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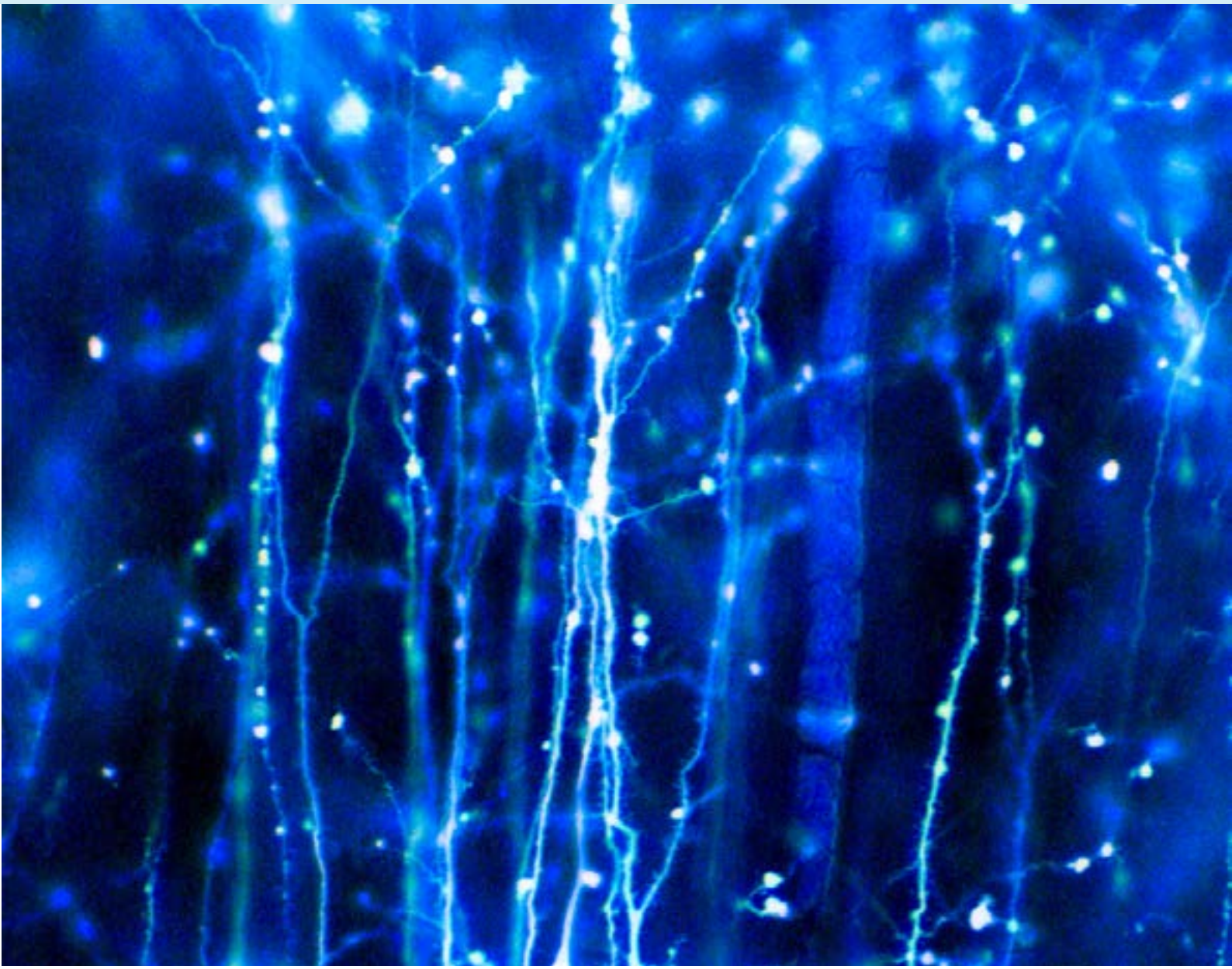

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For the second year in a row, Physiological Mini Reviews serves as the official journal of the Latin American Society of Physiological Sciences. The last volume featured physiological articles by the presidents of different Latin American Societies. The current volume will contain several contributions by members of different Physiological Societies from around the world. The first issue has been written by Gary Sieck, former president of the North American Society. We hope you will enjoy reading the contents of the volume.

