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Expression of the adiponectin receptors AdipoR1 and AdipoR2 in lean rats and in obese Zucker rats

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Abstract

The adiponectin receptors, AdipoR1 and AdipoR2, are thought to transmit the insulin-sensitizing effects of adiponectin, an adipokine secreted by adipocytes. Modifications of their expression in insulin-sensitive tissues (skeletal muscle, liver, and adipose tissue) could therefore play a role in the control of insulin sensitivity and the development of insulin resistance. Recent data in mice supported this possibility. We examined whether the expression of adiponectin receptors (messenger RNA [mRNA] concentrations) is controlled in vivo in rats (Wistar) by nutritional factors (high-fat [HF] vs high-carbohydrate diet, fasting vs fed state) and whether this expression is decreased in an experimental model of insulin resistance, the obese Zucker rat. In Wistar rats, neither an HF diet nor fasting modified the mRNA concentrations of AdipoR1 in muscle, liver, or adipose tissue; the only modification observed was a decrease ($P < .05$) in AdipoR2 mRNA level in the liver of rats fed with an HF diet. In obese Zucker rats compared with their lean controls, neither AdipoR1 nor AdipoR2 expression was modified in muscle. AdipoR2 expression was slightly decreased in adipose tissue, whereas the expression of both AdipoR1 and AdipoR2 was increased ($P < .05$) in the liver of obese Zucker rats. In conclusion, contrary to what was reported in mice, the expression of adiponectin receptors in rats is poorly responsive to changes in nutritional conditions and is not decreased in a model of insulin resistance. These results do not support an important role for the expression of AdipoR1 and AdipoR2 in the modulation of sensitivity to insulin.

1. Introduction

In addition to its role of storage of energy in triglyceride (TG) droplets, adipose tissue communicates with other tissues and participates in the regulation of important physiological functions through the secretion of various humoral mediators [1,2]. Adiponectin is one of the numerous proteins secreted by adipocytes that have effects on glucose and lipid metabolism and can therefore modify insulin sensitivity and, for some of them, energy balance [2,3]. The expression of adiponectin is reduced in human obesity [4] and in rodent models of insulin resistance [5]. Its plasma concentration decreases during the development of obesity-associated insulin resistance in rhesus monkeys [6]. Moreover, high plasma adiponectin levels in humans appear to reduce the risk of development of type 2 diabetes mellitus [7,8]. Lastly, adiponectin reverses insulin resistance in several rodent models [5]. Therefore, adiponectin improves sensitivity to insulin and has protective effects against the development of type 2 diabetes mellitus. In addition, it has some anti-inflammatory and anti-atherogenic properties [9,10]. Adiponectin exerts its metabolic effects at least in part through a stimulation of the adenosine 5′-monophosphate–activated protein kinase, which then increases both glucose uptake and fatty acid oxidation rates [11,12], and of the nuclear receptor peroxisome proliferator–activated receptor (PPAR) α [3], which promotes lipid oxidation. These effects are considered to be mediated by 2 related but distinct receptors for adiponectin, AdipoR1 and AdipoR2, that have been recently cloned and characterized [13]. They are expressed in liver, adipose tissue, skeletal muscle [13], macrophages [14], and pancreatic beta cells [15]. Interfering with the expression of these receptors impairs the metabolic effects of adiponectin [13]. Therefore, in addition to adiponectin expression and plasma concentration levels, the expression level of the receptors AdipoR1 and AdipoR2 in target tissues may play a role in the control of insulin sensitivity. Actually, the expression of adiponectin receptors was found reduced in insulin-resistant *ob/ob* mice

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[16] and in diabetic *db/db* mice [17]. In humans, Civitarese et al [18] found that skeletal muscle *ADIPOR1* and *ADIPOR2* expression levels were reduced in people with a family history of type 2 diabetes mellitus and that these expression levels were correlated positively with insulin sensitivity. On the other hand, Debard et al [19] found no decrease of *ADIPOR1* and *ADIPOR2* messenger RNA (mRNA) concentrations in the skeletal muscle of type 2 diabetic patients compared with healthy subjects. Taken collectively, however, these results support the idea that increasing the expression of AdipoR1/AdipoR2 could improve insulin sensitivity and reduce the risk of appearance of type 2 diabetes mellitus.

