Syncytin-1 Expression is Increased in Skeletal Muscle of Humans with Obesity and is Inversely Correlated to Muscle Protein Synthesis

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Research

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Abstract

Background: Various pathophysiological conditions alter protein metabolism in skeletal muscle, with obesity being one of them. Obesity impairs regeneration of skeletal muscle, and the same biological mechanism(s) may adversely affect protein metabolism in the muscle of these individuals.

Methods: We used C2C12 cell line to evaluate the effects of the anabolic hormone insulin on the expression of protein syncytin-1, which regulates regeneration of muscle, and in the presence of fatty acids whose metabolism is altered in obesity. We used muscle biopsy samples from obese humans with lower muscle protein synthesis and lean controls to evaluate expression of syncytin-1 in obesity and its correlation with protein synthesis in muscle.

Results: Insulin upregulated syncytin-1 expression in C2C12 cells and this response was impaired in the presence of the fatty acid palmitate, but not oleate. Expression of the protein 4E-BP1, which signals increase in protein synthesis in muscle, showed response similar to that of syncytin-1. Humans with obesity characterized by lower muscle protein synthesis had higher expression of syncytin-1 in muscle compared to lean humans ($P < 0.01$). The rate of synthesis of protein in skeletal muscle across humans subjects correlated inversely ($r = -0.51$; $P = 0.03$) with the expression of syncytin-1 in muscle.

Conclusions: Our studies provide novel insights in the regulation of syncytin-1 in skeletal muscle, and describe potential link between syncytin-1 expression and protein metabolism in skeletal muscle of humans. Altered syncytin-1 expression in muscle may mediate lower protein turnover in muscle of humans with obesity.

Background

Understanding the biological mechanisms impairing protein metabolism in skeletal muscle under various pathophysiological circumstances constitutes an area of active investigation. Although not a consistent finding among studies, there is evidence for lower protein synthesis in the muscle of humans with obesity [1–4]. Lower protein synthesis in muscle of humans with obesity can mediate lower muscle mass, a phenomenon that is evident in the clinical condition described as “sarcopenic obesity”. However, the underlying mechanisms that impair protein synthesis in muscle of humans with obesity remain elusive, complicating our understanding of the effects of obesity on muscle protein metabolism. In addition to lower protein synthesis [1–4], current evidence shows that the biological processes of muscle maintenance and regeneration are also impaired in obesity, an effect attributed to impaired cell fusion in skeletal muscle [5].

The protein syncytin-1, encoded by the endogenous retrovirus group W envelope member 1 (ERVW-1) gene, regulates cell fusion, and its role to date has been largely been described with respect to placental development [6]. However, syncytin-1 is found also in skeletal muscle, and specifically in the sarcolemma of the muscle fibers [7], where it regulates muscle cell fusion [7–9]. Given the key role of syncytin-1 in myogenesis [7] and that this physiological process is impaired in obesity [5], investigating the expression

of syncytin-1 in the muscle of humans with obesity can possibly provide novel insights into the development of sarcopenic obesity. Because of the scarcity of relevant evidence, currently it is not known whether biological signals known to affect protein metabolism alter the expression of syncytin-1 in muscle. In this regard, and within the metabolic context of obesity and associated insulin resistance, insulin and fatty acids are among the most relevant biological signals. Insulin induces muscle anabolism, whereas exposure of muscle to increased levels of fatty acids impairs stimulation of protein synthesis by reducing signaling through the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) [10]. Palmitate, but not oleate, impairs 4E-BP1 in C2C12 cells [11]. Along these lines, palmitate, but not oleate, impairs protein synthesis in C2C12 cells [12]. Therefore, insulin, fatty acids, or their combined effects may have distinct effects on syncytin-1 expression in muscle.

We sought to evaluate first the effects of biological signals known to modify muscle protein metabolism on syncytin-1 expression in myotubes, a cell culture model that can describe independent effects of these signals on muscle. We hypothesized that insulin stimulates syncytin-1 expression and that this effect is not evident in the presence of fatty acids. Given the role of syncytin-1 in myogenesis and the evidence for impaired muscle regeneration and protein synthesis in obesity (as discussed above), we then tested the hypothesis that expression of syncytin-1 in muscle is lower in humans with obesity.