The Editorial Team

MOTOR NEURON LOSS IN AGING AND AMYOTROPHIC LATERAL SCLEROSIS: DIFFERENT FUSE LENGTHS, SAME EXPLOSION

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ABSTRACT
Advanced age and amyotrophic lateral sclerosis (ALS) are both associated with a loss of motor neurons resulting in muscle fiber atrophy and muscle weakness. Aging associated muscle fiber atrophy and weakening is termed sarcopenia, but the association with motor neuron loss is not as clearly established as in ALS, probably related to the prolonged time course of aging-related changes. Although aging and ALS effects on limb muscle strength and neuromotor performance are serious, such effects on the diaphragm muscle can be life threatening. Converging evidence indicates that larger phrenic motor neurons, innervating more fatigable type IIx and/or IIb diaphragm muscle fibers (fast fatigue intermediate, FInt and fast fatigable, FF motor units) are more susceptible to degeneration with both aging and ALS compared to smaller phrenic motor neurons innervating type I and IIa diaphragm muscle fibers (slow and fast fatigue resistant motor units, respectively). The etiology of ALS and age-related loss of motor neurons appears to involve mitochondrial function and neuroinflammation, both chronic and acute exacerbation. How mitochondrial dysfunction, neuroinflammation and motor neuron size intersect is the focus of continuing investigation.
Keywords: Motor neurons, diaphragm muscle, mitocondria.

RESUMEN
La edad avanzada y la esclerosis lateral amiotrofica (ALS) están asociadas con una pérdida de neuronas motoras que produce atrofia de las fibras musculares y debilidad muscular. El envejecimiento asociado a atrofia y debilitamiento de las fibras musculares se denomina sarcopenia, pero la asociación con la pérdida de neuronas motoras no está tan claramente establecida como en la ALS, hecho probablemente relacionado con el curso prolongado de los cambios que ocurren durante el envejecimiento. Aunque el envejecimiento y los efectos de la ALS sobre la fuerza muscular de las extremidades y el rendimiento neuromotor son graves, tales efectos sobre el músculo del diafragma pueden ser potencialmente mortales. La evidencia convergente indica que las neuronas motoras frénicas más grandes, que inervan fibras musculares de diafragma tipo IIx y / o IIb más fatigables (unidades motoras FF de fatiga rápida intermedia, FInt y fatigable rápida) son más susceptibles a la degeneración con el envejecimiento y la ALS en comparación con las neuronas motoras más pequeñas del nervio frénico que inervan las fibras musculares del diafragma tipo I y IIa (unidades motoras lentas y rápidas resistentes a la fatiga, respectivamente). La etiología de la ALS y la pérdida de neuronas motoras relacionadas con la edad parece implicar la función mitocondrial y la neuroinflamación, tanto la exacerbación crónica como la aguda. La forma en que se cruzan la disfunción mitocondrial, la neuroinflamación y el tamaño de la neurona motora es el foco de una continua investigación.
Palabras clave: neuronas motoras, músculo diafragma, mitocondria.

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Introduction

The phenomenon of age-associated loss of muscle mass (sarcopenia) has been refined over the past three decades to describe the atrophy of skeletal muscle fibers and the reduction in skeletal muscle force generation [1]. Sarcopenia is suggested to occur over a protracted period in humans, with gradual losses (<0.5-1% per year) until the age of 65, after which a more precipitous decline occurs [1].

