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MOLECULAR MECHANISMS OF NITRIC OXIDE-MEDIATED DOWN-REGULATION OF BRAIN-DERIVED NEUROTROPHIC FACTOR SECRETION

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Neurotrophins (NTs), such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-4/5 (NT-4/5), and neurotrophin-3 (NT-3), regulate neuronal survival and differentiation during embryonic development and participate in brain functions such as modulation of synaptic transmission and memory formation [1]. NT secretion is initiated either by neurotransmitters and/or by NTs themselves by a positive-feedback mechanism. This process depends on calcium release from intracellular stores [2]. Little is known, however, about potential pathways that down-regulate NT secretion. Several evidences has been recently collected about the interplay which takes place between BDNF and nitric oxide (NO). Growth of retinal axons has been reported to be controlled by the balance between these two neuromodulators. Inhibition of NOS has been shown to potentiate the neurotrophic effect of BDNF. An additive effect of a NOS inhibitor together with BDNF administration on the survival of neurons has been described. Finally, BDNF appear to function as a positive regulator of NO synthesis and NO in turn, down-regulates BDNF expression in neural cells. Here we demonstrate that NO induces a rapid down-regulation of BDNF secretion in cultured hippocampal neurons. Similar effects occur by activating a downstream target of intracellular NO, the soluble guanylyl cyclase, or by increasing the levels of its product, cGMP. Furthermore, down-regulation of BDNF secretion is mediated by cGMP-activated protein kinase G, which prevents calcium release from inositol 1,4,5-trisphosphate-sensitive stores. Our data indicate that the NO/cGMP/protein kinase G pathway represents a signaling mechanism by which neurons can rapidly down-regulate BDNF secretion and suggest that, in hippocampal neurons, NT secretion is finely tuned by both stimulatory and inhibitory signals [3]. In addition to their classical effects in the central nervous system it has also been shown that NTs may act as intercellular messengers on non-neuronal cells. In the cardiovascular system NTs have been shown to modulate synaptic transmission between sympathetic neurons and cardiac myocytes, to regulate heart development, and to be required for intramyocardial vessel stabilization through a direct angiogenic action on endothelial cells. It has been demonstrated that significant levels of circulating neurotrophins are present in human serum and their genes are expressed in the vascular endothelial EC [4] and smooth muscle [5] cells. Both these cells population do also express members of the high-affinity neurotrophin receptors. These evidences suggest that locally produced NTs might exert some degree of control on the viability and the proliferation of the cells in the vessel wall. The ability of NO to control NTs local avalaibilty might be a potentially useful pharmacological tool and is currently under investigation.

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