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Riluzole's role in treatment of spinal cord injuries – overview of studies on animals and humans

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Abstract

Injuries in the spinal cord are responsible for disabling a great number of people each year. The primary and secondary damage varies in pathomechanisms, the latter one being heavily associated with excitotoxicity caused by excess extracellular glutamate. Riluzole, a drug used in amyotrophic lateral sclerosis, lowers the amount of released glutamate, thus making it a

possible candidate for treatment in spinal cord injuries. Several studies have been performed on animals and humans, although their results do not always align. In controlled environments, when injuries to the neural tissue in the spinal cord are mechanical or ischemic, the drug's usage shows promising effects in treated rats. Tests on humans are much harder to conduct and so the research has focused on already ill individuals. Their conditions vary, however, and not all of the people could recover, even to a small degree. Further studies need to be performed in order to qualify riluzole as a remedium to injuries of the spinal cord.

Keywords: Riluzole; Spinal Cord Injury (SCI); Glutamate

Introduction

Spinal Cord Injury (SCI) is a condition greatly reducing the quality of life in those affected. Depending on its severity, it can impair some or all functions of spinal cord neurons. The level of the spine at which the injury occurred also dictates the clinical image of this condition, with the cervical region being most severe, producing tetraplegia and even death by affecting neurons responsible for diaphragm contractions. [1] Injuries located lower may present with different more or less clinically severe outcomes. [2] Such a debilitating condition requires urgent care and sufficient treatment in hopes of stopping the damage from progressing and hopefully maintaining the functionality of the spinal cord. Unfortunately, our ability to sufficiently treat SCI is severely lacking so far. People with varying levels of disablement caused by SCI go through their days and cannot be fully recovered. This leads to a worsening psychic state and may ultimately lead even to suicide. [3] Thus, finding a proper way to reverse the injury is a very nagging predicament. Various therapeutic approaches have been suggested throughout the years, one of them being the use of a molecule known as riluzole, a substance already in use for some neurological disorders. In this review we examine the research done on animals and studies, although sparse, conducted on human subjects.

Purpose

SCIs create irreversible changes in the spinal cords, and thus make affected people injured for life. This kind of damage is not only physical, but also invades the psyche, greatly lowering the quality of life. That is why it is so important to find a way to help these people. Looking into one of the possible therapeutic methods may pave a path for finding a remedium to at least some forms of SCIs. We chose riluzole as our focus because of its already proven beneficial impact on the neural tissue.

Spinal Cord Injury – description, types and progression

As of 2021 the prevalence of SCI worldwide was estimated to be within the range of 10.4 to 83 people per million, while that of the USA was 54 per million. Men were more likely to sustain such injuries and there was a bimodal distribution of occurrence as a function of age, with one peak in adolescence, and another in the age over 65 years. Starting from the most common ones and continuing in a descending order, the causes were: vehicle accidents, falls, violent activities, sport-related activities, surgery, and others. [4] The prevalence of SCI originating as non-traumatic lesions is not known. Different causes behind these non-traumatic events and the absence of federal registers make it impossible to get accurate measurements. [5]

Based on epidemiological studies, the most common spine segment in which SCI takes place, was at the cervical level Since it is the most mobile part of the human spine and it is found between much more stationary structures, these being the cranium and the thoracic spine, it is more prone to injuries. Depending on the level on which the SCI has taken place, as well as the severity of the injury and portions of the spinal cord which were affected, the clinical state of a patient can vary. The most characteristic symptoms, however, include: paralysis, paresthesia, spasticity, pain, and various dysfunctions of cardiovascular, gastrointestinal, urinary and reproductive systems. [6] For this reason, The American Spinal Injury Association (ASIA) developed The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), with the purpose of standardizing different types of SCI, guiding the

radiographic assessment and treatment, and determining if the damage is complete or incomplete. Such classification can aid in proper diagnosis and treatment. [7]

The damage done to the spinal cord can be divided into two phases: The initial primary injury, and the following secondary injury. At the onset of SCI, as a result of a physical insult, bone fractures, broken-off vertebrae fragments, joint dislocation and tearing of ligaments may be present. In the spinal cord itself, the destruction of neural parenchyma, severing of axons and haemorrhage take place. [8] Afterwards, the second phase occurs. The destruction of tissues leads to severing of blood vessels which causes local haemorrhage and edema, which further pushes against the surrounding tissue, closing nearby unaffected vessels, and thereby stopping oxygen and nutrient supply. Moreover, the inflammatory state and disruption of blood-spinal cord barrier promotes the influx of inflammatory cells, such as macrophages, T-leukocytes, and neutrophils. [9]

