Perspective

Application of Passive Stretch and Its Implications for Muscle Fibers

To increase range of motion, physical therapists frequently use passive stretch as a means of gaining increased excursion around a joint. In addition to clinical studies showing effectiveness, thereby supporting evidence-based practice, the basic sciences can explain how a technique might work once it is known to be effective. The goal of this article is to review the potential cellular events that may occur when muscle fibers are stretched passively. A biomechanical example of passive stretch applied to the ankle is used to provide a means to discuss passive stretch at the cellular and molecular levels. The implications of passive stretch on muscle fibers and the related connective tissue are discussed with respect to tissue biomechanics. Emphasis is placed on structures that are potentially involved in the sensing and signal transduction of stretch, and the mechanisms that may result in myofibrillogenesis are explored. [De Deyne PG. Application of passive stretch and its implications for muscle fibers. *Phys Ther.* 2001;81:819–827.]

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Decreased joint range of motion can occur as a result of many different types of pathology (eg, as a sequela of orthopedic procedures[1–4]; from inactivity, especially as we age[5]; as a result of chronic dysfunction of the musculoskeletal apparatus[6,7]). Decreased range of motion can result from bony deformations or ectopic ossifications around the joint (osteophytes).[3] Lack of mobility also can originate from compromised soft tissues around a joint (eg, tight or shortened ligaments, sclerosis in the connective tissue).[3,8]

Physical therapy interventions often are used to restore normal mobility, and physical therapists use a variety of techniques, such as passive range of motion, stretching by the therapist or by the patient, splinting, and serial casting.[5,7–11] Underlying these approaches appears to be a belief that longer muscles (including muscle fibers and the related connective tissue) will have greater excursion ability; thus, there will be increased range of motion around the joint, especially if any shortened periarticular tissues are also stretched.[12,13]

These interventions have in common the use of passive stretch, which is thought to elongate shortened tissues. These interventions, often in combination with an exercise program, are claimed to lead to a sustained increase in range of motion.[5,9,10,14] Despite their widespread use and some evidence of their effectiveness,[5,9,10,14] an explanation as to why these stretch-based rehabilitation methods may be effective is lacking. In this article, I use an example of the application of a passive force to the foot and ankle and analyze the effects of this force on the soleus muscle (Fig. 1). A biomechanical rationale is used to dissect the effects of passive stretch at the tissue and cellular levels.

Applying Passive Stretch to the Soleus Muscle

Figure 1 illustrates an example in which a patient has a lack of dorsal flexion. The therapist applies a passive force of 100 N (approximately 22.3 lb; Fig. 1, F_1) to the ball of the foot, located 150 mm (Fig. 1, moment arm a) from the joint axis, and moves through a 30-degree arc of motion to end at a neutral ankle position. The joint axis of the talocrural joint goes through the ankle medially 10 mm caudal and 2 mm posterior to the distal tip of the medial malleolus,[15] and the Achilles tendon is located 5 mm (Fig. 1, moment arm b) posterior to the talocrural joint axis.[16]

The cellular and molecular adaptive mechanisms of a muscle fiber may provide the scientific basis for stretching with the goal of improving range of motion.

In this example, the Achilles tendon will undergo a passive force of 300 N (Fig. 1, F_2). Assuming that the Achilles tendon has a circular shape (which is not the case at its calcaneal insertion, but this assumption makes it easier to calculate stress in the tendon) with a diameter of 6.3 mm in a young adult,[17] the stress that is generated is 30 MPa ($300 \text{ N} / 9.9 \times 10^{-6} \text{ m}^2$). With respect to the dense connective tissue, this amount of stress results in an increase in length of approximately 1% to 2% based on the stress-strain curve of organized dense connective tissues.[18] The use of these numbers is primarily for illustration, and exact lengths cannot actually be known. Thus, the application of such an amount of stress leads to deformations in the "toe" region of the stress-strain curve of connective tissues, also known as the "take-up-the-slack" region, in which the crimp pattern of the ligaments is straightened out.[18] Moreover, Young's modulus (the unit of stiffness, defined as stress/strain) of dense connective tissues is in the 1-GPa range, and that of muscle (as a whole) is in the 200-kPa range.[19] This means that passive muscle (muscle fibers, epimysium, and perimysium) is 4 orders of magnitude more compliant than is tendon. The muscle fascicles and fibers, therefore, are likely to receive most of the mechanical stress that is generated by the passive stretching. The stress will be propagated in the muscle according to the muscle's anatomy, and the amount of stress that individual muscle fibers will experience will depend on their orientation relative to the longitudinal axis of the muscle (angle of pinnation). The average angle of pinnation (Fig. 1, α) is 30 degrees,[19] and with the cosine of 30 degrees being 0.866, this means that nearly 85% of the stress applied to the Achilles tendon is passed on to the muscle fascicles.