Methods

Cell culture experiments

C2C12 mouse myoblasts were grown in growth media containing Dulbecco's modified Eagle's medium (DMEM) with 20% fetal bovine serum and 1% antibiotic-antimycotic at 37^{o}C. After 95% confluency, cells were differentiated in differentiation media containing DMEM with 2% horse serum and 1% antibiotic-antimycotic for 5 days, and until the cells were spindle-shaped [11]. A 200 mM stock solution of palmitate and oleate were prepared using sodium oleate and palmitate dissolved in 50% ethanol for 30 minutes at 70 °C. A 10% solution of fatty acid-free bovine serum albumin (BSA) was prepared in phosphate-buffered saline for conjugation purposes. Then, 5 mM stock solution of BSA conjugated fatty acid solutions (i.e., palmitate and oleate) were prepared by adding 200 mM stock solution of oleate and palmitate in 10% fatty acid-free BSA. Conjugation of the fatty acids and BSA was performed at 37 °C for 1 hour before cell treatment. C2C12 cells were incubated in serum-free DMEM media for 2 hours before treatment. The conjugated fatty acid-BSA serum was filtered and added to serum-free DMEM media. Cells were treated with either 300 μm palmitate, 300 μm oleate, their combination, and with or without 20 nM insulin for 24 hours. Before harvesting, cells were stimulated with 100 nM of insulin for 15 minutes. Myotubes were harvested as described by Kwon and Querfurth [11]. Protein concentration was measured using Coomassie® protein assay reagent kit purchased from Pierce™ Biotechnologies (Rockford, IL), and by following the manufacturer's protocol.

Human subject experiments

We measured syncytin-1 expression in muscle biopsy samples collected from human subjects with body mass index (BMI) < 25 kg/m^2 (i.e., humans with obesity) and BMI > 30 kg/m^2 (i.e., lean humans). The muscle biopsies were collected as part of a previous study that found that humans with obesity have lower protein synthesis in skeletal muscle compared to lean humans [2]. The experimental procedures in the study were approved by the Institutional Review Board at Mayo Clinic, and all subjects provided written informed consent before study participation. Details about the study participants and the experimental procedures employed are provided previously [2]. Briefly, during subject screening, we collected data describing the anthropometric and clinical characteristics of the subjects. Table 1 displays these characteristics of the obese and lean subject populations. Body composition was determined using bioelectrical impedance analysis (BIA 310e, Biodynamics Corp., Shoreline, Washington), and the Matsuda insulin-sensitivity index was calculated from plasma insulin and glucose responses to an oral glucose tolerance test [13]. The rate of synthesis of overall protein in skeletal muscle was determined over 3 hours in the morning after an overnight fast using a d_{10}-leucine (L-[2,3,3,4,5,5,5,6,6,6-$^2H_{10}$]leucine) tracer in combination with muscle biopsies [14]. Analyses of samples for stable isotope enrichment in blood amino acids and mixed-muscle protein (i.e., overall muscle protein) were performed following procedures we have previously described [14]. The rate of synthesis of muscle protein, expressed as fractional synthesis rate (%/hour), was calculated from the stable isotope enrichments measured in these samples, and following procedures we have also previously described [14].

