Changes in adiponectin, its receptors and AMPK activity in tissues of diet-induced diabetic mice

C. Bonnard a,b,c,d,e, A. Durand a,b,c,d,e, H. Vidal a,b,c,d,e, J. Rieusset a,b,c,d,e,∗

a Inserm, U870, IFR62, 165, chemin-du-grand-Revoyet, 69600 Oullins, France
b Inra, UMR 1235, 69600 Oullins, France
c Insa de Lyon, RMND, 69621 Villeurbanne, France
d Université de Lyon-1, 69003 Lyon, France
e Hospices civils de Lyon, 69608 Lyon, France

Received 12 July 2007; received in revised form 19 September 2007; accepted 22 September 2007
Available online 25 January 2008

Abstract

Aim. – A high-fat and high-sucrose diet (HFHSD) is usually used to induce type 2-like diabetes in animal models. We investigated the effect of HFHSD on serum and tissue levels of adiponectin, its receptors and AMP-activated protein kinase (AMPK) activity in adipose tissue, skeletal muscle and the liver.

Methods. – C57Bl/6 male mice were fed either a standard diet or an HFHSD for four and 16 weeks, during which time glucose and insulin tolerance tests were performed.

Results. – After four weeks, the HFHSD-fed mice were obese and glucose-intolerant and, after 16 weeks, they were obese and diabetic. In general, four weeks of HFHSD feeding did not modify either circulating or tissue adiponectin levels, nor adiponectin receptors or AMPK activity in the tissues studied. A significant increase of circulating adiponectin was observed after 16 weeks of HFHSD feeding, whereas adiponectin expression was decreased in adipose tissue. Muscle expression of adiponectin was increased at 16 weeks in terms of both mRNA and protein levels, and correlated to adipose-specific gene expression. However, AdipoR1 mRNA levels and AMPK activity were decreased in muscle at 16 weeks, suggesting decreased sensitivity to adiponectin in the muscle of diabetic mice. Finally, liver adiponectin expression was detectable only at protein levels and was increased in HFHSD mice at 16 weeks, suggesting “contamination” by circulating adiponectin. AdipoR2 mRNA levels were significantly decreased, whereas AMPK was increased, in the liver at 16 weeks.

Conclusion. – Overall, our data suggest that HFHSD-induced diabetes is not associated with adiponectin deficiency, but with tissue-specific defects of adiponectin-receptor expression and AMPK activity.

© 2007 Elsevier Masson SAS. All rights reserved.

Résumé

Modification des niveaux d’adiponectine, de ses récepteurs et de l’activité AMPK dans les tissus de souris diabétiques.

Objectifs. – Les régimes hyperlipidiques et hyperglucidiques (RHLHG) sont classiquement utilisés pour induire un diabète de type 2 chez l’animal. Nous avons étudié les effets d’un tel régime sur les niveaux d’adiponectine, de ses récepteurs et sur l’activité AMPK dans le tissu adipeux, le muscle squelettique et le foie de souris.

Méthodes. – Des souris mâles C57Bl/6 ont été nourries, soit avec une diète standard, soit une diète RHLHG, pendant quatre et 16 semaines et des tests de tolérance au glucose et à l’insuline ont été réalisés.

Résultats. – Les souris RHLHG 4s sont obèses et intolérantes au glucose, alors que les souris nourries pendant 16 semaines sont obèses et diabétiques. Le régime RHLHG 4s n’affecte globalement pas les concentrations circulantes et tissulaires d’adiponectine, ni les niveaux d’ARNm de ses récepteurs et ni l’activité de l’AMPK, quel que soit le tissu étudié. En revanche, on observe une augmentation significative des concentrations circulantes d’adiponectine après 16 semaines de régime, alors que l’expression de l’adiponectine est diminuée dans le tissu adipeux des souris.

© 2007 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 19/05/2019 Il est interdit et ilégal de diffuser ce document.

