Proliferative and Protective Effects of the GH/IGF-I Axis on Cardiomyocytes and Neural Progenitor Cells

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I I. Pettersson, G. Muccioli, R. Granata, R Deghenghi, E. Ghigo, C Ohlsson, J. Isgaard
Natural (Ghrelin) and Synthetic (Hexarelin) Growth Hormone Secretagogues Stimulate H9c2 Cardiomyocyte Cell Proliferation
Journal of Endocrinology (2002) Vol 175: 201-209.

II I. Johansson, S. Destefanis, N. D. Åberg, M.A.I. Åberg, K. Blomgren, C. Zhu, C. Ghe, R. Granata, E. Ghigo, G. Muccioli, P.S. Eriksson and J. Isgaard
Proliferative and Protective effects of Growth Hormone Secretagogues on Adult Rat Hippocampal Progenitor cells
Endocrinology (2008) Vol 149(5): 2191-2199

III N. David Åberg, Inger Johansson, Maria A. I. Åberg, Johan Lind, Ulf Johansson, Christiana M. Cooper-Kuhn, Fred H. Gage, H. Georg Kuhn, Jörgen Isgaard
Peripheral Administration of GH Induces Cell Proliferation in the Adult Hypophysectomized Rat Brain
Manuscript

Proliferative and Protective Effects of the GH/IGF-I Axis on Cardiomyocytes and Neural Progenitor Cells

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Cardiovascular disease is the most common cause of mortality in the Western world and the majority of cardiovascular deaths are caused by coronary artery disease or cerebrovascular disease.

Growth hormone (GH) is a growth-promoting hormone synthesized by the pituitary. Most of the effects of GH are mediated by local- or liver-produced insulin-like growth factor-I (IGF-I) but GH receptors have been found in a number of extra-hepatic tissues, suggesting direct, IGF-I-independent effects of GH. Synthetic and endogenous GH secretagogues (GHS) release GH from the pituitary and may also exert direct effects in various tissues.

Recent data suggest the GH/IGF-I system to improve cardiac performance and to be tissue protective after myocardial infarction. In the brain, the activity of the GH/IGF-I axis has been suggested to improve cognitive function, to exert cell protection after ischemic injury and to stimulate neurogenesis.

The aim of this thesis was to investigate direct proliferative and protective effects of compounds of the GH/IGF-I axis on cells or tissue from organs that are exposed to ischemic injury or degenerative disease, such as heart and brain. .

Our results suggest that the GH/IGF-I axis is involved in the generation of new cells, both in the heart and in the brain, and that some of these effects are independent of IGF-I. More specifically, the synthetic GHS hexarelin and the endogenous GHS ghrelin were found to have proliferative effects both in rat cardiomyocyte-like cells and in adult rat hippocampal progenitor (AHP) cells *in vitro*. In addition, hexarelin exerted protective effects in AHP cells after induction of apoptosis. Furthermore, peripheral administration of bovine GH (bGH) to hypophysectomized rats *in vivo* had proliferative effects in several brain regions and a proliferative effect was also found when AHP cells were incubated with bGH *in vitro*.

The results in this thesis may have potentially important clinical implications in ischemic and degenerative cardiac and cerebral disease, when cell protection and recruitment of new cells are desirable.

Keywords: GH, IGF-I, GH secretagogues, ghrelin, cardiovascular, neurogenesis, hippocampus, proliferation, protection

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