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Mechanisms of compensatory plasticity for respiratory motor neuron death

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ABSTRACT

Respiratory motor neuron death arises from multiple neurodegenerative and traumatic neuromuscular disorders. Despite motor neuron death, compensatory mechanisms minimize its functional impact by harnessing intrinsic mechanisms of compensatory respiratory plasticity. However, the capacity for compensation eventually reaches limits and pathology ensues. Initially, challenges to the system such as increased metabolic demand reveal subclinical pathology. With greater motor neuron loss, the eventual result is de-compensation, ventilatory failure, ventilator dependence and then death. In this brief review, we discuss recent advances in our understanding of mechanisms giving rise to compensatory respiratory plasticity in response to respiratory motor neuron death including: 1) increased central respiratory drive, 2) plasticity in synapses on spared phrenic motor neurons, 3) enhanced neuromuscular transmission and 4) shifts in respiratory muscle utilization from more affected to less affected motor pools. Some of these compensatory mechanisms may prolong breathing function, but hasten the demise of surviving motor neurons. Improved understanding of these mechanisms and their impact on survival of spared motor neurons will guide future efforts to develop therapeutic interventions that preserve respiratory function with neuromuscular injury/disease.

1. Introduction

Multiple neuromuscular disorders arising from traumatic, infectious, autoimmune, neurotoxic or genetic neuromuscular conditions induce loss of motor neurons (i.e. α-motor neurons innervating and providing cholinergic input to motor end plate) at different time-scales and severities. Motor neuron death during neurodegenerative diseases versus advanced age occur with very different time-scales; for example, polio kills motor neurons rapidly (Kennedy, 1990), amyotrophic lateral sclerosis (ALS) kills motor neurons over years, and aging (or post-polio syndrome) causes motor neuron loss over decades. At the onset of neurodegenerative disease, motor deficits induced by motor neuron death can be difficult to detect since the degeneration is incremental, and compensatory plasticity preserves function to a considerable extent. However, once compensatory plasticity reaches its limits with advancing pathology, challenges to the respiratory control system are aggravated, leading to respiratory failure, ventilator dependence, life-threatening lung infections and death (Johnson and Mitchell, 2013). Trauma causes the quickest functional decline, detectable immediately after the initial impact but with gradual alleviation or exacerbation of functional deficits with time. Despite the importance of respiratory motor neurons to breathing, we know little concerning compensatory mechanisms in respiratory control during neuromuscular clinical disorders, the factors limiting compensation, and physiological costs associated with employing each strategy.

Compensatory plasticity is based on two main principles: i) utilization of remaining functional reserve, and ii) regeneration of lost force generating capacity. For example, increased central drive, strengthening of existing synapses and accessory muscle recruitment facilitates the use of remaining functional reserve of the respiratory system, which normally utilizes only about 20% of its capacity during resting breathing (Mantilla et al., 2010). Re-innervation of denervated muscle fibers via motor neuron end-terminal sprouting with motor neuron death and re-innervation of motor neurons following loss of descending medullary input in high cervical spinal cord injury exemplify regeneration of lost force generating capacity.

The goal of the present review is to emphasize common mechanisms of compensatory plasticity preserving ventilatory function across different neuromuscular disorders involving respiratory motor neuron death. Here, we elaborate on the conceptual framework initially described by Johnson and Mitchell (2013) to improve our understanding of compensatory plasticity via the unique perspectives and approaches focused on different diseases (e.g. ALS, spinal cord injury, post-polio syndrome).

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2. Respiratory deficits with motor neuron death

2.1. ALS

ALS is a neurodegenerative disease characterized by progressive and preferential loss of motor neurons, with attendant respiratory and limb muscle paralysis. ALS is caused by genetic or sporadic (e.g. β-methylamino-L-alanine-induced) causes often associated with familial or environmental risk factors (Kiernan et al., 2011; DeJesus-Hernandez et al., 2011; Karamyan and Speth, 2008). Patients with ALS typically exhibit progressive respiratory muscle weakness, as evident by reduced maximum inspiratory and expiratory pressures, and sniff nasal or transdiaphragmatic pressures. Eventually, hypoventilation is observed especially during sleep (Lyall et al., 2001; Polkey et al., 1998; Bourke et al., 2001; Fallat et al., 1979; Park et al., 2013; Ferguson et al., 1996). The ability to generate respiratory-related behaviors such as coughing and swallowing is also impaired in ALS, leading to impaired airway defense and risk of respiratory infections (Polkey et al., 1998; Chetta et al., 2007; Plowman et al., 2016).

