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Early postprandial low-grade inflammation after high-fat meal in healthy rats: possible involvement of visceral adipose tissue☆

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Abstract

In the postprandial period, low-grade inflammation may contribute to vascular endothelial dysfunction, a hallmark of atherogenesis. Little is known about the involvement of the adipose tissue in the initiation of the postprandial inflammatory response such as obtained after a high-saturated fat meal (HFM). In the present study, we first studied the time course of appearance of systemic inflammation after a HFM in healthy rats, and then we investigated whether a HFM activates the inflammatory signaling in the visceral adipose tissue, with a focus on the key component, nuclear factor-κB (NF-κB). Two hours after the HFM, plasma IL-6 and PAI-1, but not plasma C-reactive protein and soluble intracellular adhesion molecule-1, showed a marked, transient increase. These changes were specific to the postprandial state as not observed after a control water load. Neutrophils count and activation markers CD11B and CD62L, assessed by flow cytometry, also rose significantly 2 h after the HFM, while remaining steady after the control. At the same time, the HFM decreased significantly B-cell count and expression of the activation marker CD62L. Interestingly, at the same early time after the HFM, in the visceral adipose tissue, there was a 2.2-fold increase in the activation of NF-κB (p65) in nuclear extract and an increase in IL-6 mRNA. As far as we know, this is the first study evidencing an acute, postprandial activation of inflammation in visceral adipose tissue. This early activation of NF-κB pathway after a HFM may play a triggering role in the initiation of the complex postprandial proatherogenic phenotype.

Keywords: Low-grade inflammation; Adipose tissue; Postprandial state; Animal model; Endothelial dysfunction

1. Introduction

In the last decade, low-grade inflammation has been recognized as a common feature in the onset and the progression of obesity, type II diabetes mellitus and cardiovascular diseases [1,2]. In close association with vascular endothelial dysfunction, the initiation of systemic low-grade inflammation is probably a major contributor to atherogenesis [3,4]. Furthermore, low-grade inflammation is also a component of the complex proatherogenic phenotype occurring during the postprandial state, as shown after a single high-saturated fat meal (HFM) in healthy humans [5,6].

The postprandial inflammatory response has been identified principally in plasma and leukocytes [7]. A HFM has been well documented to increase the concentrations of circulating proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and the soluble adhesion molecules such as soluble intracellular adhesion molecule-1 (sICAM-1) in plasma [8]. Likewise, more recently, it has been reported that postprandial hypertriglyceridemia increases circulating leukocytes [9,10] and results in the activation of the proinflammatory nuclear factor-κB (NF-κB) in monocytes [11,12]. However, our current knowledge of the postprandial inflammatory response remains fragmentary and incomplete [13].

One important gap in our knowledge concerns the potential role of the adipose tissue in the postprandial low-grade inflammation. This has little been investigated, although the adipose tissue is known as an important source of proinflammatory cytokines [14,15]. In particular, the visceral adipose tissue, which is believed to account for most of the fat deposit-related inflammation that may favor the initiation or accelerate atherosclerosis [16,17], is expected to be very sensitive to the nutrient flux [7,18]. However, because no animal model of postprandial pathophysiological dysregulations under healthy conditions has been used to date, our understanding of the potential role of the visceral adipose tissue in systemic postprandial

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inflammation only builds on *in vitro* approaches [19]. Recently, Suganami et al. [20] have demonstrated that saturated fatty acids could directly activate the Toll-like receptor-4 (TLR4)/NF-κB pathway, inducing proinflammatory changes in adipocytes. Therefore, a fatty acid-induced activation of NF-κB in adipose tissue may be involved in postprandial inflammation and atherogenesis, but direct evidences for a postprandial activation of inflammatory signaling in the adipose tissue under *in vivo* nutritional conditions are still lacking.

In the present study, using a rat model of postprandial dysfunction in which we previously evidenced the occurrence of postprandial vascular dysfunction after a HFM [21], we first sought to study the time course of appearance of systemic low-grade inflammation after a HFM. To rule out any role of the circadian variations or experimental-related effect on the inflammatory markers during the postprandial state, i.e., ascertain that the observation can be specifically attributed to the postprandial situation, we used a water load as a control. After this characterization of the postprandial inflammatory response in this animal model, we investigated the postprandial activation of the NF-κB pathway activation in visceral adipose tissue.

