

# 6 Nitric Oxide in Experimental Allergic Encephalomyelitis

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<b>1</b>	<b>Introduction</b> .....	<b>2</b>
<b>2</b>	<b>Biochemistry of NO</b> .....	<b>3</b>
2.1	Nitric Oxide Synthases .....	3
2.2	Molecular Targets of NO .....	3
2.2.1	Soluble Guanylyl Cyclase: A Major Physiological Target .....	3
2.2.2	Activation of MAP Kinases .....	3
2.2.3	Peroxynitrite Formation .....	4
2.2.4	Protein Tyrosination .....	4
2.2.5	Protein Nitrosylation .....	4
2.2.6	Alteration of Oxidative Stress .....	4
<b>3</b>	<b>Role of NO in the Disease Process of EAE</b> .....	<b>5</b>
3.1	Involvement of NO in the Pathogenesis of EAE .....	5
3.2	Role of NO in the Switching of Th Cells .....	5
3.3	Role of NO in CNS Infiltration .....	6
3.3.1	Involvement of NO in Blood-Brain-Barrier Permeability .....	6
3.3.2	Effect of NO on Adhesion Molecules .....	7
3.4	NO in Gliosis .....	7
3.4.1	Induction of Inducible Nitric Oxide Synthases in Microglia .....	8
3.4.2	Involvement of NO in Microgliosis .....	9
3.4.3	Induction of Inducible Nitric Oxide Synthases in Astrocytes .....	10
3.4.4	Involvement of NO in Astrogliosis .....	11
3.5	Role of NO in Demyelination .....	11
3.5.1	Oligodendrocyte Damage by Peroxynitrite and Oxidative Stress .....	11
3.5.2	Cysteine modifications by NO: Damage to Myelin Sheath .....	12
3.5.3	NO-Mediated Glutamate Excitotoxicity and Oligodendrocyte Damage .....	13
3.6	Protective Role of NO in EAE .....	14
3.6.1	Inhibition of Leucocyte Infiltration by NO .....	14
3.6.2	Role of NO as an Inhibitor of NF- $\kappa$ B in Glial Cells .....	15
3.6.3	Immunosuppressive Role of NO .....	15
<b>4</b>	<b>Clinical Perspective of NO in EAE</b> .....	<b>16</b>
<b>5</b>	<b>Conclusion</b> .....	<b>16</b>

**Abstract:** Nitric oxide (NO) is a biologically precious molecule responsible for diverse functions in physiology and pathophysiology of many organs including the brain. Accordingly, NO contributes significantly to both neurodegeneration and neuroprotection in experimental allergic encephalomyelitis (EAE), the animal model of multiple sclerosis (MS). The neurodegenerative aspects of NO in EAE are marked by enhanced CNS infiltration, gliosis, and demyelination whereas the neuroprotection is mainly attributed by diminished adhesion and CNS infiltration, inhibition of proinflammatory factors, and immunosuppression. In this chapter, we have made an attempt to illuminate this bidirectional role of NO in EAE and discuss the therapeutic importance of this molecule in EAE and MS.

**List of Abbreviations:** AOE, antioxidant enzymes; AP-1, activator protein-1; APC, antigen-presenting cell; BBB, blood-brain barrier; cGMP, cyclic guanosine-3', 5'-monophosphate; CNS, central nervous system; LPS, lipopolysaccharides; EAE, experimental allergic encephalomyelitis; ERK, extracellular signal-regulated kinase; GAPDH, glyceraldehydes-3-phosphate dehydrogenase; GC, guanylate cyclase; GPX, glutathione peroxidase; GSNO, S-nitroso glutathione; ICAM, intercellular cell adhesion molecule; iNOS, nitric oxide synthase; IFN- $\gamma$ , interferon-gamma; IL-12R, interleukin-12 receptor; IL-1 $\beta$ , interleukin-1beta; LFA1, lymphocyte function-associated antigen 1; MAPK, mitogen-activated protein kinase; MBP, myelin basic protein; MEK, MAP kinase kinase; MS, multiple sclerosis; MMP-9, matrix metalloproteinase-9; NO, nitric oxide; NF- $\kappa$ B, nuclear factor-kappaB; NMDA, N-methyl-D-aspartate NMDA; ONOO<sup>-</sup>, peroxynitrite; PKG, protein kinase G; PARP, poly (ADP-ribose) polymerase; Raf, MEK kinase; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; SCI, spinal cord injury; SNAP, S-nitroso-N-acetylpenicillamine; SNP, sodium nitroprusside; SOD, superoxide dismutase; TNF- $\alpha$ , tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule; VLA4, very-late antigen 4

## 1 Introduction

Multiple sclerosis (MS) is the most common T cell-mediated autoimmune demyelinating disease of the central nervous system (CNS) that specifically devastates younger population of the northern European ancestry (Martin et al., 1992). Experimental allergic encephalomyelitis (EAE) is an animal model for MS that can be induced in mice or rodents by immunization with myelin proteins or by adoptive transfer of myelin-reactive T cells (Tuohy et al., 1988; Banik, 1992; Benveniste, 1997). In particular strain of mice, the relapsing-remitting type of EAE and its pathophysiology closely resemble with the human disease MS (Benveniste, 1997). Induction of the disease is primarily characterized by generation of autoreactive T cells recognizing myelin proteins as self-antigens, infiltration of these T cells and associated mononuclear cells into the CNS, followed by inflammation, and gliosis and oligodendrocyte damage. Similar to MS, various proinflammatory molecules are also implicated in the disease process of EAE. This model is widely used to identify new therapeutic approach against MS.

Among several molecules implicated in the disease pathology of EAE, nitric oxide (NO) has been discussed most widely. Since its discovery, the physiological importance of this molecule is gradually increasing. Several literatures indicate that this molecule plays a vital role in the pathogenesis of MS and other neurological diseases including Alzheimer's disease, Parkinson's disease, and HIV-associated dementia. Although the involvement of NO in the pathophysiology of EAE is evident from many previous studies, the accurate role of this molecule in this disease is still ambiguous because of its complex biochemistry and multiple actions. NO plays critical roles at almost all the pathophysiological stages of EAE, beginning with CNS infiltration of lymphocytes to demyelination. However, the role of NO in developing inflammation in the CNS appears to be the most significant. Although, NO has been identified as a primary proinflammatory signal in the pathogenesis of EAE, it does not necessarily commit NO to be only neurodegenerative. Neuroprotective role of NO has also been suggested in many literatures. Diversity of NO in its physiological manifestations may underlie its contradictory role in the pathogenesis of EAE. In this chapter, we will illustrate cellular, molecular, and biochemical perspectives of the involvement of NO in both physiology and pathophysiology of EAE. Our ultimate goal is to unravel the functional complicity of NO in EAE pathogenesis in order to consider NO as a potential target for designing new drugs.