PPARδ mediates IL15 metabolic actions in myotubes: Effects of hyperthermia

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Abstract. C2C12 cells exposed to hyperthermia (41˚C) experienced an increase in both protein synthesis and degradation. The addition of IL15 under hyperthermic conditions resulted in an important increase in protein synthesis with no changes in protein degradation, except when cells overexpressed PPARδ. The PPARδ agonist GW501516 exerted similar effects on protein synthesis to IL15. Expression of a mutant dominant negative form of PPARδ prevented the effect of the cytokine on protein synthesis, suggesting that this transcription factor is involved in the anabolic action of IL15. The present study also suggests that the effects of IL15 on lipid oxidation could be mediated by PPARδ.

Introduction

Muscle wasting is a common feature in many pathological states including infection and cancer (1). While the main events related to muscle wasting are known [activation of myofibrillar protein degradation, induction of apoptosis, activation of uncoupling proteins (UCPs)] (2,3), little information on the intracellular signaling pathways is available. These may play a key role, from a therapeutic point of view, especially if different mediators are involved. Some reports have postulated a role for NF-κB (nuclear factor-κB) in muscle wasting associated with cytokines (4) and tumour-derived factors (5). Other transcription factors, such as AP-1 (activator protein-1) and C/EBP (CCAAT-enhancer binding protein), have also been involved in sepsis-induced muscle cachexia (6). Data from our laboratory indicate that the transcription factor AP-1 could also be involved during cancer cachexia (7,8). Not much attention has been focused on the role of PPARs in skeletal muscle. These transcription factors are associated with changes in lipid metabolism as well as UCP expression (9) and apoptosis (10).

PPARs are transcription factors belonging to the superfamily of nuclear receptors. Three isoforms (α, γ and δ) have been described. The PPARs are the major regulators of lipid and glucose metabolism, allowing adaptation to the prevailing nutritional environment (11). PPARδ has a broad expression pattern in the adult and is expressed very early during embryogenesis (12). During the past few years it has been demonstrated that treatment with PPARδ agonists normalizes blood lipids and also reduces insulin resistance and adiposity both in rodents and primates (12). Work utilizing cellular and animal models revealed that this nuclear receptor plays a central role in the control of fatty acid burning in adipose tissue and skeletal muscle (12). Furthermore, PPARδ appeared to be important for the adaptive response of skeletal muscle to environmental changes, such as physical exercise (12).

We have previously demonstrated that interleukin-15 (IL15) can act as an anabolic factor for skeletal muscle influencing protein metabolism both *in vivo* (13) and *in vitro* (14). In connection to lipid metabolism, in the course of *in vivo* studies regarding the effects of IL15 on skeletal muscle, a 33% decrease in WAT mass was observed in rats, with no changes in food intake (15). In another study using obese rodent models, a correlation was found between the sensitivity to the fat-inhibiting effects of IL15 and the fat expression of mRNA for key signaling subunits of the IL15 receptor in WAT (16), suggesting that IL15 may have a direct effect on this tissue. Additionally, a direct inhibition by this cytokine of adipogenesis has been reported in 3T3-L1 cells, confirming the direct action of IL15 in adipose tissue (17). Recent data from our research group point out a novel mechanism of IL15 action, suggesting that this cytokine increases *in vivo* fatty acid oxidation by upregulation of PPARδ and other lipid

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oxidation-related genes in both muscle and liver (18). The aim of the present investigation was to elucidate the possible role of PPARδ in the actions of IL15 on cultured muscle cells exposed to hyperthermia.

