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Molecular and Electrical Abnormalities in the Mouse Model of Amyotrophic Lateral Sclerosis

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating, fast progressing and fatal disease for which there is little treatment. It is marked by loss of spinal and cortical motoneuron function. Many parameters are altered in the time leading up to this loss, including electrical properties, endoplasmic reticulum (ER) stress, glial functioning, glutamate signaling, protein degradation, mitochondrial functioning, axonal transport, and immune response. This chapter concentrates on the interplay between altered electrophysiological properties and molecular events. Emphasis is placed on the changes that precede overt symptom onset and results are mainly drawn from studies using the rodent models of ALS.

2. ALS animal models

Most cases of ALS are spontaneous (sALS), while the heritable form, familial ALS (fALS), represents about 5% of total ALS cases (Byrne et al., 2011). Of fALS patients, 20% have a mutation in the gene that encodes for the superoxide dismutase 1 (SOD1) copper/zinc enzyme (Rosen et al., 1993), 5% have a mutation in the TARDBP gene which encodes DNA-binding protein 43 (TDP-43), another 5% have a mutation in the FUS gene which encodes for the fused in sarcoma FUS/TLS protein (Mackenzie et al., 2010), some possess a mutation in the gene encoding vesicle-associated membrane protein (VAPB) (Nishimura et al., 2004), and a new study shows that some of those remaining have a mutation in the gene coding for the ubiquitin-like protein ubiquilin-2 (Deng et al., 2011). Transgenic mice expressing one of the various mutations of human SOD1, hereafter referred to as SOD1 mice; (Gurney et al., 1994, Bruijn et al., 1997, Zhang et al., 1997) are very common animal models of ALS; numerous other models of fALS are reviewed by Van Den Bosch (2011). It is not known how the SOD1 mutation leads to the degeneration of motoneurons, though it is probably not due to loss of its normal function converting superoxide into hydrogen peroxide. The mutant, misfolded protein likely possesses a toxic gain-of-function, as some mouse lines retain nearly normal levels of SOD1 enzymatic activity and still develop the disease, while SOD1

knockout mice, which do not possess any SOD1 enzymatic activity, do not develop the disease (Gurney et al., 1994, Reaume et al., 1996, Wong et al., 1995). Whatever the mechanism(s) leading to neurodegeneration, it is not immediate. The SOD1 enzyme is present throughout the nervous system (Pardo et al., 1995) starting embryonically, but does not lead to onset of overt symptoms until well into adulthood, even in mice that express high levels of the protein (Gurney et al., 1994). And within the nervous system, only certain neurons show susceptibility to the disease. This chapter will explore the earliest signs of malfunction in the neurons that are most vulnerable to the disease.

3. Timeline of deficits

In ALS, it is difficult to assess which of all the processes that have been found to be altered are causal to neurodegeneration and which are homeostatic, adaptive mechanisms that are actually allowing the maintenance function. Despite this, it is useful to map out the timing of the various altered properties collected from the mouse models, as presented in Figure 1. Depending on the particular SOD1 mouse model studied, the magnitude and timing of alterations observed does vary (reviewed in Elbasiouny et al, previous chapter). However, for this chapter, the deficits in these mice will be considered in their entirety and not separated based on the particular model from which the results were obtained.