Table 1
– Subject characteristics

	Lean	Obese
n (F/M)	8 (5/3)	10 (4/6)
Age (years)	34.5 ± 10.8	36.3 ± 8.8
Weight (kg)	65.0 ± 13.5	101.9 ± 14.6*
BMI (kg/m^2)	22.4 ± 2.7	34.4 ± 3.3*
FFM (kg)	49.5 ± 11.3	67.8 ± 9.7*
Body fat mass (%)	23.9 ± 7.3	33.1 ± 7.5*
Fasting plasma glucose ($mg{\cdot}dl^{-1}$)	85.6 ± 6.7	98.4 ± 13.9*
Fasting plasma insulin ($uIU{\cdot}ml^{-1}$)	3.6 ± 0.8	10.9 ± 6.0*
HOMA-IR	0.8 ± 0.2	2.7 ± 1.8*
Matsuda-ISI	9.4 ± 2.2	4.6 ± 4.3*
HbA1c (%)	5.4 ± 0.3	5.7 ± 0.4*
Plasma triglycerides ($mg{\cdot}dl^{-1}$)	70.9 ± 28.3	191.0 ± 140.8*
Plasma total cholesterol ($mg{\cdot}dl^{-1}$)	174.1 ± 34.6	178.8 ± 32.2
Plasma HDL-Cholesterol ($mg{\cdot}dl^{-1}$)	71.5 ± 18.4	40.9 ± 8.8*
Total Cholesterol:HDL-cholesterol	0.4 ± 0.1	0.2 ± 0.1*
Plasma LDL-Cholesterol ($mg{\cdot}dl^{-1}$)	88.4 ± 28.3	98.4 ± 21.6
Values are mean ± SD. BMI, body mass index; FFM, fat-free mass; HOMA-IR,		
homeostatic model assessment of insulin-resistance; Matsuda-ISI, Matsuda		
insulin-sensitivity index (as discussed in text); HbA1c, glycated hemoglobin;		
HDL, high-density lipoprotein; LDL, low-density lipoprotein;		
*P < 0.05 between groups.		

Immunoblotting

Lysates of human muscle and C2C12 myotubes were prepared following procedures we have previously described [1]. Approximately 40 μg of protein from human muscle lysate and 15 μg of protein from myotube lysate were separated by gel electrophoresis on Any kD™ precast polyacrylamide gels (Mini-PROTEAN, Bio-Rad Laboratories, Inc.) to identify and quantify the proteins of interest. Primary antibodies

used were: anti-syncytin-1 (Biorbyt; Cat# orb100573; RRID:AB_2857960), anti-GAPDH (Rockland Immunochemicals; Cat# 600-401-A33; RRID:AB_2107593), anti-4E-BP1 (Cell Signaling Technology; Cat# 9452; RRID:AB_331692), anti-phospho-4E-BP1 ($Thr^{37/46}$) (Cell Signaling Technology; Cat# 9459; RRID:AB_330985), anti-myosin (Santa Cruz Biotechnology; Cat# sc-32732; RRID:AB_670118). We chose myosin (instead of GAPDH) as the housekeeping gene for the cell culture experiments because GAPDH showed considerable variation across the experimental conditions (discussed in Results section). A dilution of 1:1000 was used for all primary antibodies in Tris-buffered saline with 0.1% Tween®-20 (TBST) + 5% BSA, except for syncytin-1, which was diluted at 1:250 in TBST. Protein bands were visualized using the Clarity™ Western ECL Blotting Substrate (Bio-Rad, Hershey, PA).

Statistical analyses

Unpaired t-test or one-way ANOVA with Dunnett's posthoc tests were employed to compare data from two or more than two experimental groups, respectively. Correlations were evaluated using the Pearson product-moment correlation coefficient (r). Data are presented as means ± SD. P-value of < 0.05 was considered statistically significant, and all statistical tests were two-sided. Statistical analyses were performed using GraphPad Prism version 8.4 (GraphPad Software, La Jolla, CA).

Results

Effects of insulin and fatty acids on syncytin-1 and 4E-BP1 expressions in myotubes

ANOVA analysis showed significant effect of cell culture treatments on GAPDH expression (P = 0.02). On the other hand, GAPDH expression was not different between humans with obesity and lean controls (P > 0.05). However, there was no significant effect of cell culture treatments on myosin expression (P = 0.66). Therefore, myosin (instead of GAPDH) was used as housekeeping gene to evaluate responses of syncytin-1 and 4E-BP1 in the cell culture experiments. Insulin treatment alone consistently increased the expression of syncytin-1, but this effect was not significant in the presence of fatty acids (Fig. 1). Either insulin treatment alone or any fatty acid treatment did not affect the response of p-4E-BP1/t-4E-BP1 (for all P > 0.05). On the other hand, p-4E-BP1 expression increased by insulin alone, but this effect was not evident when either palmitate or oleate was present together with insulin (Fig. 2B). However, there was significant effect of combined palmitate and oleate (i.e., without the presence of insulin) on increasing p-4E-BP1 expression (Fig. 2B). The effects of insulin and fatty acid treatments on t-4E-BP1 were identical to those on p-4E-BP1 (Fig. 2C).