Materials and methods

Cell culture. C2C12 mouse skeletal muscle cells were obtained from the American Type Culture Collection. Construction of the retroviral expression vectors for PPARδ and PPARδ dominant negative mutant and establishment of C2C12 populations overexpressing either PPARδ (referred as C2C12-PPARδ) or PPARδ dominant negative (referred as C2C12-PPARδDN), have been previously described (19,20). Cells were passaged in high-glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin, 100 μg/ml streptomycin, 25 ng/ml fungizone, 110 μg/ml sodium pyruvate, and 2 mM L-glutamine, and in the case of genetically modified cells also with 0.4 mg/ml of geneticin, in a humidified atmosphere of 5% CO_2 and 95% air at 37˚C. For experimental analyses, cells were seeded at $3.7x10^4$ cells/cm^2 in 10% FBS/DMEM until they reached 90-100% confluence 24 h later. At this time, the medium was replaced by DMEM containing 10% horse serum for induction of differentiation for genetically modified cells. Abundant myotube formation, monitored microscopically, occurred after 4 days in 10% horse serum (HS)/DMEM. Such fused myotube cultures were utilized for experimental analyses 5 days after transferring cells to 10% HS/DMEM.

Punctual hyperthermia and measurement of protein degradation and protein synthesis. Parental C2C12, C2C12-PPARδ and C2C12-PPARδDN myotubes were pre-labelled with L-[2,6-^{3}H]phenylalanine as described (21) for a 24-h period, after which they were washed extensively in PBS, and incubated in fresh DMEM for a 2-h period at 37˚C, until no more radioactivity appeared in the medium. Protein degradation was measured by the release of [2,6-^{3}H]phenylalanine into the medium after 6-h incubation at 37˚C or 41˚C in the presence of 2 mM cold phenylalanine to prevent reincorporation of the radio-label. The punctual hyperthermia method to induce protein degradation has been previously described by Smith and collaborators (22). Cultures were incubated with or without murine IL15 added at 10 ng/ml in PBS (PeProtech, London, UK) and the PPARδ agonist GW501516 at 0.1 μM (Alexis Biochemicals, Lausen, Switzerland) in DMSO:PBS (1:10000).

To determine the rate of protein synthesis, parental C2C12, C2C12-PPARδ and C2C12-PPARδDN myotubes were incubated in fresh DMEM for a 2-h period at 37˚C, after which they were incubated for a 6-h period at either 37˚C or 41˚C in DMEM-supplemented with 1% glutamine, 1% penicillin-streptomycin-fungizone and 10% HS. One hour before the end of the incubation, the culture medium was replaced with experimental medium containing [2,6-^{3}H]phenylalanine. After the incubation, the cells were rinsed twice in PBS. The protein synthesis rate was measured by the presence of [2,6-^{3}H]phenylalanine in cell protein extracts and the protein content was determined by the BCA method (Pierce, USA).

Fatty acid oxidation and uptake. In order to measure palmitate oxidation, parental C2C12 and genetically modified myotubes were incubated for 3 h in a KHB medium containing [1-^{14}C]-palmitate with or without 10 ng/ml IL15. The cells were incubated in a 25 cm^2 flask with a special stopper in order to trap the $^{14}CO_2$ generated by oxidation of the labelled substrate. At the end of the 3-h incubation period, 200 μl of 0.5 M H_2SO_4 were added to the medium and 200 μl of 1 M hyamine hydroxyde were added to the stopper's wells in order to collect the $^{14}CO_2$ produced. Cells were washed and lipids were extracted with a chloroform:heptane mix; heptane was added to the samples and the organic phase was collected to measure the palmitate incorporation into the lipid fraction. Palmitate utilization was estimated taking into account both palmitate oxidation and incorporation into the lipid fraction.

RNA isolation and real-time PCR (polymerase chain reaction). Total RNA from C2C12 cells was extracted by TriPure™ kit (Roche, Barcelona, Spain), a commercial modification of the acid guanidinium isothiocyanate/phenol/chloroform method (23).

First-strand cDNA was synthesized from total RNA with oligo dT15 primers and random primers pdN6 by using a cDNA synthesis kit (Transcriptor Reverse Transcriptase, Roche). Analysis of mRNA levels for PPARδ was performed with primers designed to detect gene products as previously described (24). To avoid the detection of possible contamination by genomic DNA, primers were designed to be located on different exons. The real-time PCR was performed using a commercial kit (LightCycler™ FastStart DNA Master^{PLUS} SYBR Green I, Roche). The relative amount of all mRNA was calculated using the comparative C_T method. 18S mRNA was used as the invariant control for all studies.

