Neuroprotective Function of PACAP and Its Molecular Mechanism

○Seiji Shioda, Tomoya Nakamachi, Hirokazu Ohtaki, Jun Watanabe, Kenji Dohi
(Dept. of Anatomy, Showa Univ. Sch. of Med.)
Hitoshi Hashimoto, Norihito Shintani, Akemichi Baba
(Lab. Mol. Neuropharmacol., Osaka Univ. Sch. Pharmac. Sci.)

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a pleiotropic neuropeptide that belongs to the secretin/glucagon/VIP family. PACAP prevents ischemic delayed neuronal cell death (apoptosis) in rat and mouse brain. PACAP inhibits the increasing activity of the MAP kinase family, especially on JNK/SAPK and p38, thereby protecting apoptotic delayed neuronal cell death. After the ischemia-reperfusion, both pyramidal cells and astrocytes increased the expression of PACAP receptor (PAC1-R). Reactive astrocytes, increased expression of PAC1-R, released interleukin-6 (IL-6) thereby protected neuronal cell death. To clarify the signaling pathway associated with the activity of PACAP and IL-6, phosphorylated STAT (signal transducer and activator of transcription) 3, ERK (extracellular signal-regulated kinase) and AKT levels were examined in $PACAP^{+/-}$ and IL-6 null mice following brain ischemia. Lower levels of pSTAT3 and pERK were observed in the $PACAP^{+/-}$ mice, while a reduction in pSTAT3 was recorded in the IL-6 null mice. These results suggest that PACAP prevents neuronal cell death after ischemia via a signaling mechanism involving IL-6. These findings strongly suggest that PACAP has pleiotropic functions such as neuroprotection as well as astrocyte differentiation during development.