PREFACE

Oxidative stress and antioxidant deficiency have been implicated in the pathogenesis of many diseases and conditions, including atherosclerosis, cancer, aging, and respiratory disease. Glutathione (L-γ-glutamyl-L-cysteinyl-glycine, GSH) is a major antioxidant acting as a free radical scavenger that protects the cell from reactive oxygen species (ROS). In addition, GSH is involved in nutrient metabolism and regulation of cellular metabolic functions ranging from DNA and protein synthesis to signal transduction, cell proliferation, and apoptosis.

By affecting the cellular reduction/oxidation status, GSH may also modulate gene expression and other cellular mechanisms. Glutathione depletion is linked to a number of disease states, including liver cirrhosis, various pulmonary diseases, myocardial ischemia and reperfusion injury, aging, Parkinson's disease, Alzheimer's disease, and sepsis, also called a systemic inflammatory response syndrome. Low intracellular levels of GSH may contribute to the immunodeficiency observed in later stages of HIV infection, as adequate concentrations of GSH are needed for proper lymphocyte function.

Virtually all mammalian cells have capacity to synthesize GSH de novo from glutamate, cysteine, and glycine by two sequential ATP-dependent reactions catalyzed by γ-glutamylcysteine synthetase (γ-GCS), recently renamed glutamate-cysteine ligase, and GSH synthetase. Furthermore, compelling evidence shows that the synthesis depends on γ-GCS activity, cysteine availability, and GSH feedback regulation. The chemical structure of glutathione provides special characteristics ranging from insusceptibility to proteolysis to redox thiols catalysis. These features, together with its high intracellular concentration, make GSH the most important redox-active thiol.

Methionine, cysteine, taurine, and homocysteine are the four common sulfur-containing amino acids. Methionine is nutritionally essential due to the inability of mammals to synthesize its carbon skeleton. It is required for protein synthesis, while its activated form, *S*-adenosylmethionine, serves as a methyl donor in numerous biological reactions. Methionine is one of the most sensitive amino acids to ROS damage, being converted to methionine sulfoxide [Met(o)]. Since the sulfur atom of Met(o) is a chiral center, oxidation of methionine by ROS results in an equal mixture of both the R and S epimers of Met(o). Further oxidation yields methionine sulfone, which has been detected in tissues, although the mechanism by which it is formed or its relevance remains unknown. One of the recently discovered systems that cells use to protect against oxidative damage is the methionine sulfoxide reductase system (Msr), which can reduce Met(o) in proteins back to methionine.

Cysteine is considered to be semiessential because it is synthesized from methionine, provided that the dietary supply of the latter is sufficient. Methionine catabolism to generate cysteine begins with its activation to *S*-adenosylmethionine, followed by transmethylation and the eventual formation of homocysteine. Thus, homocysteine is synthesized in vivo as an intermediate in methionine metabolism. Elevated plasma homocysteine has been associated with such chronic diseases as atherosclerosis, Alzheimer's disease, and osteoporosis. Homocysteine has been proposed as an additional risk factor related to cardiovascular illness. The theory of a relationship between the sulfur moiety and cardiovascular disease has been present since the late 1960s. However, the evidence presented in this volume indicates that the role of homocysteine as either a mediator or marker of cardiovascular risk remains unclear.

Taurine is synthesized from cysteine by most mammals, but the ability to do so varies markedly. Its synthetic activity is very low in humans and there is evidence that taurine is a conditionally essential nutrient, particularly in premature infants, in patients who are on very long term parenteral nutrition, and possibly in those who are vegans, since fruits, vegetables, grains, legumes, and nuts do not contain measurable amounts of taurine. Taurine is the most abundant free nitrogenous compound in cells, and it has a variety of functions, including its role as a membrane stabilizer, calcium flux regulator, and immune function modulator.

Finally, the nutritional aspects of sulfur compounds must be considered. Amino acid deficiency remains a significant nutritional problem, so new knowledge regarding the utilization and metabolism of dietary amino acids is essential for the development of nutritional strategies. In this regard, the deleterious effects exerted by sulfur amino acids at high intakes must be addressed.

This complex network of roles, functions, and effects makes GSH and sulfur amino acids a fascinating subject for protein chemists, biochemists, nutritionists, and pathologists. However, few publications are targeted at giving a multifaceted view highlighting their biological significance by different focal points.

This book, written by an international panel of experts, is a primary reference book that provides a comprehensive, state-of-the-science, in-depth review of the biochemistry, absorption, metabolism, biological activities, disease prevention, and health promotion of glutathione and sulfur amino acids. The complexity of the relationship between GSH and sulfur amino acids, their physiological role, as well as the possible role exerted by their principal metabolites, in the pathogenesis of chronic-degenerative diseases have been addressed and extensively discussed. In 22 outstanding chapters, this book provides up-to-date information on the following topics:

1. Chemistry, absorption, transport, and metabolism of GSH and sulfur amino acids
2. Antioxidant and detoxification properties of GSH and sulfur amino acids, highlighting the enzymatic systems involved in antioxidant defenses
3. Biological activities of GSH and sulfur amino acids and their role in modulating cell processes

4. Role of GSH and sulfur amino acid deficiency and alteration in the onset of diseases and in aging
5. Protective effects exerted by GSH and sulfur amino acids when used as drugs, functional foods and nutraceuticals in humans and animals

Special attention has been paid to the molecular mechanisms by which sulfur amino acids and GSH can regulate cell processes through the modulation of transcription factors and enzyme activities; and the nutritional and therapeutic significance of dietary sulfur amino acids has been carefully addressed through studies in humans and animal models.

With over 2000 scientific references, this book provides our readers (food scientists, nutritionists, biochemists, food technologists, chemists, molecular biologists, and public health professionals) with a most comprehensive and up-to-date publication on glutathione and sulfur amino acids in human health and disease.

We express our sincere thanks and appreciation to all the contributors who by freely and willingly giving their knowledge and expertise have made this book possible. Our gratitude is also extended to colleagues who have reviewed various chapters, and the editorial staff and publishers at Wiley for their contribution in bringing this work to publication.

We hope that this book will serve to further stimulate the understanding of the role of glutathione and sulfur amino acids in human health and disease, stimulate the development of functional foods and nutraceuticals rich in these important biochemicals and provide consumers worldwide with products that prevent diseases and maintain a healthier life.

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