Biochemicals and radiochemicals. Biochemicals were all reagent grade and obtained either from Roche S.A. or from Sigma Chemical Co. (St. Louis, MO, USA); culture media were obtained from Invitrogen (Carlsbad, CA, USA) and radiochemicals were purchased from Amersham (Buckinghamshire, UK).

Statistical analysis. Statistical analysis of the data was performed by means of one-way analysis of variance.

Results and Discussion

Previous studies have shown that increasing the culture temperature from 37˚C to 41˚C results in profound alterations in protein metabolism (22). Our objective was to investigate the protective effect of the cytokine in this particular catabolic condition in murine C2C12 cells submitted to punctual hyperthermia and to study the role of PPARδ in mediating IL15 effects (for more details see Materials and methods). For this purpose, we used C2C12 cells overexpressing this transcription factor (C2C12-PPARδ) together with cells where the activity of PPARδ was completely blocked by overexpression of a PPARδ dominant negative mutant (C2C12-PPARδDN). Experiments carried out with these genetically modified cells establish the direct implication of

Table I. Effect of IL15 and GW501516 on protein degradation in C2C12 myotubes after hyperthermia.

	Protein degradation at 37˚C	Protein degradation at 41˚C	ANOVA
Parental C2C12	100±6 (5)[a]	139±6 (4)[b]	p<0.05
C2C12-PPARδ	100±3 (6)[a]	150±8 (5)[b]	p<0.001
C2C12-PPARδ + IL15	109±6 (6)[a]	172±6 (6)[b]	
C2C12-PPARδ + GW501516	128±6 (6)[a]	166±18 (4)[b]	
C2C12-PPARδDN	100±5 (6)[a]	188±15 (6)[b]	p<0.001
C2C12-PPARδDN + IL15	104±1 (6)[a]	177±5 (6)[b]	
C2C12-PPARδDN + GW501516	115±2 (5)[a]	182±12 (4)[b]	

Values for protein degradation are presented as the percentage of the respective control value at 37˚C of the amino acid radioactivity in the medium versus the total radioactivity incorporated into protein. All data are means ± SEM. Statistical significance of the results by one-way analysis of variance (ANOVA) in each type of cells separately. Values that are significantly different by ANOVA p<0.05 and <0.001, and statistically significant difference by post-hoc Duncan test. [a,b]Different superscripts indicate significant differences (p<0.05) between groups.

PPARδ in the regulation of lipid metabolism in C2C12 myotubes (20).

The results presented in Table I clearly show that hyperthermia resulted in a general increase in protein degradation in all the groups studied. Control parental C2C12 cells had a 40% increase in protein degradation while the increase was above 50% in the genetically-modified cells (C2C12-PPARδ and C2C12-PPARδDN). Interestingly, neither IL15 nor the PPARδ agonist GW501516 were able to inhibit the increase of protein degradation promoted by hyperthermia. As expected, the same lack of effects for the cytokine and the agonist were observed in the C2C12-PPARδDN cells. The actual overexpression of PPARδ and PPARδDN was determined using real-time PCR in comparison to the control parental cells [100±22 (4)[a]] C2C12-PPARδ cells [3533±489 (4)[b]] and C2C12-PPARδDN [1193±174 (4)[c]].

