The effects of exercise and adipose tissue lipolysis on plasma adiponectin concentration and adiponectin receptor expression in human skeletal muscle
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Abstract
Objective: It has been suggested that adiponectin regulates plasma free fatty acid (FFA) clearance by stimulating FFA uptake and/or oxidation in muscle. We aimed to determine changes in plasma adiponectin concentration and adiponectin receptor 1 and 2 mRNA expression in skeletal muscle during and after prolonged exercise under normal, fasting conditions (high FFA trial; HF A) and following pharmacological inhibition of adipose tissue lipolysis (low FFA trial; LF A). Furthermore, we aimed to detect and locate adiponectin in skeletal muscle tissue.

Methods: Ten subjects performed two exercise trials (120 min at 50% VO2max). Indirect calorimetry was used to determine total fat oxidation rate. Plasma samples were collected at rest, during exercise and during post-exercise recovery to determine adiponectin, FFA and glycerol concentrations. Muscle biopsies were taken to determine adiponectin protein and adiponectin receptor 1 and 2 mRNA expression and to localise intramyocellular adiponectin.

Results: Basal plasma adiponectin concentrations averaged 6.57±0.7 and 6.63±0.8 mg/l in the HF A and LF A trials respectively, and did not change significantly during or after exercise. In the LF A trial, plasma FFA concentrations and total fat oxidation rates were substantially reduced. However, plasma adiponectin and muscle adiponectin receptor 1 and 2 mRNA expression did not differ between trials. Immunohistochemical staining of muscle cross-sections showed the presence of adiponectin in the sarcolemma of individual muscle fibres and within the interfibrillar arterioles.

Conclusion: Plasma adiponectin concentrations and adiponectin receptor 1 and 2 mRNA expression in muscle are not acutely regulated by changes in adipose tissue lipolysis and/or plasma FFA concentrations. Adiponectin is abundantly expressed in muscle, and, for the first time, it has been shown to be present in/on the sarcolemma of individual muscle fibres.

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Introduction
Adiponectin, also known as Acrp30 (1, 2), adipoQ (3), apM-1 (4) and GBP28 (5) is a circulating hormone secreted by adipose tissue. Correlation studies have demonstrated that reduced adiponectin expression and/or low plasma adiponectin concentrations are associated with obesity (6), insulin resistance (7) and/or coronary artery disease (8). Moreover, exogenous adiponectin administration has been shown to improve insulin sensitivity in obese diabetic (9) and adiponectin-knockout mice (10). Although the exact physiological function of adiponectin remains to be established, it has been suggested that adiponectin plays a regulatory role in substrate metabolism in liver (11) and skeletal muscle (2).

Both weight loss and exercise have proven effective in the prevention and treatment of arteriosclerosis and skeletal muscle insulin resistance (12–14). Whereas weight loss and/or energy intake restriction have been associated with elevated plasma adiponectin concentrations (7, 8), studies investigating the effects of exercise on adiponectin release have provided inconsistent findings (15–22). Kraemer et al. (15) investigated the acute effects of short-term, running exercise on plasma adiponectin secretion in healthy subjects but observed no changes. Other studies, exploring the more long-term benefits of exercise training, also reported no changes in basal plasma adiponectin concentration (16–18, 22). In contrast, Kriketos et al. (19) recently reported substantially elevated fasting plasma adiponectin levels (260% above baseline...
values) after 2–3 bouts of low to moderate intensity exercise. Studies investigating the acute effects of prolonged, moderate intensity exercise are presently lacking. Therefore, the first aim of the present study was to determine plasma adiponectin concentrations during and after a single bout of prolonged, moderate intensity exercise in healthy, lean men. In rodent studies, adiponectin has been reported to regulate plasma free fatty acid (FFA) clearance by stimulating skeletal muscle FFA uptake (10) and/or oxidation (2, 9). In line with these findings, it has been suggested that adiponectin release is acutely regulated by circulating plasma FFA concentrations (23, 24). Consequently, we speculated that pharmacological inhibition of adipose tissue lipolysis during and after exercise likely reduces plasma FFA availability and, as such, could prevent any exercise-induced changes in adiponectin release. As such, our second aim was to determine plasma adiponectin concentrations during and after prolonged exercise following administration of a nicotinic acid analogue.

