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Prostaglandin E_2 induces transcription of skeletal muscle mass regulators interleukin-6 and muscle RING finger-1 in humans

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Abstract

Cyclooxygenase (COX) inhibiting drugs augment muscle mass and strength improvements during resistance exercise based treatment of sarcopenia in older individuals. Initial evidence suggests a potential mechanism of COX inhibitor blunted prostaglandin (PG) E_2 stimulation of interleukin (IL)-6 and the ubiquitin ligase MuRF-1, reducing their inhibition on muscle growth. The purpose of this investigation was to determine if PGE_2 stimulates IL-6 and MuRF-1 transcription in skeletal muscle. Muscle biopsies were obtained from 10 young individuals and incubated *ex vivo* with PGE_2 or control and analyzed for IL-6 and MuRF-1 mRNA levels. PGE_2 upregulated ($P<0.05$) expression of both IL-6 (195%) and MuRF-1 (51%). A significant relationship was found between IL-6 and MuRF-1 expression after incubation with PGE_2 ($r=0.77$, $P<0.05$), suggesting regulation through a common pathway. PGE_2 induces IL-6 and MuRF-1 transcription in human skeletal muscle, providing a mechanistic link between COX inhibiting drugs, PGE_2, and the regulation of muscle mass.

Keywords

PGE2; Skeletal muscle; IL-6; MuRF-1

1. INTRODUCTION

The prostaglandin (PG) producing cyclooxygenase (COX) pathway has been shown to be a key regulator of skeletal muscle protein turnover through the actions of $PGF_{2\alpha}$ and PGE_2 [1–5]. Recent evidence shows that blocking this pathway with common COX inhibitors (i.e., acetaminophen and ibuprofen) in older humans during resistance exercise training over several months promotes substantial additional skeletal muscle hypertrophy [6]. The mechanism underlying this effect is not completely clear, but COX inhibitor suppression of intramuscular levels of the myokine interleukin-6 (IL-6) and the ubiquitin ligase muscle RING finger-1 (MuRF-1) appears to play a central role [7]. This purported mechanism is based on findings that low level elevation of IL-6 reduces human muscle protein synthesis and increases net muscle protein degradation [8], is associated with a reduction in muscle mass and functional independence in older individuals [9–12], and retards growth and

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promotes muscle atrophy in animals [13, 14]. In addition, MuRF-1 is a central mediator of skeletal muscle proteolysis [15–17]. Thus, a COX inhibitor mediated reduction in the intramuscular levels of these two factors would reduce their inhibitory effects on muscle growth.

A connection between the COX pathway and IL-6 and MuRF-1 production in skeletal muscle has not been established. However, studies in non-skeletal muscle cells suggest PGE_2 can stimulate IL-6 transcription [18–21]. No such evidence exists connecting PGs to MuRF-1 transcription. Therefore, the goal of the current investigation was to address the hypothesis, using *ex vivo* incubation studies, that PGE_2 stimulates the transcription of IL-6 and MuRF-1 in human skeletal muscle. If true, these findings would have implications for understanding how COX inhibiting drugs promote muscle hypertrophy in older individuals and provide insight into PG regulation of inflammation in the development and treatment of sarcopenia, the age related loss of skeletal muscle mass and function [22–24].

2. MATERIALS AND METHODS

Participants

Ten male subjects (Age: 24±1y; Height: 181±2cm; Weight: 80.3±3.3kg; BMI: 24.2±1.1kg/m^2) were recruited to participate in this investigation and before enrollment each subject completed a detailed health and exercise history questionnaire. Subjects were excluded if they had any known acute or chronic illness, cardiac, pulmonary, liver, or kidney abnormalities, uncontrolled hypertension, insulin- or non-insulin dependent diabetes or other metabolic disorders, arthritis, a history of neuromuscular problems, if they used tobacco or regularly consumed analgesics/anti-inflammatory drug(s), prescription or non-prescription. All subjects were considered moderately physically active. This study was approved by the Ball State University Institutional Review Board. All procedures, risks, and benefits associated with the experimental testing were explained to the subjects before providing written consent to participate.

