ANTIOXIDANTS & REDOX SIGNALING
Volume 28, Number 18, 2018

DOI: 10.1089/ars.2018.7509

Discoveries

FORUM EDITORIAL

# Redox Biology in Neurological Function, Dysfunction, and Aging

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**Abstract**

Reduction oxidation (redox) reactions are central to life and when altered, they can promote disease progression. In the brain, redox homeostasis is recognized to be involved in all aspects of central nervous system (CNS) development, function, aging, and disease. Recent studies have uncovered the diverse nature by which redox reactions and homeostasis contribute to brain physiology, and when dysregulated to pathological consequences. Redox reactions go beyond what is commonly described as oxidative stress and involve redox mechanisms linked to signaling and metabolism. In contrast to the nonspecific nature of oxidative damage, redox signaling involves specific oxidation/reduction reactions that regulate a myriad of neurological processes such as neurotransmission, homeostasis, and degeneration. This Forum is focused on the role of redox metabolism and signaling in the brain. Six review articles from leading scientists in the field that appraise the role of redox metabolism and signaling in different aspects of brain biology including neurodevelopment, neurotransmission, aging, neuroinflammation, neurodegeneration, and neurotoxicity are included. An original research article exemplifying these concepts uncovers a novel link between oxidative modifications, redox signaling, and neurodegeneration. This Forum highlights the recent advances in the field and we hope it encourages future research aimed to understand the mechanisms by which redox metabolism and signaling regulate CNS physiology and pathophysiology. *Antioxid. Redox Signal.* 28, 1583–1586.

**Keywords:** redox, oxidative stress, neuroinflammation, neurotoxicity, neurodevelopment, neurodegeneration

THE TRANSFER OF ELECTRONS between two chemical species is defined as an oxidation (loss of electron)–reduction (gain of electrons) or redox reaction. The species that accepts electrons is called the oxidizing agent, becoming reduced, whereas the species that donates electrons is called the reducing agent and is oxidized. The oxidizing and reducing agent pair involved in a redox reaction is called a redox pair, whereas a redox couple refers to the corresponding reduced or oxidized species. Redox reactions are central to basic functions of life, including metabolism and respiration. Redox biology is then defined as all aspects in life that are mediated or influenced by redox reactions.

In this Forum titled ''Redox Biology in Neurological Function, Dysfunction, and Aging,'' we aim to highlight and review different aspects of neural function regulated by redox biology and find how alterations in redox balance contribute to aging and disease progression (Fig. 1).

The driving force for redox reactions is determined by the free energy cost for the electron transfer (redox potential or E°(V)). The E°(V) refers to the tendency of a chemical species to be oxidized (negative values) or reduced (positive values). The term oxidation originally refers to the reduction of oxygen (O) to an oxide and the oxidation of the secondary chemical species that is targeted. Oxygen is considered one of the most common oxidizing agents (E°: +816 mV) and its reduction is essential for aerobic life, as it is required for energy production during respiration.

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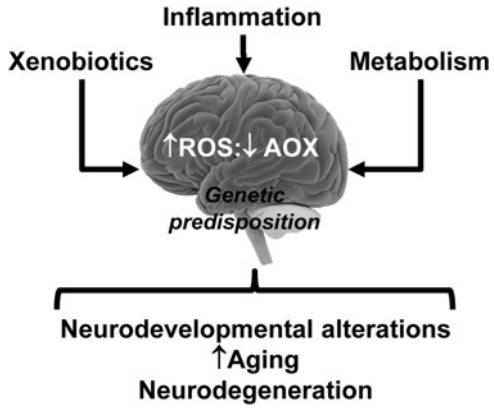


**FIG. 1. Redox biology in neurological function, dysfunction, and aging.** In the brain, redox homeostasis is recognized to be involved in all aspects of CNS development, function, aging, and disease. Although genetic predisposition is an important contributor to the overall redox capacity of brain cells, the presence of xenobiotics (toxicants), inflammatory processes (injury), and high metabolic rates (glycative stress and oxidative metabolism) contribute to the onset/trigger of brain disorders linked to aging, neurodevelopmental alterations, and neurodegeneration. This Forum highlights the recent advances in our understanding regarding the mechanisms by which redox metabolism and signaling regulate CNS physiology and pathophysiology. AOX, antioxidants; CNS, central nervous system; ROS, reactive oxygen species.

Oxygen is also the main source for reactive oxygen species (ROS). Within the mitochondria, transfer of electrons from cytochrome C to $O_2$ *via* cytochrome C oxidase (complex IV) generates $H_2O$ and the proton (H+) gradient required for energy production. However, when electrons leak before the reduction of $O_2$ to $H_2O$, direct one-electron reduction of $O_2$ generates superoxide anion ($O_2^{\bullet-}$). $O_2^{\bullet-}$ production occurs largely in complexes I and III of the mitochondrial respiratory chain *via* mechanisms that have been reviewed elsewhere (4). $O_2^{\bullet-}$ contributes to the generation of different ROS and reactive nitrogen species that can act as signaling molecules or exert toxic effects within the cell.

