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Riluzole for the treatment of acute traumatic spinal cord injury: rationale for and design of the NACTN Phase I clinical trial

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In the immediate period after traumatic spinal cord injury (SCI) a variety of secondary injury mechanisms combine to gradually expand the initial lesion size, potentially leading to diminished neurological outcomes at long-term follow-up. Riluzole, a benzothiazole drug, which has neuroprotective properties based on sodium channel blockade and mitigation of glutamatergic toxicity, is currently an approved drug that attenuates the extent of neuronal degeneration in patients with amyotrophic lateral sclerosis. Moreover, several preclinical SCI studies have associated riluzole administration with improved functional outcomes and increased neural tissue preservation. Based on these findings, riluzole has attracted considerable interest as a potential neuroprotective drug for the treatment of SCI. Currently, a Phase I trial evaluating the safety and pharmacokinetic profile of riluzole in human SCI patients is being conducted by the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury. The current review summarizes the existing preclinical and clinical literature on riluzole, provides a detailed description of the Phase I trial, and suggests potential opportunities for future investigation. Clinical trial registration no.: NCT00876889. *(http://thejns.org/doi/abs/10.3171/2012.4.AOSPINE1259)*

Key Words • **spinal cord injury** • **riluzole** • **clinical trial** • **North American Clinical Trials Network**

Most therapeutic interventions that have been hypothesized to improve neurological outcomes after SCI fall into one of two broad categories with respect to mechanism of action. The first group of therapies aims to promote regeneration of neural tissue within the spinal cord postinjury. Such therapies include emerging drug treatments such as Cethrin, as well as stem cell implantation therapies.[14,18,25] The second group of treatments, instead of generating new tissue, operate to protect viable spinal cord tissue early on after the injury by mitigating the evolution of secondary injury events. These therapies, which include methylprednisolone and GM-1 (Sygen), have been the subject of the largest clinical trials in SCI performed to date.[9–11,15] Although treatments from both of the described categories have shown exceptional promise at the preclinical stages of investigation, none have proven to be uniformly effective in the treatment of human patients with SCI.[18]

Riluzole, a sodium channel–blocking drug with putative neuroprotective properties gleaned from the preclinical literature, falls into the second group of therapies described above.[5] As of this writing, data are being analyzed from a multicenter Phase I trial investigating the safety and pharmacokinetic profile of this agent in patients with SCI (clinical trial registration no. NCT00876889). In this article we explore the relevant preclinical evidence evaluating riluzole in SCI, provide a detailed description

Abbreviations used in this paper: ALS = amyotrophic lateral sclerosis; ASIA = American Spinal Injury Association; NACTN = North American Clinical Trials Network for Treatment of Spinal Cord Injury; SCI = spinal cord injury.

of the current Phase I trial, and outline potential options for future investigation.

Pathophysiology and Existing Preclinical/Clinical Evidence

Initiated by the primary spinal cord trauma, the evolution of secondary injury mechanisms begins within seconds and continues for several weeks.[3,13,28] An important occurrence early on within this secondary injury cascade is the development of neuronal ionic imbalance, particularly increased intracellular sodium concentration, as a result of trauma-induced activation of voltage-sensitive sodium channels.[2,33] The increased intracellular sodium concentration leads to a concomitant rise in intracellular calcium levels and also acts to stimulate intracellular acidosis and the development of cytotoxic edema.[16,17,23] The influx of sodium and calcium lead to an increased neuronal release of excitotoxic glutamate, resulting in excitotoxicity-mediated secondary injury and local cell death.[20,30] One approach investigated to attenuate these specific injury events has been the delivery of pharmaceutical agents that block the constitutive neuronal sodium channel activation seen after SCI. A variety of sodium channel–blocking compounds, including locally administered tetrodotoxin, as well as systemically administered lidocaine and phenytoin, have been shown to preserve neural tissue as well as improve behavioral outcomes in several preclinical animal models of SCI.[1,24,31] In spite of these promising findings, none of these compounds have been subject to systematic evaluation in the context of human SCI.

