Neuroprotective Effects of Riluzole in Neurotrauma Models: A Review

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Summary

Physical injury to the central nervous system (CNS) remains one of the main causes of mortality and disability in young adults. Numerous therapies have been successfully evaluated in experimental traumatic brain or spinal cord injuries (TBI, SCI) and, although some of them are currently under clinical trials for these indications, no drug therapy is at present available. Thus, an interesting approach to reduce the CNS injury-induced damage could be the blockade of Na⁺-channels by drugs such as riluzole which is neuroprotective in models of TBI or SCI as summarized in this review. Repeated doses ranging from 2 to 8 mg/kg were administered between 24h to 10 days post-injury, with a first administration given either at 15 min or up to 6h post-injury. In these models riluzole was found to reduce both the size of spinal cord and brain lesions as well as brain edema, and to restore the neurological, motor and cognitive impairments consequent of these injuries. The largest therapeutic time window obtained was 1 to 6h in TBI. Thus such a compound should be considered as an interesting candidate for the treatment of SCI or TBI.

Keywords: Riluzole; traumatic brain injury; spinal cord injury; Na⁺-channels.

Introduction

Physical injury to the CNS like TBI or SCI remains one of the main causes of mortality and disability in young adults. A considerable number of molecules acting on various pathophysiological events engendered by CNS injury have been successfully evaluated in experimental research in different models and species [see 25]. Although some of them have been or are under clinical trials for this indication, up to now no drug therapy has been available for TBI or SCI patients [10, 11]. Briefly these include mannitol, corticosteroids like methylprednisolone, barbiturates, Ca²⁺-channels blockers such as nimodipine, free radical scavengers including PEG-SOD and tirilazad, and glutamate receptor antagonists like Selfotel or Cerestat [see 10, 11]. However none of these drugs has demonstrated a real benefit in phase III studies [11]. Discrepancies between experimental research and clinical trials have been reviewed by Doppenberg [10], and may be mainly related to the (i) physiopathological heterogeneity of the patient population; (ii) differences in the physiopathology of injured animals and patients; (iii) differences in the therapeutic window between animals and human; (iv) poor CNS penetration of drugs; (v) safety and tolerance problems which may only be revealed in phase I-II studies. Another interesting approach to treat the CNS injuries could be the blockade of Na⁺-channels. Indeed, blockers of voltage-dependent Na⁺ channels like the pyrimidine derivative sipatrigine [23, 34, 39], the benzothiazole derivatives lubeluzole [7] and riluzole [33], are neuroprotective in models of acute neurodegenerative diseases including TBI, SCI or stroke. If clinical trials in stroke with sipatrigine have been halted because of adverse effects [11], in contrast a clinical trial with lubeluzole demonstrated a slight benefit in stroke patients 12 weeks post infarct [16]. As reviewed by Stutzmann [33] several studies have demonstrated that riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a potent anticonvulsant drug found to be neuroprotective in acute and chronic neurodegenerative disease models in rodents, including hypoxia, cerebral ischemia, SCI, TBI, Parkinson’s and Huntington’s diseases, as well as in a model of amyotrophic lateral sclerosis (ALS) in mice [17]. Moreover, riluzole prolongs the survival of patients with ALS [41]. The mechanisms by which riluzole may be active on these models will be discussed in this review which aims to summarize the effects of riluzole in SCI and TBI in rats.
Table 1. Effect of Riluzole (2 × 2 mg/kg/day for 10 days) in Rats Subjected to SCI. The Amplitude, Duration and Latency of the SEP was Measured Just Before and at Day 7 Post-SCI (n = 10 per Group) in SCI-Vehicle and SCI-Riluzole Rats. SEP Latency was Cut-Off at 30 msec. *p < 0.05 vs SCI Vehicle