2. Materials and methods

2.1. Animals

Male Wistar-Kyoto rats (9 weeks old, Harlan, France) were housed four per cage in a temperature-regulated room (22±2°C) on a 12:12h light/dark cycle, with free access to tap water and standard rat chow. A total of 40 rats were used in two series of studies reported here.

The study protocol was approved by the Regional (Ile de France Sud) Animal Care and Ethics Committee, and all procedures were performed in accordance with the guidelines issued by the French National Animal Care Committee.

2.2. Study design

During 3 weeks before postprandial studies, 16 rats were accustomed to the experimental conditions. The HFM consisted in a 5-ml emulsion made of palm oil, sucrose, milk protein and 2.5 ml water. The fatty acid composition of the refined palm oil was 43–46% palmitate, 37–41% of oleate, 9–12% linoleate, 4–6% stearate and <2% other fatty acids. The energy nutrient content of the HFM was (% total energy, 25 kcal) 60% lipids, 20% carbohydrates and 20% protein. This lipid level, which slightly exaggerates the fat content of a real high-fat meal in humans (such as a fast-food meal), has been reported to ensure the substantial onset of a series of acute postprandial pathophysiological dysregulations in postprandial models [13]. Likewise, we chose a HFM that included carbohydrates and proteins so that the postprandial processing of dietary triglycerides would occur under the metabolic conditions of the postprandial state. A 2.5-ml water load was used as a control to assess whether circadian variations and experimental conditions due to handling, gavage and blood sampling may affect the postprandial parameters.

All tests began after a 12-h fast. An indwelling catheter, filled with heparinized 2% NaCl (50 U/ml), was inserted into a lateral tail vein to allow frequent blood sampling with minimal discomfort for the conscious animal. Venous blood was sampled before, 2, 4 and 6 h after the HFM (n=10) or the water load (n=6). Fresh whole blood was collected into heparinized prechilled tubes and was used immediately for determination of leukocyte activation markers. All other blood samples were drawn into sodium EDTA (2 mg/ml) prechilled tubes and were centrifuged for 5 min at 3500×g at 4°C. Plasma was stored at −80°C for further determinations (as described below).

In a last experiment, 24 rats were killed 2 or 6 h after the HFM (n=12) or the water load (n=12) and the liver and epididymal adipose tissue were rapidly sampled on ice for the determination of NF-κB activation, as described below, or frozen immediately in liquid nitrogen and stored at −80°C until gene expression analysis.

2.3. Biochemical analysis

Plasma triglyceride concentrations were determined using an enzymatic method (TG PAP150, Biomerieux). Plasma concentrations of IL-6, PAI-1, interleukin-1β (IL-1β) and monocyte chemoattractant protein-1 (MCP-1) were determined simultaneously by multiplex immunoassay (Linco) on a Luminex-200 analyzer (Biorad). Plasma concentrations of sICAM-1 and C-reactive protein (CRP) were quantified using commercial ELISA kits (R&D Systems and Helica Biosystem, respectively).

2.4. NF-κB p65 activation assay

After the homogenization of adipose tissue and liver in a dounce homogenizer on ice, nuclear fractions were isolated using a nuclear extract kit (Active Motif). A 10-μg protein sample of nuclear extract was used to assess NF-κB activation with a NF-κB p65-DNA binding assay kit (Active Motif) according to the manufacturer's recommendations. The specificity of the detection of NF-κB activation was checked using a consensus sequence provided by the manufacturer.

2.5. Quantitative real-time RT-PCR

Total RNA was extracted from adipose tissue using Trizol reagent (Invitrogen). Four hundred nanograms of total RNA was converted into cDNA using the High Capacity cDNA Reverse-Transcription Kit (Applied Biosystems) on a PTC-200 thermocycler (MJ Research). Real-time PCR amplifications were performed with a Prism7300 sequence detection system using SYBRGreen MasterMix (Applied Biosystems). PAI-1, IL-6, TNF-α, NADPH oxidase subunit gp91phox (NOX2) and TLR4 mRNA levels were expressed as a ratio of ribosomal 18S RNA levels.

