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Preface

Free Radicals and Cell Signaling in Alzheimer's Disease

Since the seminal discovery of superoxide dismutase in the 1960s by McCord and Fridovich, it has been recognized that free radical species, including reactive oxygen species (ROS) and, latterly, reactive nitrogen species (RNS), can be potentially dangerous to normal cellular metabolism. Natural antioxidant defenses which protect cells against elevated levels of ROS and RNS were found to be exhausted in many pathologies including neurodegenerative conditions such as Alzheimer's disease (AD), and under these conditions, the damaging effects of ROS and RNS on cells are elevated. A large body of research has characterized the cellular mechanisms by which free radical species can be generated in organisms and the antioxidant defense systems by which cells can mitigate the effects of free radical damage to constituent macromolecules such as lipids, proteins and carbohydrates.

The damaging effects of ROS and RNS which may cause cell death under abnormal cellular conditions or even in normal circumstances, such as in the aging processes, have been well-documented. However, in contrast to these deleterious aspects of ROS and RNS biochemistry, in recent years it has become clear that some free radical species such as the NO radical (a RNS) and superoxide anion (a ROS) may have beneficial effects in cell metabolism by acting as messengers or transducers in a number of cell signaling pathways. Initially, acceptance of the hypothesis of signal functions of cellular ROS and RNS was hampered by the absence of information on specific receptors for these species, and many scientists felt that their only signaling function was for cell death. However, intracellular sensors for free radicals have recently been identified including ion channels which are activated by superoxide anion, a ouabain-sensitive Na/K-ATPase which is regulated through reversible inhibition by hydroxyl radical and the NO-Fe-glutathione complex, and ROS-stimulated protein kinases involved in the activation of NFκB and other factors regulating gene expression. These findings indicate that free radical species must play important signaling roles in cellular metabolism even when free radical species concentrations are not abnormally elevated.

Because it is recognized that AD has many of the attributes of an "oxidative disease", interest has focused on the involvement of free radical species in the etiology and sequelae of the disease. However, in view of the normal involvement of some free radical species in cell signaling, it seemed to us appropriate to bring together a number of reviews which would present different aspects of how signal transduction involving free radical species might contribute to or be affected in AD, and which would present new hypotheses about the etiology of AD. Accordingly, this special edition of JAD contains papers which discuss selected aspects of free radical damage and signaling related to AD involving both ROS and RNS. Topics in the papers include analyses of signaling cascades, molecular theories of normal and abnormal aging, the role of metal ions, the involvement of natural metabolites which might affect the development of AD through interference with signal transduction processes, changes in proteome expression, protective mechanisms against oxidative stress, and normal and abnormal organelle function.

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