The role of redox biology in health and disease has for the most part been related to the homeostasis of ROS. However, a variety of redox reactions involving the transfer of electrons between redox pairs and the cycling of redox couples from their oxidized to reduced state have long been demonstrated to regulate cell metabolism and signaling.

Redox cofactors are classified as coenzymes or metallic ions. Coenzymes such as nicotinamide adenine dinucleotide and its phosphorylated form (redox pairs NAD+/NADH and NADP+/NADPH [E°: −320 mV]), glutathione disulfide/glutathione (GSSG/GSH [E°: −230 mV]), coenzyme Q (ubiquinone/ubiquinol [E°: +100 mV]), and the prosthetic groups flavin mononucleotide (oxidized/reduced) or flavin adenine dinucleotide (oxidized/reduced) (FMN/$FMNH_2$ or FAD+/$FADH_2$ [E°: +31 to −220 mV depending on the protein's prosthetic group]) are essential electron carriers involved in the transfer of electrons in a number of metabolic pathways involving oxidoreductases (dehydrogenases or reductases), such as nutrient metabolism to energy and biomolecule synthesis, antioxidant defenses, and metabolite/xenobiotic detoxification.

Redox-active metal ions in metalloenzymes and prosthetic groups (hemeproteins [E°: +400 to −100 mV], iron–sulfur proteins [E°: +400 to −700 mV], and copper centers [E°: +200 to +800 mV]) are also essential for the activity of enzymes that function as oxidoreductases or are involved in oxygen transport, storage or activation, electron transport, and antioxidant defenses.

Electron-deficient reactive metabolites (electrophiles), when not properly detoxified, can react with electron-rich biomolecules (nucleophiles) impairing biological processes. An example of these reactions are xenobiotics (*e.g.*, foreign chemical entities including metals) and electrophilic molecules generated as byproducts from oxidative stress (*e.g.*, 4-hydroxynonenal) or from endogenous metabolism (*e.g.*, methylglyoxal and prostaglandins), and their covalent binding with sulfur (S) atoms in thiolates (GSH or redox-sensitive cysteines) that can also modulate redox balance, reactive species detoxification, and enzymatic function (6).

The regulation and maintenance of central nervous system (CNS)'s function require high amounts of energy. The brain accounts for ∼20% of total body energy consumption (25% of glucose and 20% of oxygen total consumption), and brain energy levels are more resistant to starvation than other organs. Brain tissue is made up of neurons and glial cells and brain bioenergetics and redox homeostasis are an integrated process between these cell populations (Fig. 1).

Neurons are high energy consumers displaying high rates of oxidative metabolism. Brain's high metabolic rate makes it highly vulnerable to oxidative damage as ∼1% to 2% of the oxygen consumed during respiration is converted into $O_2^{\bullet-}$. Neurons utilize most of their energy (>80%) at the synapse to maintain and restore ionic gradients, and for the uptake and recycle of neurotransmitters. Interestingly, astrocytes have the same oxidative capacity as neurons, but are resilient to mitochondrial dysfunction as they can upregulate glycolysis to meet energy demands. Recent reports suggest that astrocytes have deficient mitochondrial respiration and increased ROS formation when compared with neurons. In addition, modest antioxidant defenses, a limited regenerative capacity, high levels of polyunsaturated fatty acids prone to peroxidation, and a redox-active metal burden render the brain, particularly neuronal cells and oligodendrocytes, highly vulnerable to oxidative damage (2).

This Forum starts with an original contribution by Pehar and collaborators that highlights the complexity of redox homeostasis, metabolism, and neurodegeneration. Glucose is the main substrate for the adult brain, and astrocytes consume a disproportionally high amount of glucose in comparison with their energy requirements, which is explained by the transfer of glycolysis-derived energy substrates (lactate) and antioxidant precursors (GSH) to neurons. Glycolysis is inevitably accompanied by the generation of methylglyoxal, a highly electrophilic glycating compound that reacts with proteins, lipids, and nucleic acids to form advanced glycation end products (AGEs) (1). Pehar and collaborators report that when nitrated or glycated, nerve growth factor (NGF) signals through the receptor for AGEs and the p75 neurotrophin receptors to

induce motor neuron cell death and that this post-translational modified NGF could participate in astrocyte-mediated motor neuron toxicity characteristic of amyotrophic lateral sclerosis.