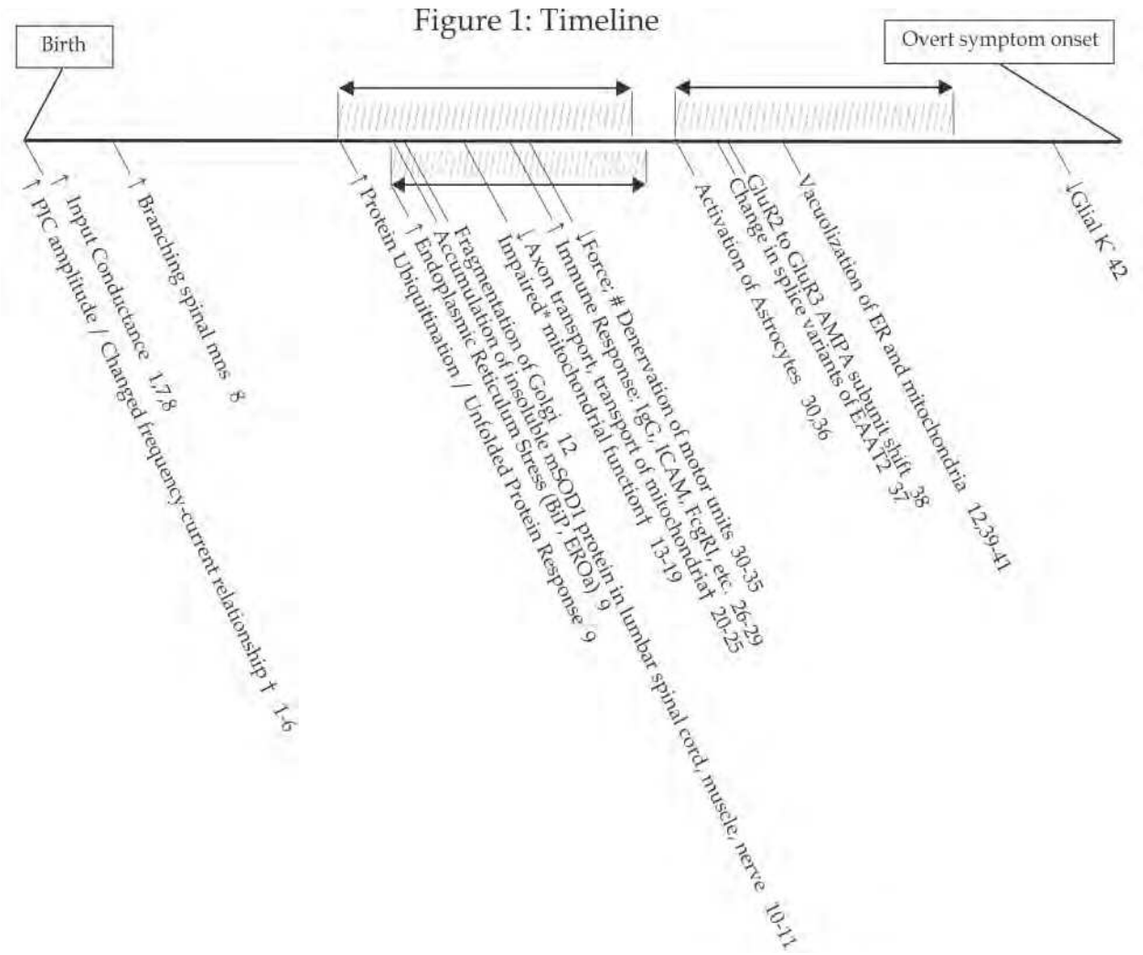
Long before the onset of overt symptoms, within the first week after birth, electrical properties are altered. These properties include an increase in excitability (as measured by both the Na^+- and Ca^{2+}– mediated persistent inward current; PIC) and an increased neuronal size (including increased dendritic branching and increased specific input conductance). Significantly larger PICs first appear in cultured embryonic spinal and cortical motoneurons (Kuo et al., 2005, Pieri et al., 2009), persist at an age of about one week in spinal and hypoglossal motoneurons (van Zundert et al., 2008, Quinlan et al., 2011) and are likely still present in the spinal and cortical motoneurons of adults (Carunchio et al., 2010, Meehan et al., 2010). Interestingly, although the PIC is upregulated very early, what might otherwise be the beginning of motoneuron hyperexcitability is instead moderated by changes in size and specific input conductance (Amendola and Durand, 2008, Elbasiouny et al., 2010, Quinlan et al., 2011). In adulthood, but still well before the onset of symptoms, there are signs of defective protein degradation, endoplasmic reticulum (ER) stress, impaired axon transport, and deficiencies in mitochondrial function. Signs of aberrant protein clearance include increased expression of genes related to ubiquitination, UPR, and ER stress (Saxena et al., 2009). As these changes might suggest, there is a buildup of insoluble SOD1 proteins at this time (Johnston et al., 2000, Turner et al., 2003a), followed shortly by fragmentation of the Golgi (Mourelatos et al., 1996). The next signs of impairment appear in the mitochondria and in the cellular transport system (Zhang et al., 1997, Warita et al., 1999, Williamson and Cleveland, 1999, Mattiazzi et al., 2002, Kieran et al., 2005, Damiano et al., 2006, De Vos et al., 2007, Bilsland et al., 2008, Jaiswal et al., 2009, Nguyen et al., 2009, Bilsland et al., 2010, Li et al., 2010). The immune response is initiated next (Alexianu et al., 2001, Chiu et al., 2008, Gowing et al., 2008, Chiu et al., 2009). After this, denervation of the motor units and loss of maximal force begins (Kennel et al., 1996, Frey et al., 2000, Fischer et al., 2004, Hegedus et al., 2007, Hegedus et al., 2008), but the impairment of normal function in the mouse is subtle and onset of overt symptoms is several weeks off, even in the most severe models. Just before the impending functional loss, several of the