Riluzole is a sodium channel–blocking benzothiazole anticonvulsant, which, like the agents described above, has demonstrated significant neuroprotective effects in preclinical SCI models (Fig. 1).[27,29] In a 2001 study by the Fehlings group, the effects of riluzole were compared with phenytoin, CNS5546A (a novel sodium channel–blocking compound), and a control compound in rats with severe compression-induced cervical SCI.[26] At 6 weeks' follow-up, while rats in all treatment groups demonstrated some degree of recovery, those in the riluzole treated group experienced a significantly larger degree of functional recovery as compared to the other treatment groups. Also in comparison to the other groups, the riluzole-treated animals exhibited a significantly reduced area of tissue cavitation at the injury epicenter on postmortem histological analysis. Riluzole's neuroprotective effects are due to its combined ability to prevent sodium and calcium influx as well as to block the synaptic release of excitotoxic glutamate. However, in light of the relative paucity of synaptic connections within the spinal cord white matter, the axon-sparing properties of riluzole are thought to be most related to its sodium channel–blocking actions.

In the clinical realm, although riluzole has not been studied extensively in the context of SCI, it has been widely used in the treatment of the neurodegenerative disorder ALS.[6,7,19,32] A 2007 Cochrane review, summarizing the findings of 4 placebo controlled randomized trials, concluded that when given at a dosage of 100 mg daily, riluzole is safe and improves median tracheostomy-free survival by 2–3 months in patients with ALS.[21] Regarding adverse events, riluzole was well tolerated, with the exception that treated patients were 2.6 times more likely to experience an increase in serum alanine transaminase levels as compared with patients treated with placebo.[21] However, this effect was found to be uniformly reversible with cessation of riluzole therapy and was only reported after several months of riluzole administration. In light of this favorable safety and efficacy profile, the FDA has approved riluzole for patients with ALS, with administration typically commenced at the time of diagnosis and continued chronically.

Given its documented efficacy in preclinical SCI studies, as well as its safety in a human ALS population, riluzole appears an attractive candidate for evaluation in human patients with SCI. Before proceeding with a comparative effectiveness study, however, it was felt prudent to first evaluate the safety and pharmacokinetic profile of this medication within an SCI-specific population.

Phase I Clinical Trial for Riluzole in Traumatic SCI

Study Objectives and Design

Beginning in the spring of 2010, a Phase I study was undertaken with the goal of developing the safety and pharmacokinetic profile of riluzole in patients with traumatic SCI. Secondary objectives were to compare neurological, functional, and pain outcomes of the enrolled participants to outcomes of patients from the NACTN prospective SCI registry, matched for injury and demographic characteristics. This trial was designed as a prospective, single-arm, open-label multicenter study with a target enrollment of 36 participants. The sample size was based on NACTN registry incidence rates of adverse events ranging from 0.15 to 0.30. Using a 1-sided exact binomial test with a Type I error rate of 5%, a case series of 36 is expected to have at least 80% power to detect a doubling of a complication rate.

The safety end point follow-up period for the study is 6 months. However, neurological, functional, and pain outcomes will continue to be assessed at 12 months postinjury.

Study Setting

The trial was undertaken by the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury. NACTN is a collaborative network of 8 North American university-affiliated departments of neurosurgery, a data management center, and a pharmacological center (Table 1).

The study protocol was reviewed and approved by the institutional review board of each participating site and by the US Army Medical Research and Materiel Command Office of Research Protections, Human Protection Office. This study is also listed in ClinicalTrials.gov, a service of the US National Institutes of Health.

Eligibility Criteria

Assessment of an individuals' study eligibility was made at hospital presentation by the site-specific princi-

