Evidence for Nervous System Degeneration with Advancing Age

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ABSTRACT Human skeletal muscle undergoes major structural and functional changes with advancing age. A progressive degeneration of the nervous system is now considered a major factor underlying these alterations. This review will briefly describe the changes that occur in the human motor unit with increasing age and focus specifically on the changes that relate to a degeneration of the nervous system. J. Nutr. 127: 1011S–1013S, 1997.

KEY WORDS: aging • central nervous system • muscle mass • motor neurons • humans

During the past 10 y, an increasing amount of interest has been focused on the effects of advancing age on the human locomotor system, the mechanisms underlying this so-called “aging atrophy,” and the importance of physical training in maintaining and improving muscle function in older men and women (Lexell 1995, Lexell et al. 1995, Porter et al. 1995). Evidence now exists that one of the major factors leading to the structural and functional changes in human muscle with aging is the progressive degeneration of the nervous system, especially after the age of 60 y. Alterations similar to those observed in humans also take place in the motor unit of other mammals (Larsson and Ansved 1995).

THE HUMAN MOTOR UNIT

The motor unit was originally described by Sherrington and colleagues in England (Eccles and Sherrington 1930, Liddel and Sherrington 1923). It is the basic component of the motor system and comprises a lower motor neuron (alpha motor neuron), and a cell body located in the ventral horn of the spinal cord, its motor axon, and all the muscle fibers that are innervated by this single neuron and axon. The motor unit is described as the “final common pathway,” because signals from different centers in the central nervous system as well as input from the peripheral nervous system lead to activation of muscles involved in all activities related to daily living.

The changes that occur with increasing age in one part of the motor unit can affect other parts of it. It is evident from the literature that increasing age has a pronounced effect on the motor unit, in particular the lower motor neuron. As a consequence, the muscle fibers innervated by these neurons will also be affected. To a great extent, normal aging can be referred to as a slowly progressive neurogenic process, and the degeneration of the nervous system is considered as a major factor underlying the reductions in muscle mass and strength that occur with advancing age.

LOWER MOTOR NEURON

One of the most prominent age-related effects on the motor unit is that on the motor neuron itself. Tomlinson and Irving (1977) provided a thorough examination of the numbers of limb motor neurons in the human lumbosacral cord throughout life. They estimated the numbers of motor neurons in the lumbosacral segments (L1–S3) from 47 previously healthy individuals, ages 13–95 y. No evidence of motor neuron loss existed up to the age of 60 y, but beyond that age there was clear and increasing evidence of a diminishing motor neuron population. The average motor neuron loss from the second to tenth decade was approximately 25%, although several people older than 60 y had counts 50% less than in early adult or middle age. The loss of motor neurons seemed to be uniform within and between the segments, and no other striking morphologic changes were detected. Similar findings were reported in a study by Kawamura et al. (1977a).

AXON

The loss of motor neurons is accompanied by a reduction in both the numbers and diameters of motor axons in the ventral roots. Kawamura et al. (1977b) estimated the numbers and sizes of motor axons in the lumbar ventral roots (L3–L5) from 17 previously healthy individuals, 17–81 y of age. They found a clear age-related reduction in the numbers of large and intermediate myelinated ventral root fibers but no significant reduction of the small nerve fibers. This loss was estimated to be approximately 5% from young age to old age. Mittal and Logmani (1987) performed a similar study on the 8th cervical ventral root and found not only a loss of myelinated large fibers but also a reduction in the fiber diameter. To distinguish changes in numbers and sizes of motor axons from a shift in the distribution of large and small fibers with increasing age, Kawamura et al. (1977a) then described a similar cell reduction, also in the motor neuron columns of the lumbar spinal cord.

Quantitative electromyography (EMG) has shown changes...
in both duration and amplitude of motor unit action potentials with increasing age (Hayward 1977, Howard et al. 1988). Doherty and Brown (1993) confirmed and extended these findings, which were summarized in a review paper (Doherty et al. 1993). They examined the range and distribution of nerve conduction velocities (CV) of single median motor fibers in younger and older subjects using a technique based on the F-response. Their findings implied that the axonal CV of all motor nerve fibers were uniformly slowed with aging. It was suggested (Doherty et al. 1993) that these alterations in CV with aging could reflect a variety of changes in the nerve fibers, such as a dropout of the largest fibers, a segmental demyelination and a reduced internodal length.

**NEUROMUSCULAR JUNCTION**

The motor end plates have been noted to undergo continuous remodeling during normal aging, with gradual changes in both pre- and postsynaptic components. Oda (1984) investigated the motor innervation and acetylcholine receptor (AChR) distribution on intercostal muscle fibers from 12 previously healthy men and women, ages 32–76 y. In the older individuals, the number of preterminal axons entering an end-plate and the length of endplates increased, and the endplate was composed of a greater number of smaller conglomerates of AChR, as compared with the younger people. Wokke et al. (1990) performed a light and electron microscopic study on end plates and related structures in samples of external intercostal muscles obtained during thoracotomy from 17 males and females, ages 4–77 y. They found few changes at the light microscopic level but more marked changes at the ultrastructural level, including increased length and branching of the postsynaptic membrane of the end plate. The significance of these changes on the transmission of action potentials and excitation-contraction coupling is, however, not fully known, and our knowledge of the underlying mechanism of these changes is also limited. It could be that these changes are compensatory rather than the result of degenerative per se, thereby preserving neuromuscular function with increasing age.

