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Antioxidant gene therapy against neuronal cell death

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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.

Keywords

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

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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; Olivares-Corichi et al., 2005; Stadtman et al., 2003; 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., 2011b) 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 et al., 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., 2007; Bienert et al.,

2006). H_2O_2 has a half-life of 1 millisecond, which allows it to react with several molecules or metals to produce the hydroxyl radical ($OH^{\bullet}$) by Fenton reaction (Christine C, 1995; Nappi et al., 1998; Reth, 2002).

Nitric oxide ($NO^{\bullet}$) 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). $NO^{\bullet}$ 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 $NO^{\bullet}$ 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 $NO^{\bullet}$, while inducible NOS (iNOS) can produce micromolar levels of $NO^{\bullet}$ (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 (Bast et al., 2013; Blumberg, 2004; Dalle-Donne et al., 2006; Halliwell, 2011). Lipid peroxidation generates mainly α,β-unsaturated reactive aldehydes, such as malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), 2-propenal (acrolein) and isoprostanes. (Dalle-Donne et al., 2006; Devasagayam et al., 2003). It is important to mention that lipid hydroperoxides and aldehydes can also be absorbed from the diet, which can confound measurements of MDA and HNE in plasma or urinary samples (Dalle-Donne et al., 2006). The determination of isoprostanes is considered now the best available biomarker of lipid peroxidation, because of their stability (Dalle-Donne et al., 2006; Halliwell, 2011; Halliwell et al., 2004).

Protein damage by oxidative stress has been mostly determined by the formation of carbonyl compounds *in vitro* and *in vivo*. Protein carbonyls are chemically stable, which makes them

suitable for postmortem samples analysis. However, carbonyls are not specific as markers of oxidative damage because bound aldehydes and glycated protein are also measured. (Dalle-Donne et al., 2006; Luo et al., 2009; Suzuki et al., 2010). Determination of 3-nitroyrosine (3-NT) is also widely used as an index of oxidative protein damage. However, its specificity is debated because nitration can occur independently of peroxynitrite exposure (Dalle-Donne et al., 2006; Duncan, 2003; Halliwell et al., 2004; Tsikas et al., 2005).

Oxidative DNA damage byproducts are also important markers assessed to evaluate oxidative stress *in vivo*. $OH^{\bullet}$ generates a wide range of base and sugar modifications in DNA. However, the initial products of free radical attack undergo transformation into stable end products, whose abundance depends on reaction conditions and more importantly, none of these modifications can identify the location of the oxidative damage is located. 8-hydroxy-2'-deoxyguanosine (8OHdG) is commonly measured as an index of oxidative DNA damage. However, artifactual oxidative damage to DNA has been shown to occur during isolation, preparation and analysis of samples. To date, there is no agreement on basal levels of 8OHdG in cellular DNA, even when standard extraction procedures have been used. (Collins et al., 2004; Dalle-Donne et al., 2006; Gedik et al., 2005; Halliwell et al., 2004; Kryston et al., 2011).

3. Oxidative stress and neuronal cell death

3.1. Neurodegenerative diseases

Neurodegenerative diseases are defined as hereditary and sporadic conditions that are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral structures of the nervous system and include: Alzheimer's Disease (AD) and other dementias, Parkinson's Disease (PD), Huntington's Disease (HD), Multiple Sclerosis, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease), Prion diseases and others. Such cell death can be induced by exogenous factors such as neurotoxicants or mutations in key genes. During neuronal cell death, diverse mechanisms are involved. Solid evidence has demonstrated that oxidative stress plays a central role in the initiation of neuronal damage in neurodegeneration (Table 1).

3.1.1. Alzheimer's Disease (AD)—An estimated of 35 million people worldwide have been diagnosed with AD, wich make it the most common neurodegenerative dementia. It is characterized by the impairment of behavioral and cognitive functions leading to death within 3 to 9 years after diagnosis. The principal risk factor for AD is age as its incidence doubles every 5 years after 65 years of age. Among the characteristics found in brains of AD patients are senile plaques, which contain amyloid-β peptide (Aβ) derived from the amyloid precursor protein (APP). Established genetic causes of AD include dominant mutations of genes encoding *APP* and presenilin 1 (*PSEN1*) and *PSEN2*. *PSEN1* and *PSEN2* mutations affect concentrations of $A\beta_{1-42}$ because presenilin proteins form part of γ secretases, which cleave APP to produce Aβ. Potential risk genes for AD include apolipoprotein E (*ApoE*), which affects Aβ aggregation and clearance. Neurofibrillary tangles are also found in postmortem brains of AD patients containing the pathologically aggregated tau protein (Mena et al., 1995). Several post-translational modifications in tau have been reported such as ubiquitination, glycation and phosphorylation, among others. Tau mutations result in tauopathies, such as corticobasal degeneration and frontotemporal dementias, but not AD (Ballard et al., 2011; Holtzman et al., 2011; Querfurth et al., 2010; Selkoe, 2011). Post-mortem human studies demonstrate the accumulation of lipid peroxidation products in multiple brain regions and in cerebrospinal fluid (CSF) of AD subjects. Protein oxidation byproducts such as carbonyls and 3-nitrotyrosine are also found increased in the frontal and parietal lobes and in the hippocampus of AD and subjects with mild cognitive-impairment (MCI). Finally, oxidative modifications in nucleic acid bases are increased in AD and MCI

brain samples (Good et al., 1996; Pratico, 2008). Several studies have indicated the presence of oxidative stress markers in the brain of most transgenic AD mouse models, suggesting that oxidative stress is an early event in the AD development that could promote the amyloid cascade by increasing Aβ synthesis and aggregation (reviewed in (Belkacemi et al., 2012).

The amyloid cascade hypothesis suggests that the deposition of Aβ triggers neuronal dysfunction and death in the brain (Figure 1). Using *in vivo* imaging of a fluorescent indicator of oxidative stress in a transgenic mouse model, Xie *et al.*, (2013) demonstrated that Aβ plaque formation precede and lead to oxidative stress in surrounding neurites, which propagates over time and leads to oxidation and degeneration of neuronal soma. These results implicate Aβ as the mediator of oxidative stress and subsequent neurodegeneration (Xie et al., 2013). It is important to state that amyloid-independent mechanisms have also been proposed to contribute to AD (Karran et al., 2011; Pimplikar et al., 2010). APP is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated as a regulator of synapse formation, neuronal plasticity and iron export. Amyloidogenic processing is initiated by a β-secretase, the beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), releasing a shortened sAPP. The C99 fragment is a γ-secretase substrate, generating Aβ and the amyloid precursor protein intracellular domain (AICD). Soluble Aβ is prone to aggregation. In a triple transgenic mouse model of AD (3xTg-AD) with human transgenes *APP* (SWE [swedish mutation]), *PSEN1* (M146V) *or PSEN2* (N141I), and Tau (P301L), an impaired oxidative phosphorylation, increased oxidative state and GSH depletion was reported to precede the onset of cognitive defects (Belkacemi et al., 2012; Ghosh et al., 2012; Rhein et al., 2009). Moreover, alterations in the glutathione redox state, an increase of GSSG together with a decrease of GSH/GSSG ratio, and an increase of mixed-disulfide (Pr-SSG) has been reported in brain tissues and blood samples at different disease stages in a double mutant AD transgenic mouse model (B6. Cg-Tg) carrying the APPswe and exon 9 deletion of the PSEN1 gene, suggesting that formation of Pr-SSG may be an early event, preceding amyloid plaque appearance (Zhang et al., 2012a).

Aβ interacts with several metal ions affecting its solubility and leading to fibrillization and cellular toxicity (Benilova et al., 2012; O'Brien et al., 2011). Elevated levels of labile copper (Cu^{+2}) that correlated with oxidative stress were found in AD brains (James et al., 2012). The morphology of Aβ aggregates is modified in a concentration-dependent manner by metal ions as iron (Fe^{+2}), Cu^{+2} and zinc (Zn^{+2}). Once Aβ is bound to metal ions such as Fe^{+2} and Cu^{+2}, the Aβ-metal complexes can mediate the production of H_2O_2 and $OH^{\bullet}$ (Su et al., 2008). It has been suggested that AD pathogenesis may be influenced by early life exposures to toxic metals such as lead, which are related to oxidative damage as well (Wu et al., 2008a; Wu et al., 2008b).

Mitochondrial dysfunction is a hallmark observed in AD and has been related to the accumulation of Aβ within mitochondria. The Aβ is transported into mitochondria via the translocase of the outer membrane (TOM) complex and localized at the mitochondrial cristae (Hansson Petersen CA, 2008). Aβ inhibits mitochondrial enzymes in the brain and in isolated mitochondria such as cytochrome oxidase (complex IV) and the key Krebs-cycle enzymes (α-ketoglutarate and pyruvate dehydrogenase) impairing ETC, ATP production, oxygen consumption, and mitochondrial membrane potential. Dysfunctional mitochondria produce ROS and as a consequence, mtDNA oxidative damage. Conversely, current evidence shows that mitochondria-derived ROS are sufficient to trigger increased Aβ production both *in vitro* and *in vivo*, and thereby initiate a vicious cycle further impairing mitochondrial function (Leuner et al., 2012). In the mitochondria, Aβ also interacts with the 17-β-hydroxysteroid dehydrogenase X (*HSD17B10*) also known as Aβ peptide-binding alcohol dehydrogenase (ABAD), an enzyme that catalyzes the oxidation of a wide variety of

fatty acids, alcohols, and steroids, exacerbating neuronal cell death by mitochondrial dysfunction and oxidative stress (Yao et al., 2011).

The receptor for advanced glycation end products (RAGE) has also been proposed to mediate Aβ's pro-oxidant effects (Yan et al., 1996). In addition, perturbations in neuronal Ca^{2+} homeostasis induced by Aβ have the potential to trigger mitochondrial dysfunction and ROS formation (Bezprozvanny et al., 2008). Aβ has a critical methionine residue at position 35, which is thought to be associated with Aβ peptide toxicity. Oxidation of Met35 produces methionine sulfoxide or methionine sulfone via irreversible oxidation. However, contradictory reports exist regarding the role of Met35 residue in Aβ toxicity and oxidative stress (Butterfield et al., 2010; Butterfield et al., 2007; Maiti et al., 2010). MPOs have been found increased in AD brains (Green et al., 2004), and the overexpression of the MPO-463G allele in astrocytes increases lipid peroxidation in a transgenic mouse model of AD (Maki et al., 2009). COX-2 inhibition is reported to improve the memory and synaptic plasticity in AD models (Jang et al., 2005; Kotilinek et al., 2008).

Increased levels of nitrated proteins are found in AD brains (Smith et al., 1997). Aβ induces an increase in iNOS expression and $NO^{\bullet}/ONOO^{-}$ generation in glial cells (Akama et al., 1998; Akama et al., 2000; Combs et al., 2001; Xie et al., 2002). However, contradictory results exist regarding the effect of iNOS knockout in AD transgenic mouse models (Colton et al., 2006; Wilcock et al., 2008). Similarly, microglial cells from ApoE epsilon 4 allele (*ApoE4*), a risk factor in AD, produce higher levels of $NO^{\bullet}$ (Brown et al., 2002; Colton et al., 2002; Ramassamy et al., 1999). In contrast, Aβ inhibits the activity of nNOS and eNOS in neuronal-like cells (Venturini et al., 2002).

3.1.2. Parkinson's Disease (PD)—PD is a neurodegenerative disorder characterized by the selective loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc). The accumulation of α-synuclein is a crucial step in the pathogenesis of PD and a key constituent of intraneuronal proteinaceous inclusions known as Lewy bodies. There is no current treatment to stop neuronal cell death and/or to cure PD. Current evidence supports a role for mitochondrial dysfunction, oxidative stress, and abnormal protein accumulation as early triggers of neuronal death in PD pathogenesis. Existing therapies available only delay the onset of PD and/or ameliorate motor symptoms by addressing dopamine deficit (Levy et al., 2009; Yao et al., 2009). A fraction of PD occurrence is related to mutations in genes such as those of α-synuclein (*SNCA*), DJ-1 (*PARK7*), PTEN-induced putative kinase 1 (*PINK1*), leucine rich repeat kinase 2 (*LRRK2*) and parkin (*PARK2*). However, 90% of PD cases occur in a sporadic (idiopathic) form without a defined genetic basis. The major risk factor identified for PD is aging as its occurrence increases exponentially from ages 65 to 90. Epidemiological evidence shows an increase in the risk of developing PD upon the exposure to environmental toxicants such as pesticides, metals, polychlorinated biphenyls, as well as early life inflammatory processes (Gao et al., 2011a). Thus, it is now being considered that PD arises from the convergence of genetic susceptibility, environmental exposures, and aging.

Oxidative damage to lipids, proteins and DNA is found in post-mortem PD brains (Alam et al., 1997a; Alam et al., 1997b; Dexter et al., 1991; Dexter et al., 1989; Dexter et al., 1994; Floor et al., 1998; Hirsch et al., 1991; Jenner et al., 1992; Perry et al., 1982; Riederer et al., 1989; Sian et al., 1994; Yoritaka et al., 1996; Zhang et al., 1999). SNpc dopaminergic cells have high levels of basal oxidative stress compared to other dopaminergic neuronal populations (Guzman et al., 2010). A decrease in the activity of the mitochondrial ETC is found in the SNpc of patients with PD (Henchcliffe et al., 2008; Schapira, 2008; Schapira et al., 1989) suggesting that oxidative stress is linked to mitochondrial dysfunction (Figure 2). Environmental pesticides such as paraquat and rotenone have been proposed to mediate

mitochondrial ROS generation via complex I and III (Castello et al., 2007; Drechsel et al., 2009; Sherer et al., 2003; Sherer et al., 2007).