Since no effects of either the cytokine or the agonist were observed on protein degradation, we studied the protein synthesis rates in the same cell culture system. It is important to note that, after hyperthermia, there is an enhanced rate of protein synthesis in cultured cardiomyocytes (25). IL15 increased the protein synthesis rate in native C2C12 cells exposed to hyperthermia (Table II). Protein synthesis rates were also determined in C2C12-PPARδ and C2C12-PPARδDN cells maintained at 37˚C or 41˚C and exposed or not to IL15 or GW501516. Treatments with IL15 or GW501516 did not affect rates of protein synthesis in both cell populations maintained at 37˚C (Fig. 1A). By contrast, IL15 and GW501516 promoted an important increase in synthesis (214% for IL15 and 195% for GW501516), this being observed only in the C2C12-PPARδ cells, while no effect was observed in the C2C12-PPARδDN cells (Fig. 1B). These data clearly show that IL15 has a protective effect during hyperthermia which relies on increasing protein synthesis. Since this effect was observed only in the PPARδ-overexpressing cells this transcription factor is involved in mediating the effects of IL15 in protein synthesis. Indeed, the incubation in the presence of the agonist of PPARδ, GW501516, generates a similar increase in protein synthesis as observed in IL15. In addition, blocking PPARδ activity (dominant negative cells) completely abolishes the effects of IL15 in protein synthesis in C2C12 under hyperthermia. These results are in agreement with data that showed a capacity of IL15 for increasing protein synthesis under catabolic conditions (13) and, in addition, clarify the transcription factor involved in this action of the cytokine. Indeed, IL15 has been shown to behave as an anabolic cytokine for skeletal muscle influencing protein turnover in this tissue, both *in vivo* (13) and *in vitro* (14) under catabolic conditions. It has to be considered that PPARδ has been related to hypertrophy at least in red muscle fibers (12,26). Indeed, PPARδ regulates PGC1α (PPARγ coactivator 1α), a protein that participates in the formation and also in the maintenance of red fibers in skeletal muscle (26). In addition, PGC1α has a protective role against loss of protein muscle present in catabolic conditions

Table II. Effects of IL15 on protein synthesis in parental C2C12 cells after hyperthermia.

Cell treatment	IL15 concentration	Protein synthesis
None	None	100±4[a]
	10 ng/ml	99±3[a]
Hyperthermia	None	109±5[a]
	10 ng/ml	123±6[b]

Values for protein synthesis are presented as the percentage of the control value at 37˚C and were assessed as radioactivity incorporated into protein/mg of total protein. All data are means ± SEM (n=5). Values that are significantly different by ANOVA p<0.05 and <0.001, and statistically significant differences were evaluated by post-hoc Duncan test. Different superscripts indicate significant differences (p<0.05 or <0.001) between groups.

