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Neuroprotective Effects of Pituitary Adenylate Cyclase-Activating Polypeptide

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Abstract

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a member of the secretin/glucagon/vasoactive intestinal peptide (VIP) super family. PACAP was first isolated from an ovine hypothalamus and named because it stimulated cAMP production in the rat pituitary cell culture. PACAP is widely expressed in the central and peripheral nervous systems. PACAP plays the roles of neurotransmitter, neuromodulator and neurotrophic factors via three G-protein binding receptors, PAC1, VAPC1 and VPAC2. A number of recent studies have discovered the neuroprotective functions of PACAP in both in vitro and in vivo models. PACAP protects the neurons from death through both direct and indirect ways. PACAP inhibits caspase-3 through cAMP-PKA or MAP kinase-signaling pathways. Moreover, PACAP can stimulate astrocytes to release neuroprotective factors, such as interleukin-6 (IL-6). The present review will briefly summarize the recent studies and provide information for the future use in the clinic.

Key words:

Pituitary adenylate cyclase-activating polypeptide; Neuroprotection; Neurodegeneration; Alzheimer's disease; Parkinson's disease

Review

Pituitary adenylate cyclase-activating polypeptide (PACAP) was first isolated from an ovine hypothalamus by Dr. Arimura and his colleagues in 1989 and demonstrated to be one of most conserved peptide through the different species [**1**]. PACAP belongs to the secretin/glucagon/vasoactive intestinal peptide family and exists in a full form (PACAP-38) and a shorter form (PACAP-27) [**2**,**3**]. PACAP and its three different receptors, PAC1, VPAC1 and VPAC2, have been demonstrated in the central and peripheral nervous system [**4-8**]. Furthermore, previous studies have proved that PACAP has pleiotropic functions, such as the regulation of neurodevelopment and protection against neuron apoptosis. The peptide exerts its physiological effects via PAC1, VPAC1 and VPAC2 receptors, which all belong to the class B, family of G protein-coupled receptors (GPCRs) [**8-10**]. The primary signaling pathways of PACAP receptors are cAMP mediated both PKA and MAPK pathways. The phospholipase D (PLD) and calcium signaling pathways can be activated by PACAP receptors as well [**11-16**].

Evidences from numbers of in vitro and in vivo experiments suggest that PACAP may enhance neuronal survival and neuronal regeneration in the nervous system [**17-19**]. The cultured cerebellar granule cell, a model of programmed cell death, is widely used for investigation of the neuroprotective factors. PACAP was demonstrated to prevent programmed cell death of cerebellar granule cell during cerebellar development [**20-22**]. PACAP has been reported to protect cerebellar granule cells against apoptosis induced by different neurotoxins including ethanol, hydrogen peroxide and ceramides. Incubating cultured granule cells with PACAP and the neurotoxins increased the number of living cells, decreased DNA fragmentation and resorted mitochondrial activity [**23-25**]. PACAP also showed its neuroprotective function in the other model systems. For example, PACAP protected neuron-like PC12 cells against cytotoxicity of b-amyloid, which is a key player in Alzheimer's disease [**26**]. PACAP has been reported to maintain the PC12 cell living under exposure of rotenone, which may cause Parkinson's disease [**27**]. The neuroprotective effects of PACAP are also observed in some in vivo models, especially in some neurodegenerative and neuron injury diseases models. PACAP has significant neurotrophic and neuroprotective effects after the cerebral ischemia or stroke, which is caused by decrease in oxygen and glucose in the brain [**28-30**]. For example, the injection of PACAP prevented the ischemic death of rat CA1 neurons in a model of transient global ischemia. In a mouse model of stroke, PACAP ameliorates neurological defects when administration begins 4 hours after middle cerebral artery occlusion [**30**]. As well PACAP appeared to be a neuroprotective factor in some animal models of Parkinson's diseases (PD) and Alzhihermer's diseases (AD). Reglodi and colleagues discovered that PACAP prevented the substantia nigra (SN) dopaminergic neurons from apoptosis and improved behavioral symptoms in a rat model of PD induced by the 6-hydroxydopamine (6-OHDA) [**31**]. In another PD model produced by the 1-methy1-4-phenyl-1, 2, 3, 6-etrahydropyridine (MPTP), several groups have showed that injection of PACAP improved memory impairment in the water maze test [**6**]. PACAP is one of three genes that are down regulated in both AD patients and AD rodent models [**32**]. Several reports suggest that PACAP stimulates the α-secretase activity, which can lead to the release of soluble N-terminal APP fragments with neurotrophic and neuroprotective properties [**33-36**].

The mechanisms of the neuroproticetive action of PACAP can be summarized to direct and indirect ways based on published manuscripts. The direct mechanism is that PACAP protects neurons via its receptors on neuronal cells to activate cAMP-PKA/MAPK

pathways [**23**,**25**,**26**,**37**]. Through the pathways, PACAP can deactivate caspase-3, an apoptotic key enzyme, and induce expression of neurotrophin such as Brain-derived neurotrophic factor (BDNF) to keep the neurons survival [**21**,**38**]. Indirectly, PACAP protects the neurons by modulating glial cells to improve the microenvironments around the neurons. For instance, the astrocytes express a lot of PACAP receptors. PACAP can induce the high secretion of interleukin-6 (IL-6) to protect CA1 neurons against apoptosis in the ischemic hippocampus [**39**].

In conclusion, a numbers of previous studies have showed that PACAP has a significant neuroprotective potential because of its neurotrophic and anti-apoptosis effect through direct and indirect mechanisms. Furthermore, PACAP has the ability to cross the blood brain barrier [**40**]. Therefore, PACAP may become a useful therapeutic agent in many brain injury and neurodegenerative diseases. In order to utilizing PACAP in clinic, researchers still need to pay more attention to delivery of PACAP into the specific region and blockade of PACAP degradation

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