Preclinical and Clinical Endeavors Targeting Mitochondria

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by the progressive loss of motor neurons, for which current treatment options are limited. Recent studies have shed light on the role of mitochondria in ALS pathogenesis, making them an attractive therapeutic intervention target.

amyotrophic lateral sclerosis | mitochondrial dysfunction | neurodegeneration

1. Approaches for Direct Enhancement of Mitochondrial Function

Metabolic enhancers represent a compelling class of therapeutic interventions in the context of ALS and other neurodegenerative disorders. These approaches aim to boost cellular energy production and stimulate mitochondrial function. As metabolic deficits are a hallmark feature in ALS, emerging research suggests that enhancing metabolic pathways within mitochondria may hold the key to slowing or mitigating disease progression.

1.1. Dichloroacetate

Dichloroacetate (DCA), investigated in multiple neurodegenerative diseases [1], represents an alternative approach for indirectly enhancing mitochondrial function. As a pyruvate dehydrogenase kinase (PDK) inhibitor, DCA stimulates the conversion of pyruvate to acetyl coenzyme A (AcCoA), supplying additional energy substrates to the TCA cycle.

Administered to mutant SOD1^{G93A} or SOD1^{G86R} mice at 500 mg/kg/day during the pre-symptomatic stage, DCA improved survival, delayed disease onset, reduced spinal motor neuron loss, and enhanced mitochondrial function [2][3]. For example, DCA treatment in SOD1^{G86R} mice not only improved glycolytic capacity but also upregulated the expression of genes associated with mitochondrial biogenesis (e.g., *Pgc-1α* and *Mfn2*), believed to impede disease progression in this animal model [2]. Moreover, DCA (5 mM) improved the mitochondrial function of abnormal glial cells isolated from the spinal cords of adult paralytic SOD1^{G93A} rats, enhancing respiratory capacity and decreasing toxicity to MNs [4].

Additionally, administering DCA (100 mg/kg for 10 days) to symptomatic SOD1^{G93A} rats reduced MN degeneration, gliosis, and the number of GFAP/S100β double-labeled hypertrophic glial cells in the spinal cord. These findings

indicate DCA's potential therapeutic strategy for ALS by modulating glial metabolism and mitigating MN degeneration [4].

However, no clinical trials have assessed DCA effectiveness in ALS patients, necessitating further research.

1.2. Ketogenic and High-Fat Diets

Various dietary interventions aim to delay ALS progression and counteract the hypermetabolism associated with the condition. Two notable approaches include the Ketogenic Diet (KD) [5][6] and the High-Fat Diet (HFD) [7][8][9][10].

A KD, characterized by high fat intake, increases circulating ketones, while restricting carbohydrates and proteins [11][12]. The primary ketones acetoacetate and D-β-3-hydroxybutyrate, produced in the liver, serve as an energy source when glucose availability is limited [13]. Studies report that a KD, comprising 60% fat, 20% carbohydrates, and 20% protein, improves motor function and safeguards MNs in SOD1^{G93A} mice [5][6].

This diet exerts its effects partially through alterations in mitochondrial function, promoting ATP synthesis, and restoring the activity of complex I in the ETC, which is often impaired in ALS [6]. Furthermore, it was demonstrated that caprylic triglyceride, a precursor to ketone bodies, enhanced motor function and protected MNs in SOD1^{G93A} mice by boosting oxidative metabolism, thereby increasing mitochondrial basal and maximum oxygen consumption [5]. Converted rapidly to caprylic acid, it easily traverses membranes, becoming β-oxidized to AcCoA in the mitochondria. Consequently, it supplies ketone bodies to the TCA cycle, serving as a rapid energy source when cellular glucose levels are low. Notably, neither the KD nor caprylic triglyceride significantly altered the survival of SOD1-^{G93A} transgenic mice [5][6].