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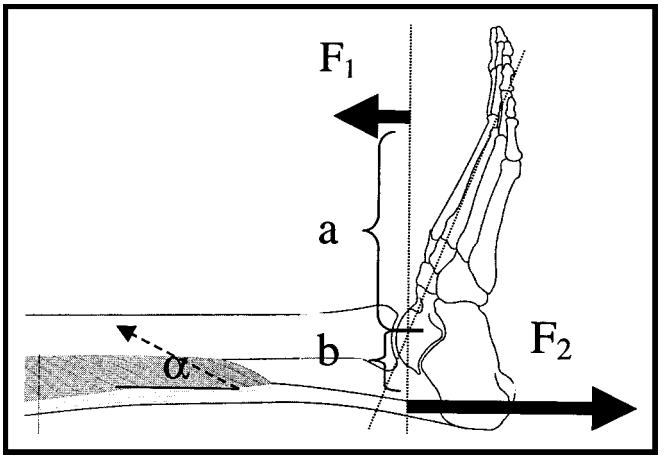

Figure 1.
Medial view of the ankle. This example shows the application of passive stretch to the human ankle. A passive force of 100 N is applied 150 mm from the joint center, and the ankle is moved through an arc of 30 degrees. The Achilles tendon and soleus muscle fascicles are stretched according to the anatomic architecture (α=pinnation angle, a and b=moment arms, F_1=stretch force, F_2=reaction force at the Achilles tendon).

In the example illustrated in Figure 1, if a physical therapist moves the ankle through an arc of motion of 30 degrees, the force at the Achilles tendon, applied 50 mm away from the joint axis, will result in a displacement of 25.8 mm (law of cosines, equilateral triangle) at the Achilles tendon. Considering a pinnation angle of 30 degrees, the muscle fascicles are displaced 22.3 mm (25.8 $\times$ cos 30). As the passive stretch is applied, however, the pinnation angle will decrease because the muscle fibers will be orientated more parallel with the longitudinal axis of the muscle. To determine the strain in the muscle fibers, the following need to be known: (1) the sarcomere length within the soleus muscle fibers at a specific joint angle, (2) the number of muscle fibers within a muscle fascicle, (3) the biomechanical properties of the perimuscular connective tissue, and (4) whether all of the sarcomeres are stretched equally. Additionally, because stretching is rarely applied to flaccid muscles, the stiffness of a muscle needs to be known, whether it is due to reflexes, active contractions, or structural changes. Stiffness of a muscle fiber is often a function of the degree of contraction.[20,21] Some of this information is available from work conducted using animal preparations, but data regarding humans are scarce.

Using cadaveric tissues, Wickiewicz et al[22] determined that throughout the whole soleus muscle, the average muscle fiber is 20 mm long (based on a sarcomere length of 2.2 μm). By using ultrasonography, some information can be generated relative to these issues.[23] This additional information is crucial for determining how a single muscle fiber can be lengthened because it allows for the calculation of the sarcomere length change per degree of range of motion. Experimental evidence from human forearm muscles shows a linear displacement of 5 to 10 nm per degree of joint rotation, with the amount of displacement varying for each muscle.[24] Given the known variability in sarcomere length between and within muscles at a specific joint angle, this must be considered a very rough estimate. At this point, we can only speculate regarding how much the sarcomere length changes in the soleus muscle in the example shown in Figure 1. For instance, if we assume that at maximal plantar flexion (40°) the sarcomere in the soleus muscle is in its most shortened position (1.5 μm) and that at maximal dorsal flexion the sarcomere is in its most extended position (3 μm), then the change in sarcomere length will not be more than 25 nm per degree, a value that is close to the experimental data.[24]

I believe that a light-to-moderate passive stretch applied to the whole muscle, as in the example illustrated in Figure 1, will affect primarily muscle fibers and not connective tissue. The effects of such an altered mechanical environment will be discussed next.

