Riluzole in the treatment of lou gehrig’s disease

Health & Medicine, Disease

Introduction

Lou Gehrig's disease is often referred to as Amyotrophic lateral sclerosis (ALS), this is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons come from the brain to the spinal cord and from the spinal cord to the muscles throughout the entire body. The progressive degeneration of the motor neurons in ALS would eventually leads to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is also lost. With voluntary muscle action progressively affected, for this reason patients in the later stages of the disease may become totally paralyzed (Choi, 1988).

ALS is led to mean no muscle nourishment. When a muscle has no nourishment, it atrophies or wastes away hence the name. In addition to this, lateral shows the areas in a person's spinal cord where part of the nerve cells that signal and control the muscles are located. As this area degenerates, it leads to scarring or hardening (sclerosis) in this particular region.

As motor neurons degenerate, this obviously means they can no longer send impulses to the muscle fibers that otherwise normally result in muscle movement. Early symptoms of ALS often include increasing muscle weakness, especially involving the arms and legs, speech, swallowing or breathing. When muscles no longer receive the messages from the motor neurons that they require to function, the muscles begin to atrophy (become smaller). Limbs begin to look thinner as muscle tissue atrophies (Choi, 1988).

Neurodegeneration is used mainly for diseases that are characterised by progressive loss of structure and function of neurons. There are many neurodegenerative diseases including amyotrophic lateral sclerosis that occurs as a result of neurodegenerative processes in selective areas. Several molecular studies have been designed both in animal models and in humans to determine the physiopathology of the disease in order to develop new approaches for neurodegeneration. ALS is a neurological disease of unknown origin which is characterised by a selective degeneration and death of upper and lower motor neurons this progresses to paralysis and death over a period of time.

ALS diagnosis is based on the El Escorial criteria carried out on mainly clinical and electrophysiological findings in four body regions. Also around 95% of ALS patients are sporadic whereas 5% are familial. In this particular group approximately 15% are caused by mutations in the SOD one gene that codes for the CuZn superoxide dismutase-1 (Bensimon, 1994). This is an enzyme that catalyzes the dismutation of superoxide to molecular oxygen and hydrogen peroxide. The symptoms and pathology of familial ALS patients with SOD1 mutations resemble those of patients with sporadic ALS. This suggests there are common mechanisms of neuron degeneration in both forms of the diseases. Several potential mechanisms of motor neuron degeneration in ALS have been projected. These include the involvement of environmental and genetic factors, autoimmune phenoma, increased oxidativestress, glutamate toxicity, viral infections, mitochondrial dysfunction and cytoskeletal abnormalities. This means that each

mechanism involvedin the pathogenesis of ALS may represent a possible thjerapeutic approach to counteract neurodegeneration.

Glutamate is the primary excitatory neuro transmitter in the central nervous system which acts at both iono-tropic and metabotropic receptors, the primary ionotropic receptor classes being N-methyl-D-aspartic acid (NMDA) and (AMPA)/kainite. Extracellular glutamate levels are regulated by transporters, they have different transporter classes on neurons and on astrocytes, however most of the glutamate uptake appears to be mediated astrocytes. Excessive glutamate exposure is toxic to neurons which is most likely that is results from glutamate triggeredCa2+ entering the neurons. Also inhibitors of glutamate uptake can cause selective motor neuron damage in organotypic slice and in dissociated spinal cordculturemodels. This suggests that the increased extracellular glutamate concentration could add to motor neuron damage in ALS. Furthermore, observations of deficient glutamate transport capacity in affected regions of spinal cord and motor cortex show a likely reason for the rises in extracellular glutamate concentration.

The only drug proven to slow the process of human ALS is the anti-excitotoxic compound Riluzole, which is an anti-convulsant and a neuro-protective agent and specifically blocks sodium channels in their inactivated states. This inhibits the release of glutamate by inactivating voltage dependent Na+ channels that are on the glutamatergic nerve terminals as well as activating a G-protein dependant signal transduction process, this slows down disease progression and in turn increases the patient's survival

rate. In addition to this Riluzole can also block some of the postsynaptic effects of glutamate, this is done by non-competitive inhibition at NMDA and AMPA receptors. For this reason a non competitive modulator of AMPA glutamate receptors has been used in clinical trials in ALS patients (Barbeito, 1996).

Several studies showed that also the clearance of glutamate from neuromuscular synapases is slowed down in patients with ALS due to the loss of a glutamate transporter which is the excitatory amino acid transporter 2, this is of huge importance for synaptic glutamate re-uptake. A loss of high-affinity glutamate transport transport has been identified in specific brain regions and spinal cord of patients with ALS (Bensimon, 1996). From the above these results suggest that the defect in glutamate transport could be responsible for high elevations in extracellular glutamate.

These results have supported the use of cephalosporins in ALS because of their antiexcitatory properties, this is done by increasing EAAT2 promoter activity. Also for human studiesthird generation ceftriaxone has been selected because of its superior CNS penetration and long half life. From this ceftriaxone observed a considerable improvement of antioxidant oxidative stress status in ALS patients after treatment.

Riluzole treatment has been tested in trials which examine tracheostomy free survival rate, this included 974 riluzole treated patients. Inrespectto this the methodological quality of the experiment was acceptable and the trails were easily comparable. The results show that riluzole 100mg per day would provide benefits to the homogenous groups of patients with no evidence of

heterogeneity. Also there was a 9% gain in the probability of surviving one year. Furthermore there was a small beneficial effect on both bulbar and limb functions but had no effect on muscle strength. Another significant effect which is represented in these results are a threefold increase in serum alanine transferase, this was more frequent in riluzole treated patients than the controls in the experiment (Wahl, 1997).

In conclusion Riluzole 100mg daily is fairly safe and most likely prolongs median surbival by around two to three months in patients with amyotrophic lacteral sclerosis. However more research needs to be done to treat Lou Gehrigs disease such as different therapeutic strategies and oxidative stress in ALS can be looked at in further depths.

References

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