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# Role of Mitochondrial Dysfunction in Motor Neuron Degeneration in ALS

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## 1. Introduction

Amyotrophic lateral sclerosis (ALS), which was described since 1869 by Jean Martin Charcot, is a devastating neurodegenerative disease characterized by the selective and progressive loss of upper and lower motor neurons of the cerebral cortex, brainstem and the spinal cord. Progressive motor neuron loss causes muscle weakness, spasticity and fasciculation, eventually paralysis and finally death by respiratory failure 3 to 5 years after diagnosis. ALS worldwide prevalence is about 2 to 8 people per 100,000, and presents two important differences with respect to other neurodegenerative diseases: the cognitive process is not affected and is not merely the result of aging because may occur at young ages (Chancellor & Warlow, 1992; Huisman et al., 2011). Two forms of ALS are known, the familial type (FALS), associated with genetic mutations, mainly in the gene encoding superoxide dismutase 1 (SOD1, enzyme responsible for superoxide dismutation to oxygen and hydrogen peroxide), and the sporadic form (SALS), of unknown origin. FALS represents only about 5-10% of cases (Rosen et al., 1993; Rowland & Shneider, 2001), and SALS comprises the remaining 90%. Despite having different origins, both ALS types develop similar histopathological and clinical characteristics.

## 2. Mechanisms of motor neuron death in ALS

After one hundred fifty years since the first ALS description of the disease, the cause of motor neuron degeneration remains unknown, but progress in neuroscience and clinical research has identified several mechanisms that seem to be involved in the cell death process, such as glutamate-mediated excitotoxicity, inflammatory events, axonal transport deficits, oxidative stress, mitochondrial dysfunction and energy failure.

### 2.1 Excitotoxicity

Based on the reduction of glutamate transporter-1 (GLT1 in rodents and excitatory amino acid transporter 2 or EAAT2 in human) content detected post-mortem in motor cortex and spinal cord of ALS patients (Rothstein et al., 1992; Rothstein et al., 1995) and on the increase of glutamate concentration in the cerebrospinal fluid (CSF) of about 40% of ALS patients (Shaw et al., 1995b; Spreux-Varoquaux et al., 2002), one proposed mechanism to explain

motor neuron death in ALS is glutamate-mediated excitotoxicity. This hypothesis has been generally accepted, although some data from our laboratory do not support it because a chronic increase in extracellular glutamate due to glutamate transport inhibition in the spinal cord in vivo was innocuous for motor neurons (Tovar-y-Romo et al., 2009b). However, overactivation of glutamate ionotropic receptors by agonists leads to neuronal death by augmenting the influx of  $\text{Ca}^{2+}$  into motor neurons. Experimental models in vivo have shown that of three major glutamate ionotropic receptor types, NMDA (N-methyl-D-aspartate), kainate and AMPA ( $\alpha$ -amino-3-hydroxy-5-isoxazolepropionate), the  $\text{Ca}^{2+}$ -permeable AMPA receptor seems to be particularly involved in motor neuron death, because the selective blockade of  $\text{Ca}^{2+}$ -permeable AMPA receptors or the chelation of intracellular  $\text{Ca}^{2+}$  prevents the motor neuron loss and the consequent paralysis induced by the infusion of AMPA into the rat lumbar spinal cord (Corona & Tapia, 2004, 2007; Tovar-y-Romo et al., 2009a). The  $\text{Ca}^{2+}$  permeability of this receptor is governed by the presence of the GluR2 subunit and its edition in the Q/R (glutamine/arginine) site of the second transmembrane domain (Burnashev et al., 1992; Corona & Tapia, 2007; Hollmann et al., 1991; Hume et al., 1991).

Increases in cytoplasmic  $\text{Ca}^{2+}$  concentration can be buffered by mitochondria, but when maintained for prolonged periods can cause mitochondrial swelling and dysfunction. These alterations are associated with deficits in mitochondrial ATP synthesis and energetic failure (this topic will be discussed later). The energetic deficits have been mainly associated with cell death process similar to necrosis (Kroemer et al., 2009; Martin, 2010). On the other hand, mitochondrial damage has also been linked to the release of proapoptotic factors such as cytochrome c and apoptosis-inducing factor (Martin et al., 2009). Cytochrome c involvement has been stressed because of its role in triggering the caspases pathway, which leads to apoptotic cellular death. In the cytoplasm cytochrome c promotes the formation of the apoptosome complex and activates caspase-3. The necrosis and apoptosis pathways are illustrated in Fig. 1.

## 2.2 Axonal transport deficits

Because of the structural and functional characteristics of motor neuron axons, the role of axonal transport is essential for the communication between the neuronal soma and the periphery, as well as for the anterograde and retrograde dispersive distribution of cargo intracellular structures such as vesicles or organelles. Changes in the speed of anterograde and retrograde transport (Breuer & Atkinson, 1988; Breuer et al., 1987; Sasaki & Iwata, 1996), as well as neurofilament disorganization and accumulation of mitochondria, vesicles and smooth endoplasmic reticulum have been described in peripheral nerves of ALS patients (Hirano et al., 1984a, b; Sasaki & Iwata, 1996). These alterations in axonal transport have been observed also in transgenic models of FALS, which have allowed the study of their progression and the molecular machinery involved (Bilsland et al., 2010; Brunet et al., 2009; Collard et al., 1995; De Vos et al., 2007; Ligon et al., 2005; Perlson et al., 2009; Pun et al., 2006; Tateno et al., 2009; Warita et al., 1999; Williamson & Cleveland, 1999). In mutant SOD1 (mSOD1) rodents, some motor proteins such as: dynein, dynactin, kinesin, myosin, actin, and microtubules and neurofilaments are affected by mSOD1 aggregates (Breuer & Atkinson, 1988; Breuer et al., 1987; Collard et al., 1995; Ligon et al., 2005; Sasaki & Iwata, 1996; Williamson & Cleveland, 1999; Zhang et al., 2007).

