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Review

Fatty acids and expression of adipokines

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Abstract

Adipose tissue has been recognised as the quantitatively most important energy store of the human body for many years, in addition to its functions as mechanical and thermic insulator. In mammals, the adipose organ is localised in several depots including white as well as brown adipose tissues. The largest depots are found subcutaneously and in the abdominal region. Several secretory proteins are synthesised in adipose tissue including leptin, resistin, adiponectin, tumor necrosis factor (TNFα), angiotensinogen, adipsin, acylation-stimulating protein, retinol-binding protein (RBP), interleukin (IL)-1b, IL-6, IL-8, IL-10, plasminogen activator inhibitor-1 (PAI-1), fasting-induced adipose factor, fibrinogen-angiopoietin-related protein, metallothionein, tissue factor (TF), complement C3, fibronectin, haptoglobin, entactin/nidogen, collagen VI α 3, pigment epithelium-derived factor (PEDF), hippocampal cholinergic neurostimulating peptide (HCNP), neutrophil gelatinase-associated lipocalin (NGAL) and adiponutrin. Fatty acids may influence the expression of adipokines like leptin, resistin or adiponectin directly by interaction with transcription factors, or indirectly via unknown mechanisms possibly linked to fatty acid oxidation, synthesis or storage. Because fatty acids are the main components of adipose tissue, it is of essential interest to clarify the biological effects of different types of fatty acids on the expression of relevant adipokines.

Keywords: Fatty acid; Adipokine; Adipose tissue; Leptin; Resistin; Adiponectin

1. Adipose tissue

Adipose tissue has been recognised as the quantitatively most important energy store of the human body for many years, in addition to its functions as mechanical and thermic insulator.

In mammals, the adipose organ is localised in several depots including white as well as brown adipose tissues. The largest depots are found subcutaneously and in the abdominal region. There is no sharp limits between the brown and white adipose tissues, and white areas contain a variable amount of brown adipocytes and their number varies with age, strain and environmental conditions [1]. Brown adipocytes have numerous small cytoplasmic lipid droplets (multilocular), whereas white adipocytes have one or two big lipid vacuoles (unilocular). Furthermore, brown adipocytes have several big mitochondria packed with cristae and expressing the thermogenic uncoupling protein 1 (UCP1). It has recently been shown that the retinoblastoma protein (pRB) regulates white vs. brown adipocyte differentiation. Functional inactivation of pRB in wild-type mouse embryo fibroblasts and white preadipocytes results in expression of the brown fat-specific uncoupling protein 1 (UCP1) in the adipose state [2]. It seems as if a physiological down-regulation of pRB may be caused by phosphorylation.

2. Endocrine function

During the last 10 years, adipose tissue has come into focus as an endocrine organ important for development many diseases related to obesity. Several secretory proteins are synthesised in adipose tissue including leptin, resistin, adiponectin, tumor necrosis factor (TNF α), angiotensinogen, adipsin, acylation-stimulating protein, retinol-binding protein (RBP), interleukin (IL)-1b, IL-6, IL-8, IL-10,

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plasminogen activator inhibitor-1 (PAI-1), fasting-induced adipose factor, a fibrinogen-angiopoietin-related protein, metallothionein, tissue factor (TF), complement C3, fibronectin, haptoglobin, entactin/nidogen, collagen VI α 3, pigment epithelium-derived factor (PEDF), hippocampal cholinergic neurostimulating peptide (HCNP), neutrophil gelatinase-associated lipocalin (NGAL) and adiponutrin [3]. Moreover, lipoprotein lipase (LPL), apolipoprotein E (apoE), cholesteryl ester transfer protein (CETP), angiotensinogen, transforming growth factor-beta (TGF-beta), nitric oxide synthase (NOS) acylation stimulating protein (ASP), adipophilin, monobutyrin, agouti protein and factors related to pro-inflammatory and immune processes have also been shown to be released by white adipocytes [4] and zinc-alpha2-glycoprotein (also named lipid mobilizing factor (LMF)) [5]. These secretory proteins from the adipose organ [1] are named adipokines and have many physiological effects on different organs including the brain, bone, reproductive organs, liver, skeletal muscles, immune cells and blood vessels [6]. The adipose organ usually accounts for 10–20% of the body weight in slim men and women, respectively, but may vary from a few % up to 70%. These dimensions make the adipose organ one of the biggest in the human body. There is a striking plasticity in the adipose organ making it possible to shrink and expand depending on the energy status, and there is an extensive integration of peripheral as well as central signals going in and out of this highly specialised tissue.