Biomechanical Rationale

The behavior of tissues exposed to altered mechanics is complex, but methods in mechanical engineering allow us to describe that behavior according to the properties of known materials.[18] When a substance is exposed to a passive force (stretch), it will deform according to its material properties, and when a relatively low force is sustained for a long period of time, most materials will deform in a time-dependent manner. This behavior is called "creep" and is a result of the viscoelastic properties of the material.[18] Nearly all tissues exhibit this property. When the force is no longer applied, the tissue will return to its original length, also in a time-dependent manner (relaxation). Such analyses are frequently used to characterize the properties of bone, cartilage, ligaments, and muscle. However, muscle is different from other tissues because it can generate force by itself (through actin/myosin interactions), which affects the stiffness.[20,21] Muscle has a number of noncontractile cytoskeletal components. One of them is titin, and it determines the elastic properties of the muscle fiber[25] and contributes to the passive resistance. The contribution of other cytoskeletal molecules (eg, dystrophin) to muscle fiber stiffness has not been fully characterized.

Increased range of motion immediately following passive stretching can be explained by the viscoelastic behavior of muscle and short-term changes in muscle extensibility.[26,27] Some authors[9] contend that passively stretching for as short a period of time as 30 seconds is sufficient to obtain increased mobility, whereas other authors[28] have found no such effect. However, clinical experience also

shows that the mobility gained with stretch-based rehabilitation protocols is maintained even when the passive stretch is removed, and this finding suggests a permanent adaptive response.[5,8–10,14] Thus, a biomechanical rationale may explain short-term, reversible changes in muscle length but fails to explain the long-term, permanent changes. Biomechanical models, in my view, because of the adaptable nature of live tissues, cannot fully explain a permanent increase in range of motion that is observed after a stretching program. Such changes, I believe, can be explained if the muscle actually becomes longer, by adding sarcomeres in series, allowing further excursion.

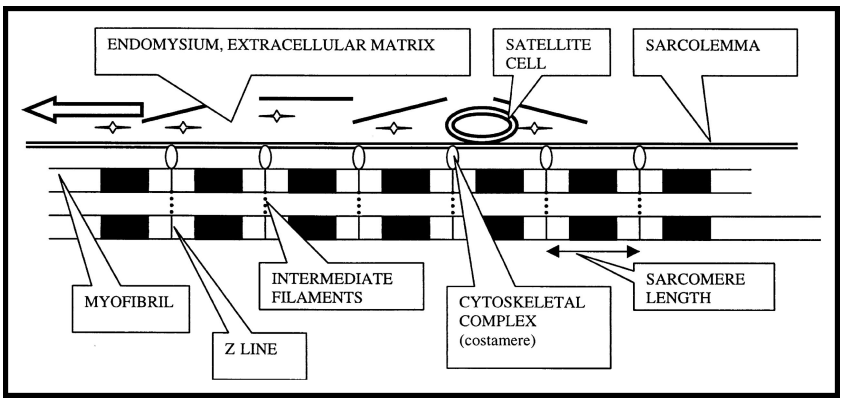

Figure 2.
Extracellular matrix, sarcolemma, and myofibrils. Passive stretch (arrow) is transmitted from the endomysium (extracellular matrix), across the muscle fiber membrane (sarcolemma), to noncontractile elements (cytoskeletal complex or costamere) at the Z line. It is thought that Z lines from adjacent myofibrils are connected by molecules that are related to intermediate filaments.