Genetic rodent models of ALS have been developed to mimic aspects of human ALS pathology. As one example, rat and mouse models overexpressing superoxide dismutase 1 (SOD1) with specific gene mutations known to elicit familial ALS in humans (Rosen et al., 1993) exhibit progressive motor neuron death, limb and respiratory muscle paralysis, and eventual death (Lladó et al., 2006; Howland et al., 2002; Wong et al., 1995; Nagai et al., 2001). In the $SOD1^{G93A}$ rat model, respiratory motor neuron cell death at disease end-stage mimics the human condition (˜75% phrenic, ˜60% intercostal motor neuron loss; (Nichols et al., 2013a; Seven et al., 2018a). At disease end-stage, spontaneous phrenic nerve activity and evoked compound diaphragm action potentials are blunted (Lladó et al., 2006; Nichols et al., 2013a). On the other hand, spontaneous diaphragm EMG activity during near-maximal reflex activation remains unchanged (Seven et al., 2018a). Nevertheless, trans-diaphragmatic pressure and the esophageal-to-gastric pressure ratio are decreased, suggesting reduced diaphragm muscle contributions to breathing. Surprisingly, ventilatory capacity is unaffected until very late in the disease progression (Nichols et al., 2013a,b). Ventilatory capacity of $SOD1^{G93A}$ mice is preserved even 2 days before overt ventilatory failure (Tankersley et al., 2007). Similarly, $SOD1^{G93A}$ rats preserve full ventilatory capacity until a defined end-stage (Nichols et al., 2013a,b).

The respiratory motor system is utilized during ventilatory behaviors (low force) and airway protective reflexes (high force). Fast-twitch muscle fibers are recruited only during near-maximal airway protective behaviors (e.g. sneezing and coughing). Ventilatory measurements are not impacted early in ALS, since motor neurons affected in the pre-symptomatic stage are only recruited during high force generating airway protective behaviors, such as sneezing and coughing; they are not likely recruited during less intense ventilatory behaviors (Mantilla et al., 2010, Seven et al., 2014, 2013). Thus, in presymptomatic ALS stages, the motor neurons innervating the most forceful and fatigable muscle fibers are preferentially affected in rodent ALS models, whereas all motor neuron pools are affected in the symptomatic stages (Hegedus et al., 2008, 2007). For example, 35% of motor neurons innervating fast-twitch-dominant extensor digitorum longus (EDL) muscle were dead in contrast to 10% loss in slow-twitch-dominant soleus muscle at presymptomatic time-points (day 50) in $SOD1^{G93A}$ mice. At symptomatic stages (day 120), EDL and soleus motor neuron loss were 45% and 35%, respectively. Therefore, muscle force and activation during near-maximal airway protective behaviors (e.g. sneezing and coughing) are likely affected earlier in ALS than ventilatory capacity, a common feature of many respiratory neuromuscular pathologies.

Respiratory insufficiency in human ALS may occur long after respiratory motor neurons and muscles are affected, although this has not been demonstrated directly. Early pathological changes can be detected prior to the functional symptomatic period, suggesting that humans with ALS have been undergoing pathology for some time before symptoms leading to diagnosis. In the $SOD1^{G93A}$ mouse model of ALS, axonal detachment of motor neuron terminals from muscle precedes symptom onset; 47 days vs. 90 days, respectively (Fischer et al., 2004). A significant drop in muscle fiber force (˜60%) is reported in pre-symptomatic $SOD1^{G93A}$ mice (Hegedus et al., 2008), suggesting secondary pathology. With progressive motor neuron death, muscle fibers are exposed to cycles of denervation and reinnervation, potentially leading to muscle fiber atrophy.

