Influence of stretch and pressure as mechanical stresses on skeletal muscle

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Abstract Mechanical forces induced by skeletal muscle contraction generate intramuscular stresses as well as external tension. Skeletal muscle cells can sense and adapt to mechanical stresses to maintain cellular homeostasis. Compared to the effects of hormone and growth factors (e.g., insulin, insulin-like growth factor, and other cytokines) on physiological and biochemical properties in skeletal muscle, the implications and molecular mechanisms concerning responses of skeletal muscle to mechanical stresses are still largely unclear. In this short review, we focus on the influences of mechanical stresses, especially intramuscular pressure and stretching, on the contraction of skeletal muscles, and review current results from studies examining the effects of mechanical stresses.

Keywords: mechanotransduction, muscle, glucose metabolism, protein synthesis, hypertrophy

Introduction

When a skeletal muscle contracts, it not only receives electrical/chemical stimulation, but is also subjected to mechanical forces. Since Vandenburgh and Kaufman1) reported in 1979 that mechanical stretching induced muscle hypertrophy, there have been many studies attempting to define the physiological effects of mechanical stresses on skeletal muscle tissues/cells with in vivo and in vitro procedures. However, compared to nerve innervation and humoral and hormonal stimulants (e.g., adrenalin, insulin, insulin-like growth factors), the molecular-level influences of mechanical stresses on skeletal muscle, despite numerous studies on this topic2-13), are still largely unclear. In the present short review, we focus on the influence of mechanical stress in contracting skeletal muscles, and thus briefly review the following issues: a) When skeletal muscle contracts, what mechanical stresses occur within the contracting muscles? b) What effects do the mechanical stresses in contracting muscles have on hypertrophic/protein synthetic responses in skeletal muscles?

Mechanical stresses during skeletal muscle contraction

When skeletal muscles contract, what types of mechanical forces are applied to contracting skeletal muscles? Although other researchers have used stretch stress, which consists of the elongation of skeletal muscle tissues/cells by external forces5,6,12), compressive (pressure) stress results from the shortening of tissues/cells within contracting muscles14,15). Sadamoto et al.16) reported in 1983 that intramuscular pressure during contraction reached 240 mmHg in a lower limb muscle. During walking and running, peak values of intramuscular pressure were recorded approximately 200 and 300 mmHg, respectively, immediately before the toe-off phase (the phase of maximal voluntary contraction) in the soleus muscle15). Intramuscular pressure is also shown to be associated with tension induced by voluntary concentric muscle contraction15-17). Collectively, these previous studies showed that when skeletal muscle voluntarily contracts and exerts tension, contracting muscle tissues/cells undergo compressive (pressure) stress. On the other hand, intramuscular pressure decreases in the phase of eccentric muscle contraction17). In this phase of muscle contraction, skeletal muscles elongated by external forces are subjected to passive stretch stress.

Most skeletal muscle that contracts during human movement undergoes a stretch-shortening cycle. Although many previous mechanical stress studies have used stretching to apply mechanical stimulation, stretching is just a part of the various mechanical forces that are observed during the stretch-shortening cycle.

Effects of stretch on skeletal muscle

Vandenburgh and his colleagues reported that stretching in vitro cultured myotubes led to increases of protein...
content and cell diameter (18). Several subsequent studies demonstrated that stretch stress induced activation of glucose metabolism, increases in protein synthesis, mRNA expression and post transcriptional responses (9-12, 18-25). Moreover, stretch stress inhibited atrophic responses (26-28). As shown in the previous review by Park et al., although there is no consensus as to the effect of stretching myocytes on cell differentiation (i.e., myogenesis), it appears that stretch stress leads to enhancement of protein synthesis in skeletal muscle.

Effects of pressure on skeletal muscle

When skeletal muscle contracts and elevates intramuscular pressure, what kinds of cellular responses take place in contracting muscles? The following two opposite responses have been reported: a) compressive/pressure stress can activate metabolic responses and protein synthesis; and b) compressive/pressure stress can lead to protein degradation. One possible reason for this inconsistency is that the various studies have used different procedures including a pressure apparatus. Hydrostatic and atmospheric pressure systems can load pressure without distortion. Compressive stress using a plate on pressurized cells applies pressure with stretch and strain. In previous studies, the magnitude of pressure used has ranged from approximately 10 mmHg (8.6 kPa) to 3 million mmHg (400 MPa) (2, 29-33). Based on results from previous studies investigating human intramuscular pressure (14, 15), we reviewed the results of the physiological level of pressure (up to 1000 mmHg).

Ishihara and his colleagues (3, 4) showed that 1.25 atm (950 mmHg) hyperbaric stress increased succinate dehydrogenase activity in rat soleus and plantaris muscle fibers. These studies used atmospheric pressure with a high oxygen concentration (36%); thus, results from the studies could be attributed to the concomitant effects of pressure and oxygen. We previously reported an in vitro study in which 160 mmHg of atmospheric pressure enhanced succinate dehydrogenase activity and glucose metabolism associated with protein synthesis in L6 myoblasts (2). The authors have also demonstrated that the same pressure treatment induced cell proliferation through extracellular signal-regulated kinase (ERK) and c-jun N-terminal kinase (JNK) activation in smooth muscle cells (31-33). These studies suggest that mechanical pressure would lead to enhancement of metabolic enzyme and protein synthesis.

On the other hand, some studies have shown protein degradation-associated responses. Pressure loading of 32 mmHg for 12 hrs was shown to lead to apoptotic responses in approximately 50% of cells in C2C12 myocytes (34). In human carcinoma cells, compressive stress (8.6 mmHg) also induced autophagy, which is a degradative response for denatured proteins and damaged organelles (see Ref. 35 reviewed by Ogata (35)). The reasons for the inconsistency between the above-mentioned pressure-induced protein synthesis and autophagic/apoptotic responses are unclear. However, it has been shown that impairments of autophagy led to a decrease in muscle mass (30) and that the cellular mechanotransduction system interacted with autophagy (37); thus, those results may not be inconsistent in mechanically loaded cells.

Differences in stretch and pressure stimulation

Both stretch and pressure were shown to increase glucose uptake into myocytes in in vitro and isolated muscles (2, 5, 19, 23, 24). Although stretch stress in the enhanced-glucose-uptake condition led to an increase of lactate efflux from myocytes to culture media, pressure stress induced a decrease in lactate efflux (19, 23). This difference suggests that aerobic metabolism can be activated by pressure stress, but not by stretching. In a recent study using single cells (40), metaphase progression was activated by compression (shortening the spindle’s long axis), but not by stretch (elongating the spindle’s long axis), suggesting that the direction of the mechanical stresses in relation to cellular components could influence cell behavior.

Perspectives

Current studies suggest that both stretch and pressure stresses to muscle tissues activate metabolism and protein synthesis in contracting muscles (Fig. 1). Our understanding of mechanical signaling and cellular responses is still
insufficient compared to our understanding of signaling by hormone and humoral factors (e.g., insulin and insulin-like growth factors). However, recent advances in microscopic technology have allowed the detection and visualization of cell behavior in living cells\(^{38-41}\). This kind of experimental technology should provide a better understanding of the molecular mechanisms involved in the responses of skeletal muscle to mechanical stresses. Future studies are expected to elucidate the dynamics of cellular mechanotransduction systems and their precise roles in governing morphogenesis, physiology and disease.

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