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# ROLE OF REDOX AND CERULOPLASMIN IN IRON DEPOSITION IN GLIAL CELLS: IMPLICATION IN NEURODEGENERATIVE DAMAGES

**Chinmay Kumar Mukhopadhyay, Som Dev, Nisha Tapryal, Reshmi Mukherjee, and Chaitali Mukhopadhyay***

*Special Centre for Molecular Medicine, Jawaharlal Nehru University, New Delhi-110 067, INDIA*

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***Corresponding author:** Email: ckm2300@mail.jnu.ac.in, mukhopc@yahoo.com; Tel: 011-26738738; Fax: 011-26741781

## ABSTRACT

***The cellular oxidation and reduction (redox) environment is influenced in presence of transition metals mainly iron and copper. They are also part of the regimen responsible for production and removal of reactive oxygen species (ROS). Interestingly, in most of the neurodegenerative diseases increased ROS generation and iron deposition were detected. However, their intrinsic relations either to cause the pathogenic condition found in neurodegenerative diseases or they are produced as a result of the condition is not clear yet. The human brain comprises only 2% of the total body weight, yet it is especially prone to ROS generation as it consumes about 20% of the resting total body oxygen. Similarly, need of glucose is also higher in active brain. Both the oxygen metabolism and glucose metabolism to gain energy are highly dependent on cellular iron metabolism. However, brain iron metabolism is so far less understood compare to the other organs. Since, ROS in presence of excess iron is highly reactive to cause oxidative damage, expression of iron homeostasis genes are usually regulated to avoid their proximity to each other. Glial cells play important role in movements of nutrients including essential metals like iron and copper to neurons as well as controlling ROS generation. Thus, it is important to understand the iron homeostasis components of glial cells in order to understand the role of redox/ROS and iron/copper mediated neurodegeneration. Ceruloplasmin (Cp) as a multicopper protein having ferroxidase ($Fe_2$+ to $Fe_3$+) activity performs a central role in body iron homeostasis. It has been described both as an antioxidant and oxidant molecule. In mammals, astroglia contains specialized membrane bound glycosyl-phosphatidyl-inositol (GPI)- anchored form of Cp that plays an important role in iron metabolism in central nervous system (CNS) by regulating iron release by maintaining stability of ferroportin. Mutation in Cp leads to iron deposition in various regions of CNS. All these evidences show a crucial role of Cp in maintaining body iron homeostasis including CNS. Here, we discuss the regulation of GPI-Cp by ROS that may be one of the potential mechanisms of iron deposition in glial cells.***

**Key words:** *Endothelial dysfunction; reactive oxygen species; oxidative stress; anti oxidants; nitric oxide; drug toxicity*

## [I] REDOX, METALS AND NEURO-DEGENERATION

Red-ox reactions represent the transfer of electrons from an electron donor (reducing agent) to an electron acceptor (oxidizing agent). The cellular redox environment is a balance between the production of reactive oxygen species (ROS) and their removal by antioxidant enzymes and small molecular weight antioxidants. ROS are oxygen-containing molecules that are highly reactive. The partial reduction of molecular oxygen results in the production of superoxide (O2.-) and hydrogen peroxide ($H_2O_2$) [1]. $O_2$.- and $H_2O_2$ react with transition metal ions (e.g., iron and copper) through Fenton and Haber-Weiss chemistry, generating the highly reactive hydroxyl radical (HO.) [2]. Redox-active metals catalyze many essential reactions for brain function as cofactors for specific enzymes, participate in electron transfer reactions required for cellular metabolism and oxygen transport [3, 4]. However, these metals can also participate in the generation of highly toxic free radicals that can cause oxidative damage to cells [5]. Iron-induced oxidative stress is par¬ticularly dangerous because it can cause further iron release from iron-containing proteins, such as ferritin (Ft), heme proteins and iron-sulfur (Fe-S) clusters, forming a destructive intracel¬lular positive-feedback loop that exacerbates the toxic effects of brain iron overload [6]. Brain iron overload is cause of, or has been associated with the development of several neurodegenerative diseases including Parkinson's, Friedreich's ataxia, aceruloplasminemia, pantothenate kinase deficiency and others. Neurodegenerative diseases and their association in iron deposition reported in the literature have summarized below in **Table-1**.

