Selected Growth Hormone Secretagogues (GHS) decrease mutant SOD1 toxicity in an in vitro model of amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is an incurable motor neuron disease whose pathogenetic mechanisms are still unclear, even though mutations of superoxide dismutase 1 (SOD1) have been linked with several variants of ALS. SOD1 is an antioxidant enzyme that, by the substitution of glycine 93 to alanine ($SOD1^{G93A}$), leads to gain/loss of function that enhances the accumulation of highly toxic hydroxyl radicals. Currently, all interventions are only symptomatic and palliative, therefore there is a strong need to characterize more effective drugs. We have focused on the potential therapeutic effects of growth hormone secretagogues (GHS), a large family of synthetic compounds as possible candidates for the treatment of ALS.
GHS are a large family of synthetic compounds which have shown endocrine functions, through the stimulation of growth hormone (GH) release, and extra-endocrine properties, including stimulation of food intake and lean mass, at least in part by the binding to GHS-R1a, the receptor of ghrelin.
Among GHS, we have investigated the effects of (i) hexarelin, which has important neuroprotective and cytoprotective activities, both *in vitro* and *in vivo*; and (ii) JMV2894, which stimulates Ca^{2+} mobilization *in vitro* and GH release *in vivo*, and modulates mitochondria functioning and ROS production.
A human neuroblastoma cell line that expresses $SOD1^{G93A}$ enzyme (SH-SY5Y $SOD1^{G93A}$ cells) was incubated for 24 h with H_2O_2 (150 µM) or with the combination of H_2O_2 and hexarelin or JMV2894 (1 µM) to study the protective effect of GHS against increased oxidative stress.
GHS, but mainly hexarelin, exert protective effects and promote cell survival processes, by the activation of molecules that regulate apoptosis. The results suggest the possibility of developing new anti-oxidant and neuroprotective drugs with improved therapeutic potential even though further investigations are required to (i) clarify GHS molecular mechanisms of action, and (ii) whether their effects are mediated by GHS-R1a.

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15-17/12/2022