Pharmacology & Therapeutics xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate Editor: M. Panagiotidis

Antioxidant gene therapy against neuronal cell death

Juliana Navarro-Yepes [a,b,e], Laura Zavala-Flores [a,b], Anandhan Annadurai [a,b], Fang Wang [c], Maciej Skotak [c], Namas Chandra [c], Ming Li [d], Aglaia Pappa [g], Daniel Martinez-Fong [f], Luz Maria Del Razo [e], Betzabet Quintanilla-Vega [e], Rodrigo Franco [a,b,*]

[a] Redox Biology Center, University of Nebraska-Lincoln, Lincoln, NE 68583, United States
[b] School of Veterinary Medicine and Biomedical Sciences, University of Nebraska-Lincoln, Lincoln, NE 68583, United States
[c] Department of Mechanical and Materials Engineering, University of Nebraska-Lincoln, Lincoln, NE 68583, United States
[d] Department of Psychology, University of Nebraska-Lincoln, Lincoln, NE 68583, United States
[e] Department of Toxicology, CINVESTAV–IPN, Mexico City, Mexico
[f] Department of Physiology, Biophysics and Neurosciences, CINVESTAV–IPN, Mexico City, Mexico
[g] Department of Molecular Biology and Genetics, Democritus University of Thrace, University Campus, Dragana, Alexandroupolis, Greece

ARTICLE INFO

Keywords:
Antioxidant gene therapy
Brain ischemia
Neurodegenerative disorders
Oxidative stress
Reactive oxygen species
Reactive nitrogen species
Virus-mediated gene delivery

ABSTRACT

Oxidative stress is a common hallmark of neuronal cell death associated with neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, as well as brain stroke/ischemia and traumatic brain injury. Increased accumulation of reactive species of both oxygen (ROS) and nitrogen (RNS) has been implicated in mitochondrial dysfunction, energy impairment, alterations in metal homeostasis and accumulation of aggregated proteins observed in neurodegenerative disorders, which lead to the activation/modulation of cell death mechanisms that include apoptotic, necrotic and autophagic pathways. Thus, the design of novel antioxidant strategies to selectively target oxidative stress and redox imbalance might represent important therapeutic approaches against neurological disorders. This work reviews the evidence demonstrating the ability of genetically encoded antioxidant systems to selectively counteract neuronal cell loss in neurodegenerative diseases and ischemic brain damage. Because gene therapy approaches to treat inherited and acquired disorders offer many unique advantages over conventional therapeutic approaches, we discussed basic research/clinical evidence and the potential of virus-mediated gene delivery techniques for antioxidant gene therapy.

© 2013 Published by Elsevier Inc.

Contents

1. Introduction . . . 0
2. Oxidative stress and generation of ROS/RNS . . . 0
3. Oxidative stress and neuronal cell death . . . 0
4. Gene delivery approaches to target the Central Nervous System . . . 0

Abbreviations: ΔΨm, mitochondrial membrane potential; 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; AADC, aromatic-L-amino decarboxylase; AAV, adeno-associated virus; Aβ, amyloid-β peptide; AD, Alzheimer's disease; AICD, amyloid precursor protein intracellular domain; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; ARE, antioxidant response element; ApoE, apolipoprotein E; BDNF, brain-derived eurotrophic factor; BBB, blood-brain barrier; CBF, cerebral blood flow; CNTF, ciliary neurotrophic factor; COX, cyclooxygenases; CSF, cerebrospinal fluid; CuZnSOD, copper-zinc superoxide dismutase; DMT1, divalent metal transporter 1; EpRE, electrophile-responsive elements; EAAT, excitatory amino acid transporter; EcSOD, extracellular superoxide dismutase; ETC, electron transport chain; bFGF, fibroblast growth factor; G-CSF, granulocyte-colony stimulating factor; G6PD, glucose-6-phosphate dehydrogenase; GAD, glutamic acid decarboxylase; GDNF, glial-cell-line-derived neurotrophic factor; GCL, glutamate-cystein ligase; GCLC, glutamate-cystein ligase catalytic subunit; GCLM, glutamate-cystein ligase modifier subunit; GSH, glutathione; GSSG, glutathione disulfide; GR, glutathione reductase; Gpx, glutathione peroxidases; Grx, glutaredoxin; GCH-1, GTP cyclohydrolase-1; HD, Huntington's disease; HO, heme-oxygenase; IMS, inner membrane space; IGF-1, insulin growth factor 1; LRRK2, leucine rich repeat kinase 2; LV, lentivirus; MetSO, methionine sulfoxide; mtHtt, mutant Huntingtin; Msrs, MetSO reductases; MnSOD, manganese superoxide dismutase; MPOs, myeloperoxidases; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NADPH, nicotinamide adenine dinucleotide phosphate; NGF, nerve growth factor; Nox, NADPH oxidase; •NO, Nitric oxide, (e) endotelial, (i) inducible, (n) neuronal; NOS, nitric oxide synthase; O_2, oxygen; $O_2^{\bullet-}$, Superoxide anion; •OH, hydroxyl radical; $ONOO^-$, peroxynitrite; ONOOH, peroxynitrous acid; PD, Parkinson's disease; Prx, Peroxiredoxin; PSEN, presenilin; RAGE, receptor for advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; SNpc, substantia nigra pars compacta; SODs, superoxide dismutases; TBI, traumatic brain injury; TH, tyrosine hydroxylase; TOM, translocase of the outer membrane; Trx, thioredoxin; TrxR, thioredoxin reductase; VEGF, vascular endothelial growth factor; VMAT2, vesicular monoamine transporter.