**MUSCLE FIBERS**

With the introduction of large cryomicrotomes and modified morphometric procedures, it is now possible to determine both the number and sizes of the different fiber types in whole human limb muscles (Lexell et al. 1983). The decrease in muscle mass seen in older people is now considered to be the result of both a loss of fibers and a reduction in size, mainly of type 2 (fast-twitch) fibers (Lexell et al. 1988). Although these results are limited in men to only one limb muscle (vastus lateralis), we can assume that other limb muscles may be affected similarly. A loss of muscle fibers can be due either to irreversible damage or to permanent denervation. Several studies have assessed the occurrence of myopathic changes vs. changes indicating a neurogenic process in muscles from older individuals. Although myopathic changes, such as central nuclei, necrosis and cell infiltration, are very rare (Aniansson et al. 1981 and 1986, Grimby et al. 1982, Lexell et al. 1983 and 1988, Lindboe and Torvik 1982), small angulated fibers and grouped atrophy are commonly seen in muscles from older men and women (Jennekens et al. 1971, Lexell et al. 1983 and 1988, Scelsi et al. 1980, Tomlinson et al. 1969, Tomonaga 1977). Larger groups of muscle fibers of the same histochemical type (fiber type grouping) are a common and striking finding in muscles that undergo continuous denervation and reinnervation, such as seen in motor neuron diseases and chronic neuropathies. Fiber type grouping can be assessed quantitatively, which may then help to diagnose an ongoing neurogenic process (Lexell et al. 1987). When the fiber type arrangement in whole muscles at various ages was assessed using the enclosed fiber method, an increased occurrence of fiber type grouping was found in muscles from individuals above the age of 70 y (Lexell et al. 1986). An extension of this study, using an improved statistical and analytical method, confirmed these findings and showed that significant fiber type grouping also occurred above the age of 60 y (Lexell and Downham 1991).

This age-related denervation and reinnervation can also be studied using EMG. Macro-EMG is a development of the conventional EMG technique and is thought to reflect the relative size of the whole motor unit (Stålberg 1980). In a study of men and women between 12 and 75 y of age, the macro-motor unit potential, and indirectly the motor unit size, was assessed in three limb muscles: the vastus lateralis, the tibialis anterior and the biceps brachii (Stålberg and Fawcett 1982). An increase in size of the motor unit was found primarily in the muscles of the lower limb, particularly in those people over 60 y of age, and more in distal than in proximal muscles. Possible factors determining the macro-EMG signal and the changes that occur with increasing age have been extensively discussed (Stålberg and Fawcett 1982), and these authors convincingly argued that the recorded age-related changes were most likely due to reinnervation after a preceding denervation.

Electrophysiologic techniques have also been used to assess the number of motor units and the changes that take place with increasing age (Brown 1972, Brown et al. 1988, Campbell et al. 1973, Doherty and Brown 1993, Doherty et al. 1993). These studies have invariably shown a reduced number of functioning motor units with increasing age, mainly after age 60 y and in both proximal and distal muscles. Some variations exist between studies and different muscles, but the estimated reduction in the number of motor units in the biceps brachii and brachialis muscles of older individuals has been reported to be as large as 50% (Doherty et al. 1993). This loss seems also to be greatest among the largest and fastest motor units, i.e., type 2 motor units (Doherty et al. 1993).

When a progressive neurogenic process reaches a phase where denervation exceeds reinnervation and/or the reinnervative capacity is diminished, some muscle fibers will become permanently denervated and thereafter lost, subsequently leading to “aging atrophy.” This loss of muscle fibers is followed by a replacement with fat and fibrous tissue and a gradual increase in non-muscle tissue, a well-known feature of the aging of human muscles (Lexell et al. 1988, Porter et al. 1995).

**CONCLUSION**

The collected evidence strongly suggests that as age increases beyond 60 y, human muscle undergoes continuous denervation and reinnervation, due to an accelerating reduction of functioning motor units. This is mediated through a loss of motor neurons in the spinal cord and myelinated ventral root fibers. Initially, reinnervation can compensate for this denervation. However, as this neurogenic process progresses, more and more muscle fibers will become permanently denervated and subsequently replaced by fat and fibrous tissue. Thus, there is substantial evidence to support the contention that an age-related degeneration of the nervous system is one of the main contributors to the gradual reduction in muscle volume and muscle strength that accompanies human aging.
LITERATURE CITED