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Review Article

Thiol redox homeostasis in neurodegenerative disease

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ABSTRACT

This review provides an overview of the biochemistry of thiol redox couples and the significance of thiol redox homeostasis in neurodegenerative disease. The discussion is centred on cysteine/cystine redox balance, the significance of the x_c^- cystine–glutamate exchanger and the association between protein thiol redox balance and neurodegeneration, with particular reference to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and glaucoma. The role of thiol disulphide oxidoreductases in providing neuroprotection is also discussed.

Contents

Abbreviations: ALS, amyotrophic lateral sclerosis; AD, Alzheimer's disease; AP1, activator protein 1; BOAA, β-N-oxalylamino-L-alanine; DAXX, death-associated receptor; GCL, ganglion cell layer; Grx, glutaredoxin; GSH, glutathione (reduced); GSR, glutathione reductase; GSSG, glutathione disulphide (oxidised glutathione); GST, glutathione-S-transferase; L-DOPA, L-3,4-dihydroxyphenylalanine; mGluR, metabotropic glutamate receptor; MMP, mitochondrial membrane potential; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-KB, nuclear factor-KB; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NRF2, nuclear factor (erythroid-derived 2)-like 2; NTG, normal tension glaucoma; POAG, primary open angle glaucoma; PD, Parkinson's disease; Prx, peroxiredoxin; SOD1, superoxide dismutase 1; Trx, thioredoxin; TrxR, thioredoxin receptor; TxNIP, thioredoxin inhibitory protein; xCT, functional subunit of the x_c^- cystine–glutamate exchanger

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Introduction

Regulation of thiol redox balance is critically important for multiple metabolic, signalling and transcriptional processes in mammalian cells. Thiol groups, whether in proteins or small molecules, are highly reactive and susceptible to oxidation that may cause significant loss of biological activity. In proteins, oxidation of free thiol groups produces modifications that, depending on their location, may impact on the structure, catalytic activity or ability to engage in protein–protein interactions. A critical function of cell-based thiol redox buffering systems is to protect thiol groups from oxidation and to repair those that may have become oxidised as a result of normal or aberrant cellular metabolism. The key components of the thiol redox buffering system are the cysteine/cystine and glutathione (GSH)/glutathione disulphide (GSSG) redox pairs, and the thiol disulphide oxidoreductases that include thioredoxin (Trx), glutaredoxins (Grx) and peroxiredoxins (Prx).

In this review, we describe the biochemistry of cellular redox couples and present recent findings on the association between thiol redox stability and neurodegenerative disease. A wealth of studies has implicated GSH redox balance in brain disorders that are the subject of several recent reviews [1–3]. Here, we focus primarily on the GSH precursor, cysteine, and the association between protein thiol redox balance and neurodegeneration, using Parkinson's disease (PD), Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) as examples. A section on thiol redox homeostasis in glaucoma is included that illustrates common disease mechanisms between this and other neurodegenerative diseases.

Cellular redox couples

Physiologically, sulphur exists in many different oxidation states ranging from +6 to −2 in an oxidative environment [4]. In cysteine, the thiol group is mildly acidic with pKa values ranging from ~4 to 9 depending on the structure of the protein and the local environment [4,5]. Its reactivity is further increased in the deprotonated thiolate anion (RS-) form. Therefore, the thiol side chain may be readily oxidised to give a variety of different post-translational modifications such as sulphenic acids and disulphides which are reversible, or higher oxidation products such as sulphinic and sulphonic acids [6]. Thiols act as depots for nitric oxide through reversible formation of nitrosothiols. Due to its high reactivity, the thiol group of cysteine plays a major role in many biological activities like catalysis, metal binding and in acting as a 'molecular switch' activating or deactivating protein activity and function [6]. Early studies of thiol reactivity were conducted in isolated chemical systems and these may be far removed from the actual cellular and organismal redox potential and it is therefore important to consider the feasibility of chemical reactions within local cellular conditions and the thermodynamic feasibility of redox reactions within biological systems.

