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# Effects of disease-afflicted and aging neurons on the musculoskeletal system

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ABSTRACT

The musculoskeletal system includes skeletal muscles, bones and innervating axons from neurons in the central and peripheral nervous systems. Together, they form the largest structure in the body. They also initiate and coordinate locomotion, provide structural stability, and contribute to metabolism and homeostasis. Because of these functions, much effort has been devoted to ascertaining the impact of acute and chronic stress, such as disease, injury and aging, on the musculoskeletal system. This review will examine the role of the nervous system in the deleterious changes that accrue in skeletal muscles and bones during the progression of neurologic diseases and with advancing age.

## 1. Introduction

The musculoskeletal system requires innervating axons to form, mature, and function. It is therefore not surprising that skeletal muscles and bones undergo deleterious morphological and functional changes when innervating axons become dysfunctional or degenerate due to diseases, old age, and injuries. Exemplifying this point, the function and size of skeletal muscles diminish in diseases that result in the degeneration of α-motor neuron axons, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) [1,2]. Skeletal muscles also atrophy following injuries that either compromise the function or result in the destruction of α-motor neuron axons [3]. A similar relationship has been established between bones and innervating axons. Bones lose mass and become weak and brittle when sensory and sympathetic neurons dysfunction [4]. Data also continue to accrue indicating that age-related deleterious changes in innervating axons contribute to the reduction of skeletal muscle and bone mass, called sarcopenia and osteoporosis respectively, as well as loss of function of the musculoskeletal system in old age [5,6]. This review will summarize published studies on the effect of diseases and aging on skeletal muscles and bones and their innervating axons. It will also propose future lines of inquiries to further understand the role of the nervous system in the myriad of pathogenic features associated with aged and disease-afflicted skeletal muscles and bones.

## 2. Impact of disease-affected and aging neurons on skeletal muscles

A skeletal muscle is a complex organ that requires the exquisite collaboration of various resident cells and innervating axons to form, function, and repair damages to remain viable. In this section, I will provide a general summary of the type, location and function of innervating axons in skeletal muscles. I will also highlight the importance of these innervating axons in the maintenance and repair of skeletal muscles. Additionally, I will review the contribution of innervating axons to pathophysiological changes that accrue in skeletal muscles during the progression of diseases and normal aging.

### 2.1. Innervation of skeletal muscles

Skeletal muscles are innervated by three neuronal types (Table 1) with distinctive roles: (1) motor neurons, which relay information from the central nervous system (CNS) to muscle to induce muscle contraction and are subdivided into α and γ subtypes; (2) sensory neurons, which relay proprioceptive (i.e. the rate and extent of contraction of a given muscle), temperature and pain signals (nociceptors), from muscles to the CNS; and (3) sympathetic neurons, which modulate a variety of adaptive cellular processes, particularly those involved in fight or flight responses. Among these neurons, α-motor neurons are essential for skeletal muscle to form, mature, contract, and survive. These neurons exert their influence on skeletal muscles primarily at the neuromuscular junction (NMJ), a synapse formed between α-motor neuron axon nerve endings (also referred as the presynaptic region) and

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**Table 1**
Neuronal types present in skeletal muscle.

| Neuron | Connection with | Function |
|---|---|---|
| α-motor | Extrafusal muscle fiber | Muscle contraction |
| γ-motor | Intrafusal muscle fiber | Muscle contraction |
| Type Ia proprioceptive sensory | Muscle spindle | Proprioception |
| Type Ib proprioceptive sensory | Muscle spindle | Proprioception |
| Type II proprioceptive sensory | Golgi organ | Proprioception |
| Nociceptive sensory | None - Free nerve endings | Pain sensation |
| Sympathetic | Blood vessels, NMJs, muscle spindles | Fight or flight response |

extrafusal muscle fibers [7]. At NMJs, α-motor neurons release acetylcholine to induce muscle contraction. They also release molecules, such as neuronal isoforms of agrin, called z-agrin, to promote the formation and stability of the postsynaptic region (the region within an extrafusal muscle fiber specialized for decoding cholinergic transmission) [8,9]. Through these actions, α-motor neurons play central roles in the function and viability of skeletal muscles, and thus in the initiation of all voluntary movement.

