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EFFECT OF CYCLOHEXIMIDE ON KAINIC ACID-INDUCED PROENKEPHALIN mRNA INCREASE IN THE RAT HIPPOCAMPUS: ROLE OF PROTO-ONCOGENES

Je-Seong. Won°, Hong-Won Suh, Dong-Keun Song, and Yung-Hi Kim

Department of Pharmacology, Institute of Natural Medicine, College of Medicine, Hallym University, Chunchon.

Previous studies have shown that kainic acid (KA) causes an elevation of hippocampal proenkephalin mRNA level. However, the role of proto-oncogene products, such as c-Fos, c-Jun and Fra proteins in the regulation of KA-induced proenkephalin mRNA increase in the hippocampus has not been well characterized.Thus, in the present study, the effect of cycloheximide (CHX) on KA-induced proenkephalin mRNA and immediate early gene products induction was examined. After pretreating with either vehicle or CHX (20 mg/kg, s.c.) for 30 min, KA (10 mg/kg) was administered s.c. The animals were sacrificed 1, 2, or 8 hrs after KA administration. Total RNA and were isolated for Northern blot assay, and proteins were isolated for Western and electrophoretic gel-shift assays. First, we found that CHX inhibited KA-induced proenkephalin mRNA increase without altering intracellular proenkephalin protein level. Secondly, Western blot assays showed that KA increased c-Fos, c-Jun and Fra proteins at 1, 2, and 8 hrs and CHX inhibited these immediate early gene products. Finally, electrophoretic gel shift assays revealed that KA increased both AP-1 and ENKCRE-2 DNA binding activities. Furthermore, CHX attenuated KA-induced AP-1 and ENKCRE-2 DNA binding activities. Both AP-1 and ENKCRE-2 DNA binding activities were abolished by cold AP-1 or ENKCRE-2 oligonucleotides, and further reduced by antibodies against c-Fos or c-Jun. Antibody against CREB reduced ENKCRE-2, but not AP-1, DNA binding activity. Our results suggest that on-going protein synthesis is required for elevation of hippocampal proenkephalin mRNA level induced by KA. All c-Fos, c-Jun, and Fra proteins appears to be involved in the regulation of hippocampal proenkephalin mRNA level induced by KA (This study was supported by a grant from KOSEF).