PD-associated genes have also been shown to modulate or induce oxidative stress in dopaminergic cells. α-Synuclein is a 140 amino acid brain protein mainly localized in pre-synaptic terminals, and gene multiplications or point mutations are associated with familial PD. Oxidative stress promotes α-synuclein oligomerization and aggregation (Giasson et al., 2000; Meloni et al., 2011). Accumulation of α-synuclein has also been suggested to trigger mitochondrial oxidative stress (Devi et al., 2008) and alterations in Ca^{2+} permeability (Furukawa et al., 2006; Goldberg et al., 2012). Extracellular α-synuclein also triggers microglia activation and Nox-mediated ROS formation (Zhang et al., 2005), which in turn increase α-synuclein aggregation (Cristovao et al., 2012). It has been proposed that α-synuclein exerts protective effects (Hashimoto et al., 2002), while the A53P mutant α-synuclein sensitizes cells upon oxidative damage (Ko et al., 2000). DJ-1 oxidation induces its mitochondrial translocation (Canet-Aviles et al., 2004), and DJ-1 knockdown or mutants render cells more susceptible to parkinsonian toxins and oxidative stress (Kim et al., 2005; Taira et al., 2004). In addition, DJ-1 has been reported to regulate GSH levels (Liu et al., 2008). Interestingly, DJ-1 seems to be primarily expressed in astrocytes (Bandopadhyay et al., 2004). PINK1 protein is a serine/threonine kinase localized in the mitochondria and the cytosol. Loss of PINK1 has been shown to induce mitochondrial dysfunction, oxidative stress and mitochondrial turnover via mitophagy (Dagda et al., 2009; Gandhi et al., 2009; Gegg et al., 2009; Heeman et al., 2011; Liu et al., 2011; Morais et al., 2009). Parkin deficiency induces mitochondrial dysfunction and oxidative stress (Palacino et al., 2004), as well as an increase in monoamine oxidase (MAO) expression (Jiang et al., 2012). On the other hand, Parkin protects cells against dopamine toxicity (Jiang et al., 2004). LRKK2 also protects against oxidative stress (Liou et al., 2008). However, gain-of-function of LRRK2 mutations disturb mitochondrial dynamics leading to increased ROS formation (Niu et al., 2012).

Metal-induced ROS generation has been postulated to contribute to oxidative damage in PD. However, controversy still exists regarding the occurrence of alterations in the levels of Fe^{+2} or Cu^{+2} in PD brains (Mariani et al., 2012). Metal ions accelerate the oligomerization/aggregation of α-synuclein, being Cu^{+2} the one that induces it faster (Paik et al., 1999; Rasia et al., 2005; Rose et al., 2011; Uversky et al., 2001; Wang et al., 2010b; Wright et al., 2009). α-synuclein-Cu^{2+} complexes have been shown to induce ROS accumulation and dopamine oxidation (Meloni et al., 2011; Wang et al., 2010a). The accumulation of Mn^{+2} in basal ganglia structures is associated with the neurodegenerative disorder commonly referred to as manganism, a condition that shares many similarities with PD, which is also linked to increased oxidative damage (Milatovic et al., 2011). However, Mn^{+2}-induced parkinsonism does not seem to involve degeneration of the nigrostriatal dopaminergic system (Guilarte, 2010).

In the brain, Fe^{+2} is most abundant in areas rich in dopaminergic neurons. Increased Fe^{+2} deposition and increased free Fe^{+2} concentrations have been found in the SNpc of PD brains, which may lead to increased generation of •OH via Fenton and Haber-Weiss reactions (Sian-Hulsmann et al., 2011). Autopsy studies found an increased total Fe^{+2} content in the SNpc of PD patients compared to age-matched controls but other studies did not confirm these findings. Fe^{+2} content in the SNpc seems to be primarily affected in advanced PD patients suggesting that it is not involved in early disease development. Alterations in Fe^{+2} distribution are also found in PD. Contrary to normal subjects, where more Fe^{+2} is deposited in the SN pars reticulata, in PD Fe^{+2} is deposited abundantly in the SNpc containing pigmented neurons (Sian-Hulsmann et al., 2011). Together with paraquat, Fe^{+2} enhances dopaminergic neurodegeneration (Peng et al., 2007). Low levels of ferritin in

the SNpc of PD patients and incidental Lewy body disease cases were reported. Overexpression of ferritin decreases oxidative stress and neuronal cell death induced by parkinsonian mimetics (Kaur et al., 2010; Lee et al., 2010; Shi et al., 2010). Neuromelanin pigmented neurons in SNpc are preferentially lost in PD, and Fe^{+2} accumulation in the SNpc is deposited within neuromelanin granules. A specific haplotype of the divalent metal transporter 1 (DMT1/*SLC11A2*) gene was found to occur at greater frequencies in PD patients suggesting that alterations in DMT1 function may contribute to PD (Dusek et al., 2012), whereas 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic cell death was associated with an increase in DMT1 and transferrin receptor levels (Kalivendi et al., 2003; Salazar et al., 2008). The levels of Fe^{+2} "handling" proteins such as ceruloplasmin have also been reported altered in PD (Hochstrasser et al., 2005; Jin et al., 2011). In the presence of Fe^{+2}, α-synuclein induces $OH^{\bullet}$ formation (Turnbull et al., 2001), whereas in other studies, oxidative damage induced by Fe^{+2} was exacerbated primarily by mutant, but not wild type (WT) α-synuclein (Chew et al., 2011; Martin et al., 2003; Ostrerova-Golts et al., 2000).

Oxidative stress in PD is also associated with the pro-oxidant properties of dopamine. Mutant α-synuclein down-regulates the vesicular monoamine transporter (VMAT2) augmenting the cytosolic dopamine levels (Lotharius et al., 2002a; Lotharius et al., 2002b), which is either metabolized by monoamineoxidase to generate H_2O_2, or auto-oxidized in the presence of Fe^{+2} generating $O_2^{\bullet -}$, H_2O_2 and dopamine-quinone species (DAQ) (Abou-Sleiman et al., 2006). α-synuclein also interacts with the dopamine transporter (DAT), although its effects in dopamine uptake and toxicity are unclear (Lee et al., 2001; Wersinger et al., 2003). Furthermore, dopaminergic cell death induced by rotenone and paraquat has been proposed to depend on dopamine oxidation (Kang et al., 2009; Liu et al., 2005). Plasma membrane NADPH- oxidases, mainly Nox1, also mediate ROS generation in dopaminergic and microglial cells upon MPP^+, rotenone or paraquat treatment (Cristovao et al., 2009; Gao et al., 2003; Gao et al., 2011b; Goldberg et al., 2012; Wu et al., 2003; Wu et al., 2005). MPOs and COX-2 have also been shown to participate in MPTP-induced oxidative stress and neurotoxicity (Choi et al., 2005; Teismann et al., 2003; Wang et al., 2005).

RNS also play an important role in oxidative stress. Both $NO^{\bullet}$ and $ONOO^-$ have been shown to participate in 6-OHDA, MPP^+/MPTP and rotenone toxicity, which are prevented by inhibition/knockout of $NO^{\bullet}$ synthases (Ara et al., 1998; Broom et al., 2011; Dehmer et al., 2000; Hantraye et al., 1996; He et al., 2003; LaVoie et al., 1999; Liberatore et al., 1999; Park et al., 2002; Przedborski et al., 1996; Schulz et al., 1995; Watabe et al., 2008). Tyrosine nitration promotes α-synuclein oligomerization and aggregation (Giasson et al., 2000; Hodara et al., 2004; Paxinou et al., 2001; Souza et al., 2000), and exposure to parkinsonian mimetics has been shown to mediate α-synuclein nitration (Przedborski et al., 2001). Interestingly, transgenic mice overexpressing α-synuclein Y39C mutant variant show age-dependent progressive neuronal degeneration (Zhou et al., 2008). Inhibition of Parkin's ubiquitin E3 ligase activity by S-nitros(yl)ation has also been found in PD brains, (Chung et al., 2004).

3.1.3. Huntington's Disease (HD)—HD is a genetic autosomal dominant neurodegenerative disorder caused by highly polymorphic CAG trinucleotide repeat expansion in the exon-1 of the huntingtin (Htt) gene (*IT15*), yielding proteins containing polyglutamine repeats that become misfolded aggregates and resist degradation. Alleles of Htt harboring between 36–40 CAGs may or may not develop HD symptoms. However, individuals with alleles containing more than 40 CAG repeats will develop symptoms. HD neuropathological changes are predominantly detected in the striatum, although marked alterations are also observed in other areas of the brain such as cerebellar cortex, thalamus

and cerebellum (Finkbeiner, 2011; Oliveira, 2010; Zuccato et al., 2010). Several biomarkers of oxidative stress including lipid peroxidation, nucleic acid and protein oxidation byproducts, are increased in HD brains (Browne et al., 2006; Browne et al., 1997; Chen et al., 2007; Hersch et al., 2006; Klepac et al., 2007; Polidori et al., 1999; Sorolla et al., 2008; Sorolla et al., 2010). However, there are some studies that have failed to detect any sign of oxidative damage in HD brains (Alam et al., 2000). Despite its ubiquitous expression, mutant HTT (mtHtt) selectively affects medium spiny striatal neurons, and oxidative stress together with mitochondrial dysfunction have been implicated in the pathology of HD (Bano et al., 2011). Oxidative DNA damage has been reported in the caudate, parietal cortex, and peripherally in the serum and leukocytes of patients diagnosed with HD (Long et al., 2012; Weir et al., 2011).

Transgenic mice expressing exon 1 of the human Htt gene with an expanded CAG repeat develop a progressive neurologic disorder and present increased levels of oxidative DNA-damage (Bogdanov et al., 2001). Striatal cells expressing mtHtt show higher basal levels of mitochondrial-generated ROS and mitochondrial DNA damage (Siddiqui et al., 2012). Impaired respiratory chain complexes and tricarboxylic acid cycle enzyme activities have also been found in the brain of HD patients (Costa et al., 2012; Mochel et al., 2011; Shirendeb et al., 2011). Succinate dehydrogenase (SDH) or complex II subunits Fp (FAD) and Ip (iron–sulphur cluster) are found reduced in HD brains and in striatal neurons overexpressing the N-terminal fragment of mtHtt (Figure 3). Accordingly, the administration of inhibitors such as malonate and 3-nitropropionic acid (3-NP) induces both the biochemical and clinical alterations *in vivo* that resemble those in HD. The iron–sulphur containing dehydratase, aconitase, is one of the most affected tricarboxylic acid cycle enzymes in HD (Costa et al., 2012). 3-NP toxicity is enhanced by dopamine (Benchoua et al., 2008; Charvin et al., 2005). In addition, 3-NP induces a decrease in ATP levels and the activation of N-methyl-d-aspartate (NMDA) receptors, which mediate ROS formation (Liot et al., 2009). Although mitochondrial dysfunction has been largely proposed as a major mechanism for ROS formation, a recent report demonstrates that aggregation of a polyglutamine Htt fragment directly causes ROS formation (Hands et al., 2011). mtHtt itself is oxidized in cysteine residues proximal to the N-terminal domain promoting oligomerization and delayed clearance (Fox et al., 2011). Interestingly, antioxidants seem to exert a deleterious effect in polyglutamine models by inhibition of autophagy (Underwood et al., 2010).

3.1.4. Amyotrophic Lateral Sclerosis (ALS)—ALS is characterized by the progressive degeneration of motor neurons in the motor cortex and lower motor neurons connecting the spinal cord and brain stem to muscle fibers. ALS typically develops between 50 and 60 years of age as a relentless progressive neuromuscular failure leading to muscle denervation and atrophy. Only ~10% of ALS cases have a clear inherited genetic component, while the majority of ALS cases are sporadic with no family history of disease, and the gene-environmental factors involved remain poorly defined. Approximately 10–20% of familial ALS cases are caused by a variety of dominant mutations in the copper-zinc SOD (CuZnSOD) gene (*SOD1*). Over 110 mutations in 153 amino acids spread throughout all five exons as well as a small number in untranslated regions of SOD1 have been described to date. Other mutations leading to ALS include genes such as the “fused in sarcoma/translated in liposarcoma” (FUS/TLS), the TAR DNA-binding protein (TDP-43), the charged multivesicular body protein 2B (CHMP2B), the vesicle-associated membrane protein (synaptobrevin-associated protein) B (VAPB), and angiogenin. Increased oxidative stress biomarkers are found in ALS postmortem tissues, such as brain and spinal cord as well as in cerebrospinal fluid (Abe et al., 1997; Beal et al., 1997; Bogdanov et al., 2000; Ferrante et al., 1997a; Ihara et al., 2005; Shaw et al., 1995{Abe, 1995 #431; Shibata et al., 2001; Simpson et al., 2004; Smith et al., 1998), and *in vivo* models (Andrus et al., 1998;

Casoni et al., 2005; Ferrante et al., 1997b; Liu et al., 1998; Poon et al., 2005). In fact, recent studies suggest that SOD1 could be pathogenic in sporadic ALS through non-heritable modifications, such as posttranslational modifications including hyperoxidation of wild type SOD1. Hyperoxidized SOD1 recapitulates mutant SOD1-like properties (Guareschi et al., 2012). However, it is now widely accepted that loss of SOD1 dismutase activity is not sufficient to cause ALS and that mutant SOD1 promotes release of toxic factors. This is demonstrated by two specific findings: 1) SOD1 knockout does not develop ALS, and 2) some ALS related mutations such as G75R and G93R do not alter dismutase activity (Barber et al., 2010).

SOD1 mutants induce Nox-dependent ROS production in microglia and neuronal death. More specifically both Nox2 and Nox1 knockdown increase survival in SOD1 mutant transgenic mice (Li et al., 2011b). Dysregulation of proteins involved in Fe^{+2} influx and sensing of intracellular Fe^{+2}, with a concomitant accumulation of Fe^{+2} iron in ventral motor neurons and increased mitochondrial Fe^{+2} load in neurons and glial cells, have been shown in mouse overexpressing human SOD1 (G37R) mutant. Similarly, aberrant coordination of Cu^{2+} by mutant SOD1 has also been demonstrated to mediate oxidative stress (Kishigami et al., 2010).

3.2. Brain Ischemia and Excitotoxicity

It is estimated that every year 15 million people suffer from an acute cerebrovascular stroke, taking the life of 5.5 million and accounting for 5 million permanently disabled patients. Ischemic stroke is characterized by a significant reduction in regional cerebral blood flow causing deprivation of O_2 and glucose resulting in brain damage. Focal ischemia is a reduction in the blood flow to a very specific brain region (for example, middle cerebral artery embolic occlusion is a frequently used experimental model), whereas global ischemia occurs when cerebral blood flow (CBF) is reduced throughout most parts of the brain (like it takes place in cardiac arrest). There are significant differences in the mode of cell death between global and focal cerebral ischemia. Brief periods of global cerebral ischemia cause delayed neuronal death with distinct morphological features characteristic of apoptosis, though the apoptotic machinery might contribute significantly to cell death progression. In focal cerebral ischemia, most of cells in the ischemic core undergo necrosis, while cell death within the ischemic penumbra region is considered to be largely dependent on the activation of apoptotic signaling (Chen et al., 2011; Nakka et al., 2008; Niizuma et al., 2009).