In the diaphragm muscle of rodents, sarcopenia selectively affects type IIx and/or IIb muscle fibers, comprising fast fatigue-intermediate (FInt) and fast-fatigable (FF) motor units, with reduced cross-sectional areas, reduced maximum force and impaired maximum transdiaphragmatic pressure (P_{di}) generation [2]. Importantly, larger phrenic motor neurons that likely innervate type IIx and/or IIb diaphragm muscle fibers comprising FInt and FF motor units [3, 4] are vulnerable to loss in old rodents [5]. Preserved ventilation in old age is consistent with the resilience of slow (S) and fast fatigue-resistant (FR) motor units in aging [2, 6, 7]. This resilience is underscored by the preserved cross-sectional areas of type I and IIa diaphragm muscle fibers and the persistence of smaller phrenic motor neurons that innervate them [2, 5, 6]. This pattern of vulnerability is similar in humans, with reduced maximum pressure generation by the diaphragm muscle, which likely contributes to impaired expulsive maneuvers (e.g. coughing and sneezing) and increased incidence of airway infections [1, 3, 8, 9]. The natural history of diaphragm muscle sarcopenia in humans is mirrored by that of rats, with unchanged diaphragm muscle force and muscle fiber cross-sectional areas between 6-month (young) and 18-month old (middle age) rats, with rapid declines occurring between 18- and 24-months (old age) of age [6].

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is an age-associated neurodegenerative condition involving the inexorable loss of motor neurons and muscle weakness [10]. In stark contrast to aging, this process is rapid, with death within three years of diagnosis the usual prognosis [10]. The majority of ALS cases (~90%) are sporadic, with no known genetic cause, while the remainder have a known genetic mutation (e.g. SOD1, TDP-43) that is often the basis of various rodent models of ALS [11]. Despite the myriad of clinical presentations and the varied disease genetics, the concomitant loss of motor neurons is pathognomic for ALS [10, 11]. Remarkably, despite the radically different timeframes of motor neuron loss the selective size-dependent vulnerability of motor neurons is similar between aging and ALS (**Figure 1**). In ALS, smaller motor neurons, likely innervating type S of FR motor units [3, 4] are resilient while larger motor neurons, likely innervating type FInt and FF motor units [3, 4] are vulnerable [11-15]. There are many proposed etiologies for ALS, mostly derived from rodent genetic models. These proposed etiologies for ALS are consistent in attributing motor neuron loss to an early and progressive dysfunction of mitochondria [10, 11, 16-18]. Subsequent to this, neuroinflammatory insults play a role in the progression of pathology towards cell death pathways and the eventual onset of symptoms (i.e., muscle weakness) [18]. Importantly, ALS patients usually die from respiratory complications associated with weak cough and ineffective airway defence measures [1, 10], associated with selective diaphragm muscle atrophy of type IIx and/or IIb fibers and related diaphragm muscle weakness [3].

The remainder of this review will address the similarities and differences in motor neuron death between aging and ALS and an examination of the interaction between mitochondrial health, neuro-inflammation and neuronal loss. A particular focus will be on diaphragm motor units, which are very well-characterised in terms of both individual motor unit properties [3, 19, 20] and in their recruitment and behavioral (both ventilatory and non-ventilatory) functions [3, 21].

