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Review

Pathologic role of glial nitric oxide in adult and pediatric neuroinflammatory diseases

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ABSTRACT

It is well established that glial cells have critical roles in the inflammatory processes in the central nervous system (CNS). These cells can be activated by a variety of endogenous and exogenous stimuli (i.e. gliosis) and can produce high levels of bioactive compounds that are noxious for neuronal cell function. One of the most important molecules released by activated glial cells is the bioactive free radical nitric oxide (NO). Although NO physiologically acts as both neuromodulator and neurotransmitter in the brain, excess production of NO by glial cells has diverse harmful effects on neuronal function, causing neuronal cell injury/death. The production of NO is induced by overexpression of the inducible isoform of NO synthase (iNOS) enzyme in glial cells. In this review, we describe the possible mechanisms that underlie the iNOS-mediated overproduction of glial NO in several pediatric and adult neuropathologic conditions such as periventricular leukomalacia (PVL), Krabbe's disease, X-linked adrenoleukodystrophy (ALD) and multiple sclerosis (MS). We specifically discuss various signaling cascades that activate several transcription factors involved in the iNOS expression in both astrocytes and microglia. We also discuss the consequences of iNOS-mediated NO production in neuroinflammatory diseases including MS. A complete understanding of the regulation of iNOS expression in glial cells and the mechanisms by which iNOS-mediated NO production is involved in neuroinflammation can provide new insights into the identification of novel targets for therapeutic intervention in NO-mediated neurologic diseases.

Abbreviations: AD, Alzheimer's disease; ALD, X-linked adrenoleukodystrophy; ALDRP, adrenoleukodystrophy-related protein; ALDP, adrenoleukodystrophy protein; ALS, amyotrophic lateral sclerosis; ATF-2, activating transcription factor 2; BBB, blood–brain barrier; AP-1, activator protein-1; CD154, CD40 ligand; C/EBP, CCAAT/enhancer-binding protein; Ca^{2+}, calcium; cNOS, constitutive nitric oxide synthase; CNS, central nervous system; COX, cyclo-oxygenase-2; CRs, cytokine receptors; CSF, cerebrospinal fluid; DEP, diesel exhaust particles; EAE, experimental allergic encephalomyelitis; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinases; GAS, IFN-γ activation site; GSK-3, glycogen synthase kinase-3; HAT, histone acetyl-transferase; HD, Huntington's disease; HIV, human immunodeficiency virus; IκB, inhibitor of NF-κB; IKK, IκB kinase; IL, interleukin; iNOS, inducible NO synthase; IRAK, IL-1 receptor-associated kinase; IRF-1, interferon regulatory factor-1; ISRE, interferon-stimulated responsive element; JAK2, Janus kinase 2; JNK, Janus kinase; LCY-2-CHO, 9-(2-chlorobenyl)-9H-carbazole-3-carbaldehyde; LPS, lipopolysaccharide; MAL, MyD88 adaptor-like protein; MAPK, mitogen-activated protein kinases; MBP, myelin basic protein; M-CSF, macrophage colony stimulating factor; MMP3, matrix metalloproteinase 3; Mn-EBDC, manganese ethylene bisdithiocarbamate; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; MyD88, myeloid differentiation primary response gene 88; NADPH, nicotinamide adenine dinucleotide phosphate; L-NAME, N^G-nitro-L-arginine methyl ester; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; L-NIL, L-N^6-(1-Iminoethyl)-lysine; NMDA, *N*-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NMDAR, NMDA receptor; NO, nitric oxide; $^{\bullet}O_2^-$, superoxide; PARP, poly(ADP-ribose) polymerase; PD, Parkinson's disease; PGE_2, prostaglandin E_2; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; PTIO, 2-phenyl-4,4,5,5-tetramethylimidazolineoxyl-1-oxyl-3-oxide; PTPase, protein tyrosine phosphatases; PVL, periventricular leukomalacia; PWMI, perinatal white matter injury; ROS, reactive oxygen species; RNS, reactive nitrogen species; SAHA, suberoylanilide hydroxamic acid; SH-2, Src homology 2; siRNA, small interfering RNA; SOCS, suppressors of cytokine signaling; STAT-1α, signal transducers and activators of transcription-1α; TIR, Toll/interleukin-1 receptor; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen-4; VLCFA, very-long-chain fatty acid.

