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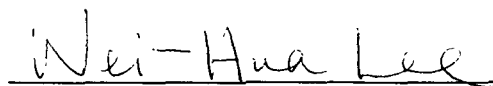
POTENTIAL MECHANISMS OF IGF-1'S EFFECT ON
HIPPOCAMPAL NEUROGENESIS

Su Huang

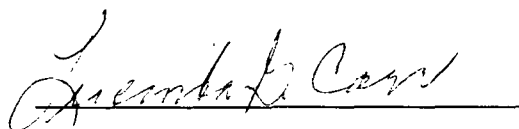
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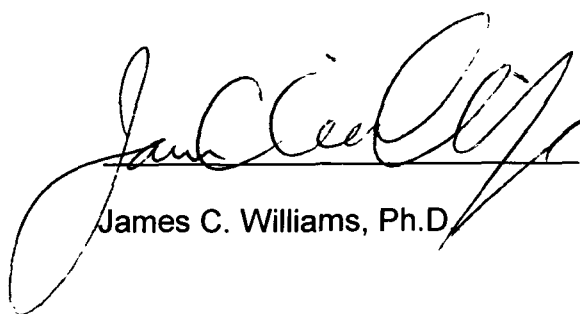
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Abstract

Su Huang

Potential Mechanisms of IGF-1's Effect on Hippocampal Neurogenesis

IGF-1 is a pleiotrophic growth factor essential for embryonic and postnatal growth of mammals. In the central nervous system, IGF-1 is known to play important roles in neuronal differentiation and survival. Although evidences from genetically manipulated mice indicate that IGF-1 levels correlate with brain sizes, whether and how IGF-1 promotes neuronal proliferation is still largely unknown. To study IGF-1's effects on this as well as underlying mechanisms of neuronal proliferation, we used IGF-1 transgenic mice and HN33 cells, which were derived from mouse hippocampal neurons. We chose to focus on the dentate gyrus in the hippocampus because it is the one of the brain regions in IGF-1 knockout mice containing low numbers of neurons. Interestingly, the dentate gyrus is also one of the brain regions where neurogenesis occurs in adulthood. First, we confirmed IGF-1's effects on neuronal proliferation in the hippocampus by comparing the number of BrdU-labeled cells and the volume of the dentate gyrus between IGF-1 transgenic mice and their wildtype littermates. Our preliminary data showed that presence of the IGF-1 transgene increased the volume of the hippocampal dentate gyrus and the number of BrdU-labeled cells. Next, we investigated potential mechanisms underlying IGF-1's effects on neuronal proliferation using HN33 cells. Our preliminary results demonstrated that IGF-1 promoted

the proliferation of HN33 cells via both the PI3 kinase pathway and the MAPK pathways. Furthermore, IGF-1 decreased p27 levels and sustained high levels of cyclin D₃ in HN33 cells, which suggests that IGF-1 has an effect on cell cycle progression. The same alteration in p27 and cyclin D was also seen in the dentate gyrus of IGF-1 transgenic mice, indicating that the same signaling mechanism is operating in vivo. Overall, our results demonstrate that IGF-1 has specific effects on the neurogenesis in dentate gyrus, which may be mediated through regulating the activity of p27 and cyclins via activating PI3 kinase and MAPK pathways.

Wei-Hua Lee, Ph.D., M.D., Committee Chair

Table of Contents

List of Figures	viii
Introduction	
I. IGF-1	
a. The Discovery of Insulin-like Growth Factors	1
b. IGF-1 Peptide and Gene Structures	2
c. IGF Binding Proteins	5
d. IGF-1 Receptor	8
e. IGF-1 Receptor Signal Transduction Pathway	10
II. The Role of IGF-1 in the Development of the Central Nervous System	
a. Growth Hormone/IGF-1 Axis	12
b. IGF-1 Gene Expression during Brain Development	14
c. IGF-1 and Brain Injury	16
d. Gene Deletion and Transgenic Mouse Models	17
III. IGF-1 and Neurogenesis	
a. Neuronal Proliferation in Vitro	20
b. Neuronal Proliferation in Vivo	21
IV. Hippocampal Dentate Neurogenesis	
a. Anatomy of Hippocampal Formation	22
b. Origin of Neurons in Dentate Gyrus	24
c. Plasticity of Hippocampal Dentate Neurogenesis in Adulthood	26
d. IGF-1 and Neurogenesis in Dentate Gyrus	27
V. Cell Cycle Regulation and Neurogenesis	28
VI. Objectives	31
Materials and Methods	
I. Materials	32
II. IGF-1 Transgenic Mice	32
III. PCR Genotyping	33
IV. HN33 Cell Lines	33
V. Tissue Preparation for Stereological Analysis	34
VI. Hemotoxylene-Eosin Staining	35
VII. Stereological Analysis of the Granule Cell Layer	35
VIII. Labeling of Proliferation Cells with BrdU in vivo	37
IX. BrdU Immunohistochemistry	38
X. BrdU labeling of HN33 cells	39
XI. Proliferation Assay for HN33 Cells	40
XII. Protein Extraction	41
XIII. Protein Assay	43
XIV. Western Blotting	44
XV. Statistical Analysis	46

Results

I. IGF-1 Transgene Expression Increases the Volume of the Granule Cell Layer in the Hippocampal Dentate Gyrus-----	47
II. IGF-1 Transgene Increases Cell Proliferation in the Subgranular Zone of Dentate Gyrus-----	48
III. IGF-1 Increases the Proliferation of HN33 cells-----	51
IV. IGF-1 Activates Both PI3/Akt and MAPK Pathways-----	53
V. IGF-1 Regulates the Activity of Foxo via Phosphorylation-----	55
VI. IGF-1 Increases the Level of Cyclin D ₃ -----	56
VII. IGF-1 Decreases the Level of p27-----	57
VIII. The Activities of pAkt and pMAPK as well as the Levels of Cyclin D ₃ are Increased in the Dentate Granule Cell Layers of IGF-1 Transgenic Mice-----	58

Discussion

I. IGF-1 Promotes Neurogenesis in the Dentate Gyrus-----	60
II. Both PI3 Kinase and MAPK Pathways Are Involved in IGF-1's Effects-----	64
III. Foxo is A Key Signaling Molecular Linking IGF-1's Action to Cell Cycle Progression-----	66
IV. IGF-1 Promotes Neurogenesis by Decreasing p27-----	67
V. IGF-1 Promotes Neurogenesis through Increasing Cyclin D ₃ -----	69

Summary and Conclusion-----	72
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Future Direction-----	73
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Figures-----	74
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References-----	94
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