# Studies on neurotoxic mechanisms by excitotoxins



# 2000 Fiscal Year Final Research Report Summary

## Studies on neurotoxic mechanisms by excitotoxins

Research Project

### Project/Area Number

10044328

### Research Category

Grant-in-Aid for Scientific Research (A).

### Allocation Type

Single-year Grants

### Section

一般

### Research Field

Biological pharmacy

### Research Institution

Kanazawa University (1999-2000)
Setsunan University (1998)

### Principal Investigator

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### Co-Investigator(Kenkyū-buntansha)

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### Project Period (FY)

**1998 – 2000**

### Keywords

Neuronal death / Neurotoxins / NMDA receptors / KA receptors / Transcription factors / CA1 and CA3 subfields / 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 particular ionotropic receptor subtypes for L-glutamic acid in mechanisms underlying neuronal toxicity by excitotoxins. 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 N-methyl-D-aspartic acid (NMDA) led to selective and drastic potentiation of DNA binding activity of the transcription factor activator protein-1 (AP1) in murine hippocampus. 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 decline within 4 h later, which occurred in a manner sensitive to antagonism by an NMDA channel blocker. 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. By contrast, kainic acid (KA) induced drastic and prolonged potentiation of AP1 DNA binding in the CA1 and CA3 pyramidal layers in addition to dentate granule layers. The administration of KA but not NMDA led to marked potentiation of AP1 binding in areas neighboring but excluding pyramidal and granule layers. KA induced severe neuronal death in the CA1 and CA3 pyramidal layers without affecting dentate granular neurons. These results suggest that modulation of de novo synthesis of particular proteins may underlie mechanisms associated with neuronal cell death induced by excitotoxins.

# Research Products (46 results)

All Other

All Publications

[Publications] T.Manabe: "Differential in vitro degradation of particular Fos family members expressed by kainic acid ……"J.Neurosci.Res.. (in press). (2001)

[Publications] K.Ogita: "Effects of glutathione depletion by 2-cyclohexen-1-one on excitatory amino acid-induced enhancement ……"J.Neurochem.. (in press). (2001)

[Publications] E.Hinoi: "Expression of GluR6/7 subunits of kainate receptors in rat adeno hypophysis"Neurochem.Int.. (in press). (2001)

[Publications] Y.Yoneda: "Consolidation of transient ionotropic signals through nuclear transcription factors in the brain"Prog.Neurobiol.. 63. 697-719 (2001)

[Publications] E.Hinoi: "Group III metabotropic glutamate receptors in cultured rat calvarial osteoblasts"Biochem.Biophys.Res.Comm.. 281. 341-346 (2001)

[Publications] E.Hinoi: "Characterization with [^3H] quisqualate of group I metabotropic glutamate receptor subtype……"Neurochem.Int.. 38. 277-285 (2001)

[Publications] T.Manabe.: "Differential expression and phosphorylation of particular Fos family members by kainic acid……"Neuroscience. 100. 453-463 (2000)

[Publications] J.Platenik: "Molecular mechanisms associated with long-term consolidation of the NMDA signals"Life Sci.. 67. 335-364 (2000)

[Publications] E.Hinoi: "Direct radio labeling by [^3H]quisqualic acid of group I metabotropic glutamate receptor in rat brain ……"Brain Res.. 881. 199-203 (2000)

[Publications] R.Janaky: "Glutathione and signal transduction in the mammalian CNS"J.Neurochem.. 73. 889-902 (1999)

[Publications] T.Kitayama: "Sensitization by prolonged glutathion depletion of kainic acid to potentiate DNA binding activity ……"Neurosci.Lett.. 269. 157-160 (1999)

[Publications] K.Ogita: "Differential inhibition by ferrous ions of [^3H]MK-801 binding to native N-methyl-D-aspartate ……"Brain Res.. 818. 548-552 (1999)

[Publications] K.Ogita: "Preventive effects of exogenous phospholigases on inhibition by ferrous ion of [^3H]MK-801 binding……"Neurochem.Int.. 34. 193-201 (1999)

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

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

[Publications] T.Kitayama: "Sustained potentiation of AP1 DNA binding is not always associated with neuronal death……"Neurochem.Int.. 35. 453-462 (1999)

[Publications] Y.Yoneda: "N-Methyl-D-aspartate signaling in nuclear activator protein-1 through mechanisms different from ……"Neuroscience. 90. 519-533 (1999)

[Publications] F.Stastny: "Ferrous iron modulates quinolinate-mediated [^3H]MK-801 binding to rat brain synaptic……"Neurosci.Lett.. 262. 105-108 (1999)

[Publications] N.Karamoto: "Correlation between potentiation of AP1 DNA binding and expression of c-Fos in association with ……"Brain Res.. 806. 152-164 (1998)

[Publications] K.Ogita: "Nitric-Oxide independent inhibition by sodium nitrogrusside of the native N-methyl-D-aspartate…"Neurochem.Int.. 33. 1-9 (1998)

[Publications] Y.Yoneda: "Possible involvement of AP1 DNA binding in mechanisms underlying is chemic tolerance in the CA1……"Neuroscience. 86. 79-97 (1998)

[Publications] Y.Azuma: "Possible invivo cross talk between transcription factors with zinc-finger and leucine-zipper……"Neurochem.Int.. 32. 325-336 (1998)

[Publications] Y.Yoneda: "Prolongation by bifemerane of potentiation of AP1 DNA binding in hippocampal CA1 subfield ……"J.Neurosci.Res.. 51. 574-582 (1998)

[Publications] T.Manabe: "Differential in vitro degradation of particular Fos family members expressed by kainic acid in nuclear and cytosolic fractions of murine hippocampus."J.Neurosci.Res.. (in press).

[Publications] K.Ogita: "Effects of glutathione depletion by 2-cyclohexen-1-one on excitatory amino acid-induced enhancement of activator protein-1 DNA binding in murine hippocampus"J.Neurochem.. (in press).

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[Publications] R.Janaky: "Glutathione and signal transduction in the mammalian CNS."J.Neurochem.. 73. 889-902 (1999)

[Publications] T.Kitayama: "Sensitization by prolonged glutathione depletion of kainic acid to potentiate DNA binding activity of the nuclear transcription factor activator protein-1 in murine hippocampus."Neurosci.Lett.. 269. 157-160 (1999)

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[Publications] Y.Azuma: "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: "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)

[Publications] T.Kitayama: "Sustained potentiation of AP1 DNA binding is not always associated with neuronal death following systemic administration of kainic acid in murine hippocampus."Neurochem.Int.. 35. 453-462 (1999)

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[Publications] N.Kuramoto: "Correlation between potentiation of API DNA binding and expression of c-Fos in association with phosphorylation of CREB in thalamus of gerbils with ischemia."Brain Res.. 806. 152-164 (1998)

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[Publications] Y.Yoneda: "Possible involvement of AP1 DNA binding in mechanisms underlying ischemic tolerance in the CA1 subfield of gerbil hippocampus."Neuroscience. 86. 79-97 (1998)

[Publications] Y.Azuma: "Possible in vivo crosstalk between transcription factors with zinc-finger and leucine-zipper motifs in murine peripheral but not central excitable tissues."Neurochem.Int.. 32. 325-336 (1998)

[Publications] Y.Yoneda: "Prolongation by bifemerane of potentiation of AP1 DNA binding in hippocampal CA1 subfield of gerbils with transient forebrain ischemia."J.Neurosci.Res.. 51. 574-582 (1998)

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