At the present time, little is known about the regulation of AdipoR1/AdipoR2 expression. Chinetti et al [14] found that LXR agonists increased the mRNA concentrations of *ADIPOR1* and *ADIPOR2* in human macrophages, whereas agonists of PPARα and PPARγ increased only the expression of *ADIPOR2*. These PPAR agonists had no effect on the expression of adiponectin receptors in human skeletal muscle [20]. Growth hormone stimulated the expression of AdipoR2 in 3T3-L1 adipocytes [21]. With respect to a possible control by metabolic and nutritional factors, oleate stimulated the expression of adiponectin receptors in pancreatic beta cells [15], and it has been reported that AdipoR1/AdipoR2 expression increased in fasted mice while decreasing in refed mice [16,17]. These last studies also provided in vivo and in vitro evidence for a suppressive action of insulin on AdipoR1/AdipoR2 expression [16,17]. On the other hand, Staiger et al [22] found no effect of insulin on *ADIPOR1* expression in human and murine myotubes. We determined in the present report whether AdipoR1/AdipoR2 expression, as appreciated by the measurement of mRNA concentrations, was modified in the liver, skeletal muscle, and adipose tissue of rats by variations in nutritional conditions (high-carbohydrate [HCHO] vs high-fat [HF] diet and fasted state vs fed state). Given the results reported in mice suggesting that a decreased expression of adiponectin receptors could participate in the development of insulin resistance [16,17], we also determined whether these mRNA concentrations were modified in a genetic model of insulin resistance, the obese Zucker rat.

2. Materials and methods

2.1. Protocols

Male Wistar rats (4 weeks old), male obese Zucker rats, and their lean littermates (10 weeks old) were obtained from Charles River (L'Arbresle, France). All rats were housed in an animal facility with controlled temperature and a 12-hour light/dark cycle (light on at 7:00 AM and off at 7:00 PM) and had unlimited access to water. Wistar rats were first fed during 4 weeks with a standard chow diet. They were then divided into 2 groups. One group was fed during 6 weeks with an HCHO diet (n = 8) (70% CHO, 10% fat, diet D12450B of Research Diets, New Brunswick, NJ) and the other group was fed for 6 weeks with an HF diet (n = 8) (20% CHO, 60% fat with saturated and monounsaturated fatty acids, diet D12492 of Research Diets). All rats had free access to food and water. Glucose tolerance test (GTT, 1 g/kg IP) was performed in all rats after 5 weeks of HCHO or HF diet, 16 hours after food withdrawal. At the end of the 6 weeks of controlled diet, Wistar rats were studied either in the fed state (n = 4) or after a 48-hour fast (n = 4). Lean (n = 10) and Zucker (n = 10) rats were fed for 1 week with a standard chow diet and were studied in the fed state (n = 5) or after a 48-hour fast (n = 5). In all rats, after anesthesia, blood was sampled, and perirenal adipose tissue, muscles of the pelvic limb (flexor digitorum superficialis), and liver were quickly removed and snap frozen in liquid nitrogen. Samples were stored at −80°C until analysis.

2.2. Measurements of mRNA levels

Total RNA was extracted from liver and adipose tissue samples using the RNeasy total RNA kit (Qiagen, Courtaboeuf, France) and from muscles by Trizol (GIBCO, Cergy Pontoise, France) with the addition of treatment with DNAse. Concentrations and purity were verified by measuring optical density at 260 and 280 nm. Their integrity was checked by agarose gel electrophoresis. AdipoR1 and AdipoR2 mRNA concentrations were measured by reverse transcriptase–polymerase chain reaction, with cyclophilin as reference, using specific primers (for Adipor1, forward AGATGGGCTGGTTCTTCCTCAT and reverse CAGACAACTCAGACTCTTCCTC; for AdipoR2, forward ATGTTTGCCACCCCTCAGTA and reverse CAGATGTCACATTTGGCAGG; for cyclophilin, forward CCTGCTTTCACAGAATTATTCCAG and reverse CATTTGGCATGGACAAGATGCCAG). The general method is comparable to the one previously published [23,24]. In short, mRNA was reverse transcripted using thermostable reverse transcriptase (*Tth* DNA polymerase, Promega, Charbonnières, France), and complementary DNA was amplified by TaqDNA polymerase (Invitrogen, Cergy Pontoise, France). The number of PCR cycles was 24 for cyclophilin and AdipoR1/AdipoR2. Products were analyzed on agarose gel.

