

Advancement of Riluzole in Neurodegenerative Disease

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ABSTRACT

Riluzole (Rilutek®) is currently achieved using off indication among the treatment of medical conditions in adult patients and a lot of and a lot of children. The scientist has gained more interest in the excitotoxic hypothesis in neurodegenerative disease. Riluzole blocks glutamatergic neurotransmission and inhibits the liberation of aminoalkanoic acid from corticostriatal neurons *in-vivo*. The effects of riluzole may be due to the effect of aminoalkanoic acid that results in the inactivation of voltage-dependent metal channels terminals in resemblance with the activation of a G-protein-dependent signal transduction technique along with the blocking of postsynaptic effects by accommodating blockade of N-methyl-D-aspartate (NMDA) receptors. Riluzole has neuroprotective properties which is responsible for the inhibition of the ischemia-evoked surge in aminoalkanoic acid that effect the glutamic-acid-uptake inhibitors.

Keywords: Riluzole, ALS, glutamate receptors, neurodegenerative diseases.

INTRODUCTION

Neurodegenerative disease could be a state of failure of formation of the nerve cell, at the side of death of neurons within the human brain¹. The core pathological mechanism is the deposition and aggregation of misfolded proteins² within the brain that results in progressive neurodegenerative illness. Though the region yet as cellular distribution and deposition of the collective proteins could vary from illness to illness, there are some links in between the illness within the pathways of super molecule aggregation. Most of the neurodegenerative illness with unknown etiology effects in aged patients. Genetic predisposition, environmental factors and aging are the most risk³ factors. The neurodegenerative illness is incurable, however illness progression is controlled.

There are completely different numbers of medication that is employed within the treatment of neurodegenerative illness; a number of the vital medicine is listed in Table I.

This article briefly reviews the advancement of Riluzole in the treatment of Neurodegenerative disease, including Amyotrophic Lateral sclerosis (ALS), and Parkinson's disease (PD) affects the people at the age above 50.

Riluzole

RILUTEK® (Riluzole), C₈H₅F₃N₂OS characterized under 4-benzothiazole category, with chemical named as 2-amino, 6-(trifluoromethoxy) benzothiazole with a molecular weight of 234.2g/mol. The melting point of the compound is found to be 119°C. The structure of riluzole is represented in Fig 1.

Riluzole could be a neuroprotective drug during which the mechanism of action is unknown. It'll block the

glutamatergic somatic cell transmission in the brain by inhibiting the discharge of aminoalkanoic acid from CNS. This mechanism blocks the post conjugation effects of aminoalkanoic acid by blocking NMDA receptor and activation of a G-protein dependent signal transduction process. It will also block the post synaptic effects of glutamic acid by the non competitive blockage of NMDA receptor⁶.

Riluzole is absorbed approximately 90%, with average absolute oral bioavailability of 60%. It will show a linear pharmacokinetics over a dose range of 25-100 mg administered every 12 hours. Fat meals will decrease the absorption. The plasma protein binding is 96% with a mean elimination half life of 12 hours after multiple doses. At least 80% of the drug being hepatically metabolized through primary metabolic pathway consisting of cytochrome P450-dependent hydroxylation and glucuronidation. The excretion is mainly through urine (90%) and through feces (5%)⁷.

Advancement of riluzole

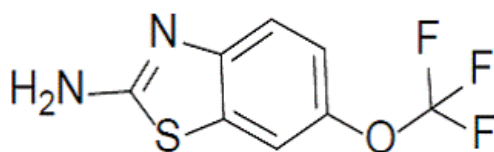
Amyotrophic Lateral sclerosis

Amyotrophic Lateral sclerosis (ALS) is characterized by weakness in the limb muscles with spasticity, atrophy weight loss and lead to the respiratory failure. There is a combination of progressive loss of upper motor neurons of the corticobulbar tract, corticospinal and lower motor neurons, which is localized in the brain stem as well as an anterior region of the spinal cord. The symptoms usually seen in smaller age, but it may become (apparent) before the age of 30 or after the age of seventy⁸. The onset of ALS is either by bulbar or spinal. The main symptoms of bulbar form include dysarthria and dysphagia. Asymmetric muscle paresis and muscle wasting either in the distal or,

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Table I: Drugs used for Neurodegenerative disease⁴.

