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Regulation of transcription factors by nitric oxide in neurons and in neural-derived tumor cells

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Abstract

Nitric oxide (NO), a diffusible molecule acting as an intercellular and intracellular messenger in many tissues, plays multiple roles in the nervous system. In addition to regulating proliferation, survival and differentiation of neurons, NO is also involved in synaptic activity, neural plasticity and memory formation. Long-lasting effects of NO, a simple and unstable molecule, occur through regulation of transcription factors and modulation of gene expression. cAMP-response-element-binding (CREB) protein is an important transcription factor that regulates the expression of several genes involved in survival and neuroprotection as well as in synaptic plasticity and memory formation. Nitric oxide promotes survival and differentiation of neural cells, both activating through cGMP signaling CREB phosphorylation-dependent transcriptional activity and promoting *S*-nitrosylation of nuclear proteins that favor CREB binding to its promoters on target genes. Among oncogenic transcription factors, N-Myc is important in neurogenesis and in regulating proliferation of neural-derived tumor cells, such as neuroblastomas and medulloblastomas. Nitric oxide negatively regulates the proliferation of neuronal precursors, as well as the proliferation of neuroblastoma cells, by downregulating N-Myc expression through cGMP signaling. Other oncogenic transcription factors, such as c-fos and c-jun, zinc-finger transcription factors, such as egr-1, and NF-κB are regulated by NO signaling in cGMP-dependent way or through nitrosative conformational changes. The present survey of how NO signaling influences neural cells through regulation of transcription factors allows us to predict that better knowledge of these interactions will provide a better understanding of the physiological role of NO in the nervous system in order to conceive novel therapies for neural-derived tumors.

Keywords: Nitric oxide; CREB; N-Myc; Neuron survival; Neurogenesis; Proliferation; Neural-derived tumor cells

Contents

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1. Introduction

1.1. Nitric oxide and its signaling

Nitric oxide (NO), first identified as endothelium-derived relaxing factor in blood vessels (Furchgott and Zawadzki, 1980; Palmer et al., 1987), has been recognized, during the following years, to play a pivotal role in intercellular communication, as well as in intracellular signaling, in many tissues (Moncada et al., 1989; Murad, 1994a; Kerwin et al., 1995). A role for NO as an intercellular diffusible messenger in the brain was demonstrated for the first time a couple of decades ago (Garthwaite et al., 1988). Since then, both its physiological role, mainly related to regulation of neuronal proliferation/survival/differentiation as well as to mediation of synaptic activity/neural plasticity, and its contribution to several neuropathological states have been addressed in thousands of papers (for comprehensive reviews see: Brenman and Bredt, 1997; Dawson and Dawson, 1998; Contestabile, 2000; Gibbs, 2003; Reif et al., 2004; Susswein et al., 2004; Cardenas et al., 2005; Guix et al., 2005). Of particular interest is the finding that NO, known to exert an anti-proliferative action towards many cell types (Garg and Hassid, 1989; Nisoli et al., 1990; Punjabi et al., 1992; Yang et al., 1994), also promotes a similar effect towards neural-derived tumor cells as well as towards neuronal precursors (Peunova and Enikolopov, 1995; Peunova et al., 2001; Murillo-Carretero et al., 2002; Packer et al., 2003; Ciani et al., 2004, 2006; Matarredona et al., 2004, 2005; Moreno-Lopez et al., 2004).

How can NO, a very simple and unstable molecule (Ford et al., 1993; Wood and Garthwaite, 1994; Lancaster Jr., 1997), affect such complex functions as the kinetics of cell division, the promotion of neuronal survival or the long-term modifications of synaptic activity in neural circuits? Two principal mechanisms have been firmly established as primary cellular targets able to explain the profound effects mediated by NO: activation of guanylate cyclase and post-translational protein modification through nitration or *S*-nitrosylation. Activation of soluble guanylate cyclase by NO, through reaction with its heme center followed by increased production of cGMP and activation of protein kinases G (PKGI and PKGII), was the first identified cellular target for transduction of NO-mediated signals (Ignarro, 1991; Murad, 1994b). This transduction pathway is involved in the response of many different cell types to NO signal and can affect the function of a wide array of proteins, as well as modulate the function of other cellular messengers, such as cAMP and calcium (Hanafi et al., 2001; Contestabile et al., 2003; Guix et al., 2005). Protein nitration is the result of reaction of peroxinitrite anion, formed by reaction of NO with superoxide radical, with residues such as tryptophan and particularly tyrosine (Kelm et al., 1997; Hanafi et al., 2001). Nitric oxide also reacts with thiol groups of several amino acidic residues, especially with cysteine, forming *S*-nitrosylated derivatives (Stamler, 1994; Hanafi et al., 2001). Both nitration and *S*-nitrosylation affect the function of the target proteins, ensuring that a multiplicity of cell-specific effects stem from the same initial signaling molecule (Hanafi et al., 2001; Jaffrey et al., 2001; Contestabile et al., 2003; Guix et al., 2005). The two main modalities able to elicit cellular responses to NO, i.e., through cGMP messenger or through conformational modification of protein function by direct chemical reaction, are not mutually exclusive even if they may preferentially occur at different concentrations of NO (Hanafi et al., 2001).

1.2. Nitric oxide and gene expression

Cellular activities regulated by cGMP are multifarious (Fiscus, 2002; Pilz and Casteel, 2003), as is the number of putative protein targets for reaction with NO. Thus, the modalities of cellular transduction of NO signal considered in the previous paragraph, may well account for the broad spectrum of effects regulated by NO in many cells, and in particular in neurons and in neural-derived tumor cells. As several effects of NO are long-lasting, affecting for instance developmental processes or memory formation, it is expected that they occur through regulation of gene expression (Bogdan, 2001; Bogdan et al., 2002; Turpaev et al., 2004, 2005). It has been indeed demonstrated that in mammalian cells NO induces temporally distinct waves of gene activation (Hemish et al., 2003). Furthermore, transgenic mice overexpressing the neuronal isoform of the NO-synthetizing enzyme, nitric oxide synthase (nNOS), show some differences in gene expression in the hippocampus of adult animals, as compared to wild type mice (Packer et al., 2005). While NO may affect gene transcription by controlling the methylation of CpG islands in the promoter regions of some genes (Hmadcha et al., 1999; Kroncke, 2003), most of its activity in regulating gene expression occurs through regulation of transcription factors (Bogdan, 2001; Bogdan et al., 2002; Kroncke, 2003; Pilz and Casteel, 2003). The aim of the present paper is to make a survey of the state of the art of our current knowledge on transcription factors mediating main effects exerted by NO towards proliferation, survival, differentiation and networking of neuronal cells. Furthermore, it has been demonstrated in several tumor cells, including tumor cells of neural origin, that NO can affect various behaviors of metastatic cells, in particular their proliferative potency, and that these effects