Evidence to support the contention that adiponectin represents one of the hormones that mediate the cross-talk between adipose tissue and skeletal muscle is accumulating (2, 9, 25, 26). As such, it has been speculated that adiponectin must be located on the surface of and/or inside skeletal muscle fibres for signalling purposes. Therefore, our third aim was to determine the presence of adiponectin in human skeletal muscle tissue. Furthermore, we applied immunohistochemical staining on muscle cross-sections to localise intramuscular adiponectin. Furthermore, following the discovery of the adiponectin receptor 1 and 2 (27), it has been suggested that the proposed effects of adiponectin on skeletal muscle metabolism might also be regulated at the receptor level. Therefore, our fourth aim was to measure adiponectin receptor 1 and 2 mRNA expression in skeletal muscle tissue obtained at rest, following exercise and after 2 h of subsequent recovery under normal, fasting conditions and following pharmacological inhibition of adipose tissue lipolysis.

Materials and methods

Subjects

Ten active male subjects (age: 23±1 years; height: 1.82±0.03 m; body weight: 74±3 kg; body fat: 13.2±0.9%; fat free mass: 64±3 kg; maximal power output (Wmax): 388±14 W; oxygen uptake capacity (VO2max): 62±3 ml/kg bodyweight/min) were selected to participate in this study, which is part of a greater project investigating the metabolic consequences of reduced plasma FFA availability. Subjects were informed about the nature and risks of the experimental procedures before their written informed consent was obtained. This study was approved by the local Medical Ethical Committee and performed according to the guidelines set by the Declaration of Helsinki.

Pre-testing

Wmax and VO2max were measured on an electronically braked cycle ergometer (Lode Excalibur, Groningen, The Netherlands) during an incremental exhaustive exercise test one week before the first experimental trial (28). Body composition was assessed using the hydrostatic weighing method in the morning after an overnight fast. Simultaneously, residual lung volume was measured by the helium-dilution technique. Body fat percentage was calculated using Siri’s equation (29). Fat free mass (FFM) was calculated by subtracting fat mass (FM) from total body weight.

Diet and activity prior to testing

All subjects maintained normal dietary and physical activity patterns throughout the experimental period. They refrained from heavy physical labour and exercise training for at least 3 days prior to each trial and filled out a food intake diary for 2 days prior to the first trial to keep dietary intake as identical as possible prior to the other trial. The evening before each trial, subjects received the same standardised meal (41.2 kJ/kg body weight; consisting of 72 energy % (En%) carbohydrate, 11 En% fat and 17 En% protein).

Experimental trials

Each subject performed two similar trials, separated by at least one week. Each trial consisted of 90 min of resting measurements, followed by 120 min of cycling exercise (50% Wmax) and a 120 min recovery period. In both trials, blood samples were collected at regular time intervals. In addition, percutaneous muscle biopsies were taken from the vastus lateralis muscle before, immediately after and 2 h after exercise. In one trial (low FFA; LFA), adipose tissue lipolysis was inhibited by oral administration of a nicotinic acid analogue (500 mg Acipimox). In the other trial (high FFA; HFA), a placebo was administered. Both trials were performed in randomised order and executed in a double blind fashion.

Protocol

After an overnight fast, subjects arrived at the laboratory at 0800 h by car or public transportation. After 30 min of supine rest, a percutaneous muscle biopsy was taken from the vastus lateralis muscle. A Teflon catheter (Baxter, Utrecht, The Netherlands) was inserted into an antecubital vein for blood sampling, after which a resting blood sample was taken. At t = 0 and t = 165 min, a capsule containing 250 mg Acipimox (Nedios, Byk, Zwanenburg, The Netherlands) was ingested in a double blind fashion.
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Blood sample analysis

Blood samples (7 ml) were collected in EDTA-containing tubes and centrifuged at 1000 × g at 4 °C for 10 min. Plasma aliquots were frozen immediately in liquid nitrogen and stored at −80 °C until analyses. Plasma glucose (Uni Kit III, Roche, Basel, Switzerland), FF A (NEF A-C, Wako Chemicals, Neuss, Germany), and free glycerol (148270, Roche, Indianapolis, IN, USA) concentrations were analysed by radioimmunoassay (Linco Diagnostics Inc., St Charles, MO, USA).

