GH/IGF-I axis regulation of cardiovascular and neuronal gene expression and function

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i:
Föreläsningssalen Förmaket, Blå stråket 5, Göteborg, Fredagen den 11:e september kl 9.00

av

Anna Barlind, MSc

Fakultetsopponent: Professor Kerstin Bismar, Institutionen för molekylär medicin och kirurgi,

Karolinska Institutet

Arbetet baseras på följande delarbeten:

I. Åsa Tivesten, Anna Barlind, Kenneth Caidahl, Natalia Klintland, Antonio Cittadini, Claes Ohlsson and Jörgen Isgaard
Growth hormone-induced blood pressure decrease is associated with increased mRNA levels of the vascular smooth muscle KATP channel
Journal of Endocrinology (2004) 183, 195–202

II. Anna Barlind*, Marion Walser*, Per-Arne Svensson, Margareta Jernås, Henrik Torp, Lena M S Carlsson, Björn Carlsson, Jan Oscarsson, H Georg Kuhn, Jörgen Isgaard, N. David Åberg
Peripheral administration of bovine GH regulates beta-globin, GABAB receptor 1, and the Lissencephaly-1 protein (LIS-1) in Adult Hypophysectomized Rats
*Equal contribution
Manuscript

III. Anna Barlind, Niklas Karlsson, Thomas Björk- Eriksson, Jörgen Isgaard, Klas Blomgren
Decreased cytogenesis in the granule cell layer of the hippocampus and impaired place learning after irradiation of the young mouse brain, evaluated using the IntelliCage® platform
Submitted

IV. Anna Barlind, Niklas Karlsson, N. David Åberg, Thomas Björk-Eriksson, Klas Blomgren, Jörgen Isgaard
The growth hormone secretagogue hexarelin increases cell proliferation in neurogenic regions of the mouse hippocampus
Submitted

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GH/IGF-I axis regulation of cardiovascular and neuronal gene expression and function

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Abstract

Cardiovascular disease is a major cause of mortality in the Western world. Another important clinical condition is brain damage due to radiation therapy in cancer patients. This has neurological impairments presenting in the survivors. For both these conditions, it is important to develop new therapeutic strategies. In the present thesis, we have gained new knowledge regarding the physiological importance of growth hormone secretagogues (GHS), growth hormone (GH) and insulin-like growth factor-I (IGF-I) and their interaction with the cardiovascular system and neuronal progenitor cells. GH/IGF-I has previously been shown to regulate vascular tone, although the precise mechanisms are not known. We have investigated the effect of two weeks of GH treatment in hypophysectomized rats on blood pressure and gene expression in the aorta. We show that both subunits (Kir6.1 and SUR2B) of the vascular smooth muscle ATP-sensitive potassium channel are regulated by GH and that the expression was negatively correlated with systolic blood pressure. This provides a novel mechanism by which GH/IGF-I could regulate peripheral resistance.

The GHS-GH-IGF-I axis has a stimulatory effect in gene expression and increases cell proliferation in the brain. By treating hypophysectomized rats with GH we studied the effect on gene expression in the cerebral cortex. This study provided three novel genes regulated by GH, GABAB receptor 1, Lis-1 and hemoglobin b. These changes might be beneficiary to brain development and function in terms of possible neuroprotection and neuronal proliferation. In a model of irradiation (IR) to the young mouse brain we have investigated place learning, cell survival and the effect of hexarelin on cell survival in the hippocampus. Place learning was evaluated in an automated, operator independent system called Intellicage®. A significant difference in place learning was detected between irradiated mice and non-irradiated litter mates. Irradiated mice had reduced ability to recognize the right corner in which water was available accompanied by reduced number of proliferating cells in the granule cell layer (GCL) of the hippocampus. When treated with hexarelin for 4 weeks, cell survival in the GCL was increased in the IR group compared to untreated mice subjected to IR. This effect was transient or too small to detect when evaluated two weeks after treatment. Further studies in these areas will hopefully form the basis for development of new therapeutic strategies in patients with cardiovascular disease or radiation induced brain damage.

Keywords: Growth hormone, rat, hypophysectomy, vascular resistance, gene expression, place learning, Intellicage, hexarelin, CNS, hippocampus, neurogenesis, cell survival, mouse.

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