Neuropeptides and retinal development: multiple roles for PACAP.

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In retinal tissue a conserved sequential order of events leads to the formation of a laminar structure with seven main cell classes and diverse neurochemical phenotypes. In this process both extrinsic and intrinsic factors are determinant. We are interested in the roles of extracellular signaling molecules upon key events of neural development, such as cell death, proliferation and differentiation. Previously, we demonstrated that PACAP (pituitary adenylate cyclase-activating polypeptide), a neuropeptide of the VIP, secretin and glucagon superfamily of peptides, is a potent neuroprotective agent in the retina (Silveira et al. J Biol. Chem. 277(18): 16075-80, 2002). This effect is dependent of cAMP/PKA pathway.

It has also been reported that this peptide may act as a modulator of the proliferative status of neuroblasts. In the cerebral cortex it showed an anti-mitogenic effect, whereas it is pro-mitogenic in sympathetic neurons. These contrasting actions were attributed to the signal transduction pathway activated, and it was suggested that cAMP production induced an anti-proliferative effect (Nicot and DiCicco-Bloom, PNAS, 98(8): 4758-63, 2001).

In this study we showed by RT-PCR that retinal tissue from postnatal day 1 (P1) rats expresses both the PAC1 and the VPAC receptors. PAC1 receptor was also detected by double immunofluorescence in retinal precursors from embryonic and neonatal retinas. The anti-proliferative effect of PACAP (10nM) was observed after 24 hours in P1 rat retinal tissue through [^{3}H]-thymidine incorporation, as well as by counting the number of cells labeled with BrdU. Both maxadilan, a specific agonist of the PAC1 receptor, and forskolin, an adenylyl cyclase activator, presented similar effects. In a search for molecular mechanisms involved in the anti-proliferative effect, we are currently analyzing key elements of the cell cycle. Our data show that, in contrast with cortical neuroblasts (Carey et al. J Neurosci. 22(5):1583-91, 2002), the expression of the CKI (cyclin- CDK inhibitor) p57 is not induced by PACAP.

Our data show that PACAP regulates progenitor cell proliferation during retinal development, and suggest that this peptide may induce cell cycle withdrawal of retinal precursors, possibly by acting in the transition from proliferation to neuronal differentiation. *(Supported by Prodoc-CAPES, CNPq, FAPERJ, Pronex).*