One important factor participating in the secondary injury is glutamate. [10] This neurotransmitter, when released from one neuron at a synapse, binds to its receptors, such as AMPA and NMDA, at another neuron. This initiates a cation influx through the postsynaptic membrane, consisting mainly of sodium and calcium ions. This creates an excitatory postsynaptic potential (EPSP), which might evoke an action potential, when a threshold potential is reached. However, in higher than normal ranges, the massive inflow and rising concentration of calcium does damage to the affected cell. [11] This process is known as excitotoxicity. Excess calcium causes a myriad of pathological cascades, leading to proteasome activation, mitochondrial endonucleases activation, disruption of intracellular homeostasis and generation of toxic levels of nitric oxide (NO). [12] Damage mediated by glutamate, as well as other factors occurring within the area of SCI and its surroundings ultimately lead to apoptosis and necrosis of damaged neurons. [12, 13] Neurons are not the only ones affected, however. All the factors destroying the neural cells might also impact glial cells, such as oligodendrocytes. Damage to those can result in demyelination within the central nervous system. [14]

Riluzole

Riluzole is a benzothiazole anticonvulsant drug with high affinity to serum albumin and lipoproteins. [15] The American Food and Drug Administration has assigned it in the treatment of several motor neuron diseases (MND), including amyotrophic lateral sclerosis (ALS). [16] Therapeutic effects of riluzole in patients with ALS brings hope in using it in those affected by various types of SCIs. The damaging processes present in the mentioned MND are similar to those occurring in other injuries of the spinal cord. Those similarities in damaging factors include: oxidative stress, mitochondrial dysfunction, presence of reactive oxygen species, damage to DNA and RNA, impaired axonal transmission, and apoptosis. A key component in this action is glutamate, released at a higher-than-normal level in the injured area. [17]

The drug's effects appear to be multimodal. It lowers sodium intracellular concentration within the neuron's body and axon, by blocking sodium channels, reversing the operation of sodium/calcium exchanger and affecting axonal sodium/hydrogen antiporters. [18] It also stops potentials arising from binding glutamate to its receptors and halts inward sodium current through the persistently open sodium channels, thus depolarizing the cell membrane. [19, 20]

Moreover, riluzole appears to be blocking release of glutamate to the extracellular space and even increasing its reuptake, not only making less of it bind to its receptor, but also shortening the time in which such action can take place. [19, 20, 21] It appears that riluzole works indirectly, not by interacting with the glutamate receptors themselves, but by affecting mechanisms around it. [19, 20] Reduced sodium concentration within the cell lowers calcium influx, which in excess is responsible for many damaging pathways, stops cellular edema, and can halt developing acidosis. [22]

Interestingly, riluzole has also been found to attenuate neuropathic pain. The mechanism behind this working seems to be associated with P2X7R, a purinergic receptor and a nonselective cation channel. It downregulates the expression of this receptor and lowers the activation of microglia. [23]

Materials and Methods

We have looked into studies on PubMed to search for papers on riluzole's effects on SCI. We evaluated them based on their accuracy on the topic, the number of subjects tested, and the amount and diversity of tests performed in order to check the results of the drug's effects. Studies of riluzole's impact on SCI were sparse in recent years. Next we show the evaluation of chosen studies from the year 2014 to 2020.

Results

I. Studies on animals

The bulk of studies done on the riluzole's effect on SCI recovery has been performed on animals as they comprise a good model for studies involved with damaging spinal cord and observing ensuing effects of performed therapies. The research was performed in order to inspect the drug's working on many aspects, such as behavioral and motor changes in injured mammals, the histological images of affected tissue, and immunohistochemical markers found in the specimen.

In a study named „Riluzole improves outcome following ischemia – reperfusion injury to the spinal cord by preventing delayed paraplegia" [24] the drug was administered intraperitoneally at a concentration of 8mg/kg 4 hours after an occlusion of the female Sprague-Dawley rats' aortae. The occlusions were performed in order to elicit damage to the spinal cord. The control group consisted of rats who also underwent surgery; they, however, received only riluzole's solution, without the drug in it. Afterwards the results were tested. In which the BBB scale was used to assess the ability of the hind limbs to properly work (BBB stands for Basso Beattie Bresnahan, and the scale ranges from 0 points, meaning no observable movements of the hind limbs, up to 21, which is given to animals with a coordinated gait, paw position parallel to the body, trunk stability, consistent tail elevation, and consistent toe movements). [25] Paraplegia was observed at first in all rats, ranging from mild to moderate. The riluzole-treated group showed, however, no decline in coordination and stepping scores. The latter one improved even over time. The rats in the control group did not appear to recover from the SCI. Number of interneurons in the intermediate zone was also higher in treated animals as compared to the untreated ones. The same was true for motor neurons.

Immunohistochemistry results showed that rats receiving riluzole had less microglia infiltration within the injury site and the apoptosis of neurons was not as prevalent as in the control group.