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**Table: 1. Neurodegenerative diseases and their association in iron deposition.**

| No | Neurodegenerative disease | Refs |
|---|---|---|
| 1 | Alzheimer's disease (AD) | [7-9] |
| 2 | Parkinson's disease (PD) | [8, 10, 11] |
| 3 | Multiple sclerosis (MS) | [12, 13] |
| 4 | Friedreich's ataxia | [14, 15} |
| 5 | Huntington's disease | [16, 17] |
| 6 | Aceruloplasminemia | [18] |
| 7 | Amyotrophic lateral sclerosis (ALS) | [19-21] |
| 8 | Hallervorden-Spatz syndrome (HSS) | [22, 23] |
| 9 | Neuroferritinopathy | [24, 25] |

## [II] REACTIVE OXYGEN SPECIES AND NEURODEGENERATION

ROS are byproducts of metabolism and considered as dangerous towards biological materials because of their roles in generating hydroxyl radical in conjunction with transition metals like iron and copper by Fenton's reaction. ROS are implicated in several metabolic disorders like atherosclerosis, cancer, neurodegenerative diseases, aging as well as in infectious diseases [26]. However, more recently, an essential role of ROS in many cellular signaling events was identified [27]. The net ROS generation is a balance between total generation and amount consumed by various non-enzymatic or enzymatic antioxidants. Various conditions leading to increased cellular ROS generation or depletion of antioxidants result into net increase in ROS generation.

Brain is thought to be particularly susceptible to ROS accumulation because of its high utilization of oxygen for metabolic processes and its relative paucity of antioxidant and regenerative properties compared to other organs [28]. ROS may arise from any number of normal or dysfunctional cellular mechanisms including auto-oxidation of catecholamines [29], disruption of mitochondrial complexes [30], inappropriate incorporation of exogenous toxins, inadequate availability of glutathione (GSH) or improperly stored or excess concentrations of free iron or copper by Fenton reaction [26, 28, 31]. Since, ROS can oxidize vital cellular components such as lipids, proteins and nucleic acid; it may cause cellular damage and subsequent cell death. The lack of regeneration capacity of neurons, once they are degenerated may lead to pathogenic conditions like AD, PD, ALS or others [32].

ROS also accumulates in brain due to exposure of pesticides (paraquat, diquat, maneb, rotenone, organochlorines) as suggested by epidemiological studies demonstrating a relationship between pesticide exposure and brain neurodegeneration [33]. Agricultural toxin paraquat is a potential neurotoxin as it has the ability to cross the blood brain barrier [34, 35]. Recent evidences show that in response to certain environmental toxins and endogenous proteins, microglia release ROS that cause neurotoxicity [36]. Strong evidences are provided to show that microglia identifies neurotoxic stimuli through pattern recognition receptors (PRRs) and activates NADPH oxidase activity to generate ROS [36]. In response to rotenone [37], paraquat [38, 39], lipopolysaccharide [40, 41], α-synuclein [42, 43], amyloid-β [44, 45], diesel exhaust particles [46] and others [36] microglia could be activated to generate NADPH oxidase induced ROS.

Glutathione is the major antioxidant present in brain tissue and the most important redox buffer in cells [47-49]. Glutathione is present in the brain in millimolar (mM) concentration [49]. Glutathione peroxidase (Gpx) is the major enzyme for the detoxification of $H_2O_2$ in the brain since the brain has comparatively lower catalase activity. Interestingly, GSH concentration appears to be higher in astrocytes than neurons [49]. Although varying in different regions of the brain, all GSH levels diminish by about 30% in age related diseases [50] suggesting a possible link with the increased ROS generation reported in AD and PD **[Table–2]**. Depletion of GSH may render cells more sensitive to toxic effects of oxidative stress and potentiate the toxic effects of reactive microglia [49, 51, 52]. Information on the origin of brain GSH and its possible transport from blood to brain is limited. A substantial uptake of 35S-labeled GSH by rat brain was found suggesting that GSH can cross blood brain barrier (BBB) by a saturable and specific mechanism [53]. Heme oxygenase-1 (HO-1) expression appears to be an excellent marker of oxidative stress related to cell injury in the brain [54] as GSH depletion induces HO-1 in the brain. Elevated GSH levels in hippocampus and midbrain were also reported in AD [55], an indication that AD neurons may be over-reacting to an oxidative load. Similarly, decreased activity of antioxidant enzymes occurs in AD brains [56], an indication that the normal handling of GSH may be altered in these cells. A 30-40% decrease in GSH concentrations without a corresponding increase in the levels of oxidized GSH (GSSG) was also reported in PD brains [57]. In almost all cases of neurodegenerative diseases substantial increase in net ROS levels were reported **[Table–2]**.