It should be recognised that >90% of the adipokine release by adipose tissue, except for adiponectin and leptin, could be attributed to non-fat cells. Visceral adipose tissue released greater amounts of vascular endothelial growth factor, IL-6, and PAI-1 compared with abdominal subcutaneous tissue [7].

3. Fatty acids

Fatty acids themselves and as part of complex lipids play a number of key roles in metabolism as a major metabolic fuel (storage and transport of energy), as essential components of all membranes and as ligands for transcription factors [8]. In addition, dietary lipids provide polyunsaturated fatty acids (PUFA) that are precursors of powerful locally acting metabolites, like the eicosanoids. Fatty acids esterified in complex lipids are also important for thermal and electric insulation, and for mechanical protection as important components of the adipose tissues.

Fatty acids or their derivatives (acyl–CoA or eicosanoids) may interact with nuclear receptor proteins that bind to certain regulatory regions of DNA and thereby alter transcription of the target genes. The receptor protein acts in combination with a fatty acid functioning as a transcription factor. The first example of this was the peroxisome proliferator-activated receptor (PPAR).

4. Leptin

Robust biological mechanisms resisting changes in body fat content are responsible for the weight regain that usually follows weight loss, provided that food is available [9]. Several hormones play important roles in keeping body weight stable. Leptin is one of the adipokines that may be of marked importance in the regulation of body fat [10]. This 16-kDa peptide is expressed and secreted in proportion to adipocyte size and number and circulates in plasma in a concentration highly correlated with body fat mass. Administration of recombinant leptin to mice with mutations in the leptin gene indicated that leptin participates in the regulation of food intake and energy expenditure. However, because there are large variations in leptin concentrations among individuals with similar body compositions, it is likely that factors other than adipose mass influence plasma leptin concentrations. Potential modifiers of leptin concentrations are energy-yielding nutrients such as fatty acids, carbohydrates, proteins, and alcohol. Moreover, physical activity is important for long-term regulation of body weight, partly because it increases the resting metabolic rate, but the effects of exercise on plasma leptin concentrations, independent of fat mass, are conflicting [11,12].

5. Prospective study of pregnant women

It has been well documented that women with pre-eclampsia have high levels of plasma lipids including cholesterol, triglycerides and free fatty acids [13]. In a prospective study of 2190 pregnant women, we compared plasma leptin, transforming growth factor-beta(1) (TGF-beta(1)) and plasminogen activator inhibitor type 2 (PAI-2) concentrations at 18 weeks' gestation in 71 women with subsequent pre-eclampsia and 71 controls matched for age, parity and first trimester body mass index [14]. Leptin and TGF-beta(1) concentrations were significantly lower and PAI-2 concentration higher in women destined to develop pre-eclampsia relative to controls. These results initiated some intervention studies among pregnant women as well as men in the time to follow.

6. Intervention studies with altered dietary fatty acids

We studied the effect of supplementation with marine n-3 fatty acids on plasma concentration of leptin among women from week 17 of their pregnancy [15]. The study was randomised and double-blinded, and the participants received either 10 mL of cod liver oil daily or the same amount of corn oil. Blood samples were taken from the mothers during pregnancy in weeks 18 and 35, and from the umbilical cord and from 4- and 14-week-old infants. We found no differences between the group receiving cod liver oil and the group receiving corn oil in any of the measured

variables; thus, the groups are treated statistically as one. The leptin levels of the mothers increased during pregnancy and correlated to BMI, but the relative leptin concentration (plasma leptin concentration/BMI) did not change. Our findings demonstrated that girls have higher plasma leptin concentrations than boys already at birth. A reduction of 61% in plasma leptin concentration was found from birth to 4 weeks of age. The increase in plasma leptin concentration from 4 to 14 weeks of age can be explained by the increase in weight during the same period.