* Corresponding author.
E-mail address: jennifer.rieusset@univ-lyon1.fr (J. Rieusset).
To gain more insight into the relationship between adiponectin, reports suggesting that adiponectin may be expressed in skeletal muscle are also equivocal. The mRNA levels of AdipoR1 and AdipoR2 have been reported as either decreased [16] or unchanged [9] or increased [10–12] in different obese and diabetic rodent models. In addition, three independent adiponectin knock-out (KO) mouse studies have had mixed results [13–15]. In two of these studies, adiponectin KO mice were insulin-resistant when challenged with a high-fat diet [13,14] and in one of these studies [14], they were insulin-resistant when maintained on a standard chow diet. However, in the third study, mice lacking adiponectin were insulin-sensitive even when challenged with a high-fat diet [15]. Moreover, data regarding the expression of adiponectin receptors in skeletal muscle are also equivocal. The mRNA levels of AdipoR1 and AdipoR2 have been reported as either decreased [16] or unchanged [17] in skeletal muscle in an obese and/or diabetic state. Furthermore, whereas some studies described adiponectin as expressed exclusively in adipose tissue, there have been several reports suggesting that adiponectin may be expressed in skeletal muscle [18,19], in cardiomyocytes [20,21] and in liver [22]. To gain more insight into the relationship between adiponectin, its signalling pathways and insulin sensitivity, we investigated these parameters in high-fat and high-sucrose (fructose) diet (HFHSD)-fed mice. The goal of our study is to determine the effects of short- and long-term HFHSD feeding on:

- circulating adiponectin levels;
- the expression of adiponectin and its receptors AdipoR1 and AdipoR2;
- the activity of AMPK in adipose tissue, skeletal muscle and the liver of C57Bl/6 male mice.

1. Introduction

Adiponectin, a hormone secreted by adipocytes, acts as an antidiabetic and antiatherogenic adipokine [1]. It is well-established that circulating adiponectin levels are reduced in patients who are obese and insulin-resistant [1]. Indeed, a strong negative correlation between plasma adiponectin levels and body mass index has been reported in humans [2], and adiponectin levels are further reduced in individuals with type 2 diabetes [3]. Also, recombinant adiponectin administration in diabetic rodents improves insulin sensitivity [4].

Circulating adiponectin acts predominantly in muscle and liver via two specific receptors (AdipoR1 and AdipoR2). AdipoR1 is ubiquitously expressed with the highest expression found in skeletal muscle, whereas AdipoR2 is mainly expressed in liver [5]. In skeletal muscle, adiponectin stimulates fatty-acid oxidation [6] and glucose transport [6,7], due in part to the activation of AMP-activated protein kinase (AMPK). In the liver, adiponectin improves the ability of insulin to suppress glucose production, also most likely through an AMPK-mediated mechanism [8].

In spite of clear evidence of the insulin-sensitizing effect of adiponectin, controversial data have been observed in animal models of obesity and diabetes. Circulating adiponectin levels were decreased [5], unchanged [9] or increased [10–12] in different obese and diabetic rodent models. In addition, three independent adiponectin knock-out (KO) mouse studies have had mixed results [13–15]. In two of these studies, adiponectin KO mice were insulin-resistant when challenged with a high-fat diet [13,14] and in one of these studies [14], they were insulin-resistant when maintained on a standard chow diet. However, in the third study, mice lacking adiponectin were insulin-sensitive even when challenged with a high-fat diet [15]. Moreover, data regarding the expression of adiponectin receptors in skeletal muscle are also equivocal. The mRNA levels of AdipoR1 and AdipoR2 have been reported as either decreased [16] or unchanged [17] in skeletal muscle in an obese and/or diabetic state. Furthermore, whereas some studies described adiponectin as expressed exclusively in adipose tissue, there have been several reports suggesting that adiponectin may be expressed in skeletal muscle [18,19], in cardiomyocytes [20,21] and in liver [22]. To gain more insight into the relationship between adiponectin, its signalling pathways and insulin sensitivity, we investigated these parameters in high-fat and high-sucrose (fructose) diet (HFHSD)-fed mice. The goal of our study is to determine the effects of short- and long-term HFHSD feeding on:

- circulating adiponectin levels;
- the expression of adiponectin and its receptors AdipoR1 and AdipoR2;
- the activity of AMPK in adipose tissue, skeletal muscle and the liver of C57Bl/6 male mice.

