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EXPERIMENTAL STUDY

Differential effects of pregnancy on contractile behavior of rat fast and slow skeletal muscles

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Abstract: *Background:* The effect of pregnancy on skeletal muscle still has not been clearly established. The aim of the present study was to investigate the effect of pregnancy on muscle weight and contractile properties of soleus and plantaris muscles.
Methods: The female Sprague-Dawley rats were divided into two groups: nonpregnant (NP, 250 ± 4 g, n = 8) and late-pregnant (LP, 305 ± 13 g, n = 8). The right plantaris and soleus muscles were liberated from the surrounding tissues. Each muscle was placed on setup to mechanical recording with electric stimulation. In the optimum length of each muscle were recorded single twitches, tetani and fatigue.
Results: The weight and cross-sectional area of soleus and plantaris muscles from pregnant rats was increased respect to nonpregnant rats. The maximal twitch tension decreased in both muscles during pregnancy respect to nonpregnant group. The soleus muscle of LP group developed lesser tetanic tension than NP group. However, the plantaris muscle showed a different behavior: to lower frequencies (5–30 Hz) the NP group developed greater tetanic tension than LP group, and for higher frequencies (40–100 Hz), the LP group developed greater tetanic tension than NP group. Finally, the soleus muscle was more resistance to fatigue than plantaris muscle in pregnant rats.
Conclusion: The fast and slow skeletal muscles show a differential contractile response during pregnancy, in tetanic tension and fatigue *(Fig. 4, Ref. 48)*. Text in PDF *www.elis.sk.*
Key words: pregnancy, skeletal muscle, fatigue, muscle mass.

Many physiological, metabolic and endocrine changes occur during pregnancy. In healthy people, the fatigue is the result from muscle activities repeated or sustained, being common in daily activities and exercise (1). In pregnancy, changes in the consumption of oxygen, fetal development, cardiovascular system, metabolism and hormone levels are physiological factors proposed as responsible for inducing fatigue. In addition, also raised other factors such as psychological stress (changes in mood, anxiety, fear, and identity), situational factors, socioeconomic status, age, number of children, hours of sleep, exercise and lifestyle (2). Also, in the last trimester of pregnancy, there is an increased perception of fatigue, probably due to the increase in body weight. At present, there is not clarity regarding the effects of gender on the magnitude of muscle fatigue. Differences in fatigability across age or gender could occur as the result of differences in neural drive, fiber-type composition, contractile function, muscle membrane excitability, metabolic capacity, or muscle mass and blood flow (3). In fact, clinically there is evidence of muscle fatigue in the pregnant woman, but to level of basic research there are few focused work in study changes in muscle contractility and the mechanisms involved. In animals models, such as the rat, a decrease in glucose transport induced by electrical stimulation in isolated epitrochlearis muscles from pregnant rats compared to non-pregnant rats has been reported, but no differences between non-pregnant rats and pregnant in terms of contractile performance (peak tension total tension, or fatigue) (4). It has been reported that in pregnant rats, the muscle tension decreases more rapidly and the vascular resistance was greater than in non-pregnant rats, this decline in tension was accompanied by an enhanced lactate production in comparison with non-pregnant rats (5). Also, a decreased activity of Na^+–K^+ ATPase pump in skeletal muscle has been reported (6), although still has not been studied how it affects the excitability and force production. During pregnancy, it is known that blood levels of estrogens are elevated (7) and some in vitro studies reported that estradiol increases the development of maximal tension in the rat soleus muscle (8). Also, in skeletal muscle, the presence of receptors to estrogens has been reported (9). However, it remains to understand the influence of the estrogens and pregnancy on the functionality of the skeletal muscle. Hence, the present study was designed to evaluate the contractile performance of fast and slow muscles in pregnant rats compared to nonpregnant rats, preserving the blood flow and motor innervation unimpaired.

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Material and methods

Animals

Animal care and experimental procedures were approved by the Ethics Committee of the University of Colima, using guidelines based on the Guide for the Care and Use of Laboratory Animals (US Department of Health, NIH). Three-month-old female Sprague-Dawley rats were separated into the two groups: controls or nonpregnant (NP, diestrus 250 ± 4 g, n = 8) and late pregnant rats (LP, 305 ± 13 g, n = 8). All rats were provided with water and food ad libitum and were maintained in individual acrylic cages on a 12:12-h light–dark cycle with an average daily temperature of 24 ± 1 °C and average humidity of 60–70 %.