To study the direct implications of respiratory motor neuron death without other complications attendant to disease, a model of respiratory motor neuron death was developed using an engineered toxin (Nichols et al., 2014), Cholera toxin beta subunit (CTB) conjugated to saporin (CTB-Saporin). CTB binds to the GM1 gangliosides present on neurons and is internalized into those neurons. Thus, intramuscular or intrapleural injection of CTB leads to its uptake at the neuromuscular junctions and retrograde transport to the motor neuron somata; this characteristic is often used in motor neuron labeling (Mantilla et al., 2009). Saporin inhibits protein translation via inhibition of 28S subunit of ribosomes, leading to cell death (Bolognesi et al., 1996; Llewellyn-Smith et al., 1999, 2000). Thus, when CTB-Saporin is delivered intrapleurally, it is internalized by motor neuron axon terminals and retrogradely delivered to motor neuron somata, where Saporin is cleaved from CTB and released into the cytoplasm where it triggers respiratory motor neuron death. Motor neuron death via intrapleural CTB-Saporin mimics some respiratory impairments observed during end-stage motor neuron disease, such as phrenic and intercostal motor neuron loss, microglial activation, diminished phrenic nerve activity, and relatively preserved tidal volume during maximum chemoreceptor stimulation (Nichols et al., 2014). The rate of motor neuron loss in CTB-Saporin model is quicker than rodent ALS models. Therefore, it is possible that plasticity mechanisms may not cope with accelerated motor neuron loss. In fact, compensatory respiratory plasticity in this model is less robust than that observed in $SOD1^{G93A}$ rats (Nichols et al., 2013b, 2014). Factors accounting for this difference remain to be investigated.

2.2. Spinal cord contusion injury

The most common cause of death after cervical spinal cord injury (SCI) is respiratory failure (Frankel et al., 1998). Cervical SCIs often cause phrenic motor neuron death and disrupt descending neural pathways to phrenic and other respiratory motor neurons. Consequently, high-cervical SCIs frequently cause respiratory failure, necessitating mechanical ventilation. Increased mortality due to lung infections occurs in ventilator-dependent patients following SCI (DeVivo and Ivie, 1995). On the other hand, mid- and low-cervical SCIs partially spare phrenic motor neurons; nevertheless, there is still potential for respiratory impairment and reliance on ventilatory support depending on the extent of spared neural tissue following injury. Most SCIs are incomplete, sparing neurons and axonal pathways that can undergo compensatory plasticity, spontaneously improving function (Mansel and Norman, 1990; Khurram et al., 2018; Goshgarian, 2009, 2003; Mantilla et al., 2013; Lane et al., 2009; Wen and Lee, 2018; Lee, 2018; Lee and Hsu, 2017; Lee and Kuo, 2017). Regardless, peak cough flow, maximal expiratory pressure, and maximal inspiratory pressure are diminished by cervical SCI especially at C5 and above (Kang et al., 2006). A greater reduction in tidal volume is observed transitioning to during sleep in those with cervical SCI and is associated with higher end-tidal CO_2 and lower O_2 (Bascom et al., 2015). Central and/or obstructive sleep apnea are highly prevalent following cervical SCI (Berlowitz et al., 2005; Sajkov et al., 1998).

Injured human spinal cord tissues show extensive gray and white matter damage at the injury epicenter, with sparing around the rim of the spinal cords (Grumbles and Thomas, 2017). Motor neuron death (˜45% loss) occurs bilaterally in multiple spinal segments starting from

1 level rostral, down to 3 levels caudal to injury epicenter. Loss of motor neurons suggest muscle fiber denervation; together with inactivity, this denervation will lead to severe muscle atrophy after SCI (Castro et al., 1999; Thomas et al., 1997).

Rodent models of cervical (contusion) SCI mimic aspects of human SCIs, including impact, hemorrhage, robust demyelination and axonal degeneration that affects multiple spinal segments surrounding the epicenter. As a result of cervical contusion injury, ~50% of phrenic motor neurons may die, leading to Wallerian degeneration and diaphragm motor end plate denervation (Nicaise et al., 2012a, 2013; Rana et al., 2017; Nicaise et al., 2012b). Phrenic motor neuron loss is associated with reduced evoked compound diaphragm muscle action potentials (Nicaise et al., 2012b), phrenic nerve activity and abnormal ventilatory patterns (Wen and Lee, 2018; Golder et al., 2011; Warren et al., 2018).