The coordination and precision of muscle movement requires the action of γ-motor neurons and type Ia/II proprioceptive sensory neurons. These neurons converge on intrafusal muscle fibers to form a structure called the muscle spindle [10]. γ-motor neurons innervate the polar region of intrafusal muscle fibers where they release ACh to cause contraction of this muscle fiber type. The nerve endings of Ia/II proprioceptive sensory neurons, on the other hand, terminate throughout the equatorial region of intrafusal muscle fibers and function to relay information to the CNS, and directly to α-motor neurons, about the tone and contraction rate of skeletal muscles. A third proprioceptive sensory neuron subtype, type Ib, innervates Golgi tendon organs and also relays information regarding the contractile status of skeletal muscles to various components of the CNS, including α-motor neurons [11]. Through these actions, either by directly or indirectly connecting with α-motor neurons in the spinal cord, these neurons influence the function and health of skeletal muscles.

Sensory neurons that sense pain and temperature, commonly referred to as nociceptors, have been found in skeletal muscles [12–18]. The axons of these nociceptors are either thinly myelinated (Aδ-fibers) or unmyelinated (C fibers), and are positive for the neuropeptide substance P (SP) and calcitonin gene-related peptide (CGRP) [19]. Unlike proprioceptive sensory neurons, nociceptors do not contact muscle fibers nor any other cell within skeletal muscles. These neurons depolarize (are activated) only when levels of potassium and ATP abruptly and significantly increase [20]. Hence, there nociceptors relay pain information to the CNS following the tearing of many muscle fibers at once, often caused by injuries. This explains the lack of pain sensation during the progressive and asynchronous atrophy of muscles, in which only a few muscle fibers die at any given time and therefore do not significantly alter potassium and ATP levels in the interstitial space, with advancing age and progression of diseases such as ALS, SMA and the spectrum of muscular dystrophies.

In addition to motor and sensory neurons, skeletal muscles are innervated by sympathetic postganglionic nerve endings positive for the neuropeptide Y (NPY) and tyrosine hydroxylase (TH) [18,21–24]. Using light microscopy, these nerve endings have been found in various locations within skeletal muscles of rabbits, rodents and humans [13,22,24,25]. They are present in muscle spindles and adjacent to extrafusal muscle fibers in addition to surrounding blood vessels [24,26]. More recently, sympathetic nerve endings were found adjacent to and directly abutting NMJs in the soleus and extensor digitorum longus muscles in developing and adult mice [22]. Their presence at NMJs and in muscle spindles suggests that they play important functions beyond modulating blood vessels. This has been supported by recent findings showing that sympathetic nerve endings activate the alpha- 1a and beta- 2 adrenergic receptors (ADRA1A and ADRB2, respectively) in skeletal muscles, leading to a marked increase in the production of 3′,5′-cyclic adenosine monophosphate (cAMP) [27] and the peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1a) [22,23,28]. These two signaling molecules have been shown to mediate a variety of cellular processes that influence mitochondrial function, satellite cell proliferation and NMJ health in skeletal muscles [29–31]. Through these and potentially other molecules, sympathetic nerve endings alter the release of ACh at NMJs, regulate the secretion and reuptake of calcium from the sarcoplasmic reticulum, and modulate glucose uptake and metabolic activity. These molecular changes are necessary for skeletal muscles to adapt to changing physiological and functional demands not only for fight or flight responses, but also associated with development, exercise, diseases, injuries and aging.