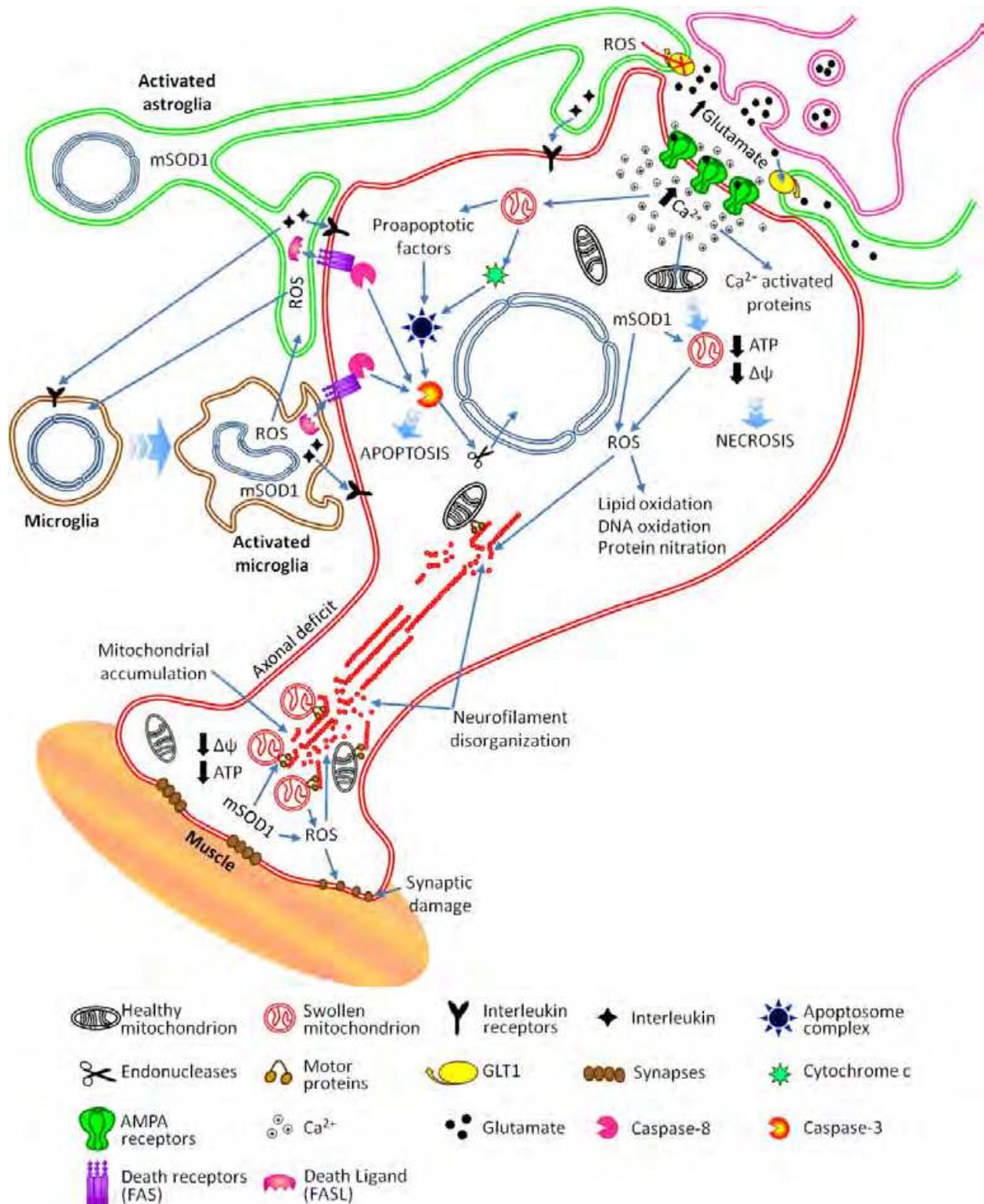


Fig. 1. Scheme of the main proposed mechanisms involved in motor neuron death. Description in the text.

These deficits may affect the renewal of organelles in the axon terminals of motor neurons, leading to accumulation of damaged mitochondria or autophagosomes, increased ROS production, disruption of microtubule formation and stability (Julien & Mushynski, 1998), as well as damage of presynaptic structure such as swelling of axon terminals (Komatsu et al., 2007). Accumulation of damaged mitochondria may result in energetic failure (Liu et al., 2004; Martin et al., 2009; Menzies et al., 2002a, b; Pasinelli et al., 2004; Wong et al., 1995; Zhu et al., 2002) and in the release of proapoptotic factors (Pasinelli et al., 2004) (Fig. 1, bottom left). These alterations may be involved in the distal neuropathy and impairment of muscular reinnervation observed in ALS.

### 2.3 Oxidative stress

Another mechanism implicated in motor neuron degeneration in ALS that involves both motor neurons and non-neuronal cells is oxidative stress. Reactive oxygen species (ROS) arise in cells as aerobic metabolism by-products, mostly due to the leakage of electrons from the mitochondrial respiratory chain, resulting in an incomplete reduction of molecular oxygen during the oxidative phosphorylation, generating the superoxide radical anion ( $O_2^{\bullet-}$ ). The  $O_2^{\bullet-}$  anion reacts quickly with the nitric oxide radical ( $NO^{\bullet}$ , produced by nitric oxide synthase, NOS) to form peroxynitrite ( $ONOO^-$ ). Meanwhile, the product of  $O_2^{\bullet-}$  dismutation,  $H_2O_2$ , slowly decomposes to form the highly reactive hydroxyl radical ( $\bullet OH$ ). Both  $ONOO^-$  and  $\bullet OH$  are highly reactive and can damage proteins, membranes and DNA by oxidation. Cellular mechanisms to combat the constant production of free radicals are: 1) enzymes such as SOD, catalase and peroxidase, which catalytically remove reactive species; 2) reducing agents synthesized *in vivo*, such as glutathione,  $\alpha$ -keto acids, lipoic acid and coenzyme Q, and compounds obtained from the diet, such as ascorbate (vitamin C) and  $\alpha$ -tocopherol (vitamin E); and 3) chaperone heat shock proteins which remove or facilitate repair of damaged proteins. Oxidative stress arises from an imbalance between ROS production and its control mechanisms.

