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Review Article

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Neurodegenerative Multioethiology Lou Gehrig's Disease – Genetic Mutations, Pharmacological Mechanisms and Applications of Rilusole

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ABSTRACT

The most severe motor neuron degenerative illness is Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's disorder). The aims of the current study are 1) a comparison of genetic and other factors for disease development, 2) an estimation of pharmacological mechanisms of Rilusole for its applications against different diseases; 3) the combinations for the symptomatic treatment of stages ALS progression stages. The investigation has been made through the existing electronical database of medical sources. The most common risk factors for ALS are mutations in genes for SOD1, SETX, FUS, VEGF, VAPB, ANG, TARDBP, FIG4, OPTN, ATXN2, VCP, UBQLN2, SIGMAR1, CHMP2B, PFN1, ERBB4, HNRNPA1, C9orf72, dynactin 1, H46R, A4V. Other risk factors are oxidative stress, glutamate toxicity, autoimmune, protein aggregation, inflammation, and viral infections. Pharmacological effects of Riluzole are a result of the mechanisms of action 1) depression of repetitive firing frequency; 2) suppression of persistent sodium current in motoneurons; 3) potentiation of calcium-dependent potassium current; 4) presynaptic reduction of neurotransmitter release; 5) suppression of postsynaptic neurotransmitter receptor responses. Applied combinations of Riluzole with antioxidants: vitamin E, vitamin C, coenzyme Q_{10}, creatine, and selenium can be used for ALS therapy. For symptomatic therapy nonsteroidal anti-inflammatory drugs are used and opioids for pain and Baclofen and Dantrolene for spasticity. Memantine, Nimesulide, and Gabapentin are considered to be appropriate for further investigations. Due to different mechanisms of action, Riluzole is applied against ALS, Parkinson, Huntington, Machado-Joseph's disease, multiple sclerosis, spinal muscular atrophy, anxiety, autistic, depression, and schizophrenic disorders.

Key words: *Amyotrophic Lateral Sclerosis, Mutations, Riluzole, Pharmacological mechanisms*

INTRODUCTION

The hallmark of neurodegenerative diseases such as Alzheimer, Huntington, Lou Gehrig, Lewy body dementia, multiple sclerosis, and mitochondrial disorders as Friedreich's ataxia and Leber's neuropathy, is the progressive malfunction of the nervous system accompanied by atrophy of the structure or function of neurons or the death of neuronal cells [1, 2]. The pathogenetic mechanisms of progressive neurological degeneration of the central nervous system are: mitochondrial disorders [3], oxidative stress [4] aggregation of proteins [5], membrane damage, and apoptosis [1].

Beta-amyloid [6, 7] and alpha-synuclein fragments, as well as hyperphosphorylated tau protein, make up the majority of neurofibrillary tangles in Alzheimer's disease, or senile plaques [6]. Alzheimer's disease with Lewy bodies, Parkinson's disease, and multiple system atrophy are all conditions where alpha-synuclein accumulates [5, 8].

Different trends for treatment of Alzheimer's disease have been applied [9] and one of the very important is acetyl-cholinesterase inhibitor Galantamine [10] with antioxidant activity [11]. As anti-Alzheimer agents are being investigated phenacyl derivatives of 9-aminoacridine [12, 13], and new synthesized 1.3-di-4-piperidylpropane derivatives with acetylcholinesterase-inhibiting properties [14]. Primary lateral sclerosis is caused from the degeneration of higher motor neurons and progressive muscular atrophy is a result from damage in lower motor neurons [15].

Amyotrophic Lateral Sclerosis (Charcot disease) [16] is characterized with the severest motor neuron disfunction, which leads to atrophy, or paralysis of the voluntary muscles in the hands, arms, and legs, as well as dysarthria and dysphagia. The upper and lower motor neurons gradually become dysfunctional and die, which causes damage to the voluntary muscles, paralysis, and the loss of senses such as sight, hearing, touch, and taste. This is what Lou Gehrig's disease is known for. Abdominal, bulbar (mouth and throat), leg, and thoracic muscles all gradually atrophy as a result of the condition, causing cramps, discomfort, paralysis, weakness, and stiffness. Bulbar signs, such as dysarthria (speech disorder) and dysphagia (swallowing difficulty), appeared in the latter stages of the illness.