Drugs	Therapeutic uses
Amantadine	Parkinson's disease
Aripiprazole	Schizophrenia
Benzatropine	Parkinson's disease
Clozapine	Schizophrenia
Donepezil	Alzheimer's disease
Galantamine	Alzheimer's disease
Rivastigmine	Dementia
Riluzole	Amyotrophic Lateral sclerosis
Olanzapine	Schizophrenia
Levodopa	Parkinson's disease

Figure 1: Chemical structure of Riluzole⁵.

less frequently, in proximal area are the main limb symptoms. Both bulbar and spinal form end up involving all voluntary muscles with the expectation of sphincters. According to U.S Food and Drug Administration the suggested dose for Riluzole is 50 mg for each 12 hours. It should be taken a two hour before or after taking meals in order to avoid gastric problems⁹. Apart from the tablet formulation, there are novel drug deliveries of Riluzole for the treatment of ALS, which includes Liquid emulsion for oral administration to reduce the anesthetic effect in the mouth and solid lipid nano particle which administered by the intra peritoneal route. The obtained system shows an optimum colloidal size and drug release is dependent on suitable pH medium¹⁰⁻¹⁴. The drug loaded solid lipid nano particles reaches higher concentrations in the CNS and passes through the blood brain barrier (BBB), when compared with the free Riluzole drug resulting in decrease drug accumulation in the liver, spleen, kidneys and lung when compared to free drug leading to less toxic¹⁵. From the recent research Riluzole (Teglutik[®]) oral suspension has been developed that may help patients with¹⁶ ALS-associated dysphagia to continue with longer drug therapy. The suspension is available in 1mL which contains 5mg of Riluzole administered 50mg (10 ml) on every 12 h, using a graduated dosing syringe. Compare to another formulation of Riluzole, oral suspension has a minimal or no anesthetic effect which will improve the patient compliance¹⁷. The intrathecal administration of Riluzole drastically increases the drug efficiency by targeting at the spinal cord segment maintaining lower plasmic levels with reduced side effects associated with oral dosage form¹⁰.

There are mainly two types of ALS, one is familiar ALS (fALS) and sporadic ALS (sALS), which are clinically undistinguishable. Approximately 23% of fALS and 7% of sALS cases are occurred by the mutation in the SOD1 gene. In other way around 8% of fALS and 1% of sALS cases are caused due to the mutation in TARDBP and

FUS/TLS, some other studies discovered that genes encoding for proteins involved in RNA process¹⁸.

Parkinson's disease (PD)

Parkinsonism disease involves the malfunctioning and death of neurons in the brain which primarily affect the neurons in the substantia producing dopamine. The production of dopamine decreases as the disease progress. One of the main symptoms of PD is Bradykinesia other main symptoms, including rigidity, tremor, Postural instability¹⁹ and this degeneration of dopaminergic neurons in neural structure pars compacta is coupled with intra cytoplasmic inclusion known as Lewy bodies. This mechanism can even be found within the locus ceruleus, hypothalamus, neural structure, cranial nerve motor nuclei, cerebral cortex and central and peripheral components of the autonomic nervous system²⁰. The mitochondrial dysfunction is one of themain important mechanisms in pathogenesis of PD²¹. The insufficiency of energy increases weakness of glutaminergic stimulation and contributes to the neurodegenerative process in PD²². In PD, neuronal activity get strengthened in the subthalamic nucleus, which is in charge of projecting to the internal regiment of the Globus pallidus²³.

So the glutamate antagonist Riluzole may useful for patients with PD. The augmentation of the synaptic efficacy of striatal ionotropic glutaminergic receptors contributes dyskinesia and it could be relieved by Riluzole through the intonation of excitatory glutaminergic transmission in strata spiny neurons²⁴. The combination of Levodopa and Riluzole is also under the development for treating PD²⁵.

In other Neurodegenerative disease

In multiple Sclerosis, Riluzole blocks the excessive glutamate in order to control the transmitting messages from one to other nerve cells²⁷. Riluzole act as a glutamate receptor blocker which can be also used to treat Psychiatric disorders and a childhood obsessive compulsive disorder²⁸. From the recent research work the scientists have also shown the advancement of Riluzole in fading memory that comes with advancing age due to the altered connection between the brain neurons²⁹. The communication circuits from neurons to neurons via glutamate decreases with excess splitout and stimulate connecting neurons in the wrong spot. In the case of age related disorder, this process damages the area of neurons which connects through synapses resulting in Alzheimers, Schizophrenia, and ALS. So in such conditions Riluzole inhibits the excessive amount of glutamate thereby preventing the memory loss in elderly patients. Riluzole can also be effective in certain neuromuscular diseases like Spinal Muscular Atrophy. The antiglutaminergic action of Riluzole reduces the amino acid neurotransmission in mood and anxiety disorders³⁰.