The involvement of oxidative stress in ALS pathogenesis is supported by abundant evidence that has been reported in both SALS and FALS patients, where several indicators of increased oxidative damage have been found: 1) In postmortem central nervous system (CNS) tissue samples (mainly spinal cord) these markers include oxidized DNA (Ferrante et al., 1997b; Fitzmaurice et al., 1996), lipid peroxidation (Siciliano et al., 2002), protein glycooxidation (Shibata et al., 2001), elevated protein carbonylation (Ferrante et al., 1997b; Shaw et al., 1995a), and increased protein tyrosine nitration; remarkably, nitrotyrosine immunoreactivity was more densely detected in motor neurons (Abe et al., 1995; Abe et al., 1997; Beal et al., 1997; Ferrante et al., 1997a). 2) Oxidation markers in CSF, plasma and blood from living ALS patients during the course of the disease have also been described. The most relevant are oxidized DNA (Bogdanov et al., 2000; Ihara et al., 2005), hydroxyl and ascorbate free radicals (Ihara et al., 2005), lipid peroxidation (Baillet et al., 2010; Bogdanov et al., 2000; Bonnefont-Rousselot et al., 2000; Ihara et al., 2005; Oteiza et al., 1997; Simpson et al., 2004; Smith et al., 1998), and a remarkable elevation of 3-nitrotyrosine levels in CSF (Tohgi et al., 1999). However, in other study, 3-nitrotyrosine was not different between the CSF of ALS patients and control subjects (Ryberg et al., 2004). Increased oxidative damage to proteins, lipids and DNA has also been demonstrated in CNS tissue of transgenic mouse model of FALS expressing mSOD1 (Andrus et al., 1998; Casoni et al., 2005; Liu et al., 1999; Liu et al., 1998; Poon et al., 2005).

Mitochondria, ROS and glutamate-induced excitotoxicity are closely related and this is relevant in ALS, because the mitochondrion is the main oxygen consumer and it is also the main producer of ROS. These species can be produced in neurons and in non-neuronal cells and can cause failure in the glutamate uptake system of both motor neurons and astroglia (Rao et al., 2003; Trotti et al., 1996, 1998; Volterra et al., 1994; Zagami et al., 2009). This may contribute to an excitotoxic condition due to increased concentration of extracellular glutamate. ROS production and its effects on motor neurons and non-neuronal cells are illustrated in Fig. 1.

#### **2.4 Inflammation**

A mechanism of non-cell-autonomous death associated with motor neuron degeneration in both FALS and SALS is the participation of non-neuronal cells in inflammatory events (Boillee et al., 2006a; Boillee et al., 2006b; Hall et al., 1998; Yamanaka et al., 2008; Yang et al., 2011). The main histopathological feature of inflammation is the proliferation of reactive astroglia and of activated microglial cells, associated with alterations in their cellular functions, such as glutamate reuptake failure and release of proapoptotic and proinflammatory factors (Sanagi et al., 2010; Sargsyan et al., 2005; Sofroniew, 2005). Molecules associated with inflammatory process, such as interleukins 6, 12, 15, 17A, 23, C4d and C3d complement proteins, as well as tumor necrosis factor-alpha, have been found in blood and CSF from ALS patients (Almer et al., 2002; Fiala et al., 2010; Henkel et al., 2004; Kawamata et al., 1992; McGeer et al., 1991; Moreau et al., 2005; Rentzos et al., 2010a, b). The finding of increased levels of granzymes A, B in serum (Ilzecka, 2011) and decrease in cytochrome c levels in the CSF (Ilzecka, 2007), suggests an apoptotic process in human disease. The proliferation of activated non-neuronal cells has been associated with the disease severity (Clement et al., 2003). Nevertheless, alteration in their functions may be more important than their proliferation (Lepore et al., 2008). In experimental models of FALS (mSOD1) it has been attempted to prevent the motor neuron loss through the use of drugs with anti-inflammatory properties, such as minocycline (Keller et al., 2010; Kriz et al., 2002; Neymotin et al., 2009; Van Den Bosch et al., 2002; Zhu et al., 2002). This drug was effective in delaying the motor neurons loss when given prior to the symptoms onset, but when given at late stages it exaggerated the neuroinflammatory response and accelerated the progression of the symptoms (Keller et al., 2010). In this transgenic ALS model, apoptosis processes can be triggered by non-neuronal cells through the extrinsic apoptotic pathway, via the release from activated glial cells of several death ligands (for example FasL) that bind to their respective death receptor (Fas) and trigger the cleavage of caspase-8 (Locatelli et al., 2007; Petri et al., 2006; Raoul et al., 2006) (Fig. 1).

### **3. Mitochondrial dysfunction in ALS and in experimental motor neuron degeneration**

A convergent point of the deleterious mechanisms discussed above is the mitochondrion. This organelle is the main energy producer in eukaryotic cells and plays a fundamental role in normal cell physiology. Among the functions mitochondria carry out, besides ATP synthesis, intracellular  $Ca^{2+}$  buffering has been recognized as another relevant factor for the protection against deleterious processes such as oxidative stress, excitotoxicity and necrotic and apoptotic death, thus playing a central role in neuronal survival.

Mitochondria are closely related to necrotic and apoptotic processes, which are the main cellular death mechanisms. During necrosis, mitochondria undergo rapid swelling and lysis. Although apoptosis is an energy-dependent active process, sometimes mitochondrial morphological alterations are associated with the intrinsic-apoptosis pathway. Furthermore, it is now recognized that apoptosis and necrosis are not two mutually exclusive processes, but they can occur simultaneously or one preceding the other (Kroemer et al., 2009; Martin, 2010; Martin et al., 2009; Shrivastava & Vivekanandhan, 2011).

