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Short Communication

Two Decades of Riluzole Showed No Clear Benefit on ALS: Case Close, or Isn't? Clinical Implication of Basic Neuroscience Research

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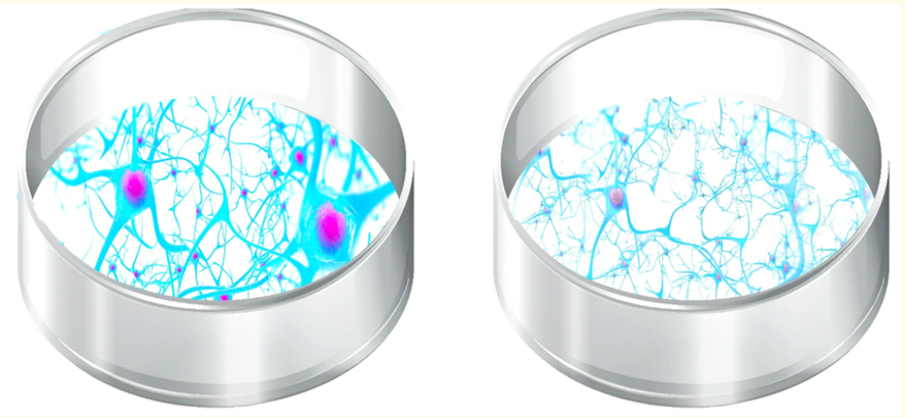
ALS is a neurodegenerative disease characterized by degeneration of the pyramidal neurons in the motor cortex (upper motor neuron) and the motor neurons in the brain stem motor nuclei and spinal cord anterior horn (lower motor neuron). The result is progressive and unrelenting weakness with the patient's demise by respiratory failure in a few years.

Riluzole and Endaravone are the only two FDA drugs approved to treat ALS with a modest effect on survival. Riluzole was first approved two decades ago and several trials and evidence-based medicine showed minimal, but consistent protective effect in survival (advantage of 3 months) [1]. Last year, Endaravone, a free radical scavenger, was also approved to treat early-stage ALS. But, showed no benefit in advanced ALS [2].

Riluzole has multiple effects in the central nervous system. This includes blocking of sodium channels, activation of G-proteins, inhibition of the P2X7 purine receptor expression, reduction of glutamate neurotransmission, and enhancement on the production of trophic factors necessary for motor neurons survival by astrocytes and other glia cells [3,4].

A recent publication showed additional effects of riluzole on trophic factors production both in vitro and in vivo [5]. Short-term administration of riluzole stimulated the production of trophic factors, whereas long-term administration blocked the enhanced production and even inhibited the production of trophic factors. Until recently the small protective effect of riluzole was attribute exclusively to low bioavailability of the drug in the spinal cord. However, these results provide an alternative explanation suggesting that the poor therapeutic activity of riluzole could be caused by opposite acute and chronic affects. If this interpretation is correct, there is the possibility that intermittent riluzole administration could have better therapeutic effects compared with the continuous treatment.

Motor neurons survival *in vitro* increases when incubated with a media previously conditioned by astrocytes or Schwann cells treated with riluzole compared to motor neurons treated with an unconditioned media. This beneficial effect on survival was mediated by trophic factors produced by astrocytes and Schwann trophic factors. The protective effect was lost by incubation of the conditioned media with antibodies against cardiotrophin-1 (CT1), brain-derived neurotrophic factors (BDNF), and glial-derived neurotrophic factor (GDNF). The study also shows that the protective effect of the conditioned media on motor neuron survival was also decreased after long-term incubation of the glial cultures with riluzole (Figure 1).



A: Intermittent Riluzole Therapy B: Continuous Riluzole therapy

Figure 1

In addition, increment in trophic factors especially CT1 protein and messenger RNA was reported in the spinal cord and sciatic nerve of mice treated with riluzole in the drinking water for up to 15 days. Chronic riluzole treatment not only eliminated the increase in the production of trophic factors, but also decreased the concentration to levels below the untreated controls for some trophic factors. The alternating on-off treatment of mice with riluzole reversed the inhibitory the long-term inhibitory effects of the drugs on the content of trophic factors. In fact, the CT1 levels in the spinal cord remained elevated as compared to the untreated control and animals that received continuous administration of riluzole for the same period. However, the effects depend on the protocol of administration, and the trophic factor investigated.

This study reveals that trophic factors such as CT-1, BDNF, and GDNF mediate the beneficial effect of riluzole on survival *in vitro*. However, riluzole stimulatory effect on trophic factor production by glial cells only occurs by short-term incubation with the drug. In contrast, long-term incubation with riluzole abolishes the enhanced production of trophic factors. These effects opposite effects on the production of trophic factors are observed also after acute and chronic administration of riluzole to mice, which are not due to desensitization to the drug because of the reduction trophic factors levels below control indicate an inhibitory effect. However, alternating on and off administration of riluzole to riluzole kept elevated the CT1 and prevents the inhibition of the trophic factors in the spinal cord. These results also demonstrated that riluzole has complex effects on the regulation of protein synthesis, which might be an important component of the therapeutic effect of the drug. Although further investigation is necessary, these results suggest that intermittent treatment with riluzole could be more beneficial than its continuous administration.

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