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Research paper

Therapeutic progress in amyotrophic lateral sclerosis-beginning to learning

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease associated with motor neuron degeneration, muscle weakness, paralysis and finally death. The proposed mechanisms of ALS include glutamate excitotoxicity, oxidative stress, inflammation, mitochondrial dysfunction, apoptosis and proteasomal dysfunction. Although numerous pathological mechanisms have been explained, ALS remains incurable disease because of failure of clinical trials and lack of any effective therapy. The rapid advancement in genetic discoveries in ALS emphasizes the point that ALS is a multi-subtype syndrome rather than a single disease. This can be argued as one of the single reason why many previous therapeutic drug trials have failed. Efforts to develop novel ALS treatments which target specific pathomechanisms are currently being pursued. Herein, we review the recent discovery and preclinical characterization of neuroprotective compounds and compare their effects on disease onset, duration and survival. Furthermore, the structure-activity relationships of these agents are analyzed with the overall goal of developing a screening strategy for future clinical applications.

1. Introduction

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a common motor neuron disease initiated by the loss of motor neurons in brain and spinal cord [1]. It progresses to muscle weakness and paralysis and ultimately to death due to respiratory failure by 2–5 years after diagnosis [2,3]. It occurs with an incidence of 1–2 in 100,000 individuals per year, with about 90% cases being sporadic (sALS) and 10% cases are characterized as familial (fALS) [4]. Several gene mutations have been identified that contribute to this disorder with more than 20% of fALS cases being linked to mutations in the Copper/Zinc Superoxide Dismutase 1 (SOD1) gene [5]. Recent studies have identified expanded repeats in an on coding region of chromosome 9 open reading frame 72(C9orf72) as the most frequent genetic cause of ALS [6].

Rapid advances in genetic studies enable the identification of new genes contributing to ALS pathogenesis. However, no effective treatment is currently available for ALS. Patient care focuses exclusively on symptomatic treatments and physical therapy. Riluzole, an anti-glutamatergic agent that blocks the presynaptic release of glutamate, is the only Food and Drug Administration (FDA)-approved drug for the treatment of ALS [7]. However, the efficacy of riluzole is questionable, with minimal therapeutic benefits of about 3–4 months of survival increase [8–11]. Thus, while there remains a major push towards identification of the new genetic factors underlie ALS; there is an urgent need to convert the genetic information we already have into effective therapy for this syndrome.

The etiology of ALS like other neurodegenerative diseases is highly multifacorial [1,12,13], being associated with but not limited to, glutamate-induced excitotoxicity, oxidative stress, inflammation, loss of neurotrophic factors, protein misfolding and aggregation, deficient protein quality control, and mitochondrial dysfunction [14]. Despite multiple preclinical studies and clinical trials, the exact mechanism of disease pathogenesis and disease progression is still largely unknown; thus, the development of targeted and effective therapy remains one of the significant issues scientists face today to treat ALS.

Recently, a retrospective review providing the overview of drug discovery in ALS has been published [15]. This review focuses on the recent advances in ALS drug discovery and highlights why drug development is proving to be so difficult in ALS. This review also highlights the importance of preclinical models from *in vitro* to in vivo translation and emphasized the importance of

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combinatorial therapy for ALS drug discovery. Another general but broad review by Mancuso et al. [16] discusses extensively the various aspects of ALS ranging from the diagnostic and evaluation methods to pathophysiology and clinical findings in ALS with emphasis on pathomechanisms of disease and the development of new therapeutic strategies.

In this review we summarize some of the known cellular pathways contributing to the disease pathology and the neuroprotective agents currently being developed to target these pathways (Fig. 1). Table 1 summarizes the drug trials discussed and clinical trial outcome. We also try to examine whether the outcomes of ALS mouse models translate well through human clinical trials. We also analyze the structure-activity relationships of some agents with the aim to developing a screening strategy for future applications in ALS drug discovery. Furthermore, we discuss the potential for different non-pharmacological therapy to connect disease modelling and drug discovery.

2. Pharmacological strategies in ALS

2.1. Excitotoxicity in ALS and therapeutic strategies

The main excitatory neurotransmitter in the central nervous system (CNS) is glutamate. Excessive activation of glutamate receptors and failure in the clearance of neurotransmitter from the synaptic cleft or increased post-synaptic sensitivity to glutamate results in accumulation of the excitatory mediators that cause injury to neurons. Such neurotoxicity due to excitatory mediators is called excitotoxicity [17,18]. This activation induces huge influx of calcium ions that damages the cell through activation of proteases, lipases and nucleases [19,20]. In fact, excitotoxicity is also responsible for other features of ALS, such as calcium disruption, activation of proteolytic and reactive oxygen species producing enzymes, mitochondrial dysfunction and energy imbalance [21]. A large number of evidences implicated excitotoxicity as a mechanism involved in causing injury to motor neurons in ALS but its involvement as a primary disease mechanism is still unknown. The increase in glutamate levels in ALS patients [22,23] and the benefits of riluzole as an anti-excitotoxic drug [8] suggest an important role of excitotoxicity in ALS.