**Table: 2. ROS and neurodegenerative diseases.**

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| No | Neurodegenerative disease | References |
|---|---|---|
| 1 | Alzheimer's disease (AD) | [58-63] |
| 2 | Parkinson's disease (PD) | [61, 64-66] |
| 3 | Amyotrophic lateral sclerosis (ALS) | [67-70] |
| 4 | Huntington's disease | [71-75] |
| 5 | Friedreich's ataxia | [76-79] |
| 6 | Multiple sclerosis (MS) | [80-83] |
| 7 | Aceruloplasminemia | [84-85] |
| 8 | Neuroferritinopathy | [86] |

## [III] CERULOPLASMIN

Ceruloplasmin (Cp), a copper containing 132-kDa acute phase α2-glycoprotein regulates body iron homeostasis by its capacity as a ferroxidase [87-88]. It binds ~95% of copper found in human plasma and is mainly synthesized and secreted from the liver [89, 90]. In the central nervous system of humans and other mammals, Cp is expressed in astroglial cells as a GPI-anchored membrane bound form [91, 92]. Cp was first isolated from plasma and characterized as a copper containing protein by Holmberg and Laurell in 1948 [93]. Other than liver and brain organs expressing Cp gene are eyes, lungs, spleen and testis [94-96]. In 1984, Putnam determined the complete amino acid sequence of human ceruloplasmin, revealing the single-chain structure of this molecule [97]. As a major ferroxidase in plasma, Cp catalyzes conversion of Fe2+ to Fe3+ for binding to apo-transferrin [98].The role of Cp in iron homeostasis is confirmed by findings of abnormal iron metabolism in patients with hereditary Cp deficiency [99] and in mice with targeted disruption of the Cp gene [100]. Patients with aceruloplasminemia have impaired iron export from certain tissues and characterized by iron overload in retina, brain and pancreas [85,101]. Also Cp-/- mice exhibit similar iron overload in brain and other visceral organs [100,102,103]. These findings, together with early organ culture studies [98, 104] suggest that Cp is required for efficient iron release from cells and tissues. In contrast, Cp has been shown to mediate inward iron flux as well in several cell culture systems including hepatic, erythroid [105,106] and glioblastoma cells [107,108]. Iron deposition in brain of aceruloplasminemia patients and related neurodegeneration strongly indicate its role as a neuroprotector in central nervous system by regulating iron transport. The ability of GPI-Cp in astrocytes to release iron was confirmed using purified astrocytes from Cp knock-out mice [109]. Subsequent studies to reveal the role of Cp in iron release illustrated that GPI-Cp co-localizes on the astrocyte cell surface with a ferrous iron transporter, ferroportin (IREG1). A recent study shows the ferroxidase activity of GPI-Cp is required for stability of ferroportin providing a molecular mechanism of iron deposition in brain in absence of or in reduced content of Cp [110]. Any reduction of Cp may, thus, affect cellular release of iron and cause oxidative damages in presence of ROS.

