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Review

Oxidative stress, DNA damage, and the telomeric complex as therapeutic targets in acute neurodegeneration

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ABSTRACT

Oxidative stress has been identified as an important contributor to neurodegeneration associated with acute CNS injuries and diseases such as spinal cord injury (SCI), traumatic brain injury (TBI), and ischemic stroke. In this review, we briefly detail the damaging effects of oxidative stress (lipid peroxidation, protein oxidation, etc.) with a particular emphasis on DNA damage. Evidence for DNA damage in acute CNS injuries is presented along with its downstream effects on neuronal viability. In particular, unchecked oxidative DNA damage initiates a series of signaling events (e.g. activation of p53 and PARP-1, cell cycle re-activation) which have been shown to promote neuronal loss following CNS injury. These findings suggest that preventing DNA damage might be an effective way to promote neuronal survival and enhance neurological recovery in these conditions. Finally, we identify the telomere and telomere-associated proteins (e.g. telomerase) as novel therapeutic targets in the treatment of neurodegeneration due to their ability to modulate the neuronal response to both oxidative stress and DNA damage.

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1. Introduction

Substantial evidence indicates that oxidative stress is a major contributor to the pathophysiology of a variety of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, and acute central nervous system (CNS) injuries such as spinal cord injury (SCI) and traumatic brain injury (TBI) which will be the focus of this review. The CNS, and neurons in particular, are especially vulnerable to oxidative stress due to their high metabolic rate, limited capacity for regeneration, and high iron/copper content. Damaging reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed as unavoidable by-products of metabolism but their damaging effects are normally counteracted by endogenous anti-oxidant enzymes (e.g. catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase) and substances (e.g. glutathione, metallothionein, vitamin A, vitamin C, and vitamin E) (Duffy et al., 1998; Suemori et al., 2006; Vatassery, 1998). However, oxidative stress represents a state in which these antioxidant defenses are overwhelmed and no longer capable of protecting the cell from oxidative damage.

Accumulation of ROS/RNS can result in a number of detrimental effects such as lipid peroxidation, protein oxidation, and DNA damage. Lipid peroxidation disrupts normal structure and function of lipid bilayers surrounding both the cell itself and membrane-bound organelles (Catala, 2011, 2012). In particular, peroxidation of lipids may alter membrane permeability, transport processes, and fluidity. In addition, lipid peroxidation may ultimately result in the production of multiple aldehyde species (e.g. acrolein, malondialdehyde (MDA)) that further contribute to toxicity associated with lipid peroxidation. Elevated markers of lipid peroxidation, including MDA, 4-hydroxynonenal (4-HNE), and acrolein, have been shown in animal models of both SCI and TBI, indicating that lipid peroxidation may be an important contributor to the pathophysiology of these disorders (Ansari et al., 2008; Hall et al., 2004; Hamann et al., 2008; Inci et al.,

Abbreviations: MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; EAE, experimental allergic encephalomyelitis; MS, mutiple sclerosis; SSB, single strand break; DSB, double strand break; 8-OxoG, 8-hydroxyguanosine; 8-NO(2)-G, 8-nitroguanine; AP, apurinic/apyrimidinic; OGG1, 8-oxoguanine DNA glycosylase; XP, xeroderma pigmentosum; ATM, ataxia-telangiectasia mutated; MP, methylprednisolone; BBB, Basso Beattie Bresnahan; APE, apurinic/apyrimidinic endonuclease; PANT, DNA polymerase I-mediated biotin-dATP nick-translation; PROG, progesterone; NEIL1, endonuclease VIII-like 1; PIKK, phosphatidylinositol 3-kinase like kinase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; Chk, checkpoint kinase; APAF1, apoptotic protease-activating factor 1; PFT-α, pifithrin-α; PARP-1, Poly (ADP-ribose) polymerase-1; NAD, nicotinamide adenine dinucleotide; AIF, apoptosis-inducing factor; CCI, controlled cortical impact; TRF, telomere repeat binding factor; POT1, protection of telomeres 1; TERT, telomerase reverse transcriptase; TERC, telomerase RNA component; DC, dyskeratosis congenita; HHS, Hoyeraal–Hreidarsson Syndrome; SOD1, superoxide dismutase 1; ALS, amyotrophic lateral sclerosis.

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1998; Lin et al., 2007; Seligman et al., 1977). Protein modifications by accumulated ROS/RNS include protein fragmentation, protein misfolding, protein–protein cross-linkages, production of protein carbonyls, and priming of oxidized proteins for proteasomal degradation (Berlett and Stadtman, 1997; Radak et al., 2011). Substantial evidence suggests that protein aggregation or misfolding may be involved in the pathogenesis of neurodegenerative conditions. Severe protein aggregation was noted in hippocampal CA1 neurons after ischemia/reperfusion injury, appearing first at 4 h. and accumulating over a period of 48 h. (Hu et al., 2000). Increases in heat shock protein 70 (HSP70), which functions as an intracellular chaperon of protein folding, have also been observed after TBI, indicating induction of HSP70 to clear misfolded or aggregated proteins (Zhao et al., 1998). Conversely, overexpression of HSP70 has been shown to reduce neuronal injury both *in vitro* and in animal models of stroke (Rajdev et al., 2000). These studies suggest that increased ROS/RNS in the context of CNS injury may also contribute to protein aggregation and misfolding. Together, these alterations can profoundly impact normal protein/enzymatic activity and disrupt a variety of biochemical processes. Given the role of oxidative stress in the pathology of acute CNS injury and disease, it is not surprising that increased levels of protein carbonyls have been demonstrated in experimental models of both SCI and TBI as well as in experimental autoimmune encephalomyelitis (EAE) an animal model of multiple sclerosis (MS) which is also characterized by a neurodegenerative component (Jin et al., 2004; Smerjac and Bizzozero, 2008; Xiong et al., 2007). Such elevated levels of protein carbonyls have also been described in both grey and white matter in tissue obtained from patients with MS. Although the importance of lipid peroxidation and protein oxidation in cellular damage resulting from CNS injuries should not be overlooked, the remainder of this review will focus on DNA damage and telomeric dysfunction as effects of oxidative stress generated as a result of acute CNS injury (Fig. 1). We use the term acute neurodegeneration to differentiate CNS injury from other, more chronic forms of neurodegenerative disorders such as AD, PD, and ALS. It should be noted, however, that it is still difficult to differentiate the biochemical pathways which are active during DNA damage/repair in the "acute" and "chronic" phases of CNS injury. For this reason, we have placed less emphasis on classifying cellular changes related to DNA damage as "acute" or "chronic" in the context of CNS injury in this review.