### 2.2. Impact of disease-afflicted neurons on skeletal muscles

Skeletal muscles must be innervated by α-motor neurons in order to function and survive. Hence, it is not surprising that diseases that affect α-motor neurons and their axons invariably result in the malfunction and atrophy of skeletal muscles. This is the case in ALS [32–36], SMA and myasthenia gravis (MG) [1,37–41], which directly target α-motor neurons, particularly their nerve endings in skeletal muscles. In ALS and SMA, α-motor neurons and their axons completely degenerate, resulting in the loss of muscle function and mass. MG is a disease that causes muscle weakness and fatigue resulting from mutations or autoimmune-related loss of function of various genes critical for the function of the presynaptic or postsynaptic region of the NMJ. Among presynaptic genes are the P/Q-type voltage-gated calcium channel (VGCC) and choline acetyltransferase [42]. The nerve endings of α-motor neurons are also affected in muscular dystrophy [43,44], diabetes, and vascular exclusion [45–48]. While the effect of these diseases on α-motor neuron nerve endings is likely indirect, their dysfunction may nevertheless further compromise the function and viability of skeletal muscles.

There is evidence that γ-motor neurons and proprioceptive sensory neurons undergo deleterious changes in ALS and SMA. In a mouse model for ALS, γ-motor neurons were found to increase the contraction rate of intrafusal muscle fibers, and thus augment the activity of Ia proprioceptive sensory neurons [49]. This heightened firing frequency of Ia proprioceptive sensory neurons has been suggested to contribute to calcium-induced cytotoxicity of α-motor neurons by augmenting levels of glutamate at synaptic sites in the spinal cord [50]. Additionally, recent findings indicate that proprioceptive sensory neurons may be directly affected and contribute to α-motor neuron degeneration in ALS and SMA. In a mouse model for SMA, the loss of proprioceptive sensory synaptic inputs correlates temporally and spatially with degeneration of α-motor neurons [51]. More recently, our lab demonstrated that Ia and II proprioceptive sensory nerve endings in the spinal cord and in skeletal muscles also degenerate in two mouse models for ALS, either harboring $SOD1^{G93A}$ or $TDP43^{A315T}$ [52]. Importantly, we showed that these neurons are intrinsically compromised in ALS [53], indicating that they may contribute to disease pathology by altering the function of α-motor neurons. Together, these published findings support roles for γ-motor and proprioceptive sensory neurons in ALS and

**Table 2**
Neuronal types present in bone.

| Neuron | Bone region innervated | Function |
|---|---|---|
| Nociceptive sensory | Periosteum, diaphysis, epiphysis, cortical bone, bone marrow | Detection of pain, bone remodeling |
| Sympathetic | Periosteum, diaphysis, epiphysis | Vasoregulation, bone remodeling |

SMA, two diseases that cause atrophy of skeletal muscles. In contrast to proprioceptive sensory neurons, the impact of diseases on nociceptive sensory neurons, and thus their contribution to skeletal muscle dysfunction and atrophy, remains unknown.

Sympathetic neurons have also been implicated in the function and health of skeletal muscles in various diseases. In this regard, drugs that augment the actions of the sympathetic system, such as ephedrine or salbutamol, provide therapeutic benefits presumably by restoring the normal function of NMJs [42]. Supporting this possibility, the inverse experiment, which relied on other chemicals to induce degeneration of sympathetic nerves, was shown to reduce the size of NMJs and density of nAChRs [23]. These changes, however, were reversed following the systemic administration of the ADRB2 agonist clenbuterol [54]. Sympathetic neurons have also been implicated in the progression of SMA and ALS, two diseases that invariably result in degeneration of the NMJ and atrophy of skeletal muscles [55–57]. Together, these published findings demonstrate important roles for sympathetic neurons in skeletal muscle pathogenesis. They have also revealed that a close anatomical and functional relationship exists between sympathetic and motor nerve endings at NMJs [54].