Surgery and experimental conditions

Rats were anaesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally). The right plantaris and soleus muscles were liberated from the surrounding tissues, leaving the bone insertion and blood supply intact. The motor nerve was cut as far away as possible from its entry into the muscle. During surgery, saline solution (125 mM NaCl; 5.4 mM KCl; 1.05 mM $MgCl_2$; 1.8 mM $CaCl_2$; and 11 mM glucose, pH = 7.4) was applied to protect the tissues. A transverse hole was made in the femur using a microdrill (F.S.T.18000 – 17; Fine Science Tools, Foster City, CA, USA), and the distal tendon of both muscles was tied to a hook. Each rat was then transferred to a mechanical recording system consisting of a plate mounted on an inclined base that allowed the muscle to be placed perpendicularly to a load transducer (FT10; Grass Co., Quincy, MA, USA). The plate had two posts to hold the steel rod passing through the hole in the femur. The transducer was mounted on an actuator driven by a computer-controlled stepper-motor and wired to an A/D converter to allow display and storage of the force signals. The tendon hook was attached to the transducer. The corresponding motor nerve was placed on stimulating electrodes wired to a stimulator (S88; Grass Co.). During the experiment, rat body temperature was maintained at 37 °C. The environmental temperature was 24 °C. At the end of the experiments, the muscles were excised from the animals, dried with absorbent paper, and weighed on an analytical balance (Sartorius, Edgewood, NY, USA).

Mechanical properties measurement

At several muscle lengths, isometric twitches were elicited by supramaximal stimuli (3 Volts) to the motor nerve until the maximal amplitude (corresponding to the optimal length, Lo) was obtained. At Lo of each muscle, (soleus and plantaris) twitches and tetani (5–100 Hz) were recorded elicited by motor nerve stimulation. The muscles were rested for 100 s between each record. Fatigue was induced applying supramaximal stimuli with trains of 300 ms in duration and frequency of 60 Hz for 3 min at a rate of 3 trains/s. For each tetanic contraction, a fatigue index was calculated as follows: (tension developed / maximal peak tension) 100 %. The mean fatigue index of the pregnant group was compared to the mean fatigue index of the nonpregnant group. Finally, the animals were sacrificed by an anesthetic overdose (150 mg/kg, intraperitoneally).

Mechanical analysis

The tensions obtained were expressed as force/CSA (N/cm^2), where CSA corresponded to cross-sectional area and was calculated using the equation CSA = MW / (1.056Lo), where MW corresponded to muscle weight (g); Lo, the muscle optimum length (cm); and 1.056, the muscle density (g/cm^3) (10, 11). Finally, a conversion to Kilopascal (KPa) was done.

Statistical analysis

Experimental groups were compared using the Mann-Whitney test with a level of significance of 95 %. Tension curves were compared to the analysis of variance of one factor and a post hoc Tukey's test. All differences were considered statistically significant with a $p \leq 0.05$. Statistical analysis was conducted with the Minitab 12 software.

Results

Muscle weight

The soleus muscles weight in LP group was significantly higher than in the NP group (NP, 123 ± 5 mg; LP, 165 ± 13 mg, $p < 0.01$). In plantaris muscle, the weight also increased significantly during pregnancy (NP, 319 ± 09 mg; LP, 418 ± 10 mg, $p < 0.01$) (Fig. 1a). When CSA was calculated, a significant increase in both muscles during pregnancy was found: Soleus (NP: 0.044 ± 0.001 cm^2; LP: 0.055 ± 0.003 cm^2, $p = 0.021$), and plantaris (NP: 0.088 ± 0.002 cm^2; LP: 0.105 ± 0.003 cm^2, $p = 0.021$) (Fig. 1b).

Tension and frequency curves

Figure 2 shows the maximal twitch tension for both muscles. The soleus declined 41 % in the LP group, while in plantaris muscle decreased 26 % respective to the NP group; differences were statistically significant ($p < 0.05$). Using repetitive stimulation, the soleus developed significantly less tetanic tension in the LP group (350 kPa) than in the NP group (450 kPa) (Fig. 3). In the case of plantaris, the NP group reached its maximum tension at 70 Hz (460 kPa), whereas the LP group reached its peak at 100 Hz (640 kPa). It was observed that at frequencies below 30 Hz that the tension developed by the LP group was lower than in the NP group, but at stimulation frequencies greater than 30 Hz the tension developed by the LP group was higher (Fig. 3).

