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Integrative Perspectives on Oxidative Stress, Anaemia, and Neurotoxicity: A Cross-Talk Between Erythropoiesis and Neural Health

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ABSTRACT

Oxidative stress is a central pathological mechanism underlying diverse complications in metabolic and systemic disorders, including anaemia and neurotoxicity. Reactive oxygen and nitrogen species generated in excess can impair erythropoiesis, shorten red blood cell lifespan, and compromise neural integrity, creating a bidirectional interplay between hematologic and nervous system health. Anaemia and oxidative stress are frequently coexistent in chronic diseases, with iron dysregulation, mitochondrial dysfunction, and inflammation contributing to erythroid impairment. Simultaneously, neural tissue is highly susceptible to oxidative injury due to high metabolic demand, limited endogenous antioxidant defenses, and excitotoxic vulnerability. Emerging evidence highlights shared molecular pathways, including mitochondrial dysfunction, redox-sensitive transcription factors, inflammatory cytokines, and nitric oxide signaling, that link impaired erythropoiesis with neurodegeneration. Therapeutic strategies targeting oxidative stress, including endogenous and exogenous antioxidants, mitochondrial protectants, and iron-modulating interventions, show potential to restore erythroid and neuronal homeostasis. This review provides an integrative analysis of the mechanistic crosstalk between oxidative stress, anaemia, and neurotoxicity, highlighting potential avenues for translational therapeutics.

Keywords: Oxidative stress, anaemia, neurotoxicity, erythropoiesis, neural health

INTRODUCTION

Oxidative stress represents an imbalance between reactive oxygen species (ROS) and reactive nitrogen species (RNS) production and the capacity of endogenous antioxidant systems to neutralize them [1]. Persistent oxidative stress is implicated in the pathophysiology of a wide array of disorders, including diabetes, chronic kidney disease, neurodegenerative diseases, and anemia. In hematopoietic tissues, excessive ROS disrupt erythropoiesis, damage developing erythroid precursors, and reduce red blood cell (RBC) lifespan, contributing to functional and absolute anemia [2]. Simultaneously, the nervous system is particularly vulnerable due to high oxygen consumption, abundant polyunsaturated lipids, and comparatively low antioxidant capacity. Oxidative insults in neurons impair mitochondrial function, disrupt ion homeostasis, and activate apoptotic pathways, leading to both central and peripheral neurotoxicity [3]. The co-occurrence of anemia and neural dysfunction is increasingly recognized as a clinical challenge in chronic disease. Iron dysregulation, inflammation-driven hepcidin elevation, and ROS-mediated cellular injury not only compromise erythropoiesis but also exacerbate neural oxidative damage [4]. This bidirectional relationship creates a vicious cycle: anemia-induced hypoxia amplifies ROS production in neural tissues, while oxidative neurotoxicity can affect systemic oxygen delivery and cognitive function [5]. Understanding the molecular crosstalk between erythropoiesis and neural health is essential for developing integrative therapeutic approaches that target shared oxidative and inflammatory pathways [6]. This review aims to consolidate mechanistic insights into oxidative stress-mediated erythroid and neural dysfunction, explore the molecular intersection of anemia and neurotoxicity, and highlight emerging strategies to restore redox balance and functional homeostasis.

2. Oxidative Stress and Erythropoiesis

Erythropoiesis, the process by which red blood cells (RBCs) are produced, is exquisitely sensitive to redox imbalances. Physiologically, reactive oxygen species (ROS) function as signaling molecules, regulating erythroid progenitor differentiation and proliferation [7]. However, chronic oxidative stress, as observed in diabetes, chronic

inflammation, or metabolic disorders, overwhelms these regulatory mechanisms, leading to impaired erythroid development, reduced RBC output, and clinically significant anemia [8].