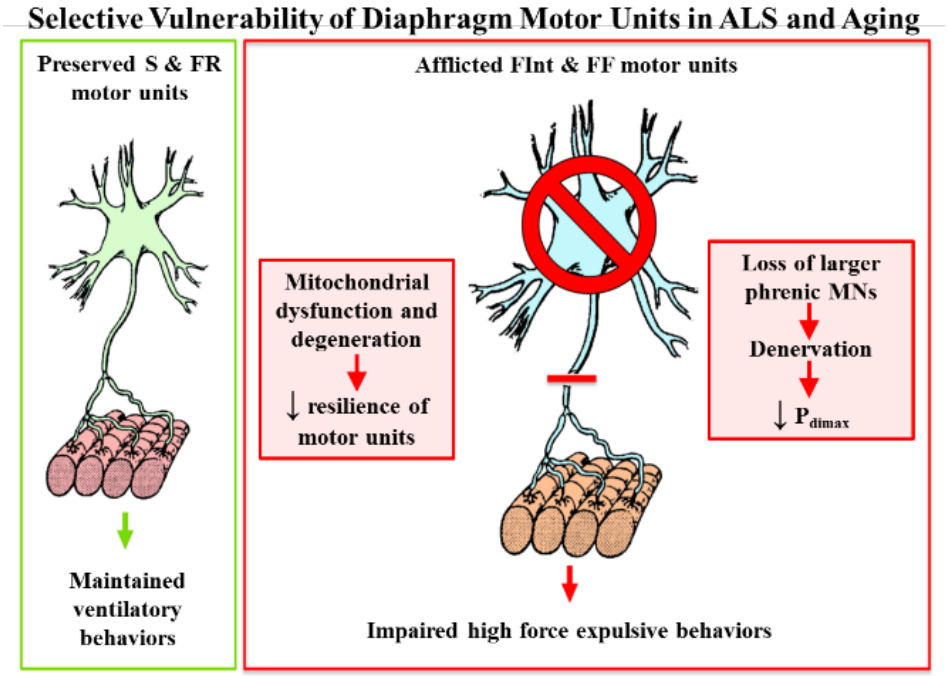

Figure 1. Selective Vulnerability of Motor units in ALS and Aging. In both aging and ALS, the loss of larger phrenic motor neurons results in disruption of neuromuscular connection to type IIx and/or IIb diaphragm muscle fibers leading to selective impairment of higher-force expulsive maneuvers that require recruitment of type FInt and FF motor units. In contrast, the resilience of smaller phrenic motor neurons that innervate type S and FR motor units ensures the preservation of life-sustaining ventilatory behaviors.

Vulnerable versus resilient motor neurons in aging and ALS – pathological and functional evidence.

There are two important distinctions when describing the relative vulnerabilities and resilience of motor neurons to various conditions, namely motor unit type specific and motor neuron pool specific susceptibilities. The most important factor with regard to susceptibility of motor neurons to degeneration is what motor unit type they comprise. In general, larger motor neurons are more vulnerable to death during aging and in ALS [5, 11-14], and these larger motor neurons comprise type FInt or FF motor units [1, 3, 4]. By contrast, smaller motor neurons that comprise type S or FR motor units [1, 3, 4] are largely resilient to loss in both aging and ALS [5, 11-14].

Susceptibility to motor neuron loss in both aging and ALS is also dependent on motor neuron pool varying across muscle. For example, motor neuron pools comprising certain cranial nuclei (oculomotor and trochlear) and Onuf's nucleus are spared in ALS [12, 22]. The effect of aging on motor neurons within these pools is unclear. In the case of the oculomotor and Onuf's nuclei, the neural circuitry and innervation patterns are remarkably different compared to other cranial and spinal motor neurons. For example, polyneuronal innervation of muscle fibers persists into adulthood, and there is continued expression of embryonic myosin heavy chain in adult muscle fibers [10-12, 22].

The functional consequences of differential susceptibilities of motor neuron to death are matched by the functional deficits observed in motor behaviors, with higher-force maneuvers more affected than endurance activities or behaviors requiring only activation of fatigue-

resistant motor units. The best way to quantify these behaviors in diaphragm motor units is by measuring transdiaphragmatic pressure (P_{di}), the pressure difference across the thoracic/abdominal surfaces of the diaphragm muscle. In healthy adults, the P_{di} during quiet breathing is ~10% of maximum P_{di} (P_{dimax}), ranging from ~120 cmH_2O in rats [1-3] to ~200 cmH_2O in humans [1, 3, 23] **(Figure 2).** In aging diaphragm muscle, fatigue resistant motor units are spared from the effects of sarcopenia, which is evident by the preservation of ventilatory behaviors (even when fatigued). However, with aging, more fatigable diaphragm motor units are affected and P_{dimax} is reduced. The reduction in diaphragm muscle strength and P_{dimax} primarily impacts expulsive motor behaviors that require activation of FInt and FF units, such as coughing and sneezing [3, 21, 24] (Figure 2). Impairments in these expulsive airway clearance behaviors leads to increased risk of pneumonias and other airway infections in aged populations [7, 9, 24]. A similar scenario is likely to occur in ALS, with FInt and FF motor units primarily afflicted [14], explaining the initial maintenance of ventilation in ALS patients and the poor correlations between ventilatory parameters and early disease progression [25]. However, ALS patients are at increased risk for airway infections and pneumonias [8], likely reflecting their inability to effectively clear their airways. Notably, a maximal nasal inspiratory transdiaphragmatic pressure of <40 cmH_2O is a sensitive dire prognostic indication in ALS patients, with death due to respiratory failure likely within <6 months [25].