Regarding the HFD, studies have indicated its potential to slow disease progression in ALS mouse models. One study employing a diet composed of 47% fat, 38% carbohydrates, and 15% protein reduced disease progression in a SOD1^{G93A} mouse model [10]. Similarly, another study utilizing a HFD comprising 21% fat and 0.15% cholesterol extended the mean survival of SOD1^{G86R} mice [7]. To investigate the impact of high-caloric diets on ALS patients, a double-blinded trial known as the LIPCAL-ALS study (NCT02306590) enrolled 201 patients; participants were assigned to receive either a high-caloric fatty diet (HCFD, 405 kcal/day, 100% fat) or a placebo in conjunction with riluzole (100 mg/day). However, the results did not provide conclusive evidence of a life-prolonging effect of the diet on the overall ALS patient population. Nevertheless, post-hoc analysis revealed a significant survival benefit for a subgroup of fast-progressing patients [14]. Given the potential influence of caloric content on the intervention's efficacy, a clinical Phase I LIPCALII study (NCT04172792) is set to explore whether an ultra-high caloric diet (UHCD), featuring twice the caloric content compared to LIPCAL-ALS, can be well tolerated by ALS patients over four weeks and if it can exceed the beneficial effects of LIPCAL-ALS. In another study [15] assessing the effects of a high-caloric nutrition protocol on ALS patients with percutaneous gastrostomy, 40 patients were randomly assigned to either a routine diet (control group) or high-caloric nutrition combined with the routine diet (Ensure group) for six months.

In summary, the mechanisms through which HFD and KD modify ALS disease progression in mouse models are unclear. However, it is suggested that the high fat content of these diets might elevate phospholipids and cholesterol, which are crucial components for axonal membrane assembly and regeneration [16]. In alignment with this hypothesis, it was demonstrated that abnormally elevated cholesterol levels were associated with increased survival in ALS patients, by more than 12 months, suggesting hyperlipidemia as a prognostic factor [17].

1.3. Acetyl-Carnitine

Acetyl-carnitine (ALC) is a crucial cellular source of acetyl groups, particularly in high-energy demanding situations, playing a pivotal role in transporting long-chain fatty acids across mitochondrial membranes and limiting β-oxidation rates [18].

Studies administering 50 mg/kg/day of ALC orally before disease onset significantly delayed symptoms, slowed motor function deterioration, and extended lifespan in mutant $SOD1^{G93A}$ mice; subcutaneous ALC injection to symptomatic mutant $SOD1^{G93A}$ mice improved survival [19].

In a randomized double-blind, placebo-controlled Phase II trial involving 82 patients receiving 3 g/day of ACL or a placebo with riluzole (100 mg/day), ALC demonstrated mild enhancements in ALSFRS score and respiratory capacity. Notably, it doubled the median survival range compared to the placebo group, indicating effectiveness, tolerability, and safety in ALS treatment [20]. A recent study involving 32 ALS patients revealed ALC's improvement in the redox state, persisting six months post-treatment, offering potential disease biomarkers and drug effects indicators in clinical practice and trials [21].

2. Antioxidants

2.1. N-acetyl-L-cysteine (NAC)

N-acetyl-L-cysteine (NAC), a membrane-permeable antioxidant, replenishes cellular cysteine and glutathione pools, mitigating free radical damage [22][23]. In a preclinical study, NAC (1 mM, 24 h) attenuated mitochondrial ROS production, restored MTT reduction rates to control levels, and elevated ATP levels in human neuroblastoma SH-SY5Y cell lines harboring the $SOD1^{G93A}$ mutation [24]. In $SOD1^{G93A}$ transgenic mice, a daily dose of 2.0 mg/kg significantly extended survival and improved motor performance [22]. However, a double-blind, placebo-controlled clinical trial involving 110 ALS patients using subcutaneous NAC infusion (50 mg/kg daily) did not show a substantial increase in 12-month survival or disease progression slowdown [25]. In G93A mice, intranasal NAC administration with the nanocarrier PEG-PCL-Tat significantly increased spinal cord accumulation, extending median survival by 11.5 days. These findings highlight the potential of this approach as a promising Drug Delivery System for ALS therapeutics [26]. However, the potential benefits of NAC in ALS remain uncertain, necessitating further clinical trials in humans. The ability of NAC to traverse the Blood–Brain Barrier (BBB) has been a subject of controversy and is likely influenced by dosage and administration routes [27]. Consequently, multiple NAC derivatives have been synthesized to overcome this limitation. Important examples include N-acetylcysteine ethyl

ester (NACET), which is proposed to improve pharmacokinetics but undergoes rapid transformation into NAC and cysteine resulting low plasma levels [28]; N-acetylcysteine butyl ester (NACBE), which is highly lipophilic and was shown to have superior effects after oxidative insult exposure compared to NAC [29]; and N-acetylcysteine amide (NACA), which was developed to enhance lipophilicity, membrane permeability, and the capability to traverse the BBB [30]. Previous studies have supported the protective properties of NACA, suggesting its potential clinical utility [31].