* Corresponding author at: Redox Biology Center and School of Veterinary Medicine and Biomedical Sciences, 114 VBS 0905, University of Nebraska-Lincoln, Lincoln, NE 68583, United States. Tel: 402-472-8547; fax: 402-472-9690.
E-mail address: rfrancocruz2@unl.edu (R. Franco).

0163-7258/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.pharmthera.2013.12.007

5. Catalytic antioxidant defenses against neuronal cell death 0
6. Conclusions and perspectives 0
Authors' disclosure statement 0
Acknowledgments. 0
References 0

1. Introduction

Oxidative stress is a cellular condition induced by the de-regulated production of reactive species of oxygen (ROS) and nitrogen (RNS), which are highly reactive molecules generated by several biochemical and physiological processes of cellular metabolism under both normal and pathological conditions. The delicate balance between the production and elimination of ROS/RNS (redox homeostasis) determines the normal function of cells. However, when cells are unable to maintain redox homeostasis via the detoxification of these reactive species produced and/or repair the damage produced, oxidative stress prevails. During oxidative stress, many cellular functions are disturbed by the reaction of reactive species with cellular components such as amino acids, carbohydrates, DNA, RNA, lipids and proteins. ROS are produced upon incomplete reduction of oxygen (O_2) by action of housekeeping enzymes and/or formed during the exposure to X-ray, γ or UV irradiation. RNS are generated under normal and pathological conditions by catalytic and non-catalytic reactions (Cooke et al., 2003; Stadtman & Levine, 2003; Olivares-Corichi et al., 2005; Tanaka et al., 2007; Yin et al., 2009).

Oxidative stress contributes to the etiology of metabolic disorders (Shibata et al., 2010) and neurodegenerative diseases (Patten et al., 2010), and it has also been established to have an important role in the acceleration of pre-existing conditions such as cell invasiveness in cancer (Shinohara et al., 2010). On the other hand, ROS/RNS are essential mediators of cellular processes such as redox signaling, immunological defense mechanism and protein folding. Over the years, the role of ROS and RNS as signaling molecules has been extensively documented. The key issue is the concentration at which these reactive species are present within the cell.

Considering the important role of oxidative stress in neuronal cell death (Franklin, 2011) and the growing knowledge about the protective role that antioxidant systems play, recent efforts have been directed to develop an efficient antioxidant approach to counteract the oxidative stress-induced neuronal cell death that is a hallmark in neurological diseases. Therefore, in this review we will discuss the advances in antioxidant gene therapy for neurodegenerative diseases as well as in brain ischemia and traumatic brain injury.

2. Oxidative stress and generation of ROS/RNS

Within the cell, there are several organelles that have the ability to produce ROS such as peroxisomes (Schönfeld et al., 2009), the endoplasmic reticulum (Liu et al., 2004), autophagosomes/lysosomes (Kubota et al., 2010), endosomes (Li et al., 2011) and the nucleus (Spencer et al., 2011). Notably, it has been amply demonstrated that one of the main sources of ROS is the mitochondria (Murphy, 2009). $O_2^{\bullet -}$ is produced by the one-electron reduction of O_2 through the complex I (Grivennikova & Vinogradov, 2006) and complex III (Chen et al., 2003) of the electron transport chain (ETC) and released to the mitochondrial matrix by complex I and to both the mitochondrial matrix and the inner membrane space (IMS) by complex III (Muller et al., 2004). A second important source of ROS production is the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family (Nox enzymes). This family of enzymes catalyzes the production of $O_2^{\bullet -}$ from O_2 and NADPH, and was originally described in polymorphonuclear neutrophils to provide host defense against bacteria via a rapid respiratory burst of $O_2^{\bullet -}$. However, distinct Nox enzymes have also been reported in distinct brain regions (Infanger et al., 2006).