2. DNA damage as a result of oxidative stress

Oxidative stress and the resultant accumulation of ROS/RNS can lead to a number of different DNA lesions including direct modification of nucleotide bases, formation of apurinic/apyrimidinic sites, DNA single strand breaks (SSBs), and, much less frequently, DNA double strand breaks (DSBs). Direct nucleotide modifications have been widely reported as consequences of oxidative/nitrosative damage to the cell. Of all the nucleotide bases, guanine is the most susceptible to oxidative modifications due to the fact that it has the lowest reduction potential. Hydroxyl radicals have been shown to interact with the C4, C5, and C8 positions in the imidazole ring of guanine. Of these, formation of 8-hydroxyguanosine (8-OxoG) is the most well studied and has been reported in a wide variety of disease states as recently reviewed in (Cooke et al., 2003). This oxidative modification represents a potentially mutagenic DNA lesion, as 8-OxoG can undergo a conformational change allowing it to aberrantly pair with adenine and thus promote G to T transversion (Bruner et al., 2000). Peroxynitrite is also capable of reacting with guanine to form 8-nitroguanine (8-NO(2)-G) which is considered a marker of nitrosative DNA damage. Like its ROS-induced counterpart, 8-NO(2)-G promotes formation of mutagenic DNA lesions due to G to T transversion (Yermilov et al., 1995). Similar oxidative/nitrosative modifications have been reported for adenine, thymine, and cytosine (reviewed in (Dizdaroglu and Jaruga, 2012)).

One common consequence of direct oxidative modification of nucleotide bases is formation of apurinic/apyrmidinic (AP) sites along the DNA. For example, the presence of 8-OxoG is known to engage the base excision repair (BER) system resulting in removal of the oxidized guanine by glycosylases including 8-oxoguanine DNA glycosylase (also known as OGG1) (Hazra et al., 2001). AP sites may also result from direct base modifications that disrupt the *N*-glycosidic bond linking them to deoxyribose and thereby resulting in spontaneous loss of nucleobases (Otterlei et al., 2000). ROS have also been shown to interact with the sugar moieties of nucleotides. In particular, hydroxyl radicals appear to target the C-1 and C-4 positions of the deoxyribose ring. Hydroxyl attack of deoxyribose may result in the formation of multiple oxidation products including 2-deoxyribonolactone, 2 deoxypentos-4-ulose, 3′-phosphates, and 3′-phosphoglycolate esters. These modifications may result in the formation of AP sites by the release of free bases or by initiating the activity of other members of the BER pathway (e.g. AP endonucleases) (Demple and DeMott, 2002; Wilson et al., 2003). It should be noted that AP sites are also formed at an estimated rate of 50,000–200,000 per mammalian cell per day under normal physiologic conditions. Interestingly, the rat CNS appears to accumulate a greater number of AP sites when compared to other organ systems (Nakamura and Swenberg, 1999).

Oxidative stress can also cause DNA damage in the form of both single-stranded breaks (SSBs) and double-stranded breaks (DSBs). SSBs form as a result of the interaction of hydroxyl radicals with deoxyribose and subsequent generation of peroxyl radicals. These peroxyl radicals are then responsible for nicking phosphodiester bonds that form the backbone of each helical strand of DNA (Dedon, 2008). In addition, SSBs have also been shown to indirectly form under oxidative/nitrosative conditions through the actions of the BER system in the repair of AP sites (Hegde et al., 2008). Topoisomerase I has also been shown to preferentially cleave nucleotides at the site of oxidative DNA lesions further resulting in the generation of SSBs (Pommier et al., 2003). SSBs found in closely associated sites on complementary DNA strands may also result in the formation of DSBs. Interestingly, peroxynitrite has also been shown as a potent mediator of DSBs *in vitro* (Jia et al., 2009).

3. Evidence for DNA damage in acute CNS injuries and neurodegeneration

3.1. DNA damage in neurodegenerative disorders

Perhaps the strongest link between neurodegeneration and DNA damage thus far comes from neurodegenerative phenotypes seen in a variety of hereditary disorders of DNA damage repair. One such example is xeroderma pigmentosum (XP) which occurs as a result of mutations in genes encoding members of the nucleotide excision repair (NER) system. Early-onset, progressive neurological symptoms in xeroderma pigmentosum include peripheral neuropathy, sensorineural deafness, mental disability, bulbar, extrapyramidal, and cerebellar disturbances (e.g. chorea, ataxia, etc.), and dysfunction of the corticospinal tract (Kassubek et al., 2012). Magnetic resonance imaging (MRI) of patients with XP demonstrates cerebral and cerebellar atrophy and accompanying ventricular enlargement (Kraemer et al., 2007). Histological examination of post-mortem tissue from XP patients demonstrates widespread neuronal loss in the corticospinal tract, basal ganglia, substantia nigra pars compacta, cerebellum, and dorsal root gan-