On a similar note, a study named: „Effect of Riluzole on Spinal Cord Regeneration with Hemisection Method Prior to Injury" [26] also provided results showing the beneficial results of using riluzole. In this study, rats after getting a hemispection of their spinal cords, were placed in separate groups and received different types of treatment, each with a variation of riluzole or just its vehicle (a solution without the drug) at different concentrations. Some groups were getting the injections prior to the procedure as well. In effect, the groups receiving riluzole, and especially those with the drug administered before the injury, recovered better as tested with the BBB scale. The neuroprotective aspect of riluzole usage was best seen in the group receiving regular doses of it prior to the injury, but not after, as described by the mean number in neurons in a histological assessment. A bigger number of glial cells in the control group was informative of higher glial proliferation in these animals and the creation of glial scar being a mechanical obstacle in neural recovery. [27]

In another study, named: „Riluzole improves functional recovery after acute spinal cord injury in rats and may be associated with changes in spinal microglia/macrophages polarization" [28] the following came to be. A laminectomy at the level of T10 was performed on rats. Later on they were divided into a riluzole-treated group and a control one, without the drug admission. The substance was administered at a concentration of 4 mg/kg intraperitoneally immediately after the surgery. Afterwards the rats were injected with the same dose of riluzole or vehicle every 12h for 7 weeks. Rats treated with riluzole showed better results on the BBB scale, and performed better on the inclined plane test. Neurofilament NF200, used as an axonal marker, and myelin basic protein (MBP), used as a myelin marker, in the immunofluorescence study, was found at lower concentrations in rats treated with riluzole.[29, 30] This suggests axon preservation and halting of myelin degradation processes. ELISA tests also showed lower levels of proinflammatory cytokines, IL-6, IL-1β, and TNF-α in the riluzole-treated rats.

II. Studies on humans

As for now, many different approaches have been tested on humans when thinking about treating SCI. Early decompression of the spinal cord by operating on the vertebrae around the affected spinal cord area has been tried. This method creates more free space for the arising haemorrhage and edema, and thus lowering the amount of injury occurring within the tissues. This procedure has led to an improvement of the clinical state of the patients. [31] Therapeutic hypothermia has also been suggested. Lowering the body temperature down to 32-34 degrees Celsius, in order to slow down the damaging mechanisms taking place in the trauma affected tissues, might help to enhance motor neuron recovery according to performed studies. [31, 32]

Based on studies on animals, riluzole appears to be a promising agent in the field of SCI treatment. However, there is not enough research done on humans to draw an ultimate conclusion on whether its functions would be sufficient. [33]

In a study named: „A Prospective, Multicenter, Phase I Matched-Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury", riluzole was administered orally or through a nasogastric tube in 36 patients. The first dose was given 12 h after SCI, and then every 12h for a total of 28 doses. A dose of 50mg twice a day showed best results. These patients showed improved mobility in the lower limbs and, in the cases of damage to the cervical portion of the spinal cord, of the upper limbs as well. Time duration between gain in motor score and the admission of riluzole showed no correlation. Pin-prick tests for cutaneous sensation testing have also improved. The tested amount of patients was however very limited, and the lack of a control group made it hard to determine the actual usage of such treatment. [34]

In a study on 16 patients with SCI an MRI and clinical parameters were assessed to show the results of treatment of riluzole on these patients. Treatment lasted for a year and consisted of 50mg of the drug administered twice a day. As a result, the spinal cord area remained stable after receiving the substance, as opposed to prior to getting it, when the spinal cord atrophy could be measured. Lesion loads in the parenchymal volume measured on T1-weighted images in the MRI scans increased at a smaller amount before receiving riluzole. On the T2-weighted images, however, the amount of its increase was higher than to the time from before the damage. The small sample group and lack of control group makes it hard to truly assess

the working of the drug on human subjects, although the clinical state of those treated has improved. The inflammation, demyelination and the axonal damage were reduced as well. [35]

In patients with SCI caused by degenerative cervical myelopathy, a group of 408 people was assembled. They have been divided into a riluzole-receiving group, and a control one, receiving placebo. The first group was administered the drug at a concentration of 50 mg twice a day for 14 days before their surgery, and then for 28 days after it. The resulting effects were assessed with the use of an mJOA score. The score was checked at the beginning of the study and after 6 months. Both patients receiving riluzole and the placebo showed improvements after the 6 months-long follow up and there was no difference between the two groups. These results, however discouraging they may look, might have been caused by the heterogeneous nature of the treated disease. In such a case, the limited scope of riluzole effects, could be not enough to affect various different pathomechanisms of the diseases. [36]

Discussion

The studies on riluzole effectiveness in treating SCI proved to be sparse, especially in the realm of research performed on humans. Given the little information from recent years that we could gather, assessing without a doubt the drug's role is not possible. However, we can still look at the data and draw interesting conclusions from them. In animals that sustained controlled damage to their spinal cord in laboratory conditions, and later on received riluzole, actual improvement could be observed. This informs us that mechanical injury, or one done by the means of ischemia, could potentially also be successfully treated in humans. On the other hand, not all research done on humans resulted in healing. When experimenting on people one cannot simply sever the cord. The only way to test riluzole in this case, was to give it to people who already had SCI. The main issue, however, is that SCI can arise in a plethora of ways, with many different pathological processes taking place. In such a situation it is to be expected that one drug cannot possibly affect all of them and improvement, if any, would be disappointing. As for now, no unified conclusion can be made, and further research is required.

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