2.6. Assessment leukocyte activation markers

Heparinized 25 μl whole-blood samples were incubated at room temperature for 5 min with 2 μl anti-rat CD32 monoclonal antibody (Fc Block, BD Pharmingen). Fluorescence-labeled monoclonal antibodies (FITC-CD11b, PE-CD62L, Cy5-CD45RA, APC-CD3, BD Pharmingen), with *ad hoc* dilutions, were added and the mixture was incubated at room temperature for 15 min in the dark. Lysis of the red blood cells was performed by adding 200 μl FACS lysing solution (BD Pharmingen). After washing and centrifugation, the samples were thoroughly mixed with 100 μl PBS and then analyzed by flow cytometry (FACSCalibur, BD Pharmingen). The leukocyte events number was considered as the leukocyte count.

2.7. Statistical analysis

Data were expressed as means±S.E.M. Data were tested for normality and homogeneity of variance. If one of these assumptions was not satisfied, the data were log transformed before analysis. When the outcomes were repeated (over time and/or meal types), data were analyzed using mixed model procedures under SAS (SAS Institute), with meal and time used as fixed effects and interaction between the two was tested. When a fixed effect or interaction was significant or tended to be (P≤1), *post hoc* testing was performed with the Tukey–Kramer adjustment. Gene expression was analyzed using two-way ANOVA with time and meal as fixed effects and one-tailed Tukey studentized t test for *post hoc* comparisons. A value of P≤.05 was determined to be statistically significant.

3. Results

When compared to the values found after the water load, mean plasma triglycerides (Fig. 1) steadily increased, being twice (198± 13%, P≤001) the baseline values 6 h after the HFM.

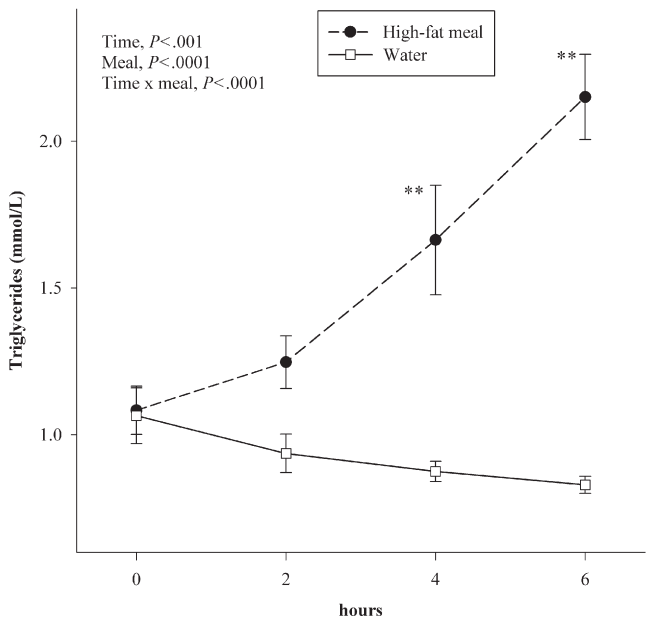

Fig. 1. Plasma triglycerides before and after the high-fat load or water load. Values are means±S.E.M. (high-fat load: n=10; water load: n=6). **P≤001 vs. baseline.

