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Neuroprotectins A and B, Two New Bicyclohexapeptides Protecting Primary Cultured Neurons from Excitotoxicity

Bong-Sik Yun, In-Ja Ryoo and Ick-Dong Yoo
Korea Research Institute of Bioscience and Biotechnology, Yusong, Taejon 305-600, Korea

Excitatory amino acids are known to induce considerable neurotoxicity in central nervous system in abnormal condition. It has been known that glutamatergic system was involved in the development of neuronal cell death following a variety of traumas including ischemia, hypoglycemia and epilepsy and certain neurodegenerative diseases such as Huntingtons chorea, Parkinsons disease, Alzheimers disease and AIDS neuropathology. The glutamatergic system is divided into two main categories depending on the agonist preference of the postsynaptic receptor system. The *N*-methyl-D-aspartate (NMDA) is one major ionotropic receptor, whereas the other comprises kainate and a-amino-3-hydroxy-5-methyl-isoxa-sol- 4-propionic acid (AMPA) receptors. Kainate is a powerful neurotoxin that produces selective neuronal damage in the CNS and is employed as a tool to destroy postsynaptic elements in the brain, while preserving presynaptic structures. Kainate preferentially destroys the CA3/CA4 hippocampal formation, when it is administered to rat intraventricularly. This region corresponds to that with high density of kainate receptors.

During the screening for novel neuroprotective compounds against kainate-induced neurotoxicity using chick primary telencephalic cell culture and mouse primary cortical cell culture, we have isolated two novel compounds neuroprotectins A and B from the fermentation broth of *Streptomyces* sp. 60910. Neuroprotectins A and B possessed oxindolylalanine moiety in their structure, which was differentiated from well known bicyclohexapeptides, complestatin and chloropeptin. Neuro- protectins protect primary cultured mouse cortical neurons from excitotoxicity induced by NMDA and AMPA as well as kainate, in a dose dependant fashion.

We also report herein the taxonomy of the producing microorganism, fermentation, isolation, physicochemical properties, structure determination, and the detailed biological activities of these compounds.