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Review

Glutathione transferases and neurodegenerative diseases

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ABSTRACT

There is substantial agreement that the unbalance between oxidant and antioxidant species may affect the onset and/or the course of a number of common diseases including Parkinson's and Alzheimer's diseases. Many studies suggest a crucial role for oxidative stress in the first phase of aging, or in the pathogenesis of various diseases including neurological ones. Particularly, the role exerted by glutathione and glutathione-related enzymes (Glutathione Transferases) in the nervous system appears more relevant, this latter tissue being much more vulnerable to toxins and oxidative stress than other tissues such as liver, kidney or muscle. The present review addresses the question by focusing on the results obtained by specimens from patients or by *in vitro* studies using cells or animal models related to Parkinson's and Alzheimer's diseases. In general, there is an association between glutathione depletion and Parkinson's or Alzheimer's disease. In addition, a significant decrease of glutathione transferase activity in selected areas of brain and in ventricular cerebrospinal fluid was found. For some glutathione transferase genes there is also a correlation between polymorphisms and onset/outcome of neurodegenerative diseases. Thus, there is a general agreement about the protective effect exerted by glutathione and glutathione transferases but no clear answer about the mechanisms underlying this crucial role in the insurgence of neurodegenerative diseases.

1. Introduction

The term oxidative stress (OS) refers to an impairment of intracellular equilibrium between oxidant species, produced by the oxidative metabolism and their efficient removal exerted by the antioxidant defense system. When the oxidant species, e.g. the reactive oxygen species (ROS), are increasing and/or the antioxidant species are diminished there is oxidative stress. Human tissues show varying degrees of susceptibility to OS. The central nervous system (CNS) is highly sensitive to OS because of low antioxidant enzyme levels, high content of oxidant substrates and the formation of many ROS (Morozova et al., 2007; Polidori et al., 2007). Neurons are among the most active cells in the oxidative metabolism demanding a fine equilibrium between supply and consumption of both glucose and oxygen. The appearance of OS is a consequence of a disequilibrium between production of ROS and the cell antioxidant defense (Ciccone et al., 2013; Smeyne and Smeyne, 2013) with potential damage to membrane (lipid peroxidation), DNA and mitochondrial complex I (Dringen et al., 2000; Spencer et al., 1994; Sugawara and Chan, 2003).

Many studies suggest a crucial role for OS in the first phase of aging (Jha and Rizvi, 2009), or in the pathogenesis of various diseases including neurological ones (Arning et al., 2004; Butterfield et al., 2007; Marco et al., 2004; Markesbery, 1997; Raichle and Gusnard, 2002).

2. Glutathione and oxidative stress in neurodegeneration

There is substantial agreement that the unbalance between oxidant and antioxidant species may affect the onset and/or the course of a number of common diseases including Parkinson's (PD) and Alzheimer's (AD) diseases. Both these diseases are considered multifactorial pathologies and a number of events may occur simultaneously after OS including mitochondrial dysfunction, accumulation of mutations in mitochondrial DNA, DNA repair

Abbreviations: OS, oxidative stress; ROS, reactive oxygen species; CNS, central nervous system; PD, Parkinson's disease; AD, Alzheimer's disease; GSH, reduced glutathione; GST, glutathione transferase; GSSG, glutathione disulfide; SN, substantia nigra; BSO, L-buthionine-(S,R)-sulfoximine; CSF, cerebrospinal fluid; MPTP, 1-methyl-4-phenyl-1,2,3,6, tetrahydropyridine; JNK, Jun Kinase; MCI, mental cognitive impairment; 4-HNE, 4-hydroxy-2-nonenal; MRP1, multidrug resistance protein 1; GPx, glutathione peroxidase; CDK-5, cyclin dependent kinase-5; RBC, red blood cells; SOD, superoxide dismutase; GCS, gamma glutamyl cysteinyl synthetase; GS, glutathione synthetase; BBB, blood–brain barrier; MRS, magnetic resonance spectroscopy; ADDS, antioxidant and detoxifying defense system; MAPEG, membrane-associated proteins in eicosanoid and glutathione metabolism; PG, prostaglandin; CLIC, chloride intracellular channel proteins; SAPK, stress-activated protein kinase; TRAF2, TNF receptor-associated factor 2; NS, nitrosative stress; GR, glutathione reductase; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor-erythroid 2 p45-related factor 2; NOS, nitric oxide synthase; ARE, antioxidant responsive element; Prx1, peroxiredoxin 1; APP, amyloid precursor protein.