### 2.3. Effect of aging neurons on skeletal muscles

The loss of skeletal muscle function and mass is a hallmark of old age in humans and animals. In humans, there is a significant and constant decline in muscle mass and strength [58], called sarcopenia, beginning in the fifth decade of life. Similar deleterious changes have been shown to occur on skeletal muscles of aging rodents. Over the last few decades, data have accrued supporting an important role for the nervous system in the erosion of skeletal muscle function and mass with advancing age [59,60]. Not surprisingly, the majority of studies have examined the role of α-motor neurons. To date, we know that aging results in significant molecular, morphological, and functional changes in α-motor neurons [61–65]. Aging also impairs the propagation of action potentials down α-motor neuron axons [66–68], alters the distribution of synaptic vesicles [69], and reduces the density of active zones at the presynaptic region of α-motor neuron nerve endings [70,71]. These destructive cellular changes with advancing age ultimately cause the nerve endings of α-motor neurons to retract from NMJs following a similar pattern as observed in ALS [32,33,72–78]. Because these deleterious changes occur progressively, it has been hypothesized that degeneration of α-motor neuron nerve endings contribute to aging of skeletal muscles, including sarcopenia. In support of this possibility, the two lifestyles best known to slow aging of skeletal muscles, a calorically restricted diet and exercise [33], attenuate the deleterious effects of aging on innervating α-motor axons. The caloric-restriction mimetic, resveratrol, was also found to delay aging of skeletal muscles partly by preventing retraction of α-motor axons from NMJs [79].

Because coordinated movements, such as gait and balance, become increasingly more difficult to properly carry out with aging [80,81], our lab recently examined the impact of aging on Ia/II proprioceptive sensory neurons in mice [82]. We found that the majority of Ia proprioceptive afferents fail to maintain their annulospiral structures and type II proprioceptive afferents degenerate in muscle spindles of the extensor digitorum longus (EDL) and soleus muscles of 11- and 15-month old mice compared to 2-month-old mice. Accompanying these changes, we found fewer proprioceptive sensory neurons populating dorsal root ganglia in old mice. Despite these findings, it remains unknown if changes in proprioceptive sensory neuron nerve endings contribute to the loss of skeletal muscle function and mass with aging. If they do, they likely act by altering the function of α-motor neurons. There is also a paucity of knowledge regarding the effect of aging on γ-motor, nociceptive, Ib proprioceptive, and sympathetic neurons innervating skeletal muscles.

## 3. Impact of disease-affected and aging neurons on bones

While bone is a hard tissue, a characteristic necessary to act as a scaffold, it is also highly adaptable to changes. Exemplifying this, bones undergo significant remodeling as they grow during development and repair damages following injuries. These features of bones, however, are compromised in diseases and in old age. Here, I will review the potential contribution of innervating axons on the deleterious morphological changes associated with disease-afflicted and aged bones.

### 3.1. Innervation of bones

Sensory and sympathetic neurons innervate various regions of bones [83,84] (Table 2). Their nerve endings are found on the periosteum, a fibrous membrane covering the entire surface of bones that contain blood vessels and lymphatic vessels. Nerve endings are also present in two distinct anatomical regions of bones, the diaphysis and epiphysis. The diaphysis is the tubular region that runs from the distal to the proximal end of bones. This area has an inner region, called the medullary canal, where yellow bone marrow resides. The medullary canal is covered by the endosteum, a delicate fibrous membrane. The epiphysis is the wider and polar region of a bone. It is made up of spongy bone filled with red marrow. Axons enter deeper regions of bones together with blood vessels through the foramen, located near the equatorial region of bones.