<table>
<thead>
<tr>
<th></th>
<th>SEP amplitude (µvols)</th>
<th>SEP duration (msec)</th>
<th>SEP latency (msec)</th>
<th>Lesion size (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control before SCI</td>
<td>10 ± 1.7</td>
<td>4.2 ± 0.03</td>
<td>11 ± 3.2</td>
<td>–</td>
</tr>
<tr>
<td>SCI vehicle</td>
<td>0</td>
<td>0</td>
<td>≥ 30</td>
<td>1.99 ± 0.23</td>
</tr>
<tr>
<td>SCI riluzole</td>
<td>5 ± 1.2</td>
<td>5.5 ± 0.8</td>
<td>18 ± 1.8</td>
<td>1.03 ± 0.12*</td>
</tr>
</tbody>
</table>

Spinal Cord Injury

SCI Procedure, Somatosensory Evoked Potentials (SEP) and Histology

SCI was induced in Wistar rats by inflation of a Fogarty balloon catheter in the cord canal at level of thoracic 10–12. The SEP were recorded before and after spinal cord injury (for details see 32). Ten days after the trauma induction, rats were killed and the spinal cord was dissected, cut with a cryostat and then stained with cresyl violet. Each slide was examined, and damage to grey or white matter was measured via an image analyzer.

Drug Treatment

Riluzole at 2 mg/kg (n = 10) or vehicle for control group (n = 10) was given intravenously (iv) twice a day for 10 days, starting 30 min post trauma, and was then given immediately post SEP recording.

Results (Table 1)

SCI produced a paralysis of the hind limbs, which persisted until euthanasia on day 10. Riluzole (2 × 2 mg/kg iv for 10 days) considerably inhibited the evolution of the behavioral deficit, as assessed qualitatively on a flat surface, with animals using their paws to sit upright. After 6 ± 2 days the majority of animals (7/10) had regained a nearly normal motor behaviour, although 3/10 animals retained a marked motor deficit beyond day 8. Control SEPs were recorded in all rats prior to trauma and were abolished in all animals immediately following intervention. In vehicle-treated animals no recovery was observed during the duration of the experiment while in the riluzole-treated group, animals showed a notable recovery of SEP amplitude, duration and latency. Treatment with riluzole also significantly reduced the lesion volume by 48% (p < 0.05), and more particularly that in the white matter.

Traumatic Brain Injury

Fluid Percussion Procedure

TBI was induced in Sprague-Dawley rats by a fluid percussion (FP) according to the techniques initially described by Toulmond [35] and McIntosh [26]; an FP of moderate severity at 1.6–1.8 bar was induced laterally to the right parietal cortex (for details see 1,40), or at 2.1–2.5 atm centered over the left parietal cortex (for details see 26).

Following different protocols of administration, riluzole was evaluated on extent of the cerebral lesions, brain edema, neurological function and cognitive impairment which were measured at various times after the injury. We also investigated the therapeutic time window of riluzole in our model for which we chose the most active dose (8 mg/kg).

Cerebral Lesions

Methods. One week after TBI rats were killed by decapitation and their brains removed and frozen in isopentane (−30°C). Coronal cryostat sections were cut and stained with hematoxylin-eosin. The lesion areas were measured with an image analyzer to calculate the volume of brain damage (for details see 40).

Drug treatment. Riluzole at 4 and 8 mg/kg or vehicle was administered 15 min (iv), and then subcutaneously (sc) at 6h and 24h post TBI (n = 15, 15 and 16, respectively).

Therapeutic window. Riluzole at 8 mg/kg (n = 11) or vehicle (n = 14) was administered at 1h (iv) and at 6h and 24h (sc) post-injury.

Results (Fig. 1). TBI induced neuronal lesions at the level of the right parietal cortex spreading out ipsilaterally along a rostrocaudal axis. Riluzole at 3 × 4 and 3 × 8 mg/kg significantly decreased the lesion size at some coronal levels [40], with an overall significant reduction in the volume of brain damage by 43% and