Muscle Biopsy

Subjects underwent a muscle biopsy of the vastus lateralis [25, 26] in the early morning (~0700) after at least 30 minutes of supine rest. Prior to the muscle biopsy, subjects were supplied their evening meals in liquid form (Ensure Plus; 57% carbohydrate, 15% protein, 28% fat) that provided 50% of the estimated daily caloric need to standardize the composition, amount, and timing (i.e., ~12h fast) of the final meal consumed prior to the biopsy. In addition, subjects were instructed to refrain from physical activity beyond their normal daily activity for three days prior to the biopsy. Following the biopsy, the muscle was cleansed of excess blood, visible fat, connective tissue and divided into ~10mg samples and immediately processed for the *ex vivo* incubation experiments.

Ex vivo PGE_2 Stimulation Experiments

Four ~10mg muscle samples were immediately placed in individual pre-weighed incubation vials containing 1ml of pre-gassed (95% O_2/5% CO_2) Krebs-Henseleit Buffer (KHB) (118.5mM NaCl, 1.2mM $MgSO_4$, 4.7mM KCl, 1.2mM KH_2PO_4, 25mM $NaHCO_3$, 2.5mM $CaCl_2$; pH 7.4) supplemented with 5mM glucose, re-weighed to determine muscle weight (11.60±0.41mg), and then completed a pre-incubation of 30min. The muscle samples were then transferred to new vials containing 1ml of fresh pre-gassed KHB, with two vials receiving PGE_2 (20μM) (PGE_2 powder dissolved in 100% ethanol; experimental samples) (BML-PG007, Enzo Life Sciences, Farmingdale, NY) and two vials receiving the same amount of ethanol (7μL; control samples). The amount of PGE_2 was chosen based on preliminary experiments on human skeletal muscle completed using various PGE_2

concentrations (data not shown) and on studies in human nerve and bone cells [19, 21, 27, 28]. The four vials were then incubated in a shaking water bath (110 cycles/min) under constant temperature (37°C) and received continuous gassing (95% O_2/5% CO_2) for 1 or 2 hours. At the end of each 1h and 2h incubation period, an experimental and control muscle sample were removed from their incubation vials, blotted on KHB soaked gauze and frozen in liquid nitrogen (−190°C). After freezing, the muscle samples were placed in RNA*later*-Ice (Ambion, Austin, TX) at −20°C until mRNA analysis.

Muscle mRNA Measurements

qPCR was completed on the incubated samples to determine the mRNA levels of IL-6 and MuRF-1 as we have previously described [7, 29]. Total RNA was extracted in TRI Reagent (Molecular Research Center, Cincinnati, OH). The quality and integrity (RIN of 7.1±0.1) of extracted RNA (88.3±5.8 ng/μl) was evaluated using a RNA 6000 Nano LabChip kit on an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA) [6, 30, 31]. Oligo (dT) primed first-strand cDNA was synthesized (150ng of total RNA) using SuperScript II RT (Invitrogen, Carlsbad, CA). Quantification of mRNA levels (in duplicate) was performed in a 72-well Rotor-Gene 3000 Centrifugal Real-Time Cycler (Corbett Research, Mortlake, NSW, Australia). Housekeeping gene GAPDH was used as a reference gene [30, 32, 33]. All primers used in this investigation were mRNA-specific (on different exons and/or crossing over an intron) and designed for qPCR (Vector NTI Advance 9 software, Invitrogen) using SYBR Green chemistry. Details about primer characteristics and sequences have been described previously [7, 29]. A melting curve analysis was generated for all qPCR runs to validate that only one product was present. A serial dilution curve (cDNA made from 500ng of total RNA of human skeletal muscle; Ambion, Austin, TX) was generated for each qPCR run to evaluate reaction efficiencies. The amplification calculated by the Rotor-Gene software was specific and highly efficient (1.03±0.02; R^2=0.99±0.00; slope=3.25±0.05). Gene expression of IL-6 and MuRF-1 was determined after 1h and 2h of incubation by using the $2^{-\Delta C_T}$ (arbitrary units) relative quantification method [31, 33, 34].

Statistical Analysis

Data were analyzed with a one-tailed paired t-test to compare gene expression between control and PGE_2 stimulated samples after 1h and 2h of incubation. Muscle sample weight between the control and PGE_2 stimulated samples was also compared with a paired t-test. The association between the IL-6 and MuRF-1 gene expression was evaluated using a Pearson r correlation. For all variables, significance was accepted at $P<0.05$. Data are presented as means ± SE.