2.2. Edaravone

Edaravone, the active component of Radicut®, is a potent free radical scavenger widely employed in the treatment of cerebral ischemia in Japan [32][33]. Its neuroprotective role arose from its ability to eliminate lipid peroxides and hydroxyl radicals [34][35]. While the precise mechanisms are not fully understood, it has been proposed that in addition to its radical-scavenging properties, edaravone might inhibit the mPTP, contributing to its neuroprotective effects [36]. It benefits various CNS cell types, including neurons, microglia [37], astrocytes [38], and oligodendrocytes [39], partly attributable to its anti-inflammatory properties [40]. Preclinical studies indicate improved motor function, slowed disease progression, and mitigated motor neuron degeneration in transgenic SOD1 rodent models of ALS treated with edaravone doses ranging from 1.5 to 15 mg/kg [41][42].

In an open-label Phase II study with 20 ALS patients, intravenous administration of edaravone (30 or 60 mg daily) was safe, well-tolerated, and slowed disease progression, as measured by the ALS-FRS scale, during the six-month treatment period compared to the six months before edaravone administration [43]. A subsequent double-blind, placebo-controlled study with 102 ALS patients showed a smaller reduction in ALSFRS-R scores in the edaravone group over a 24-week treatment period [33].

In a recent Phase III study (NCT01492686), a 24-week, double-blind, parallel-group study of edaravone showed less decline in ALSFRS-R scores at 6 months and less deterioration in quality of life in patients receiving edaravone compared to those receiving standard care [44]. Currently, edaravone is approved for ALS treatment in Japan and South Korea and it was also approved by the FDA in May 2017 [45]. However, the precise mechanism of action of edaravone in ALS treatment remains to be fully elucidated.

A Phase I trial of an oral formulation of edaravone (TW001) developed by the Treeway company demonstrated safety, tolerability, and adequate exposure levels [46]. Furthermore, in a Phase III trial (NCT04165824), oral edaravone showed a favorable safety profile in ALS patients after 48 weeks of treatment [47]. A recent meta-analysis [48] suggests potential clinical benefits of edaravone in ALS treatment, with no significant increase in adverse events or deaths in compiled randomized clinical trials. However, more high-quality research is needed for further confirmation due to the small sample sizes in the included studies.

2.3. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine), a neurohormone secreted by the pineal gland, possesses ROS-scavenging activity and amphiphilic properties, permeating both lipophilic and hydrophilic cellular environments [49].

Its potential as an experimental drug has been explored in various neurodegenerative diseases characterized by excessive ROS production owing to its robust antioxidant properties [50].

In addition to acting as a potent free radical scavenger, melatonin augments cellular antioxidant defenses by stimulating vital antioxidant enzymes (SOD, glutathione peroxidase, and glutathione reductase) and elevating GSH levels [51]. Furthermore, melatonin plays a role in preserving mitochondrial homeostasis, decreasing free radical generation, and protecting mitochondrial ATP synthesis by stimulating the activities of complexes I and IV [52].

In transgenic $SOD1^{G93A}$ mice, the oral administration of melatonin (57–88 mg/kg/day) at the pre-symptomatic stage delayed disease progression and extended survival [53]. The same study demonstrated that the rectal administration of 300 mg/day of melatonin in 31 sALS patients was well tolerated over 2 years, reducing circulating serum protein carbonyl levels. However, it did not show upregulation of genes encoding antioxidant enzymes [53]. The decreased oxidative damage in ALS patients under melatonin treatment, coupled with its established safety in humans, emphasizes the need for further clinical trials to elucidate its neuroprotective effects in ALS.

More recently, it was reported that administering melatonin (30 mg/kg) to pre-symptomatic $SOD1^{G93A}$-transgenic mice significantly delayed disease onset, neurological deterioration, and mortality [54]. These effects involved inhibition of the caspase-1/cytochrome c/caspase-3 pathways and the loss of melatonin receptor 1A. Conversely, melatonin administration (0.5, 2.5, and 50 mg/kg, i.p.) to pre-symptomatic $SOD1^{G93A}$-transgenic mice reduced their survival [55].

2.4. Mitochondria-Targeted Antioxidants

One promising avenue in ALS research involves mitochondria-targeted antioxidants, such as 10-(60-ubiquinonyl) decyltriphenylphosphonium, known as MitoQ. This compound features a triphenylphosphonium (TPP) functional group linked to the antioxidant ubiquinone [56] that penetrates biological membranes and selectively accumulates within mitochondria, driven by the $\Delta\Psi_m$ [57]. Positioned within mitochondria, MitoQ effectively shields these critical organelles from oxidative damage [56][58].