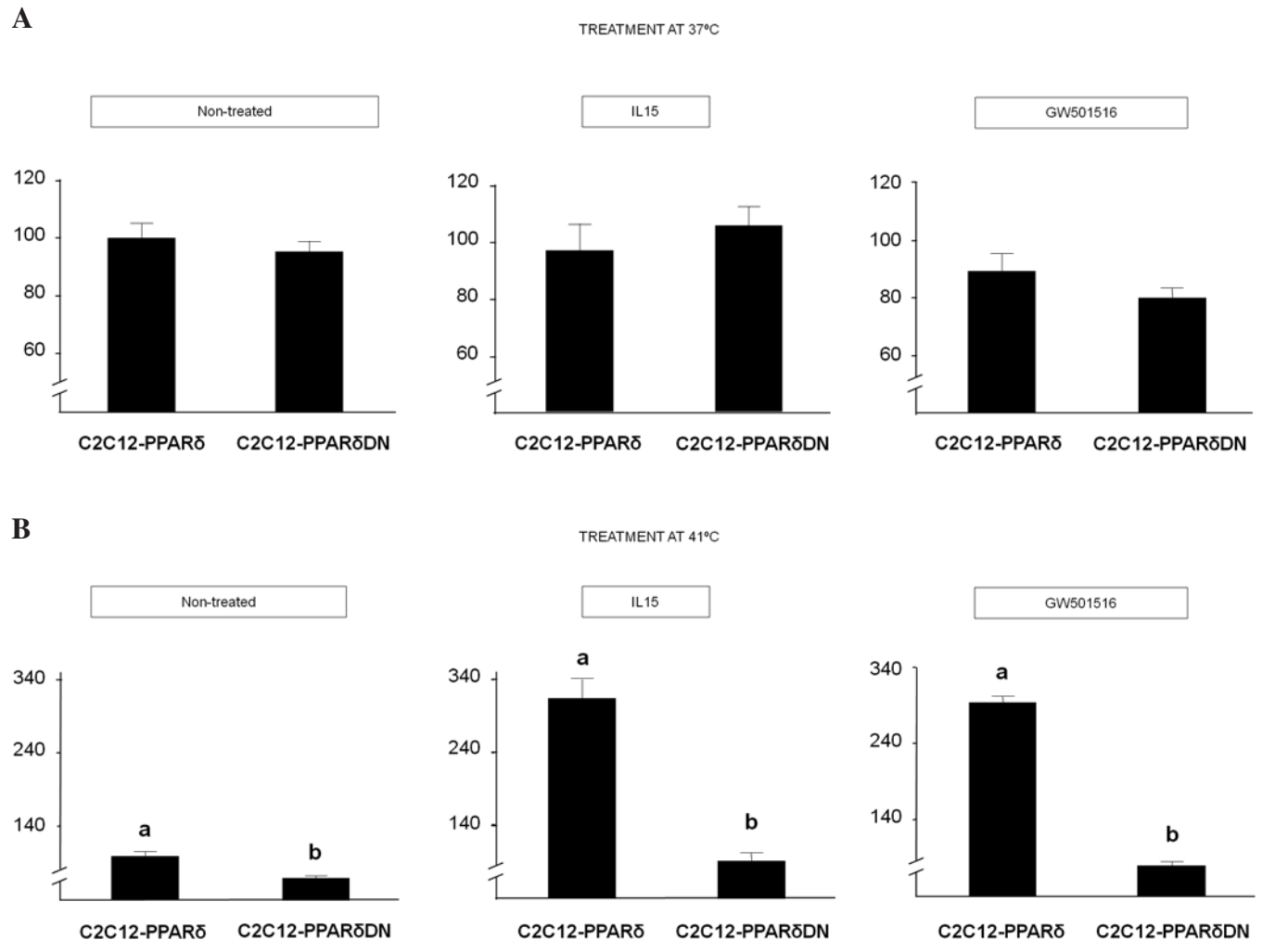

Figure 1. Rates of protein synthesis in C2C12 cells after hyperthermia. (A), Values for protein synthesis are presented as the percentage of the respective control value at 37˚C and were assessed as radioactivity incorporated into protein/mg of total protein. (B), Values for protein synthesis are presented as the percentage of the respective control value at 41˚C and were assessed as radioactivity incorporated into protein/mg of total protein. All data are means ± SEM (n=5). Values that are significantly different by ANOVA $p<0.05$ and <0.001, and statistically significant differences were evaluated by post-hoc Duncan test. Different superscripts indicate significant differences ($p<0.05$ or <0.001) between groups.

(27). All these studies agree with the results observed here, supporting a relation between the anabolic effect of IL15 on muscle cells and PPARδ. Taking into account all this information, it could be suggested that IL15 activation of PPARδ could be upregulating PGC1α and, consequently, promoting some of the characteristics of type I muscle fiber phenotype.

In addition to its effects on muscle cell protein metabolism, IL15 has been shown to have effects on both carbohydrate (28) and lipid (18,29,30) metabolism; thus IL15, reduces intestinal lipid absorption (30) and, at the level of adipose tissue, it decreases lipogenesis and diminishes lipid uptake (18,29). In the present study we decided to analyze the effects of the cytokine on palmitate uptake and oxidation of this fatty acid in C2C12 cells and, as can be seen in Fig. 2, IL15 did not influence either uptake or oxidation in control parental cells. However, the overexpression of PPARδ is associated with a higher tendency for palmitate utilization and an increased palmitate oxidation in the IL15-treated cells. Interestingly, the results presented here are in agreement with previous results showing an enhanced oxidative capability in muscle (presence of more oxidative fibers) (31) and in C2C12 cells overexpressing PPARδ (12). These results suggest that this transcription factor could also be involved in some of the actions of this cytokine on lipid metabolism in skeletal muscle. Altogether, the results of this study support a role for IL15 in protecting muscle cells during hyperthermia and that the intracellular mechanism involved in this action of the cytokine implicates the transcription factor PPARδ.