When $O_2^{\bullet -}$ suffers natural or enzymatic dismutation, hydrogen peroxide (H_2O_2) is arisen. The enzymatic generation of H_2O_2 is catalyzed by $O_2^{\bullet -}$ dismutases (SODs). H_2O_2 is thought to diffuse across membranes. In addition, it has been demonstrated that the diffusion of H_2O_2 is facilitated by members of the aquaporin family (Bienert et al., 2006, 2007). H_2O_2 has a half-life of 1 ms, which allows it to react with several molecules or metals to produce the hydroxyl radical (OH•) by Fenton reaction (Christine, 1995; Nappi & Vass, 1998; Reth, 2002).

Nitric oxide (NO•) is formed from L-arginine by the enzyme nitric oxide synthase (NOS) and is a small hydrophobic molecule that freely diffuses across membranes (Miersch et al., 2008). NO• has been recognized to act as a paracrine signaling molecule playing an important role as second messenger in processes as diverse as cell survival (Patel et al., 2010), proliferation (Magalhães et al., 2006), apoptosis (Wei et al., 2000) and neuronal differentiation (Ciani et al., 2004). $O_2^{\bullet -}$ reacts three times faster with NO• than with MnSOD leading to the production of the most oxidant specie peroxynitrite ($ONOO^-$), which is able to cross membranes through the anion channel in the anionic form ($ONOO^-$) and by passive diffusion in its protonated form, peroxynitrous acid (ONOOH) (Denicola et al., 1998). Three NOS genes have been described, all of which are found in distinct brain regions. Endothelial (eNOS) and neuronal NOS (nNOS) are classically calcium (Ca^{2+})/calmodulin-dependent and generate nanomolar concentrations of NO•, while inducible NOS (iNOS) can produce micromolar levels of NO• (Brown, 2010).

Myeloperoxidases (MPOs) produce hypochlorous acid (HOCl) from H_2O_2 and chloride anion (Cl^-) using heme as a cofactor. MPOs also oxidize tyrosine to tyrosyl radical using H_2O_2 as an oxidizing agent. Until recently, phagocytic cells were thought to be the only cellular sources of MPOs. However, recent studies demonstrate that several cell types including neuronal cells, express MPOs under certain pathological conditions (Green et al., 2004; van der Veen et al., 2009). Cyclooxygenases (COXs) are also known to generate ROS as a byproduct of the metabolism of arachidonic acid. COXs metabolize arachidonic to prostaglandin G2 (PGG_2) utilizing two O_2 molecules and producing peroxyl radicals. COXs also possess a heme-containing active site that provides peroxidase activity, converting PGG_2 to prostaglandin H2 (PGH_2) by removing O_2, which might be a source of oxygen radicals. In the presence of H_2O_2, the peroxide activity of COXs may oxidize various co-substrates such as NADH and glutathione (GSH), which could reduce O_2 to $\bullet O_2^-$ (Im et al., 2006). Several studies have demonstrated COX-immunoreactivity in neuronal populations from different regions, where COX-2 is found in postsynaptic cell bodies and dendritic spines (Mancuso et al., 2006).

An increasing amount of evidence suggests that oxidative/nitrosative stress is linked to the pathophysiology of multiple human diseases. However, definitive evidence for this association has been controversial because of shortcomings found in methods available to assess oxidative stress in vivo. Measuring oxidative stress can be difficult because the biological half-life of free radicals and other reactive species is too short for direct detection. Therefore, evidence has to rely on indirect measurements. These indirect measurements are based on byproducts of oxidative damage to lipids, proteins and DNA, which provide an extensive array of potential biomarkers (Blumberg, 2004; Dalle-Donne et al., 2006; Halliwell, 2011; Bast & Haenen, 2013). Lipid peroxidation generates mainly α,β-unsaturated reactive aldehydes, such as

UNCORRECTED PROOF

Please cite this article as: Navarro-Yepes, J., et al., Antioxidant gene therapy against neuronal cell death, *Pharmacology & Therapeutics* (2013), http://dx.doi.org/10.1016/j.pharmthera.2013.12.007

Download English Version:

https://daneshyari.com/en/article/5844019

Download Persian Version:

https://daneshyari.com/article/5844019

Daneshyari.com