2.3. Metabolite and hormone concentrations

Plasma insulin concentrations were measured by enzyme-linked immunosorbent assay (Crystal Chem, Downers Grove, IL). Plasma glucose, nonesterified fatty acids (NEFAs), cholesterol, and TG concentrations were measured by enzymatic method [25].

2.4. Statistics

Results are shown as mean and SEM. Comparisons between groups were performed by 1-way analysis of variance followed by the Newman-Keuls test to locate the specific differences.

3. Results

3.1. Wistar rats

The body weight gain and the final weight of the rats fed with the HF or the HCHO diet were not different either in the fed state or after a 48-hour fasting (data not shown). Glucose and insulin concentrations were decreased by fasting in both groups, without differences between the HF and HCHO groups (Table 1). Plasma TG was also decreased by fasting and not different between the HF and HCHO groups. However, rats fed with the HF diet had higher plasma NEFA concentrations in the fed state ($P < .05$); this difference disappeared after the 48-hour fast (Table 1), which induced a rise in NEFA levels in both groups. Compared with the HCHO group, the HF group had a decrease in glucose tolerance (Fig. 1) with higher glucose levels at 15 and 30 minutes ($P < .05$) and increased area under the curve ($P < .05$).

The mRNA concentrations of AdipoR1 and AdipoR2 are shown in Fig. 2. In the fed HCHO group, AdipoR1 and AdipoR2 were expressed to comparable levels in adipose tissue as well as in liver without difference between these tissues despite a trend for lower AdipoR1 mRNA concentrations in liver. AdipoR1 mRNA levels were much higher in muscles than those of AdipoR2 mRNA ($P < .05$) and were higher than AdipoR1 mRNA concentrations in both liver and adipose tissue ($P < .05$). There were no differences in AdipoR2 mRNA concentrations between muscles, liver, and adipose tissue. Compared with the HCHO diet and the fed state, respectively, neither the HF diet nor a 48-hour fast modified AdipoR1 or AdipoR2 mRNA concentrations in muscle or adipose tissue despite a trend for higher muscle AdipoR2 mRNA levels in the HF group. AdipoR1 expression was also unchanged in liver by the fasting or the HF diet. The only modification observed was a decrease of AdipoR2 mRNA concentrations in the liver of rats fed with an HF diet; this decrease was found both in the fed ($P < .01$) and fasted ($P < .05$) states.

3.2. Zucker fatty and lean rats

Obese Zucker rats had, as expected, higher concentrations of plasma TG (2.2 ± 0.3 vs 0.6 ± 0.1 mmol/L, $P < .01$, in the fed state and 2.0 ± 0.3 vs 0.4 ± 0.1 mmol/L, $P < .05$, in the fasted state) and cholesterol (4.40 ± 0.17 vs 2.25 ± 0.11 mol/L, $P < .001$, in the fed state and 3.31 ± 0.18 vs 1.51 ± 0.09 mmol/L in the fasted state) than their lean controls. The mRNA concentrations of adiponectin receptors are shown in Fig. 3. AdipoR1 was also the predominant form of adiponectin receptors in the muscle of both lean and obese rats ($P < .05$ vs AdipoR2 in both fed and fasted states) and was more expressed than in liver and adipose

Table 1
Concentrations of plasma insulin and metabolites in Wistar rats

	HCHO groups		HF groups	
	Fed (n = 4)	Starved (n= 4)	Fed (n = 4)	Starved (n = 4)
Glucose (mmol/L)	7.77 ± 0.22	4.13 ± 0.17[a]	6.71 ± 0.12	4.44 ± 0.21[a]
Insulin (ng/mL)	5.5 ± 1.8	1.8 ± 0.8[a]	5.2 ± 0.6	0.8 ± 0.1[a]
NEFA (μmol/L)	288 ± 55	1665 ± 198[a]	641 ± 100*	1281 ± 145[a]
TG (mmol/L)	3.32 ± 0.87	0.97 ± 0.28[a]	3.18 ± 0.66	0.75 ± 0.12[a]

[a] $P < .05$ vs the fed group.
* $P < .05$ vs the corresponding group of rats fed with an HCHO diet.