During reperfusion, when O_2 is replenished, pro-oxidant enzymes and mitochondria utilize O_2 as a substrate to generate ROS (Figure 4). Multiple markers of oxidative damage are increased immediately after ischemic stroke, and remain elevated for several days (Seet et al., 2011). Mitochondria have been reported to act as major sources of ROS in ischemia and the inhibition of the mitochondrial complex I inhibits both hypoxic- (ischemic) and reperfusion-mediated oxidative damage (Niatsetskaya et al., 2012). Current data provide evidence suggesting Nox2 as the most important NADPH oxidase mediating cerebral injury (Kahles et al., 2013; Lu et al., 2012). Nox2 has also been shown to contribute to ischemic/reperfusion injury in hippocampal cells *in vitro*, and neuronal cell death and microglial activation *in vivo* (Chen et al., 2009a; Kahles et al., 2013). Nox1 contributes to ischemic injury in mice (Kahles et al., 2010). However, a comparative study between Nox1, 2 and 4 demonstrated that Nox4 is the major contributor to oxidative damage and neuronal cell death after both transient and permanent ischemia (Kleinschnitz et al., 2010). Interestingly, neither the knockout of Nox2 nor the inhibition of Nox activity prevents perinatal brain injury in newborn mice (Doverhag et al., 2008).

Ischemia/reperfusion injury depletes energy stores impairing ATP-dependent processes. Malfunction of the Na^+/K^+-ATPase leads to disruption of ionic gradients of potassium (K^+),

sodium (Na^+), chloride (Cl^-), and calcium (Ca^{+2}). These alterations in ionic homeostasis induce plasma membrane depolarization, Ca^{+2}-dependent exocytosis, and reversal of excitatory amino acid uptake. The release of excitatory amino acids (glutamate) and the activation of ionotropic NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors promote Ca^{+2} overload and cell death progression by a variety of signaling mechanisms involving mitochondrial dysfunction (Figure 4). ROS formation upon ischemic conditions (O_2-glucose deprivation) has been shown to be specific for neuronal populations in CA1 region of the hippocampus, and this was associated with NMDA receptor and NOS activation (Fekete et al., 2008). In cortical neurons, glutamate excitotoxicity and ROS formation are also mediated by Nox4 (Ha et al., 2010).

3.3. Traumatic Brain Injury (TBI)

TBI is a pathological condition resulting from occupational activity (sports or accidents) in civil population and is the leading cause of death and disability for people under the age of 45. The annual burden associated with TBI is estimated at over $60 billion dollars. In the United States, it has been estimated that more than 1.7 million individuals annually suffer a TBI event that results in the development of complex neurological deficits caused by both primary and secondary injuries. Primary injury events encompass the mechanical damage that occurs at the time of trauma as a result of shearing, tearing or stretching, while the secondary injury develops progressively as a result from chronic biochemical, metabolic and cellular effects. Secondary injury is associated with progressive development of a number of neurological deficits. Brain traumatic insults are classified as: 1) focal, caused by direct impact with solid object with subsequent pathologies developing locally in the vicinity of the site of impact, or 2) diffuse, caused by forces acting inside the entire volume of brain parenchyma and resulting from head acceleration-deceleration. An emerging field of research are military brain injuries, in particular blast-induced TBI, whose pathobiology has characteristics not seen in other types of TBI (Cernak et al., 2010; Tyler, 2012).

Glutamate excitotoxicity and ischemia have been shown to participate in oxidative stress upon TBI (Figure 4). Direct tissue damage and impaired regulation of CBF and metabolism lead to ATP depletion, ionic gradient homeostasis and release of excitatory neurotransmitters (Cheng et al., 2012). Oxidative stress is known to play an important role in the pathology of TBI (Ansari et al., 2008; Tyurin et al., 2000), and both mitochondria and Nox enzymes have been reported to mediate ROS formation (Singh et al., 2006). A biphasic generation of ROS by Nox2 has been reported in TBI *in vivo* models (Zhang et al., 2012b). In addition, iNOS inhibition reduces neuronal damage induced by brain contusion (Gahm et al., 2006).

Characterization of oxidative stress in blast TBI models is a relatively unexplored area of research. Recently, Abdul-Muneer and colleagues performed an extensive characterization of ROS/NOS in the rat model of primary blast mild TBI (Abdul-Muneer et al., 2013). They found that after exposure to a moderate intensity (130 kPa peak overpressure) single blast, the oxidative damage of the cerebrovascular barrier interface (the blood–brain barrier, BBB) was manifested by induction of Nox1 and inducible nitric oxide synthase (iNOS), and corresponding elevated levels of the signatures of oxidative and nitrosative damage, 4-hydroxynonenal (4-HNE) and 3-nitrotyrosine (3-NT). Similarly, the effects of blast exposure with moderate intensity (120 kPa) in rats resulted in reduced neurological function immediately following exposure to blast. Quantitative immunostaining revealed the temporal course of brain oxidative and nitrosative stress following the injury. An increase in the levels of 4-HNE and 3-NT were observed at 3 hours, and returned to base levels at 24 hr post exposure (Readnower et al., 2010).

4. Gene delivery approaches to target the Central Nervous System

Gene therapy is the process of delivering genes to cells. Most gene therapy studies employ viral vectors because they are highly efficient and can support lifetime protein expression in the brain (Figure 5). Virions can carry and protect viral genetic information, and can be designed to possess determinants on their surface to specify which cells to infect, minimizing immunostimulatory potential within the host. An ideal therapeutic viral vector will: 1) show specific tropism and highly efficient transduction of target tissues with minimal off-target transduction; 2) express the transgene for a length of time and at a level as to exert maximal therapeutic impact; and 3) show minimal side effects such as vector related pathologies or host immune responses (Manfredsson et al., 2012).

Viral vectors such as adenovirus, lentivirus (LV) and adeno-associated viral (AAV) have been designed for gene transfer (Figure 5). Adenoviruses display a rather promiscuous tropism and have significant immunological issues, thus, they have not been employed clinically for neurological diseases (Manfredsson et al., 2012). LV vectors have excellent safety and efficacy in rodent and primate models of neurodegenerative diseases. However, because they insert their genetic material into the host genome they present an oncogenic risk. Major advantages of LV vectors are their ability to transduce non-dividing cells including differentiated neurons, and that large genes can be inserted and permanently incorporated into the host cell (Dreyer, 2011).

Recombinant AAV (rAAV) are non-pathogenic, have low immunogenicity and high efficiency transducing brain cells. rAAV can in fact support transgene expression in post-mitotic cells for the lifetime of an individual. One of the major limitations of rAAV vectors is that they only support a genomic/gene carrying capacity of ~6 kb. AAVs can integrate into the host genome with lower frequency than LV. AAV safely integrate at the AAVS1 site found at chromosome 19q13.4 qtr mapped to the first exon of the myosin binding subunit 85 of protein phosphatase 1. However, rAAV vectors have the potential to lose their site-specific integration and can instead integrate randomly introducing point mutations (Manfredsson et al., 2012). Recombinant AAV vectors form stable episomal concatemers, and in postmitotic cells, episomal AAV genomes can provide long-term (>1 yr) transgene expression. AAV vectors have been used in animal models and clinical trials showing more specificity at transducing certain brain areas compared to LV (Ramaswamy et al., 2012). Twelve different serotypes of AAV have been discovered with distinct affinities for different cell types depending on the proteins displayed on the surface of their capsids that recognize different cell-surface receptors. Cells in the brain are transduced by AAV serotypes 1, 2 and 4–9. Most studies in the brain have been carried out with AAV-2 and 5. While AAV5 conveys a more wide-spread infection of neurons and astrocytes, AAV2 is more neuronal-specific. AAV2 transduces neurons by binding to the heparan sulfate proteoglycan receptor and using bFGF (basic Fibroblast Growth Factor) receptor as a co-receptor. Distinct rAAV have been created in which the genome of the AAV2 serotype is packaged in the capsid protein of other AAV serotypes that better bind to receptors on neurons, glia and ependymal cells (Manfredsson et al., 2012). Interestingly, AAV9 has been shown to produce global expression in the brain and spinal cord neurons after a peripheral, systemic route of administration to neonatal mice, while in adult mice the transduction is mainly observed in glial cells, which reduces its use as a therapeutic alternative in aging-related diseases (Dayton et al., 2012).

The design, production, and efficiency of viral vectors have been improved remarkably, leading to safer transduction, long-term and robust transgene expression. Most clinical vector-based gene-therapy trials have shown success regarding vector safety. However, clinical efficacy attributed to the gene transfer has been lacking in many cases. Despite a

number of successful phase I therapy clinical trials, only few have reached phase II. One potential reason is that experimental therapeutics is often not applied until later stages of the disease, when it can no longer provide a benefit. Other reasons might be associated with the lack of a clear understanding of the underlying molecular mechanisms associated with neuronal cell death and the neuropathology of specific neurological diseases, including the lack of animal models that fully recapitulate the etiology of the disease states, and not with our current ability to efficiently and safely deliver gene targeting (Manfredsson et al., 2010).

An increased focus in gene-therapy research has been directed to the development of clinical regulatable vectors (on/off switches), tissue specific (tyrosine hydroxylase promoter for catecholaminergic cells), or conditional promoters (hypoxia [HRE] or antioxidant response elements [ARE]) in order to address safety concerns, tissue specificity and responsiveness to appropriate local factors that are related to disease. To date, none of the vectors in clinical use have any direct way to reverse or control their transgene product in the event continued protein expression should become problematic (Manfredsson et al., 2012).

Viruses offer excellent gene expression efficiency. However, non-viral gene therapy offers the potential to target specific cells, being less immunogenic and non-integrating into the host genome. Delivery agents utilized in non-viral gene therapy include complexes consisting of DNA/RNA and carriers such as cationic agents, modified silica nanoparticles, cationic lipids and peptides, polymeric micelles and receptor targeting peptides or proteins (Figure 5). Similar to viral therapy, tissue-specific promoters have been used to direct non-viral transgene expression to neurons following gene delivery to the brain (Rogers et al., 2012). Non-viral delivery systems can target specific cell populations by the incorporation of receptor binding agents, ligands (glycosylated molecules), peptides, proteins or antibodies. The pathway followed by receptor mediated gene delivery is known to involve endocytosis, endosomal escape and nuclear entry prior to transcription. Although the BBB precludes the entry of therapeutic molecules from the circulation to the brain, the use of endogenous receptor-mediated transport systems or retrograde machinery that viruses “hijack”, allows the delivery of non-viral agents across the BBB and their delivery to neurons (Rogers et al., 2012).

Exosomes are extracellular vesicles produced constitutively by most cell types that contain mRNAs and non-coding micro RNAs (miRNAs) as well as proteins, and are naturally used as a mechanism of horizontal gene transfer. Exosomes have been re-engineered for targeted gene therapy. Because they are comprised of non-synthetic and non-viral components, exosomes are in principle ideal vectors for gene therapy delivery. The small size and flexibility of exosomes allows them to cross biological membranes, while the RNA and protein cargo is protected from degradation by their bi-lipid structure (Figure 5). A recent study demonstrated the ability of modified systemic intravenous delivery of murine exosomes to deliver short interfering RNA (siRNA) in the brain with the aid of a rabies virus glycoprotein peptide, without major effects in peripheral organs or adverse immune responses (Alvarez-Erviti et al., 2011; Lee et al., 2012b).

4.1. Current strategies used for gene therapy in neurological diseases

Major advances in gene-therapy research for neurological disorders have been achieved in recent years. By overexpressing pro-survival growth factors or targeting endogenous mutant or wild type genes associated with disease pathogenesis (Figure 5), different research groups have demonstrated the feasibility of gene-therapy approaches against neurological diseases. We next summarize the research in this area in order to highlight some examples and routes of administration.

4.1.1. Growth factors—One of the major successful areas of research in gene therapy has been the use of pro-survival growth factors. Gene delivery of Brain-Derived Neurotrophic Factor (BDNF) using a LV vector decreases learning and memory impairment in AD animal models (Nagahara et al., 2009). Similarly, AAV2/1 delivery of basic Fibroblast Growth Factor (bFGF) restores hippocampal functions in an APP+PSEN1 bigenic mice model of AD (Kiyota et al., 2011). Nerve growth factor (NGF) is known to enhance the function and survival of basal forebrain cholinergic neurons that are vulnerable in AD. A clinical trial is ongoing using AAV2-mediated overexpression of NGF for the treatment of AD (Mandel, 2010).

Anterograde transport of AAV vectors from the putamen to the substantia nigra is widely used as therapeutic approach in PD. LV delivery of Glial-cell-line-Derived Neurotrophic Factor (GDNF) prevents nigrostriatal degeneration induced by MPTP (Kordower et al., 2000). An AAV2 vector encoding human Neurturin (NTN) injected into the striatum and/or substantia nigra decreased neurodegeneration in primate and rodent models of PD (Gasmi et al., 2007; Kordower et al., 2006). Preliminary data disclosed from ongoing clinical trials using bilateral intraputaminal AAV2-NTN injection, reports significant improvement in patients at 18 months post-administration, but NTN expression does not seem to reach the substantia nigra (Bartus et al., 2011; Berry et al., 2011; Marks et al., 2010).

Similarly, the overexpression of BDNF using AAV reduces motor impairment and neuronal damage induced by quinolinic acid as a model for HD (Kells et al., 2008). The adenoviral delivery of Ciliary Neurotrophic Factor (CNTF) also reduces neuronal damage induced by 3-NP (Mittoux et al., 2002). However, opposite effects have been observed when LV or AAV have been used to deliver CNTF to HD transgenic mice (Denovan-Wright et al., 2008; Zala et al., 2004). AAV delivery of GDNF protects rats against 3-NP toxicity and also reduces degeneration in the N171-82Q transgenic mouse model of HD (McBride et al., 2003; McBride et al., 2006). AAV2-NRTN also exerts protective effects against 3-NP in the N171-82Q transgenic mouse model (Ramaswamy et al., 2012).

