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Title (max 35 parole):
Selected Growth Hormone Secretagogues (GHS) as disease modifiers in an *in vitro* model of Amyotrophic Lateral Sclerosis: a proof-of-concept study

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Introduction: ALS is a disease characterized by rapid deterioration of both upper and lower motor neurons in the brainstem, motor cortex and spinal cord. The mutation in SOD1 with the replacement of glycine 93 by alanine is responsible for a conformational change that leads to a gain of function resulting in oxidative stress, mitochondrial alterations, and apoptosis [1].
GHS are a family of synthetic compounds capable to stimulate the release of GH, but they also exert neuroprotective effects and participate in the regulation of skeletal muscle mass, in animals and humans. Their pleiotropic roles on neurons and muscle cells suggest that GHS could be developed for the treatment of ALS. Among them, hexarelin has important neuroprotective and cytoprotective activities, both in vitro and in vivo; and JMV2894 stimulates Ca^{2+} mobilization in vitro and GH release in vivo, and modulates mitochondria functioning and ROS production [2].
Methods: human neuroblastoma cells overexpressing the $SOD1^{G93A}$ mutated protein (SH-SY5Y $SOD1^{G93A}$ cells) were treated with H_2O_2 and GHS for 24h to study the protective effect of GHS against increased oxidative stress. The mRNA expression levels were quantified by real-time PCR, whereas protein levels were measured by western blot.
Results: Morphometric evaluation 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.
Conclusions: Hexarelin and JMV2894 are capable of protecting cells from oxidative stress-caused cytotoxicity, suggesting the possibility of developing new anti-oxidant and neuroprotective drugs with improved therapeutic potential.

References:

[1] S.T. Ngo, H. Wang, R.D. Henderson, C. Bowers, F.J. Steyn, Ghrelin as a treatment for amyotrophic lateral sclerosis, J Neuroendocrinol. (2021). https://doi.org/10.1111/jne.12938.
[2] Meanti R, Bresciani E, Rizzi L, Coco S, Zambelli V, Dimitroulas A, Molteni L, Omeljaniuk RJ, Locatelli V, Torsello A. Potential Applications for Growth Hormone Secretagogues Treatment of Amyotrophic Lateral Sclerosis. Curr Neuropharmacol. 2023;21(12):2376-2394. doi: 10.2174/1570159X20666220915103613.