GSH is the major cellular thiol antioxidant. It operates within an important biological network of redox couples comprising NAD^+/NADH, $NADP^+$/NADPH and GSH/GSSG that work in concert with GSH/ glutathione reductase (GSR), Grx/GSH, Trx/oxidised Trx and thioredoxin reductase (TrxR) and Prx to maintain redox homeostasis (see Fig. 1). In neurons, oxidation of glucose via the pentose phosphate pathway provides the NADPH needed by GSR to regenerate GSH from GSSG [7]. Moreover, neurons preferentially oxidise glucose for antioxidant defence rather than energy production, due to low activity of the key activator of glycolysis, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 [8]. The abundance of GSH in cells and the ready conversion of sulphenic acids and S-nitroso derivatives to S-glutathione mixed disulphides suggests that reversible S-glutathionylation may be a common feature of redox signal transduction and regulation of the activities of redox sensitive thiol-proteins [9].

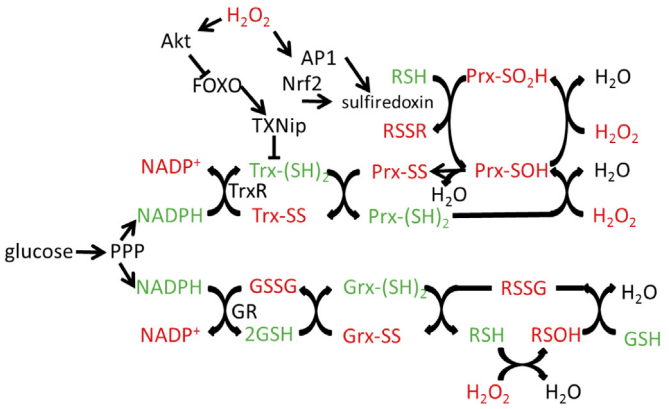

Fig. 1. Cellular redox couples in biological systems that show the link between reducing nucleotides (NADPH) derived from the pentose phosphate pathway (PPP) and maintenance of cellular redox state through reduction of hydrogen peroxide and oxidised proteins.GSH, glutathione; GSSG, glutathione disulphide; GR, glutathione reductase; Grx, glutaredoxin; Prx, peroxiredoxin; PrxSOH, peroxiredoxin sulphenate; PrxSOOH, peroxiredoxin sulphinate; PrxSS, oxidised peroxiredoxin; RSH, protein; RSSG, glutathionylated protein; RSOH, protein sulphenate; RSSR, protein disulphide; trx, thioredoxin; TrxR, thioredoxin reductase.

Cysteine is the precursor for GSH, hydrogen sulphide and taurine, each of which has significant antioxidant, neuroprotective or neuromodulatory properties. Free cysteine readily oxidises to the corresponding disulphide, cystine. In normal cells, cysteine is the dominant form, due to electron transfer from other cellular thiol/disulphide systems, particularly GSH/GSSG. The cytosolic cysteine/cystine redox potential (Eh) is typically −140 to −160 mV, whereas extracellularly, the oxidised form prevails and the cysteine/cystine ratio is close to 1:5, with an Eh of −80 mV. The GSH/GSSG redox potential is more reduced than that of cysteine/cystine and has an intracellular mean value of −230 mV, compared to −140 mV extracellularly. The steady-state redox potential for reduced/oxidised Trx in cells is the most reduced at −280 mV. The intracellular concentration of cysteine is typically in the low micromolar range and is an order of magnitude lower than the concentration of GSH. Extracellularly, the concentration of cystine (40–50 μM) is greater than either GSH (2.8 μM) or GSSG (0.14 μM).

The extracellular cysteine/cystine ratio shifts towards a more oxidised value during ageing in humans and is viewed as a significant risk factor for disease [10]. For example, a more oxidised cysteine/cystine redox potential significantly increases metabotropic glutamate receptor 5 (mGluR5)-mediated phosphorylation of extracellular signal-regulated kinase (ERK) in astrocytes, leading to increased expression of the transcription factor, nuclear factor-KB (NF-KB), and inducible nitric oxide synthase, release of reactive oxygen and nitrogen species and increased neurotoxicity [11]. It is believed that the extracellular portion of mGluR5, which contains a cysteine-rich domain incorporating many disulphide bridges, alters to facilitate interaction between glutamate and the receptor at the more oxidised potential. Based on studies using the 6-hydroxydopamine rodent model of PD, it has been proposed that nutritional strategies aimed at manipulating the extracellular cysteine/cystine redox potential may prove beneficial in slowing the rate of neurodegeneration in this and other age-related neurodegenerative diseases [12].