2. Materials and methods

2.1. Mice

Four-week-old male C57Bl/6J mice were purchased from Harlan (n = 48) and housed, under standard conditions, at the animal community centre in Laennec (IFR62, Lyon). All animal procedures were conducted in accordance with the institutional guidelines for the care and use of laboratory animals. After acclimatization, half the mice were fed a standard chow diet [SD, 5% (wt/wt) fat, Harlan] and the other half, an HFHSD [36% (wt/wt) fat, 19% (wt/wt) sucrose, Harlan], for four and 16 weeks (n = 12 mice per group). After both periods of feeding, intraperitoneal (IP) glucose and insulin tolerance tests (IPGTT and IPITT, respectively) were performed on two different groups of 8-h fasted mice (n = 6 mice per group). Animals were injected IP with 2 mg/g body weight of glucose or 0.75 mU/g body weight of insulin. Blood was taken by tail puncture immediately before and at different times after injection for measurements of plasma glucose. Three days later, whole blood was withdrawn, in the fed state, from the orbital sinus of anaesthetized animals. The animals were then sacrificed, and the gastrocnemius muscle, epididymal adipose tissue and liver rapidly excised, and frozen in liquid nitrogen.

2.2. Measurement of hormones and metabolites

Blood glucose levels were measured using a glucometer (Roche Diagnostics). Serum levels of insulin (Linco Research), leptin and adiponectin (Abcys) were determined using the murine ELISA kit. Total serum triglycerides (TG; Biomérieux)
and free fatty acids (FFA; Roche Diagnostics) were assayed using enzymatic methods.

2.3. Extraction of RNA and real-time quantitative RT-PCR analysis

Total RNA was extracted with the TRIzol reagent (Invitrogen). Concentrations of target mRNA were measured by reverse-transcription (RT) followed by real-time PCR using a LightCycler (Roche Diagnostics). We also measured hypoxanthine guanine phosphoribosyl transferase (HPRT) mRNA as a reference gene, and expressed the results as a ratio to HPRT. The following primer combinations were used: 5′-AGGCCGTGATGGCAGAGATG-3′ and 5′-CTTCTCCAGGTITTCTCTTTCTGC-3′ for adiponectin; 5′-AAGCACCGCCAGACAAGAGC-3′ and 5′-AGGAGAGAGAAGCATCTG-3′ for adiponectin; 5′-AGCCCTCATGGCTCAACTCCTTCC-3′ and 5′-TTGCTGACCTGCTGATTAC-3′ for leptin; and 5′-TTGCTGACCTGCTGATTAC-3′ and 5′-AGTTGAGAGATCATCTCCAC-3′ for HPRT.

2.4. Extraction of proteins and Western blotting

Tissues were lysed in ice-cold lysis buffer (1% NP40, 20 mM tris–HCl, 138 mM NaCl, 2.7 mM KCl, 1 mM MgCl₂, 5 M glycerol, 5 mM EDTA, 1 mM Na₃VO₄, 20 mM NaF, 1 mM DTT, protease inhibitors, pH = 8). Proteins were separated under denaturing conditions by SDS-PAGE and electrotransferred onto PVDF membranes. The membranes were incubated in blocking buffer for 1 h at room temperature and then probed with different primary antibodies: adiponectin (1/1000, Abcam) and phospho-Thr172 AMPKα (1/1000, Ozyme). After washing, the membranes were further incubated with horseradish peroxidase-conjugated secondary antibodies. Signalling was detected using an enhanced chemiluminescence detection system. To normalize for equal protein amounts, the blot was stripped and probed again with tubulin (1/100, Santa-Cruz) and/or AMPKα (1/1000, Ozyme).
3.1. Metabolic effects of high-fat and high-sucrose feeding

The characteristics of the mice are summarized in Table 1. Four weeks of HFHSD feeding induced an increase in body weight (27.5%, \( P < 0.01 \)), epididymal fat-pad mass (343%, \( P < 0.01 \)), circulating leptin (770.4%, \( P < 0.01 \)) and insulin (87.5%, \( P < 0.05 \)) levels, whereas no significant differences in plasma levels of glucose, FFA and TG were observed. In addition, the mice were glucose-intolerant (Fig. 1(A)), while their response to insulin injection remained unaltered compared with SD mice Fig. 1(B). After 16 weeks of HFHSD feeding, there were marked increases in body weight (54.1%, \( P < 0.01 \)), epididymal fat-pad mass (242.8%, \( P < 0.01 \)) and plasma leptin levels (554%, \( P < 0.01 \)). In addition, at 16 weeks, HFHSD mice were hyperglycaemic (\( P < 0.01 \)) and hyperinsulinaemic (\( P < 0.01 \)), with increased circulating FFA (\( P < 0.01 \)) and TG (\( P < 0.01 \)) levels compared with SD mice, indicating impaired glucose and lipid metabolism. Plasma glucose levels at 16 weeks in the HFHSD mice were significantly higher (\( P < 0.01 \)) than at four weeks, and there was an altered response to both glucose and insulin injection compared with SD mice Fig. 1(A and B), indicating that the 16-week HFHSD mice were clearly insulin-resistant. Altogether, these data demonstrate that both the four-week and 16-week HFHSD mice were obese, but were in two different metabolic states in terms of insulin sensitivity.

