Contribution Details

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Submission Type / Conference Track: Poster Abstract Submission

Development of Growth Hormone Secretagogues as new therapeutical tools for Amyotrophic Lateral Sclerosis

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Congress Topics: Muscle and motor neuron disorders
Symposia: Amyotrophic Lateral Sclerosis: From Molecular Mechanisms To Clinical Trial Design (ID 138)

Abstract

GHS are a large family of synthetic compounds originally developed for their capability to stimulate the release of GH. It has been proven that GHS also exert neuroprotective effects and participate in the regulation of skeletal muscle mass, in animals and humans. Their pleiotropic role on neurons and muscle cells suggest that these compounds could be developed for the treatment of ALS. The mutation in SOD1 with the replacement of glycine 93 by alanine is a well-known pathogenetic mechanism of ALS, responsible for a conformational change that leads to a gain-of-function resulting in oxidative stress, mitochondrial alterations, and apoptosis.

This research aims to investigate the potential protective effects of two selected GHS, hexarelin and JMV2894, against massive oxidative stress conditions. Hexarelin has important neuroprotective and cytoprotective activities, both in vitro and in vivo; JMV2894 stimulates Ca^{2+} mobilization, modulates mitochondria functioning and ROS production in vitro, and GH-release in vivo. To study the neuroprotective effects of hexarelin and JMV2894, human neuroblastoma cells overexpressing $SOD1^{G93A}$ enzyme were incubated for 24h with 150µM H_2O_2 or with the combination of H_2O_2 and 1µM hexarelin or 1µM JMV2894.

Morphometric quantification showed that H_2O_2-treatment induced an apoptotic phenotype that was rescued by both GHS. The quantification of mRNA levels of the BCL-2 family and those of the effector caspase proteins suggest that GHS have anti-apoptotic effects: both GHS significantly decreased Bax/Bcl-2 ratio and hexarelin also inhibited the activation of caspase-3.

The molecular pathways involved in GHS neuroprotection include the modulation of MAPKs and PI3K/Akt phosphorylation, probably through epigenetic mediation. Immunofluorescence visualization of γH2AX nuclear foci showed that hexarelin and JMV2894 significantly decreased the percentage of γH2AX-positive cells compared to the H_2O_2-treated group.

These findings suggest the possibility of developing new GHS-based anti-oxidant and neuroprotective drugs with improved therapeutic potential that may be useful in ALS therapy.