acids in these strains. Previous reports have suggested that S5B rats are more sensitive to the satiating effects of a HFD, and therefore the increase in CD36 expression in S5B rats may reflect this increase in sensitivity and increase in satiety [2, 8]. However, the OM rats have an apparent dysregulation of the satiety signals released by the GI tract [2, 8]. Therefore, the increased expression of duodenal CD36 may not be able to adequately detect and signal the duodenum to produce and release satiety hormones. Overall, the increased potential for diet-induced obesity in OM rats may be influenced by the ability of CD36 to adequately detect the presence of the HFD at various topographical levels in the GI tract.

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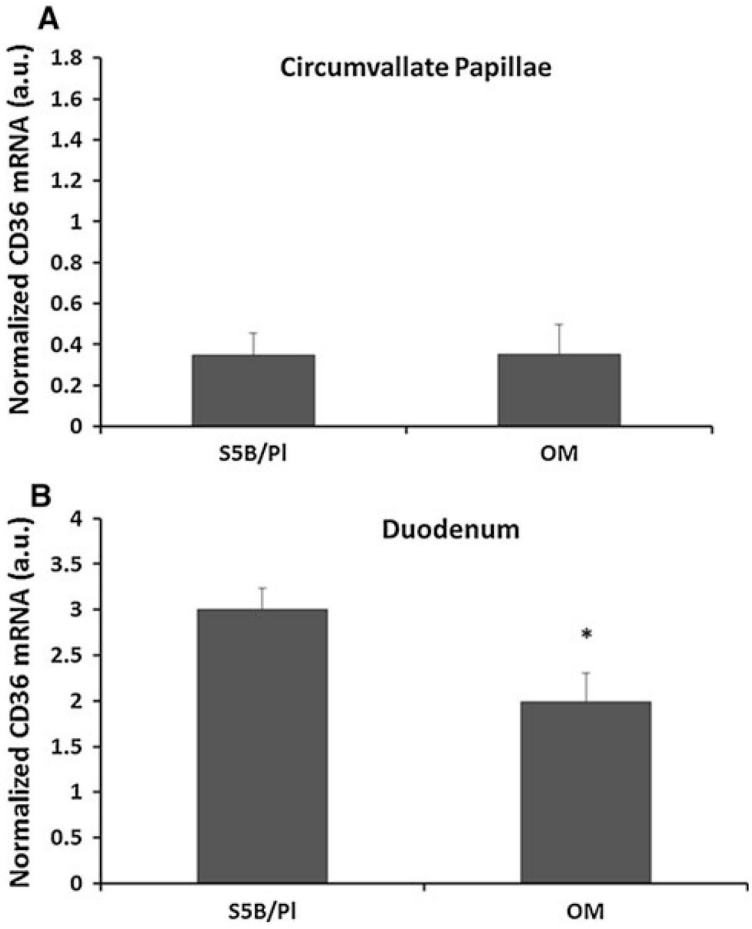

Fig. 1.

Basal levels of CD36 mRNA expression in two regions of the GI tract were measured in OM and S5B rats fed a standard chow diet. **a** CD36 mRNA levels on the circumvallate papillae of the tongue did not differ between OM and S5B rats. **b** Duodenal CD36 mRNA levels were higher in the obesity-resistant S5B rats, compared with the OM rats (n = 4–5/group). Data shown as mean ± standard error of the mean (SEM). *p <.05; arbitrary units (a.u.)

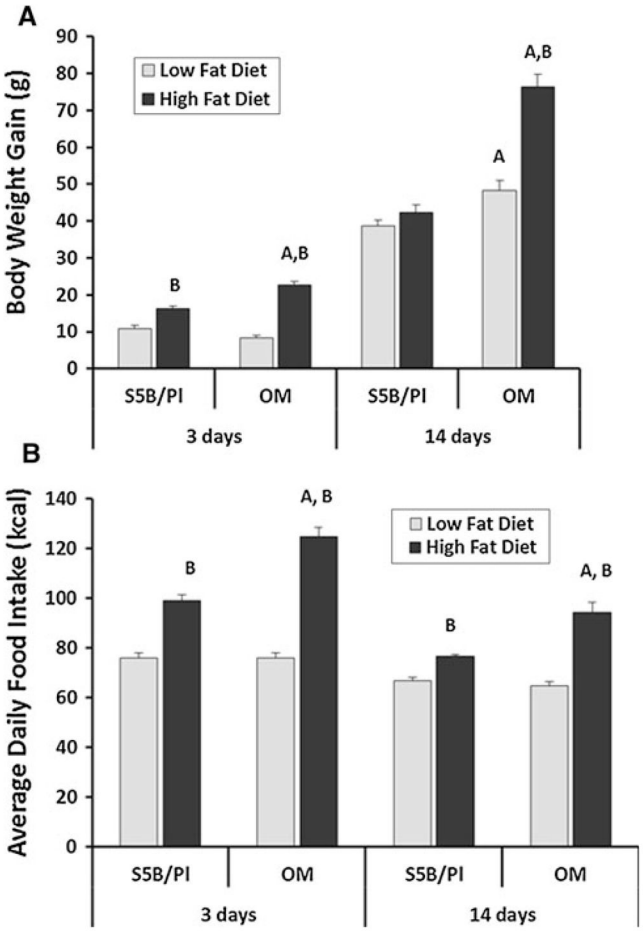

Fig. 2.