3.2. Long-term HFHSD feeding increases circulating adiponectin levels

After four weeks of HFHSD feeding, there was no significant difference in circulating adiponectin concentrations between...
the groups (Table 1). However, 16-week HFHSD-fed mice had higher plasma adiponectin levels than SD mice (66.5%, $P < 0.02$). In addition, 16-week SD-fed mice had significantly higher plasma adiponectin levels ($P < 0.01$) than four-week SD mice, indicating that circulating adiponectin concentrations are increased with age.

Plasma adiponectin levels did not correlate to serum glucose, insulin or FFA levels, whereas they did positively correlate to serum leptin ($r = 0.252$, $P = 0.01$) and TG levels ($r = 0.187$, $P = 0.036$).

3.3. Adiponectin expression in adipose tissue, skeletal muscle and liver of HFHSD mice

To better understand the causes of the increased circulating adiponectin levels in HFHSD mice, we measured the levels of
expression of the hormone in adipose tissue, skeletal muscle and the liver. As expected, we found that adiponectin mRNA levels were expressed at higher levels in adipose tissue than in skeletal muscle (adiponectin:HPRT ratio: 3.85 ± 0.3 versus 0.45 ± 0.07, respectively) or in liver (adiponectin mRNA is undetectable). Both adiponectin mRNA (Table 2, \( P < 0.03 \)) and total adiponectin protein (Fig. 2(A), \( P < 0.05 \)) levels were decreased in adipose tissue of the 16-week HFHSD mice compared with SD mice, whereas no differences had been observed at four weeks of feeding. Interestingly, we noted an increase of adiponectin mRNA levels in skeletal muscle of HFHSD mice compared with SD mice at both 4 (\( P = 0.03 \)) and 16 weeks (\( P = 0.04 \)) of feeding (Table 2). The total adiponectin protein levels were significantly increased only after 16 weeks of HFHSD feeding in muscle (Fig. 2(B), \( P = 0.02 \)). To test whether muscle adiponectin expression is related to an increased adipose tissue content in muscle, we measured leptin and HSL mRNA levels, two adipose tissue-specific genes. Adiponectin mRNA levels were positively correlated to both leptin (\( r = 0.217, P = 0.02 \)) and HSL (\( r = 0.697, P = 0.0001 \)) mRNA levels in skeletal muscle, suggesting an increase in intramuscular adipose tissue in HFHSD-fed mice. Consistent with this was the histological analysis, which revealed white adipocytes beneath the perimysium and epimysium of skeletal muscle in the 16-week HFHSD-fed mice (Fig. 3). As for the liver, total adiponectin protein levels were also increased in the 16-week HFHSD mice compared with SD mice, whereas no differences had been observed at four weeks Fig. 2(C). However, liver adiponectin mRNA levels were too low to be accurately measured by real-time PCR, suggesting that there was no expression of adiponectin in liver and that the measured adiponectin protein content might have been due to circulating adiponectin.

3.4. Adiponectin receptor expression in adipose tissue, skeletal muscle and liver of HFHSD mice

In adipose tissue, AdipoR1 mRNA was slightly more abundantly expressed than AdipoR2 (AdipoR:HPRT ratio: 0.27 ± 0.03 versus 0.13 ± 0.02, respectively; \( P < 0.0001 \)). As shown in Table 2, AdipoR1 and AdipoR2 mRNA levels remained unchanged with HFHSD. As for skeletal muscle, AdipoR1 mRNA was clearly more abundantly expressed than AdipoR2 (AdipoR:HPRT ratio: 2.74 ± 0.28 versus 0.35 ± 0.04, respectively; \( P < 0.0001 \)). Interestingly, AdipoR1 mRNA levels were decreased in skeletal muscle at 16 weeks of HFHSD compared with SD, whereas AdipoR2 mRNA levels remained unchanged (Table 2). There was more AdipoR2 expression in liver than AdipoR1 (AdipoR:HPRT ratio: 1.33 ± 0.3 versus 0.67 ± 0.1, respectively; \( P < 0.05 \)), and the level of AdipoR2 mRNA was decreased at 16 weeks of HFHSD.
feeding whereas AdipoR1 expression remained unchanged (Table 2).