last changes before overt onset of symptoms involve the glia: activation of astrocytes, expression of different splice variants of EAAT2, decreased expression of the GluR2 subunit, and decreased number of glial K^+ channels (Bruijn et al., 1997, Bendotti et al., 2001, Sasaki et al., 2001, Munch et al., 2002, Warita et al., 2002, Fischer et al., 2004, Ignacio et al., 2005, Kaiser et al., 2006).

It is tempting to assume that the order of appearance of the altered parameters represents a chain reaction of events, but this is not necessarily the case. There is considerable interplay between these components within the neurons, such that one pathway cannot be altered without affecting any other aspect of cellular or synaptic function. These interactions will be considered next.

4. Calcium: No buffer for increased currents

Entry of Ca^{2+} occurs through voltage-gated Ca^{2+} channels and through ligand-gated channels activated by glutamate, particularly the NMDA-type glutamate receptors and those AMPA-type glutamate receptors which lack the Ca^{2+}-impermeable GluR2 subunit. Most voltage-gated Ca^{2+} channels open only when the cell depolarizes; however, the L-type $Ca_v1.3$ channels, which contribute to the PIC, open near the resting membrane potential (-40mV) and allow some Ca^{2+} influx even when the neuron is at rest (Xu and Lipscombe, 2001). There is very little expression of $Ca_v1.3$ channels in spinal motoneurons at birth, but $Ca_v1.3$ channels are increasingly present as the motoneurons mature, reaching adult levels by postnatal day 18 (P18) in mice, (Jiang et al., 1999, Quinlan et al., 2011). The PIC sets the level of excitability in neurons: PICs allow neurons to repetitively fire action potentials, and with large PICs, neurons can sustain firing long after the depolarizing stimulus is removed (Heckman et al., 2008). In addition, motoneurons from SOD1G93A-high-expressor mice show a significantly larger PIC during postnatal development, including significantly larger amplitudes of both Ca^{2+} and Na^+ currents (Quinlan et al., 2011). Larger PICs can increase the overall excitability of a neuron (though other factors, like size, can mitigate this), and the influx of Ca^{2+} could have many other consequences in cell-signaling. An increased PIC is found in cultured, embryonic, SOD1G93A-high motoneurons (both spinal and cortical), though at this point the PIC is completely Na^+-based (Kuo et al., 2005, Pieri et al., 2009). Postnatally, both spinal and brainstem SOD1 motoneurons show an increased PIC (van Zundert et al., 2008, Quinlan et al., 2011), and indirect evidence suggests larger PICs persist into adulthood in SOD1 cortical and spinal motoneurons (Carunchio et al., 2010, Meehan et al., 2010). In addition to the maturation of the PIC, there is an increase in AMPA-type glutamate receptors on motoneurons (Vinay et al., 2000). These receptors normally would not contribute to Ca^{2+} influx since, due to a single amino acid in the pore-forming GluR2 subunit they are impermeable to Ca^{2+}. However, in presymptomatic SOD1 motoneurons, there are fewer Ca^{2+}-impermeable GluR2 subunits; and more Ca^{2+}-permeable GluR3 subunits (Tortarolo et al., 2006). In sALS patients, AMPA receptors also are more Ca^{2+}-permeable, but through a different mechanism. Spinal motoneurons of symptomatic sALS patients, but not SOD1 rats, showed inefficient editing of the mRNA, resulting in mutant, GluR2Q subunits that are Ca^{2+}-permeable (Kawahara et al., 2004, Kwak and Kawahara, 2005, Kawahara et al., 2006). As motoneurons mature they must cope with an ever-increasing burden of Ca^{2+} influx through voltage-gated Ca^{2+} channels (as the Ca^{2+} PIC increases with age) and SOD1 motoneurons have a heavier burden due to potentiation of the Ca^{2+}PIC and altered AMPA receptors which are more Ca^{2+}-permeable.



