Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol10Issue2abst044P.pdf

Effects of PACAP on signaling pathways in the retina exposed to oxidative stress or ischemia

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Pituitary adenylate cyclase activating polypeptide (PACAP) has well-established protective effects in the nervous system, including the retina. PACAP exerts retinoprotective effects against several types of injuries in vivo, including optic nerve transection, retinal ischemia, excitotoxic injuries, UVA-induced lesion and diabetic retinopathy. In a recent study we have proven that PACAP is also protective in oxidative stress-induced injury in human pigment epithelial cells (ARPE-19 cells). The aim of the present study was to investigate mechanisms of the retinoprotective effects of PACAP in oxidative stress-induced injury in human ARPE cells in vitro and hypoperfusion-induced injury in vivo. ARPE cells were exposed to 24 h hydrogen peroxide treatment, while the in vivo hypoperfusion was induced by 24 h-bilateral carotid artery occlusion in rats. Expressions of kinases were studied Western blot, while changes in apoptotic, angiogenetic markers and cytokines were studied by complex array kits. Oxidative stress of ARPE cells induced the activation of several apoptotic markers, including bad, bax, HIF-1α, several heat shock proteins, Trail and Fadd, while PACAP treatment decreased them. The changes in the expression of MAP kinases showed that PACAP activated the protective ERK1/2 and downstream CREB, and decreased the activation of the pro-apoptotic p38MAPK and JNK, an effect opposite to that observed with only oxidative stress. These changes were observed in both the in vitro stress model and the in vivo ischemic injury. Furthermore, PACAP increased the activation of the protective Akt pathway in both models. In addition, the effects of oxidative stress on several other signaling molecules were counteracted by PACAP treatment (e.g. HIF1alpha, Chk2, Yes, Lyn, paxillin, p53, PLC, STAT4, RSK). In ischemia-induced injury in vivo, PACAP treatment counteracted the ischemia-induced changes in several cytokines, such as IL-1, CINC, fractalkine, sICAM, MIP, VEGF, selectin, TIMP, CNTF, RANTES and thymus chemokine. These play a role in cell death, cell cycle, angiogenesis, inflammation, adhesion, differentiation and proliferation. In summary, PACAP, acting at different levels, counteracts changes in several stress-induced inflammatory, apoptotic/survival and angiogenetic markers, thereby providing protection in oxidative stress-induced injury of human retinal pigment epithelial cells and ischemia-induced injury in vivo.

Supported by OTKA (K72592, 75965, CNK78480), SROP 4.2.1.B-10/2/KONV-2010-002, 4.2.2.B-10/1-2010-0029, Bolyai Scholarship, Richter Foundation, PTE-MTA “Lendulet” Program.