GASTRIC INHIBITORY POLYPEPTIDE IN THE BRAIN

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av
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Avhandlingen baseras på följande delarbeten:

I. Ekaterina Perfilieva, Anette Risedal, Jenny Nyberg, Barbro J. Johansson, Peter S. Eriksson. Gender and strain influence on neurogenesis in dentate gyrus of young rats.
J. Cereb. Blood. Flow. Metab. (2001), 21: 211-217.

II. Jenny Nyberg, Michelle F. Anderson, Björn Meister, Ann-Marie Alborn, Anna-Karin Ström, Anke Brederlau, Ann-Christin Illerskog, Ola Nilsson, Timothy J. Kieffer, Max Albert Hietala, Anne Ricksten, Peter S. Eriksson. Glucose-Dependent Insulinotropic Polypeptide Is Expressed in Adult Hippocampus and Induces Progenitor Cell Proliferation
Journal of Neuroscience (2005), 25(7):1816 –1825.

III. Jenny Nyberg, Calle Jacobsson, Michelle F. Anderson, Peter S. Eriksson
Immunohistochemical distribution of gastric inhibitory polypeptide in the adult rat brain.
J. Neurosc.i Research (2007), 85(10):2099-119.

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ABSTRACT

The hippocampus is an area of active cell proliferation and neurogenesis within the adult mammalian brain. Adult neurogenesis is of great importance for the brain, since it increases neuroplasticity and the ability to respond to environmental stimuli. It also provides a possible mechanism for the brain to replace lost cells that have died due to injury or disease. However, the molecular events controlling adult cell genesis in hippocampus remain largely unknown. One way of obtaining a deeper understanding of the mechanisms contributing to adult neurogenesis is to study the naturally occurring genetic variance in different inbred strains of rats while keeping the environment constant. In this thesis, we investigated differences in adult hippocampal neurogenesis between male and female rats of 2 different strains: Sprague-Dawley and Spontaneously Hypertensive. The aim of this project was to identify and investigate potential modulators of cell proliferation in the adult rat hippocampus. Combining BrdU, a marker of cell proliferation, with cell-specific markers, we found that Spontaneously Hypertensive rats had a higher rate of cell proliferation in the hippocampus than Sprague-Dawley rats. Moreover, male rats had more newborn cells than their female counterparts in both strains. To investigate this natural difference in proliferation rate and to identify potential regulators of cell genesis in the hippocampus, gene expression in the hippocampus was compared between the same groups of rats, using a cDNA array approach. Results revealed that hippocampal expression of the gene encoding glucose-dependent insulinotropic polypeptide (GIP) varied strongly in parallel with cell proliferation rates in the adult rat hippocampus. GIP is a polypeptide belonging to the secretin-glucagon family of gastrointestinal regulatory polypeptides, and it was the only member of this peptide family that had not been described in the brain. To support our DNA results, we used immunohistochemistry and *in situ* hybridization to show that GIP mRNA and protein is expressed in the adult hippocampus and in cultured adult hippocampal progenitors. Furthermore, we found that the GIP receptor is also expressed by cultured adult hippocampal progenitors and throughout the granule cell layer of the dentate gyrus including progenitor cells *in vivo*. To confirm the proliferative capacity of GIP, we demonstrated that exogenously-delivered GIP induces proliferation of hippocampal progenitors *in vivo* as well as *in vitro*. Moreover, adult GIP receptor knockout mice exhibited a significantly lower number of newborn cells in the hippocampal dentate gyrus compared to wild-type mice. In order to investigate the localization of GIP-producing cells, we used immunohistochemistry on sections of the adult rat brain. We observed a widespread distribution of GIP-immunoreactive cells in the brain, with the highest level in the olfactory bulb, hippocampus and Purkinje cells of the cerebellum. This investigation demonstrates for the first time the presence of GIP in the brain and provides evidence for a regulatory function of GIP in progenitor cell proliferation. Although the importance of GIP in the different brain structures remains to be established, its widespread distribution suggests that it may play an important modulatory function in the brain.

Keywords: neural progenitor cells, neural stem cells, hippocampus, cell proliferation, GIP, neuropeptides, neurogenesis, insulinotropic, gastrointestinal
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