While cervical SCI can significantly impact phrenic output or diaphragm activity; tidal volume does not consistently change across different studies following cervical contusions. For example, tidal volume was either recovered or not changed at 2 weeks post-injury (Nicaise et al., 2012a, 2013; Nicaise et al., 2012b; Golder et al., 2011; Lane et al., 2012). On the other hand, some reports demonstrated a long-term decrease in tidal volume (Lee and Kuo, 2017; Warren et al., 2018). It is possible that the level and severity of injury affect the potential for functional compensation and long-term recovery. Therefore, it is critical to provide and compare detailed information about parameters characterizing the contusion impact and the extent of injury by reporting (e.g. applied peak force, impulse, tissue displacement due to impact, hemorrhage, tissue sparing at the epicenter etc.). In addition, there are important considerations in the plethysmographic assessment of respiratory behaviors. First, proper acclimatization and 'reminder' protocols should be applied before the first and subsequent measurements, respectively. Second, because dysfunction of thermoregulation is very often observed after SCI (Khan et al., 2007; Schmidt and Chan, 1992), body temperatures should be carefully monitored and reported during plethysmographic measurements; tidal volumes should be corrected for actual body temperatures with the Drorbaugh-Fenn Equation (Drorbaugh and Fenn, 1955).

3. Mechanisms of compensatory plasticity

There is no single answer to how the central nervous system compensates to maintain ventilatory capacity in neuromuscular pathologies causing respiratory motor neuron loss. In many cases of disease or trauma, multiple compensatory mechanisms are employed. With a physiological process as critical as breathing, it would be surprising if the affected individual did not use every potential form of compensation at their disposal. Potential mechanisms compensating deficiencies in phrenic motor output include (Fig. 1): 1) increased central respiratory drive, 2) spinal synaptic enhancement within the phrenic motor nucleus, 3) enhanced neuromuscular transmission, and 4) shifting respiratory muscle utilization from more affected to less affected motor pools (Johnson and Mitchell, 2013; Seven et al., 2018a; Nichols et al., 2013b).

3.1. Increased central drive

Respiratory motor neurons receive central mono- and poly-synaptic glutamatergic input (central drive) via descending bulbospinal connections from medulla, where respiratory rhythm and pattern are generated. Both respiratory rhythm and pattern are determined via afferent input from chemoreceptors sensing changes in O_2, CO_2, and pH, as well as mechanoreceptors sensing changes in lung and chest wall volume/pressure. For example, increased CO_2 stimulates the central chemoreceptors at the brainstem, increasing tidal volume and frequency. Therefore, chemoreceptor feedback could compensate for challenges such as respiratory motor neuron loss, but only after disease progression is severe enough to cause overt hypoventilation. Animal models of cervical SCI often present decreased tidal volume compensated by increased respiratory frequency (Golder et al., 2011; Warren et al., 2018). This pattern shift may be due to mechanoreceptor feedback and/or neuroplasticity since baseline minute ventilation is not affected by the injury severity reported in these studies.

In rodent ALS models, ventilation is not affected, hypoglossal motor neuron numbers and motor output are maintained until the disease end-stage (Nichols et al., 2013a), suggesting that increased central drive is not employed until late in disease progression. In fact, it may not be practical to maintain high levels of glutamate release for long periods, particularly with neurodegenerative diseases. Motor neuron survival depends on proper function of surrounding glial cells, which maintain the extracellular milieu and provide trophic and nutritional support. Demise of interneurons and motor neurons in ALS is a consequence of dysfunction of multiple cell types in the CNS and can be facilitated by endogenous toxic insults such as glutamate excitotoxicity. Glutamate is one of the most important mediators of excitatory synaptic neurotransmission. However, at high concentrations of extracellular glutamate, excess glutamate receptor activation can cause excitotoxic neuron death (Lewerenz and Maher, 2015; Foran and Trotti, 2009; Shaw and Ince, 1997; Rothstein et al., 1996). Glutamate uptake at the synaptic cleft by astrocytic glutamate transporters is impaired in ALS (Bruijn et al., 1997; Rothstein et al., 1992). In addition, loss of inhibitory spinal interneurons is also implicated to contribute to excitotoxicity (Martin and Chang, 2012; Chang and Martin, 2009; Martin et al., 2007). Thus, multiple mechanisms can contribute to excitotoxic motor neuron death.

If the central respiratory drive is chronically increased and glutamate scavenging mechanisms cannot cope with the demand, chronically increased extracellular glutamate concentrations would likely hasten motor neuron death. Mounting evidence from in vitro and in vivo models suggest that glutamate receptor antagonism can be neuroprotective (Shaw and Ince, 1997). In fact, riluzole prolongs survival in ALS patients possibly via modulation of glutamatergic system (Bellingham, 2011; Doble, 1996). Thus, increased central drive may be detrimental to motor neuron survival ALS; thus, with increased descending drive in late-stage disease, increased central respiratory drive and glutamate release within respiratory motor nuclei is expected to accelerate motor neuron death, leading to the impression that patients "fall off a cliff" as they move towards ventilator dependence.