As the organelle responsible for energy production in the cell, mitochondria possess the enzymatic machinery to catalyze the oxidation of various substrates generated inside and outside mitochondria, including pyruvate through pyruvate dehydrogenase, fatty acids through  $\beta$ -oxidation, and carbon chains from amino acids. Energy is obtained by oxidation of all these biomolecules to finally  $\text{CO}_2$  and  $\text{H}_2\text{O}$  through the tricarboxylic acid cycle and the respiratory chain. The tricarboxylic acid cycle is the converging point because the carbon skeletons of carbohydrates and fatty acids are metabolized to yield the acetyl group of acetyl-Coenzyme A, and many of the carbons of the amino acid skeleton also enter the cycle via its conversion to some cycle intermediates. The reducing equivalents generated in the tricarboxylic acid cycle reactions reduce pyridine and flavin nucleotides to NADH and  $\text{FADH}_2$ . These electron transporters enter the respiratory chain, where electron flux through various redox carriers and centers in the enzyme complexes located in the inner mitochondrial membrane finally reduces  $\text{O}_2$  to  $\text{H}_2\text{O}$ ; this flux is coupled to ATP synthesis through oxidative phosphorylation.

The energy released by the electron flux through respiratory chain complexes is used to pump protons through the inner mitochondrial membrane, producing an alkaline and negatively charged mitochondrial matrix, as compared to the intermembrane space, thus creating a proton gradient. This proton gradient generates an electrochemical potential called proton-motive force ( $\Delta p$ ), which supplies the energy to ATP synthase for ATP synthesis from ADP and inorganic phosphate. The  $\Delta p$  depends mainly on the mitochondrial transmembrane potential ( $\Delta\psi_m$ ), which is the electric potential (negative inside), but it also depends on the transmembrane pH gradient ( $\Delta\text{pH}$ ), which is the chemical potential (alkaline inside). Energy stored in the proton gradient can also transport solutes against concentration gradient across the membrane. The  $\Delta\psi_m$  is a central parameter that controls three fundamental and highly relevant cellular processes for neuronal survival: ATP synthesis, mitochondrial  $\text{Ca}^{2+}$  sequestration, and mitochondrial ROS generation. On the other hand,  $\Delta\psi_m$  is controlled by substrate availability, ATP demand, respiratory chain capacity, mitochondrial proton conductance, and mitochondrial  $\text{Ca}^{2+}$  sequestration (Nicholls & Budd, 2000). Therefore, mitochondrial bioenergetic status is crucial for controlling the susceptibility of neurons to chronic or acute stress and also in determining cellular fate (survival, apoptosis or necrosis).

Owing to the great relevance of mitochondria, their morphological, ultrastructural and functional characteristics have been studied in ALS patients. Deficits in respiratory chain complexes I and IV activities have been detected in the spinal cord and skeletal muscle (Borthwick et al., 1999; Crugnola et al., 2010; Vielhaber et al., 2000; Wiedemann et al., 2002; Wiedemann et al., 1998), and a temporal study of mitochondrial respiratory function in skeletal muscle in SALS demonstrated that respiratory complex IV activity is progressively altered as the disease develops (Echaniz-Laguna et al., 2006). Some cases of ALS have been described as a mitochondriopathy (Finsterer, 2002, 2003) including a mitochondrial DNA

mutation in the gene encoding subunit I of the mitochondrial respiratory chain complex IV (Comi et al., 1998). The electron transport chain proteins FAD synthetase, riboflavin kinase, cytochrome C1, and succinate dehydrogenase complex subunit B expression were significantly decreased in some ALS patients (Lin et al., 2009).

In the mSOD1 mice or cell culture familial ALS model, complexes I, II and IV of the electron transport chain exhibit decreased enzyme activities, even at early stages of the disease (Jung et al., 2002; Mattiazzi et al., 2002; Menzies et al., 2002a,b). In G93A-SOD1 mice the association of cytochrome c with the inner mitochondrial membrane was reduced and there was a significant decrease in respiratory chain complex IV (Kirkinezos et al., 2005). SOD-containing aggregates (Higgins et al., 2002; Jaarsma et al., 2001; Pasinelli et al., 2004) and decreased oxygen consumption, lack of ADP-dependent respiratory control, and decreased membrane potential (Cassina et al., 2008), were observed in mitochondria from spinal cord of transgenic mSOD1 rodents.

In neuronal cultures, glutamate-mediated excitotoxicity caused significant changes in mitochondrial function, such as decline in ATP levels, mitochondrial transmembrane potential collapse, decreased mitochondrial and cellular oxygen consumption, and oxidative phosphorylation uncoupling, all these events preceding cell death (Ankarcona et al., 1995; Atlante et al., 1996; Maus et al., 1999; Monje et al., 2001). There is a link between excitotoxicity-induced intracellular  $\text{Ca}^{2+}$  overload and the collapse of  $\Delta\psi_m$ , since intracellular  $\text{Ca}^{2+}$  increase and its accumulation in mitochondria are sufficient to induce prominent and persistent depolarization, leading to mitochondrial dysfunction and to neuronal death in vitro (Schinder et al., 1996; White & Reynolds, 1996).

Few studies on excitotoxicity have been carried out in vivo. In our laboratory we have developed two experimental models of spinal motor neurons degeneration by overactivation of AMPA receptors, both by infusing AMPA directly in the lumbar spinal cord of rats. In the first one AMPA is administered through microdialysis cannulas during short time periods (Corona & Tapia, 2004) and in the other AMPA is infused chronically during several days, using osmotic minipumps (Tovar-y-Romo et al., 2007). These models reproduce the main histopathological features of ALS: loss of lumbar motor neurons, astroglial activation and motor deficits that progresses to complete paralysis of the rear limbs. The main difference between the two models is the time required for the occurrence of motor neuron degeneration and the development of the paralysis. AMPA perfusion by microdialysis causes a rapid loss of motor neuron and paralysis, occurring within the initial 12 hours, while chronic AMPA infusion with osmotic minipumps triggers a progressive motor neuron loss and motor deficits throughout three to four days. For these reasons, the microdialysis model is defined as an acute model and the minipumps model as a chronic model of spinal motor neuron degeneration by excitotoxicity (Tovar-y-Romo et al., 2009a). The most important feature of both models is that motor neuron loss occurs without the influence of a genetic factor and thus presumably can be used to study the mechanisms that may be involved in motor neuron loss occurring in SALS, which accounts for over 90% of ALS cases.