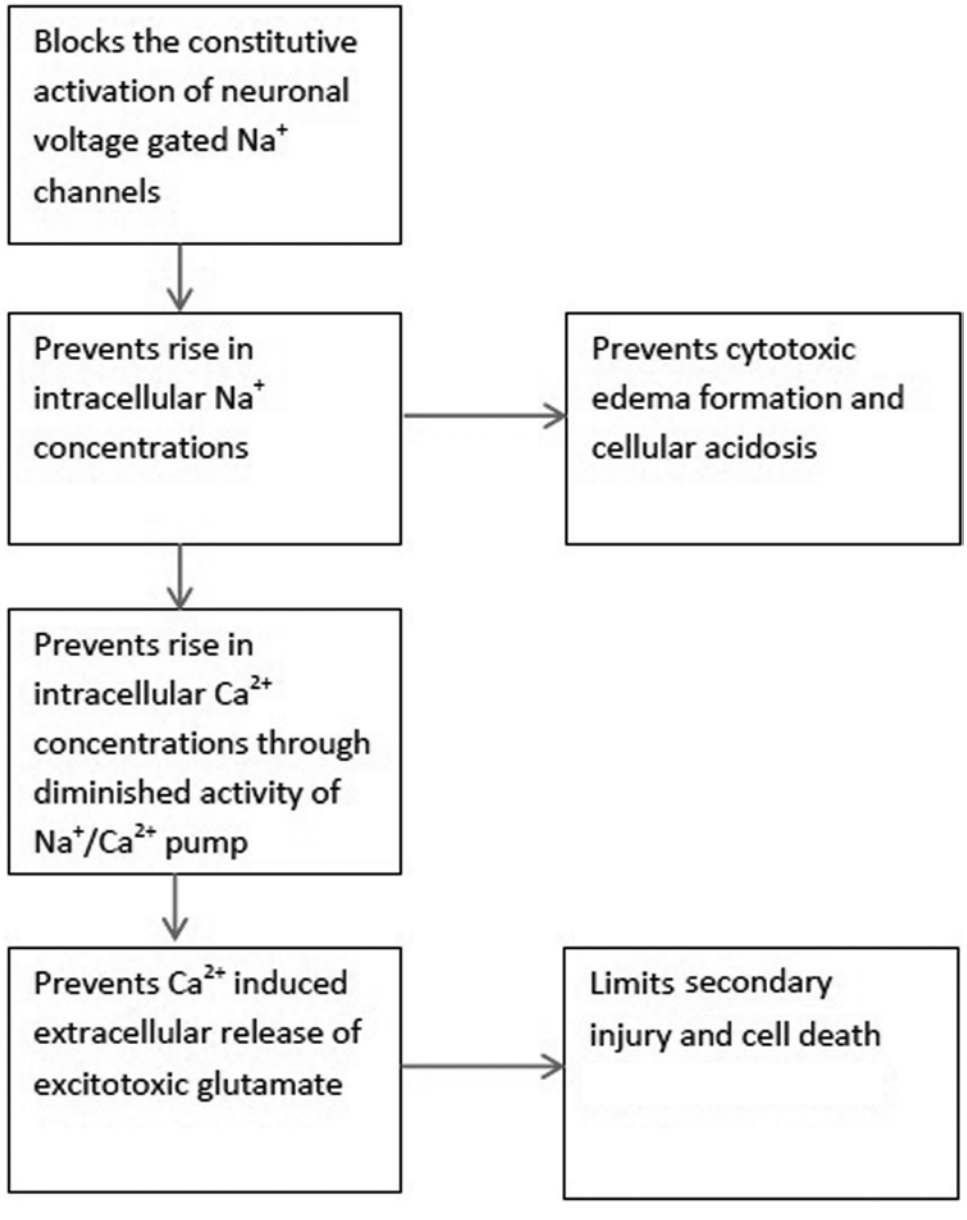

Fig. 1. Flow diagram summarizing the putative neuroprotective mechanisms of riluzole in SCI.

pal investigator or study coordinator according to the inclusion and exclusion criteria shown in Table 2.

Intervention Details

Participants received riluzole 50 mg every 12 hours for a total of 14 days, with treatment initiated within 12 hours of injury. The 12-hour drug window, as well as the 2-week duration of therapy, was chosen based on a desire to match the period of drug administration to the known period of sodium- and glutamate-induced secondary injury after SCI (several minutes after injury until 2 weeks after injury).[22] Riluzole was administered either orally or enterally through a nasogastric tube. When given orally, a single 50-mg tablet was given; however, if a nasogastric route was required, the 50-mg tablet was crushed and then dispersed in water prior to administration. Although riluzole is well absorbed in the stomach and proximal intestine, coadministration of the drug with food can reduce absorption up to 20%. As a result, feeding, whether via an oral or nasogastric route, was not permitted within 2 hours before and was delayed until at least 1 hour after riluzole was given. Since riluzole undergoes hepatic metabolism, primarily by cytochrome P450 1A2, coadministration with other pharmacological agents metabolized by this enzyme (such as quinolone antibiotics, amitriptyline, or omeprazole) was prohibited to prevent variations in serum drug concentration.