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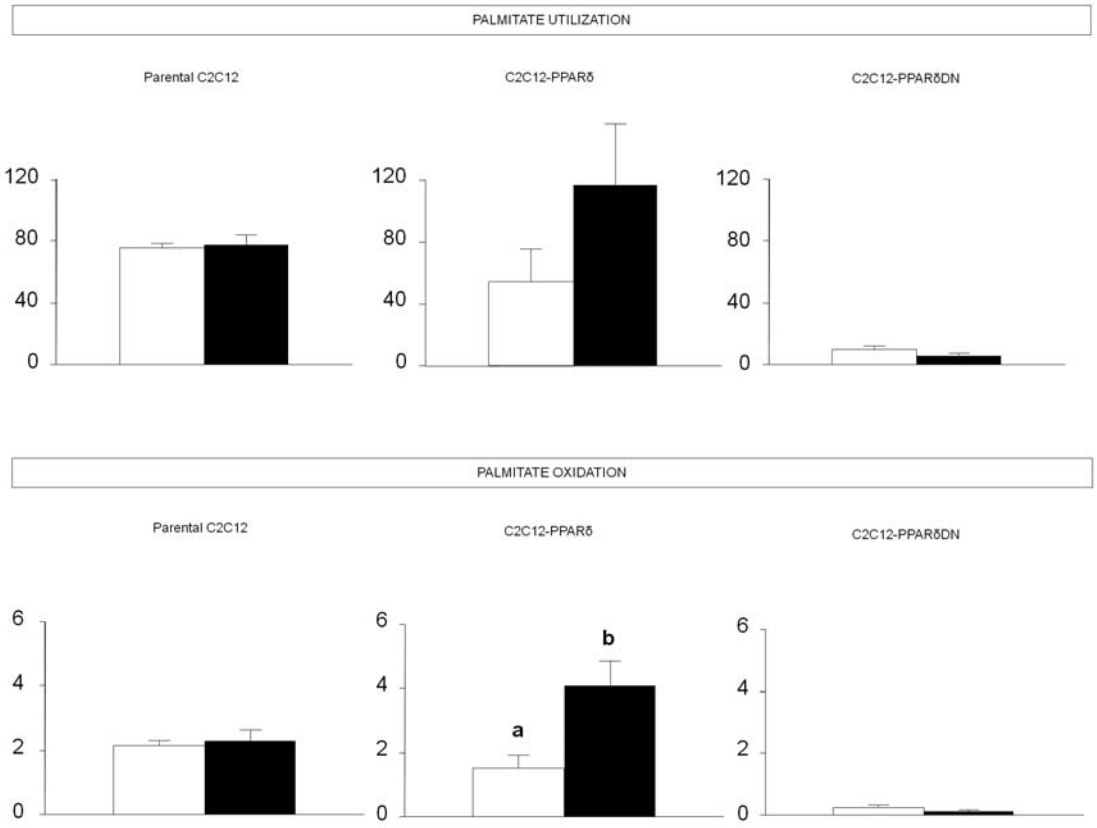

Figure 2. Palmitate oxidation and utilization by C2C12 cells. The cells were incubated for 3 h. The results are expressed as nmol of palmitate either metabolized or oxidized to CO_2 per mg of protein. White bars, non-treated cells. Black bars, IL15-treated cells. All data are means ± SEM (n=5). Values that are significantly different by ANOVA $p<0.05$ and <0.001, and statistically significant differences were evaluated by post-hoc Duncan test. Different superscripts indicate significant differences ($p<0.05$) between groups.

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