3.2. Spinal synaptic plasticity at the phrenic motor nucleus

Respiratory spinal networks exhibit considerable plasticity (Dale-Nagle et al., 2010a, b; Turner et al., 2018). For example, activation of Gq and Gs-protein coupled metabotropic receptors elicit phrenic motor facilitation (pLTF), a long-lasting increase in phrenic nerve activity (Golder et al., 2008; MacFarlane and Mitchell, 2009; Hoffman et al., 2010; Hoffman and Mitchell, 2011; Dale et al., 2012; Dale-Nagle et al., 2011; Nichols et al., 2012; Huxtable et al., 2014; Seven et al., 2018b). pLTF is a form of phrenic motor facilitation induced by moderate or severe cute intermittent hypoxia (mAIH and sAIH, respectively). mAIH-induced pLTF results from a 5-HT-2 receptor-dependent mechanism, which requires new BDNF synthesis and TrkB receptor activation (Hoffman et al., 2012). In contrast, sAIH-induced pLTF results from an adenosine 2 A (A_{2A}) receptor-dependent mechanism (Nichols et al., 2012).

Although central serotonergic neurons degenerate in rodents models (El Oussini et al., 2017) and patients with ALS (Dentel et al., 2013), mAIH-induced pLTF is enhanced in late-stage $SOD1^{G93A}$ rats, and the underlying mechanisms remain 5-HT-2 receptor and BDNF-dependent, suggesting that it arises from amplification of the same fundamental mechanism (Nichols et al., 2017). Enhanced pLTF is also observed following intrapleural CTB-Saporin-induced phrenic motor neuron death (Nichols et al., 2018), suggesting that motor neuron death per se

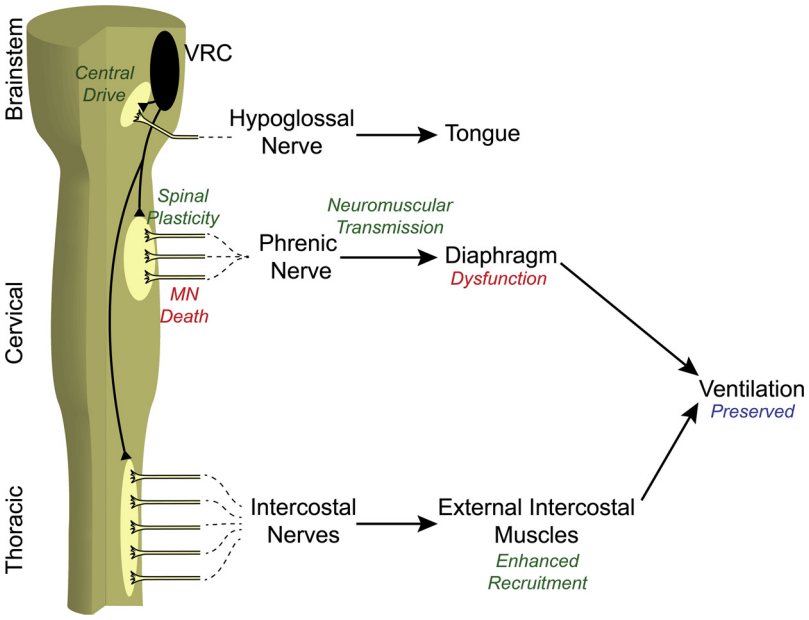

Fig. 1. Overview of Compensatory Plasticity Mechanisms after Phrenic Motor Neuron Death. Phrenic motor neuron death leads to diaphragm dysfunction, which can be compensated by 1) increased central drive, 2) spinal plasticity at the phrenic nucleus, 3) improved neuromuscular transmission, and 4) enhanced accessory muscle recruitment. These mechanisms preserve ventilatory and airway protective functions of respiratory motor network.

is sufficient to elicit certain forms of spinal respiratory motor plasticity. The relevant trigger to this form of plasticity/metaplasticity remains unknown (Fields and Mitchell, 2015). The impact of AIH-induced phrenic motor plasticity on the **spontaneous** compensatory plasticity remains to be elucidated. Further, it is unknown if this same trigger is sufficient to elicit spontaneous plasticity not linked to AIH. Since ˜20% of spared phrenic motor neurons at disease end-stage elicit 55% of normal phrenic nerve activity during maximal chemoreflex activation In end-stage SOD1^{G93A} rats, there must be some form of spontaneous compensatory plasticity that amplifies descending synaptic inputs onto spared phrenic motor neurons (Nichols et al., 2013b).