The rapid disease progression of ALS is a major concern for therapeutic intervention. Different injection pathways have been used to deliver transgenes to spinal motor neurons including peripheral delivery via intramuscular or intraneural routes of administration, or systemic delivery via intravascular or intrathecal administration (Federici et al., 2012). Injection of an AAV2 vector encoding human Insulin Growth Factor-1 (IGF-1) into the ventral gray matter in the lumbar region slows disease onset and increases the survival of SOD1G93A mice (Lepore et al., 2007). Viral vector delivery of IGF-1 or Vascular Endothelial Growth Factor (VEGF) to the CNS through bilateral injection into the deep cerebellar nuclei also significantly improves lifespan in SOD1G93A mice (Dodge et al., 2008); these results were confirmed in presymptomatic SOD1G93A rats (Franz et al., 2009). AAV4-mediated delivery of IGF-1 or VEGF into the ventricular system and spinal cord central canal delays motor decline and death in SOD1G93A mice (Dodge et al., 2010). Intramuscular delivery of IGF, GDNF or VEGF using viral vectors delays the disease progression in SOD1G93A mice (Azzouz et al., 2004; Kaspar et al., 2003; Wang et al., 2002). AAV-mediated delivery of the Cytokine Granulocyte-colony Stimulating Factor (G-CSF) to the spinal cord improves the motor function and also delays the disease progression in SOD1G93A mice (Henriques et al., 2011).

Direct vector administration into the cerebrospinal fluid within the ventricular or perivascular systems, or into the brain parenchyma via the striatum has been used in stroke animal models (Gabriel et al., 2007). Gene therapy studies using viral delivery of bFGF-2 have also demonstrated a protective effect of this approach against cerebral stroke (Leker et al., 2007; Watanabe et al., 2004). A number of studies also report that viral delivery of

GDNF protects against brain ischemia (Hermann et al., 2001; Iwai et al., 2001; Tsai et al., 2000; Zhang et al., 2002). AAV-VEGF transduction prior to cerebral ischemia also exerts a protective effect (Bellomo et al., 2003; Shen et al., 2006).

Non-viral gene therapy has also been explored to mediate transgene overexpression of growth factors. Cationic carriers conjugated to neurotensin can carry DNA plasmids into dopaminergic neurons (Hernandez-Baltazar et al., 2012) and have been used as a potential therapeutic approach in PD (Gonzalez-Barrios et al., 2006; Martinez-Fong et al., 2012). Use of transferring receptor (TrfR) antibodies conjugated to immunoliposomes, have been proven to be a viable route to deliver DNA plasmid encoding GDNF encapsulated in pegylated liposomes to reverse TH depletion *in vivo* and to protect against experimental PD (Zhang et al., 2009; Zhang et al., 2004). Liposome-mediated NGF cDNA transfer also increases the number of surviving cholinergic neurons in a TBI model (Zou et al., 1999).

4.1.2. Targeting of endogenous/mutant genes—Neurodegenerative diseases are in many cases associated with specific gene mutations. In these cases, the modification of endogenous levels of wild type or mutant genes might represent a more direct approach for gene therapy. LV-delivered of siRNA against BACE1 (APP beta secretase 1) decreases amyloid plaque levels and neurodegeneration in APP transgenic mice (Singer et al., 2005). Overexpression of ApoE2, whose allele is associated with a decreased risk for developing AD, reduces Aβ burden in transgenic mice models of AD (Dodart et al., 2005). Viral delivery of parkin to the substantia nigra protects against α-synuclein mediated neurodegeneration (Lo Bianco et al., 2004; Yamada et al., 2005), while effective knockdown of α-synuclein in rats using viral delivery of shRNA ameliorates motor dysfunction in rats overexpressing human α-synuclein (Khodr et al., 2011). AAV2 encoding a rotenone-insensitive genetic variant of the mitochondrial complex I NADH–quinone oxidoreductase (NDI1) has also been shown to protect against MPTP toxicity (Barber-Singh et al., 2009).

The identification of the huntingtin gene allows for the identification carriers well before symptom onset. Because neuronal dysfunction precedes cell death in HD, genetic testing and disease state evaluation could allow early therapeutic intervention to be initiated prior to onset of symptoms to prevent neuronal cell death (Ramaswamy et al., 2012). Normal huntingtin protein deletion is lethal and thus, RNA interference approaches to treat HD should preferably target knockdown of mHtt. A number of studies using siRNA, shRNA or miRNA to down-regulate the production of the mHtt protein have shown effectiveness in transgenic HD mouse models (Ramaswamy et al., 2012). Similar to HD, familial ALS arises through a toxic gain-of-function of mutant SOD1. Knockdown of mutant SOD1 via viral vectors leads to increase lifespan in the G93ASOD1 ALS mice (Federici et al., 2012; Ralph et al., 2005; Raoul et al., 2005).

4.1.3. Other genetic targets—Aβ deposition and inflammation are major components in AD pathology. LV-mediated expression of the lysosomal cysteine protease cathepsin B in APP transgenic mice reduced preexisting Aβ deposits (Mueller-Steiner et al., 2006). LV-mediated overexpression of neprilysin (NEP), the dominant Aβ peptide-degrading enzyme in the brain, also reduces Aβ peptide levels and ameliorates neurodegeneration in AD mouse models (El-Amouri et al., 2008; Marr et al., 2003; Spencer et al., 2008). AAV2/1 delivery of anti-inflammatory interleukin-10 was shown to ameliorate cognitive dysfunction in an APP +PSEN1 bigenic mice model of AD (Kiyota et al., 2012).

Dopamine deficiency is the hallmark feature in PD and gene therapy studies have aimed to correct this by overexpression of enzymes involved in dopamine synthesis. An AAV2 vector encoding human aromatic-l-amino decarboxylase (AADC), the enzyme responsible for dopamine synthesis, reduces motor deficits in MPTP-treated primates and these results have

led to a phase I clinical trial (Bankiewicz et al., 2006; Christine et al., 2009; Muramatsu et al., 2010). Because the restoration of AADC still requires L-dopa supplementation, other approaches have aimed to transduce enzymes involved in its synthesis. Triple transduction of TH, AADC and GTP cyclohydrolase 1 (GCH1) in rats using AAV vectors reduces 6-OHDA-induced neurodegeneration (Shen et al., 2000). A LV that delivers GCH1, TH and AADC in patients with PD is currently in use (Azzouz et al., 2002). Another explored strategy is increasing the expression of glutamic acid decarboxylase (GAD) (that mediates GABA synthesis) to inhibit the synchronous oscillatory activity of the globus pallidus and subthalamic nucleus observed in PD patients. AAV2-GAD decreases neurodegeneration induced by 6-OHDA and MPTP (Emborg et al., 2007; Lee et al., 2005; Luo et al., 2002). These results led to phase I/II trials in PD patients that demonstrated a significant improvement of PD patients (Kaplitt et al., 2007; LeWitt et al., 2011). Importantly, the safety and tolerability analysis of unilateral subthalamic injection of the AAV2-GAD65/67 in 12 patients reported no adverse effects related to the procedure and no change in the patients' immunity against AAV or GAD were reported after 12 months.

Neuronal cell death in neurodegenerative diseases and upon brain ischemia and TBI insults is mediated by apoptotic signaling. Delivery of anti-apoptotic Bcl-2 or Bcl-xl proteins using rAAV also reduces degeneration in transgenic ALS mice (Azzouz et al., 2000; Yamashita et al., 2002). In TBI, gene therapy research uses different routes of delivery. Extravascular delivery of viral vectors via direct injection into the injured brain conveys precise focus positioning. However, the area transfected is limited, repeated injections are not allowed, and the injected volume has to be minimized to prevent extrusion and distortion of the surrounding brain tissues. In contrast, intraventricular injection of gene vectors has a smaller invasion area and wider tissue distribution through the cerebrospinal fluid circulation. Intravascular delivery is more acceptable in clinical use, but delivered viral vectors do not permeate the BBB. A recombinant adenovirus vector expressing Bcl-2 has also been used as a therapeutic approach in a TBI experimental model (Yang et al., 2006). Similarly, AAV delivery of the anti-apoptotic protein Bcl-w improves the neuronal function in cerebral ischemia (Sun et al., 2003)

5. Catalytic antioxidant defenses against neuronal cell death

Cells have evolved intrinsic antioxidant mechanisms to maintain a tight homeostatic control of the ROS/RNS generated under physiological conditions, and to detoxify their excessive accumulation in pathological conditions. Under physiological conditions a balance exists among the activities of enzymatic antioxidant defenses, the intracellular levels of non-enzymatic antioxidants, and the production of ROS/RNS as signaling molecules essential for proper cellular function. In addition to their ability to scavenge ROS/RNS, antioxidants systems modulate cell signaling pathways by redox dependent mechanisms (Figure 6).

Based on the evidence highlighted above regarding the role of oxidative stress in neuronal cell death associated with a number of neurological diseases (neurodegeneration, brain ischemia and TBI), a number of clinical trials have aimed at using antioxidant supplementation in the diet as therapeutic approach. However, the clinical trial results so far have been mostly negative. Indeed, most antioxidants tested have been chosen based on their easy availability rather than because they have proved to be the best antioxidant candidates. Not only their efficiency to scavenge ROS/RNS, but many other factors such as absorbability, metabolism, ability to penetrate the BBB and distribution should also be considered to identify potential antioxidant candidates. Other possibility for the lack of benefit of antioxidants might be that the clinical trials have not lasted long enough or have not started early enough to prevent disease progression, our failure to understand their basic mechanisms of action in relationship to human diseases, and to conduct preclinical studies to

identify concentration and time parameters relevant to the clinical setting of each pathology. In addition, it is clear that multiple pathogenetic factors other than ROS/RNS participate in neuronal cell death in distinct neurological disorders suggesting that an integrated approach might prove to be more successful (Giustarini et al., 2009; Kamat et al., 2008; Shen et al., 2010).

Another possibility that has not been taken into account is that experimental evidence demonstrates that ROS/RNS formation, oxidative stress and redox signaling involved in neuronal cell death show a high degree of selectivity regarding the ROS/RNS implicated and their subcellular compartmentalization. With the technological advance in the design of viral vectors leading to safer transduction as well as selective, long-term and robust transgene expression, together with the progress in using gene therapy in clinical trials, we consider that the targeted expression of specific catalytic antioxidants might be a more selective therapeutic approach to counteract oxidative stress, compared to dietary supplementation of non-selective antioxidants. We next summarize the *in vivo* experimental evidence demonstrating the potential of selective regulation of endogenous catalytic antioxidant enzymes to counteract oxidative damage and neuronal cell death.

5.1. Superoxide dismutases (SODs)

The most important cellular defense against $O_2^{\bullet -}$ are SODs. In mammals, there are three isoforms specifically compartmentalized, which catalyze the dismutation of $O_2^{\bullet -}$ to O_2 and H_2O_2 by cycling of the transition metal ion at the active site: MnSOD (*SOD2*) localized in the mitochondrial matrix (Sutton et al., 2003), CuZnSOD or *SOD1* in the IMS, peroxysomes, nucleus or cytosol (Okado-Matsumoto et al., 2001), and the extracellular SOD (EcSOD or *SOD3*) anchored to the cells' surface through an heparin-binding domain (Hjalmarsson et al., 1987). MnSOD contains one manganese atom at the active site (Bakthavatchalu et al., 2011), while CuZnSOD and EcSOD contain a metal cluster of copper and zinc atoms (Crapo et al., 1992; Oshikawa et al., 2010).

Genetic ablation of one copy of the MnSOD allele SOD2(+/−) in mutant human APP (hAPP) transgenic mice exacerbates the Aβ burden and significantly increases the levels of phosphorylated tau and oxidative stress (Esposito et al., 2006; Lee et al., 2012a; Li et al., 2004; Melov et al., 2007). Conversely, the overexpression of MnSOD in hAPP mice reduces oxidative stress and amyloid deposition (Dumont et al., 2009). Similar to MnSOD, CuZnSOD deficiency in hAPP accelerates the Aβ oligomerization, memory impairment and oxidative damage (Murakami et al., 2011).

In experimental PD models, the overexpression of CuZnSOD (Barkats et al., 2006; Przedborski et al., 1992) or MnSOD (Klivenyi et al., 1998) has been shown to decrease MPTP toxicity, while MnSOD or CuZnSOD deficiencies increase it (Andreassen et al., 2001; Zhang et al., 2000). However, contradictory results also report that overexpression of MnSOD or CuZnSOD does not prevent MPP^+ or rotenone toxicity (Rodriguez-Rocha et al., 2013; Sanchez-Ramos et al., 1997). Adenoviral-mediated overexpression of MnSOD but not CuZnSOD protects against paraquat toxicity suggesting a specific role for mitochondrial ROS formation (Rodriguez-Rocha et al., 2013).

Ischemic brain damage and TBI, as well as 3-NP/malonate (HD models)-induced oxidative stress are also exacerbated in SOD2(+/−) mice (Andreassen et al., 2001; Fujimura et al., 1999; Kim et al., 2002a; Kim et al., 2002b; Lewen et al., 2001; Mehta et al., 2011; Murakami et al., 1998; Noshita et al., 2001), while in transgenic mice overexpressing MnSOD or CuZnSOD, mitochondrial dysfunction induced by TBI is reduced (Xiong et al., 2005). In contrast, while MnSOD deficiency decreases the lifespan of G93ASOD1 (pseudo-wildtype) ALS mice, it had no effect on H46R/H48QSOD1 (metal-deficient) mice,

suggesting that different mechanisms other than mitochondrial $O_2^{\bullet -}$ formation mediate ALS caused by mutations in SOD1 (Andreassen et al., 2000; Muller et al., 2008).

5.2. Catalase

Catalase enzymatically decomposes H_2O_2 to H_2O and O_2 and is primarily localized in the peroxisomes. It contains four porphyrin heme (iron) groups that allow the enzyme to react with H_2O_2. A reduction in Aβ levels and oxidative stress is found in hAPP mice overexpressing catalase targeted to the mitochondria, using the first 25 amino acids of the ornithine transcarbamylase leader sequence (Mao et al., 2012). Similarly, mitocatalase also decreases MPTP-induced mitochondrial ROS accumulation and dopaminergic cell death (Perier et al., 2010). We have not been able to observe any effects of adenoviral-mediated overexpression of catalase or mitocatalase on MPP^+-induced toxicity in human neuroblastoma cells (unpublished data).