Inside mitochondria, complex II reduces the ubiquinone moiety of MitoQ to its active ubiquinol form, bolstering the defense against oxidative damage [58]. Various oxidants can convert ubiquinol back to ubiquinone, efficiently reversed by the respiratory chain [59] and ensuring continual recycling. MitoQ efficiently mitigates oxidative damage in chronic hepatitis C virus patients, decreasing liver damage [60]. Additionally, it has shown promise in neurodegenerative diseases like Parkinson's [61][62] and Alzheimer's [63][64], by decreasing oxidative damage. However, a Phase II clinical trial for Parkinson's disease (NCT00329056) yielded disappointing results [65].

Despite the setback in Parkinson's disease trials, MitoQ has shown potential in ALS; it ameliorated nitroxidative stress and mitochondrial dysfunction in astrocytes expressing $SOD1^{G93A}$, decreasing toxicity to MNs in co-cultures [66]. In $SOD1^{G93A}$ mice, MitoQ (500 µM) administration improved the ALS phenotype by slowing mitochondrial function decline in the spinal cord and quadriceps muscle, increasing the lifespan of the animals [67]. This treatment reduced nitroxidative markers and pathological signs in the spinal cord along with the recovery of neuromuscular

junctions and a marked increase in hindlimb strength [67]. MitoQ rapidly crosses the BBB [63] and is well tolerated in animals and humans [60], with nausea being the most common side effect [68].

These findings underscore the potential of mitochondria-directed antioxidants as a strategy to delay ALS symptoms, warranting further development.

Another mitochondria-targeted antioxidant in ALS research is the mitochondria-targeted carboxy-proxyl (Mito-CP). Like MitoQ, this features a TPP cation covalently coupled to carboxy-proxyl nitroxide, accumulating within mitochondria [69]. Low doses of Mito-CP (1–10 nM) effectively prevented MN death expressing $SOD1^{G93A}$ induced by proapoptotic stimuli that trigger ROS formation [70]. It also prevented mitochondrial dysfunction, decreasing $O_2^{\cdot -}$ production in $SOD1^{G93A}$ astrocytes and promoting MN survival [66].

While these results are promising, further investigations are necessary to explore other mitochondriotropic compounds, focusing on reducing toxicity and enhancing therapeutic efficacy.

In addition, it is crucial to prioritize investment in the development of ALS models that faithfully represent the diverse subtypes of the disease. This approach aims to address the challenge of translating positive effects observed in preclinical trials with antioxidants into meaningful efficacy during clinical trials. These models should serve as robust platforms for conducting preclinical trials before advancing to clinical trials [71]. Human induced pluripotent stem cells have opened avenues to explore therapeutic development relevant to human diseases [72] [73]. An example is the generation of MNs from a patient-derived iPSC line carrying the SOD1-A4V mutation that demonstrated significant disease phenotypes, including proteinopathy, structural attrition, axonopathy, synaptic pathology, and functional defects. This model holds the potential to emerge as a robust preclinical platform for evaluating the therapeutic efficacy of diverse molecules in addressing this disease [74].

3. Antiapoptotic Agents

3.1. mPTP-Targeting Agents

As discussed in Section 2.8, emerging evidence points towards the involvement of mPTP in ALS pathogenesis. Initial studies used CsA, which, when administered intracerebroventricularly (25 µg every other day) at the symptomatic stage in $SOD1^{G93A}$ mice, extended their survival [75]. Similarly, intracerebroventricular administration of CsA (20 µg/mouse/week) in pre-symptomatic $SOD1^{G93A}$ mice delayed the onset of hindlimb weakness, prolonged the time from onset to paralysis, and extended life span [76]. However, it is important to note that CyA struggles to cross the BBB [76][77] and its benefits could be confounded by its immunosuppressant effects due to calcineurin inhibition. Therefore, it is advisable to explore other mPTP inhibitors that lack calcineurin effects.