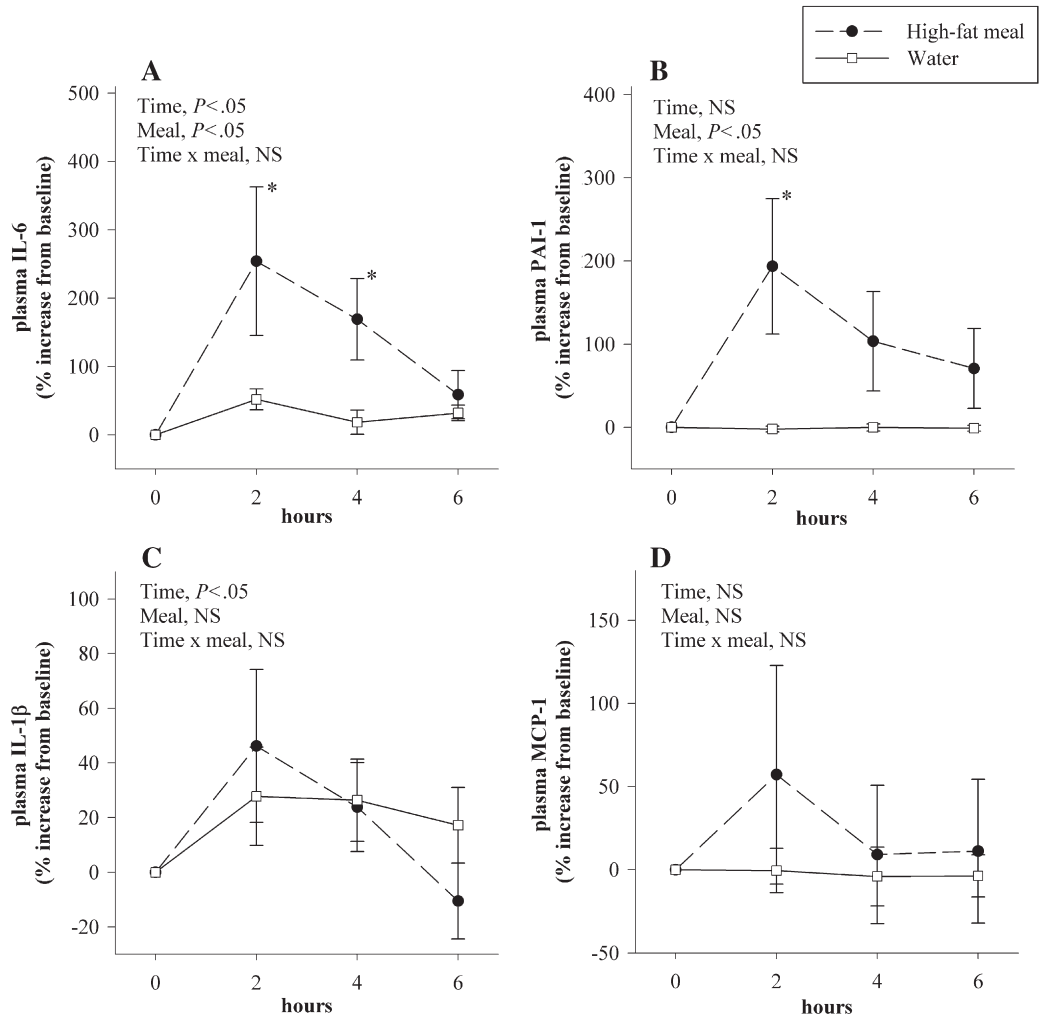

Fig. 2. Systemic markers of low-grade inflammation before and after the high-fat meal or water load. Plasma IL-6 (A), PAI-1 (B), IL-1β (C) and MCP-1 (D) values are means±S.E.M. (high-fat load: n=10; water load: n=6). *P<.05, **P<.001 vs. baseline.

3.1. Systemic markers of low-grade inflammation

Plasma IL-6 and PAI-1 (Fig. 2A and B) significantly increased after the HFM, when compared to baseline values and the values found after the water load. Two hours after the HFM, plasma IL-6 and PAI-1 (Fig. 2A and B) displayed a maximum increase of 254±109% and 197±81%, respectively, as compared to the water load (P<.05). Changes in plasma IL-1β (Fig. 2C) did not differ after the HFM as compared to the water load. Plasma MCP-1 (Fig. 2D) and plasma sICAM-1 and CRP (data not shown) did not vary significantly after the HFM.

3.2. Leukocyte activation markers

The HFM increased neutrophil count (P<.05 vs. water load; Fig. 3A) and decreased B-cell count (P<.05 vs. water load), while not significantly affecting monocyte and T-cell counts. The number of neutrophils expressing CD62L and CD11B (Fig. 3B and C) increased significantly after the HFM (P<.05 vs. water load), while remaining unchanged for monocytes. A significant decrease in B-cells expressing CD62L (Fig. 3B) was observed after the HFM (P<.05 vs. water load).

