Effect of bone matrix protein osteocalcin on proliferation and neuronal differentiation of PC12 cells

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Bone matrix protein osteocalcin (OC) was recently reported to support the development of learning and memory and also prevent anxiety-like behaviors in mice. Although the mechanism through which OC affects systemic energy expenditure and glucose homeostasis has been relatively well studied, the direct actions of OC on neurons in detail are still uncovered. Therefore, we here investigated the effect of OC on neurons using rat pheochromocytoma cell line PC12, with special reference to the neurite outgrowth, cell proliferation and survival, as well as intracellular signaling. The number of PC12 cells cultured for four days in the presence of 5 to 50 ng/mL of OC was increased compared to the cells cultured in the absence of OC. The length, but not the number of NGF-induced neurite outgrowth was enhanced by OC. NGF-induced phosphorylation of Akt and ERK was both affected by pretreatment of the cells with OC. RT-PCR analysis for candidates of OC receptor revealed that mRNA expression of Gpr158, but not Gprc6a, was detected in PC12 cells. These results suggested that OC may exerts direct effect on cell growth and differentiation by binding to Gpr158 and modulation of downstream intracellular signaling.