One such strategy involves mPTP stabilization using cholest-4-en-3-one oxime, known as olesoxime (TRO19622), which binds to VDAC and TSPO [78][79]. Subcutaneous administration of TRO19622 (3 or 30 mg/kg) in pre-symptomatic $SOD1^{G93A}$ mice improved motor function and prolonged survival [80]. Additionally, administration of

TRO19622 (600 mg/kg of food pellets) in pre-symptomatic SOD1^{G93A} mice delayed muscle denervation, decreased astrogliosis, prevented microglia activation, and protected MNs in the lumbar spinal cord, suggesting its potential as a neuroprotective agent to delay ALS neurodegeneration [81]. However, a Phase II–III clinical trial failed to demonstrate efficacy in 512 ALS patients receiving 330 mg TRO19622 daily compared to a matching placebo group receiving 50 mg riluzole twice a day for 18 months. None of the assessed parameters, including slow vital capacity, manual muscle testing, and rates of deterioration of ALSFRS-R scores, revealed a significant clinical benefit of TRO19622 treatment compared with the placebo, except for a minimal increase in the ALSFRS-R global score over 9 months [82]. Several factors may explain the absence of clinical efficacy, including differences in the timing of administration relative to disease onset, the limitations of animal models in predicting clinical outcomes [83], and the need for further investigation into the survival-promoting effects of TRO19622 on human MNs derived from ALS patient induced pluripotent stem cells [84].

Another compound of interest is GNX-4728, a cinnamic anilide derivative that inhibits mPTP opening and has shown promise in the SOD^{G93A} mouse model. Systemic treatment with GNX-4728 (15 mg/kg) in C57BL/6 mice significantly increased mitochondrial calcium retention capacity (CRC) in the heart and brain. Importantly, the increase in CRC in the brain suggests its potential to cross the BBB [85]. Furthermore, systemic administration of GNX-4728 (300 µg every other day, i.p.) in pre-symptomatic SOD1^{G37R} mice delayed disease onset, increased lifespan, protected against motor neuron and mitochondrial degeneration, attenuated spinal cord inflammation, and preserved neuromuscular junction (NMJ) innervation in the diaphragm in ALS mice [85].

These findings highlight the potential of mPTP-targeting agents as a therapeutic approach in ALS, with the need for further research to optimize their clinical translation.

3.2. Rasagiline

Rasagiline, a monoamine oxidase B inhibitor primarily used to treat Parkinson's disease [86][87], has shown neuroprotective properties beyond its MAO inhibitory activity [88]. In vitro studies suggest its neuroprotective role, partly mediated by anti-apoptotic properties [89][90][91]. Rasagiline may protect mitochondria by preventing mPTP opening, inhibiting caspase 3 activation [90], or by upregulating the anti-apoptotic Bcl-2 and Bcl-xL genes and downregulating the pro-apoptotic Bad and Bax genes [91].

In ALS, oral rasagiline (0.5–2 mg/kg/day), administered alone or with riluzole (30 mg/kg/day) at the pre-symptomatic stage, improved motor performance and extended survival in SOD1^{G93A} mice [92]. A Phase II clinical trial involving 23 ALS patients receiving rasagiline (2 mg/day) showed increased $\Delta\Psi_m$ and oxygen radical antioxidant capacity (ORAC) in lymphocytes and a decrease in the apoptotic marker Bcl-2/Bax ratio [93]. While this trial did not find significant improvements in the rate of ALSFRS-R score decline, it did identify differences in symptom duration among patients administered who received rasagiline compared to placebo controls (NCT01232738) [93]. This raises the question of whether rasagiline-induced mitochondrial changes could slow motor function decline and extend ALS patient survival.

However, another Phase II clinical trial involving 80 ALS patients receiving rasagiline (2 mg/day for 12 months) did not demonstrate improvements in mitochondrial and molecular biomarkers ($\Delta\Psi_m$, ORAC, and Bcl-2/Bax ratio) or differences in the average 12-month ALSFRS-R slope between the rasagiline and placebo groups. Variability among patients and differences in sample processing timing at various centers involved in this clinical trial (NCT01786603) may explain the discrepant results regarding rasagiline's impact on mitochondrial markers [94].

Post-hoc analysis of a Phase II clinical trial involving 252 patients (NCT01879241) suggested that 1 mg of rasagiline, in addition to riluzole (100 mg/day), could slow disease progression in patients with normal to fast disease progression. This effect was observed in function (ALSFRS-R decline at 6, 12, and 18 months) and survival (at 6 and 12 months) [95].

In conclusion, rasagiline's effects in ALS research reveal its complex potential as a therapeutic agent, with varying outcomes in clinical trials. Further research and careful patient stratification are essential to unlock its full therapeutic benefits in ALS treatment.

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