Neuroprotective potential of three neuropeptides PACAP, VIP and PHI

Agnieszka Dejda¹, Paulina Sokolowska¹, Jerzy Z. Nowak¹.²

¹Centre for Medical Biology, Polish Academy of Sciences, Lodowa 106, PL 93-232 Łódź, Poland
²Department of Pharmacology, Medical University, Żeligowskiego 7/9, PL 90-752 Łódź, Poland

Correspondence: Agnieszka Dejda, e-mail: adejda@cbmim.pan.pl

Abstract:
Pituitary adenylate cyclase activating polypeptide (PACAP), vasoactive intestinal peptide (VIP) and peptide histidine-isoleucine (PHI), are structurally related endogenous peptides widely expressed in the central and peripheral nervous system and showing rich profile of biological activities. They act as neurotransmitters, neuromodulators and neurotrophic factors. Recently, their neuroprotective potential has been revealed in numerous in vitro and in vivo models. Thus, PACAP and VIP protected the cells from neurotoxic effects of ethanol, hydrogen peroxide (H₂O₂), β-amyloid and glycoprotein 120 (gp120). Moreover, PACAP showed neuroprotection against glutamate, human prion protein fragment 106–126 [PrP(106–126)] and C2-ceramide. Both peptides reduced brain damage after ischemia and ameliorated neurological deficits in a model of Parkinson’s disease. Neuroprotective potential of PHI has not been thoroughly investigated yet, but several results obtained in the last years do not exclude it. The mechanism underlying neuroprotective properties of PACAP seems to involve activation of adenylyl cyclase (AC) → cyclic adenosine 3',5'-mono-phosphate (cAMP) → protein kinase A (PKA) and mitogen-activated protein (MAP) kinase pathways, and inhibition of caspase-3. PACAP can also, yet indirectly, stimulate astrocytes to release neuroprotective factors, such as regulated upon activation normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein 1 (MIP-1) chemokines. Neuroprotective activity of VIP seems to involve an indirect mechanism requiring astrocytes. VIP-stimulated astrocytes secrete neuroprotective proteins, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP), as well as a number of cytokines. However, in the activated microglia, VIP and PACAP are capable of inhibiting the production of inflammatory mediators which can lead to neurodegenerative processes within the brain.

In conclusion, studies carried out on the central nervous system have shown that PACAP, VIP, and likely PHI, are endowed with a neuroprotective potential, which renders them (or their derivatives) promising therapeutic agents in several psychoneurological disorders linked to neurodegeneration.

Key words: pituitary adenylate cyclase activating polypeptide, vasoactive intestinal peptide, peptide histidine-isoleucine, activity-dependent neurotrophic factor and activity-dependent neuroprotective protein, neuroprotection

Introduction

Pituitary adenylate cyclase activating polypeptide (PACAP), vasoactive intestinal peptide (VIP) and peptide histidine-isoleucine (PHI), belong to structurally related family of polypeptides, comprising also peptide histidine-methionine (PHM), secretin, glucagon, glucagon-like peptide (GLP), glucose-dependent insulinotropic polypeptide (GIP), growth hormone releasing hormone (GHRH) and helodermin [87]. PACAP, originally isolated from the sheep hypothalamic extracts and described as a factor potently