Immunohistochemistry

Muscle samples were dissected and frozen in liquid nitrogen. About 15 mg muscle were frozen in nitrogen-cooled isopentane and embedded in Tissue-Tek (Sakura Finetek, Zoeterwoude, The Netherlands). Multiple serial sections (5 µm) were thaw mounted on uncoated, pre-cleaned glass slides, fixed in formaldehyde and incubated overnight with a Acrp30/adiponectin monoclonal antibody (MAB 10 651, R&D Systems Inc, Minneapolis, MN, USA), and a laminin polyclonal antibody (Sigma Diagnostics, Steinheim, Germany). After washes with PBS, sections were incubated with appropriate conjugated secondary antibodies: GAMlgG2B Alexa555, GARlgGAlexa488 (Molecular Probes, Leiden, The Netherlands). Thereafter, sections were embedded in Mowiol-Tris (Calbiochem, Omnilabo, Etten-Leur, The Netherlands) containing 0.5 µg/ml 4′,6′-diamino-2-phenylindole (DAPI, Molecular Probes). Slides were examined using a Nikon E800 fluorescence microscope (Uvikon, Bunnik, The Netherlands) coupled to a Basler A113 C progressive scan colour charge-coupled device (CCD) camera. Appropriate controls, applying only primary or secondary antibodies, showed no signal.

Immunoblotting

About 30 mg muscle tissue were sonicated in ice-cold buffer (20 mmol/l HEPES (pH 7.4), 100 mmol/l KCl, 50 mmol/l beta-glycerophosphate, 50 mmol/l NaF, 1 mmol/l dithiothreitol, 0.5 mmol/l Na3VO4, 0.2 mmol/l EDTA, 2 mmol/l EGTA, 0.1 mmol/l PMSF and 1 mmol/l benzamidine). Homogenates were centrifuged for 5 min at 10 000 × g and at 4 °C. Thereafter, the supernatant was centrifuged (at 10 000 × g and at 4 °C for 10 min) and resolved in SDS-buffer. Human plasma was used as a positive control for adiponectin protein expression. First, albumin was filtered from the plasma sample, using the SwellGel Blue albumin removal kit (89 845, Pierce Biotechnology, Rockford, IL, USA). After boiling the samples, denatured protein from a subset of 20 plasma samples (each containing ~6 µg protein) and 10 different muscle samples (each containing ~50 µg protein) were run on 15% SDS-polyacrylamide gels and transferred onto 0.45 µm nitrocellulose membranes. Membranes were exposed to a 1:1000 dilution of a monoclonal anti-human Acrp30/adiponectin antibody (MAB 10 651) and incubated in a 1:10 000 dilution of horseradish peroxidase-conjugated antibody (Pierce). Light sensitive film (CL-Xposure; Pierce) was used to detect immunoreactive bands using chemiluminescent substrate (SuperSignal CL; Pierce).

PCR methodology

Total RNA was extracted from 10–15 mg wet muscle as previously described (30). cDNA was obtained using AMV Reverse Transcriptase and Oligo (dT)15 Primers (Promega, Madison, WI, USA). Samples were analysed in triplicate to detect adiponectin 1 and 2 receptor and cyclophilin mRNA transcripts using real time RT-PCR (Gene Amp 5700 sequence detection system, Applied Biosystems, Foster City, CA, USA) as previously described (30) using primer sequences obtained from GenBank (adiponectin receptor 1 – NM_0159999: forward primer, cgccatggaagatggga; reverse primer, tcatatggagtacctctca; adiponectin receptor 2 – NM_024551: forward primer, ggtatccc- gaacgttttt; reverse primer, ttagacaccatggaattg). A BLAST search confirmed homologous binding (31). Input cDNA concentrations were normalised for the housekeeping gene (cyclophilin-X52851: forward primer, catatgcaatgcagaagctga; reverse primer, tcatgccttcttaccttgc).

Calculations

From respiratory measurements, total fat and carbohydrate oxidation rates were calculated using the
non-protein respiratory quotient (32).