3. RESULTS

On average, IL-6 was upregulated by PGE_2 (165%) at 1h ($P<0.05$) but was similar to control after 2h ($P>0.05$) and MuRF-1 expression in response to PGE_2 was similar to control at 1h and 2h ($P>0.05$) (Figure 1). However, not all subjects had their largest induction of IL-6 or MuRF-1 at the same time points; therefore, the largest induction from each subject was grouped (Peak), resulting in an upregulation ($P<0.05$) of IL-6 (195%) and MuRF-1 (51%) (Figure 1). A significant relationship was found between IL-6 and MuRF-1 gene expression after 1h and 2h of incubation with PGE_2 ($r=0.77$, $P<0.05$). There were no differences in muscle weight between the control and PGE_2 samples (control: 11.77±0.62; PGE_2: 11.42±0.56mg) ($P>0.05$).

4. DISCUSSION AND CONCLUSIONS

The primary findings from this investigation were prostaglandin E_2 induces intramuscular transcription of IL-6 and MuRF-1, both regulators of human skeletal muscle mass, and this transcriptional activation may be regulated through a common pathway.

The PGE_2 stimulated IL-6 gene transcription response in the current study (Figure 1) is similar to studies that have examined this response in cultured human nerve and bone cells [19, 21]. The fact that some subjects had their highest induction of IL-6 with PGE_2 at 1h while others responded more at 2h suggests a variation in sensitivity to PGE_2 simulation among the subjects. To a greater extent this variation in response was also seen in the MuRF-1 expression increase with PGE_2 stimulation, as 40% of the subjects had a peak response at 1h while 60% had their peak expression at 2hrs. The specific basis for the variability of MuRF-1 (and to some degree IL-6) expression induced by PGE_2 *ex vivo* is unclear. Differences in the number of PGE_2 receptors on the incubated muscle and components associated with the stimulated receptor pathway would likely alter the responsiveness of the muscle to PGE_2. Exercise training does impact human skeletal muscle PGE_2 receptor levels [7], although the training status of the current subjects was relatively similar (~30min/day of exercise). Considering the known fiber type influence on metabolic and molecular processes [35–38], including IL-6 and MuRF-1 levels [39, 40], it is possible that differences in fiber type among the subjects or between the different incubated muscle samples contributed to the variable transcription response. This variability raises interesting questions regarding the PG/COX pathway in human skeletal muscle and further investigation into these issues is clearly warranted.

The significant relationship between IL-6 and MuRF-1 expression in response to PGE_2 suggests that activation of the PGE_2 receptor may stimulate both IL-6 and MuRF-1 gene transcription through a similar mechanism in human skeletal muscle. In support of this notion, PGE_2 stimulates IL-6 transcription in non-skeletal muscle cells through a NF-κB-mediated mechanism [18, 20, 21, 41], and MuRF-1 has been shown to be regulated via NF-κB [17, 42]. Based on these studies and the current data it is reasonable to speculate that PGE_2 stimulates IL-6 and MuRF-1 transcription through a common PGE_2 receptor - NF-κB linked mechanism.

The findings from the current *ex vivo* studies of adult human skeletal muscle provide strong support for the proposed mechanism of COX inhibitors augmenting muscle growth by up to 50% in resistance training older individuals through a reduction in PGE_2 stimulation of IL-6 and MuRF-1 [6, 7]. This mechanism is based on the findings that: 1) Intramuscular levels of IL-6 and MuRF-1 are lower after several months of resistance training in individuals consuming COX inhibitors (e.g., acetaminophen and ibuprofen) daily compared to a placebo group [7], 2) IL-6 and MuRF-1 are elevated after exercise [29] and generally exhibit the aforementioned inhibitory effects on muscle growth, and 3) The elevation in intramuscular PGE_2 in response to exercise can be eliminated with consumption of a COX inhibitor [2]. Further support comes from studies that show NF-κB activation and binding to the IL-6 promoter is elevated with resistance exercise in humans [43], and NF-κB regulators (i.e., IKKβ) appear to be reduced in skeletal muscle from individuals consuming a COX inhibitor [7].

It is unclear if the PGE_2 and COX inhibitor regulated effect on muscle mass is age-specific, as might be expected if differences existed between young and old in their production of intramuscular PGE_2 or their PGE_2 stimulation of IL-6 and MuRF-1 in response to repeated resistance exercise sessions. While the studies in the current investigation were limited to young males to establish whether or not the proposed pathway was present in skeletal

muscle, there is no evidence to suggest this pathway would not be intact in both young and old men and women. Further studies examining potential gender and aging differences are needed. In addition, the current methodology opens the possibility to test further hypotheses in this area and should greatly expand our insight into PG regulation of metabolic and molecular processes in human skeletal muscle.