3.3. NF-κB activation and inflammatory gene expression in adipose tissue

The amounts of activated NF-κB in nuclear extract from liver were below the lower limit of quantification of the method whatever the meal and the time of sampling. When compared to the values found after the water load, activated NF-κB (Fig. 4) was 2.2-fold higher (P<.05) in adipose tissue collected 2 h after the HFM. By contrast, 6 h after the HFM, activated NF-κB no longer differed from those after the water load.

When compared to the water load, IL-6 gene expression in adipose tissue (Fig. 5) was 3.6-fold higher (P=.06) 2 h after the HFM, while being similar 6 h after the HFM. By contrast, TNF-α, NOX2 and TLR4 gene expressions in adipose tissue remained very similar, 2 and 6 h after the HFM, to those after the water load (data not shown).

4. Discussion

It has been well documented that the adverse postprandial effects of a HFM, in particular vascular endothelial dysfunction, are generally associated with increase in proinflammatory markers [4,6,7]. In this context, the post-meal increase in plasma IL-6 and PAI-1 was expected and is consistent with the general proinflammatory and prothrombotic effects of hypertriglyceridemia [6]. Nevertheless, it is noteworthy that this increase in circulating markers of low-grade inflammation was transient and occurred very early (2 h after the HFM) when compared to the gradual increase in plasma triglycerides. Conversely, we observed no changes in plasma CRP after the HFM, but to our knowledge, there has been no report of an acute effect of high-fat meal on plasma CRP in healthy subjects [6]. Very recently, Dekker