Baseline Assessment

On patient admission to a study center, the site prin-

TABLE 1: Summary of participating centers in NACTN Phase I riluzole trial

Center	Location
clinical centers	
The Methodist Hospital*	Houston
University of Toronto	Toronto
University of Texas Health Science Center	Houston
University of Virginia Health System	Charlottesville
University of Louisville	Louisville
University of Maryland	Baltimore
University of Miami	Miami
Thomas Jefferson University	Philadelphia
data management center	
University of Texas School of Public Health	Houston
pharmacologic center	
University of Houston College of Pharmacy	Houston

* Coordinating center.

cipal investigator or designee performed a neurological examination in accordance with the ASIA/International Medical Society of Paraplegia recommendations.[4] This examination established the baseline ASIA Impairment Scale grade, ASIA motor score, and ASIA sensory score. Additional clinical information, such as age, sex, Glasgow Coma Scale score, injury mechanism information, the time of injury, and medical history, were also assessed and recorded. All personnel performing neurological assessments underwent a 2-day training course in performing ASIA examinations. Also at the time of initial assessment, a comprehensive set of trauma blood work was obtained including a pregnancy test and a serum liver panel as detailed below.

Outcome Data and Follow-Up

Adverse Events. Throughout the course of this study, adverse events were carefully monitored for each participant. Particular care was made to track adverse events previously associated with riluzole administration in the ALS literature, particularly hepatotoxicity. Baseline blood work included alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptide, and bilirubin levels as well as prothrombin time and international normalized ratio. Liver enzyme tests were repeated on Days 3 and 14 after the start of riluzole. Data were recorded on a wide range of adverse events including infections, respiratory complications, cardiovascular events, deep vein thrombosis/pulmonary embolus, skin breakdown, and neuropathic pain. All serious adverse events were reported to the coordinating center and to the central medical monitor. There were no deaths among the 36 patients enrolled in the study.

Neurological, Functional, and Pain Outcome Assessment. The ASIA Impairment Scale grade, ASIA motor score, and ASIA sensory score are the primary neurological outcome measures used in this study. The Spinal Cord Independence Measure and Brief Pain Inventory short form were used to assess functional status and pain outcomes, respectively.[8,12] Outcome measures are assessed at 6 weeks, 3 months, 6 months, and 1 year postinjury.

Follow-up data on adverse events as well as neurological, functional, and pain outcomes will be compared between enrolled riluzole-treated patients and non–riluzole-treated patients enrolled in the NACTN prospective SCI registry in the final study analysis.

Collection of Pharmacological Data. Blood samples for determining the peak and trough serum riluzole concentrations were drawn on Day 3 and Day 14 of riluzole administration for all participants. Complete details of pharmacological data collection and analysis can be

TABLE 2: Summary of objectives and inclusion and exclusion criteria for Phase I riluzole trial

Study Objectives	Inclusion Criteria	Exclusion Criteria
primary objective: to evaluate the safety & pharmacokinetic profile of riluzole in patients w/ traumatic SCI secondary objective: compare neurological, functional, & pain outcomes of enrolled participants w/ outcomes of matched patients from the NACTN SCI registry	traumatic SCI & an ASIA Impairment Scale grade of A, B, or C neurological level of injury from C-4 to T-12 btwn the ages of 18 & 70 yrs able to receive riluzole w/in 12 hrs of injury able to cooperate in completion of informed consent	preexistent liver or kidney disease injuries arising from penetrating mechanisms moderate or severe traumatic brain injury pregnant or nursing women preexistent neurologic or mental disorder that would preclude accurate evaluation and follow-up (e.g., Alzheimer disease, Parkinson disease, or schizophrenia) life-threatening injuries, the management of which would delay drug administration past 12 hrs postinjury unable to receive medication via an oral or nasogastric route recent history of illicit drug or alcohol abuse

found in the pharmacological review by Chow et al. in this supplement.