We have recently assessed mitochondrial function in our acute model of spinal excitotoxic motor neuron degeneration, by studying mitochondrial oxygen consumption and transmembrane potential in mitochondria isolated from the lumbar spinal cord of rats perfused with AMPA. The AMPA-treated group showed decreased oxygen consumption, ADP-dependent respiratory control and transmembrane potential, as compared to control

rats perfused only with Krebs-Ringer medium (Santa-Cruz and Tapia, in preparation). These results suggest that mitochondrial dysfunction plays a crucial role in spinal motoneuron degeneration induced by overactivation of AMPA receptors *in vivo*. These mechanisms could be involved in ALS motoneuron degeneration.

### 3.1 Ca<sup>2+</sup>, mitochondria and motor neuron degeneration

Under physiological conditions, Ca<sup>2+</sup> participates as intracellular messenger in many normal cellular functions, such as cell growth, differentiation, signal transduction, membrane excitability regulation, exocytosis and synaptic activity. Cytoplasmic Ca<sup>2+</sup> concentration in resting neurons is maintained at low concentrations (~100 nM), 10,000 times lower than extracellular space concentration. To achieve this, neurons possess specialized homeostatic mechanisms, such as regulation of Ca<sup>2+</sup> input and output, Ca<sup>2+</sup> binding proteins, mitochondrial and endoplasmic reticulum storage, and Ca<sup>2+</sup>-ATPases. Moreover, neurons not only control intracellular Ca<sup>2+</sup> levels, but also its location in the cell by means of complex interactions among Ca<sup>2+</sup> input, output, buffering and internal storage. Under physiological conditions, these processes maintain spatial and temporal location of Ca<sup>2+</sup>, so that multiple Ca<sup>2+</sup>-regulated signaling pathways can take place independently within the same cell.

Excessive intracellular Ca<sup>2+</sup> concentration damages neurons through several mechanisms, including mitochondrial damage, energy metabolism deficit, toxic ROS generation, membrane depolarization, and activation of lytic enzymes such as proteases, lipases, phosphatases and endonucleases. Intracellular Ca<sup>2+</sup> accumulation also stimulates ROS production through NOS activation and the conversion of xanthine dehydrogenase to xanthine oxidase through proteases activation. All these events eventually produce membrane destruction and neuronal death (Arundine & Tymianski, 2003; Shaw, 1999).

Intracellular Ca<sup>2+</sup> regulation is an expensive process from the energy point of view. Ca<sup>2+</sup> is extruded from the cell and sequestered into the endoplasmic reticulum through active transport using Ca<sup>2+</sup>-ATPases, and it is also removed by secondary active transport using the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, which activates Na<sup>+</sup>/K<sup>+</sup>-ATPases to take out Na<sup>+</sup>. Mitochondria also play a critical role in the regulation of cytosolic Ca<sup>2+</sup> concentration, since they sequester this cation through a Ca<sup>2+</sup> uniporter located in the inner mitochondrial membrane and driven by the electric potential (Nicholls, 1985). To prevent a potentially lethal Ca<sup>2+</sup> accumulation in mitochondrial matrix, there is an output system that exchanges Na<sup>+</sup>/Ca<sup>2+</sup>, besides a mitochondrial Na<sup>+</sup>/H<sup>+</sup> transporter that extrudes Na<sup>+</sup>, so that ion flux under a constant Ca<sup>2+</sup> entrance to mitochondria involves a sequential transfer of Ca<sup>2+</sup>, Na<sup>+</sup> and H<sup>+</sup>, the latter driven by the respiratory chain (Crompton & Heid, 1978; Nicholls & Budd, 2000). When Ca<sup>2+</sup> concentration surpasses a certain critical point, under physiological phosphate concentration an osmotically inactive and rapidly dissociable Ca<sup>2+</sup>-phosphate complex is formed in the mitochondrial matrix, so that mitochondria work as efficient buffers of extramitochondrial Ca<sup>2+</sup> by accumulating this cation (Becker et al., 1980; Nicholls, 1978). Apparently, this organelle acts as a temporary Ca<sup>2+</sup> store during high cytoplasmic concentrations peaks, as suggested by the kinetics of mitochondrial Ca<sup>2+</sup> transport; because the Ca<sup>2+</sup>-phosphate complex is rapidly dissociable, mitochondria can release Ca<sup>2+</sup> back to the cytoplasm when its concentration decreases below the critical point. As long as mitochondria are polarized, cytosolic Ca<sup>2+</sup> accumulates within the mitochondrial matrix through the Ca<sup>2+</sup> uniporter. Mitochondrial Ca<sup>2+</sup> uptake is driven by  $\Delta\psi_m$ , so it will compete with ATP synthase for proton gradient, in such a way that Ca<sup>2+</sup> uptake could dominate due

to the fact that ATP synthesis requires a thermodynamic threshold for  $\Delta\psi_m$ , while  $\text{Ca}^{2+}$  transport can proceed at much lower  $\Delta\psi_m$  and excessive  $\text{Ca}^{2+}$  concentrations reduce  $\Delta\psi_m$  dramatically. When  $\text{Ca}^{2+}$  concentration does not recover below the critical point, excessive  $\text{Ca}^{2+}$  overload in the mitochondrial matrix can lead to mitochondrial swelling, loss of respiratory control, increased mitochondrial ROS generation,  $\Delta\psi_m$  collapse (depolarization) diminished ATP synthesis, and  $\text{Ca}^{2+}$  release from the mitochondrial matrix caused by inner mitochondrial membrane permeabilization through the mitochondrial permeability transition pore (MPTP, a large protein complex forming a non-selective pore through the inner mitochondrial membrane) (Al-Nasser & Crompton, 1986; Nicholls & Budd, 2000; Peng & Jou, 2010). When mitochondrion depolarizes, accumulated  $\text{Ca}^{2+}$  goes back into the cytoplasm, either through the  $\text{Ca}^{2+}$  uniporter, the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, or through the MPTP. Since  $\Delta p$  depends mainly on  $\Delta\psi_m$ , its collapse causes  $\Delta p$  collapse, which results not only in halting ATP synthesis but also in a rapid cytoplasmic ATP hydrolysis because ATP synthase catalytic function reverses in an attempt to restore  $\Delta p$ .