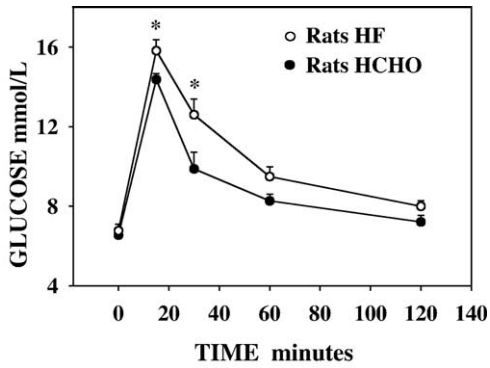

Fig. 1. Evolution of blood glucose concentration during the GTT (1 g/kg IP) in Wistar rats fed for 6 weeks with an HCHO or an HF diet. *$P < .05$ vs the corresponding sampling time of the other group.

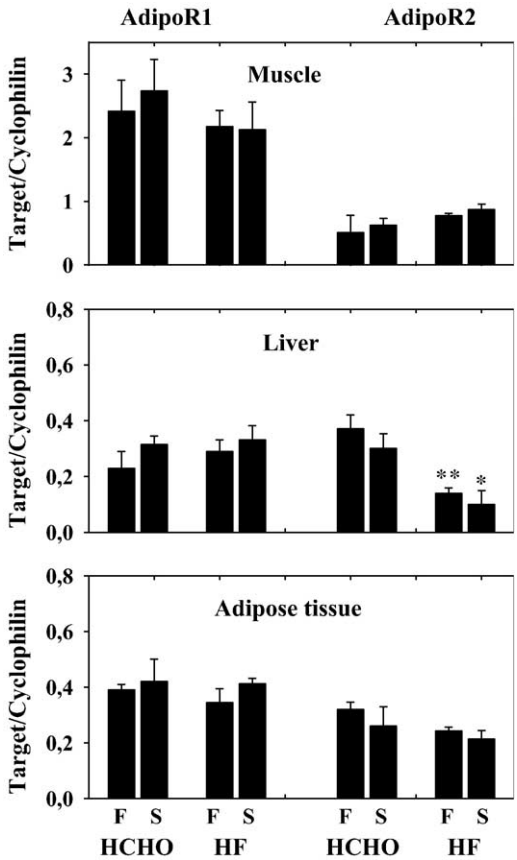

Fig. 2. Concentrations of AdipoR1 and AdipoR2 mRNA in muscle, liver, and adipose tissue of Wistar rats. *$P < .05$, **$P < .01$ vs the corresponding HCHO group of rats. F indicates fed state; S, starved state.

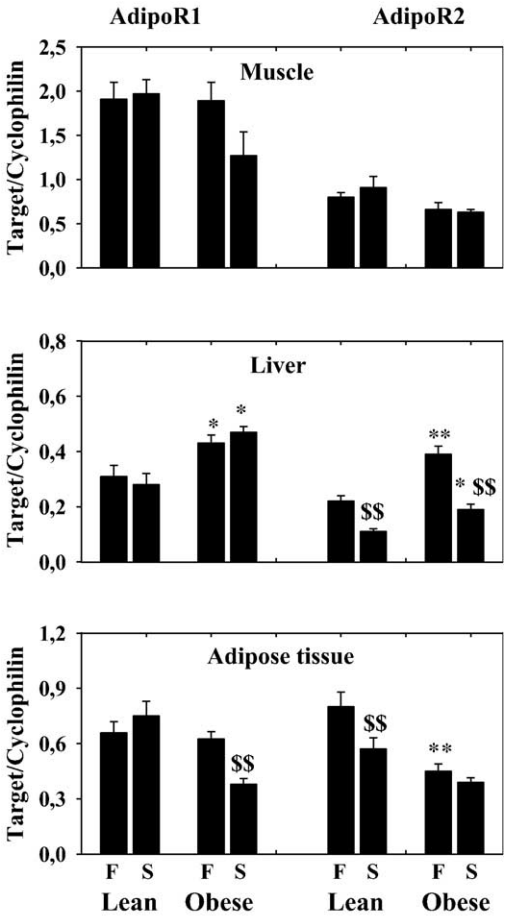

Fig. 3. Concentrations of AdipoR1 and AdipoR2 mRNA in muscle, liver, and adipose tissue of lean and obese Zucker rats. *$P < .05$, ** $P < .01$ vs the corresponding group of lean rats. $^{\$\$}P < .01$ vs the corresponding fed state.

