Promotion of Neurogenesis and Brain Repair by Bradykinin

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BK stimulating kinin-B2 receptors (B2BKR) do not only participate in inflammation and blood pressure regulation, but also in neurotransmission and neuromodulation. Novel functions for BK were obtained using neural progenitor cells (NPC) isolated from fetal rat as in vitro models for neural differentiation. Functional B2BKR and secretion of BK medium suggested the existence of an autocrine loop participating in neural differentiation. Chronic exposure of differentiating neurospheres to the B2BKR antagonist HOE-140 resulted in reduced migration and neurogenesis and enhanced gliogenesis. These results were confirmed in migration and differentiation assays with neurospheres isolated from B2BKR-knockout mice. Our findings indicate a previously unidentified role of BK action in inducing neuron-generating division in vitro and in vivo, since B2BKR activation lengthened the G1-phase of the NPC cycle and increased TIS21 (PC3/ BTG2) expression in the hippocampus from newborn mice. This effect was due to ERK activation by BK. Moreover, immunohistochemistry analysis of hippocampus showed that the percentage of Ki67+ cells were markedly increased in BK-treated mice and ERK inhibition affected this neurogenic response. The progress of neurogenesis depended on sustained ERK phosphorylation and resulted in MAPK translocation to the nucleus in NPCs and PC12 cells, changing expression of genes such as Hes1. In agreement with the function of ERK in integrating signaling pathways, effects of BK in stimulating neurogenesis were reversed following removal of PKC-mediated sustained phosphorylation. Together, these results compose mechanisms of action for BK during neurogenesis. Neurogenic actions of bradykinin were further studied in an animal model of Parkinson’s disease induced by nigrostriatal injection of 6OH-dopamine. Degeneration of dopaminergic neurons and clinical symptoms, such as apomorphine-induced rotations, in a rat model of Parkinson’s disease were mostlyreversed following a single BK injection, providing novel strategies for brain repair.

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