Neuroscience Approach

In this article, I focus on the effects of passive stretch in people without pathology of the nervous system. Passively stretched muscles have intact afferent and efferent pathways connecting to the central nervous system. For people with an intact nervous system, interventions such as proprioceptive neuromuscular facilitation, which is sometimes used to increase mobility, may be considered logical because they are supposed to use the function of the central nervous system to allow for increased movement.[29] According to proponents of proprioceptive neuromuscular facilitation, the application of passive stretch can alter the muscle spindle (Ia and II afferents) and perhaps the Golgi tendon organ (Ib afferents) output to the central nervous system. Such an altered afferent drive is supposed to influence the activity of the α-motoneurons.[30,31] Whether this technique helps to increase motion and whether central nervous system influences are effective in a passively stretched muscle are yet to be determined. Research in this area is needed. In this article, I do not address the neurophysiological implications of passive stretch.

Cellular and Molecular Biological Approach

To reach the muscle, passive stretch (Fig. 2, arrow) is transmitted via the connective tissue (perimysium and endomysium) to the muscle fiber. To lead to immediate increased sarcomere length, the contractile apparatus must be linked with the noncontractile apparatus (Figs. 2 and 3). To explain whether a stretched muscle fiber ultimately leads to a longer muscle fiber with more sarcomeres in series (myofibrillogenesis), signal sensing, signal transduction, and subsequent gene transcription must take place, resulting in sarcomere assembly. In this article, I focus on signal sensing and signal transduction.

Some examples of stretch-induced myofibrillogenesis come from an orthopedic procedure in which the muscle is indirectly lengthened (distraction osteogenesis).[32–34] If the extensor digitorum lateralis muscle is lengthened 3 mm (by distraction in rabbits), laser diffraction studies show an increase in sarcomere length from 3.1 to 3.5 μm.[35] When that stretch is maintained for several days, the sarcomere length returns to a value of 3.1 μm, suggesting the addition of sarcomeres. Similar observations were made in muscle when the joint was immobilized in different positions.[36–38] The investigators who documented these observations also noted that when muscles are immobilized in a stretched position, they initially undergo less atrophy than when muscles are immobilized in a shortened position. These observations have led to a stretch-induced hypertrophy hypothesis. This hypothesis states that, if stretched, a muscle responds by adding more sarcomeres.[32,39,40]

Some researchers[36–38,41] have suggested that stretch-induced hypertrophy occurs at the fiber ends (toward the insertion into the tendon) of the muscle. This adaptation of muscle (ie, making more sarcomeres in series, thus creating a longer muscle by myofibrillogenesis) provides the theoretical basis for a new treatment for strabismus.[42] A surgical technique entails the shortening of the rectus lateralis muscle, leading to a lengthened rectus medialis muscle. Both muscles, in theory, adapt to the new length, and, ultimately, similar sarcomere lengths and contractile properties are found in both muscles.[42] To summarize, there are a number of experiments that support the concept that sustained passive stretch leads to the generation of a longer and functionally intact muscle, albeit by unknown mechanisms.

Whether specific training methods induce myofibrillogenesis is not known. Use of training with eccentric muscle contraction is thought to lead to the generation of sarcomeres in series,[43] but some authors[44] do not share this view.

In some studies of passive stretch, a constant amount of passive stretch was applied for several days[36–38] or incrementally increased over a 2-week period during fracture healing.[35] The methods used in these experiments did not exactly parallel the stretching methods often used by physical therapists (manual stretches or assisted range of motion) and others in rehabilitation. The methods used in these experiments, however, have some similarities to rehabilitation methods such as serial casting and splinting. In addition, in vivo models cannot be used to independently determine the individual contributions of the altered mechanics or the altered afferent and efferent neurophysiology. To make this research more relevant, an appropriate model is needed, one that can be used to test several possibilities. Is myofibrillogenesis more efficiently induced by a cyclic or static passive stretch? For how long (time) and to what intensity (percentage of stretch) must the stretch continue before myofibrillognesis is induced? What are the contributions of mechanical variables and contractile variables to myofibrillogenesis?