Syncytin-1 expression and protein synthesis in human skeletal muscle

Subjects with obesity had higher expression of syncytin-1 in skeletal muscle (Fig. 3A), and in the presence of lower muscle protein synthesis compared to the lean controls (obese: 0.060 ± 0.014, lean: 0.084 ± 0.019 %/hour; P = 0.01). Across study subjects, muscle protein synthesis correlated inversely and

significantly with the expression of syncytin-1 in muscle (Fig. 3B). Among the anthropometric and clinical characteristics presented in Table 1, syncytin-1 expression displayed positive correlation with HbA1c (r = 0.56; P = 0.01) and negative correlation with Cholesterol:HDL-C (r = -0.59; P = 0.01). Syncytin-1 expression did not correlate significantly with indices of obesity or insulin resistance.

Discussion

Myotube experiments showed that insulin stimulates syncytin-1 expression in muscle. To our knowledge, this is novel finding concerning the regulation of syncytin-1 in skeletal muscle. The findings of the effects of insulin on syncytin-1 expression are supported by relevant literature showing that syncytin-1 is target gene for expression through the insulin-like growth factor signaling pathway [15]. Insulin may regulate muscle growth through increased syncytin-1 expression along with its effects on increasing other muscle growth factors, such as myogenin and MyoD [16, 17]. In addition to the effects of insulin on syncytin-1, treatment of myotubes with insulin enhanced the 4E-BP1 pathway, whose activation plays an important role in upregulating protein synthesis in muscle. Therefore, concurrent upregulation of syncytin-1 and 4E-BP1 expression by insulin suggests the possibility for coordination of the processes of myogenesis and protein synthesis in skeletal muscle.

The finding that expression of syncytin-1 was higher in skeletal muscle of humans with obesity when compared to that of lean humans was rather surprising. This is because, and as stated in our hypothesis, syncytin-1 upregulates muscle maintenance and regeneration/myogenesis [7], but these processes are suppressed in the presence of obesity [5, 18]. In is possible that biological mechanisms downstream of syncytin-1 in muscle are adversely affected by obesity in a way that impair muscle maintenance. However, and in support of our data showing higher expression of syncytin-1 in a pathophysiological circumstance, syncytin-1 expression is higher in neuronal cells of patients with multiple sclerosis, which is an inflammatory state [19]. Similarly, the inflammatory state of obesity [20] may induce expression of syncytin-1 in the skeletal muscle of humans with obesity. Relevant evidence shows that the treatment of neuronal cells with the pro-inflammatory molecule TNF-α, which is increased in muscle in obesity [21], increases syncytin-1 gene expression [22]. Therefore, increased syncytin-1 expression in skeletal muscle of humans with obesity could be secondary to the pro-inflammatory milieu in skeletal muscle of these individuals.

Contrary to the evidence discussed above, other studies show that syncytin-1 induces the production of pro-inflammatory molecules and redox reactants toxic to tissues [19]. In this case, increased expression of syncytin-1 in skeletal muscle would induce lower protein synthesis, because increased inflammation is linked to reduced protein synthesis in muscle [23]. These latter lines of evidence appear to explain the inverse correlation we observed between the expression of syncytin-1 and protein synthesis in skeletal muscle. At this stage, it remains to be determined whether increased expression of syncytin-1 and concurrent lower muscle protein synthesis are both induced by an inflammatory state in obesity or increased expression of syncytin-1 in the muscle of humans with obesity directly mediates lower protein synthesis by inducing pro-inflammatory state in muscle of these individuals.