In summary, we have established a connection between the COX pathway product PGE_2 and the stimulation of IL-6 and MuRF-1 transcription in human skeletal muscle. These findings establish a novel mechanism regulating skeletal muscle adaptation in humans, add to our understanding of the molecular and metabolic effects of the most commonly consumed drugs, COX inhibitors, and identify a new pathway and potential targets for the treatment of sarcopenia.

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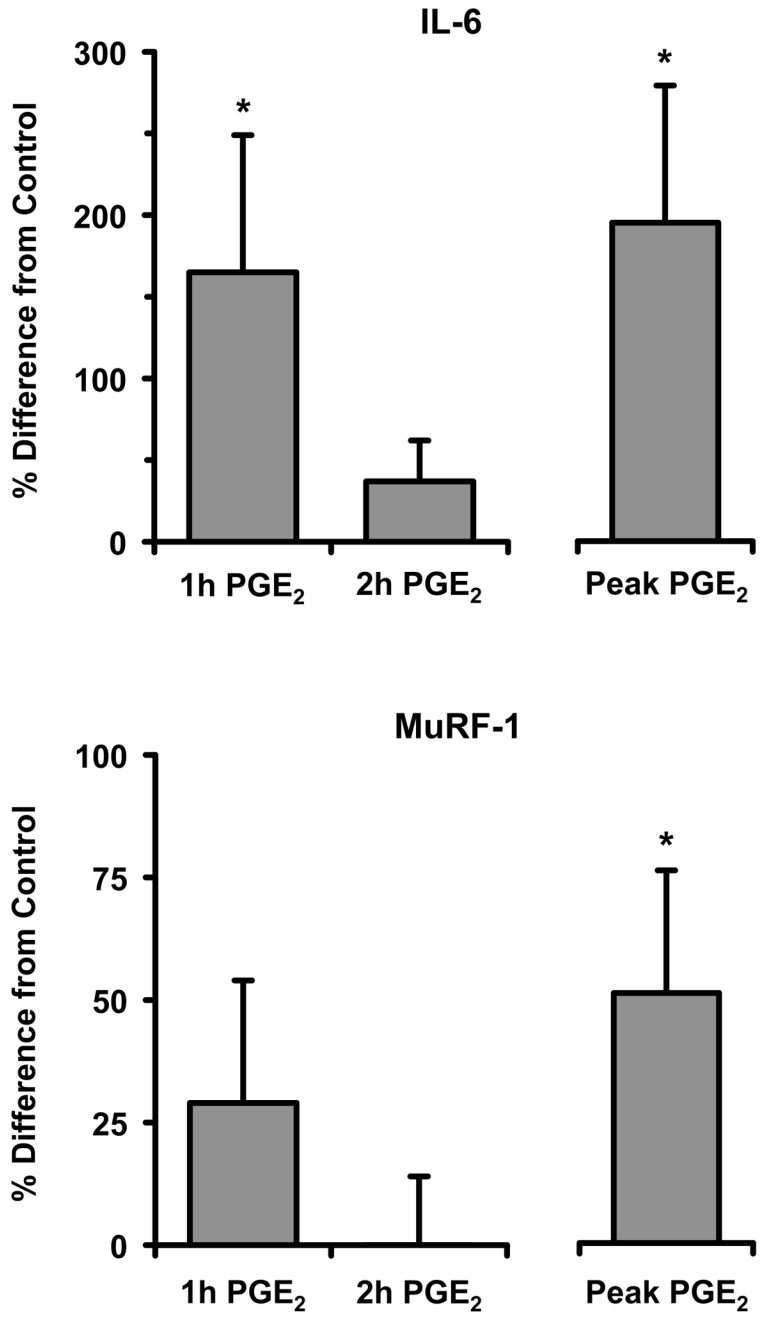

Figure 1.

Percent difference in IL-6 and MuRF-1 gene expression from control after human skeletal muscle samples (~10mg) were incubated (Krebs-Henseleit Buffer, shaking 37°C water bath, continuous gassing (95% O_2/5% CO_2)) with and without PGE_2 (20μM) for 1h or 2h. Not all subjects had their largest induction at the same time points; therefore, the largest induction of gene expression that occurred for both genes from either the 1h or 2h experiments by each subject were grouped together to determine peak expression independent of time (Peak). IL-6 and MuRF-1 mRNA expression was determined by qPCR. Data are means ± SE from 10 subjects. * $P<0.05$ from control.