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Can inadequacy of rest between high-intensity exercises predispose for glutamate excitotoxicity among people at risk of motor neuron disease?

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ABSTRACT

Motor neuron disease (MND) is characterized pathologically by degenerative changes in the anterior horn cells, motor nuclei of the brainstem, and the corticospinal tracts. Several theories have been proposed to understand the etiology of MND. Glutamate excitotoxicity is one of the important theories that explain the pathogenesis of MND. Theories have argued participation in high-intensity exercises leads to excessive glutamate production and glutamate excitotoxicity which further leads to neuronal death and incidence of MND. However, to date, none of the studies/authors have explored the importance of rest periods in glutamate reabsorption. We argue that lack of adequate rest periods between the bouts of high-intensity exercises can be a potential risk factor for developing MND, rather than engaging in high-intensity exercise itself. In this short communication, we propose an interesting postulate on the role of rest periods in the prevention of glutamate excitotoxicity.

Keywords:

Amyotrophic lateral sclerosis, Anterior horn cell disease, High intensity exercises, Neuronal cell death, Pathogenesis

Motor neuron disease (MND) is characterized pathologically by degenerative changes in the anterior horn cells, motor nuclei of the brainstem and corticospinal tracts, and manifested clinically by muscle weakness, wasting, and corticospinal tract signs in varying combinations [1,2]. Amyotrophic Lateral Sclerosis (ALS) is the most prevalent MND that results from the progressive degeneration of the motor neurons in the spinal cord, brainstem, and motor cortex [1]. Numerous theories have been proposed to explain the pathogenesis of ALS that include free radical oxidative stress, cortical hyper excitability, autoimmunity, apoptosis, cytoskeletal abnormalities, a deficiency of neurotrophic factor, altered superoxide dismutase, decline in ascorbate availability [3], clostridial motor neuron toxin [4], viral infection, autoimmunity, and glutamate excitotoxicity [1,5].

Glutamate is one of the essential functional neurotransmitters in the human body [6]. Glutamate plays a role in a multitude of functions such as protein structure, nutrition, metabolism, and signaling [6]. In the central nervous system, glutamate has a major excitatory effect, whereas the product of glutamate, Gamma-aminobutyric acid (GABA), has a significant inhibitory effect. When the nerve cells transmit a signal to another nerve cell, glutamate is released into the synaptic cleft. Dysfunction of transporter cells (Astrocytic excitatory amino acid transporter 2 or Glial Glutamate transporter 1) in the postsynaptic nerve cells or astrocytes results in reduced uptake of glutamate from the synaptic cleft and leads to glutamate excitotoxicity [7]. Excessive glutamate in the synaptic cleft causes activation of Ca²⁺ dependent enzymatic pathways that results in mutation of genes (C9orf72, TDP-43, FUS, and SOD-1), disruption of RNA metabolism, formation of intracellular aggregates, oxidative stress, mitochondrial dysfunction, abnormal axonal transportation, neurotoxicity, and neuronal degeneration [5].

Participation in physical exercise has been considered as a risk factor for MND [8,9]. Vigorous or high-intensity exercises increase the synthesis of glutamate and GABA [10]. Impaired breakdown of glutamate can lead to excessive accumulation of glutamate in the synaptic cleft, glutamate excitotoxicity, and neurodegeneration. Theories have broadly argued that high-intensity exercises cause excessive glutamate production and glutamate excitotoxicity which may further lead to neuronal death and incidence of ALS, however, the findings are largely inconclusive. A larger research study revealed that individuals who regularly engaged in soccer are at high risk for ALS [11]. Among the soccer players, the risk of ALS was higher for midfielders and those with careers lasting more than 5 years [12]. Higher incidence of ALS among the midfielders could be due to their nature of job that requires increased number of motor units' recruitment and higher rate of action potential discharge (rate coding) without rest periods interspersed between the bouts of action potential discharge.

Short rest intervals between the sets of resistance training have been shown to produce higher lactate levels in contrast to long rest intervals among human participants following resistance training [13]. Though rest periods during the exercises have shown to assist in replenishing the energy stores, promote recovery and washout metabolic waste products [13], till date, none of the studies have explored the importance of rest periods between high-intensity exercises for effective glutamate reabsorption. Extrapolation of the aforementioned may suggest that long rest intervals may reduce the glutamate accumulation and the plausibility of glutamate toxicity between the bouts of high-intensity exercise.

Therefore, we argue that lack of adequate rest period between the bouts of high-intensity exercises as a potential risk factor for developing MND than the high-intensity exercises themselves. Incorporating adequate rest periods between the sessions of high-

intensity exercises may minimize the potential deleterious effects of glutamate accumulation and prevent neuronal cell death among those vulnerable for developing MND, especially in the presence of defective transport or reuptake of glutamate. However, this hypothesis needs to be substantiated by evaluating through future studies in animal models or human participants.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

AMJ and ZM were involved in conceptualization and manuscript writing. AJP and SP were involved in manuscript proofreading and editing. PN was involved in literature search, manuscript writing, proofreading, and editing.

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