Fat oxidation rate = 1.695 VO₂ – 1.701 VCO₂

Carbohydrate oxidation rate

= 4.585 VCO₂ – 3.226 VO₂

with VO₂ and VCO₂ in l/min and oxidation rates in g/min.

Statistics

All data are expressed as means±S.E.M. To compare substrate utilisation rates and plasma metabolite concentrations over time within a trial, a one-way repeated measures analysis of variance (ANOVA) was applied. To enable comparisons between trials, a two-way repeated measures ANOVA was applied. A Scheffe’s post-hoc test was applied in case of a significant F-ratio to locate specific differences. For non-time-dependent variables, a Student’s t-test for paired observations was used.

Results

Plasma metabolites

Plasma FFA concentrations increased substantially during exercise in the HFA trial (P < 0.001). During recovery, plasma FFA levels declined but remained well above pre-exercise resting levels (P < 0.001). In contrast, in the LFA trial, plasma FFA levels declined following Acipimox administration at rest, after which they remained below or at near baseline values throughout exercise and post-exercise recovery. Plasma FFA levels were significantly lower in the LFA versus the HFA trial (P < 0.001; Fig. 1A). Plasma glycerol concentrations increased substantially during exercise in the HFA trial (P < 0.001). During recovery, plasma glycerol levels declined but remained well above pre-exercise resting values (P < 0.001). In the LFA trial, a small but significant increase in plasma glycerol was observed following the onset of exercise (P < 0.01). Thereafter, glycerol levels declined to pre-exercise resting values. Plasma glycerol levels were significantly lower in the LFA compared with the HFA trial (P < 0.001; Fig. 1B). Plasma glucose concentrations declined during exercise in both trials (P < 0.001). During post-exercise recovery, plasma glucose levels remained below pre-exercise resting values. No significant differences in plasma glucose concentrations were observed between trials (Fig. 1C).

Substrate utilisation

Total fat and carbohydrate oxidation rates as well as total energy expenditure at rest, during exercise and during post-exercise recovery are provided in Table 1.

Total fat oxidation rates were substantially lower at rest, during exercise as well as during recovery in the LFA compared with the HFA trial (P < 0.05). Total carbohydrate oxidation rates were greater in the LFA trial when compared with the HFA trial. Energy expenditure at rest, during exercise and during subsequent recovery were similar between trials (Table 1).
Plasma adiponectin concentrations

Fasting plasma adiponectin concentrations averaged $6.57 \pm 0.7$ and $6.63 \pm 0.8$ mg/l before the HF A and LF A trials respectively (not significantly different). No significant changes in plasma adiponectin concentrations were observed over time in the LF A or HF A trial. No differences in circulating adiponectin were observed between trials ($P=0.989$) (Fig. 2).

Immunolocalisation

Immunohistochemistry performed on skeletal muscle cross-sections showed adiponectin present in the sarcolemma of skeletal muscle fibres (Fig. 3A). As we applied an antilaminin antibody as a marker for the sarcolemmal and vascular walls (Fig. 3B), adiponectin is shown to be present on the sarcolemma of the individual muscle fibres as well as in/on the vascular endothelial lining of the interfibrillar arterioles (Fig. 3A). Adiponectin does not seem to be present in the cytosol nor does it seem to be associated with the muscle fibres’ nuclei (Fig. 3C). These findings have been verified with two different anti-human adiponectin antibodies (MAB 10651 and AF1065; R&D Systems, Inc.). No differences in adiponectin signal intensity or localisation were observed between biopsies collected before, immediately after or 2 h after exercise. No differences were observed between trials.

Adiponectin protein expression

Adiponectin protein expression in plasma and skeletal muscle tissue was visualised by Western blotting. Membranes probed with a primary monoclonal antibody (MAB 10651) raised against an epitope in the globular domain (gAcrp30, amino acids 104–244) of full-length adiponectin protein showed three bands at 28 kDa, 55 kDa and 85 kDa according to the molecular weight marker. These three bands likely correspond with the adiponectin monomeric (1, 5, 33, 34), dimeric (2, 5, 34) and trimeric (1, 6, 34) forms. The band observed between 28 and 34 kDa likely represents one (or more) of the glycolysated isoforms (35). Whereas in plasma all three bands were shown, only the 28 kDa and 85 kDa bands were observed in muscle (Fig. 4). The blot depicted is representative for the muscle samples analysed.