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impairment (Ciccone et al., 2013), alteration of glutathione (GSH) metabolism and GSH related enzymes (Smeyne and Smeyne, 2013). However, a clear overview of a multiple connection between OS and neurodegeneration is beyond the scope of this article as it deals mainly with GSH and glutathione transferases (GSTs).

2.1. Parkinson's disease(PD)

PD is an age-related neurodegenerative disease clinically associated with impairment of motor and cognitive functions. Despite the etiology of this disease being unknown, all PD patients show in the central and peripheral nervous systems the so-called "Lewy bodies" which are intracellular aggregates of misfolded α-synucleine (Jenner et al., 1992; Owen et al., 1996). The most characteristic anatomic lesion is the loss of dopaminergic neurons located in the pars compacta of substantia nigra (SN). This region is particularly sensitive to OS probably because of the presence of endogenous dopamine, iron and neuromelanine. Moreover, it is apparent that in this area the antioxidant and detoxifying defense system (ADDS) (Fig. 1) is weak because of low levels of GSH (Pearce et al., 1997; Sian et al., 1994) and low activity of γ-glutamylcysteine synthetase (GCS), the enzyme responsible for the *de novo* synthesis of GSH (Kang et al., 1999). The analysis of SN, in the post-mortem brain of PD patients, has revealed an increase of lipid peroxidation, in particular of malonaldehyde and lipid hydroperoxides along with a substantial reduction of GSH levels. This seems to be specific to this area and this pathology since there is no change in GSH in other areas of the brain or in other neurodegenerative diseases (Di Monte et al., 1992). The association between depletion of GSH and PD onset has been confirmed by *in vitro* studies carried out in murine cells of neuroblastoma (NS20Y). Treatment of these cells for different times with L-buthionine-(S,R)-sulfoximine (BSO), a specific inhibitor of GCS, depletes GSH and is responsible for cell death (Andersen et al., 1996). Depletion of GSH, in cells treated with BSO, is accompanied by loss of intracellular connections and of neurites, changes of morphology of the cellular body, reduction of the total cell number, block of cell proliferation, DNA fragmentation and eventually cell apoptosis (Nicole et al., 1998). In a genetic study of a Drosophila model of PD it was shown that parkin mutants produced a neurodegenerative phenotype enhanced by loss-of-function mutations of GSTs. Overexpression of these latter genes in these neurons suppressed neurodegeneration and suggested a protective effect of these antioxidant enzymes (Whitworth et al., 2005). In a murine cellular model (HT22 murine hippocampal cells) GSH was depleted by homocysteic acid treatment, at the same time there was an increase in the levels of mRNAs encoding three different proteins: heavy and light ferritin and GST (Morozova et al., 2007). In a search for proteins involved in PD progression by using proteomic approach on postmortem samples of PD patients it was found that GST P1-1 is intimately associated with several critical cellular processes directly related to PD progression (Shi et al., 2009). When comparing postmortem ventricular cerebrospinal fluid CSF from PD and normal control subjects by using two dimensional gel electrophoresis (2D-DIGE) six proteins were found to be different in PD individuals in respect to control ones. Among them there was GST P1-1 and apolipoproteins E and A1 (Maarouf et al., 2012). The molecular mechanisms underlying the regulation of Jun Kinase (JNK) activity under stress conditions were studied in C57BL/6 wild type and GSTP knockout mice, both treated with 1-methyl-4-phenyl-1,2,3,6, tetrahydropyridine (MPTP), a potent neurotoxin. The results showed that GSTP knockout mice were more susceptible to the neurotoxic effects of MPTP and indicated that *in vivo* GST P may act as an endogenous regulator of stress by controlling JNK activity (Castro-Caldas et al., 2012). In addition to GSTs, many other GSH-related enzymes have been connected with antioxidative defense in the brain and with OS. Especially GSH peroxidases (GPx) are here important because of their role in removing hydroperoxides or by balancing H_2O_2 homeostasis in signaling cascades (Brigelius-Flohé and Maiorino, 2013). Also the peroxidase activity of some GST isoforms (e.g. class Alpha GST) should be mentioned (Hurst et al., 1998) and in general the antioxidant function of GSTs in the removal of short-lived lipid hydroperoxides that break down to yield