In motor neurons, the damage produced by these alterations may be enhanced because they do not have sufficient mitochondrial  $\text{Ca}^{2+}$ -buffering capacity, due in part to a lower mitochondrial density per volume compared to non-motor neurons (Grosskreutz et al., 2007). In addition, other buffering mechanisms are deficient in spinal and cortical motor neurons because they lack the  $\text{Ca}^{2+}$ -binding proteins calbindin D-28K and parvalbumin. This may explain why other motor neurons that express these proteins, such as those located in oculomotor and Onuf's nuclei, are not usually affected in ALS (Alexianu et al., 1994; Celio, 1990; Ince et al., 1993; Palecek et al., 1999). For all these reasons, mitochondrial  $\text{Ca}^{2+}$  overload plays a key role in glutamatergic excitotoxicity (Nicholls et al., 2003), given that overactivation of  $\text{Ca}^{2+}$ -permeable AMPA receptors, which are abundant in spinal motor neurons, confers to these cells a special vulnerability to AMPA receptor-mediated excitotoxicity (Corona & Tapia, 2007; Grosskreutz et al., 2010). AMPA exposure to spinal motor neuron cultures results in an intracellular  $\text{Ca}^{2+}$  concentration increase that triggers mitochondrial  $\text{Ca}^{2+}$  overload, depolarization and ROS generation (Carriedo et al., 2000). So, there is abundant evidence that suggest that mitochondrial damage, probably related to  $\text{Ca}^{2+}$  homeostasis disturbances, is involved in SALS and FALS (Manfredi & Xu, 2005; Menzies et al., 2002a; Swerdlow et al., 1998; von Lewinski & Keller, 2005).

### 3.2 Energy deficits

Due to the large size of motor neurons and their long processes reaching muscles, they have an expensive energy cost and this renders them very vulnerable to energy deficits. Much of the ATP demand in neurons is used in the ion pumping through plasma membrane to maintain membrane potential. Thus,  $\text{Na}^+/\text{K}^+$ -ATPase is the most demanding ATP process in neurons (Scott & Nicholls, 1980) in order to expel  $\text{Na}^+$  excess resulting from excitation. Intracellular  $\text{Ca}^{2+}$  regulation by  $\text{Ca}$ -ATPases is also highly energy consuming, as previously discussed.

There is abundant evidence both in vitro and in vivo that any restriction in the ability of the cell to generate ATP can exacerbate or even induce glutamatergic excitotoxicity. The energy-linked excitotoxic hypothesis (Beal et al., 1993; Greene & Greenamyre, 1996; Novelli et al., 1988) proposes that the correlation between excitotoxic damage and energy restriction is due to plasma membrane depolarization. Diminished ATP levels cause a decrease in  $\text{Na}^+/\text{K}^+$ -ATPase and  $\text{Ca}^{2+}$ -ATPase functions, lessening  $\text{Na}^+$  and  $\text{Ca}^{2+}$  removal. This triggers plasma

membrane depolarization and as a consequence  $\text{Ca}^{2+}$  enters the cell through voltage-dependent  $\text{Ca}^{2+}$  channels and glutamate is released to the extracellular space by exocytosis. This in turn activates  $\text{Ca}^{2+}$  influx through the NMDA receptor, which is also voltage-dependent. Further, under energetic failure conditions, glutamate transporters operate in reverse because  $\text{Na}^+/\text{K}^+$  electrochemical gradient collapse due to ATP decrease, resulting in diminished glutamate uptake and non-vesicular glutamate release into extracellular space (Jabaudon et al., 2000; Longuemare & Swanson, 1995).

The observation that inhibition of mitochondrial respiratory chain complexes activity can induce pathological changes similar to those observed in some neurodegenerative diseases in specific CNS regions has generated great interest. Association among glutamatergic excitotoxicity and bioenergetic limitation has been proposed for Alzheimer, Parkinson, Huntington's disease and ALS (Beal, 1998), and in many cases specific respiratory chain complexes are involved. In organotypic spinal cord cultures, motor neurons are selectively vulnerable to chronic mitochondrial blockade by inhibitors of mitochondrial respiratory chain complex II and complex IV and this motor neuron degeneration displays structural changes similar to those seen following excitotoxicity (Brunet et al., 2009; Kaal et al., 2000).

In our acute model of excitotoxic motor neuron degeneration previously described (Corona & Tapia, 2004, 2007) we have demonstrated the importance of  $\text{Ca}^{2+}$ -permeable AMPA receptors and of intracellular  $\text{Ca}^{2+}$  overload in motor neuron death process. Using this model, we aimed to study the importance of energy deficits and oxidative stress in AMPA-induced degeneration. With this purpose, we assessed the potential neuroprotection of various energy substrates and antioxidants at different concentrations, co-perfusing them with AMPA in the rat lumbar spinal cord. We observed protection at different degrees depending on the concentration of each compound, but in general antioxidants only partially protected, while various energy substrates prevented the AMPA-induced motor impairment and the spinal motor neuron loss (Santa-Cruz and Tapia, in preparation). These findings suggest that intracellular  $\text{Ca}^{2+}$  overload *in vivo* disrupts mitochondrial energy metabolism. On the other hand, energy substrates can directly prevent  $\Delta\Psi_m$  collapse and thus prevent mitochondrial dysfunction. Because one of the factors that control  $\Delta\Psi_m$  is substrate availability, excess mitochondrial substrates administered exogenously can stimulate respiratory chain and increase oxidative phosphorylation, maintaining the electrochemical proton gradient and thus preventing the collapse of ATP synthesis.