[1](Quinlan et al., 2011),[2](Kuo et al., 2005), [3](van Zundert et al., 2008), [4](Meehan et al., 2010), [5](Carunchio et al., 2010), [6](Pieri et al., 2009), [7](Bories et al., 2007), [8](Amendola and Durand, 2008), [9](Saxena et al., 2009), [10](Johnston et al., 2000), [11](Turner et al., 2003b), [12](Mourelatos et al., 1996), [13](Li et al., 2010), [14](Jaiswal and Keller, 2009),[15](Mattiazzi et al., 2002), [16](Nguyen et al., 2009), [17](Jaiswal et al., 2009), [18](Bilsland et al., 2008), [19](Damiano et al., 2006), [20](Bilsland et al., 2010), [21](De Vos et al., 2007), [22](Williamson and Cleveland, 1999), [23](Zhang et al., 1997), [24](Kieran et al., 2005), [25](Warita et al., 1999), [26](Alexianu et al., 2001), [27](Gowing et al., 2008), [28](Chiu et al., 2008), [29](Chiu et al., 2009), [30](Fischer et al., 2004), [31](Frey et al., 2000), [32](Pun et al., 2006), [33](Hegedus et al., 2007), [34](Hegedus et al., 2008), [35](Kennel et al., 1996), [36](Bruijn et al., 1997), [37](Munch et al., 2002), [38](Tortarolo et al., 2006), [39](Bendotti et al., 2001), [40](Dal Canto and Gurney, 1995), [41](Dal Canto and Gurney, 1994), [42](Kaiser et al., 2006).

Fig. 1. Timeline of deficits in mutant SOD1 mice. Earliest reported deficits in the above properties are used. Different SOD1 mutants were normalized to dates of overt symptom onset. When differences in timing between mouse lines were large (as it was for protein ubiquitination, stress of the ER, and activation of astrocytes), the range is indicated in the timeline with (///). † Also found in embryonic cultured motoneurons. * Different aspects of mitochondrial function were impaired at different time points. The first alteration in function is decreased Ca^{2+} storage capacity[19]. Another property, mitochondrial membrane potential, is not altered until just before symptom onset[17], while the function or regulation of the electron transport chain is impaired slightly before membrane potential[16].

While Ca^{2+} currents are increased in SOD1 motoneurons, large spinal and hypoglossal motoneurons do not have Ca^{2+}-binding proteins calbindin and parvalbumin and thus cannot quickly neutralize large influxes of Ca^{2+}. Instead, they depend heavily on mitochondrial uptake of Ca^{2+} (Ren and Ruda, 1994, Lips and Keller, 1998, Palecek et al., 1999, Bergmann and Keller, 2004). Small ocular motoneurons which have calbindin, parvalbumin and high Ca^{2+}-buffering capacities are unaffected by ALS (Vanselow and Keller, 2000, von Lewinski and Keller, 2005). Ca^{2+}-binding ratio, Ks, depends on Ca^{2+}-binding proteins, the intracellular $[Ca^{2+}]_i$, and the size and geometry of the cell (Neher, 1995). Although Ca^{2+} buffering at the soma of neonatal SOD1 and WT motoneurons was similar (von Lewinski et al., 2008), buffering has not been measured in adult motoneurons or in the processes, where Ca^{2+} channels are located (Sukiasyan et al., 2009). Ca^{2+} buffering could also change postnatally in motoneurons, as in rat Purkinje cells in which the Ca^{2+}-binding ratio more than doubles between P6 and P15 (Fierro and Llano, 1996). The increasing Ca^{2+} entry with postnatal maturation combined with the lack of Ca^{2+}-buffering proteins seems likely to contribute to motoneuronal vulnerability in adulthood.

5. Impaired transport, more places to go

The lack of Ca^{2+}-buffering proteins in vulnerable motoneurons make the mitochondria even more critical to their function. Mitochondria are normally highly mobile both in axons and dendrites (MacAskill et al., 2010). Mitochondrial movement can be halted by increased concentrations of ADP, so they tend to remain in compartments which are highly metabolically-active (Mironov, 2007). Mitochondrial movements are also regulated through Ca^{2+} signaling and synaptic activity (Rintoul et al., 2003, Yi et al., 2004, Macaskill et al., 2009). When glutamate binds NMDA- or certain AMPA-type receptor-channels, it allows the influx of Na^{+} and Ca^{2+} into the cell. The Ca^{2+}-sensitive domain of Miro, the mitochondrial trafficking protein, then interacts with Ca^{2+} and the transport factors TRAK and KIF5, and pauses in its movement at active synapses (Rintoul et al., 2003, MacAskill et al., 2009). Postsynaptic NMDA receptors are also associated with PSD95 and with nitric oxide synthase (NOS) which, through nitric oxide (NO), also pauses mitochondrial movement (Rintoul et al., 2006). Once at a synapse, the mitochondria are probably tethered by neurofilaments, a process that depends both on the state of phosphorylation of the neurofilaments and a high mitochondrial membrane potential which indicates a high level of activity (Wagner et al., 2003).