tissue ($P < .05$ for lean and obese rats). AdipoR2 was less expressed in liver than in muscles or adipose tissue of lean rats ($P < .05$). In both groups of rats, there were no modifications of muscle AdipoR1 or AdipoR2 mRNA concentrations between the fed and fasted state, and there were no differences between the lean and obese groups. In the liver, there was no difference either in AdipoR1 expression between the fed and fasted states in both groups of rats, but obese rats had higher expression levels ($P < .05$) in both the fed and fasted states. AdipoR2 was also more expressed in the liver of obese rats, both in the fed ($P < .01$) and fasted state ($P < .05$), but the 48-hour fast induced in both groups of rats a large decrease ($P < .01$) in this expression level. In adipose tissue, obese and lean rats had comparable mRNA concentrations of AdipoR1 in the fed state; however, these concentrations were decreased by fasting only in the obese group ($P < .01$) and reached values lower than in the fasted lean group ($P < .01$). AdipoR2 mRNA levels were on the contrary lower in obese than in lean rats in the fed state ($P < .01$) and were decreased by fasting ($P < .01$) only in the lean group.

4. Discussion

The main objective of the present study was to determine whether variations of the expression of adiponectin receptors could play a role in the decreased sensitivity to insulin in experimental situations of insulin resistance, either acquired (nutritionally induced) or of genetic origin. We first examined whether variations of nutritional conditions, that is, fasting vs fed state and HF diet vs HCHO diet, modified the expression of adiponectin receptors in insulin-sensitive tissues. Feeding rats an HF diet rich in saturated fatty acids induced, as expected, a decrease in glucose tolerance. The only modification of adiponectin receptor expression observed when feeding rats this HF diet was a decrease in liver AdipoR2 mRNA concentration. One of the metabolic effects of adiponectin is to decrease the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production [26,27]. Inhibition of glucose production is one of the main mechanisms limiting the increase of plasma glucose during a GTT. Therefore, it is conceivable that the decrease in liver AdipoR2 expression that we observed had a role in the decrease in glucose tolerance induced by the HF diet. The lack of modifications of AdipoR1/AdipoR2 mRNA levels in muscle and adipose tissue suggests that variations of the expression of these receptors play, on the contrary, no role in the fat-induced insulin resistance of extrahepatic tissues.

Compared with the fed state, fasting induced no modifications of white adipose tissue AdipoR1/AdipoR2 expression in Wistar rats, whereas AdipoR2 expression was decreased in lean Zucker rats and AdipoR1 in obese Zucker rats. To our knowledge, the only other study examining the effects of fasting on adipose tissue adiponectin receptor expression is the recent report of Blücher et al [28]. These authors found that fasting induced in mice an increase in AdipoR1 and AdipoR2 expression in epididymal adipose tissue. In subcutaneous adipose tissue, on the contrary, AdipoR1 and AdipoR2 expressions were, respectively, decreased and unchanged. Therefore, the regulation of adiponectin receptor expression appears to be different from one site of adipose tissue to another. Besides species differences and variations in genetic background, this could explain the difference between our results and those of Blücher et al [28] because we investigated perirenal and not subcutaneous or epididymal adipose tissue. Blücher et al found a circadian rhythm of AdipoR1/AdipoR2 expression in adipose tissue with high mRNA concentrations between 10:00 AM and 6:00 PM and low concentrations between 8:00 PM and 6:00 AM. Whether this rhythm is present in other tissues in mice and also in other species is unknown. During our study, all tissues were collected at the same hour and, therefore, at the same period of a circadian rhythm, if this rhythm exists in rats. We also observed no modifications of muscle AdipoR1/AdipoR2 expression during fasting, either in Wistar or in lean and obese Zucker rats. In liver, fasting induced only a decrease in AdipoR2 mRNA