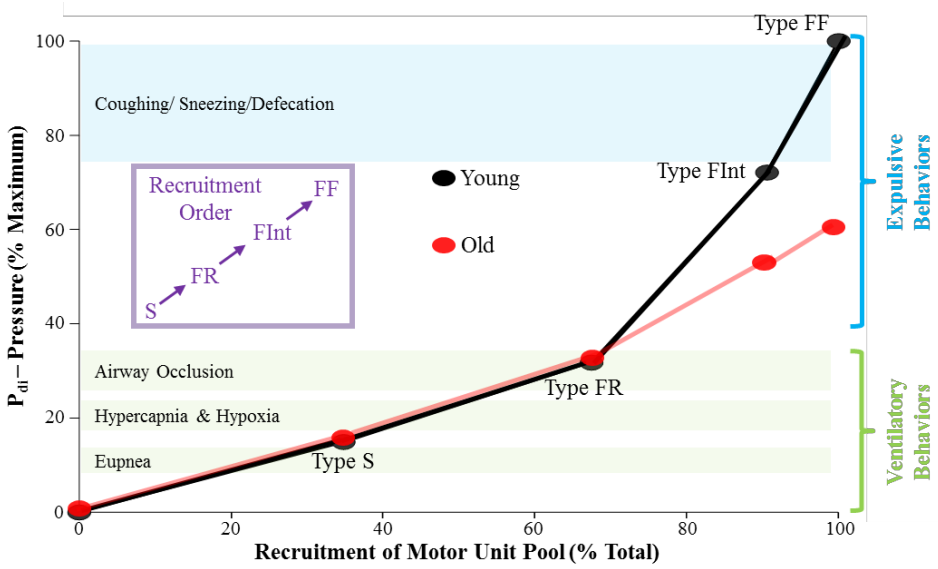

Figure 2. During lower force ventilatory behaviors to more forceful expulsive, airway clearance behaviors, diaphragm muscle motor units are recruited in an orderly fashion depending on the size of phrenic motor neurons. Smaller phrenic motor neurons are recruited first to accomplish lung ventilation from quiet breathing (eupnea) to ventilatory efforts stimulated by hypoxia and/or hypercapnia to more forceful efforts against an occluded airway (e.g., as occur during obstructive sleep apnea). These ventilatory efforts must be sustained and therefore are accomplished by recruitment of fatigue resistant type S and FR diaphragm motor units. By contrast higher-force airway clearance behaviors and straining/expulsive maneuvers (including coughing, sneezing and defecation) require recruitment of higher force but more fatigable type FInt and FF motor units. In young rodents, the recruitment of the FInt and FF units provides for markedly increased transdiaphragmatic pressure (P_{di}) during maximum recruitment. In old rodents, the pathology present in FInt and FF motor units limits accomplishing those behaviors that require their their recruitment. The sparing of type S and FR motor units with age allows for the adequate generation of P_{di} for ventilatory behaviors.