In axons, but not in the soma of cultured SOD1 motoneurons, mitochondria are more sparsely distributed (De Vos et al., 2007), and *in vivo* mitochondria show more frequent pauses in their movements in pre-symptomatic SOD1 mice (Bilsland et al., 2010). Unfortunately, movement of mitochondria and other membrane-bound organelles has not yet been well studied in the dendrites of SOD1 motoneurons. If the mitochondria are similarly sparse in the dendrites, where most Ca^{2+} channels are located, this could have serious consequences for Ca^{2+} buffering. Spinal motoneurons of SOD1 mice show a significant proliferation in dendritic branches (Amendola and Durand, 2008) and an increased Ca^{2+} PIC (Quinlan et al., 2011), which could make mitochondrial motility in the dendrites more challenging. Without mitochondria to take up Ca^{2+} at the synapses, this would further exacerbate the low Ca^{2+} buffering in vulnerable motoneurons and any increased Ca^{2+} entry with synaptic inputs (Tortarolo et al., 2006). It is also worth noting that

the motoneurons that are vulnerable are the largest: the fast, fatiguable alpha motoneurons (Pun et al., 2006, Hegedus et al., 2007, Hegedus et al., 2008). Evidence for further increases size in SOD1 motoneurons is reviewed in the previous chapter by Elbasiouny et al. Perhaps the size of the motoneuron and deficits in transport go hand in hand to produce vulnerability.

Axon transport has been extensively studied and is likely to contribute to ALS and to several neurodegenerative diseases, reviewed by (De Vos et al., 2008). In ALS, both slow and fast axon transport appear to be altered (Zhang et al., 1997, Warita et al., 1999, Williamson and Cleveland, 1999, Kieran et al., 2005, De Vos et al., 2007, Bilsland et al., 2010). Excessive glutamate could cause these deficiencies: high levels of glutamate activate a family of mitogen-activated protein kinases that phosphorylate neurofilaments, thereby decreasing transport (Ackerley et al., 2000, Hiruma et al., 2003, Stevenson et al., 2009). This process can be induced by NMDA or AMPA, blocked by removal of extracellular Ca^{2+}, or reduced by application of riluzole (Hiruma et al., 2003, Stevenson et al., 2009). The protein kinases JNKs, cdk/p35 and p38, which phosphorylate heavy and light chains of kinesin and medium and heavy neurofilament sidearms, may link glutamate neurotransmission and axon transport deficits (Kawasaki et al., 1997, Schwarzschild et al., 1997, Ackerley et al., 2000, Brownlees et al., 2000, Lee et al., 2000). Further suggesting this, p38 has been found to be activated in SOD1 mice and ALS patients (Raoul et al., 2002, Tortarolo et al., 2003, Ackerley et al., 2004). Axon transport deficiencies occur early, with reports of impaired axonal integrity and die-back from the neuromuscular junction occurring weeks in advance of onset of symptoms in SOD1 mice, and appearing in cultured embryonic neurons (Kennel et al., 1996, Zhang et al., 1997, Williamson and Cleveland, 1999, Frey et al., 2000, Fischer et al., 2004, Pun et al., 2006, De Vos et al., 2007, Hegedus et al., 2007, Hegedus et al., 2008, Bilsland et al., 2010). Strengthening these results, transgenic TDP-43 mice show significantly lower levels of expression of heavy and light neurofilaments, though axon transport itself has not yet been assessed (Swarup et al., 2011).