concentration in lean and obese Zucker rats. These results in rats contrast with those reported in mice [16,17]. Tsuchida et al [16] found in the liver of fasted mice a large increase in AdipoR1 mRNA level and a moderate rise of AdipoR2 mRNA; mRNAs for both receptors were moderately increased by fasting in skeletal muscle. Inukai et al [17] also found in mice an increase in skeletal muscle AdipoR1 mRNA during fasting, whereas AdipoR2 mRNA in liver was unchanged (values for muscle AdipoR2 mRNA and liver AdipoR1 mRNA were not reported). These authors [16,17] provided evidence for an inhibitory effect of insulin on adiponectin receptor expression, suggesting that the decrease in insulinemia during fasting played a role in the rise in adiponectin receptor mRNA levels. A role for raised plasma NEFA levels during fasting would also be conceivable because fatty acids stimulated the expression of adiponectin receptors, at least in pancreatic beta cells [15]. In the present experiments in rats, fasting induced, however, no increase in adiponectin receptor expression despite the expected fall in insulinemia and rise in plasma NEFA concentrations. There is no clear explanation to this discrepancy. It may represent differences between species. Another explanation could be differences in the timing of tissue sampling between our study and those of Tsuchida et al and Inukai et al. We sampled all our samples, in fed and fasted rats, at the same hour and, therefore, at the same period of a possible cycle of AdipoR1/AdipoR2 expression in rats. Precise timings of sampling are not given in the studies of Tsuchida et al and Inukai et al. Therefore, it cannot be determined whether differences in the sampling time between fed and fasted mice could have a role in the difference in AdipoR1/AdipoR2 expression between these nutritional states reported by these authors.

Lastly, we measured adiponectin receptor expression in a genetic model of insulin resistance, the obese Zucker rat. We found only a decrease in adipose tissue AdipoR2 mRNA in fed obese rats and in adipose tissue AdipoR1 mRNA in fasted obese rats. Both mRNA were unchanged in muscle and increased in liver. These results do not support a role for decreased expression of adiponectin receptors in the development of insulin resistance in this experimental model, contrary to what was observed in *ob/ob* mice [16]. It should be pointed out that these results in *ob/ob* mice (decreased AdipoR1 and AdipoR2 mRNA concentrations in muscles, liver, and adipose tissue) differ in part from those found in *db/db* mice [17] (unchanged expression of AdipoR2 in liver, muscle, and adipose tissue). Therefore, it is probable that modifications of adiponectin receptor expression, and the role of these receptors in the development of insulin resistance, vary from one experimental model to another. It should also be stressed that we, like others [16,17,28], investigated only male rodents. There are sex differences in plasma levels of adiponectin, in rodents and in humans, with higher values in females than in males [29-31]. Whether there are also differences in the regulation of the expression of adiponectin receptors between males and females remains to be determined. However, Debard et al [19] and Civitarese et al [18] reported no difference in the expression level of adiponectin receptors between men and women.

In conclusion, we found that adiponectin receptor expression in rats is poorly responsive to modifications of nutritional conditions and that this expression is not decreased in a genetic model of insulin resistance. As in most previous studies [14,16,18-22,28], the expression of adiponectin receptors was appreciated only by the measurement of their mRNA concentrations; however, Inukai et al [17] showed recently that variations of adiponectin receptor mRNA and protein amounts were parallel. Our results do not support an important role for variations of adiponectin receptor expression in the modulation of sensitivity of tissues to the actions of insulin. They do not preclude a role in situations of insulin resistance for modifications of the action of adiponectin at the postreceptor level, as suggested by the recent study of Chen et al [32] in cultured human skeletal muscle cells from type 2 diabetic subjects.

References

[1] Fruhbeck G, Gomez-Ambrosi J, Muruzabal F, Burrell M. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. Am J Physiol 2001;280: E827-47.
[2] Guerre-Millo M. Adipose tissue and adipokines: for better or worse. Diabetes Metab 2004;30:13-9.
[3] Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439-51.
[4] Kern P, Di Gregorio G, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin-resistance, and TNF alpha expression. Diabetes 2003;52:1779-85.
[5] Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin-resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-6.
[6] Hotta K, Funahashi T, Bodkin N, et al. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001;50:1126-33.
[7] Duncan B, Schmidt M, Pankow J, et al. Adiponectin and the development of type 2 diabetes: the Atherosclerosis Risk in Communities study. Diabetes 2004;53:2473-8.
[8] Lindsay R, Funahashi T, Hanson R, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002;360:57-8.
[9] Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 2003;14:561-6.
[10] Shimada K, Miyazaki T, Daida H. Adiponectin and atherosclerotic disease. Clin Chim Acta 2004;344:1-12.
[11] Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288-95.
[12] Tomas E, Tsao T, Saha A, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci U S A 2002;99:16309-13.
[13] Yamauchi T, Kamon J, Iot Y, et al. Cloning of adiponectin receptors that mediate antidiabetic effects. Nature 2003;423:762-9.