Sensory axons are most prevalent in the periosteum, and surround this area in a fishnet-like pattern presumably to better detect mechanical distortion of the underlying cortical bone that can result from injuries, diseases, and even aging [85]. Sensory nerves are also present in cortical bone, as well as, bone marrow but at a lower density compared to the periosteum. To date, the preponderance of evidence indicates that bones are innervated largely by nociceptive sensory neurons, which is not surprising given the sharp and intense pain sensation following an injury to this tissue [86]. As expected, these nociceptive axons are small in diameter, unmyelinated or thinly myelinated, and exhibit electrical conduction velocities of less than 2 m/s or between 2 and 30 m/s. In contrast to skeletal muscles, nociceptors innervating bones are heterogenous, and can be subdivided based on expression of various combinations of SP, CGRP, the tyrosine receptor kinase A (TrkA), and isolectin B4 (IB4). Suggesting that sensory innervation affects bone development, in addition to relaying painful sensation, there is a strong correlation between sprouting of developing sensory nerves and formation of new bone [87]. Moreover, the destruction of sensory nerves slows the formation of new bone and increases fragility of bones [88]. More recently, Chen et al. [89] established that sensory neurons play an active and direct role in the maintenance and repair of bones. The authors found that osteoblasts release prostaglandin E2 (PGE2) to activate the PGE2 receptor 4 (EP4) located in sensory nerves. Importantly, they demonstrated that inhibiting this communication, between osteoblasts and sensory nerves, has deleterious effects on the

integrity and mass of bones.

Sympathetic postganglionic neurons positive for TH, NPY and dopamine-beta-hydroxylase also innervate bones [21,88,90,91]. These nerve endings are found sparsely on the periosteum compared to the inner regions of the bone, the epiphysis and diaphysis. In addition to regulating vasomotor function, sympathetic nerves play important roles in developing and adult bones. They directly affect bones by releasing norepinephrine to activate ADRB2 in osteoblasts and osteoclasts. Highlighting the functional role of this sympathetic signaling axis in bone, deletion of ADRB2 increases the formation of cancellous bone [92], the spongy bone located in the epiphysis region of long bones. Similarly, blocking ADRB2 with propranolol, a non-selective antagonist, increases cancellous bone [93,94]. Conversely, constitutively stimulating the ADRB2 using agonists, such as isoproterenol, clenbuterol, and salbutamol, results in the loss of bone mass in mice and rats [93]. Furthermore, Chen et al. [89] recently demonstrated that sympathetic hyperactivation promotes bone loss. There is also evidence indicating that sympathetic nerves regulate bone through the beta-1 adrenergic receptor (ADRB1). Specifically, Khosla et al. [95] found a strong correlation between selective blockers of the ADRB1 with better structural integrity and higher metabolic activity in bones of postmenopausal women. The role of sympathetic nerves in bones, however, varies depending on their location. For example, stimulation of the sympathetic nervous system in bone marrow promotes the differentiation of resident stem cells, and the subsequent egress of hematopoietic stem and progenitor cells [92], in contrast to inhibiting the actions of osteoblasts in other bone regions. Nevertheless, these and other published evidence have established a central role for sympathetic nerve endings in the formation, maintenance, and repair of bones.

### 3.2. Impact of disease-afflicted neurons on bones

Sensory and sympathetic neurons are affected in various diseases known to compromise the structural integrity and reduce the mass of bones. In the reflex sympathetic dystrophy syndrome (RSDS; also called complex regional pain syndrome), damaged sympathetic nerves extensively sprout within bones leading to osteoporosis and osteopenia [96]. In hereditary sensory and autonomic neuropathies (HSAN), a broad spectrum disease with different etiologies, the degeneration of sensory and sympathetic nerves cause deleterious changes on bones residing in the distal portions of the lower extremities [97]. Sensory and sympathetic neurons are also affected in a number of genetic bone disorders such as osteogenesis inperfecta, Paget's disease, and juvenile arthritis [83]. In these genetic bone diseases, sensory and sympathetic nerve endings also extensively sprout, partly explaining the severe pain and loss of bone mass resulting from heightened sympathetic innervation that accompanies such disorders. In addition, the high incidence of osteoporosis and bone fractures in neurological disorders with a CNS etiology, including Alzheimer's disease, Parkinson's disease, ALS, and SMA, suggest roles for sympathetic and sensory nerve endings in the deterioration of bones [98]. However, sensory and sympathetic nerve endings innervating bones have yet to be examined prior to and during the progression of such neurological diseases.