6. Mitochondrial deficiency and energy balance

In motoneurons under normal conditions, the mitochondrial membrane potential powers both the Ca^{2+} uniporter and ATP synthase, so in periods of heavy Ca^{2+} influx, ATP production could be impaired (Mattson et al., 2008, Nguyen et al., 2009). The increased Ca^{2+} influx in SOD1 motoneurons is likely to further impair the function of mitochondria under these conditions. In addition, SOD1 mitochondria appear to be impaired in function under basal conditions (Mattiazzi et al., 2002, Nguyen et al., 2009, Li et al., 2010). Before the onset of symptoms, SOD1 mitochondria show decreased protein import, altered Ca^{2+} sequestering, and an exaggerated response of the electrical gradient of the inner membrane to stimulation-induced Ca^{2+} influx (Damiano et al., 2006, Bilsland et al., 2008, Jaiswal et al., 2009, Nguyen et al., 2009, Li et al., 2010). By the time symptoms appear there is severe damage to mitochondrial membrane potentials, respiration, the electron transport chain and ATP synthesis (Mattiazzi et al., 2002, Jaiswal and Keller, 2009). Another impairment is misfolded SOD1 binding to VDAC1, the general diffusion pore for anions and cations, including Ca^{2+}. Both mitochondrial conductance and the uptake of ADP are thereby reduced, however, this is not observed until after the onset of symptoms (Israelson et al., 2010). Early alterations in SOD1 mitochondria must take place though another mechanism.

In summary, not only are there fewer mitochondria present in the processes of SOD1 neurons (De Vos et al., 2007, Bilsland et al., 2010), but those that are present are impaired in functioning. This is likely to have dire consequences for both Ca^{2+} buffering and ATP production in the large and metabolically-active SOD1 motoneurons.

7. Protein degradation and endoplasmic reticulum stress

Misfolded proteins are degraded through autophagy (Yang and Klionsky, 2010). When the capacity of the cellular machinery in the ER to properly fold proteins is exceeded, cells react with the unfolded protein response (UPR) and signs of ER stress (reviewed by Ron and Walter, 2007). The UPR decreases most protein synthesis in the cell while upregulating synthesis of some ER proteins that assist in proper folding and processing of proteins. Another pathway, known as ER-associated protein degradation (ERAD), helps to clear the ER of misfolded proteins by exporting them to proteasomes where they are broken down (Bernasconi and Molinari, 2011). Proteins to be exported and degraded are marked by ubiquitination, a process in which ubiquitin molecules bind to the protein, tagging it for destruction (Bingol and Sheng, 2011). Normal ER function can be disrupted by blocking the ER-resident proteins from folding properly, inadequate functioning of the ubiquitin-proteosome system, or failure to maintain a high level of Ca^{2+} inside the lumen of the ER (Paschen, 2003).

It is known that mice with the highest expression levels of mutant SOD1 protein have the earliest disease onset (Wong et al., 1995), and that markers for ER stress have been found in the spinal cords of sALS patients (Ilieva et al., 2007, Atkin et al., 2008, Ito et al., 2009). However, recent studies have shed more light on the role of protein degradation and ER stress in the pathology of ALS. In the first study, gene expression patterns from 3 different SOD1 mouse lines all showed an early increase in protein ubiquitination only in those motoneurons that are vulnerable to the disease. This is followed shortly by the UPR and signs of ER stress by P30 in SOD1G93A-high expressor mice (see Fig 1) (Saxena et al., 2009). In another study, cortical motoneurons from SOD1 mutant mice were compared to those from wild type mice that were fed a diet high in branched-chain amino acids (Carunchio et al., 2010). These branched chain amino acids are part of protein supplements that some athletes consume. Like mutant SOD1 neurons, cortical neurons from mice fed the high-protein diet were hyperexcitable compared with neurons from wild type mice on a normal diet. A return to normal levels of excitability after treatment with rapamycin was achieved for both the SOD1 and the amino- acid-supplement-treated cortical neurons (Carunchio et al., 2010). The protein kinase known as the mammalian target of rapamycin (mTOR) serves as an integration point for several cell signaling pathways. As its name suggests, mTOR is inhibited by rapamycin; it also inhibits protein degradation, and promotes increased cell size in some neurons (Lee et al., 2007). These results indicate that promoting autophagy with rapamycin can reduce abnormal excitability and could be beneficial for treatment of the disease (Carunchio et al., 2010). The third, most recent study described a mutation found in 5 different families, located in the gene encoding ubiquilin-2 as a novel genetic cause of fALS (Deng et al., 2011). The function of ubiquilin is to clear certain misfolded proteins during ERAD by shuttling ubiquitinated proteins from the ER to the proteasome, such that loss of ubiquilin leads to ER stress (Kim et al., 2008, Lim et al., 2009). The mutations in ubiquilin-2 found in ALS patients were also found to impair proteosome- mediated protein degradation *in vitro,* suggesting these mutations could be causing similar impairments in the

families from whom they were isolated (Deng et al., 2011). Even in sALS patients, ubiquilin-2 was found in abnormal protein aggregates in degenerating neurons, indicating it could play a broad role in both fALS and sALS pathology (Deng et al., 2011). These studies suggest a key role for protein degradation and ER stress in ALS pathology.