The most prevalent motor neuron illness, Lou Gehrig's disease, is more frequent in men. It affects people of all racial and ethnic origins: 2 people for 100000 per year in Europe [17], in Caucasian populations [18] it is estimated 4 cases per 100000, and in Filipinos 3 per 100000. Cognitive dysfunctions occur in 20% -50% of cases and dementia is developed in 5%-15 % of patients [19]. Some of the important data for Amyotrophic Lateral Sclerosis are shown in **Table 1**.

Table 1. Important data for Amyotrophic Lateral Sclerosis [17, 19].

1824	The descriptions of the disease by Charles Bell
1850	The discovery of shriveled nerve fibers by the English scientist Augustus Waller
1869	Firstly, a description of the connection between the symptoms and the neurological problems by Jean-Martin Charcot [19]
1874	Introduction of the term Amyotrophic Lateral Sclerosis from Jean-Martin Charcot [19]
1941	The death from ALS of baseball player Lou Gehrig [19]
1950	ALS epidemic occurred among the Chamorro people on Guam
1993	The discovery of mutations of the SOD1 gene on chromosome 21 for familial ALS (FALS) [19]
1996	The first ALS treatment authorized by the FDA is riluzole [20].
1998	The creation of criteria to serve as the industry standard for categorizing ALS in clinical research [18]
2011	Frontotemporal dementia and ALS have both been linked to noncoding repeat expansions in the C9ORF72 gene [21].

The disease starts around 60 years of age and in inherited cases at around 50 [17]. Lower motor neuron degeneration's initial signs and symptoms include muscular cramping in the arms or legs, weakness, atrophy, hyporeflexia, and hypotonicity. Unusual symptoms include dementia and pain [22]. Depending on the site of neuronal degeneration, a patient exhibit initial bulbar symptoms (speech, swallowing, and chewing difficulties) and limb symptoms (fatigue and weakness). Weakness, delayed movement, stiffness, pathological reflexes, increased reflexes (hyperreflexia), and an aberrant Babinski's reflex are signs of upper motor neuron injury. Approximately 45% of people suffer from defeneration of upper motor neurons (pseudobulbar affect), which is accompanied by uncontrollable laughing, and sobbing. This condition causes an amplification of motor displays of emotion. Frontotemporal dementia, a respiratory condition, and bulbar dementia all have a quicker rate of deterioration. The most frequent ALS-causing mutation in North America is the mutant SOD1 gene, which is characterized by a quick transition from start to death. Younger people under 40 who are somewhat obese and have symptoms exclusively in their upper motor neurons are known to have a slower problem development [23]. The most prevalent mutation in Scandinavian nations is D90A-SOD1, which has a moderate rate of advancement and an 11-year survival rate. Mutation in gene forAsp90Ala CuZn-superoxide dismutase is related to the development of autosomal recessive type of the disease [24].

The inability to move, swallow (dysphagia), talk or form words (dysarthria), and lose tongue movement all progress with time. The oculomotor nerve that regulates the motions of the eye is impacted in the late stages by ophthalmoplegia (a loss of neurons in and around the ocular motor nucleus), making it difficult to produce quick voluntary eye movements and slowing down eye movement speed [25].

In later stages of the disorder increases the risk of development of aspiration pneumonia and loss of breathing due to affected intercostal muscles that support breath. Respiratory failure, which occurs when intercostal muscles that assist breathing are impacted by nerve injury, is the most prevalent cause of mortality. After diagnosis, the usual survival period is three to five years, with a 10-year survival rate of 10%. From the time of diagnosis until death, the median survival time is around 39 months, and only 4% of patients live for more than 10 years. Even though physicist Stephen Hawking has lived for more than 50 years, this situation is exceptional. In ALS, cachexia develops without significant muscular loss [26].

