Potential Applications for Growth Hormone Secretagogues Treatment of Amyotrophic Lateral Sclerosis: the case of hexarelin and JMV2894

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Introduction:

Amyotrophic lateral sclerosis (ALS) is an incurable motor neuron disease, whose therapeutic strategies result in only minimal effects on the disease course and patient's survival.
Ghrelin and its synthetic derivatives, the growth hormone secretagogues (GHS), have been demonstrated to stimulate GH secretion and exert neuroprotective, anticonvulsant and anti-inflammatory effects. Moreover, they increase food intake and body weight, and participate in the regulation of skeletal muscle mass by stimulating insulin-like growth factor 1 (IGF-1) production, all aspects that are altered in ALS.
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.

Materials and Methods:

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. Apoptotic and cell survival markers were quantified by real-time PCR and western blot.

Results:

The treatment of SH-SY5Y $SOD1^{G93A}$ cells with H_2O_2 induces important changes in cell morphology which can be antagonize by hexarelin and JMV2894 incubation.
In addition, GHS exert anti-apoptotic effects by antagonizing cell morphology changes, modulating the mRNA levels and proteins belonging to the BCL-2 family as well as the activation of effector caspases.

Discussion:

The two selected GHS, 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. Further investigations are required to (i) clarify GHS molecular mechanisms of action, and (ii) to envisage the development of new GHS that may be useful in ALS therapy.

Breve Lay summary

ALS is a highly debilitating neurodegenerative disease for which there are no effective therapies to date, so research toward identifying promising molecules for new drug development is in constant flux. Given the evidence of hypermetabolism, weight loss, altered appetite, muscle atrophy, mitochondrial dysfunction and neurodegeneration in ALS patients, we have supposed that ghrelin and cognate growth hormone secretagogues (GHS) may constitute potential therapies for ALS.

In fact, ghrelin, a 28-amino acid hormone, binds to the pituitary GHS-R1a and stimulates GH secretion, but it is also endowed with multiple extra endocrine bioactivities. Likewise, the GHS, a large number of synthetic compounds encompassing short peptides, peptoids, and non-peptidic moieties, are capable to mimic several biological activities of ghrelin, including stimulation of GH release, appetite, and elevation of blood IGF-I levels. Moreover, GHS have demonstrated neuroprotective and anticonvulsant effects in experimental models of pathologies both *in vitro* and *in vivo*. To illustrate, some GHS, currently under evaluation by regulatory agencies for the treatment of human cachexia, have a good safety profile and are safe for human use.

In this context, comprehensive investigations of ghrelin and GHS modulation of apoptosis, inflammation, and mitochondrial dysfunction are timely.