5.3. Enzymes involved in GSH recycling and synthesis

Glutathione (L-γ-glutamyl-L-cysteinyl-glycine, GSH) is the most abundant non-protein thiol in mammalian cells acting as a major reducing agent and antioxidant defense maintaining a tight control of the redox status. GSH synthesis is initiated by the generation of γ-glutamylcysteine from glutamate and cysteine via glutamate-cysteine ligase (GCL), with the subsequent addition of glycine by the activity of GSH synthetase (GS) (Franco et al., 2009, 2012; Jones, 2006; Meister, 1995; Schafer et al., 2001; Sies, 1999). GCL is a heterodimer composed of a catalytic subunit (GCLC) and a modifier subunit (GCLM), and knockout of GCLM decreases the survival of G93ASOD1 ALS mice (Vargas et al., 2011).

Brain GSH concentration is approximately 2–3 mM. The cysteine availability is rate limiting for the synthesis of GSH. In neurons, cysteine uptake is mediated primarily by the Na^+-dependent excitatory amino acid transporter (EAAT), also known as system X_{AG}^- (Aoyama et al., 2008; Dringen et al., 2003). EAAT3 (or EAAC1) can transport cysteine at a rate comparable to that of glutamate. Extracellular cysteine is unstable and has neurotoxic effects mediated by oxidative stress (Janaky et al., 2000). However, the CSF cysteine concentration is much higher than in plasma. A major extracellular source for cysteine is the dipeptide cystine. Cystine uptake occurs by a Na^+-independent heteroexchange mechanism denominated X_c^-, which is found in immature neurons, astrocytes, microglia, retinal Muller and Bergmann glial cells (Lewerenz et al., 2012). An inter-relationship exists between astrocytes and neurons where neurons rely on extracellular cysteine provided by GSH efflux from astrocytes via GAP junction hemichannels, multidrug resistance protein transporters or EAAT1 (GLAST) (Fernandez-Fernandez et al., 2012; Minich et al., 2006; Rana et al., 2006; Stridh et al., 2010; Stridh et al., 2008). Interestingly, while mice deficient in X_c^- system have no alterations in brain GSH content, EAAT3-deficient mice have reduced GSH levels (Aoyama et al., 2006; Aoyama et al., 2008). EAAT3 knockout mice are more susceptible to ischemia-induced oxidative stress (Li et al., 2011a).

GSH reductase (GR), which reduces glutathione disulfide (GSSG) back to GSH, requires reduced NADPH) as the electron donor reductant, and glucose-6-phosphate dehydrogenase (G6PD) is indispensable for the regeneration of NADPH from $NADP^+$(Ho et al., 2007). Mice overexpressing G6PD are more resistant to MPTP-induced PD-like neurodegeneration (Mejias et al., 2006).

5.4. Glutathione peroxidases (Gpx)

Gpx are selenoproteins that reduce peroxides. Gpx isozymes are encoded by different genes and vary in their cellular location and substrate specificity. While GPx1, found primarily in the cytoplasm, preferably scavenges H_2O_2, Gpx4 hydrolyses lipid hydroperoxides and can

be found in both cytosolic and mitochondrial compartments. Gpx1 transgenic mice and LV-mediated expression of Gpx1 in nigral dopaminergic neurons *in vivo* significantly protect against 6-OHDA toxicity, but these results could not be reproduced *in vitro* using adenoviral vectors (Barkats et al., 2002; Bensadoun et al., 1998; Ridet et al., 2006). MPTP toxicity is increased in mice deficient in Gpx1 (Klivenyi et al., 2000; Zhang et al., 2000). Malonate-induced striatal cell loss is also decrease in transgenic Gpx1 mice (Zeevalk et al., 1997). A number of studies from independent research groups demonstrate that Gpx1 knockout exacerbates, while Gpx1 overexpression protects against ischemic injury (Crack et al., 2006; Keller et al., 2000; Sheldon et al., 2008; Taylor et al., 2005; Weisbrot-Lefkowitz et al., 1998; Wong et al., 2008), and increases the survival of G93A SOD1 mice (Cudkowicz et al., 2002). Contradictory results exist regarding the protective effect of Gpx1 overexpression in TBI (Potts et al., 2009; Tsuru-Aoyagi et al., 2009). Gpx4 deficiency increases lipid peroxidation and Aβ levels in hAPP mice (Chen et al., 2008).

5.5. Peroxiredoxins (Prxs)

Prxs are ubiquitous thiol peroxidases comprising up to 1% of soluble cellular proteins that scavenge peroxides in cells (Figure 6). The catalysis of H_2O_2 is initiated by the reaction of their active site cysteine residue with H_2O_2, and recent studies have demonstrated that the reaction rate for Prxs with H_2O_2 is comparable to that of catalase (Cox et al., 2010; Hall et al., 2009). Mammals have six Prxs, with Prx1, 2 and 6 found in the cytoplasm, Prx4 in the ER, Prx3 in the mitochondria, and Prx5 in various compartments within the cell, including peroxisomes and mitochondria. Prx3 transgenic mice are resistant to oxidative damage and mitochondrial dysfunction induced by paraquat in hAPP mice (Chen et al., 2012). Transgenic mice overexpressing Prx2 showed reduced neuronal injury and oxidative stress induced by ischemia (Gan et al., 2012). LV-mediated over-expression of Prxs2 protects against 6-OHDA toxicity *in vivo*. In addition, a comparable degree of protection was observed *in vitro* by overexpression of Prx1 and Prx4 (Chen et al., 2012).

5.6. Thioredoxins (Trxs)

Trxs are thiol-redox proteins with a conserved Cys-Gly-Pro-Cys catalytic site that reduce or bind to proteins modifying their function. The Trx redox system depends on thiol-disulfide exchange reactions at the active site. Thioredoxin reductase (TrxR), a homodimeric selenium containing flavoprotein, transfers reducing equivalents from NADPH to Trxs reducing them. While the Trx1/TrxR1 system is localized in the cytoplasm, the Trx2/TrxR2 system is mitochondrial. In addition, Trxs provide reducing equivalents for the peroxide scavenging activity of Prxs (see section above). Trx1 has also been shown to reduce and activate a number of transcription factors. Overexpression of Trx1 decreases the neuronal cell apoptosis induced by ischemia (Takagi et al., 1999; Zhou et al., 2009).

5.7. Glutaredoxins (Grxs)

Glutathionylation is a reversible post-translational oxidative modification observed upon oxidative stress involving the formation of a mixed disulfide bond between GSH and protein cysteines. Grxs are oxidoreductases that utilize the reducing power of GSH to catalyze protein deglutathionylation. However, Grxs can induce both glutahionylation/deglutathionylation depending on the GSH/GSSG ratio and the presence of thiyl radicals (GS•). Grx1 is localized in the cytosol and intermembrane space, whereas mitochondrial Grx2 is localized in the matrix (Beer et al., 2004; Mieyal et al., 2008). *In vivo* down-regulation of Grx1 using anti-sense oligonucleotides exacerbates the impairment of complex I by MPTP, while *in vitro* adenoviral delivery of Grx1 protects against paraquat and 6-OHDA toxicity (Kenchappa et al., 2003; Rodriguez-Rocha et al., 2012). Grx2 overexpression protects against MPP^+-induced toxicity (Karunakaran et al., 2007).

5.8. Methionine sulfoxide reductases (Msrs)

Methionine (Met) is one of the most vulnerable amino acid residues to oxidation. The addition of an oxygen atom oxidizes Met to methionine sulfoxide (MetSO), and its further oxidation leads to methionine sulfone ($MetSO_2$) formation. Two different stereoisomers of MetSO, L-Met-S-SO and L-Met-R-SO are found at physiological conditions and they are reverted by Msrs. In humans, there are two different Msrs, MsrA and MsrB. MsrA is specific to the S-stereoisomer, and human MsrA is localized in the mitochondria, whereas MsrB reduces the R- stereoisomer. Mammals have three MsrB proteins. MsrB1 is a selenoprotein that contains selenium (Se) in the catalytic cysteine residue. MsrB1 is primarily located in the cytosol and nucleus, while MsrB2 is located in the mitochondria. MsrB3A is located in the ER and MsrB3B is targeted to the mitochondria (Lee et al., 2011). In AD a high percentage of Aβ aggregates contain MetSO at position 35, and the oxidation of Met(35) to Met(35)SO decreases the extent of Aβ aggregation and toxicity, whereas the oxidation of Met(35) to $MetSO_2$ yields a toxicity similar to that of unoxidized Aβ. In MsrA(−/−) mice, the toxicity between native Aβ and Aβ-Met(35)SO is similar suggesting that the lower toxicity of Aβ-Met(35)SO might be a result of MsrA-mediated reduction (Moskovitz et al., 2011).

5.9. Heme-oxygenase (HO)

HO is a microsomal enzyme that catalyzes the first rate-limiting step in the heme degradation playing an important role in Fe^{2+} recycling. HO cleaves the carbon bridge of heme, yielding equimolar quantities of carbon monoxide (CO), Fe^{2+} and biliverdin. HO activity results in decreased oxidative stress by removal of heme, a potent pro-oxidant. Although Fe^{2+} can give rise to •OH radicals, simultaneous up-regulation of ferritin and cytosolic Fe^{2+} efflux protect cells from oxidative stress. Biliverdin and bilirubin are also potent antioxidants, capable of attenuating oxidative injury by scavenging peroxyl radicals (Jozkowicz et al., 2007). HO-1 is an inducible isoform in response to stress, whereas HO-2 is a constitutive isoform that is expressed under homeostatic conditions. HO-1 transgenic mice are protected against cerebral ischemia (Hung et al., 2008). Adenoviral-mediated overexpression of HO-1 also reduces oxidative brain injury induced by cerebral ischemia (Chao et al., 2013), and dopaminergic cell death triggered by MPTP (Hung et al., 2008). However, another study reports that HO-1 deficiency does not affect MPTP toxicity (Innamorato et al., 2010). HO-2 knockout mice exhibit increased neuronal loss after TBI insult (Chang et al., 2003).

5.10. Transcriptional regulation of antioxidant defenses

Oxidative stress activates the transcription of a variety of antioxidant genes through cis-acting sequences known as antioxidant response elements (ARE) or electrophile-responsive elements (EpRE). Nuclear factor (erythroid-derived 2)-like 1 (Nrf1) and 2 (Nrf2), members of the Cap-N-Collar family of transcription factors bind ARE. Nrf2 regulates the expression of antioxidant proteins and proteins that mediate GSH synthesis or recycling. Nrf2 is kept in a cytosolic complex with the kelch-like ECH-associated protein 1 (Keap1), where it is subjected to proteasomal degradation. Oxidants or electrophiles induce a conformational change in Keap1 that allow the translocation of Nrf2 to the nucleus (Brigelius-Flohe et al., 2011). Accordingly, *in vivo* activation of Nrf2 has been linked to the protective effects of triterpenoids (MPTP-PD model) (Kaidery et al., 2013), sulforaphane (MPTP-PD model and TBI) (Hong et al., 2010; Jazwa et al., 2011), histone deacetylase inhibitors, and carbon monoxide (brain ischemia) (Wang et al., 2011; Wang et al., 2012). Nrf2 deficiency exacerbates dopaminergic degeneration induced by α-synuclein (Lastres-Becker et al., 2012), MPTP (Burton et al., 2006; Innamorato et al., 2010; Rojo et al., 2010), 6-OHDA (Burton et al., 2006), as well as 3-NP/malonate-induced striatal cell loss (Calkins et al.,

2005), ischemic injury (Shah et al., 2007; Shih et al., 2005), and neuronal cell death in TBI (Hong et al., 2010; Jin et al., 2009). Interestingly, the selective overexpression of Nrf2 in astrocytes protects against MPTP-induced toxicity (Chen et al., 2009b) and increases survival of G93ASOD1 ALS mice (Vargas et al., 2008). Viral-mediated delivery of Nrf2 also improves cognitive function but not Aβ burden in an APP/PS1 AD mouse model (Kanninen et al., 2009).

6. Conclusions and Perspectives

Oxidative stress has been largely reported to trigger and/or regulate neuronal cell death in a number of neurological disorders such as neurodegenerative disorders, brain ischemia and TBI (Franklin, 2011). A large number of studies have reported the beneficial effects of antioxidant approaches on counteracting oxidative stress-induced neuronal cell death in different experimental models. However, clinical trials aimed at using antioxidant supplementation in diet as a therapeutic approach have been largely unsuccessful. Indeed, many factors can explain the lack of success of such clinical interventions including: 1) intrinsic characteristics of the antioxidant studied (absorption, metabolism, ability to penetrate the BBB, and distribution); 2) caveats in the design of clinical trials (duration, concentration and time of intervention); 3) a gap in our understanding of their basic mechanisms of action in relationship to human disease progression; and 4) the existence of multiple pathogenic factors other than ROS/RNS contributing to neuronal cell death (Giustarini et al., 2009; Kamat et al., 2008; Shen et al., 2010). However, with the advances in the design of viral vectors leading to safer transduction as well as selectivity, long-term and robust transgene expression, and the recent successes in recent gene therapy clinical trials, we consider that the targeted expression of specific catalytic antioxidants might be a more selective therapeutic approach to counteract oxidative stress. This is also supported by experimental evidence demonstrating that the ROS/RNS formation and redox signaling involved in neuronal death on neurodegenerative disorders, as well as the subcellular compartmentalization of oxidative stress, is specific and different to each neurological diseases. The experimental evidence supporting a role for oxidative stress in neuronal cell loss/damage associated with neurological diseases is strong. However, it is necessary to carefully consider the biomarkers of oxidative stress and methods employed for their evaluation in the clinic. Attention to confounding factors must be taken to objectively measure and evaluate biomarkers of oxidative stress as indicators of normal biological processes, pathogenic processes, or responses to therapeutic intervention.

We have summarized here the *in vivo* experimental evidence demonstrating the potential for selective regulation of endogenous catalytic antioxidant enzymes to counteract the oxidative damage and neuronal cell death observed in neurodegeneration and ischemia/TBI insults. We have included in this discussion both experimental studies *in vivo* using viral expression vectors and transgenic/knockout models. However, we need to consider that the experimental evidence gathered using transgenic/knockout animals has to be corroborated using viral delivery approaches. Long-term modification of gene expression might induce compensatory mechanisms during development that could not be observed during transgene overexpression in adulthood. The experimental work reviewed here aims to encourage future experimentation in this are with the potential to be translated in the design of clinical trials. The question now is…what are we waiting for?