### 3.5. AMPK activation in adipose tissue, skeletal muscle and liver of HFHSD mice

We investigated the phosphorylation of AMPKα on threonine 172 in tissues of both SD- and HFHSD-fed mice. As shown in Fig. 4(A), we were able to detect both isoforms of AMPKα1 and α2 by Western blotting, and we found similar protein expressions of both isoforms in adipose tissue. In addition, we observed an increase in basal phosphorylation of both AMPKα isoforms in adipose tissue at 16 weeks in the HFHSD mice, whereas no effect was observed at four weeks Fig. 4(A). In skeletal muscle, only the α2 isoform of AMPK was detectable by Western blotting. As shown in Fig. 4(B), phosphorylation of AMPKα2 was reduced in skeletal muscle at 16 weeks in the HFHSD compared with SD mice, whereas no differences were observed at four weeks. As regards the liver, only the α1 isoform of AMPK was detectable by Western blotting. After 16 weeks of HFHSD feeding, AMPK phosphorylation was increased in the liver of HFHSD mice compared with SD mice, whereas no effect was observed at four weeks Fig. 4(C). Finally, to verify whether basal AMPKα protein levels were modified during HFHSD feeding, we normalized them with tubulin protein levels and found that, for all tissues investigated, HFHSD feeding did not modify basal AMPKα protein levels (data not shown).

### 4. Discussion

Adiponectin has attracted considerable interest in the area of obesity and diabetes over the last few years. However, conflicting results have often been observed concerning adiponectin, its receptor levels and AMPK, one of its major signalling proteins. One possible explanation is that all these parameters have been investigated separately in different obesity and/or diabetes models. Therefore, we have studied adiponectin levels, its receptor expression and AMPK activity in parallel in three insulin-sensitive tissues (adipose tissue, skeletal muscle and the liver) in HFHSD-induced obese and diabetic mice. In addition, we have studied two durations of feeding to dissociate obesity from diabetes. After four weeks of feeding, HFHSD mice were...
obese and glucose-intolerant whereas, after 16 weeks, HFHSD mice showed hyperglycaemia and altered in vivo insulin responsiveness, indicating a diabetic state.

Overall, four weeks of HFHSD feeding did not modify circulating and tissue adiponectin levels, adiponectin-receptor expression or APMK activity in any of the tissues investigated. As the animals were markedly obese at this stage, these data suggest that diet-induced obesity per se is not associated with alterations of adiponectin secretion and sensitivity. In contrast, we observed a significant increase in circulating adiponectin levels in the 16-week HFHSD-fed mice, suggesting alteration of adiponectin secretion and/or turnover. On measuring adiponectin expression in fat tissue, we found a marked decrease in adiponectin mRNA and total protein levels in epididymal adipose tissue in the 16-week HFHSD-fed compared with SD-fed mice. These data demonstrate that the decreased adiponectin expression does not translate to a parallel decrease in plasma adiponectin concentration, suggesting the possibility of post-transcriptional control mechanism(s). However, we cannot exclude that adiponectin expression was increased in other non-investigated fat depots [23] or that diet-increased fat mass counterbalanced the reduced adiponectin secretion from adipocytes.

Interestingly, a similar increase in circulating adiponectin has been observed in other diet-induced models of diabetes [10–12], suggesting a possible role of altered lipid and/or glucose metabolism in its regulation. In agreement with this, we observed a significantly positive correlation between circulating TG and adiponectin levels, and different lipids have been shown to increase plasma adiponectin concentration [24,25]. Nevertheless, as adiponectin expression has been reported in skeletal muscle and liver [17,18], we have also investigated the

---

Fig. 4. (Continued).
role of these tissues in adiponectin production. We found an increase of both adiponectin mRNA and protein levels in gastrocnemius muscle, whereas only protein was measurable and increased in the liver of 16-week HFHSD mice. Regarding skeletal muscle, the increased adiponectin expression was due to intramuscular ectopic adipocyte accumulation, as revealed by histological analysis. Consistent with this, adiponectin mRNA levels in muscle were correlated to leptin and HSL mRNA levels, two fat tissue-specific genes. This result does not contradict the decreased expression of adiponectin in epididymal adipose tissue of HFHSD mice. Indeed, the presence of adipocytes, which express high levels of adiponectin, in skeletal muscle, which does not express this cytokine, explains the increase of adiponectin in the skeletal muscle of 16-week HFHSD-fed mice. As for the liver, the fact that adiponectin mRNA was not detectable suggests that the presence of the protein in liver was due to “contaminating” circulating adiponectin.