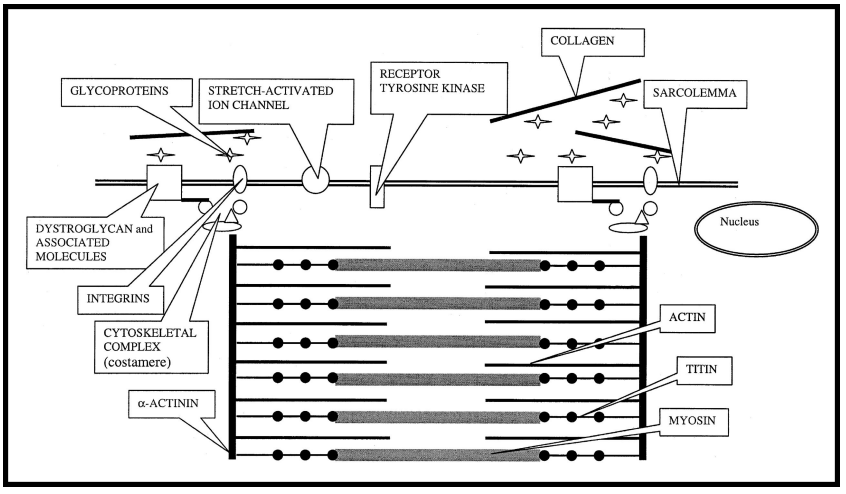

Figure 3.
Model of force transduction in a muscle fiber. Stretch is transmitted through components of the extracellular matrix (collagen and glycoproteins). Glycoproteins (laminin, fibronectin) have the capacity to bind integral membrane proteins (integrins, dystroglycan complex). The intracellular portion of the latter molecules forms the basis for a chain of protein-protein interactions (including dystrophin, β-spectrin, talin, vinculin, desmin, and perhaps some as yet unidentified molecules) ending at the Z line in structures called "costameres." This model is able to link the contractile molecules with the noncontractile molecules in muscle.

Potential Mechanisms for Myofibrillogenesis

Implications of Altered Mechanics at the Sarcolemma

To understand how passive stretch may lead to myofibrillogenesis, I believe it is necessary to study the individual components that are involved in force sensing and force transduction. Passive stretch is transmitted to a muscle fiber via its surrounding connective tissue (Fig. 2, arrow). At a higher level of detail, I believe that the stretch must be transmitted from the extracellular matrix, via the basement membrane, across the sarcolemma, to intracellular molecules, and ultimately to the contractile apparatus in the myofiber (Fig. 2). The physical link between the outside of the muscle fiber and the contractile apparatus inside the muscle fiber should be characterized if we are to understand the process. Figure 3 shows a schematic overview of potential interactions, based on several review articles and models.[45–47] For the transduction of a force generated within the muscle fiber to the connective tissue, a similar model, in my view, is valid. The general idea is that molecular interactions between the contractile and noncontractile elements provide the link with the contractile apparatus. Starting outside the muscle fiber, a passive force is transmitted to the contractile apparatus by the molecular interactions of the following:

- collagen,
- glycoproteins,
- integral membrane proteins, such as integrins or dystroglycan,
- cytoskeletal complexes, such as talin, vinculin, desmin, dystrophin, β-spectrin, and other related molecules,
- noncontractile cytoskeleton, such as α-actinin and intermediate filaments (eg, synemin),
- contractile apparatus.

Structures Thought to Be Involved in Force Transmission

Longitudinal force transduction. Most biomechanical models describing movement use the tendon as an anchoring point for the muscle-generated force. The force generated by the whole muscle is ultimately transmitted to the tendon, and the importance of the myotendinous junction has been shown by experiments involving the study of muscle injury.[26] In these studies, a longitudinal force applied to the muscle resulted in trauma at the muscle–connective tissue interface. People with muscle overuse syndromes are believed by some authors to have symptoms mostly at the myotendinous junction.[48] The myotendinous junction is a structure that changes its morphology in response to altered loading.[49–51] The molecular composition of the myo-