In healthy neurons, the resting [Ca^{2+}] in the ER remains high. When ER [Ca^{2+}] drops, the Ca^{2+}-sensing STIM proteins promote Ca^{2+}-channel formation (Luik et al., 2008). Blocking this ER-mediated Ca^{2+}-entry affects neuronal activity and under conditions of chronic hyperexcitability, STIM proteins are upregulated (Steinbeck et al., 2011). Contributions to electrophysiological excitation-mediated Ca^{2+} transients from ER Ca^{2+} release have been documented in motoneurons (Scamps et al., 2004, Jahn et al., 2006). Supporting the possibility that neuronal excitability and neuronal protein processing and ER function could share common pathways, blocking L-type Ca^{2+} channels has been reported to increase autophagy (Williams et al., 2008). To summarize, due to the large role Ca^{2+} plays in cell signaling, (McCue et al., 2010, Pivovarova and Andrews, 2010), even small changes in electrophysiological properties could have broad consequences in cellular function.

8. Non-cell autonomous deficits: Astrocytes and glutamate excitotoxicity

Recent work has shown that the vulnerability of motoneurons is not cell autonomous, and that glia play critical roles in neurodegeneration in SOD1 mice. The involvement of astrocytes and microglia in the disease were elegantly demonstrated in a series of studies using mice with deletable mutant SOD1, mice with a selective knockdown of SOD1, and SOD1/WT chimera mice (Clement et al., 2003, Boillee et al., 2006, Yamanaka et al., 2008, Wang et al., 2009). Simply culturing WT motoneurons on mutant SOD1 astrocytes was sufficient to confer toxicity to motoneurons (Nagai et al., 2007). Glia have this effect on motoneurons through a variety of pathways, including activation of astrocytes, microglia, and T cells shortly after the first signs of pathology appear. The glial response is thought to influence the progression, but not the onset, of the disease (Beers et al., 2006, Boillee et al., 2006, Yamanaka et al., 2008, Wang et al., 2009, Philips and Robberecht, 2011). Presymptomatic involvement of the glia includes a reduction of glial K^+ channel expression shortly before the onset of symptoms (Kaiser et al., 2006) and later in the course of the disease, a reduced expression of astroglial glutamate transporters, GLT1/EAAT2 which mediate glutamate reuptake at synapses and help prevent glutamate excitotoxicity (Bruijn et al., 1997, Bendotti et al., 2001, Warita et al., 2002). Earlier alterations in EAAT2 function are likely due to expression of different splice variants rather than decreased expressions levels (Sasaki et al., 2001, Munch et al., 2002, Ignacio et al., 2005). Some ALS patients also show abnormal splice variants of EAAT2, which could lead to decreased glutamate transport (Rothstein et al., 1992, Maragakis et al., 2004, Lauriat et al., 2007). Stimulation of the expression and transporter activity of EAAT2/GLT1 increases the lifespan of mutant SOD1 mice (Rothstein et al., 2005). An additional, critical function of the glia is regulation of the glutamate receptor's pore-forming GluR2 subunit (Van Damme et al., 2007). The challenges of Ca^{2+} buffering are exacerbated by alterations in the glutamate signaling across disease models of ALS. In SOD1 motoneurons, expression of subunits in the AMPA-type glutamate receptors is shifted from Ca^{2+}-impermeable to Ca^{2+}-permeable (Tortarolo et al., 2006). In TDP mice, levels of RNA that encode proteins involved in synaptic activity, including glutamate receptors, ion channels and voltage gated Ca2+ channels, are altered, with unknown consequences on synaptic transmission (Polymenidou et al., 2011). Lastly, in sALS