2.1 Iron Dysregulation and Hepcidin

Inflammatory states and metabolic dysregulation stimulate hepatic hepcidin synthesis, a peptide hormone that binds to and degrades the iron exporter ferroportin. This mechanism traps iron within macrophages and enterocytes, limiting its availability for hemoglobin synthesis [9]. Simultaneously, labile intracellular iron promotes Fenton reactions, generating highly reactive hydroxyl radicals. These radicals directly damage erythroid precursors and mature RBCs, exacerbating anemia [10]. Iron dysregulation therefore contributes to a feed-forward cycle in which oxidative stress and functional iron deficiency reinforce one another, compromising erythropoiesis at multiple levels.

2.2 Oxidative Damage to Erythroid Precursors

Excessive ROS directly injure the membranes, mitochondria, and nuclear material of developing erythroid cells [11]. Lipid peroxidation decreases membrane fluidity and integrity, while oxidative modifications of DNA interfere with transcription factors essential for erythropoiesis, including GATA-1 and NF-E2. These disruptions reduce progenitor proliferation, impair differentiation, and decrease overall RBC output [12]. Mitochondrial dysfunction within erythroid precursors further impairs heme biosynthesis and energy production, leading to ineffective erythropoiesis and diminished oxygen-carrying capacity.

2.3 Reduced RBC Lifespan

Mature RBCs lack nuclei and mitochondria, rendering them dependent on intrinsic antioxidant systems, such as glutathione, catalase, and peroxiredoxins, for protection against oxidative damage. ROS-mediated modifications of membrane proteins and cytoskeletal elements increase susceptibility to hemolysis and premature clearance by the spleen, further aggravating anemia even when erythropoiesis remains partially intact [13].

3. Oxidative Stress and Neural Health

Neurons are highly vulnerable to oxidative injury due to their high metabolic demand, abundant polyunsaturated fatty acids, and relatively low levels of endogenous antioxidants. Chronic oxidative stress in conditions such as diabetes, anemia, and systemic inflammation contributes to both structural and functional neural deficits, spanning the peripheral and central nervous systems [14].

3.1 Mitochondrial Dysfunction and Bioenergetic Failure

ROS and reactive nitrogen species (RNS) damage mitochondrial DNA, proteins, and membranes, disrupting oxidative phosphorylation and ATP production [15]. Energetic failure compromises ion homeostasis, axonal transport, and synaptic function, predisposing neurons to degeneration and impaired signaling.

3.2 Excitotoxicity and Calcium Dysregulation

Elevated ROS exacerbate glutamate-mediated excitotoxicity, leading to intracellular calcium overload. This calcium dysregulation activates proteases, phospholipases, and endonucleases, resulting in structural and functional neuronal damage, including dendritic spine loss and axonal degeneration [16].

3.3 Neuroinflammation

Oxidative stress primes microglia toward a pro-inflammatory phenotype, promoting the release of cytokines and additional ROS. This neuroinflammatory loop perpetuates neuronal injury, contributing to cognitive deficits, peripheral neuropathy, and heightened susceptibility to neurodegenerative disorders [17].

3.4 DNA and Protein Damage

ROS and RNS induce oxidative modifications to DNA, RNA, and proteins, impairing transcription, translation, and post-translational signaling pathways [18]. Accumulated oxidative lesions trigger apoptosis and cellular senescence, further reducing neuronal viability and functional reserve. Together, these mechanisms illustrate how systemic oxidative stress simultaneously compromises erythropoiesis and neuronal integrity, creating a pathophysiological link between anemia and neurotoxicity [19]. Understanding this interplay provides a rationale for interventions targeting redox balance to preserve both hematologic and neural health.