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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

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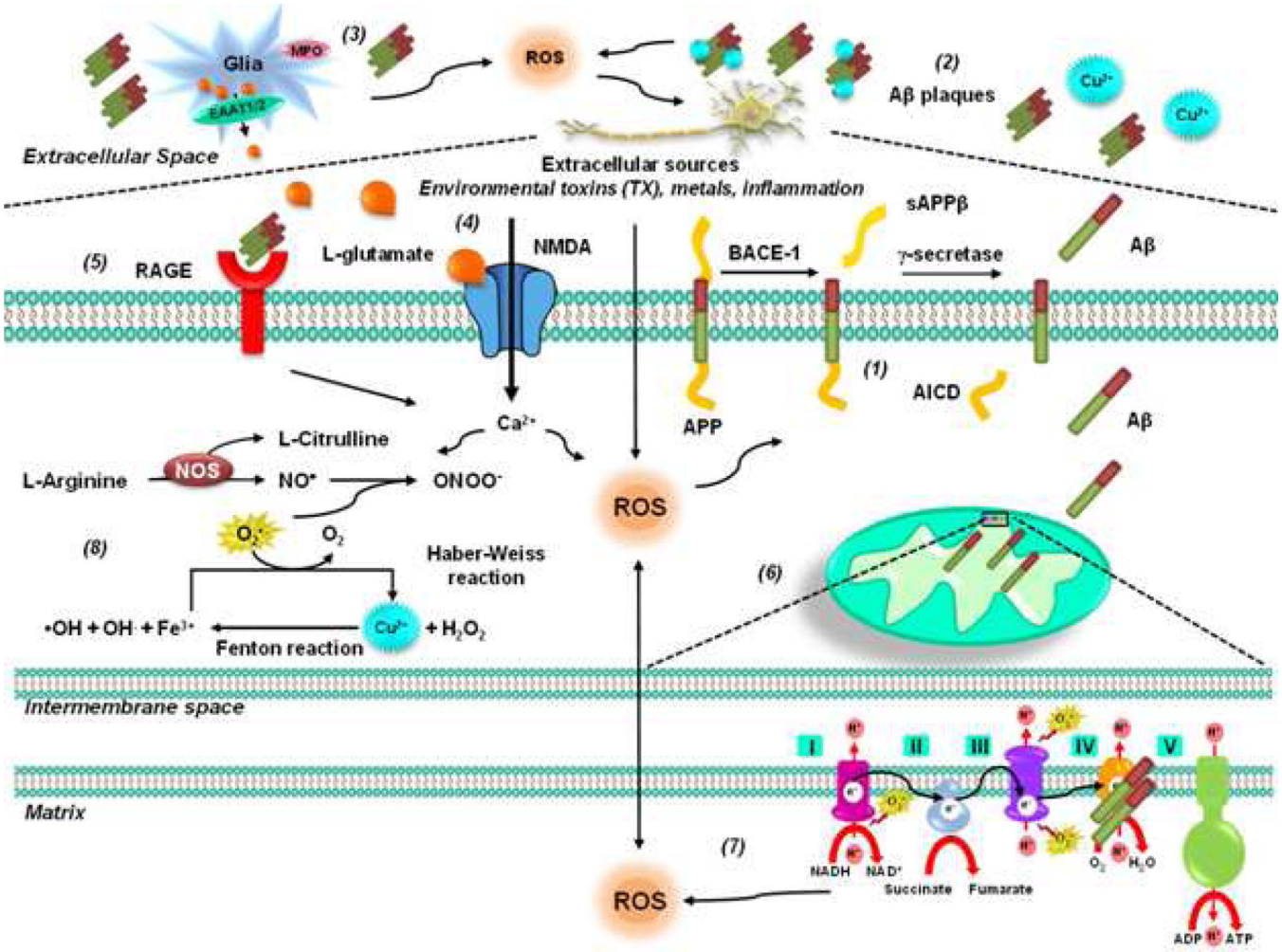

Figure 1. Oxidative stress in AD

The amyloid cascade hypothesis suggests that deposition of Aβ triggers neuronal dysfunction and death in the brain. APP is an integral membrane protein concentrated in the synapses of neurons. **(1)** Amyloidogenic processing is initiated by β-secretase beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), releasing a shortened sAPP. The C99 fragment is a γ-secretase substrate, generating Aβ and AICD. *PSEN1* and *PSEN2* mutations affect concentrations of $A\beta_{1-42}$ because presenilin proteins form part of γ secretase, which cleaves APP to produce Aβ. **(2)** Soluble Aβ is prone to aggregation. In addition, Aβ interacts with several metal ions affecting its solubility and leading to fibrillization and cellular toxicity. The Aβ-metal complex triggers ROS production. **(3)** Activation of glial cells has also been proposed to contribute to ROS formation via MPO. **(4)** In addition, accumulation of extracellular levels of the exicitatory amino acid glutamate leads to perturbations in neuronal Ca^{2+} homeostasis that have the potential to trigger mitochondrial dysfunction and ROS formation. **(5)** The RAGE has also been proposed to mediate Aβ's pro-oxidant effects. **(6)** Aβ has been shown to be transported into mitochondria via the outer membrane (TOM) complex and localized at the mitochondrial cristae. **(7)** In the mitochondria, Aβ inhibits mitochondrial cytochrome oxidase (complex IV) and the key Krebs-cycle enzymes (α-ketoglutarate and pyruvate dehydrogenase) impairing ETC, ATP production, oxygen consumption, and mitochondrial membrane potential. Dysfunctional mitochondria produce ROS and mtDNA oxidative damage. Conversely, mitochondrial ROS

also trigger increased Aβ production. **(8)** Aβ induces an increase in iNOS expression and $NO^{\bullet}$ $ONOO^{-}$ generation in glial cells, whereas it inhibits the activity of nNOS and eNOS in neuronal-like cells.

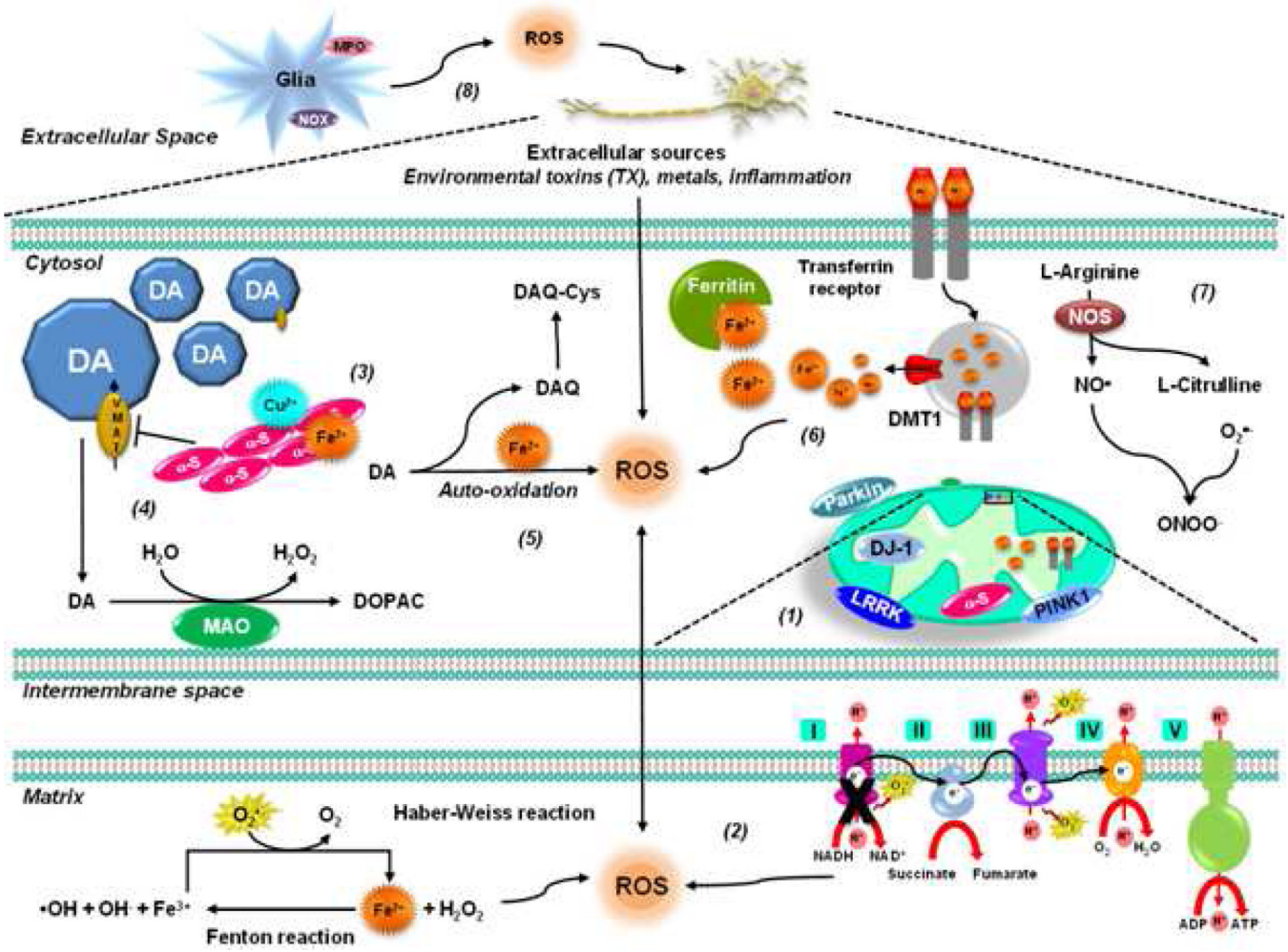

Figure 2. Oxidative stress in PD

(1) A fraction of PD cases are related to mutations in genes such as those encoding α-synuclein, DJ-1, PINK1, LRRK2 and parkin. Most of these gene products have been found to interact with mitochondrial components to different extent and under pathological conditions, impair its function leading to ROS formation (*see text for further details*). **(2)** Oxidative stress in PD is linked primarily to mitochondrial dysfunction. Decreased activity of mitochondrial complex I is found in the SNpc of PD patients. **(3)** Metal ions accelerate α-synuclein oligomerization / aggregation, Cu^{2+} being the one that induces it faster. **(4)** Mutant α-synuclein and environmental toxins impair VMAT2 augmenting cytosolic dopamine, which dopamine is metabolized by MAO or auto-oxidized generating ROS and DAQ. **(5)** DAQs are highly reactive products which can inactivate proteins by reacting with protein thiols. **(6)** Increased iron deposition and free iron concentration have been found in the SNpc of PD brains, which leads to increased generation of •OH via Fenton and Haber-Weiss reactions. Low levels of ferritin in PD patients have been reported. Alterations in DMT1 function and transferrin receptors have also been proposed to contribute to PD. **(7)** RNS also play an important role in PD. Parkinsonian mimetics have been shown to mediate $NO^{\bullet}$ and $ONOO^{-}$ generation as well as nitration of α-synuclein that promotes its oligomerization and aggregation. **(8)** Environmental toxins have also been shown to induce oxidative damage through Nox and MPO activation in glial cells.

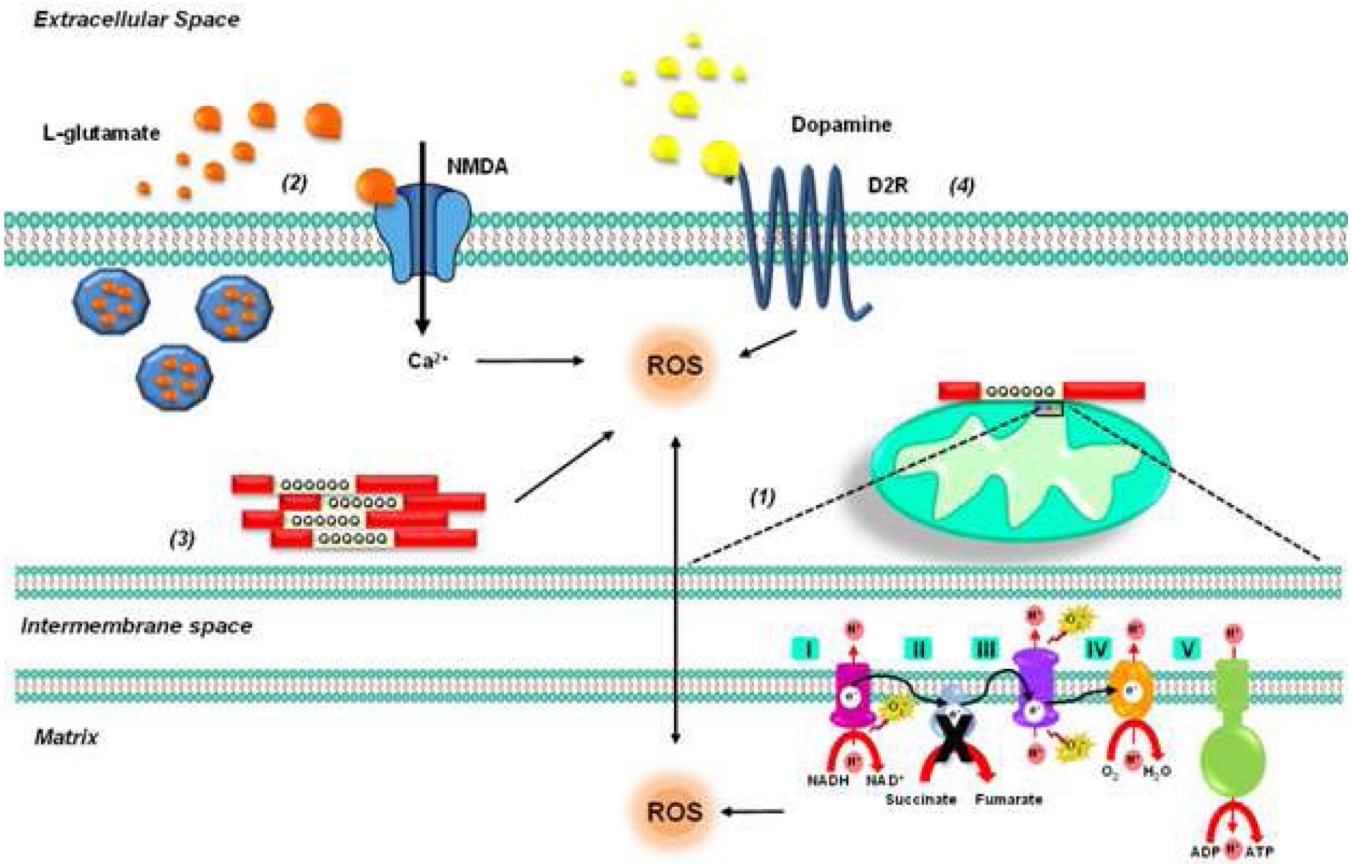

Figure 3.