Mitochondrial mechanisms of motor neuron death, lessons learned from ALS

Mitochondria are essential organelles in all living cells. Besides producing ATP, they are important in numerous cellular signalling processes and for the maintenance of homeostasis [18]. Mitochondrial dysfunction in neurons has been implicated in various neurodegenerative diseases, including Alzheimer's, Parkinson's, Frontotemporal Dementia, and ALS [10, 18]. Accumulating evidence also points to a role of mitochondrial dysfunction in the pathogenesis of ALS, with mitochondrial degeneration in motor neurons preceding death of vulnerable motor neurons [16, 17, 26]. In humans, mitochondrial dysfunction in ALS has been associated with genetic mutations and pathology. In 20% of ALS patients with a familial form of the disease (~10% of all sufferers), there is a mutation in the SOD1 gene, leading to a toxic gain of function and the overloading of mitochondria with excessive production of reactive oxygen species (ROS) [10, 11, 18]. Excessive ROS formation is consistent with increased oxidative damage in ALS leading to instrinsic and synaptic hyper-excitability of motor neurons that occurs prior to neuronal death [10, 11, 22, 27-29]. In patients, there is a remarkable amount of morphological and other abnormalities in mitochondria, including vacuolations, breakdown of the outer mitochondrial membrane and reduced mitochondrial DNA copy number [18, 26, 30].

In aging motor neurons, much less is known about the 'normal' mitochondrial state of affairs, let alone how aging-associated related changes may underlie sarcopenia. In many respects our knowledge is limited by the fact nearly all of the age-matched controls used in rodent models of age-related neurodegenerative conditions are barely old enough to be considered as 'young' rodents in aging studies. For example, for the most validated and highly characterised high-expresser SOD1 model of ALS, the humane endpoint is ~150 days of age (barely 5 months-old) [11, 12, 14-17]. By comparison, 6 month-old rodents are routinely classified as 'young' in aging studies [1-3, 5-7]. In aging skeletal muscle, the oxidative capacity muscle fibers declines [31, 32]. This age-related decrease in mitochondrial volume density and oxidative capacity also occurs in diaphragm muscle, where these effects are exclusive to the type IIx and/or IIb fibers that constitute FInt and FF motor units [6]. Our lab is currently exploring age-related changes in mitochondrial volume density and morphological derangement of mitochondria (e.g., fragmentation) in phrenic motor neurons. It appears that age-related changes in mitochondria are selectively found in larger phrenic motor neurons that innervate type FInt and FF motor units, consistent with the overall phenotype of diaphragm muscle neuromotor control.

Inflamm-aging and motor neuron death.

Human aging and the accrual of tissue damage over time is thought to be caused by a state of chronic low-grade inflammation. This is sometimes termed inflamm-aging, which was first coined by Franceschi in 2000 [33]. Aging is considered a major risk factor for all chronic diseases, including neurodegenerative disorders like ALS. There is evidence that inflammatory biomarkers are predictors of morbidity and mortality from chronic diseases in the aging population [34]. However, whether inflammation is causal or consequential to the deleterious age-associated diseases remains unresolved [10, 18, 22]. Indeed, inflammation is in many cases a beneficial process for cells, but gone awry can lead to cellular and mitochondrial damage [18, 22, 31, 33]. There is little to suggest that the overall aging process is devoid of low grade inflammation. However, manifestations of unhealthy aging, including sarcopenia and frailty are not fully explained by low-level inflammation. Acute-on-chronic inflammatory assaults could explain these disruptions, with the nervous system experiencing a punctuated equilibrium, whereby chronic low-grade inflamm-aging is exacerbated by a

severe bout of acute inflammation. Aged cells are less able to repair the damage from inflammation, exacerbating any effects of additional inflammatory challenge. In ALS models, measures to mitigate the haywire inflammatory response of microglia preserve spinal motor neurons [35].

Conclusions

It is evident that the pattern of motor unit pathology is remarkably similar between ALS and aging-associated sarcopenia (Figure 1). The resilience of type S and FR motor units and the selective vulnerability of FInt and FF units is consistent with the behavioural deficits observed in clinical cohorts and rodent models (Figure 2). However, the temporal scale is different between the two conditions, with ALS being characterised by an incredibly rapid loss of motor neurons and decline in muscle function. There is some optimism that our expanding knowledge of the pre-clinical period of ALS and identification motor neuron protective therapies may prove of cross-utility with aging. With painstaking untangling of the fuses that lead to the explosion of motor neuron death in aging, we may be able to separate cause from effect. To this end, understanding the nexus between inflammation, mitochondrial dysfunction and aging is of great importance.

Acknowledgements

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