Progress Made to Date and Future Directions

As of January 2012, the target enrollment of 36 participants has been achieved. Complete analysis of the trial data is underway, and we anticipate that the final results will be available in the summer of 2012. Assuming that the safety profile of riluzole in SCI patients is confirmed, we will use the findings of this study to plan a Phase II trial evaluating the effects of riluzole on long-term neurological and functional outcomes. To this end, data from the current Phase I trial will be used to determine an appropriate treatment effect size for future sample size calculations.

Conclusions

Initiated by the primary spinal cord trauma, a host of secondary pathological processes combine to expand the area of neurological tissue injury after SCI. As part of this process, posttraumatic constitutive activation of neuronal voltage-gated sodium channels leads to increased intracellular sodium and calcium concentrations with concomitant cellular swelling and increased release of excitotoxic glutamate. Riluzole, a sodium channel–blocking anticonvulsant drug, has shown efficacy in preclinical SCI studies and has proven safe and effective in the treatment of human patients with ALS. To initiate the translation of this therapy to the clinic for SCI patients, we have undertaken an open-label Phase I trial to define the safety and pharmacokinetic profile of riluzole in this population. We look forward to publishing the final results of this study later this year.

Disclosure

Dr. Shaffrey reports a consultant relationship with Medtronic, NuVasive, and Biomet; being a patent holder with Medtronic and Biomet; receiving clinical or research support for the study described from the National Institutes of Health, the Department of Defense, NACTN, and AOSpine; and receiving honoraria from Globus.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fehlings. Drafting the article: Wilson. Critically revising the article: Fehlings, Wilson, Frankowski, Toups, Aarabi, Harrop, Shaffrey, Guest, Grossman. Reviewed submitted version of manuscript: Fehlings, Wilson, Toups, Aarabi, Harrop, Shaffrey, Harkema, Guest, Tator, Burau, Johnson, Grossman. Statistical analysis: Tator, Burau, Johnson.

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References

1. Agrawal SK, Fehlings MG: The effect of the sodium channel blocker QX-314 on recovery after acute spinal cord injury. **J Neurotrauma 14:**81–88, 1997
2. Agrawal SK, Fehlings MG: Mechanisms of secondary injury to spinal cord axons in vitro: role of Na+, Na(+)-K(+)-ATPase, the Na(+)-H+ exchanger, and the Na(+)-Ca2+ exchanger. **J Neurosci 16:**545–552, 1996
3. Amar AP, Levy ML: Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. **Neurosurgery 44:**1027–1040, 1999
4. American Spinal Injury Association, International Spinal Cord Society: **International Standards for Neurological Classification of Spinal Cord Injury.** Chicago: American Spinal Injury Association, 2000
5. Baptiste DC, Fehlings MG: Emerging drugs for spinal cord injury. **Expert Opin Emerg Drugs 13:**63–80, 2008
6. Bensimon G, Lacomblez L, Delumeau JC, Bejuit R, Truffinet P, Meininger V: A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis. **J Neurol 249:**609–615, 2002
7. Bensimon G, Lacomblez L, Meininger V: A controlled trial of riluzole in amyotrophic lateral sclerosis. **N Engl J Med 330:** 585–591, 1994
8. Bluvshtein V, Front L, Itzkovich M, Aidinoff E, Gelernter I, Hart J, et al: SCIM III is reliable and valid in a separate analysis for traumatic spinal cord lesions. **Spinal Cord 49:**292–296, 2011
9. Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, et al: Efficacy of methylprednisolone in acute spinal cord injury. **JAMA 251:**45–52, 1984
10. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. **N Engl J Med 322:**1405–1411, 1990
11. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al: Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. **JAMA 277:** 1597–1604, 1997
12. Cleeland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. **Ann Acad Med Singapore 23:**129–138, 1994
13. Fehlings MG, Sekhon LSH: Cellular, ionic and biomolecular mechanisms of the injury process, in Tator CH, Benzel EC (eds): **Contemporary Management of Spinal Cord Injury: From Impact to Rehabilitation.** Park Ridge, IL: American Association of Neurological Surgeons, 2000, pp 33–50
14. Fehlings MG, Theodore N, Harrop J, Maurais G, Kuntz C, Shaffrey CI, et al: A phase I/IIa clinical trial of a recombinant Rho protein antagonist in acute spinal cord injury. **J Neurotrauma 28:**787–796, 2011
15. Geisler FH, Coleman WP, Grieco G, Poonian D: The Sygen multicenter acute spinal cord injury study. **Spine 26 (24 Suppl):**S87–S98, 2001
16. Haigney MC, Lakatta EG, Stern MD, Silverman HS: Sodium channel blockade reduces hypoxic sodium loading and sodium-dependent calcium loading. **Circulation 90:**391–399, 1994
17. Haigney MC, Miyata H, Lakatta EG, Stern MD, Silverman HS: Dependence of hypoxic cellular calcium loading on Na(+)-Ca2+ exchange. **Circ Res 71:**547–557, 1992
18. Hawryluk GW, Rowland J, Kwon BK, Fehlings MG: Protection and repair of the injured spinal cord: a review of completed, ongoing, and planned clinical trials for acute spinal cord injury. **Neurosurg Focus 25(5):**E14, 2008
19. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V: Dose-ranging study of riluzole in amyotrophic lateral sclerosis. **Lancet 347:**1425–1431, 1996
20. Li S, Mealing GA, Morley P, Stys PK: Novel injury mechanism in anoxia and trauma of spinal cord white matter: gluta-

