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And what about Gaba Magnetic Resonance Spectroscopy as an Indirect Tool to Evaluate Riluzole Efficacy in Amyotrophic Lateral Sclerosis?

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive muscular paralysis connected with degeneration of the human motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord [1]. ALS has been related to a complex multifactorial aetiology [1-3]. The machinery responsible for motor neuron degeneration remains largely unknown [1]. The development of ALS has been related to the glutamatergic neurotransmitter system, with destruction of motor neurons triggered through excessive activation of glutamate receptors at the synaptic cleft [4]. Glutamate is an essential component of synaptic transmission that is localized both at excitatory synapses, where it is the neurotransmitter, and at inhibitory synapses, where it serves as the substrate for Gamma-Aminobutyric Acid (GABA) synthesis [3,5]. Glutamate transporters supply GABAergic terminals with glutamate [4]. GABA is synthesized by decarboxylation of glutamate by Glutamic Acid Decarboxylase (GAD) [3,5]. Glutamate transporters tightly regulate glutamate concentration in the synaptic cleft maintaining stimulatory but non-toxic levels of free intra-synaptic L-glutamate in the area adjacent to neurons [3,5]. Dysfunction of glutamate transporters has been involved in the process of glutamate excitotoxicity that has been described as a major cause of brain injury [5]. Glutamate excitotoxicity has been implicated as a pathophysiologic mechanism in many neurodegenerative syndromes, including ALS [1,2]. A lack of neuroinhibitory function may result in unopposed excitotoxic neuronal damage in Amyotrophic Lateral Sclerosis (ALS) [6]. It has been reported that glutamate levels in cerebrospinal fluid are elevated in patients with ALS [1]. Five Excitatory Amino Acid Transporters (EAAT1-5) have been identified [3,5]. Impaired expression of EAAT3 also called Excitatory Amino-Acid Carrier 1(EAAC1) has been linked to a decrease in both tissue GABA levels and de novo synthesis from glutamate [3,5]. Decreased levels of GABA have been found in the motor cortex of patients with ALS compared to healthy controls suggesting a GABAergic deficit in ALS [7]. In addition, decreases in GABAergic inhibition has been correlated with cortical hyperexcitability [8]. Riluzole is the only FDA-approved drug to treat ALS [1,2]. It has been reported to have clearly proven efficiency on mortality with a 35 percent reduction in death or tracheostomy at 18 months [1,2]. Riluzole seems to exert a beneficial effect through different properties, including action on glutamatergic transmission increasing extracellular glutamate uptake with neuroprotection against excitotoxic damage [9]. Intriguingly, it has been found that riluzole significantly enhances glutamate uptake in a dose-dependent manner increasing the affinity of glutamate for the transporters including EAAC1 [9]. Magnetic Resonance Spectroscopy (MRS) is a powerful methodology that allows to quantify neurotransmitter concentrations in discrete regions of the human brain non- invasively in vivo [4,10]. Over recent years there has been a particular interest in using this technique to detect biologically relevant alterations in GABA concentrations [10,11]. High field strengths have improved signal-to-noise with a better separation of metabolic peaks, such as glutamate and GABA, which play an important role in the ALS pathogenesis [6,11,12]. MRS studies have confirmed the finely tuned balancing act between glutamate and GABA in the human brain both biochemically, as the huge majority of GABA is metabolized from glutamate, and functionally, with regard to the strict control of the inhibitory/excitability balance in healthy [6,12]. However, it has been reported that MRS gives a less accurate reflection of glutaminergic actions than GABAergic activity [10,11]. All these contentions led us to hypothesize that GABA MRS may represent an indirect promising tool to evaluate riluzole efficacy with timely detailed description of the dynamics of changes in GABA levels due to drug-induced effects on extracellular glutamate uptake. Longitudinal studies are needed to verify the applicability of GABA MRS in the management of the patients with ALS on treatment with riluzole. What's more, in vivo disease –specific GABA MRS changes may be utilized as potential biomarkers for upper motor neuron degeneration allowing to better assess disease progression expanding the knowledge and the comprehension of the natural history of ALS.

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