Serotonergic mechanisms of plasticity in the respiratory neural network after cervical spinal injuries are often studied using hemisection injuries. Following cervical hemisection, serotonergic input to motor neurons is often impaired transiently at 2 weeks (Golder and Mitchell, 2005) consistent with mAIH-induced pLTF impairment at 2 weeks post-injury. At 8 weeks post-injury, serotonergic innervation is partially recovered and pLTF is restored. Pharmacological activation of 5-HT-1 or 5-HT-2 receptors is sufficient to enhance phrenic nerve activity after cervical hemisection injuries (Zhou et al., 2001; Teng et al., 2003; Zimmer and Goshgarian, 2006). Repetitive exposure AIH is currently being explored as a minimally invasive therapeutic intervention in rodents and humans. Repetitive exposure to AIH improves respiratory function via adenosinergic mechanisms at 2 weeks post-injury (the time-point serotonergic pathways are still impaired) and via serotonergic mechanisms at 8 weeks post-injury (the time-point serotonergic pathways are partially recovered). Thus, serotonin plays a significant role in plasticity following cervical hemisection injuries, however, these findings should be tested in cervical spinal contusion.

Involvement of interneurons was implicated in spinal compensatory processes after cervical contusion injury using pseudo-rabies virus (Lane et al., 2012) and C2 hemisection injury using Alexa-488 conjugated wheat germ agglutinin (Buttry and Goshgarian, 2014). Both studies reported higher number of interneurons innervating the phrenic motor neurons, consistent with increased terminal sprouting or synaptic strengthening. A recent study support functional significance of excitatory interneurons in recovery of function after cervical SCI. While VGLUT2+ excitatory interneurons are not necessary for normal breathing, they increase their innervation of phrenic motor neurons and contribute to breathing after non-traumatic spinal cord compression injury (Satkunendrarajah et al., 2018). A similar effect is observed with inhibition of inhibitory neurotransmission in the spinal cord. For example, a latent spinal network generating phrenic bursting is revealed after inhibition of GABAergic and glycinergic transmission suggesting that inhibitory interneuronal networks can be harnessed to promote spinal compensatory plasticity (Cregg et al., 2017). Furthermore, interneurons may also underlie/mediate the contralateral compensatory muscle activity following lateralized injuries such as spinal hemisection (Mantilla et al., 2013; Lee and Hsu, 2017) and unilateral denervation (Khurram et al., 2017). Thus, it is likely that interneurons play a significant functional role in respiratory motor network via a suite of mechanisms enhancing respiratory motor function (Fig. 2, see review (Zholudeva et al., 2018).

3.3. Improved neuromuscular transmission

There is a one-to-one relationship between motor neuron discharge and muscle fiber activity. Each time a motor neuron discharges, the muscle fibers it innervates are also activated. However, with progressive motor neuron death, denervated muscle fibers remain silent until they are reinnervated by surviving motor neurons via end-terminal sprouting (Fig. 3). A motor neuron can increase the number of

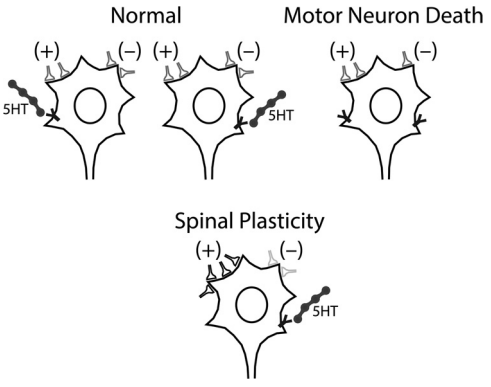

Fig. 2. Spinal Plasticity after Motor Neuron Death. To preserve ventilatory and airway protective functions of respiratory motor network, the following remodeling strategies can be employed: 1) strengthening/weakening existing excitatory/inhibitory synapses and 2) form new synapses or prune existing synapses. 3) Restoration of neuromodulatory (e.g. 5H-T) innervation. Consequently, phrenic nerve output can be at least partially be restored following phrenic motor neuron death.