We can only speculate on the mechanism(s) that may link increased expression of syncytin-1 to reduced protein synthesis in skeletal muscle. Overexpression of syncytin-1 in neuronal cells suppresses its two receptors, alanine/serine/cysteine transporter 1 (ASCT1) and ASCT2 [22], two proteins that serve as cell membrane amino acid transporters [24, 25]. Furthermore, evidence in humans shows downregulation in the gene expressions of ASCT1 and ASCT2 in muscle occurring concurrently with an increase in the expression of syncytin-1 in muscle in response to exercise training [7]. Experimental blockade of these two proteins reduces amino acid uptake into the cells [26]. Along with this evidence, reduction in amino acid transporters in myotubes by ceramide treatment, a condition that mimics the metabolic environment of obesity in muscle, reduces muscle protein synthesis [27]. Although relevant evidence in humans is currently lacking, lower protein synthesis in the muscle of obese Zucker rats [28] occurs in parallel with lower uptake of amino acids in muscle [29]. Therefore, decrease in amino acid transport into muscle due to suppression of muscle amino acid transporters that results from higher syncytin-1 expression may explain the inverse correlation we observed between syncytin-1 and protein synthesis in skeletal muscle.

Conclusions

We found increased expression of syncytin-1 in skeletal muscle of obese humans with reduced muscle protein synthesis, along with significant inverse correlation between syncytin-1 expression and protein synthesis in muscle. It remains to be determined whether increased expression of syncytin-1 in muscle of humans mediates lower protein synthesis in muscle.

Declarations

Competing interests

None declared.

Authors' contributions

The authors were involved in the conception of the work, acquisition and analysis of the data, as well as drafting and revising the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Ethical Approval

All the experimental procedures in the study conformed to the standards set by the Declaration of Helsinki, were approved by the Institutional Review Board at Mayo Clinic (IRB #: 12-004000), and all subjects provided written informed consent prior to study participation.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

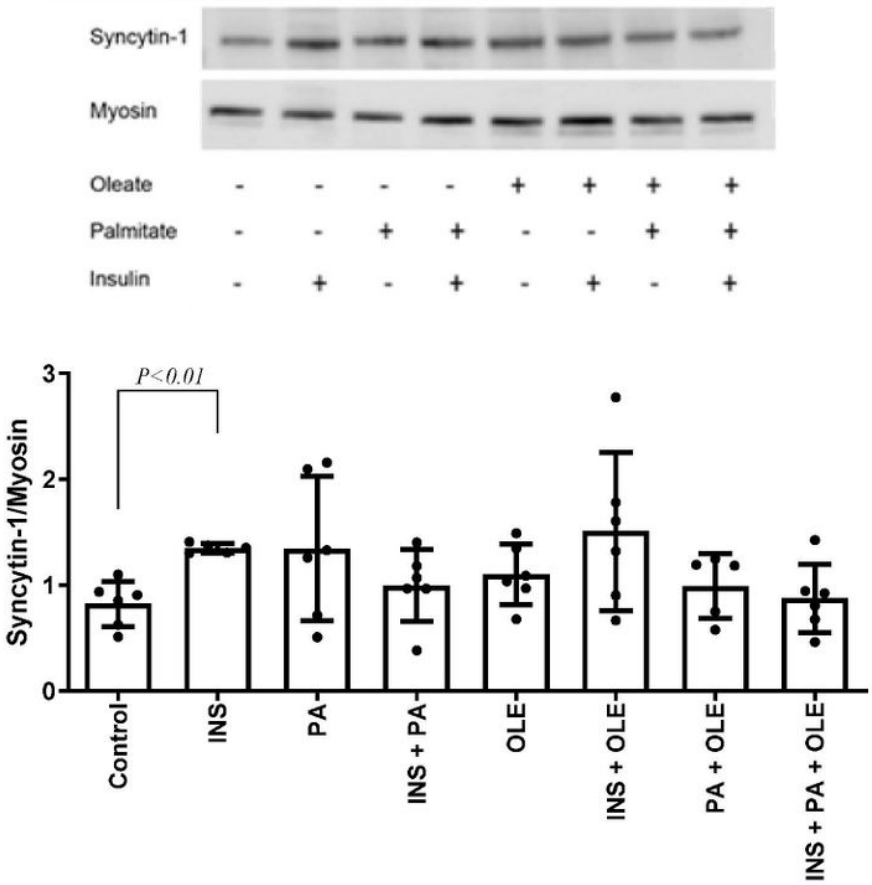

Figure 1

Western blot analysis of syncytin-1 expression in myotubes treated with either insulin (INS; 20 nM), palmitate (PA; 300 uM), oleate (OLE; 300 uM), or their combinations, and compared with the no treatment (i.e., Control) condition. Individual data points are depicted in the graphs along with mean ± SD values.