4. Crosstalk Between Erythropoiesis and Neural Health

Anemia and oxidative neurotoxicity are intimately interlinked, forming a bidirectional pathological loop. Reduced RBC-mediated oxygen delivery leads to tissue hypoxia, which stimulates mitochondrial ROS production in neurons and glial cells [20]. Hypoxia-inducible factor-1α (HIF-1α) signaling is activated under these conditions, further promoting oxidative stress, inflammatory cytokine release, and mitochondrial dysfunction. Conversely, systemic oxidative stress arising from chronic inflammation, hyperglycemia, or neurodegeneration exacerbates erythroid precursor damage in the bone marrow, impairing differentiation, proliferation, and hemoglobin synthesis [21]. Shared molecular mediators reinforce this crosstalk. Mitochondrial ROS contribute to both erythroid and neural cell injury, while activation of NF-κB and upregulation of inflammatory cytokines, including IL-6 and TNF-α, drive erythropoietic suppression and neuronal inflammation [22]. Nitric oxide species generated during oxidative and nitrosative stress further impair iron metabolism, erythropoietin signaling, and neuronal function. Lipid peroxidation and protein oxidation affect cell membrane integrity in RBCs and neurons alike, while DNA damage

triggers apoptosis in both systems [23]. These intersecting pathways demonstrate that disruption in one system can amplify injury in the other, emphasizing the necessity of integrative therapeutic strategies targeting oxidative stress across erythroid and neural compartments.

5. Therapeutic Strategies Targeting Oxidative Stress

5.1 Endogenous Antioxidant Enhancement

Activation of endogenous defense mechanisms, primarily through Nrf2 and related transcriptional pathways, increases the expression of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [24]. Enhanced enzymatic activity protects erythroid precursors from ROS-induced apoptosis, maintains RBC membrane integrity, and stabilizes mitochondrial function in neurons, preserving synaptic activity and axonal transport. Pharmacologic Nrf2 activators or phytochemicals with similar effects can bolster intrinsic cellular defenses and reduce the burden of oxidative injury [25].

5.2 Exogenous Antioxidants

Dietary and supplemental antioxidants, including vitamins C and E, polyphenols such as resveratrol and quercetin, and thiol donors like N-acetylcysteine, directly scavenge free radicals [26]. These compounds restore redox balance, reduce lipid peroxidation, and protect mitochondrial and cellular structures. In erythroid cells, they improve survival and maturation, while in neurons they mitigate excitotoxicity, preserve energy metabolism, and reduce neuroinflammation.

5.3 Mitochondria-Targeted Therapies

Mitochondria-targeted antioxidants and bioactive compounds, designed to accumulate selectively in mitochondria, reduce ROS generation at the source. By maintaining mitochondrial membrane potential and ATP synthesis, these agents enhance erythropoietic efficiency, preserve neural bioenergetics, and improve synaptic function, directly addressing a central node in the cross-system pathology [27].

5.4 Anti-Inflammatory and Iron-Modulating Approaches

Modulating inflammatory signaling through cytokine inhibition or reducing hepcidin activity improves iron availability for erythropoiesis while simultaneously attenuating ROS-mediated neural injury [28]. Controlling systemic inflammation also reduces microglial activation, protecting neurons from chronic oxidative and inflammatory insults.

5.5 Combination Strategies

Integrative therapeutic strategies that combine antioxidant supplementation, iron therapy, erythropoiesis-stimulating agents, and neuroprotective interventions show the greatest promise in mitigating cross-system oxidative damage [29]. These approaches target multiple pathogenic mechanisms simultaneously, addressing the interconnected nature of erythropoietic suppression and neurotoxicity, and potentially improving both hematologic and cognitive outcomes in patients with metabolic and inflammatory disorders [30].

CONCLUSION

Oxidative stress is a central mediator linking anemia and neurotoxicity. Excess ROS damages erythroid precursors and mature RBCs, impairs heme synthesis, and shortens RBC lifespan, while concurrently compromising neural structure and function through mitochondrial dysfunction, excitotoxicity, and inflammation. Shared molecular pathways underline the bidirectional crosstalk between erythropoiesis and neural health. Therapeutic strategies enhancing endogenous antioxidants, providing exogenous ROS scavengers, targeting mitochondrial dysfunction, and modulating inflammation and iron metabolism hold promise to restore redox balance and functional homeostasis. An integrative approach addressing both hematologic and neural systems is critical for mitigating oxidative stress-related complications in chronic disease.

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