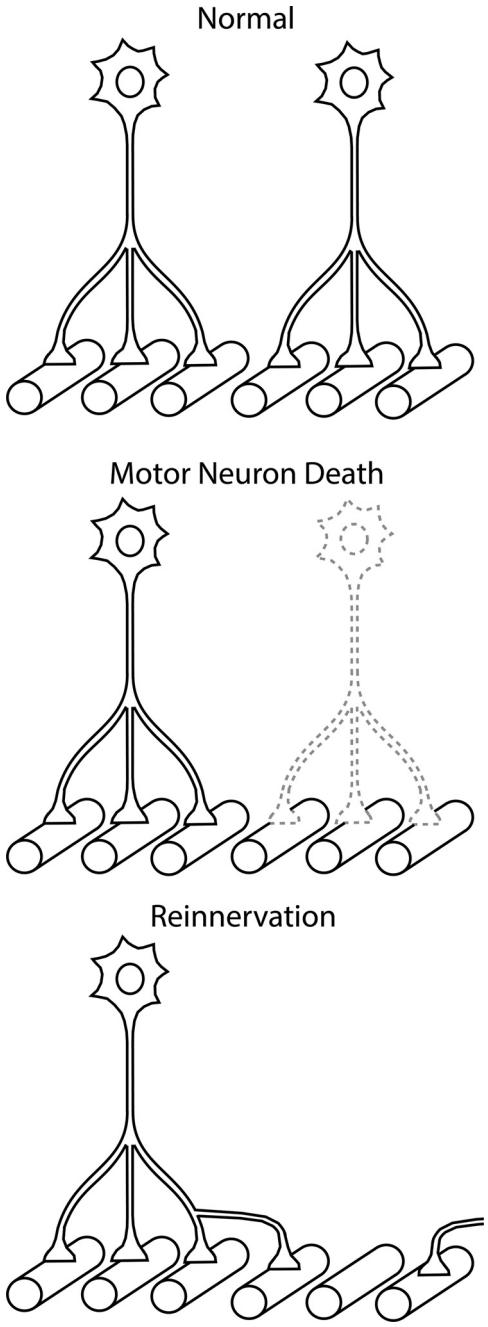

Fig. 3. Increased Motor Neuron Terminal Sprouting after Motor Neuron Death. In healthy adults, each muscle fiber is innervated by a single motor neuron. With neurodegenerative disease or trauma, some motor neurons die (or undergo axonal detachment) and their muscle fibers are denervated. The adjacent motor neuron terminals sprout to reinnervate the denervated muscle fibers. As the pathology progresses, the number of muscle fibers innervated by each motor neuron increases up to 5- to 8-fold preserving ventilatory and airway protective functions of respiratory motor network, However, further sprouting and increased discharge activity may lead to neuromuscular transmission problems and muscle dysfunction.

muscle fibers it innervates (i.e. innervation ratio) by up to ~5- to 8-fold within a year (Gordon and Tyreman, 2010), amplifying neural output to the muscle and effectively compensating for early-stages of motor neuron loss both in animal models and clinical populations (Gordon et al., 2004). This compensatory mechanism has may have the advantage that the same glutamatergic input to motor neurons can generate greater force without inducing excitotoxicity.

In SOD1^{G93A} rats, although only ~50% of phrenic nerve activity is maintained, diaphragm EMG activity is fully preserved (Seven et al., 2018a; Nichols et al., 2013b) consistent with improved neuromuscular transmission from phrenic nerve to diaphragm muscle. Increased motor unit innervation ratio (i.e. average number of muscle fibers innervated per motor neuron) is mediated by axon terminal sprouting and motor end-plate reinnervation (Schaefer et al., 2005). In pre-symptomatic SOD1^{G93A} mice, the tibialis anterior innervation ratio was increased by 44% (Hegedus et al., 2008). We speculate that diaphragm muscle innervation ratio may further increase until the end-stage ALS, compensating for phrenic motor neuron death. Unfortunately, as each surviving motor neuron expands its muscle fiber innervation, it has more neuromuscular junctions to maintain via axonal transport, which can be severely impaired in neurodegenerative diseases and/or neurotrauma (De Vos and Hafezparast, 2017). Extensive sprouting observed when motor neuron loss or muscle fiber denervation exceeds 85% and increased duty cycle for motor neuron discharge increase oxidative stress, which impairs sprouting capacity and may weaken existing and newly innervated presynaptic terminals leading to neuromuscular transmission fatigue and decreased muscle force generation (Gordon et al., 2004; Rizzuto et al., 2015; Rafuse et al., 1992). Regardless of preserved diaphragm EMG activity, repeated denervation and reinnervation cycles likely cause muscle fiber atrophy. In pre-symptomatic SOD1^{G93A} mice, force per muscle fiber decreased ~60% (Hegedus et al., 2008). Consequently, trans-diaphragmatic pressure (in vivo surrogate of diaphragm force) in rats was reduced by ~30%, suggesting secondary diaphragm dysfunction (Seven et al., 2018a).