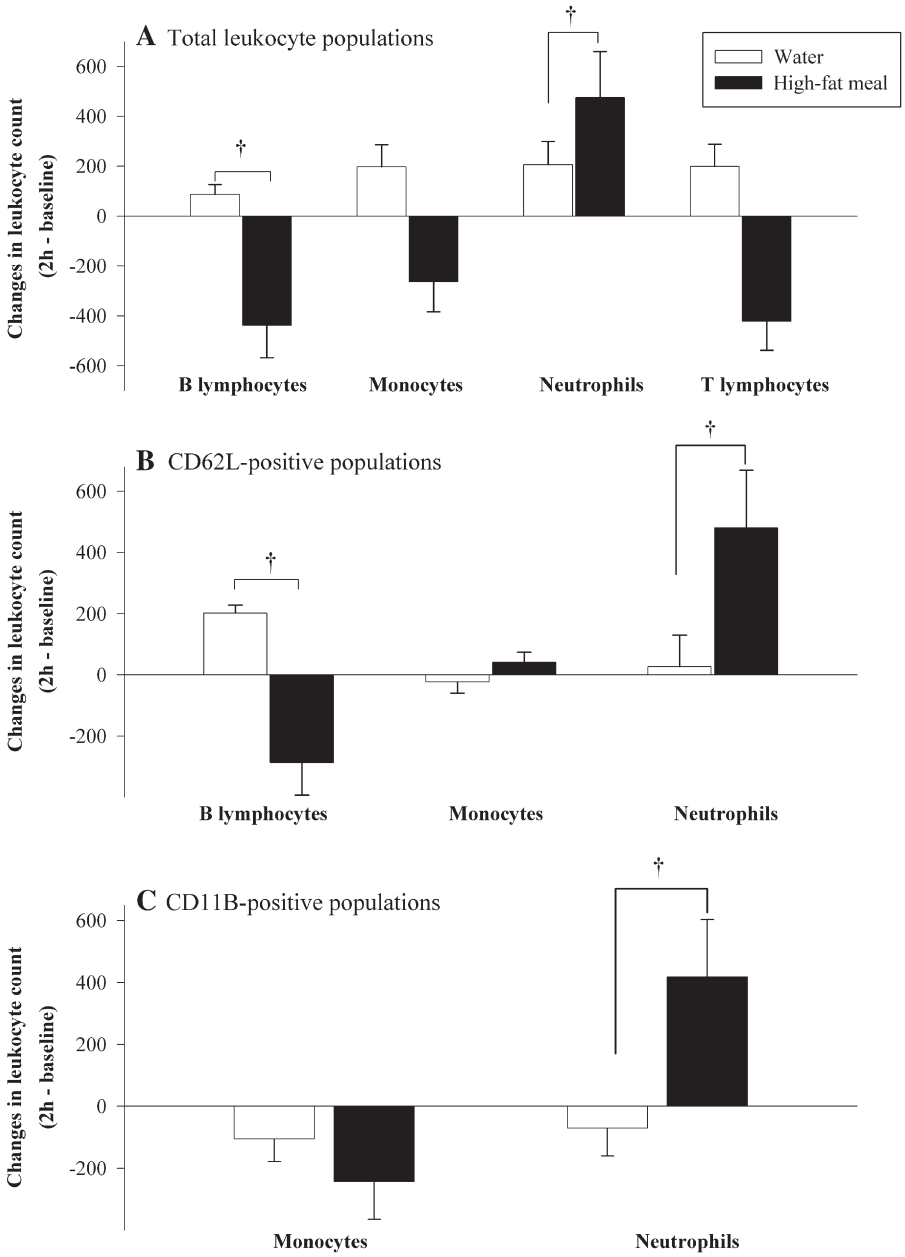

Fig. 3. Total leukocyte population (A) and activated population as characterized by CD62L-positive populations (B) and CD11B-positive populations (C), 2 h after the high-fat meal or water load. Values are means±S.E.M. (n=5) and are expressed as changes from baseline. †P<.05 vs. water load.

et al. [22] have demonstrated that the postprandial rate of change in plasma CRP slightly increased only in subjects with high-fasting triglycerides as compared with low-fasting triglycerides. This finding strengthens the idea that plasma CRP may be more relevant in predicting the risk of cardiovascular disease in conditions of chronic low-grade inflammation.

To further inspect the postprandial inflammatory response in the early hours after the HFM, we examined leukocyte activation markers, such as the integrin CD11B and the selectin CD62L, which are implicated in the leukocyte adherence to the endothelium [23]. Two hours after the load, the HFM increased the neutrophil count concomitantly with enhancing the expression of the adhesion proteins CD11B and CD62L on neutrophils. These results are in line with those obtained by Van Oostrom et al. [9,24] indicating that neutrophils, which displayed a postprandial increase in their capability for adhesion and recruitment, may be actively involved in postprandial low-grade inflammation. Incidentally, our study shows a decrease in B-cell count and expression of CD62L 2 h after the HFM. However, to the best of our knowledge, no data on B cells' involvement in atherogenesis have ever been reported and this result may rather support the hypothesis that B-cells can be recruited by the gut after a meal [25].

To examine the mechanisms underlying postprandial inflammatory signaling, *in vitro* studies have suggested that triglyceride-rich lipoproteins isolated from human plasma after a HFM may directly induce inflammatory changes affecting both endothelial cells and leukocytes [26]. Concomitant with postprandial endothelial activation, Suganami et al. [20] recently suggested that saturated fat could activate the TLR4/NF-κB pathway in a coculture of adipocytes and macrophages, suggesting a contribution of adipose tissue to postprandial inflammation. For the first time in an *in vivo* model, our study shows that a HFM can evoke an early transient activation of the

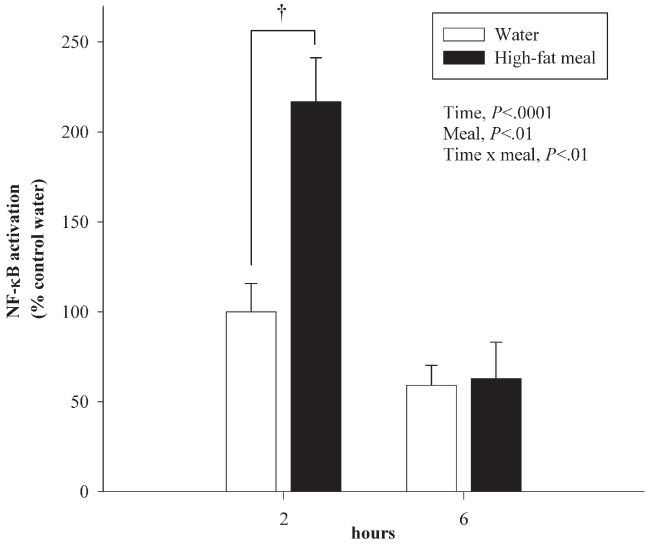

Fig. 4. NF-κB activation in adipose tissue 2 and 6 h after the high-fat meal or water load. Values are means±S.E.M. (n=6). †P<.05 vs. water load.