Adiponectin is present as species of different molecular weights [1]. However, as we measured tissue adiponectin protein levels after reduction and heat denaturation, we observed only a single 30-kDa band on SDS-PAGE gels corresponding to the conversion of all molecular-mass species into monomers. Consequently, we cannot determine whether the diet-induced diabetes affected tissue adiponectin oligomeric distribution, as previously suggested by other studies [26]. Taken together, this part of the study suggests that increased circulating adiponectin levels in 16-week HFHSD-fed mice could be related to:

- diet-induced increased adipose mass, which could counterbalance the reduced adiponectin production by adipocytes;
- diet-induced increased intramuscular adipose-tissue accumulation;
- a possible increase of adiponectin expression and secretion by non-investigated fat depots;
- decreased clearance of adiponectin through an unknown mechanism.

The adiponectin receptors are thought to transmit the insulin-sensitizing effects of adiponectin. In this study, we found – in agreement with previous work [5] – a predominant expression of AdipoR1 in skeletal muscle and AdipoR2 in liver, whereas adipose tissue expressed low levels of both receptors. In addition, we showed that an HFHSD produced a tissue-specific effect on AdipoR1–R2 expression, with no effects on adipose tissue, specific decreases of AdipoR1 mRNA level in skeletal muscle and specific decreases of AdipoR2 expression in liver. Thus, these results suggest that HFHSD-induced diabetes could be associated with a tissue-specific decreased adiponectin response. Although other studies have reported increased expression of AdipoR1 in skeletal muscle in high-fat diet-fed mice [27], similar decreases of AdipoR1 in skeletal muscle were reported in different genetically obese and diabetic mice [16,28]. In contrast to observations in mice, the expression of AdipoR1–R2 was poorly regulated by a high-fat diet in rats [29]. Nevertheless, as it has been previously demonstrated that the expression of AdipoR1–R2 is inversely correlated to plasma insulin levels in vivo [16], the decreased expression of AdipoR1 and AdipoR2 in gastrocnemius muscle and liver, respectively, could be partly linked to the hyperinsulinaemia observed in 16-week HFHSD-fed mice.

Peripheral effects of adiponectin are in part mediated by activation of AMPK [1]. AMPK is a heterotrimer of three subunits – α, β and γ – and the α subunit, which contains the kinase domain, has two isoforms – α1 and α2. In the present study, we observed tissue-specific expression of both isoforms of AMPKα, with similar expression levels of both isoforms in adipose tissue and a preferential expression of AMPKα2 in muscle, and of AMPKα1 in liver. This tissue-specific expression profile of AMPKα isoforms is consistent with previous reports [30–32]. In addition, we found that 16 weeks of an HFHSD promotes tissue-specific effects on AMPK activity, as basal phosphorylation of both AMPKα isoforms was increased in adipose tissue and liver, and decreased in skeletal muscle. Thus, it is tempting to speculate that the impaired expression of AdipoR1, in combination with decreased basal AMPK activity in skeletal muscle, might reflect adiponectin resistance, as has also been suggested by others [33], which could contribute to the decreased lipid oxidation and/or glucose transport observed in diet-induced diabetes [34]. Similar decreases in basal AMPK activity in skeletal muscle have already been reported in obese and diabetic rodents [35] and humans [36]. As for the liver, we observed an increase in basal AMPK activation, which could be related to increased diet-induced lipid levels, as suggested in other studies [37,38].

In summary, we have demonstrated that long-term high-fat feeding is associated with:

- an increase in circulating adiponectin contributing to the detection of adiponectin protein in the liver;
- an increase in intramuscular ectopic adipocyte accumulation, leading to adiponectin detection in skeletal muscle;
- a decrease of adiponectin receptors and/or AMPK activity in skeletal muscle and liver.

Altogether, these data suggest that HFHSD-induced diabetes is not associated with adiponectin deficiency but, rather, with tissue-specific defects of adiponectin-receptor expression and AMPK activity, which could contribute to the alterations in glucose and lipid metabolism observed in diet-induced diabetic mice.

Acknowledgements

This work was supported in part by grants from INSERM. C.B. received fellowships from the Rhônes-Alpes region. The authors thank the community imaging centre of Laennec and the IFR62 for access to platforms, and J. Tirard and Dr F. Rajas for their contributions to the experimental protocol.

References