OM and S5B rats were fed the HFD or LFD diet for 3 or 14 days. **a** At 3 days, the HFD increased weight gain in OM and S5B rats. Following 14 days of HFD intake, body weight increased in OM rats only. **b** OM and S5B rats consuming the HFD consumed more kilocalories per day than rats consuming the LFD (n = 5/group for 3 days; n = 10/group for 14 days). Data shown as mean ± SEM. *A* strain difference; *B* diet difference within strain; p <.05

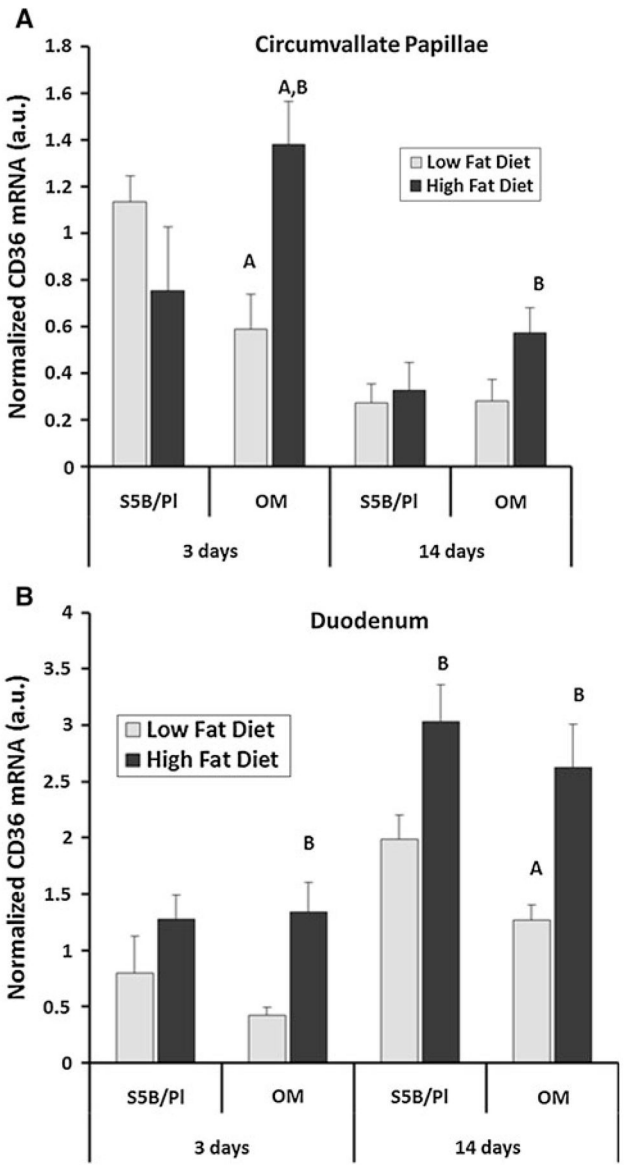

Fig. 3.

CD36 mRNA expression was assessed in OM and S5B rats fed the HFD or LFD for 3 or 14 days in two regions of the GI tract. **a** On the circumvallate papillae of the tongue, CD36 mRNA levels were selectively increased by HFD consumption for 3 days and for 14 days in the OM rats. CD36 mRNA levels on the circumvallate papillae were not altered by HFD intake in the S5B rats. **b** Duodenal CD36 mRNA levels were increased by consumption of the HFD for 3 days in the OM rats and following 14 days consumption in the OM and S5B rats (n = 4–5/group for 3 days; n = 8–9/group for 14 days). Data shown as mean ± SEM. *A* strain difference; *B* diet difference within strain; $p < .05$; arbitrary units (a.u.)

Table 1

Correlational analyses conducted in OM and S5B rats consuming the HFD or LFD for 3 or 14 days

CD36 mRNA	Body weight gain	Kilocalories consumed	CD36 mRNA duodenum	CD36 mRNA tongue
Osborne–Mendel—3 days				
Duodenum	.712*	.904*	1	.530
Tongue	.804*	.753*	.530	1
Osborne–Mendel—14 days				
Duodenum	.471	.392	1	.491
Tongue	.405	.500	.491	1
S5B/Pl—3 days				
Duodenum	.325	.377	−.363	1
Tongue	−.552	−.262	1	−.363
S5B/Pl—14 days				
Duodenum	.668*	.463*	1	−.299
Tongue	−.181	.004	−.299	1

* $p < .05$