HD is caused by highly polymorphic CAG trinucleotide repeat expansions in the exon-1 of the Htt gene, yielding proteins containing polyglutamine repeats that become misfolded aggregates and resist degradation. **(1)** Levels of SDH or complex II subunits Fp (FAD) and Ip (iron–sulphur cluster) are found reduced in HD brains and in striatal neurons overexpressing the N-terminal fragment of mtHtt. Accordingly, complex II inhibitors such as malonate and 3-NP induce both biochemical and clinical alterations *in vivo* that resemble those in HD. **(2)** 3-NP induces a decrease in ATP levels, a reduction in the uptake of the excitatory amino acid glutamate and the activation of NMDA receptors, which mediate ROS formation. **(3)** A recent report demonstrates that aggregation of polyglutamine Htt fragments directly causes ROS formation. **(4)** 3-NP toxicity is enhanced by dopamine, which mediates and exacerbates ROS production.

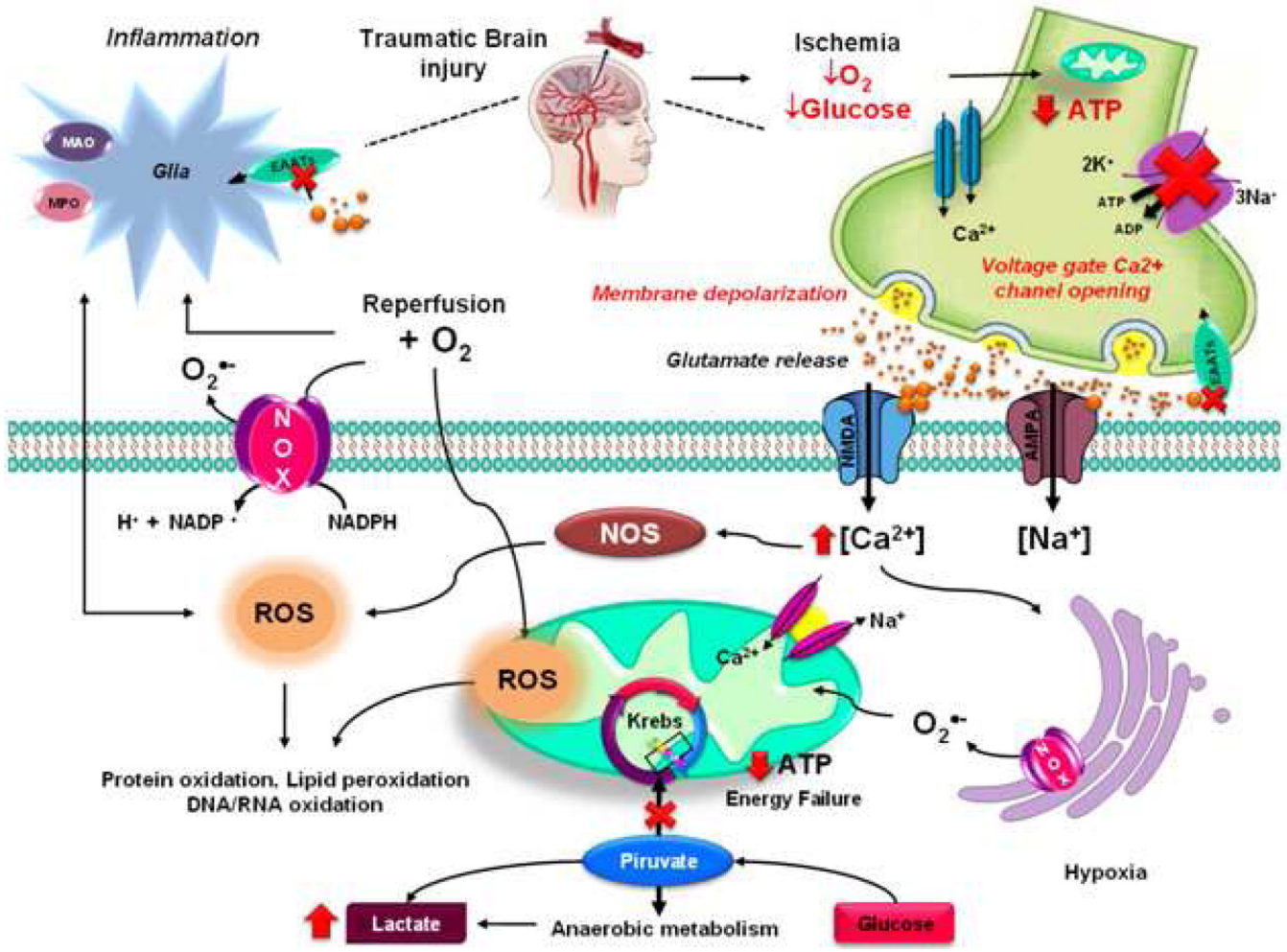

Figure 4. Oxidative stress during Brain Ischemia, Excitotoxicity and Traumatic Brain Injury (TBI)

TBI produces a direct tissue damage and impaired regulation of cerebral blood flow (CBF) causing deprivation of O_2 and glucose resulting in brain damage by Ischemia. Ischemic injury is mediated by depletion in energy stores impairing ATP-dependent processes. Malfunction of the Na^+/K^+-ATPase leads to the disruption of ionic gradients of K^+, Na^+, Cl^-, and Ca^{+2}. This leads to plasma membrane depolarization, reversal of excitatory amino acid uptake and Ca^{+2}-dependent exocytosis. The presynaptic cell releases excitatory amino acid (glutamate) that activates NMDA and AMPA receptors, which permit Ca^{+2} entry/overload in the postsynaptic cell, which is partially buffered by mitochondrial $2Na^+/Ca^{2+}$ exchanger. Mitochondrial Ca^{+2} overload leads to a loss of mitochondrial membrane potential ($\Delta\Psi m$) and an increase in ROS generation. Energy failure caused by mitochondrial dysfunction leads to a metabolic switch towards anaerobic metabolism leading to increased lactate production. The elevated cytosolic Ca^{+2} levels also activate nNOS and increases •NO. During reperfusion, when O_2 is replenished, pro-oxidant enzymes, such as Nox, and mitochondria utilize O_2 as a substrate to generate additional ROS. Inflammation also contributes to oxidative damage and release of excitatory amino acids.

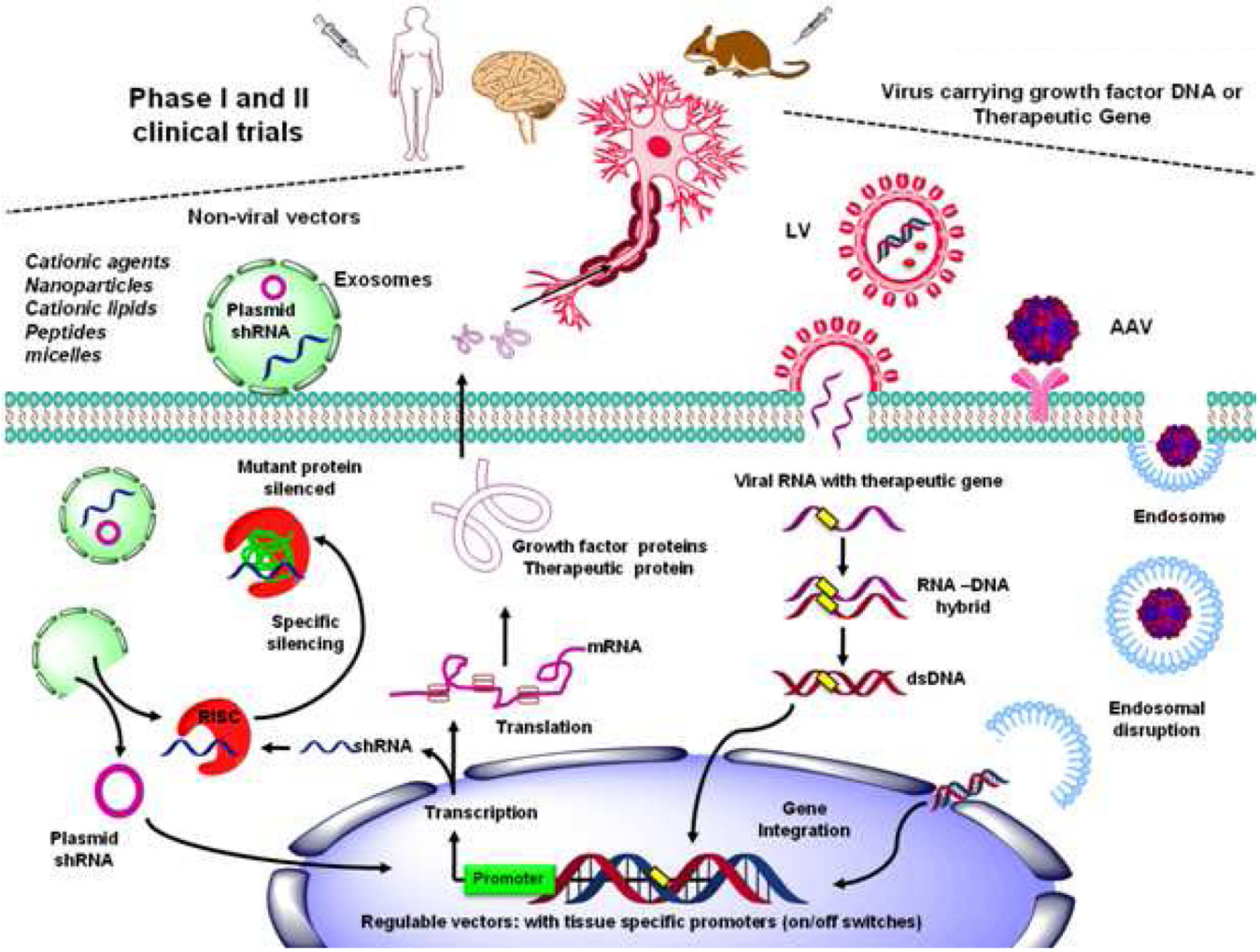

Figure 5. Target delivery of therapeutic genes in neuronal populations

Adenovirus, lentivirus (LV) and adeno-associated viral (AAV) have been used as viral vectors for gene transfer. Viral vectors carrying therapeutic genes **(1)** can be bonded to cell surface receptors to selectively allow entry of DNA into neurons by receptor-mediated endocytosis, which then becomes encapsulated in endosomes, from which they must escape to inject the corresponding new gene into the nucleus to promote the expression of the therapeutic protein of interest. In addition **(2)**, viruses can inject the viral RNA, which by reverse transcription produces a dsDNA that could be integrated in host genome. Although viruses offer excellent gene expression efficiency, non-viral gene therapy offers the potential to target specific cells, being less immunogenic and non-integrating into the host genome. An example are exosomes that have been re-engineered for targeted gene therapy, their small size and flexibility allows them to cross biological membranes, while the “cargo” is protected from degradation by their bi-lipid structure. Major advances in gene-therapy research for neurological disorders have been achieved in recent years by overexpressing pro-survival growth factors or targeting endogenous mutant or wild type genes associated with disease pathogenesis.