The same compensatory strategy was observed in the rat model of cervical contusion injury. Following cervical contusion, an initial reduction in diaphragm compound muscle action potential (CMAP) amplitudes was partially recovered over time consistent with partial reinnervation of diaphragm motor end plates (Nicaise et al., 2013). However, diaphragm CMAP was not fully restored in agreement with the observation of immature neuromuscular junctions as evident by high percentage of partially or multiply innervated diaphragm motor end plates.

3.4. Accessory respiratory muscle recruitment

Diaphragm muscle dysfunction or paralysis elicits compensatory increases in the activity of accessory respiratory muscles (e.g. intercostal, neck, abdominal muscles), in part due to the release of inhibition originating from phrenic afferents (Brichant and De Troyer, 1997). Neck muscle recruitment following diaphragm paralysis is vital in people with ALS. Preserved inspiratory sternocleidomastoid activation during REM sleep is associated with longer REM sleep duration in ALS patients with diaphragmatic dysfunction (Arnulf et al., 2000). On the other hand, sternocleidomastoid muscle weakness is associated with lower sniff and maximum inspiratory pressures in ALS patients (Pinto and de Carvalho, 2008). Neck muscle weakness is the most significant prognostic factor for the necessity for mechanical ventilation or death in ALS patients (Nakamura et al., 2013). Other neuromuscular disorders such as Pompe disease and Duchenne muscular dystrophy require accessory muscle function to avoid ventilatory insufficiency (Carlier et al., 2011; Barbé et al., 1994).

Accessory muscle recruitment is a compensatory response utilized during other pathological conditions involving diaphragm paralysis (Brichant and De Troyer, 1997; Katagiri et al., 1994; Maskrey et al., 1990; Ninane et al., 1989; Teitelbaum et al., 1993). In SOD1^{G93A} rats, trans-diaphragmatic pressure is impaired at the late stages of disease leading to powerful recruitment of external intercostal muscles that are normally quiescent, likely compensating for diaphragm dysfunction (Seven et al., 2018a). A class of glutamatergic neurons (V2a neurons) were implicated in the recruitment of accessory respiratory muscles in SOD1^{G93A} mice suggesting that degeneration of V2a neurons would induce decompensation and likely lead to respiratory failure (Romer

et al., 2017).

Compensatory intercostal muscle activation is also utilized in rodent models of cervical contusion injury as early as 20 min post-injury (Wen and Lee, 2018). However, increased intercostal muscle activation was far from reaching its functional reserve, which is utilized via therapeutic modalities. In fact, intercostal muscle pacing via epidural stimulation was reported to be beneficial in ventilator-dependent patients (DiMarco et al., 1994). When combined with diaphragm pacing, intercostal muscle pacing enabled ventilator-dependent patients to forego mechanical ventilation for 16 to 24 h per day (DiMarco et al., 2005).

4. Conclusion

Respiratory motor neuron loss imposes major challenges to the respiratory control system. Powerful and diverse compensatory responses preserve ventilatory capacity, even with major motor neuron death. However, as metabolic workload of spared motor neurons increase, maladaptive decompensation may accelerate motor neuron death, leading patients to sudden respiratory failure. Here, we outline spontaneous compensatory processes preserving ventilatory capacity, despite their potential to compromise motor neuron survival. This appears to be a decision between preservation of life for the patient or animal model versus accelerated motor neuron death. Improved understanding of these processes may enable development of new strategies to slow progression towards respiratory impairment with neurological injury or disease.

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Conflicts of interest

The authors declare no competing financial interests.

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