Frontotemporal dementia develops in 5% of ALS. Of all cases, up to 90%-95% are sporadic and 5%-10% are familial forms inherited from parents [17] with mutations in 40 ALS-related genes. 10% to 20% of hereditary ALS cases and 7% of spontaneous ALS cases, respectively, are caused by mutations in the copper-zinc superoxide dismutase gene [24]. Gene mutations in TARDBP and FUS/TLS account for around 8% of familial ALS cases and 1% of sporadic ALS cases [27].

Astrocytes cause toxic effects on the motor neurons. The autosomal dominant transmitted mutation in astrocytes on chromosome 21 [28, 29], which codes for the antioxidant Cu-Zn superoxide dismutase (SOD1) enzyme, was found to be the cause of 20% of familial ALS diseases in 1993. This enzyme prevents the organism from oxidative stress, which is a result of the formation of superoxide radical in the mitochondria. A SOD1 deficiency results in a lack of SOD1 function, which triggers a buildup of superoxide and damages cells' DNA and proteins [24]. SOD1 has more than 110 distinct mutations, with H46R having a protracted clinical course and A4V having an aggressive nature. The most common cause of sporadic forms of ALS are mutations on chromosome 9 (C9orf72) and FUS protein aggregates [27].

The genetic abnormality in the gene C9orf72 leads to hexanucleotide repeat and is associated with a 2011 discovery in 6 % of Europeans and Filipinos of ALS combined with frontotemporal dementia (ALS-FTD) [21]. The most common forms of ALS and their associated mutations are presented in **Table 2**.

Table 2. Forms of ALS and their associated mutations

1	ALS1	SOD1 [24]	10	ALS13	ATXN2
2	ALS2	ALS2	11	ALS14 [29]	L106F
3	ALS4	SETX	12	ALS15 [30]	UBQLN2
4	ALS6	FUS [27]	13	ALS16 [31]	SIGMAR1
5	ALS8	VAPB	14	ALS17	CHMP2B
6	ALS9	ANG	15	ALS18 [32]	PFN1
7	ALS10	TARDBP [27]	16	ALS19 [33]	ERBB4
8	ALS11	FIG4	17	ALS20 [34]	HNRNPA1
9	ALS12	OPTN	18	ALS-FTD [21]	C9orf72

Gene mutations VEGF at chromosome 6p21.3 (VEGF121, VEGF145, VEGF 165, VEGF 183, VEGF 189, VEGF206) [35] decrease vascular perfusion, leading to:

1. Mitochondrial reactive oxygen and nitrogen species are produced as a result of an oxygen shortage (hypoxia) [36].
2. Decreased glucose levels (limited energy production for cells).

The effects resulting from some gene mutations in ALS are summarized in **Table 3**.

Table 3. Effects from gene mutations in ALS.

Gene mutation	Effect
Superoxide dismutase 1 (SOD1) [24]	familial ALS (FALS)
CHMP2B (charged multivesicular protein 2B) [37]	involved in cellular transport
VEGF at chromosome 6p21.3 [35]	deficiency of oxygen [36]
VAPB - vesicle-associated membrane protein B [38]	providing protein response to the endoplasmic reticulum
dynactin 1 [39]	involved in the axonal transport of nerve cells
SETX - senataxin	role in DNA repair in the brain and muscle
Angiogenin [40, 41]	role in neovascularisation

In the multifactorial etiology of ALS other risk factors include [19]:

