精神分裂病の発症を規定する脳内蛋白質の探索とその治療領域への応用

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Search for proteins associated with schizophrenia in the brain and its therapeutic application

Research Project

Project/Area Number

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Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

展開研究

Research Field

応用薬理学・医療系薬学

Research Institution

Kanazawa University (1999)
Setsunan University (1997-1998)

Principal Investigator

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Schizophrenia / Negative syndromes / NMDA receptor / Transcription factors / DNA binding activity / Hippocampus / Dentate granule cells / c-Fos protein

Research Abstract

The present study deals with modulation of gene transcription in the brain, in order to evaluate possible involvement of N-methyl-D-aspartate (NMDA) receptor in mechanisms underlying the crisis of negative syndromes of Schizophrenia. Transcription factors are nuclear proteins with high affinity for a particular core nucleotide sequence to modulate the activity of RNA polymerase II that is responsible for formation of mRNA from genomic DNA in the nucleus. The systemic administration of NMDA led to selective and drastic potentiation of DNA binding activity of the transcription factor activator protein-1 (AP1) in murine brain. Frozen coronal sections were made with the aid of a cryostat, followed by punching out of the desired regions by a plastic capillary on dry ice under a binocular microscope. The potentiation was only seen in the dentate granule cells, but not in the CA1 and CA3 pyramidal cells. The potentiation in the dentate gyrus was transient with a peak at 2 h after administration and a diminution within 4 h later, which occurred in a manner sensitive to antagonism by an NMDA channel blocker. However, NMDA failed to markedly potentiate AP1 DNA binding in the CA1 and CA3 pyramidal neurons up to 4 h after administration. Immunohistochemical analysis revealed that NMDA induced expression of both c-Jun and c-Fos proteins in the dentate gyrus, but not in the CA1 and CA3 subfields. Moreover, a systemic injection of NMDA resulted in a variety of abnormal behaviors, such as tail biting, in mice for 2 h. These results suggest that modulation of de novo synthesis of particular proteins may underlie mechanisms associated with long-lasting alterations of brain functions such as Schizophrenia.

Research Products (8 results)

All | Other

All | Publications (8 results)

[Publications] Kiyokazu Ogita: "Differential inhibition by ferrous ions of ['H]MK-801 binding to native N-methyl-D-aspartate …"Brain Research. 818. 548-552 (1999)

[Publications] Kiyokazu Ogita: "Preventive effects of exogenous phosphalipases on inhibition by ferrous ions of [^3H]MK-801 binding …"Neurochemistry International. 34. 193-201 (1999)

[Publications] Yasutaka Azuma: "Constitutive expression of cytoplasmic activator protein-1 with DNA binding activity …"Neuroscience. 92. 1295-1308 (1999)

[Publications] Yukio Yoneda: "Predominant expression of nuclear activator protein-1 complex with DNA binding …"Neuroscience. 93. 19-31 (1999)

[Publications] K. Ogita et al.: "Differential inhibition by ferrous ions of [イイD13イエD1H]MK-801 binding to native N-methyl-D-aspartate channel in neonatal and adult rat brains."Brain Res.. 818. 548-552 (1999)

[Publications] K. Ogita et al.: "Preventive effects of exogenous phospholipases on inhibition by ferrous ion of [イイD13イエD1H]MK-801 binding in rat brain synaptic membranes."Neurochem. Int.. 34. 193-201 (1999)

[Publications] Y. Azuma et al.: "Constitutive expression of cytoplasmic activator protein-1 with DNA binding activity and responsiveness to ionotropic glutamate signals in murine hippocampus."Neuroscience. 92. 1295-1308 (1999)

[Publications] Y. Yoneda et al.: "Predominant expression of nuclear activator protein-1 complex with DNA binding activity following systemic administration of N-methyl-D-aspartic acid in dentate granule cells of murine hippocampus."Neuroscience. 93. 19-31 (1999)