Fatigue

Figure 4 shows the fatigue index of the soleus. The fatigue index in the soleus muscle of the LP group was 60 %, while for the NP it was 49 %, so that the LP group was more resistant to fatigue than the NP group. However, for the plantaris muscle, the fatigue index was similar for both groups (Fig. 4).

Discussion

It known that there are differences between the skeletal muscles of males and females. For example, in the study between males and females subjected to restriction in the supplying food, it was observed a significant decrease in the weight of the muscles extensor

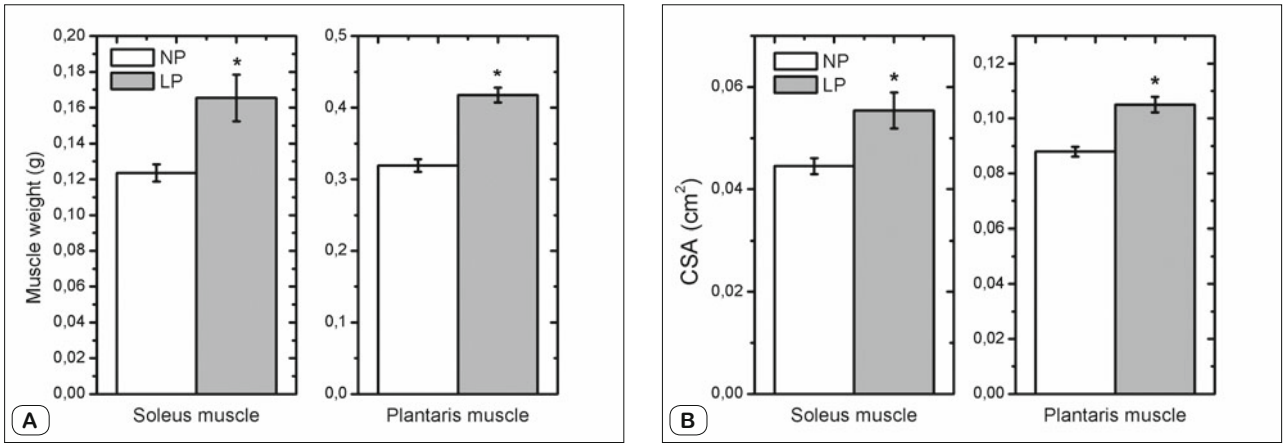

Fig. 1. Soleus and plantaris muscles weight from nonpregnant rats (NP) and late-pregnant rats (LP). (A) Shows the weight and (B) the cross sectional area. In general, the two parameters it increased significantly during pregnancy in both muscles (*p < 0.05). Data correspond to means ± error standard (n = 8 by group).

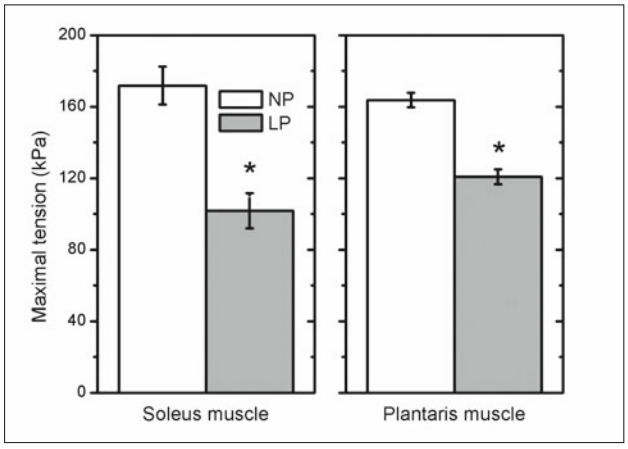

Fig. 2. Maximal twitch tension in the soleus and plantaris muscles of nonpregnant rats (NP) and late-pregnant rats (LP). The tension decreases significantly during pregnancy in both muscles (*p < 0.05) (Soleus: 41 %, Plantaris: 26 %). Data correspond to the means ± error standard (n = 8 by group).