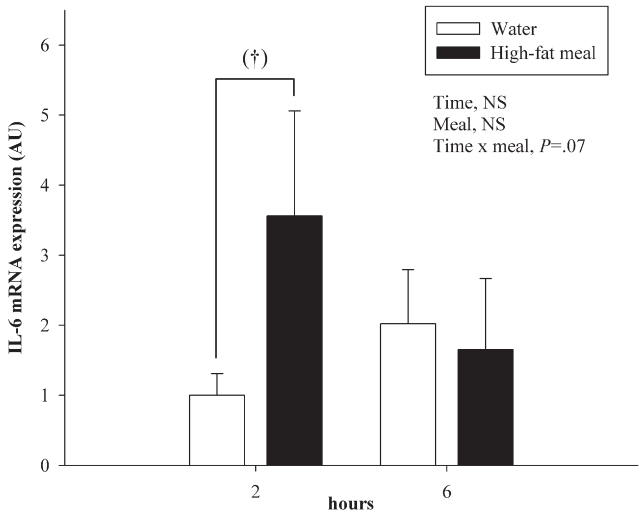

Fig. 5. IL-6 mRNA expression in adipose tissue 2 and 6 h after the high-fat meal or water load. Values are means±S.E.M. (n=6). †P=.06 vs. water load.

transcription factor NF-κB, a primary effector of inflammatory signaling activation, in visceral adipose tissue. This activation of NF-κB pathway in adipose tissue is supported by an acute increase in IL-6 gene expression (a NF-κB target gene) in visceral adipose tissue. It is noteworthy that postprandial activation of NF- κB and IL-6 up-regulation in adipose tissue is consistent with the marked increase of IL-6 in plasma. In fact, the adipose tissue, and particularly the visceral adipose tissue, is an endocrine organ [14,27], and a significant part of IL-6 recovered in the circulation is secreted by the adipose tissue [28,29]. Emerging data have recently suggested that macrophages of adipose tissue may play an important role in chronic inflammation and obesity [30,31]. As we studied here the whole visceral adipose tissue, further studies are needed to understand which type of cells is specifically involved in the inflammatory response reported here.

Furthermore, in accordance with the importance of NF-κB pathway-related functions including inflammatory responses, cellular growth and apoptosis, the activity of NF-κB pathway is highly regulated in the organism [32]. This tight control of NF-κB signaling may explain why, in healthy rats, during the postprandial state, the marked activation of this inflammatory pathway was transient. Interestingly, in a previous study, Patel et al. [33] have observed that, in mononuclear cells, the postprandial activation of NF-κB was more prolonged in obese individuals than in lean individuals. This finding is in line with the idea that the repeated exposure to proinflammatory HFM, in synergy with obesity, paves the way to a chronic low-grade inflammation and to the series of dysregulations and dysfunctions that cluster together [34]. Therefore, understanding the mechanisms underlying the regulation of the postprandial activation of NF-κB in the adipose tissue would be of particular interest in comprehending the pathogenesis of obesity. Given the importance of this pleitropic modulator of inflammation, our findings may drive future investigations to further delineate the early postprandial initiation of inflammation in visceral adipose tissue and its contribution to systemic low-grade inflammation during the postprandial state.

In conclusion, in this animal model of postprandial acute pathophysiological dysregulations, we revealed for the first time that a HFM early induces a transient activation of NF-κB in visceral adipose tissue. Taken together, the results suggest that the very early activation of inflammatory pathways in the adipose tissue may play a central role in the initiation of systemic low-grade inflammation, which is an early feature in the postprandial proatherogenic phenotype. Further studies are needed to inspect the role of the visceral adipose tissue in postprandial inflammation and atherogenesis.

Acknowledgments

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