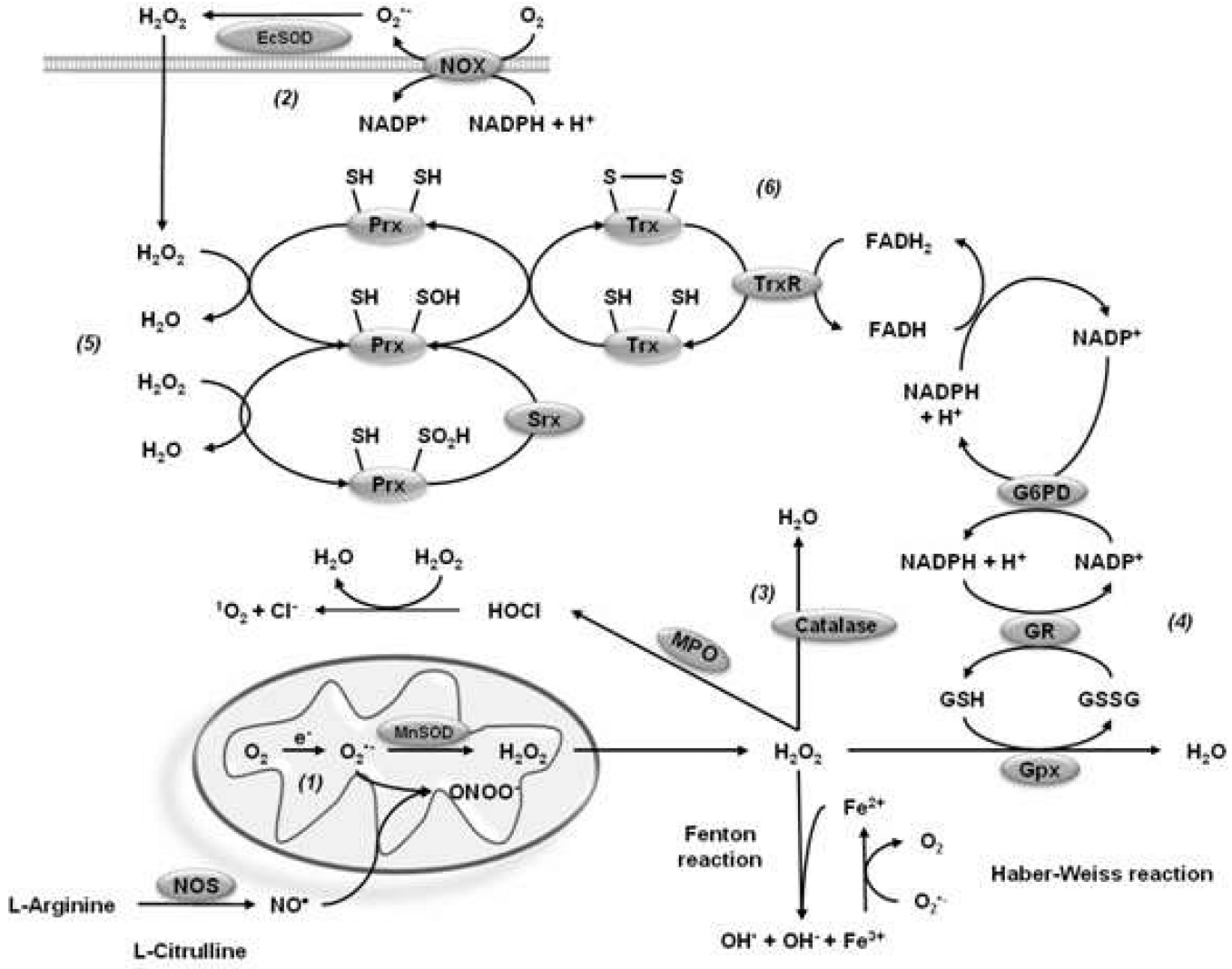

Figure 6. Catalytic antioxidant systems

Cells have intrinsic antioxidant mechanisms to maintain a tight homeostatic control of ROS/RNS generated under physiological conditions, and also detoxify their excessive accumulation in pathological conditions. SODs dismutate $O_2^{\bullet -}$ to O_2 and H_2O_2. **(1)** MnSOD is localized in the mitochondrial matrix, CuZnSOD in the IMS, peroxysomes, nucleous or cytosol, and EcSOD in the extracellular space **(2)**. **(3)** Catalase catalyzes the decomposition of H_2O_2 to water and oxygen and is primarily localized in the peroxisomes. **(4)** Gpx are selenoproteins that reduce peroxides using GSH as substrate. Gpx isozymes encoded by different genes vary in their cellular location and substrate specificity. For example, Gpx1 preferably scavenges H_2O_2, whileGpx4 hydrolyses lipid hydroperoxides. GR, which reduces GSSG back to GSH, requires NADPH as electron donor reductant, and G6PD is indispensable for the regeneration of NADPH from $NADP^+$ in then cytosol. **(5)** Prxs are ubiquitous thiol peroxidases that scavenge peroxides. Catalysis of H_2O_2 is mediated by the reaction of their active site cysteine residue with H_2O_2 with a rate comparabale to that of catalases. The catalytic activity of Prxs requires reducing equivalents provided by the Trx/TrxR system. **(6)** In addition, Trxs can directly bind to proteins modifying their function.

Table 1

Clinical and experimental (*in vivo*) findings linking oxidative stress to neurological diseases.

Disease	Model	Findings	Reference
Alzheimer's disease (AD)	Human postmortem brain tissues	Increase 3-NT in neurofibrillary tangles (NFTs) of postmortem brain tissues with respect to control cases lacking NFTs, where nitrotyrosine was not detected.	Good et al., 1996
		Increased 3-NT in neurons of brain tissues. 3-NT was undetectable in the cerebral cortex of age-matched control brains. The distribution is essentially identical to that of free carbonyls.	Smith et al., 1997
		Iron has been found accumulated in the hippocampus and cerebral cortex, colocalizing with AD lesions. RNA-bound iron plays a pivotal role in RNA oxidation. The cytoplasm of hippocampal neurons showed significantly higher redox activity and Fe^{2+} staining than age-matched controls and only AD rRNA contains 8-hydroxyguanosine in reverse transcriptase-PCR.	Su et al., 2008; Honda et al., 2005
		Elevated levels of labile Cu^{2+} that correlated with oxidative damage were found in AD brains in postmortem cortical tissue when compared with non-demented elderly controls.	James et al., 2012
		High Cu^{2+} concentrations are found within Aβ plaques; Aβ binds Cu^{2+} in AD tissue, and Aβ: Cu^{2+} complexes form a catalytic source of H_2O_2 that could enhance the production of •OH.	Su et al., 2008
	In vivo models	*In vivo* imaging using the fluorescent redox sensor roGFP in the APP/PS1 transgenic mice identifed susceptible neurons by their increased redox potential. The oxidative stress was most prevalent in neurites near plaques and propagated to cell bodies.	Xie et al., 2013
		An oxidized redox state (NADPH/FAD), lower NADH regenerating capacity, lower GSH levels, and excessive ROS were found in 3xTg-AD compared with non-Tg neurons.	Ghosh et al., 2012
		Using triple transgenic AD mice a massive dysregulation of mitochondrial proteins mainly related to complexes I and IV of the oxidative phosphorylation system (OXPHOS) were found. These mitochondrial defects were associated with an increase of $O_2^{\bullet -}$, as well as cytosolic ROS levels.	Rhein et al., 2009
		Alterations in the GSH/GSSG redox state and an increase of mixed-disulfide (Pr-SSG) were found in both brain tissues and blood samples of a double mutant AD transgenic mouse model.	Kahles et al., 2013
		Developmental exposure to Pb altered the levels, characteristics, and intracellular distribution of Aβ staining and plaques in the cortex of aged monkeys. These effects were accompanied by higher levels of oxidative damage to DNA.	Wu et al., 2008
Parkinson's Disease (PD)	Human postmortem brain tissues	A significant increase in protein carbonyl levels was found in brain areas associated with PD	Alam et al., 1997a; Floor and Wetzel 1998
		An increase in 8-hydroxyguanine (8-OHdG) was found in the SNpc of PD brain.	Alam et al., 1997b Zhang et al., 1999
		Increased levels of malondialdehyde (MDA; an intermediate in the lipid peroxidation process) were found in PD SNpc compared with other brain regions and control tissue.	Dexter et al., 1989; Yoritaka et al., 1996

Disease	Model	Findings	Reference
		Deficiency in the activity of the ETC in the substantia nigra of patients with PD.	Schapira et al., 1989, 2008
		Extensive and widespread accumulations of nitrated a-synuclein in the inclusions of PD, dementia with Lewy bodies and the Lewy body variant of AD.	Giasson et al., 2000; Hodara et al., 2004
		Mitochondria of SNpc from PD subjects showed a significant accumulation of α-synuclein, which was associated with impairment in complex I activity and increased oxidative stress.	Devi et al., 2008
		Postmortem analysis of PD brain tissues showed a considerable increase in total Fe, Zn, and Al content when compared with control tissues, with significantly lower GSH levels.	Uversky et al., 2001; Hirsch et al., 1991; Dexter et al., 1989, 1991; Riederer et al., 1989
		Parkin is S-nitrosylated *in vivo* in a mouse model of PD, and in brains of patients with PD and diffuse Lewy body disease.	Chung et al., 2004
		GSH levels were reduced in the PD SNpc (40% compared to control subjects).	Sian et al., 1994; Jenner et al., 1992; Dexter et al., 1994; Perry et al., 1982
	In vivo models	Mitochondrial oxidative stress was found increased in dopaminergic neurons within the SNpc compared to those of the ventral tegmental area (VTA), which are much less affected in PD.	Guzman et al., 2010
		The loss of PINK1 impairs mitochondrial fission, which causes defective assembly of the ETC complexes, leading to oxidative stress and abnormal bioenergetics.	Liu et el., 2011; Morais et al., 2009
		A reduction in respiratory capacity of striatal mitochondria isolated from parkin −/− mice. Parkin −/− mice also exhibited decreased levels of proteins involved in protection from oxidative stress, serum antioxidant capacity and increased protein and lipid peroxidation.	Palacino et al., 2004
Huntington's Disease (HD)	Human postmortem brain tissues	HD patients had higher levels of lipid peroxidation in plasma levels and lower levels of GSH compared to age and sex-matched controls.	Klepac et al., 2007
		An Increase in protein-carbonyls was found in human brain postmortem samples obtained from striatum and cortex of patients with HD when compared to samples of age- and sex-matched controls. Carbonylated proteins found included enzymes involved in the glycolytic pathway and mitochondrial proteins related to ATP production. Oxidation resulted in decreased catalytic activity, in agreement with energy deficiency observed in HD.	Sorolla et al., 2008, 2010
		A signifcant increase in 8-OHdG in mtDNA was found in the parietal cortex of HD patients as compared to controls.	Polidori et al., 1999
		Serum 8-OHdG levels were markedly elevated in HD.	Hersch et al., 2006
		Leukocyte 8-OHdG and plasma MDA were elevated, and the activities of Cu/Zn-SOD and Gpx were reduced in 16 HD patients when compared to 36 age- and gender-matched controls.	Chen et al., 2007
	In vivo models	mtHtt is oxidized in cysteine residues proximal to the N-terminal domain promoting oligomerization and delayed clearance.	Fox et al., 2011
		Increased concentrations of 8-OHdG were found in the urine, plasma and striatal microdialysates of HD mice.	Bogdanov et al., 2001

Disease	Model	Findings	Reference
		Increased concentrations of 8-OHdG were also observed in isolated brain DNA at 12 and 14 weeks of age. Immunocytochemistry showed increased 8-OHdG staining in late stages of the illness.	
Amyotrophic Lateral Sclerosis (ALS)	Human Patients samples	Derivatization analysis of oxidized carbonyl compounds performed on immunoprecipitated SOD1 identified a hyper-oxidized SOD1 that recapitulates mutant SOD1-like properties and damages mitochondria by forming a toxic complex with Bcl-2.	Guareschi et al., 2012
		The mean protein carbonyl level in the lumbar spinal cord from patients with sporadic motor neuron disease was increased by 119% ($p < 0.02$) when compared to normal control subjects and by 88% ($p < 0.04$) compared to the neurological disease control subjects.	Shaw et al., 1995
		Protein carbonyl and OH8dG levels were increased in sporadic ALS but not in autosomal dominant familial ALS patients.	Ferrante et al., 1997a
		Immunoreactivity for 3-NT was detected in motor neurons of ALS but was not or was only minimally found in those of controls. The staining was also localized in the axons of motor neurons of ALS, but was not found in the corresponding controls.	Abe et al., 1995, 1997; Beal et al., 1997
		4-HNE was elevated in the cerebrospinal fluid (CSF) of a patient with sporadic amyotrophic lateral sclerosis (sALS) compared with that of most patients with other neurological diseases	Smith et al., 1998; Simpson et al., 2004
		8-OHdG levels were significantly elevated in plasma, urine, and cerebrospinal fluid (CSF) from subjects with ALS when compared to controls. Plasma and urine 8-OHdG levels increased significantly with time in the ALS group only. The rate of increase in urine 8-OHdG levels with time was significantly correlated with disease severity.	Bogdanov et al., 2000; Ihara et al., 2005
	In vivo models	The deletion of the Nox2, and to a lesser extent Nox1, can prolong survival in the SOD1 G93A transgenic mice.	Li et al., 2011b
		A significant increase in the concentrations of 3-NT in upper and the lower spinal cord and in the cerebral cortex of the SOD1 G93A transgenic mice was found. MDA was increased in cerebral cortex. 3-NT and MDA-modified protein immunoreactivities were increased throughout the transgenic mice spinal cord but particularly within motor neurons.	Ferrante et al., 1997b; Casoni et al., 2005
		Protein carbonyl content in 30-day-old SOD1-G93A mice was twice as high as the level found in age-matched nontransgenic mice. The levels in the SOD1-G93A mice increased dramatically (557%) between 100 and 120 days of age, compared with either the nontransgenic mice or transgenic animals that overexpress the wild-type human SOD1.	Andrus et al., 1998
		Transgenic mice expressing mutant SOD1-G93A show enhanced free radical content in spinal cord but not brain. This increase precedes motor neuron degeneration	Liu et al., 1998
Brain Ischemia and Excitotoxicity	Human Patients	Multiple markers of oxidative damage are increased immediately after stroke and remain elevated for several days in 66 stroke subjects with respect to 132 control subjects.	Seet et al., 2011
	In vivo models	Nox inhibition or scavenging reduced brain injury H_2O_2 in a neonatal rat model of hypoxia/ischemia demonstrating that Nox contributes to oxidative stress mediating cerebral injury during ischemia/reperfusion.	Lu et al., 2012; Kahles et al., 2010; Kleinschnitz et al., 2010

Disease	Model	Findings	Reference
		Hypoxic-ischemic insult was produced in p10 mice. Administration of the complex I inhibitor pyridaben significantly decreased the extent of HI injury. Mitochondria isolated from the ischemic hemisphere in pyridaben-treated animals showed reduced H_2O_2 formation and decreased oxidative damage to the mitochondrial matrix. A protective effect of pyridaben administration was also observed when the reperfusion-driven oxidative stress was augmented by the exposure to 100% O_2.	Niatsetskaya et al., 2012
Traumatic Brain Injury (TBI)	In vivo models	Biochemical damage of the cerebral vasculature is initiated by the induction of the free radical-generating enzymes Nox1 and iNOS. Induction of these enzymes by shock-wave exposure increased oxidative and nitrosative damage.	Abdul-Muneer et al., 2013
		Levels of 4-HNE and 3-NT were significantly increased at 3 h post-exposure to blast and returned to control levels after 24 h.	Readnower et al., 2010
		Significant time-dependent changes in antioxidant levels were observed as early as 3 h post-trauma and paralleled increases in oxidants (4-HNEl, acrolein, and protein carbonyls), with peak values obtained at 24–48 h.	Ansari et al., 2008
		Lipid peroxidation in brain extracts were increased at 6 and 24 h after trauma compared with sham-operated controls. The total antioxidant reserves of brain homogenates and water-soluble antioxidant reserves as well as tissue concentrations of ascorbate, GSH, and protein sulfhydryls were reduced after TBI.	Tyurin et al., 2000
		Nox activity in the cerebral cortex and hippocampal CA1 region increases rapidly following controlled cortical impact in male mice, with an early peak at 1 h, followed by a secondary peak from 24–96 h after. In situ localization using oxidized hydroethidine and the neuronal marker, NeuN, revealed that the $O_2^{\bullet -}$ induction occurred in neurons at 1 h after TBI.	Zhang et al., 2012b
		Selective inhibition of iNOS after trauma protected the injured brain by limiting $ONOO^-$ formation.	Gahm et al., 2006