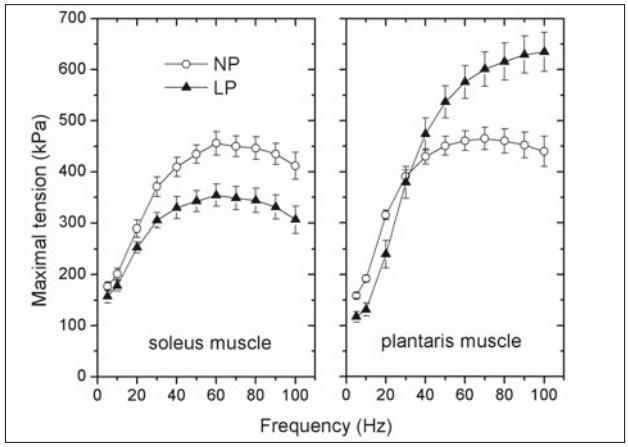

Fig. 3. Maximal tetanic tension reached different stimulation frequency in the soleus and plantaris muscles of nonpregnant rats (NP) and late-pregnant rats (LP). At low frequencies, the tension in the soleus and plantaris muscles decreases significantly during pregnancy (*p < 0.05). At high frequencies, the muscles showed a different behavior: in the soleus, the tension was less during pregnancy while in the plantaris increased (*p < 0.05). Data correspond to the means ± error standard (n = 8 by group).

digitorum longus (EDL) and soleus (12). In other study, the CSA was measured in the elbow and knee extensor and flexor muscles of women and men, and the women had significantly smaller muscle CSA than men in both the upper arm and thigh (13). Also, there are differences in energy metabolism, fiber type composition, and contractile speed (14–18). Besides, also it has been reported differences in the skeletal muscle functionality between males and females subjected to immobilization (19). However, although there are studies to understand sex-based differences in skeletal muscle, little is known regarding the effects on fast and slow skeletal muscles in other conditions physiological as the pregnancy characterized by high levels of estrogens (20). In the present investigation, we studied the effect of pregnancy on the skeletal muscle and the experiments showed that the cross-sectional area and the mass of fast and slow muscles increased during pregnancy.

It is known that the muscle mass is determined by the protein synthesis and degradation ratio (21). Consequently, during pregnancy, some mechanism implicating in these processes are affected, then it could explain the differences observed in the muscle mass. It is known that myostatin induces skeletal muscle atrophy, and there is evidence that the estrogens inhibit this protein to promote muscle growth. On the other hand, the estrogens also stimulates the expression of insulin-like growth factor-1 (IGF-1) (22) and, IGF-1 is a modulator of skeletal muscle hypertrophy by activating the calcium-dependent calcineurin signaling pathway (23). Also, it has been reported that IGF-1 can played a crucial role in the regulation of skeletal muscle growth through of a signaling cascade that actived the kinase Akt (also called Protein Kinase B, PKB). Akt regulates both synthesis and protein degradation, the synthesis is mediated via the kinases mammalian target of rapamycin (mTOR) and glycogen synthase kinase 3β (GSK3β), while the

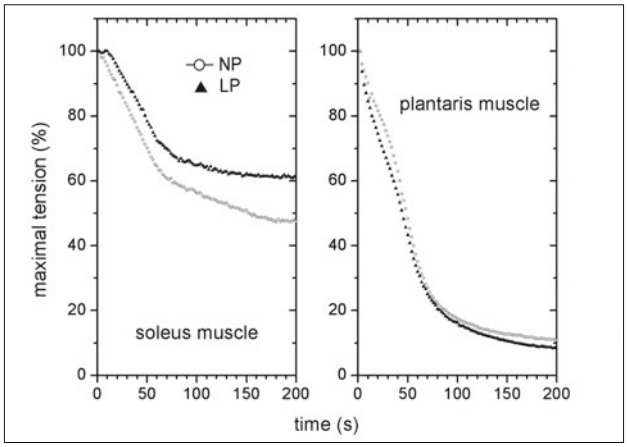

Fig. 4. Fatigue in the soleus and plantaris muscles of nonpregnant rats (NP) and late-pregnant rats (LP). The traces show the declined of tension average (n = 8 by group). The soleus muscle is significantly more resistance to fatigue in LP group than the NP group (*p < 0.05), while the plantaris muscle not showed changes to fatigue.

proteins degradation is regulated by the transcription factors of the FoxO family (24). Pollanen et al (25) suggested that the estrogens could be regulating an increase in the muscle mass through of IGF-1. Recently, it has been reported that activation of the Akt/mTOR signaling was increased higher in females than in males (26); this difference could be caused by the amount of estrogens in females supporting the participation in the increases of the muscle mass.

