Pathophysiology of Muscle Contractures in Cerebral Palsy

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KEYWORDS

• Cerebral palsy • Skeletal muscle • Extracellular matrix • Sarcomere • Fiber
• Gene expression • Pathophysiology

KEY POINTS

- Muscle from patients with cerebral palsy shows functional deficits such as decreased force production and range of motion.
- Muscle is altered at a structural level, with decreased muscle body size, smaller-diameter fibers, and highly stretched sarcomeres (the force-producing unit of muscle).
- Muscle from patients with cerebral palsy has altered extracellular matrix and connective tissue.
- Decreased muscle stem cell numbers and altered gene expression have been reported in cerebral palsy.

INTRODUCTION

Nature of the Problem

Cerebral palsy (CP) is a motor disorder caused by a nonprogressive injury to the developing brain.[1] The injury occurs perinatally and, though causes are rarely known,[2,3] CP is common in infants born preterm with small birth weights.[4] CP occurs in 2 to 3 of every 1000 live births[5] and has heterogeneous symptoms, anatomic involvement, and functional impairment, including lifelong changes in motor function.[1,2] These

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alterations stem from both changes in the neural drive to muscles[6] and changes to muscles themselves.

Symptoms

Spastic CP, which involves injury to the pyramidal system, is the most common form of CP, making up nearly 75% of all cases.[3] Spasticity has been defined as a "velocity dependent resistance to stretch."[7] Limb involvement varies, with patients showing symptoms in either all 4 limbs (tetraplegia or quadriplegia), primarily on one side of the body including one upper and lower extremity (hemiplegia), or primarily in the lower extremities (diplegia).[8] Patients' functional mobility can be classified using several rating scales, including the Gross Motor Function Classification System (GMFCS), which rates patient mobility on a scale of 1 to 5 from high to low function, respectively.[1,3] Although the injury associated with CP initially occurs in the developing brain, symptoms are commonly treated at the muscle level. Because the population affected with CP is large and heterogeneous, a better understanding, especially among clinicians and therapists, of muscular adaptations in CP may lead to improvements in treatment or even development of completely novel therapeutic strategies.

To understand the adaptations that occur in muscle from CP patients, it is important to review the function of typically developing muscle.

HEALTHY SKELETAL MUSCLE STRUCTURE AND FUNCTION

Muscle Structure

The fundamental unit of muscle force production is the sarcomere. Sarcomeres produce force by the interaction between 2 proteins, actin and myosin. Force production is affected by both muscle velocity and the amount of overlap between these 2 proteins, or sarcomere length. The sarcomere length-tension relationship has been characterized in the length-tension curve.[9] Sarcomeres are joined end to end (in series) to form myofibrils. Bundles of myofibrils form myofibers, or multinucleated muscle cells. These muscle fibers are joined into muscle fiber bundles, or fascicles (**Fig. 1**).

At each increasing size scale, extracellular matrix (ECM), the surrounding connective tissue, encapsulates muscle structures. Endomysium surrounds individual myofibers,[10] perimysium surrounds muscle fascicles,[11] and epimysium surrounds the whole muscle (see **Fig. 1**).[12,13] The composition and arrangement of these structures is important to muscle function, and can vary in muscle disorders.

The extensive growth and regeneration capacity seen in muscle is due to its intrinsic stem cell population. Most of these stem cells are called satellite cells[14] and are found below the basal lamina of myofibers; they are normally quiescent except when activated during times of muscle disease or injury.[15] Satellite cell number and viability, rather than being constant throughout life, decreases with age or diseases that are characterized by extensive regeneration.[16] Conditions such as muscular dystrophy, which require constant regeneration of muscle fibers, are believed to eventually lead to exhaustion of the satellite cell population[17] and the concomitant loss in a muscle's ability to adapt to the new functional demand.

Plasticity

Muscle has strong regenerative capacity, and can respond and change based on functional demands; for example, muscle fibers atrophy (leading to a decrease in muscle fiber size) when subject to decreased use, aging, and some diseases. Serial sarcomere number can also change in response to growth[18] as well as limb immobilization with the muscle in a shortened or lengthened position. This serial change in sarcomere