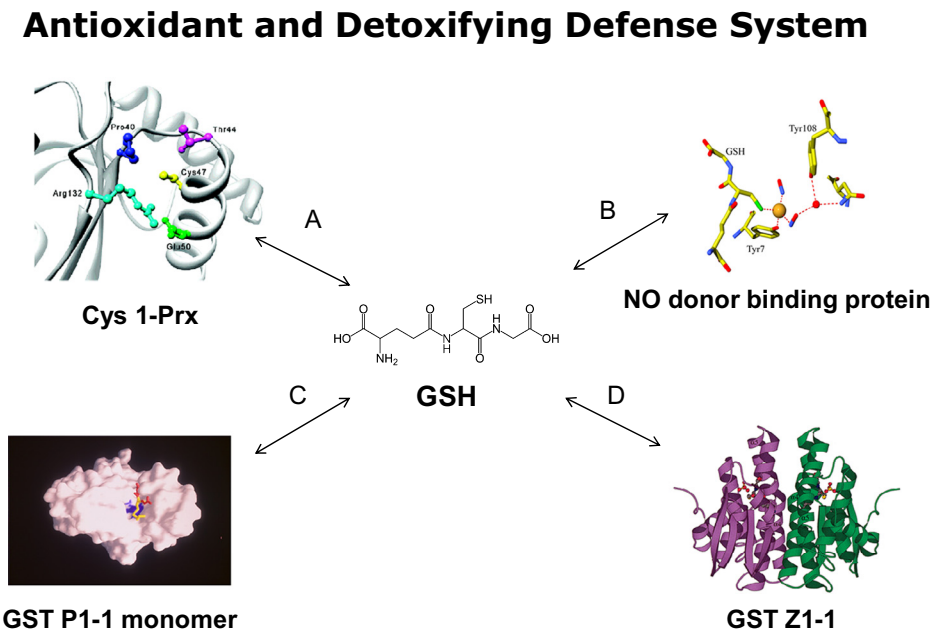

Fig. 1. GSH and GSH-based antioxidant systems are important regulators of neurodegeneration associated with PD (Garcia-Garcia et al., 2012) and AD (Saharan and Mandal, 2014). This picture emphasizes the concept that GSH homeostasis and its cellular functions are mediated by a number of different enzymes involved in the ADDS (Carvalho et al., 2014; Satoh et al., 2014). A. Cys 1-Peroxiredoxin (Cys 1-Prx) removes peroxides by the aid of GSH/GST system (Manevich et al., 2003). B. GST (NO donor binding protein) binds tightly NO carriers at the active site (Cesareo et al., 2005). C. Surface representation of GST P1-1 monomer with bound GSH (courtesy of Prof. Michael Parker). D. GST Z1-1 utilizes GSH for the isomerization of maleylacetoacetate to fumarylacetoacetate in the tyrosine degradation pathway (Polekhina et al., 2001).