1. Lead, cadmium, and arsenic, as well as organophosphates, electromagnetic fields, smoking, consuming glutamate-rich and high-fat diets, and mitochondrial dysfunction, are variables that contribute to systemic oxidative stress by producing free radicals [42].
2. Glutamate toxicity – the excessive release from presynaptic nerve terminals in the CNS of excitatory glutamic acid
3. Lack of trophic growth factors
4. Aggregates of insoluble intracellular proteins in astrocytes and motor neurons [43]
5. Autoimmune-mediated attack
6. Susceptibility of motor neurons to neurodegeneration
7. Protein aggregation, inflammation, cytoskeletal abnormalities
8. Viral infection

Reactive oxygen species are byproducts of mitochondrial respiratory chain activity, and the quantity of these substances is controlled by the mitochondrial antioxidants manganese superoxide dismutase and glutathione peroxidase. Oxidative stress which is characterized with the loss of equilibrium between the formation of free radicals and mitochondrial antioxidants, is a significant contributing factor to neurodegenerative diseases. One of the key pathophysiological processes involved in the development of neurodegenerative illnesses is oxidative damage to proteins, nucleic acids, and lipids [4, 5].

It has been found that there is a dynamic balance between free radical formation and the function of protective antioxidant systems (superoxid dismutase, catalase, glutathione-peroxidase, glutathione-reductase, glucose-6-phosphate dehydrogenase). The increased levels of free radicals lead to oxidative stress, which is at the base of the pathogenesis of severe diseases [44]: autism [45], atherosclerosis, diabetes type 1 and 2, Daun syndrome [46], hypertension, schizophrenia, vascular diseases, macular degeneration [47], psoriatic arthritis [48], neurodegenerative diseases [49]: Alzheimer Alzheimer [50, 51], Parkinson, Huntington, amyotrophic lateral sclerosis (Lou-Gerich's disease) [19]. Because it consumes a lot of oxygen, has unsaturated fatty acids, and has low levels of endogenous antioxidant systems, the brain is particularly vulnerable to the effects of free radicals. In ALS and Alzheimer's disease, oxidative stress develops as a result of an imbalance between endogenous or exogenous overproduction of reactive free radicals and the decline of antioxidant protection systems [52].

Increased reactive oxygen and nitrogen species (ROS, RNS) harm the motor neurons' cellular components as well as the cells around them, causing motor neuron degeneration in sporadic ALS [52-54]. CSF, plasma, and urine levels are all raised in ALS. Indicators of enhanced lipid peroxidation include the DNA damage marker 8-hydroxy) deoxyguanosine (8-oxodG) [53] and the product 4-hydroxy-2,3-nonenal [52], which is raised in the serum.

The only drug approved by the Food and Drug Administration in 1995 for therapy of ALS is the neuroprotective agent Riluzole [54], which also slows the progression of disease symptoms [55], lengthens survival [56, 57] by increasing the median survival time [58] in both the long-term and short-term survival periods [59], and slows the progression of the disease [60]. Long-term drug usage improves the prognosis for the sporadic type of the condition [61].

Excessive excitatory glutamic acid release from presynaptic nerve terminals in the central nervous system, which causes excessive postsynaptic glutamate receptor activation (also known as "excitotoxicity"), is a significant risk factor for ALS. [62]. The glutamate receptor-gated ion channels the sodium ion influx into neurons is increased and induces the overproduction of free radicals, resulting in degeneration, necrosis, and apoptosis of motor neurons [19].

The mechanism of action of Riluzole has included the activation of the G-protein-dependent process, inhibiting the presynaptic release of glutamic acid. By noncompetitive blockage of the N-methyl-D-aspartate receptors the drug inhibits the postsynaptic effects of glutamic acid and this action reduces the effects of glutamate on motor neurons. Reduced cerebral glucose consumption is a result of Riluzole's neuroprotective action, which enhances resistance to hypoxia by inactivating voltage-dependent sodium channels on glutamatergic terminals [63].

For slowing the progression of ALS are important the low dose (< 1-10 μM) effects of Riluzole, including [63]:

1. depression of repetitive firing frequency [64]
2. suppression of the persistent sodium current in motoneurons, which increasing is associated with neuronal hyperexcitability
3. potentiation of calcium-dependent potassium current

4. presynaptic reduction of neurotransmitter release
5. suppression of postsynaptic neurotransmitter receptor responses.