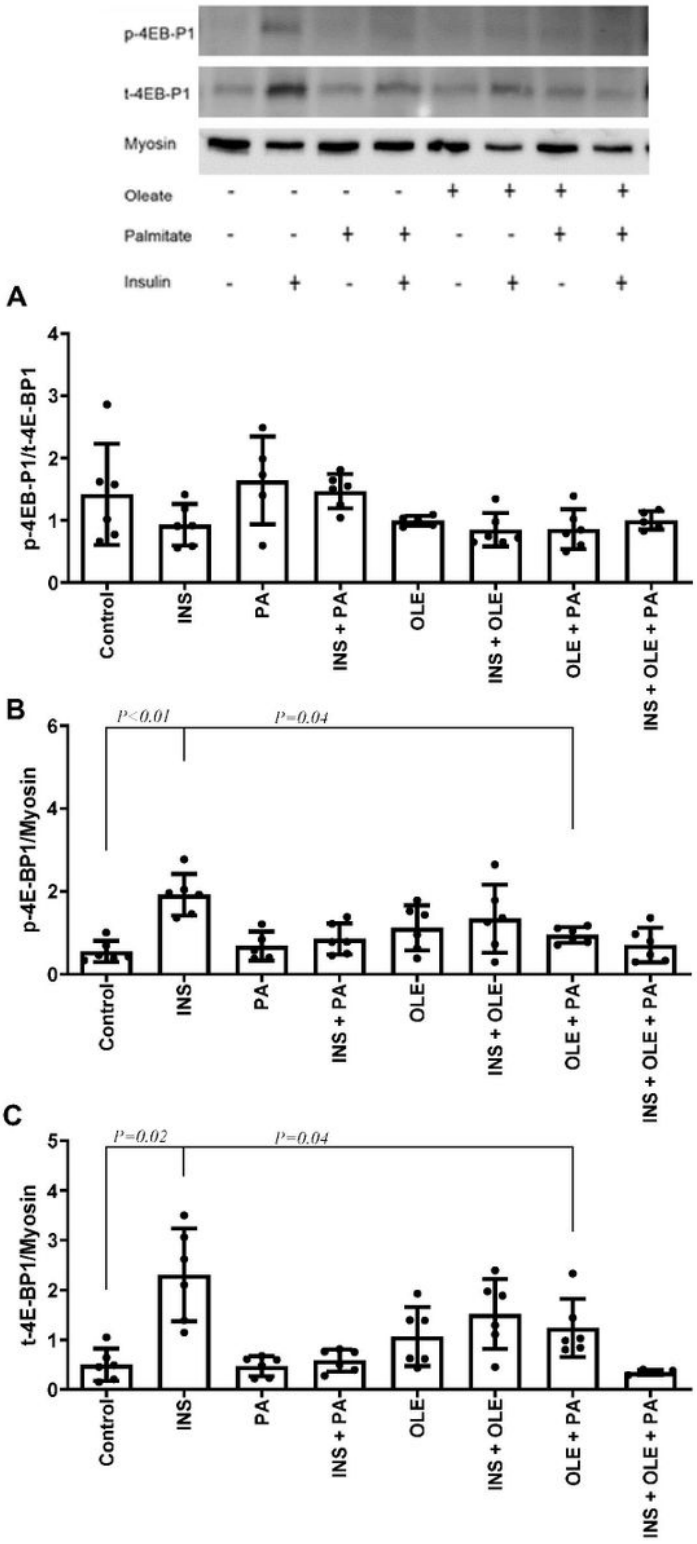

Figure 2

Western blot analysis of p-4E-BP1/t-4E-BP1 (A), p-4E-BP1 (B) and t-4E-BP1 (C) in myotubes treated with either insulin (INS; 20 nM), palmitate (PA; 300 uM), oleate (OLE; 300 uM), or their combinations, and compared with the no treatment (i.e., Control) condition. Individual data points are depicted in the graphs along with mean ± SD values.