### 3.3. Effect of aging neurons on bones

There is a paucity of knowledge regarding the effect of aging on sensory and sympathetic nerve endings innervating bones. In one of the few studies published to date, Jimenez-Andrade et al. [99] visualized sensory axons in the femur periosteum of young, middle-aged and old rats using antibodies against CGRP and neurofilament (NF). This study found no difference in the density of sensory axons across ages. More recently, Chartier et al. [83] examined sensory axons in the femur of young and aged mice. In the periosteum, bone marrow, and cortical bone, the density of sensory nerve endings was unchanged. These findings partly corroborate observations in humans indicating that the number of sensory nerve endings increases in aged and degenerating vertebrae [100]. Together, these published observations indicate that sensory nerve endings remain unchanged or potentially sprout to occupy more territory even though bones clearly undergo deleterious structural changes in old age. Interestingly, sensory neurons also extensively sprout in fractured adult bones, a morphological change associated with increased pain sensation. Thus, the exuberant sprouting of sensory nerve endings may underlie the increased sensitivity to bone pain in the elderly population [20,101]. While the aforementioned studies provide insights into the effect of aging on sensory neurons innervating bones, there is still much to learn about the effect of aging on these nociceptors. For example, the impact of aging on the functional and molecular characteristics of sensory nerve endings remains unknown. This information is essential to further understand the role of these neurons in aging bones.

Chartier et al. [83] also examined sympathetic nerve endings in different regions of the femur of aging mice using an antibody against TH. Similar to sensory nerve endings, the density of sympathetic nerve endings was found unchanged in the periosteum and bone marrow of aged femurs. This was not the case in cortical bone where the density of sympathetic nerve endings was found to be decreased by over 75% in the femur of aged mice. While the contribution of sympathetic nerves to age-related changes in bones remains unknown, severing or blocking the function of these nerve endings promotes bone growth in adulthood. Thus, the loss of sympathetic nerve endings in cortical bone, which constitutes over 80% of long bones such as the femur, may contribute to the progressive enlargement of bones with advancing age. In support of this possibility, deletion of adenylyl cyclase 5, a downstream target of beta-2AR, was shown to increase bone mass with advancing age [102].

## 4. Concluding remarks

The nervous system clearly plays a central role in the pathogenic changes that accumulate in bones and skeletal muscles due to diseases and with advancing age. Because of this, it is critical to answer a number of outstanding questions to target neurons that innervate bones and skeletal muscles. These include: 1) What are the initial molecular, subcellular, and functional changes that precipitate dysfunction and degeneration of motor, sensory, and sympathetic neuron nerve endings in bones and skeletal muscles?; 2) Does aging of innervating neurons precede, cause, or contribute to pathophysiological changes in skeletal muscles, and bones?; 3) Does aging simultaneously affect innervating neurons, skeletal muscles, and bones?; 4) Do agents that preserve the function of sympathetic and sensory neurons delay or prevent musculoskeletal aging?; and 5) What underlies the disparate effect of altering the function of sympathetic neurons on bones compared to skeletal muscles? Additionally, it will be important to understand if and how different neuronal populations innervating skeletal muscles and bones cross-talk in the periphery and in the CNS. This question is particularly relevant given the evidence that sympathetic neurons potentially interact with sensory neurons in bones [89,103] and motor neurons and proprioceptive sensory neurons in skeletal muscles [22–25]. The fact that connected bones and skeletal muscles adapt in concert to different functional demands and pathological insults raises the possibility that neuronal circuits in the CNS coordinate changes between these two components of the musculoskeletal system. Answering these questions is essential to understand the contribution of the nervous system to pathophysiological changes in the musculoskeletal system. This knowledge may also reveal broader relationships between different neurons that innervate bones and skeletal muscles that were not appreciated in the past, and pave the path to better mitigate disease and age-related deleterious changes in the musculoskeletal system.

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