The mechanisms for the reduction of neurotransmitter release by Riluzole (1-20 μM) are [63]:

1. inhibition of voltage-gated presynaptic calcium channels (10-40 μM) and decrease of presynaptic calcium influx
2. reduction of fast and persistent sodium currents, leading to the suppression of presynaptic terminal excitability.

Enhancement of calcium-dependent potassium currents is observed from Riluzole (2-20 μM). The high dose (20-100 μM) effects of Riluzole include the inhibition of voltage-gated potassium current [63]. The recommended dose of the drug is 50 mg twice daily and is applied in oral tablets [65] and in oral 5 mg/ml suspension [66].

Neurodegenerative Parkinson's and Huntington's diseases, atypical parkinsonism, and hereditary ataxia, which are characterized by neuron loss and clinical motor symptoms [67, 68], can be effectively treated with Rriluzole [69, 70]. The drug is effective in early Parkinson's disease and dyskinesia and duration of the state in Parkinson's disease [71, 72]. In Huntington's disease, the drug protects from brain glucose hypometabolism and increases the production of neurotrophins [73]. Riluzole is applied in patients with cerebellar ataxia [74], hereditary cerebellar ataxia [75], and ataxia type 3 [76].

The most prevalent autosomal dominantly inherited ataxia in the world [77, 78] and a spinocerebellar ataxia type 3 called Machado-Joseph's disease are polyglutamine diseases that also include Huntington's disease, dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy, and spinocerebellar ataxia types 1, 2, 3, 6, 7, and 17 [79].

As a glutamate receptor blocker, the drug can be applied for the therapy of childhood obsessive-compulsive disease and psychiatric disorders [80]. Children with persistent schizophrenia [81] and autistic disorder [82] who are irritable can be treated with riluzole as an additional therapy to risperidone. By the inhibition of the excessive amount of glutamate, the drug prevents memory loss in elderly patients. The anti-glutaminergic action of Riluzole reduces the amino acid neurotransmission in mood and anxiety disorders [83]. The drug possesses antidepressant-like properties [84].

In multiple sclerosis, by blocking the excessive glutamate, Riluzole controls the transmission of information between neurons [85]. Since glutamate-related excitotoxicity contributes to the pathology of neuromuscular disease Spinal Muscular Atrophy [86], a glutamate receptor blocker Riluzole is effective against this disease. For acute spinal cord injury and early cervical myelopathy, the medication may be used as a pharmacotherapeutic therapy option [87, 88].

The potential benefit in the treatment of ALS is the combination of Riluzole with antioxidants: vitamin E, vitamin C, coenzyme Q_{10}, [89] a combination of L-methionine, vitamin E, and selenium. Creatine with antioxidant and neuroprotective properties and may enhance mitochondrial function [90]. Lithium delays the progression of amyotrophic lateral sclerosis too [68].

For the therapy of pain in Lou Gerich disease, they are used as nonsteroidal anti-inflammatory drugs and opioids [91] and Baclofen and Dantrolene are applied for spasticity. The agents considered appropriate and suitable for further investigation in patients with ALS are Memantine, Nimesulide, and Gabapentin [17].

CONCLUSION

Amyotrophic Lateral Sclerosis is the most severe degenerative disease of the upper and lower motor neurons. Risk factors are genetic mutations, oxidative stress, glutamate toxicity, lack of trophic growth factors, autoimmune-mediated attack, protein aggregation, inflammation, cytoskeletal abnormalities; viral infection.

Riluzole protects against memory loss, has antidepressant-like qualities, and is used to treat chronic schizophrenia, autistic disorder, Parkinson's disease, and hereditary ataxia as an adjuvant therapy to risperidone. It is also used to treat amyotrophic lateral sclerosis, Parkinson's disease, and hereditary ataxia.

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