This Forum then proceeds with a series of reviews that highlight the role of redox signaling and metabolism in different aspects of CNS function. The work from Moran and collaborators reviews the role of redox signaling in neurodevelopment, making emphasis in neuronal and oligodendrocyte differentiation and in dendritic and axonal growth guidance, topics that have not been extensively reviewed before. The authors review evidence that alterations in the balance between oxidative metabolism, ROS, and antioxidants act as signaling events regulating differentiation, maturation, and cytoskeleton dynamics. Research toward further understanding these processes has the potential to lead to the design of regenerative therapies based on stem cell differentiation.

The role of oxidative stress, ROS, and mitochondrial dysfunction in neurodegeneration has been reviewed extensively elsewhere (3). In this Forum, three review articles now focus on more specific and novel aspects of the mechanisms by which alterations in redox metabolism and signaling promote neurodegeneration and neurotoxicity.

NAD+ is a coenzyme that participates in the transfer of electrons in a number of redox reactions involved in cellular metabolism. NAD+ also participates in nonredox reactions involved in cellular signaling regulating DNA damage and metabolism. NAD+ acts as a substrate for the enzymatic addition (ADP ribosylation), removal (deacyation) of post-translational modifications, or generation of second messengers (cyclic ADP ribose). Importantly, changes in the balance between NAD+ consumption/depletion and synthesis/recycling are thought to alter cellular bioenergetics, metabolism, and redox homeostasis (9). Vargas and co-authors address the role of NAD+ metabolism in neurodegeneration. In particular, they focus on the role of NAD+-dependent signaling and its protective role against mitochondrial dysfunction and oxidative stress in neurodegeneration and aging.

Microglia are probably the least abundant of all CNS cell types (10% or less). Although other immune cells can migrate into the CNS during injury or disease, microglia are the primary immune cells of the CNS. It is now well recognized that microglia activation and neuroinflammation contribute to neuronal cell loss during neurodegeneration (Fig. 1) (5), but how redox signaling regulates these processes is far from being understood. Santamaría's research group reviews the mechanistic basis of how inflammation is triggered under pathological conditions and how both inflammatory and redox signaling regulate neurodegeneration.

Metals are essential for the maintenance of cellular homeostasis as they participate as signaling molecules or cofactors (micronutrients), and as activators or components of redox systems. Although essential metals participate in important biological functions, alterations in their handling or their increased accumulation are well reported to exert neurotoxicity. In addition, long-term effects of either xenobiotic metal exposure or alterations in metal homeostasis in the CNS have been proposed to play a role in neurodegenerative disorders (Fig. 1). The role of metals in neurodegeneration or the mechanisms by which metals induce oxidative stress and neurotoxicity have been extensively reviewed (8). Franco and collaborators now present an integrated review on the recent advances in the metabolism of essential and xenobiotic metals, the mechanisms by which these metals determine or modify cellular redox homeostasis, and the link between their redox activity and function in neural systems. Finally, they present an overview of how alterations in metal homeostasis and contant are thought to participate in neurotoxicity and neurodegeneration.

The last two review articles address how changes in the redox environment and signaling are affected during aging and their pathological consequences (Fig. 1). Aging is the major risk factor for neurodegeneration and loss of cognitive function, and it is paralleled by the accumulation of oxidative damage. Aging is associated with a state of growth arrest named cellular senescence, which in the brain has been primarily described for glial cells (7). Königsberg and collaborators review evidence suggesting that not only glial cells but also postmitotic neurons senesce as well, and summarizes the alterations in redox homeostasis associated with this phenomenon. Finally, Foster and coauthors provide a review of the mechanisms by which senescence-associated oxidative damage leads to cognitive impairment by inducing alterations in neuronal excitability, plasticity, and neurotransmission.

Overall, we hope the contributions of this Forum will encourage future research aimed to better understand the mechanisms by which redox metabolism and signaling regulate brain physiology and pathophysiology. We would like to thank all authors for submitting their exciting contributions to this Forum, the reviewers for their critical and constructive comments, and Dr. Chandan K. Sen (Editor-in-Chief), and the Editorial Board members of ARS for their kind invitation, outstanding cooperation, and patience throughout this process.

## Acknowledgments

This work was supported by the P20RR17675 Centers of Biomedical Research Excellence (COBRE), the University of Nebraska-Lincoln (R.F.), and NIH grant NS089640 (M.R.V.).

## Author Disclosure Statement

No competing financial interests exist.

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Date of first submission to ARS Central, March 12, 2018; date of acceptance, March 13, 2018.

**Abbreviations Used**

AGE = advance glycation end products
AOX = antioxidants
CNS = central nervous system
E°(V) = redox potential
GSH/GSSG = glutathione/glutathione disulfide
NAD+/NADH = nicotinamide adenine dinucleotide (oxidized/reduced)
NGF = nerve growth factor
$O_2^{\bullet -}$ = superoxide anion
ROS = reactive oxygen species