

Commentary

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Commentary: Calcium in the pathomechanism of amyotrophic lateral sclerosis - Taking center stage?

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ABSTRACT

Amyotrophic lateral sclerosis is a rare and fatal neurodegenerative disorder characterized by the progressive loss of motor neurons in the central nervous system and neuromuscular junctions in the periphery. The pathomechanism behind the disease, except from some familiar cases associated with genetic mutations, remains unclear, however, numerous mechanisms contributing to the disease have already been disclosed. The key components are the oxidative stress, excitotoxicity, mitochondrial dysfunctions and inflammatory processes. In addition, increased intracellular calcium, which is another identified pathological event, could merge these individual toxic mechanisms into a single, escalating and self-perpetuating cycle of neuronal degeneration. Our previous results suggest that calcium homeostasis might be preserved by modulating the transmembrane calcium flux with therapeutic compounds or via altering the calcium binding protein content to maintain an enhanced calcium buffer capacity. The scope of this commentary is to accentuate the reciprocal calcium dependence of the pathological events associated with amyotrophic lateral sclerosis and to discuss possible therapeutic strategies based on the restoration of calcium homeostasis.

Introduction

French neurologist, Jean Martin Charcot, was the first who defined amyotrophic lateral sclerosis (ALS) as „*la sclérose latérale amyotrophique*” which is a French expression for a pathological manifestation of the disease. Pioneering work of Professor Charcot was the autopsy report of the scar tissue in the anterolateral fasciculus of the spinal cord which manifested as spasticity and paralysis in the patients¹. Nowadays amyotrophic lateral sclerosis is known as a non-cell autonomous², multifactorial³ and multisystem disease⁴, however its exact origin and all the details of the development of the disorder, relentlessly leading to death, are still unclear. Several pathophysiological processes contributing to the progression of the disease have been disclosed in the last five decades, for instance genetic mutations in more than a dozen of genes⁵, excitotoxicity⁶, oxidative stress⁷, immune/inflammatory processes⁸, mitochondrial dysfunctions⁹ and disruption in calcium homeostasis¹⁰. Significance of calcium ions in different physiological and pathological conditions is a well-known phenomenon, since it has got a prominent biological property in reversible complex formations¹¹ and second messenger function. As a rule in biochemical reactions, a limited concentration range characterizes the optimal conditions of the calcium-mediated processes: either too low or too high concentration values are irreconcilable with life. At low concentration values, the vital