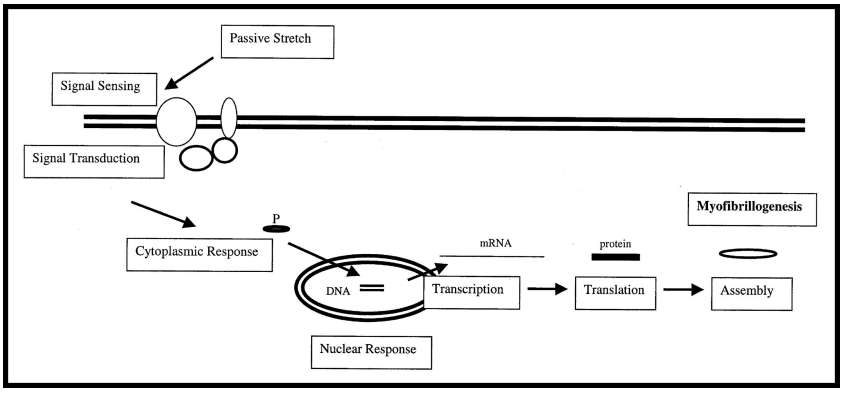

Figure 4.
Conceptual overview how passive stretch can affect a muscle fiber. The biological response of passive stretch in a muscle fiber entails several basic steps. First, the stretch has to be sensed at the sarcolemma, most likely by a complex of integral membrane protein, before it is transduced to generate a cascade of one or more intracellular signaling molecules. Such events can lead to several cytoplasmic responses. The one illustrated is the phosphorylation (P) of a transcription factor, resulting in its translocation to the nucleus. Specific genes (DNA) are then transcribed, and the messages (mRNA) are translated into specific proteins. Especially important for a muscle fiber is a coordinate assembly of contractile and noncontractile proteins giving rise to functional sarcomeres.

tendinous junction contains a high amount of desmin,[52] dystrophin,[53,54] vinculin,[55] talin,[56] and integrin[57] molecules that are also present at structures thought to be responsible for lateral force transmission, called "costameres."

Lateral force transmission. Ultrastructural and biochemical studies of the sarcolemma (muscle fiber membrane) show the presence of structures identified as costameres (Figs. 2 and 3).[55,58–60] Because costameres are associated with the Z disk, they are thought to play an important role in the mechanism of lateral force transduction,[59] and it is possible that as much as 80% of the force generated by a single muscle fiber is transmitted laterally rather than longitudinally. Costameres contain numerous biologically important proteins, which are also at the myotendinous junction. This suggests an important role for the costameres.

Dystrophin, spectrin, ankyrin, vinculin, and certain integrins[61] are some of the molecules found at costameres. Dystrophin, together with dystroglycan, forms a complex that spans the sarcolemma and links the cytoskeleton with the extracellular matrix.[62] Integrins, which also are membrane-spanning proteins with the capacity to bind to both the extracellular matrix and the intracellular cytoskeleton, are present at Z lines.[63] The presence of the dystroglycan complex and integrins in the sarcolemma is of particular importance (Fig. 3). These groups of molecules have the capability of binding both intracellular and extracellular molecules and thus provide a link between the basement membrane and the cytoskeleton. The presence of these molecules at both the myotendinous junction and costameres suggests they have a role in the force transmission mechanism at both sites, although there is no direct evidence of such a role.

Transducing the Altered Mechanics to an Intracellular Signal

Not only is it necessary to identify the molecules that provide the physical continuum, but the identification of the biological and chemical interactions between these molecules is important to provide physiological evidence. The study of the transmission of stretch to a muscle, in my view, must entail studies on signal transduction (Fig. 4). The intracellular pathways, which supposedly are activated by passive stretch, ultimately reach the nuclei of the muscle fiber where stretch-induced gene transcription is initiated (Fig. 4). Stretch-induced gene transcription has been described in experimental paradigms of altered muscle loading[39] and is not discussed in this article. In this article, I review 3 concepts: integrin-based signal transduction, growth factor–based autocrine/paracrine control, and ion channel–based events.