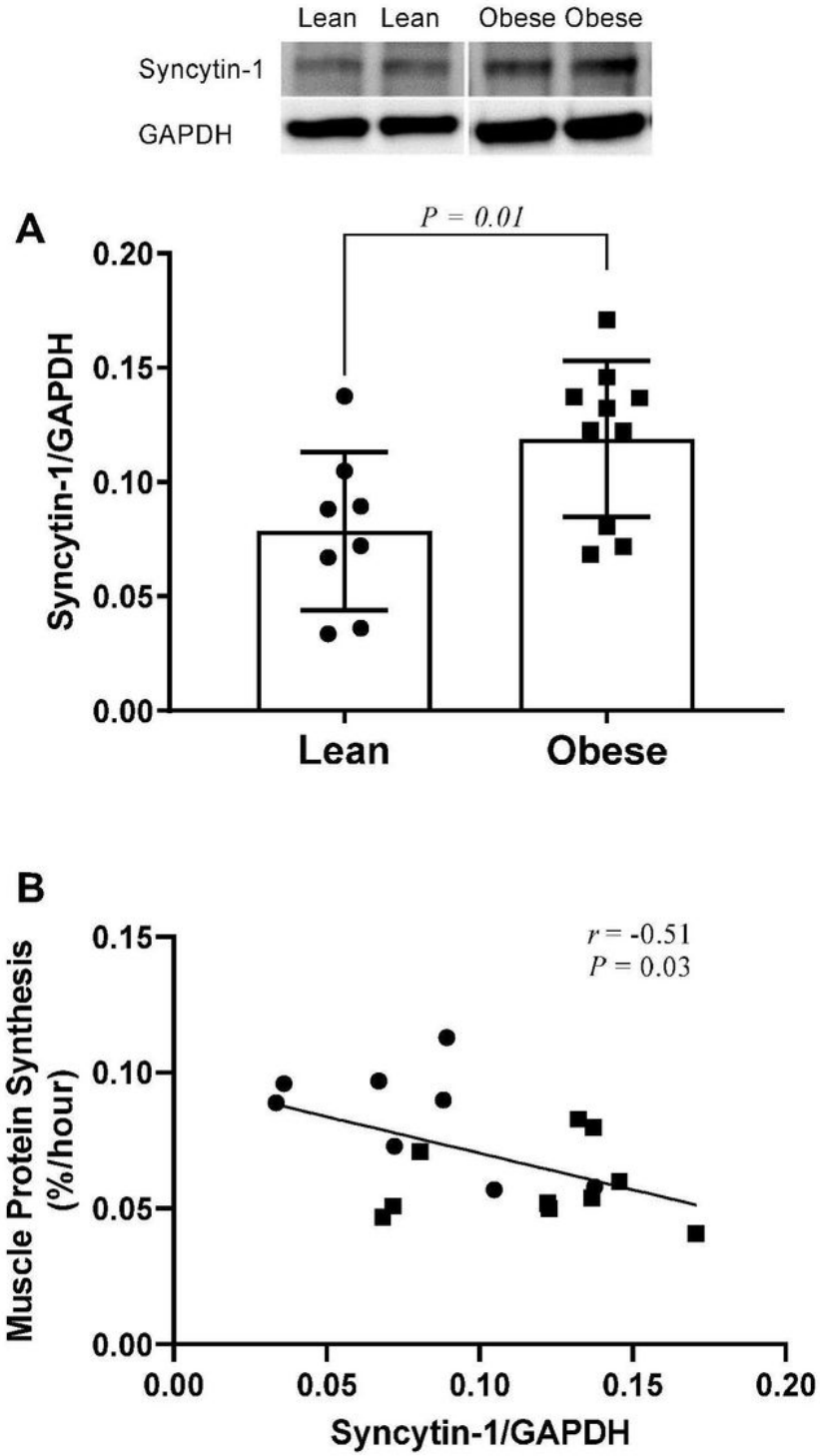

Figure 3

Western blot analysis of syncytin-1 expression in skeletal muscle from humans with obesity and lean controls with individual data points shown in the graph along with mean ± SD values (A). Pearson product-moment correlation (r) between syncytin-1 expression and protein synthesis in skeletal muscle across subjects.