7. Diet and exercise

We performed another human intervention study to examine whether changes in lifestyle among sedentary individuals [16] had any effects on plasma leptin concentrations [17].

In a randomized, 2×2 factorial trial, 186 men with the metabolic syndrome were divided into four groups: diet, exercise, a combination of diet and exercise, and control. Data on dietary intake, physical fitness, and demographics were collected and plasma leptin concentrations were measured before and after a 1-year intervention period. We observed that plasma leptin concentrations, body mass index, and fat mass decreased in association with long-term reductions in food intake as well as increased physical activity. By adjusting for either body mass index or fat mass, we observed a highly significant reduction in plasma leptin concentration after both the diet and the exercise interventions. There was no interaction between the interventions, suggesting a direct and additive effect of changes in diet and physical activity on plasma leptin concentrations. Thus, long-term changes in lifestyle consisting of decreased intake of dietary fat and increased physical activity reduced plasma leptin concentrations in humans beyond the reduction expected as a result of changes in fat mass [17].

Because the dietary intervention in the ODES study included less saturated fatty acids and more polyenes, we proceeded to examine the effect of different dietary fatty acids on the plasma concentration of leptin [18]. The study was carried out as a randomised, double-blinded, placebo-controlled trial to assess the effects of marine n-3 FA and antioxidants, alone or in combination, over a period of 6 weeks. The participants were randomly allocated to one of four groups receiving supplementation with either 5 g of EPA (20:5 n-3) and DHA (22:6 n-3); a mixture of 75 mg vitamin E, 150 mg vitamin C, 15 mg β-carotene, and 30 mg Coenzyme Q10; a combination of n-3 FA and antioxidants; or control oil. The FA control capsule contained 5 g of oil with a FA pattern similar to an ordinary Norwegian diet, whereas the antioxidant control capsule contained peanut oil only. We observed no significant effects of placebo-controlled dietary supplementation with n-3 FA and/or antioxidants on plasma leptin concentration or body weight in men. Baseline leptin concentration for all individuals correlated to body weight (r=0.477, P<0.001) and body mass index (r=0.534, P<0.001).

Plasma leptin concentration correlated negatively with dietary intake of PUFA, but failed to be statistically significant. No correlation was found with the intake of total energy or other nutrients. Furthermore, we observed a positive correlation (P=0.003) between the changes (difference between week 6 and baseline values) in dietary intake of saturated FA (as % of total fat) and the change in plasma leptin concentration in the n-3 FA group. A significant negative correlation was found between changes in the intake of PUFA and changes in plasma leptin concentration. In the combined n-3 FA/antioxidant group, no correlation between change in plasma leptin concentration and change in dietary intake of fat was observed. When combining the two groups receiving n-3 FA supplementation, the changes in dietary intake of saturated FA correlated positively (P=0.03), and changes in dietary intake of PUFA correlated negatively (P=0.02), to changes in plasma leptin concentrations [18].

8. Feeding marine fatty acids to rats

Because changes in n-3 fatty acid intake correlated negatively to changes in plasma leptin concentration among men, we examined the effect of n-3 FA-enriched diets on plasma leptin concentration in rats. We observed a non-significantly lower plasma leptin level in rats fed an n-3 FA-enriched diet as compared with a lard-enriched diet but the relative expression of leptin mRNA in epididymal adipose tissue was lower in the n-3 FA group than in the lard group (P=0.012). No significant differences in weight gain was found between the two feeding groups.