Other studies had shown that a reduction in the levels of estrogens and expression of estrogen alpha receptor (αER) is associated with a decrease in the muscle mass in the soleus muscle (27). Therefore, increases in the levels of estrogens as occuring during pregnancy could be associated with an increase in the expression of estrogen alpha receptor (αER) and promoting the muscle growth. Also, there are data suggesting that a reduction in the oxidative enzyme content in the muscle fibers are correlated with the loss weight and cross-sectional area in fast and slow muscles (28). This information suggests that oxidative enzymes are important in the control of the size of the skeletal muscle. Studies recent shown that estrogens increased the amount of type I fibers in the soleus muscle (29), which are characterized by a high content of oxidative enzymes, so considering the possibility that this mechanism could be involved in the regulation of the size of the muscle during pregnancy. Finally, estrogens will promote muscle growth via satellite cell activation and proliferation (30). However, although experimental studies designed to understand the mechanisms involving of the estrogens in the muscle atrophy and hypertrophy exist, more investigations is required to explore signaling pathways involved in the regulation of the muscle mass during pregnancy, until today this has been not studied.

Tetanic and twitch tension

In late pregnancy, we found that the maximal twitch tension decreased in soleus and plantaris muscles. On the other hand, when a repetitive electric stimulation was used, the soleus muscle of pregnant rats developed less maximal tetanic tension than the nonpregnant rats. The plantaris showed a differential response, at low frequencies, the pregnant rat muscle developed less maximal tetanic tension compared to the control group, and high frequency pregnant-rat muscle developed more tension than the control group. Studies reported in literature on the effects of estrogens on the maximal tension of fast and slow skeletal muscle have shown discrepancy in their results. The decrease in maximal tension observed in present experiments was similar to the results obtained in assays in vitro where the effect of estrogens on the maximal tension in soleus muscle was evaluated (8). However, McCormick et al (31) did not find changes in the maximal tension of soleus muscle in ovariectomized rats with estrogens replacement. Other research performed by Moran et al (32) found that skeletal muscle contractility (soleus and extensor digitorum longus muscles) and myosin function declined following ovariectomy in female mice, and the estrogens replacement evoked a reversion of the changes induced by ovariectomy. Also, it has been reported that estrogens increase relaxation time in soleus muscle (31), this change in the relaxation kinetic could explain a decrease in the maximal tetanic tension observed in the soleus muscle during late pregnancy by effect of estrogens. On the other hand, in the study performed in fast muscle (epitroclearis muscle) no change was found in the maximal tension after the administration of estrogens (4), while we reported in this work that during pregnancy the plantaris muscle (fast muscle) showed changes significant in the maximal tension with electric stimulation to low and high frequency.

Muscle fatigue

The muscle fatigue is defined as the muscle inability to maintain the expected force or power, whether or not the task can be sustained (33). There are studies that shown differences in muscle fatigue between females and males. For example, it was reported in the muscles: adductor pollicis (34–35), elbow flexors (36–37), extrinsic finger flexors (38–39) and knee extensors (40). The women may have several times longer endurance than the males (resistance to fatigue) when performing isometric contractions at low to moderate intensity. In a study to compare the pressor response and muscle activation patterns of men and women, during a fatiguing contraction performed with the elbow flexor muscles, it was found that the endurance time of women was longer than men and the endurance time was inversely related to the absolute force sustained during the contraction (41). Skeletal muscle fatigue may be related to sex differences, this is due to the difference in muscle mass and strength between men and women (42–43). However, little is known regarding the effect of pregnancy on the fatigue of fast and slow skeletal muscle. In the present study, we found that soleus muscle is less fatigable in pregnant rats than in nonpregnant rats; this suggested that estrogens protect to muscle. In the plantaris muscle, the fatigue level was not modified by pregnancy. One possible explication to the increased fatigue resistance observed in soleus muscle during pregnancy is that the estrogens increases the myosin cross bridges in strong binding states during contraction by a reduction in oxidative stress (30, 44–45). Other possibility is that estrogens increases the amount of type I fiber

in soleus muscle (29) and this fiber are more resistance to fatigue; this increasing in type I fiber could be mediated by peroxisome proliferator-activated receptor β/δ (PPARβ/δ) (46), which are expressed in skeletal muscle (47) and its expression is increased by estrogens action (48). Finally, this finding also could suggest that estrogens improve more muscle quality than quantity (45).

In conclusion, during pregnancy, a physiological state with a high level of estrogens, soleus and plantaris muscles increased the weight and showed the effect benefitial to the contractile properties. The soleus muscle increased its resistance to fatigue, and the plantaris muscle increased the maximal tetanic tension with repetitive electric stimulation at high frequency. Finally, to elucidate the mechanisms involved in the changes in muscle mass, maximal tension as well as in fatigue during pregnancy, future investigations are required.

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