[14] Chinetti G, Zawadski C, Fruchart J, Staels B. Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPAR alpha, PPAR gamma and LXR. Biochem Biophys Res Com 2004;314:151-8.
[15] Kharroubi I, Rasschaert J, Eizirik D, Cnop M. Expression of adiponectin receptors in pancreatic beta cell. Biochem Biophys Res Commun 2004;312:1118-22.
[16] Tsuchida A, Yamauchi T, Ito Y, et al. Insulin/Foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. J Biol Chem 2004;279:30817-22.
[17] Inukai K, Nakashima Y, Watanabe M, et al. Regulation of adiponectin receptor gene expression in diabetic mice. Am J Physiol 2005;288:E876-82.
[18] Civitarese A, Jenkinson C, Richardson D, et al. Adiponectin receptors gene expression and insulin sensitivity in non-diabetic Mexican American with or without a family history of type 2 diabetes. Diabetologia 2004;47:816-20.
[19] Debard C, laville M, Berbe V, et al. Expression of key genes of fatty acid oxidation, including adiponectin receptors, in skeletal muscle of type 2 diabetic patients. Diabetologia 2004;47:917-25.
[20] Kaltenbach S, Staiger H, Weisser M, et al. Adiponectin receptor gene expression in human skeletal muscle cells is not regulated by fibrates and thiazolidinediones. Int J Obes Relat Metab Disord 2005;29:760-5.
[21] Fasshauer M, Klein J, Kralisch S, et al. Growth hormone is a positive regulator of adiponectin receptor 2 in 3T3-L1 adipocytes. FEBS Lett 2004;28035:27-32.
[22] Staiger H, Kaltenbach S, Staiger K, et al. Expression of adiponectin receptor mRNA in human skeletal muscle cells is related to in vivo parameters of glucose and lipid metabolism. Diabetes 2004;53:2195-201.
[23] Letexier D, Pinteur C, Large V, Frering V, Beylot M. Comparison of the expression and activity of the lipogenic pathway in human and rat adipose tissue. J Lipid Res 2003;44:2127-34.
[24] Forcheron F, Cachefo A, Thevenon S, Pinteur C, Beylot M. Mechanisms of the triglyceride and cholesterol-lowering effect of fenofibrate in hyperlipidemic type 2 diabetic patients. Diabetes 2002;51:3486-91.
[25] Diraison F, Dusserre E, Vidal H, Sothier M, Beylot M. Increased hepatic lipogenesis but decreased expression of lipogenic gene in adipose tissue in human obesity. Am J Physiol 2002;282:E46-E51.
[26] Combs T, Berg A, Obici S, Scherer P, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest 2001;108:1875-81.
[27] Berg A, Combs T, Du X, Brownlee M, Scherer P. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947-53.
[28] Blücher M, Fasshauer M, Kralisch S, Schön M, Krohn K, Paschke R. Regulation of adiponectin receptor R1 and R2 gene expression in adipocytes of C5BL/6 mice. Biochem Biophys Res Commun 2005;329:1127-32.
[29] Gui Y, Silha J, Murphy L. Sexual dimorphism and regulation of resistin, adiponectin and leptin expression in the mouse. Obes Res 2004;12:1481-91.
[30] Bottner A, Kratzsh J, Muller G, Kapellen T, Bluher S, Keller E, et al. Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. J Clin Endocrinol Metab 2004;89:4053-61.
[31] Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 2002;51:2734-41.
[32] Chen M, McAinch A, Macaulay S, et al. Impaired activation of AMK-kinase and fatty acid oxidation by globular adiponectin in cultured human skeletal muscle from obese type 2 diabetics. J Clin Endocrinol Metab 2005;90:3665-72.