In another feeding study, we supplied rats with high levels of fatty acids in the diet including lard as well as marine n-3 fatty acids [19]. Two groups of male Wistar rats were fed either a high-fat diet [28% (w/w) of saturated fat] or a high-fat diet containing 10% n-3 PUFA and 18% saturated fat for 3 weeks. The hypotriglyceridemic effect of n-3 PUFA was accompanied by increased hepatic oxidation of palmitoyl-CoA (125%, P<0.005) and palmitoyl-L-carnitine (480%, P<0.005). These findings were corroborated by raised carnitine palmitoyltransferase-2 activity (154%, P<0.001) and mRNA levels (91%, P<0.01) as well as by simultaneous elevation of hepatic peroxisomal acyl-CoA oxidase activity (144%, P<0.01) and mRNA content (82%, P<0.05). In contrast, hepatic carnitine palmitoyltransferase-1 activity remained unchanged despite a twofold increased mRNA level after n-3 PUFA feeding. Skeletal muscle FA oxidation was less affected by dietary n-3 PUFA, and the stimulatory effect was found only in peroxisomes. Dietary intake of n-3 PUFA was followed by increased acyl-CoA oxidase activity (48%, P<0.05) and mRNA level (83%, P<0.05) in skeletal muscle. The increased FA oxidation after n-3 PUFA supplementation of the high-fat diet was

accompanied by lower plasma leptin concentration (−38%, $P<0.05$) and leptin mRNA expression (−66%, $P<0.05$) in retroperitoneal adipose tissue, and elevated hepatic mRNA level for the leptin receptor Ob-Ra (140%, $P<0.05$). Supplementation of the high-fat diet with n-3 PUFA enhanced in vivo insulin sensitivity, as shown by normalisation of the glucose infusion rate during euglycemic hyperinsulinemic clamp. Our results indicate that the hypotriglyceridemic effect of dietary n-3 PUFA is associated with stimulation of FA oxidation in the liver and to a smaller extent in skeletal muscle. This may ameliorate dyslipidemia, tissue lipid accumulation, and insulin action, in spite of decreased plasma leptin level and leptin mRNA in adipose tissue. Another interpretation is that reduced fatty acid synthesis and/or increased fatty acid oxidation may promote the reduced plasma leptin concentration.

9. Effects of fatty acids on leptin expression in cultured cells

These findings led us to perform in vitro experiments where we examined the effects of fatty acids directly on cultured cells expressing leptin [18]. In cultured BeWo cells, we observed that both EPA (20:5 n-3) and DHA (22:6 n-3) reduced the relative expression of leptin mRNA significantly, whereas palmitic or oleic acid had no significant effect. We observed similar results in the murine 3T3-L1 cells. Incubation with FA had no effect on the expression of the long signal transducing form of the human leptin receptor (OB-Rb) in BeWo cells. Constructs of the leptin promoter linked to a luciferase reporter gene were used in transiently transfected BeWo cells to study human leptin promoter activity in response to different FAs. Leptin promoter activity of the pGL3-ob1 construct (containing 2.9 kb of the human leptin promoter) was reduced by incubation with EPA to 28±1% ($P<0.001$) and DHA to 17±9% ($P<0.001$) of control, whereas incubation with palmitic and oleic acid had no significant effects. A similar expression pattern was found for the pGL3-ob2 construct (containing 0.2 kb of the proximal human leptin promoter).

The pGL3-ob2 construct of the leptin promoter contains an E-box with the potential to bind SREBP and a functional C/EBP element, but no sequence similarity was observed to any known peroxisome proliferator-activated receptor element (PPRE). The PPAR agonist BRL 49653 reduced the luciferase activity in BeWo cells transfected with the pGL3-ob2 construct in a time- and dose-dependent manner. After 72-h incubation with 1 and 10 μM BRL 49653, the activity of the proximal part of the leptin promoter was reduced to 53±13% and 35±3% of control, respectively. Northern blot analysis showed that incubation with 0.5 mM oleic acid, EPA, and DHA for 48 h reduced the expression of PPAR mRNA to 55±7%, 28±6%, and 31±11%, respectively. SREBP-1 expression was also reduced to 55±15%, 24±10%, and 27±4% by oleic acid, EPA, and DHA, respectively, whereas no significant effect on C/EBP expression was observed. The mature, nuclear form of SREBP-1 is known to increase when cells are starved of cholesterol. After activation of SREBP by starving the cells for cholesterol in LPDS-supplemented medium, we observed that most of the effect of DHA on leptin mRNA expression was abolished. DHA reduced the leptin mRNA level to 24±15% in BeWo cells cultured in FCS-supplemented medium, whereas the leptin mRNA level was not significantly different from the basal expression (82±16%) when DHA was added to the LPDS-supplemented medium. This indicates that leptin expression is not reduced by DHA when cells are grown under cholesterol-deficient conditions.