Integrins and tyrosine phosphorylation. Integrins are integral membrane molecules in a variety of cells and are associated with both extracellular and intracellular molecules.[64–66] The fact that they contact both the extracellular and cytoplasmic surfaces, combined with their presence in muscle fibers at costameres and the myotendinous junction,[57] could indicate that they play a role in force transduction. Whether mechanical stimulation activates specific enzymes (kinases such as tyrosine kinases and perhaps serine/threonine kinases) and, subsequently, second messenger pathways is not well known, but such a mechanism was recently described in association with cardiac fibroblasts[67] and in systems other than muscle.[68] Whether such a mechanism exists in muscle fibers as a result of passive stretch is relevant to furthering our knowledge.

Growth factors and their cognate receptors. Another possibility of how muscle may adapt to passive stretch is based on the autocrine (ie, the muscle fiber itself) or paracrine (ie, the fibroblasts or other cells contiguous with the muscle fiber) regulation of muscle growth. Growth factors are molecules, secreted by cells, and have a potent biological activity.[69–72] In addition to specific effects, growth factors, in general, stimulate cell proliferation.[69–72] Several growth factors are involved in muscle development and have been identified. Insulin-like growth factor 1 (IGF-1),[69,70] platelet-derived growth factor (PDGF),[71] and fibroblastic growth factor (FGF)[72]

have been documented to stimulate either myoblast proliferation or, to a certain extent, muscle maturation.

The release of an IGF-1–like molecule from muscle fibers during passive stretch was described by Goldspink and colleagues,[70] and these findings provide support for the theory that a similar mechanism might occur during the passive stretching of a muscle. Whether IGF-1 is directly involved in stretch-induced hypertrophy needs to be verified, and the molecular mechanisms of a stretch-sensitive increase in IGF-1 or other molecules during stretch-based rehabilitation protocols is not known. Insulin-like growth factor 1 (secreted with passive stretch)[69] and PDGF (there are relatively more PDGF receptors at the myotendinous junction than at the nonjunctional membrane)[71] are the likeliest candidates to regulate satellite cell proliferation during stretch-based rehabilitation. These growth factors could stimulate cell division of the myosatellite cells. The addition of more sarcomeres (ie, myofibrillogenesis) could be the result of the proliferating myosatellite cells, which have fused with preexisting muscle fiber cells. The proliferation of myosatellite cells is proposed to explain overload-induced muscle enlargement,[73–75] and perhaps they could also be stimulated by passive stretch as it is applied therapeutically to function in a manner similar to how they behave during limb lengthening (growth).[33] Such adaptation seems to occur preferentially at the distal portion of the muscle.[34] Based on the literature, it seems that the distal portion of a muscle, and the myotendinous junction in particular, is important in the adaptive response of muscle to altered loading. However, the role of satellite cells and the formation of *de novo* muscle fibers in response to a changed nontraumatic mechanical event is not fully known and needs more study.

Ion channels. Transmission of a mechanical stimulus could lead to changes in ion flux (eg, mechanical transduction similar to the hair cells in the inner ear). Stretch-activated ion channels have been found in muscle cells and in many other systems.[76–78] The electrophysiological characteristics (determined by patch clamping) of these channels have been well documented, but their function in muscle remains unclear. Mechanosensitive ion channels may be organized by a submembranous actin cytoskeleton. Whether these ion channels play a role in passively stretched muscle fibers is not yet fully determined, in part because few reagents are available that could analyze the mechanosensitive ion channels. Undoubtedly, as more of the gene sequences are discovered, specific reagents (eg, cDNA and antibodies) can be made, providing researchers with the necessary tools.

Conclusion

The increase in range of motion often reported after passive stretching may involve biomechanical, neurological, and molecular mechanisms. The biological and molecular consequences of the application of passive stretch to muscle appear to be known. Force transmission is likely to occur through a chain of protein-protein interactions and may lead to a chain of biological signals and ultimately to myofibrillogenesis. The potential mechanisms may be as follows: (1) the phosphorylation of integral membrane proteins and associated cytoskeletal molecules, (2) the secretion of selective growth factors, regulated by an autocrine or paracrine mechanism, and (3) changes in the intracellular ion flux through stretch-activated ion channels. The scientific basis of the traditional rehabilitation technique of stretching with the goal of improving range of motion may actually be found in the cellular and molecular adaptive mechanisms of a muscle fiber.

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