### 3.3 Oxidative stress

Since mitochondria are the organelles where oxidative phosphorylation is accomplished, they consume about 98 % of the cell oxygen requirement and constitute a major site for intracellular ROS production. Some steps along mitochondrial oxygen reduction pathway have the potential to produce, and indeed generate free radicals, due to the fact that electron flux along respiratory chain may have leakage of electrons to oxygen. The intermediate radical ubiquinone, involved in the transfer of electrons through respiratory complexes III and I, can grant an electron to oxygen, forming the superoxide radical  $\text{O}_2^{\bullet-}$ , a powerful oxidant and a very reactive intermediate (Turrens et al., 1985) that must be rapidly removed by antioxidant enzymes to avoid its lethal effects. About 0.1-4% of the  $\text{O}_2$  used by actively respiring mitochondria is converted to  $\text{O}_2^{\bullet-}$ . Nevertheless, respiratory chain enzymes defects or other mitochondrial perturbations could be responsible of an excessive mitochondrial

ROS production, triggering or increasing cellular injury. Among them, mitochondrial  $\text{Ca}^{2+}$  overload resulting from NMDA, AMPA or kainate receptor overactivation (Carriedo et al., 1998; Carriedo et al., 2000; Dugan et al., 1995) increases ROS production (Dykens, 1994; Peng & Jou, 2010); thus, an initial excitotoxic event might also contribute to increased oxidative stress.

In addition, it is important to consider that mitochondria are not only ROS producers but also that they are a susceptible target of them. Thereby, in a pathologic situation where an increased ROS production occurs initially, oxidative damage to mitochondrial lipids, nucleic acids and proteins can reduce mitochondrial respiration, disturb normal function and seriously damage this organelle (Lenaz et al., 2002). Furthermore, mitochondrial DNA is more susceptible to oxidative damage than nuclear DNA, due to its close location next to an important ROS production site, to the lack of protective histones and to less effective repair mechanisms, as compared to the nuclear DNA (Richter et al., 1988). Mitochondrial redox status also influences the opening of the MPTP, since it is enhanced by oxidative stress in isolated mitochondria (Saxena et al., 1995).

#### **4. Mitochondrial structural damage in ALS and experimental motor neuron degeneration**

The death process involved in the motor neuron loss characteristic of ALS is not yet fully understood. Several functional alterations present in both human disease and experimental models have been reviewed in the previous sections, but several studies have shown also morphological and ultrastructural changes in motor neurons that may be associated with apoptosis and/or necrosis.

Postmortem examination of ALS patients tissues has revealed morphological and ultrastructural abnormalities in mitochondria. Atypical mitochondrial aggregates were found in skeletal muscle subsarcolemmal region and in intramuscular axons (Afifi et al., 1966; Atsumi, 1981), and morphological abnormalities were also detected in proximal axons, as well as dense clusters of mitochondria in the ventral horn of spinal cord SALS patients (Hirano et al., 1984a; b; Sasaki & Iwata, 1996). Giant mitochondria with intramitochondrial inclusions were observed in the liver of some ALS patients and these alterations were disease specific (Nakano et al., 1987). Further, mitochondria with increased volume and with high  $\text{Ca}^{2+}$  concentration were found in motor nerve terminals in muscle biopsies of alive ALS patients, which were not observed in patients with other neuropathies or in control subjects (Siklos et al., 1996). Ultrastructural damage of mitochondria, characterized by swelling and rounding, was recently described in platelets of ALS patients (Shrivastava & Vivekanandhan, 2011; Shrivastava et al., 2011a,b).

The main problem with pathological studies in human ALS is the difficulty in determining whether the alterations observed are a cause or a consequence of the disease. This highlights the importance of developing experimental models of motor neuron death to study the temporal progress of the morphological changes, including the alterations of mitochondrial structure. With this objective, we have recently studied the ultrastructural changes of mitochondria in both our acute and chronic models of spinal motor neuron death described above. In the acute model we observed motor neurons with mitochondrial swelling as soon as 2 h after AMPA perfusion, followed in a few hours by the rupture of mitochondrial, nuclear and plasma membranes, which led to total neuronal disruption. These ultrastructural alterations are characteristic of a necrotic process. In contrast, in the chronic

model we observed by day one swelling of the endoplasmic reticulum and only later progressive alterations in mitochondrial internal and external membranes that generated mitochondrial swelling. So, the initial mitochondrial integrity might indicate an apoptotic process, although motor neurons eventually probably die by a slow necrotic process (Fig. 2; Ramírez-Jarquín and Tapia, in preparation). The mitochondrial swelling observed in both models may be associated with energy failure, which as discussed above causes ATP depletion, oxidative stress and inflammatory events, leading to cell death.

