EDITORIAL

Recognition of Functional Roles of Free Radicals

Although free radicals are traditionally regarded as harmful by-products of aerobic cellular metabolism, this view has recently essentially changed and it is now evident that production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are strongly regulated processes that play central roles in most cell signaling. During physiological and pathophysiology processes, ROS and RNS can act as secondary messengers and control gene expression, apoptosis, cell growth, cell cycle, cell adhesion, chemotaxis, protein-protein interactions and enzymatic functions, Ca^{2+} and redox homeostasis, to name but a few functions [1, 2]. In addition, the generation of reactive oxygen species is cell-specific [3].

ROS and RNS also act as signaling molecules in cerebral circulation and are required for signal processes such as synaptic plasticity, memory formation, and regulated production, release, and uptake of neurotransmitters [4, 5]. In addition, it is less known and seldom stressed that catecholamines and serotonin have significant free radical scavenging and neuroprotective abilities [5] that indicate redox regulation can also play key roles in neurotransmission.

The average lifetime of free radicals is 10^{-9} - 10^{-6} sec, but under physiological conditions, in tissues and cells, it may be 1-2 orders of magnitude greater, because the physiological oxygen concentration is ≈ 10 -25 μM , while in *in vitro* experiments oxygen concentration is ≈ 220 μM [6]. Thus, under physiological circumstances, ROS could carry long-distance signals in cells.

Several recent studies suggest that regulated radical signal formation can be realized, for example, by redoxosomes (*redox-active endosomes*) that can spatially and temporally control ROS production to generate precise ROS gradients at sites of receptor signaling [7]. Lipid rafts (*plasma membrane-localized microdomains*) can have significant roles in formation of redoxosomes.

It appears, however, that antioxidant supplements do not provide adequate protection against oxidative stress and do not lead to an increase of the lifespan. Some current studies revealed that antioxidant treatment has either no effect or can even enhance mortality [2]. Because ROS plays a key signaling role in cells, the imbalance of the increased antioxidant potential, (*antioxidative stress*), can also be dangerous. Recent experiments revealed that integral mitochondrial Manganese superoxide dismutase (MnSOD) protein possesses peroxidase activity when the enzyme is overexpressed in mitochondria [8].

It may seem paradoxical that diverse ROS-mediated mechanisms protect cells against ROS-induced oxidative stress and can restore redox homeostasis. Based on the classical physiological concept of hormesis (*hormesis is a biological response when a beneficial effect (stress tolerance, longevity, etc.) is due to the exposition to low doses of an agent that is otherwise toxic or lethal at higher doses*), Finkel and Holbrook [9] claim that the best strategy to enhance endogenous antioxidant capacity may be oxidative stress itself. ROS with low doses and short dynamic duration can exhibit hormesis effects, although higher ROS doses are indisputably detrimental [10].

Ca^{2+} and ROS are two cross-talking secondary messengers in numerous cellular processes. Functionally, interactions between Ca^{2+} and ROS signaling systems can be both stimulatory and inhibitory. There is a delicate balance between the beneficial and detrimental consequences of Ca^{2+} and ROS regarding the mitochondrial function [11].

It is probable that free radical generation is one of the most regulated processes in cells and that oxidative stress is a secondary consequence of cellular malfunctions produced by intrinsic and extrinsic factors. Protein-folding malfunctions play key roles in numbers of disorders and the metal coordination is a key structural and functional factor in most proteins [12]. It is more probable that various stresses, for example, can produce defective structure formations of proteins that perturb homeostasis of transition metals (*mainly Cu^+ or Fe^{2+}*). Subsequently, perturbed homeostasis produces free metal ions (*or labile ions* [13]), which create an unregulated production of extremely reactive hydroxyl radicals that can damage carbohydrates, DNA, lipids and proteins. However, it is highly unlikely that evolution could not have taken care of precise and regulated production of the most reactive signaling molecules in cells.

It seems that the redox age (*recognition of functional roles of free radicals*) has opened new avenues for investigations of basic research, therapies, and drug development. We hope this special issue may significantly contribute towards these goals so that we can understand regulated free radical mechanisms in neural processes that work for us.

ABOUT PAPERS IN THIS SPECIAL REDOX ISSUE

Pomytkin in his review shows the importance of insulin-induced H_2O_2 signaling pathway that creates a bridge between insulin receptor and mitochondrial function in neurons. The paper by **Martinc, Grabnar, and Vovk** examines the evidence for the initial function of fine disturbance in Ca^{2+} and ROS cellular balance (*disorder of ROS - Ca^{2+} crosstalk*) in epileptogenesis. In addition, they propose that many antiepileptic drugs may prejudice the endogenous antioxidative ability to prevent oxidative stress. The article by **Hernandes and Britto** summarizes the state of current research on NADPH oxidase (*Nox generates large superoxide through the reduction of molecular oxygen*) and its involvement in neurodegeneration, with a special focus on Parkinson's and Alzheimer's diseases. Work by **Gyengesi, Paxinos, and Andrews** emphasizes the role of ROS and calcium signaling/stress in hypothalamic arcuate neurons controlling feeding. These authors suggest that calcium binding protein (CBP)

in hypothalamic neurons may buffer Ca^{2+} and ROS in NPY/AgRP (*neuropeptide Y (NPY)* and *agouti-related peptide (AgRP)* neuron to sustain prolonged firing during negative energy equilibrium and that Ca^{2+} signaling through N-Methyl-D-aspartate receptors (NMDARs) plays a significant role in the control of energy homeostasis. **Contestabile, Monti, and Polazzi** discuss functional interactions between Nitric oxide (NO) radicals produced by neurons and NO produced by glial cells and emphasize the physiological aspects of these interactions. **Kovacic and Somanathan** present a review concerned with many neurodegenerative diseases which is based on extensive recent literature from a redox point of view, which can be applied to a large number of illnesses in this class, such as Parkinson's, Huntington's, Alzheimer's, prions, Down's syndrome, ataxia, multiple sclerosis, Creutzfeldt-Jacob disease, amyotrophic lateral sclerosis, schizophrenia, and tardive dyskinesia. In their review, **Thompson, Narayanan, and Perez-Pinzon** examine the origin and mechanisms of ROS and RNS species production with subsequent ischemic/reperfusion and the roles of free radicals in modulating proteins associated with ischemic preconditioning neuroprotection. They point out that the ROS and RNS production may be a crucial trigger in activating survival or death signaling pathways in cells following ischemia. Ischemic preconditioning can be a neuroprotective procedure that is activated by means of a brief sublethal ischemic exposure and is sufficient to offer protection against a subsequent lethal ischemic insult.

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