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Contents

1. Introduction

Nitric oxide (NO) is a bioactive free radical that plays a critical role as both neurotransmitter and neuromodulator in the central nervous system (CNS). At low concentrations, NO has physiological roles in the function of neuronal and vascular cells, whereas at higher concentrations, it is implicated in the pathogenesis of various neurologic diseases including stroke, neurodegenerative diseases, demyelination and neuroinflammatory diseases (Calabrese et al., 2007). NO is enzymatically produced from the amino acid L-arginine by the activity of the NO synthase (NOS) enzymes. Three subtypes of NOS have been identified. Neuronal NOS (nNOS or NOS1) and endothelial NOS (eNOS or NOS3), constitutive forms of NOS, are calcium (Ca^{2+})-dependent enzymes (Bredt et al., 1991; Bredt and Snyder, 1990; Schmidt et al., 1991; Sessa et al., 1992). Neuronal NO is synthesized by the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR)-mediated activation of nNOS, the principal isoform present in the CNS (Bredt et al., 1991; Bredt and Snyder, 1990; Schmidt et al., 1991; Sessa et al., 1992). The name of the third subtype, inducible NOS (iNOS or NOS2), indicates that expression of the enzyme is induced by acute inflammatory stimuli (Geller et al., 1993; Lyons et al., 1992). iNOS does not require Ca^{2+} for its activity and is expressed in various cell types especially the glial cells, astroglia and microglia (Galea et al., 1992). Astrocytes and microglia do not constitutively express iNOS but they express the enzyme in pathological conditions such as ischemia, trauma, neurotoxic and inflammatory damage (Galea et al., 1992). Several lines of evidence have demonstrated that glial NO is involved in the pathophysiology of a variety of neurological diseases including demyelination (e.g. multiple sclerosis [MS], experimental allergic encephalopathy, and X-linked adrenoleukodystrophy [ALD]), neuronal death during ischemia (e.g. stroke) and trauma, and neurodegenerative diseases (e.g. Alzheimer's disease [AD], Parkinson's disease [PD], Huntington's disease [HD], human immunodeficiency virus [HIV]-associated dementia, and amyotrophic lateral sclerosis [ALS]) (Nakamura et al., 2012).

Therefore, determination of intracellular signaling pathways that cause glial iNOS-derived NO overproduction can provide novel therapeutic approaches for targeting these pathways in order to decrease NO overproduction and thereby decrease neuronal injury/death. In this review, we describe the possible mechanisms that underlie the overproduction of glial NO in several neuropathologic conditions in the adult and the developing brain and discuss the consequences of such events in neuroinflammatory diseases such as MS.

2. Glial NO and neuroinflammation

The brain has traditionally been considered as an "immunologically privileged site," mainly because the blood–brain barrier (BBB) normally restricts the access of immune cells from the blood. However, it is now known that immunological reactions occur in the CNS, particularly during brain inflammation, differing from inflammation in the periphery by relative absence of leukocytes and antibodies. Brain inflammation contributes to the pathology of many neurologic diseases including neurodegenerative diseases (e.g. PD, AD, MS and AIDS dementia), stroke, brain trauma and meningitis (Engelhardt and Ransohoff, 2005; Klegeris et al., 2007; Lucas et al., 2006; Zipp and Aktas, 2006). This process primarily involves the participation of the two types of glial cells, microglia and astrocytes. Microglia are the resident monophagocytic cells of the brain and spinal cord (Block et al., 2007). In response to certain cues (e.g. brain injury or immunological stimuli) resting ramified microglia are readily activated to an amoeboid form and present an upregulated catalog of surface molecules, receptors, and a range of new proteins including iNOS and cyclo-oxygenase-2 (COX-2) (Kettenmann et al., 2011; Nimmerjahn et al., 2005; Oehmichen and Gencic, 1975). Activated microglia fulfill a variety of different physiologic tasks within the CNS which include cellular maintenance (e.g. clearing toxic cellular debris (Kettenmann et al., 2011; Streit, 2002)), innate immunity (Jack et al., 2005; Kettenmann et al., 2011), release of trophic and anti-inflammatory factors necessary for brain development (Liao et al., 2005; Morgan et al., 2004), and facilitation of stem cell migration to the site of inflammation and injury (Aarum et al., 2003). Astrocytes, on the other hand, act to maintain ionic homeostasis, buffer the action of neurotransmitters, and secrete nerve growth factors (Simard and Nedergaard, 2004). Activated astrocytes release some trophic factors in order to enhance neuronal survival. Under pathologic circumstances microglia can induce a robust detrimental neurotoxic effect by the excess generation of a variety of cytotoxic and noxious factors such as NO (Liu et al., 2002a; Moss and Bates, 2001), superoxide anion ($^{\bullet}O_2^-$) (Colton and Gilbert, 1987), tumor necrosis factor-α (TNF-α) (Sawada et al., 1989) and interleukin (IL)-1β (Banati et al., 1993). NO and IL-1β are also produced by activated astrocytes (Liu et al., 2002a).

2.1. Glial activators

Glial overactivation and dysregulation can be induced by diverse stimuli, ranging from environmental toxins to neuronal damage/death products (Fig. 1). In neurodegenerative diseases, overactivated microglia present in large numbers. Activated microglia cluster at sites of aggregated β-amyloid and penetrate the neuritic plaques and this event occurs even before the development of symptoms in AD patients (Block et al., 2007). β-Amyloid is pro-inflammatory (Ii et al., 1996) and its toxicity in neurons in co-culture with glia is prevented by iNOS inhibitors (Brown, 2007). Macrophage colony stimulating factor (M-CSF), a classical