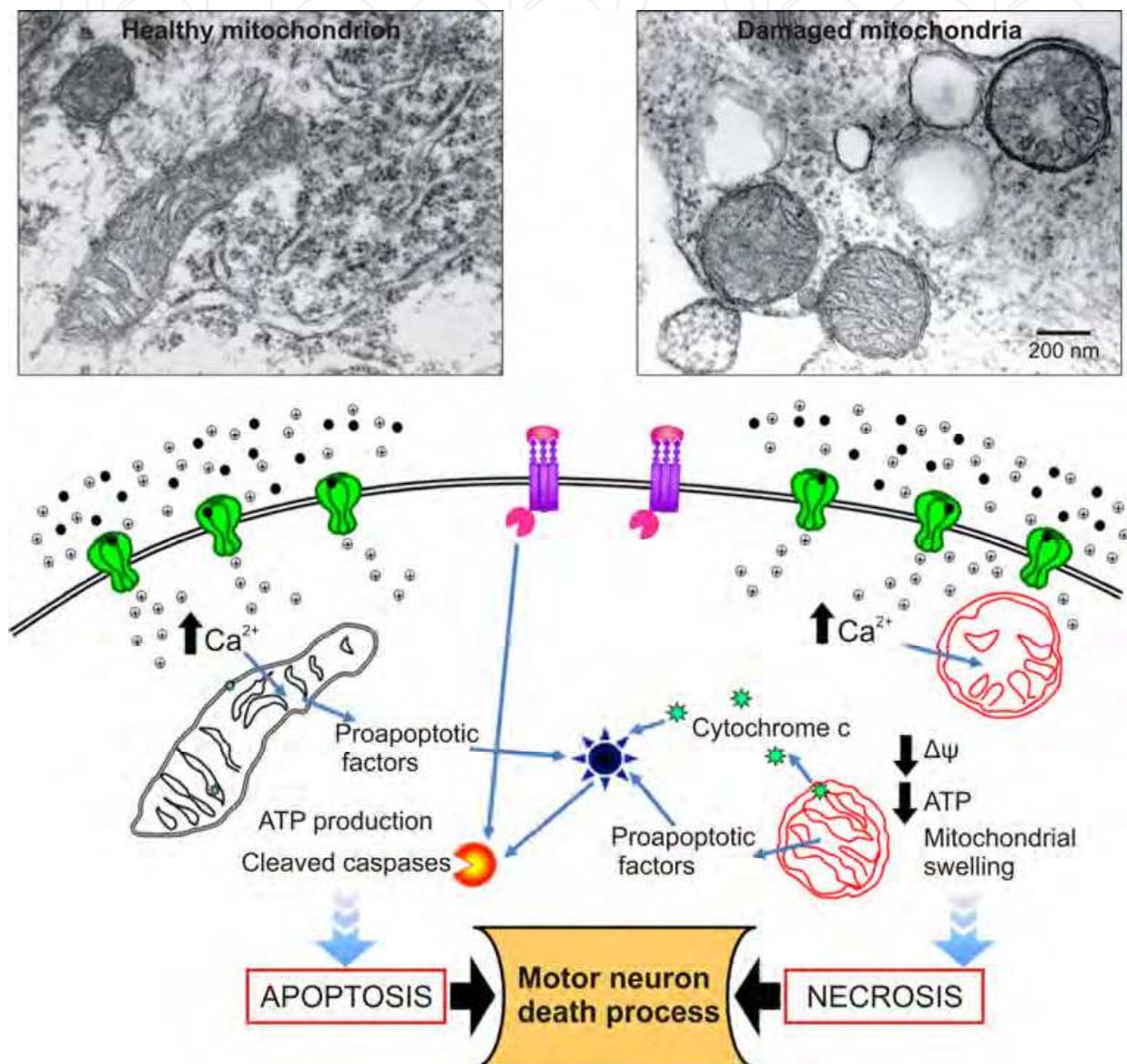


Fig. 2. Role of mitochondrial damage in motor neuron excitotoxicity. The electron-micrographs show normal mitochondria and endoplasmic reticulum in a spinal motor neuron of a control rat (left), and swollen mitochondria with altered cristae observed 2 h after perfusion of AMPA by microdialysis (right) (Ramírez-Jarquín and Tapia, unpublished). Bottom: proposal of the involvement of mitochondrial damage in the apoptosis and necrosis processes leading to motor neuron death. The symbols are the same as in Fig. 1. Description in the text.

The mitochondrial damage seen in our models is similar to those observed in the human disease and also in muscle and spinal cord of mSOD1 rodent models, namely mitochondrial fragmentation, enlargement, vacuolization, rearrangement of the cristae and swelling (Bendotti et al., 2001; Kong & Xu, 1998; Martin et al., 2009; Menzies et al., 2002b; Wong et al., 1995). The observed rearrangement of the inner membrane to form small vacuoles has been associated with an alteration in the MPTP permeability and also with the trigger of intrinsic-apoptosis pathway by release of proapoptotic factors, such as cytochrome c (Bendotti et al., 2001; Martin, 2010; Martin et al., 2009; Ohta et al., 2008) followed by the cleavage of caspases (Li et al., 2000; Pasinelli et al., 2000) Fig. 2 illustrates the ultrastructural mitochondrial damage and shows a schematic representation of the mechanisms associated with these alterations.

## 5. Conclusions

Altogether the foregoing data suggest that mitochondrial respiratory chain damage is a relevant event in ALS pathogenesis, although it is still unknown if mitochondrial abnormalities are the cause of the disease process or if they are consequence of neuronal degeneration. However, it is clear from the evidence reviewed here that mitochondria definitely play a central role in determining the fate of motor neurons and in their degeneration process. This evidence comes from studies in several tissues of ALS patients, both from biopsies or from postmortem observations, and from direct measurements of mitochondrial function in experimental models of motor neuron degeneration, both *in vitro* and *in vivo*. These experiments clearly point to energy deficits and disruption of  $\text{Ca}^{2+}$  homeostasis and axonal transport.

Integrity of the mitochondria morphology and structure is pivotal for their function and for cellular health. It is interesting that similar structural alterations have been observed in ALS tissues and in *in vitro* and *in vivo* models of motor neuron degeneration, including transgenic mSOD1 rodents and excitotoxicity. Clearly, this damage can be associated with the mitochondrial functional deficits, which trigger deleterious process resulting in cellular death by apoptosis, necrosis or a combination of these mechanisms. Although there is biochemical evidence of an apoptotic process involving the mitochondria, no ultrastructural evidence of classic apoptosis, such as apoptotic bodies, has been found. Rather, mitochondrial swelling and membrane disruption are frequently observed, suggesting the predominance of a necrotic process.

The evidence for a role of calcium homeostasis disruption in the induction of neuronal death is vast, and the involvement of mitochondria in this mechanism seems determinant. The advances in the elucidation of this process should help to understand the importance of the preservation of mitochondrial structure and function, which hopefully can lead to the design of preventive and therapeutic measures for ALS.

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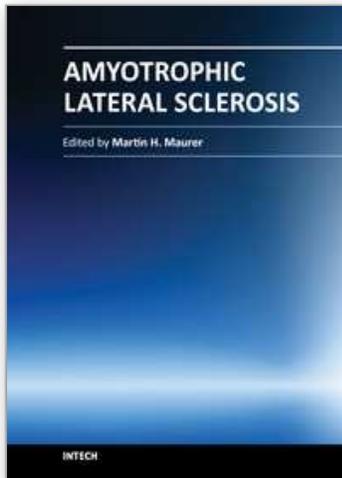
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## **Amyotrophic Lateral Sclerosis**

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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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