Damaging effects of excitotoxicity are mainly mediated through calcium-dependent pathways. A possible explanation for the role of excitotoxicity is that ALS-susceptible spinal and brain stem motor neurons has decreased Ca^{2+} buffering capacity, making them more vulnerable to excitotoxicity [24,25]. Increase activation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors is considered to be one of the main causes of excitotoxicity [25]. It was demonstrated that motor neurons are especially vulnerable to AMPA-mediated excitotoxicity *in vitro* [26], while some evidence also suggest the contribution of NMDA-receptor to excitotoxicity in ALS [27]. Moreover, Sunico et al. [28] have shown an excitatory imbalance in motor neurons of $SOD1^{G93A}$ mice, a mouse model of ALS with an increased density of glutamatergic synapses, which could lead to an excitatory imbalance. As mentioned earlier, excitotoxicity can also occur if the clearance of glutamate from the synaptic cleft is altered. The excitatory amino-acid transporters (EAATs) located at the synaptic junction in CNS translocate glutamate from the synaptic cleft into astrocytes [29]. ALS pathogenesis also results in defect in glutamate transport in the motor cortex and the spinal cord of ALS patients, especially affected astroglial specific EAAT2 [30]. Furthermore, loss of EAAT2 has also been reported in mutant SOD1 models of ALS [31,32]. Mutant SOD1 can directly alter calcium homeostasis. Misfolded A4V SOD1 aggregates form pores that integrate in the membrane resulting in calcium influx [33], suggesting that mutant SOD1 can contribute to excitotoxic damage without contribution of other glutamatergic-related elements. Below we summarize a number of neuroprotective agents targeting excitatory pathways in ALS (see Table 1).

As pointed out earlier, riluzole **(1)** inhibits the release of glutamate and noncompetitively inhibits post-synaptic NMDA and AMPA receptors, as well as activating a G-protein dependent signal transduction process. Thus slows down disease progression in $SOD1^{G93A}$ transgenic mice [10] and significantly increase patient's

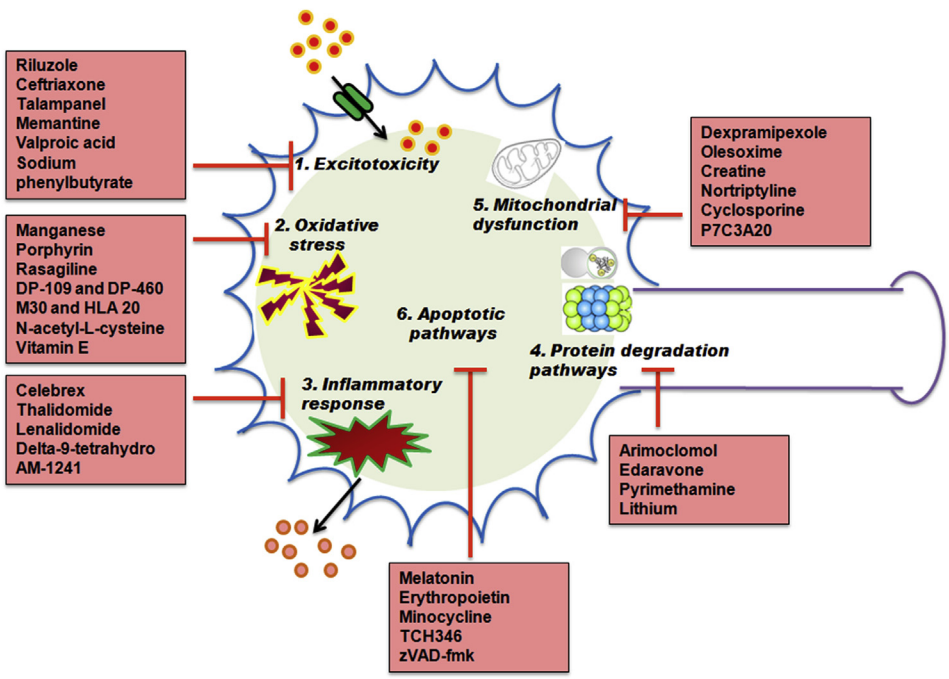

Fig. 1. Neuroprotective agents and their target in the pathogenic pathways in ALS.

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