Adiponectin receptor 1 and 2 mRNA expression

Skeletal muscle adiponectin receptor 1 and 2 mRNA content at rest, after exercise and after 2 h recovery are shown in Fig. 5A and B respectively. Adiponectin receptor 1 mRNA was more abundantly (25- to 70-fold) expressed compared with receptor 2. Muscle mRNA contents are expressed relative to corresponding

![Graph](image-url)
baseline values, set to equal 1. Adiponectin receptor 1 mRNA expression did not change with time in the HF A or LF A trial and did not significantly differ between groups (P > 0.05). Adiponectin receptor 2 mRNA content decreased significantly in the HF A trial only (P = 0.02). Differences in adiponectin receptor 2 mRNA content between trials did not reach statistical significance (P = 0.08).

Discussion
Since the discovery of the various adipocytokines, it has become apparent that adipose tissue is actively involved in the regulation of skeletal muscle metabolism. Recently, adiponectin has received much interest due to the observation that plasma adiponectin levels are reduced in the obese and/or type 2 diabetic state (3, 6–8, 36–43). In line with these observations, dietary interventions (8, 20, 44) as well as pharmacological treatment with thiazolidinediones (34, 45–50) to improve insulin sensitivity have been shown to elevate adiponectin concentrations. Although an acute bout of exercise and exercise training substantially improve insulin sensitivity (13, 14), their effect on plasma adiponectin remains to be elucidated (15–22). In rodent studies, adiponectin has been shown to regulate plasma FFA clearance by stimulating skeletal muscle FFA uptake (10) and/or oxidation (2, 9). With adipose tissue lipolysis and plasma FFA appearance rates reaching maximal levels during prolonged, low to moderate intensity exercise (51, 52), we speculated that potential exercise-induced changes in plasma adiponectin concentration would be most prominent during or immediately after such exercise tasks. However, in accordance with earlier observations in athletes during short, high-intensity running exercise (15), we did not observe any...
changes in plasma adiponectin concentration under exercise conditions. Even though adipose tissue lipolysis and fat oxidation rates were substantially elevated in the placebo trial (HF A; Table 1 and Fig. 1), plasma adiponectin concentrations remained unaffected during or after prolonged exercise (Fig. 2).

In accordance, studies exploring the benefits of participation in a long-term exercise training regimen generally report no changes in basal plasma adiponectin concentrations (16 – 18, 22). In contrast, Kriketos et al. (19) reported a massive increase in fasting plasma adiponectin levels after 2 – 3 bouts of low to moderate intensity exercise performed within a one-week period. Although it could be speculated that the inclusion of overweight, sedentary males in their study could be responsible for the apparent discrepant findings (19), others have failed to report such changes in a similar population after 6 months of exercise training (18). Therefore, further research is warranted to confirm the proposed effects of a short period of exercise training on plasma adiponectin levels. We conclude that adiponectin release is unrelated to the acute, temporary increase in adipose tissue lipolytic rate, plasma FFA concentration and/or whole-body fat oxidation rate during and immediately after prolonged, moderate intensity exercise in healthy, lean males.