Thus, n-3 FA decreased leptin gene expression both in vivo and in vitro. The direct effects of PUFA on leptin promoter activity indicate a specific regulatory action of FA on leptin expression. This is accordance with newer observations in rat adipocytes [20].

10. Resistin

The resistin gene is expressed in adipocytes and encodes a protein proposed to link obesity and type 2 diabetes [21]. Elevated plasma FFA is associated with insulin resistance. We examined the effect of separate FFAs on the expression of resistin mRNA in cultured murine 3T3-L1 adipocytes [22]. The FFAs tested did not increase resistin expression, whereas both arachidonic acid (AA) and eicosapentaenoic acid (EPA) reduced resistin mRNA levels. AA was by far the most potent FFA, reducing resistin mRNA levels to ~20% of control at 60–250 μM concentration. Selective inhibitors of cyclooxygenase (COX)-1, and of mitogen-activated protein kinase (MAPK) kinase (MEK), counteracted AA-induced reduction in resistin mRNA levels. Transient overexpression of sterol regulatory element-binding protein (SREBP)-1a activated the resistin promoter, but there was no reduction in the abundance of ~65 kDa mature SREBP-1 after AA-exposure. Actinomycin D as well as cycloheximide abolished AA-induced reduction of resistin mRNA levels, indicating dependence on de novo transcription and translation. Our data may suggest that reductions in resistin mRNA levels involve a destabilisation of the resistin mRNA molecule. An inhibitory effect of AA and EPA on resistin expression may explain a beneficial effect of ingesting PUFA on insulin sensitivity.

11. Adiponectin

Plasma concentration of adiponectin is lower in subjects with obesity, type-2 diabetes mellitus, and coronary heart

disease as compared to healthy controls [10,11,23,24]. These findings indicate that adiponectin may represent a biological link between obesity and obesity-related disorders such as atherosclerosis and diabetes. Moreover, adiponectin has been found to increase with weight loss, and be negatively correlated with changes in body mass index (BMI), waist and hip circumference and plasma glucose levels [25]. Lifestyle parameters like diet composition and physical activity are linked to obesity, type-2 diabetes mellitus, and cardiovascular diseases. We have previously reported on a clinical trial in men with clear signs of the metabolic syndrome, in which 1-year changes in physical activity and diet, alone or in combination, decreased plasma leptin concentration beyond the expected reduction due to changes in body weight and fat mass [17]. Furthermore, blood pressure, plasma triglycerides, C-peptide, HDL cholesterol, and carbohydrate metabolism, including insulin variables, were also significantly and favorably improved, demonstrating that simple intervention measures can be beneficial in reducing risk of disease [4,5,26]. The present study was carried out to investigate the influence on plasma adiponectin concentration of the 1-year program of dietary and exercise intervention, in which the control group maintained body mass index and fat mass during the year, while all three intervention groups lost about 1 kg/m^2 of BMI and 1 kg of fat mass [17]. We observed a significantly higher plasma concentration of adiponectin among the men that reduced their body fat mass by exercise and diet, largely explained by reduced body fat mass [27].

12. Final conclusions

Fatty acids may influence the expression of adipokines like leptin, resistin, or adiponectin directly by interaction with transcription factors, or indirectly via unknown mechanisms possibly linked to fatty acid oxidation, synthesis, or storage. Because fatty acids are the main components of adipose tissue, it is of essential interest to clarify the biological effects of different types of fatty acids on the expression of relevant adipokines. Moreover, it is important to describe the precise mechanisms by which fatty acids execute their effects on adipokines, to gain enough knowledge to intelligently interfere with harmful effects of adipokines.

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