Besides its role in iron homeostasis, Cp is also reported to have other functions including participation in several biological oxidation reactions that include role in copper transport, coagulation, angiogenesis, defense against oxidant stress as antioxidant and role in low density lipoprotein oxidation [111]. Cp was described as an antioxidant because of its ability to inhibit the oxidation of lipids [26] as well as for its ability to scavenge superoxide radical (O2.-) and sequestering of free copper ions [112]. The ferroxidase activity may also contribute to the antioxidant capacity of Cp, because conversion of Fe2+ to Fe3+ may reduce oxidant capacity of iron by inhibition of the Fenton reaction. In contrast, several other studies have shown that Cp to contain pro-oxidant activity and ability to oxidize low density lipoprotein (LDL) in presence of vascular cells like endothelial, smooth muscle cells or monocytes and implicated in atherosclerosis [111, 113, 114]. Recently, its role as a nitrite oxidase has also been established [115].

### *3.1. Gene structure*

Human Cp is encoded by 20 exons encompassing approximately 65 kb of DNA localized to chromosome 3q23-q24 [116, 117]. In hepatocytes, Cp gene is expressed as two transcripts of 3.7 and 4.2 kb, which arise from use of alternative polyadenylation sites within the 3' untranslated region [118]. Cloning and characterization of Cp from rat and mouse reveals 90% amino acid homology with the human sequence and similar patterns of gene expression in all three species [94, 95]. Within the human central nervous system Cp is expressed in astrocytic glia lining the brain microvasculature, surrounding dopaminergic neurons in the substantia nigra and within the inner nuclear layer of the retina [91]. Recent studies demonstrate that Cp is synthesized as a GPI-anchored protein generated by alternative splicing of exons 19 and 20 in astrocytes, sertoli cells and lymphocyte [92, 119-121, 122]. As a result, the 5 C-terminal amino acids found in secretory form of Cp are replaced by a 30-amino acid stretch in GPI-Cp. The spatial structure of human Cp and the precise total amount of six copper ions in its molecule were elucidated when a crystallographic picture at 3.1A° resolution was obtained [123]. Although copper has no effect on the rate of synthesis or secretion of Cp, failure to incorporate this metal during synthesis results in the secretion of an unstable apoceruloplasmin moiety that is devoid of ferroxidase activity [124, 125].

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### 3.2. Ceruloplasmin and neurodegeneration

Cp is a key protein involved in the regulation of the redox state of iron by converting the ROS catalytic Fe(II) to a less reactive Fe(III) by virtue of its ferroxidase activity. Iron deposition in brain of aceruloplasminemia patients and related neurodegeneration strongly indicate its role as a neuroprotector in the central nervous system by regulating iron transport [126-130]. Initially, it was suggested that GPI-anchored Cp in astrocytes could promote iron release [102] that was later confirmed using purified astrocytes from Cp knock-out mice [109]. Ferroportin is a unique and ubiquitous iron exporter of mammalian cells including astroglia [131]. GPI-anchored Cp is co-localized on membrane of astrocytes with ferroportin. It was demonstrated that ferroxidase activity of Cp is required for the stability of ferroportin [110]. Cp-knockout mice exhibit severe defects in iron release from astrocytes, probably resulting from the lack of ferroxidase activity, which is necessary for the exporter function and stability of ferroportin. In absence of Cp, ferroportin loses its ability to export iron that may explain iron accumulation in astroglia in aceruloplasminemia. Taken together, these results suggest a role for Cp in the regulation of cellular iron efflux implying its role in the pathogenesis of neurodegeneration involving increased iron and oxidative damage, such as PD and AD.

### 3.3. Reactive oxygen species decrease ceruloplasmin expression

We recently demonstrated a novel negative regulation of Cp synthesis by ROS in rat C6 glial and human astroglia U373MG cells by mRNA decay mechanism. Cp is reported to predominantly express a GPI-anchored membrane bound form in glial cells [103]. We demonstrated that ROS generated either intracellularly by inhibition of mitochondrial electron transport chain as may happen by environmental toxins or extracellularly as may be generated by NADPH oxidases of activated macrophages, neutrophils or microglial cells could decrease Cp synthesis. The study further revealed the involvement of its 3'-untranslated region (3'UTR) in ROS mediated regulation of Cp as verified by conferring a promotion of mRNA decay using heterologous reporter, where addition of Cp 3'UTR downstream of CAT gene cause decay of CAT mRNA in astroglial cells [130]. We further demonstrated that in response to ROS, a decrease in binding of yet unidentified protein to 3'UTR makes it apparently susceptible to endonuclease mediated cleavage. The complete blocking of the reduction of RNA-protein complex by antioxidant N- acetyl cysteine shows the actual role of ROS is to regulate the complex formation of the protein with the Cp 3'UTR.