Several groups have speculated on the proposed negative association between basal circulating adiponectin and plasma FFA and/or triglyceride concentrations (7, 53) and suggested that adiponectin release might be under acute negative feedback control by plasma FFA concentrations (23, 24). To investigate this, Staiger et al. (23) reduced plasma FFA availability in vivo in healthy males by administration of a nicotinic acid analogue (Acipimox) which specifically inhibits adipose tissue lipolysis (54, 55). The decline in plasma FFA levels observed in that study did not reduce plasma adiponectin concentrations (23). In contrast, Bernstein et al. (24) recently performed a similar study in which they reported a ~40% decline in plasma adiponectin concentrations following Acipimox administration. In the present study, plasma FFA availability was reduced at rest, during exercise and during post-exercise recovery by Acipimox administration in the LF A trial. We observed a pronounced reduction in plasma FFA and glycerol concentrations (Fig. 1) and whole-body fat oxidation rates (Table 1). However, the latter did not affect plasma adiponectin concentrations (Fig. 2). Furthermore, no differences were observed between the HFA and LF A trials. In accordance with Staiger et al. (23), we conclude that adiponectin release is unrelated to an acute, temporary decline in adipose tissue lipolytic rate, plasma FFA concentration and/or whole-body fat oxidation rate in healthy, lean males. As such, our data imply that there are other, more important, factors that mediate adiponectin production and/or release by adipose tissue. The latter likely include adipocyte size and/or lipid content of the adipocyte, circulating catecholamines, glucocorticoids, tumour necrosis factor α, and/or interleukin-6 (56). As animal work and human correlation studies still point towards an important regulatory role of circulating plasma adiponectin concentration on skeletal muscle metabolism (2), we speculated that adiponectin may be present in human skeletal muscle tissue. In accordance, Western blotting analyses showed adiponectin protein to be abundantly expressed in both plasma and skeletal muscle tissue (Fig. 4). Subsequently, we performed immunohistochemical staining on skeletal muscle cross-sections to show the presence of adiponectin on the sarcolemma of individual muscle fibres and within the endothelial lining of the interfibrillar arterioles (Fig. 3). The finding of adiponectin within the sarcolemma is surprising and has not been reported previously. The presence of adiponectin in the interfibrillar arterioles in human skeletal muscle tissue is consistent with the known actions of...
adiponectin as a potent anti-inflammatory and atheroprotective agent in vascular tissue (8, 57–59). Moreover, adiponectin has been reported to stimulate vasodilatation and/or angiogenesis (57). As such, these findings seem to suggest that adiponectin could represent an important link between skeletal muscle tissue perfusion and substrate use.

The presence of adiponectin on the sarcolemmal membrane of the individual muscle fibre implies that adiponectin is bound to adiponectin receptors in muscle tissue for signalling purposes. In that context, the recently cloned adiponectin receptor 1 (expressed abundantly in muscle) and receptor 2 (expressed predominantly in the liver) are likely to play a key role (27). These receptors mediate the elevated glucose uptake and FFA oxidation induced by adiponectin through activation of AMP kinase and peroxisome proliferator-activated receptor-α ligand activities (27). The latter could potentially stimulate the translocation and/or expression of the various skeletal muscle fatty acid transporters (9, 60). As plasma adiponectin concentrations were not affected by either exercise or pharmacological inhibition of adipose tissue lipolysis, we speculated that the effects of adiponectin on muscle metabolism could be mediated at the receptor level. As such, we measured adiponectin 1 and 2 receptor mRNA expression in muscle tissue in both conditions. As expected, adiponectin receptor 1 was more abundantly expressed in muscle tissue than receptor 2. Prolonged exercise and/or lipolytic inhibition did not change adiponectin receptor 1 mRNA expression (Fig. 5A). Interestingly, adiponectin receptor 2 mRNA content decreased significantly following exercise in the control trial (HPA; Fig. 5B). However, differences in adiponectin receptor 2 mRNA expression between trials did not reach statistical significance ($P = 0.08$). Although these data tend to suggest that there is some negative feedback inhibition of circulating FFA concentrations at the level of the adiponectin receptor, it should be noted that the adiponectin receptor 2 is predominantly expressed in liver and not in muscle tissue. As such, we can only speculate on the physiological relevance to muscle metabolism. It is tempting to hypothesise that more long-term regulation of substrate metabolism is co-regulated by adiponectin production and/or release in adipose tissue, whereas more short-term regulation is also realized at the level of the adiponectin receptor in skeletal muscle tissue and/or the intercellular arterioles. More research is warranted to elucidate the physiological role of the adiponectin receptors in various tissues.

In conclusion, prolonged moderate intensity exercise does not affect plasma adiponectin concentrations or skeletal muscle adiponectin receptor 1 and 2 mRNA expression in healthy, lean males. Furthermore, adiponectin concentrations and adiponectin receptor 1 mRNA expression in muscle are not modulated by acute changes in adipose tissue lipolysis, circulating plasma FFA levels and/or whole-body fat oxidation rate. Adiponectin is abundantly expressed in human skeletal muscle tissue, and is located in the sarcolemma of individual muscle fibres and within the endothelial lining of the arterioles. The latter findings imply that there is a regulatory role for adiponectin and/or adiponectin receptors in skeletal muscle metabolism.

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