1868 DIETARY METALS AND GENE EXPRESSION.

R. J. Cousins. *University of Florida, Food Science & Human Nutrition, Gainesville, FL.*

We have undertaken a broad spectrum analysis of zinc regulated gene expression using differential mRNA display and cDNA array analysis. Using diets below and above the zinc requirement for both mice and rats, it is clear that this micronutrient influences expression of genes in both thymus and small intestine, respectively. Genes that clearly relate to the physiology of zinc deprivation include cholecystokinin and uroguanylin, both peptide hormone genes in a variety of functional categories, including signal transduction. These experiments strongly suggested metals influence expression of genes, either directly by the transcription factor-metal interaction mode, or indirectly by perturbation of metal responsive systems. Many zinc transporter genes have been cloned. Some of these have been in genomic databases for years. Most of our attention has been directed at ZnT-1, the first in a family of four proteins. We have found that ZnT-1 is zinc regulated and has a cellular localization favoring export from enterocytes and renal tubular cells, and maternal to fetal placental transfer. All of these favor zinc retention. ZnT-2 is also zinc regulated and has properties suggesting a vesicular localization. The ZnT-2 gene is markedly upregulated by a zinc load. ZnT-4 is constitutively expressed, and is responsible for zinc secretion into milk during lactation. The ZnT transporter family may help to regulate zinc homeostasis. The metabolism and functions of zinc are clearly such that they could be perturbed by toxic insults from a variety of metals and other factors.

1869 PHENOLIC COMPOUNDS: FREE RADICAL MECHANISMS OF TOXICITY, CATALYSIS, AND PROTECTION. INTRODUCTION.

V. E. Kagan[1] and R. P. Mason[2]. [1]*University of Pittsburgh, Department of Environmental and Occupational Health, Pittsburgh, PA and* [2]*NIEHS, National Institutes of Health, Laboratory of Pharmacology and Chemistry, Research Triangle Park, NC.*

Cells contain a number of phenolic metabolites and are exposed to an overabundance of different phenolic compounds originating from food, drugs, industrial products, and environment. While some of these phenolics are extremely toxic, others are said to be protective or even vitally important as intracellular constituents. The mechanisms underlying these different functional role(s) of phenolic compounds are poorly understood. In addition to the interactions with estrogen receptors, phenolic compounds are critically involved in intracellular redox reactions. The common intermediate of their enzymatic and non-enzymatic one-electron oxidation pathways is a free radical intermediate, phenoxyl radicals. These free radicals are difficult to detect, identify, and quantitate because of their reactivity. Recent work established that it is the reactivity of the free radical intermediates that ultimately determines the potential of phenolic compounds to act as a cytotoxin, an effective and selective catalyst, or an antioxidant protector. This symposium will elaborate our current understanding of specific free radical mechanisms responsible for different toxic and/or functional roles and pathways of phenolic compounds in cells.

1870 PHENOLIC ANTIOXIDANTS AND PROOXIDANTS: ARE THEY REALLY SO DIFFERENT?

V. E. Kagan[1] and A. A. Shvedova[2]. [1]*University of Pittsburgh, Department of Environmental and Occupational Health, Pittsburgh, PA and* [2]*NIOSH-HELD, Pathology and Physiology Research Branch, Morgantown, WV.*

Hydroxy-function of phenolic compounds renders them effective donors of reducing equivalents for radicals providing for their radical scavenging role. The reducing potency of phenolic compounds is also utilized in enzymatic peroxidase-catalyzed reactions. In both cases, the one-electron oxidation intermediate, the phenoxyl radical, determines further pathways through which phenolic compounds participate in cell metabolism. If phenoxyl radicals are not indiscriminately reactive towards biomolecules, they can be selectively reduced by electron transport enzymes or redox cascades to yield antioxidant recycling. The most prominent example of this is the interaction of vitamin E phenoxyl radicals with coenzyme Q, ascorbate and thiols (*e.g.*, dihydrolipoic acid). If the reactivity of phenoxyl radicals is high enough to directly oxidize critical biomolecules (proteins, lipids, nucleic acids), these reactions may overwhelm capacities of protective redox regulation and trigger redox-cycling cascades. The latter can catalytically generate huge amounts of new reactive radicals as exemplified by metabolism of such molecules as phenol and etoposide in myeloperoxidase-rich human leukemia HL60 cells and human epidermal keratinocytes. Thus a high radical scavenging activity of phenolic compounds is a necessary but not sufficient prerequisite for their protective antioxidant role. Detailed studies of the redox reactivity of phenoxyl radicals should be mandatory for antioxidant evaluations.