Increase in cellular ROS generation was previously shown to increase HO-1 content suggesting HO-1 mediated heme degradation during ROS generation [132]. The resultant increase in intracellular labile iron pool (LIP) was confirmed by EPR analysis [132]. Increase in cellular ferritin synthesis is reported in hepatic cells probably to protect cells from iron-mediated cellular damage by storing the excess intracellular iron [132]. In contrast, both the ferritin-H and-L chains are degraded in presence of ROS in microglial cells [133]. In fact, that would also increase the intracellular iron pool and may lead to iron mediated injury. To avoid this iron-mediated injury Cp should help release iron through ferroportin. There is so far no report on ferroportin status in astrocytes, microglia or neurons by ROS. In fact, our work shows GPI-Cp is decreased in presence of ROS that would affect ferroportin status and resultant increase in intracellular iron pool.

The presence of AU-rich responsive element (ARE) or stem-loop structure like iron responsive element (IRE) is often reported in 3'UTR of genes those are regulated by mRNA decay/stability mechanism [134]. The absence of any ARE or IRE in Cp 3'UTR opens the intriguing possibility of finding a novel response element involving mRNA stability/decay mechanism in mammalian cells. We hypothesize that a redox protein normally remains bound to the 3'UTR and provides stability to Cp transcript in glial cells. In response to ROS, this redox-sensitive protein may undergo oxidative modification and eventually leaves 3'UTR. As a result, the unoccupied 3'UTR becomes a better substrate for endonuclease cleavage. The region of Cp 3'UTR responsible for binding the protein and the mechanism by which ROS affect the binding of this protein remains to be determined.

This ROS mediated regulation of Cp could also explain iron accumulation and related injury in neurodegenerative diseases. Generations of ROS in neuronal and glial cells by inflammation, injury or by environmental toxins like pesticides **[Table–2]** are implicated in developing these neurodegenerative diseases [36, 135-137]. Thus, in a condition, when ROS generation is increased either by environmental toxins like pesticides or by inflammation, concomitant decrease in GPI-Cp synthesis in glial cells would result into accumulation of iron within the cell probably by simultaneous decrease of ferrous iron transporter ferroportin as described recently [110]. Thus, generated ROS and resultant accumulated iron can form highly reactive hydroxyl radical by Fenton reaction and damage glial cells. The role of glial cells is well appreciated in neuroprotection [138]. Therefore, any damage in glial cells can lead into damages of associated neurons. Thus, our finding could explain how neuronal damage might happen by increased ROS generation in glial cells by environmental toxins or other pathological conditions, a likely scenario in most of the neurodegenerative diseases. Very recent demonstration of increased neurotoxicity and lipid peroxide products in brains of rotenone treated, Cp-deficient mice strongly support our finding [139].

## [IV] CONCLUSION AND FUTURE PERSPECTIVE

Iron plays a crucial role in maintaining several functions of brain but in increasing concentration can act as a catalyst for detrimental oxidative damages to elevate the chances of neurodegenerative diseases. Generation of ROS and iron deposition both are found to be increased in most of the

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neurodegenerative diseases. Although role of iron in elevating oxidative damage in conjunction with ROS is well appreciated, the role of ROS in dysregulation of iron homeostasis has not been explored much. The recent finding of down-regulation of GPI-Cp by ROS thus opened a new avenue of understanding iron deposition detected in neurodegenerative diseases. The detail molecular mechanism of this novel mRNA decay mechanism may identify newer players important for maintaining iron homeostasis in brain. The new knowledge and technology of proteomics and bioinformatics will be highly helpful to identify these new molecular players responsible for iron deposition in brain. This knowledge also may be helpful in predicting iron deposition in individuals by examining status of these molecules in younger age of any individual. Developing newer iron chelators that can cross blood brain barrier may also open novel therapeutic strategies to prevent or slow the progression of these neurodegenerative diseases.

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