patients, there is inefficient editing of AMPRA receptor GluR2Q subunit mRNA which also causes a shift from Ca^{2+}-impermeability of the receptors to Ca^{2+}-permeability (Kawahara et al., 2004, Kwak and Kawahara, 2005, Kawahara et al., 2006). Glutamatergic signaling is probably a significant factor in the onset of symptoms since reducing excitatory sensory input delayed the onset of disease in SOD1 mice (Ilieva et al., 2008), and intrathecal administration of the glutamate agonist kainic acid in normal rats produced slow, selective motoneuron death similar to ALS (Sun et al., 2006). If changes in the transmission of glutamate are taking place early enough, it could alter the activity of spinal networks during normal development (Blankenship and Feller, 2010, Landmesser and O'Donovan, 1984, Marder and Rehm, 2005, Gonzalez-Islas and Wenner, 2006). Some evidence for alterations in network activity has been shown in SOD1 hypoglossal motoneurons (van Zundert et al., 2008) and spinal motoneurons (Amendola et al., 2004, Bories et al., 2007) in juvenile mice. After symptom onset, increased network activity has also been shown in the spinal cord (Jiang et al., 2009). However, considering all the documented changes in glutamate-mediated neurotransmission, there has been surprisingly little research into the overall effects on cortical, brainstem and spinal network activity throughout the lifespan of the SOD1 mouse.

9. Future directions

There are many possibilities to explore for new treatments of ALS besides the now-standard drug riluzole (Bellingham, 2011). The neuroinflammation response is a promising approach (Philips and Robberecht, 2011); another could be to manipulate neuromodulatory input to the spinal cord. Serotonin (5HT) and norepinephrine (NE) have potent effects on motoneurons, including increasing PIC amplitude, decreasing input conductance, hyperpolarizing spike threshold, and depolarizing resting potential (Hounsgaard and Kiehn, 1989, Lee and Heckman, 1999, Powers and Binder, 2001, Alaburda et al., 2002, Hultborn et al., 2004, Perrier and Delgado-Lezama, 2005, Heckman et al., 2008). Furthermore, neuromodulators are constantly scaling the level of activation of motoneurons as needed (Heckman et al., 2004). Activation of $5HT_2$ receptors strongly depresses high-voltage-activated Ca^{2+} channels while probably increasing basal $[Ca^{2+}]_I$ by potentiating the Ca^{2+} PIC (Hounsgaard et al., 1988, Bayliss et al., 1995, Hsiao et al., 1998, Ladewig et al., 2004, Li et al., 2007). Both 5HT and dopamine (DA) modulate KIF-5-dependent cellular transport, including transport of mitochondria. Acting through the GSK3 regulator of KIF-5, 5HT is observed to increase transport, while DA decreases it (Chen et al., 2007, Chen et al., 2008). Other neuromodulators, such as nitric oxide, $GABA_B$, and adenosine, could also be worth investigating as modulators of motoneuron synaptic strength, reduction of the Ca^{2+} PIC, and modulation of both high-voltage-activated Ca^{2+} channels and input conductance, respectively (Marks et al., 1993, Mynlieff and Beam, 1994, Li et al., 2004, Moreno-Lopez et al., 2011). Another useful target of neuromodulators that modify Ca^{2+} influx is protein clearance; inhibition of L-type Ca^{2+} channels has been found to increase autophagy (Williams et al., 2008).

10. Conclusions

Factors causing neurodegeneration in ALS are present long before motor function is adversely affected. From research on the animal models of ALS, it is thought that excessive

Ca^{2+} entry, increased motoneuronal size, altered glutamate neurotransmission, astrocyte dysfunction, mitochondrial deficits, failures in axon transport, and problems in protein degradation act in concert and gradually push motoneurons outside the parameters under which they can function properly. The fact that motoneurons are able to remain functioning for as long as they do under adverse conditions suggests that there is a large window of time and intrinsic conditions within which motoneurons can maintain normal function. Hopefully future treatments can target these altered pathways to extend the time motoneuron properties remain within these parameters.

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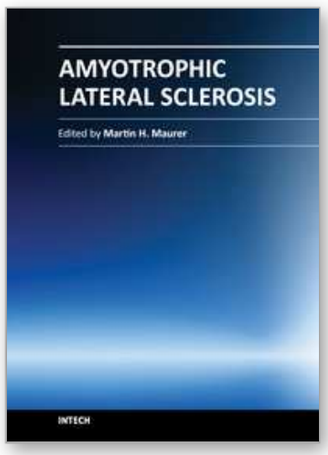

Amyotrophic Lateral Sclerosis

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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