mate release via reverse Na+-dependent glutamate transport. **J Neurosci 19:**RC16, 1999
21. Miller RG, Mitchell JD, Lyon M, Moore DH: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). **Cochrane Database System Rev (1):**CD001447, 2007
22. Park E, Velumian AA, Fehlings MG: The role of excitotoxicity in secondary mechanisms of spinal cord injury: a review with an emphasis on the implications for white matter degeneration. **J Neurotrauma 21:**754–774, 2004
23. Regan RF, Choi DW: Glutamate neurotoxicity in spinal cord cell culture. **Neuroscience 43:**585–591, 1991
24. Rosenberg LJ, Teng YD, Wrathall JR: Effects of the sodium channel blocker tetrodotoxin on acute white matter pathology after experimental contusive spinal cord injury. **J Neurosci 19:**6122–6133, 1999
25. Rowland JW, Hawryluk GW, Kwon B, Fehlings MG: Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. **Neurosurg Focus 25(5):**E2, 2008
26. Schwartz G, Fehlings MG: Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole. **J Neurosurg 94 (2 Suppl):**245–256, 2001
27. Schwartz G, Fehlings MG: Secondary injury mechanisms of spinal cord trauma: a novel therapeutic approach for the management of secondary pathophysiology with the sodium channel blocker riluzole. **Prog Brain Res 137:**177–190, 2002
28. Tator CH, Fehlings MG: Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. **J Neurosurg 75:**15–26, 1991
29. Tator CH, Koyanagi I: Vascular mechanisms in the pathophysiology of human spinal cord injury. **J Neurosurg 86:**483–492, 1997
30. Taylor CP, Geer JJ, Burke SP: Endogenous extracellular glutamate accumulation in rat neocortical cultures by reversal of the transmembrane sodium gradient. **Neurosci Lett 145:**197–200, 1992
31. Teng YD, Wrathall JR: Local blockade of sodium channels by tetrodotoxin ameliorates tissue loss and long-term functional deficits resulting from experimental spinal cord injury. **J Neurosci 17:**4359–4366, 1997
32. Yanagisawa N, Tashiro K, Tohgi H, Mizuno Y, Kowa H, Kimura J, et al: Efficacy and safety of riluzole in patients with amyotrophic lateral sclerosis: double-blind placebo-controlled study in Japan. **Igakuno Ayumi 182:**851–866, 1997
33. Zhang Y, Lipton P: Cytosolic Ca2+ changes during in vitro ischemia in rat hippocampal slices: major roles for glutamate and Na+-dependent Ca2+ release from mitochondria. **J Neurosci 19:**3307–3315, 1999

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