CONCLUSION

Investigations in the field of neurodegenerative disease appear to have several restrictions. What is patently mirrored within the diminutive growth accomplished within the neurodegenerative medical care of the studies illustrates the mechanisms concerned within the

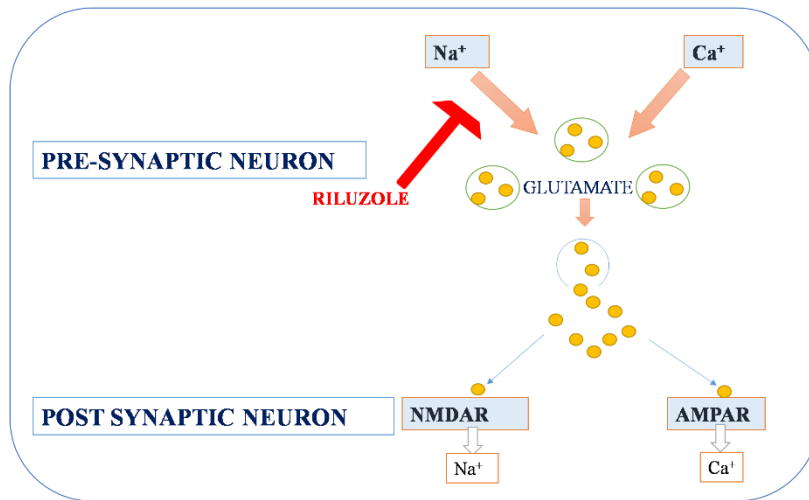


Figure 2: Mechanism of Riluzole in ALS.

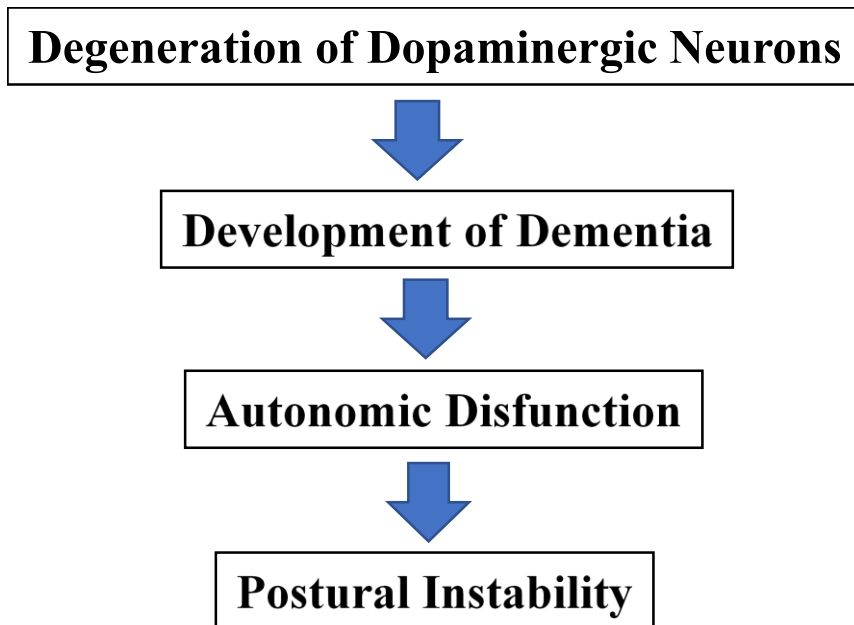


Figure 3: Schematic diagram to represent the disease progression²⁶.

pathogenesis process of the familial form of neurodegenerative, that accounts for a minority of all the neurodegenerative cases³¹.

However, number of the assumptions presently below analysis may additionally elucidate however the pathology develops within the irregular types of sickness within the last twenty years. Many experimental models for in vitro and in vivo studies have been used to explain the pathogenesis of the disease. Many potential mechanisms are involved within the origin of of neurodegenerative disease and progression as well as aerophilic stress, excitotoxicity, mitochondrial pathology, intestinal tissue activation, protein abnormalities and RNA-processing. Whether or not these mechanisms link³², effort in comparable or in sequence to cause somatic cell/death remains to be investigated. Riluzole appears to being interested by the researcher in the field of vast area in neurodegenerative disorders. On the basis of different novel drug delivery, the drug can be used in extended

release formulations for further advancement in the research field.

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