1871 PHENOXYL RADICAL MEDIATED PROOXIDANT AND CYTOTOXIC MECHANISMS.

G. Galati[1], A. G. Siraki[1], T. S. Chan[2], M. Y. Moridani[2] and P. J. O'Brien[1,2]. [1]*University of Toronto, Pharmacology, Toronto, ON, Canada and* [2]*University of Toronto, Pharmacy, Toronto, ON, Canada.*

Phenolic compounds chosen for free radical mechanisms of toxicity and protection include phenolic xenobiotics, dietary flavonoid antioxidants and biogenic catecholamines. Phenoxyl radicals (PR) generated by the oxidation of phenolic agents by H_2O_2 and peroxidases, hemoproteins or cytochrome P450 were shown to oxidize GSH, lipids, ascorbate and DNA to their respective radicals with an effectiveness related to their redox potential. High redox potential PR were found to oxidize GSH whereas low redox potential PR formed GSH conjugates likely from quinones or quinone methide metabolites formed by PR disproportionation. Although most PR were effective antioxidants, high redox potential PR were prooxidant and initiated lipid peroxidation. They also oxidized ABTS (2,2'-azino-bis(3-ethylbenz- thiazoline-6-sulfonic acid)) to the ABTS radical cation instead of reducing the ABTS radical cation as in the Trolox Equivalent Antioxidant Capacity (TEAC) assay. PR were also likely responsible for phenolic compound induced erythrocyte oxidative stress toxicity including GSH oxidation, lipid oxidation, increased osmotic fragility and hemolysis. Hepatocyte cytotoxicity induced by peroxidase generated PR resulted in GSH oxidation/conjugate formation and mitochondrial toxicity. Catecholamine induced myocardial necrosis may be initiated by semiquinone radicals and o-quinones formed by myoglobin/cytochrome P450 and H_2O_2 (from catecholamine metabolism by mitochondrial monoamine oxidase). Evidence for the involvement of PR in catecholamine induced cytotoxicity in striatal brain slices used as a model for Parkinson's disease will also be discussed.

1872 TYROSYL RADICAL GENERATION BY MYELOPEROXIDASE: A PATHWAY FOR PROTEIN AND LIPID OXIDATION DURING ATHEROGENESIS.

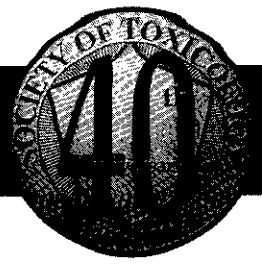
J. W. Heinecke. *Washington University School of Medicine, Lipid Research, St. Louis, MO.* Sponsor: V. Kagan.

Phagocytes secrete the heme protein myeloperoxidase, which is present and active in human atherosclerotic tissue. These cells also generate hydrogen peroxide (H_2O_2), thereby allowing myeloperoxidase to generate a range of oxidizing intermediates and stable end products. When this system acts on L-tyrosine *in vitro*, it forms o,o'-dityrosine, which is enriched in atherosclerotic lesions. Myeloperoxidase therefore may oxidize artery wall proteins in vivo, cross-linking their L-tyrosine residues. Myeloperoxidase also promotes lipid peroxidation by a pathway that requires tyrosine and H_2O_2. We used electron paramagnetic resonance spectroscopy to investigate the nature of the reactive intermediate generated from L-tyrosine by myeloperoxidase. Using an EPR flow system to rapidly mix and examine solutions containing peroxidase, H_2O_2, and L-tyrosine, we detected free tyrosyl radical. We used spin trapping to further identify this intermediate as tyrosyl radical. Collectively, these results indicate that peroxidases use H_2O_2 to convert L-tyrosine to free tyrosyl radical. They also support the idea that free tyrosyl radical initiates cross-linking of L-tyrosine residues in proteins. We suggest that this pathway may play an important role in protein and lipid oxidation at sites of inflammation and in atherosclerotic lesions.

1873 QUINOIDS AND QUINOID RADICALS FROM ESTROGENS AND ANTIESTROGENS: ROLE IN CARCINOGENESIS.

J. L. Bolton. *University of Illinois at Chicago, Medicinal Chemistry, Chicago, IL.*

Estrogens and antiestrogens have been implicated in hormone dependent cancers; however, the carcinogenic mechanism(s) remains both controversial and elusive. One mechanism could involve metabolism of these compounds to reactive intermediates such as quinones, quinone methides, and/or semiquinone radicals which leads to oxidation and/or alkylation of DNA. Quinone methides and carbocations



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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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