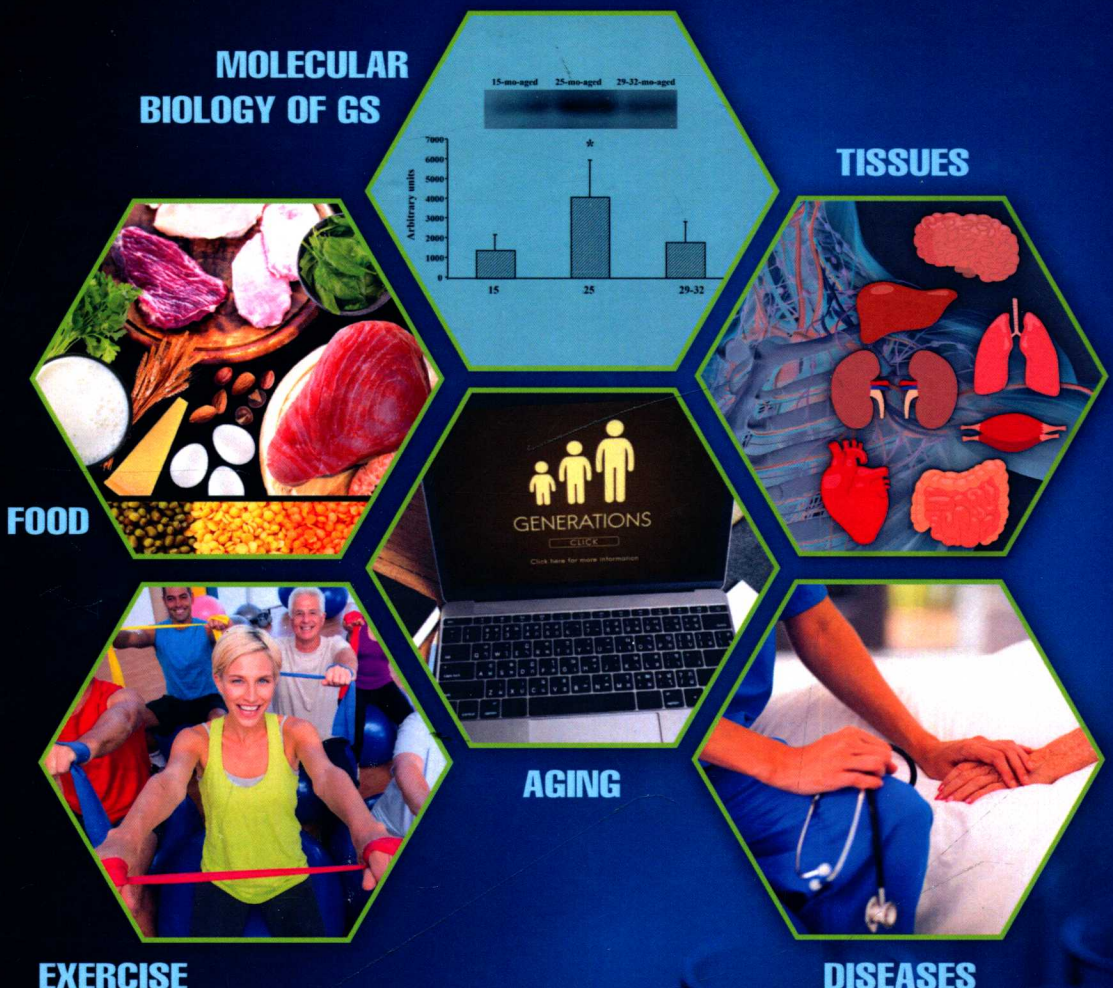
Glutamine

Biochemistry, Physiology, and Clinical Applications



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This book is dedicated to the memory of Dr. Maurice Arnal and Professor Bernard Beaufrère. Gifted with imagination and vision and exemplars of scientific rigor, both were renowned scientists in the field of amino acid and protein metabolism, to which they made outstanding contributions. In spirit they were humanists and at all times retained a sense of humility. In 1992, Dr. Arnal created the Human Nutrition Research Center in Clermont-Ferrand, which is now one of the most active in France. Professor Bernard Beaufrère joined Dr. Arnal's project to become assistant director and then director until his untimely death in 2002.

For me, it was a privilege and a pleasure to work with two men of such exceptional qualities and throughout my career as a scientist I have attempted to apply their high standards to all areas of my work.

Preface

This book gathers advanced expertise on the most significant aspects of glutamine metabolism and its health implications. Its aim is to present fully up-to-date coverage of research in this field.

This book is didactically orientated and addressed to nutritionists with a research interest in amino acids, glutamine, or catabolic states; graduate students in nutrition; medical students and postdoctoral researchers in nutrition, biology, and medicine; dieticians and pharmacists looking for a comprehensive update on glutamine; and clinicians with an interest in catabolic states and/or artificial nutrition. Readers will be interested in finding out about experimental research in the most advanced areas of glutamine metabolism, and in its designation as conditionally essential, as a regulator of cellular function, as a therapeutic nutrient to improve mucosal recovery in the intestine during certain diseases or aging, as a potential adjuvant in patient therapy, and as a potential metabolic target in cancer therapy and imaging.

Such a book can only come into being through the efforts of many people. I would like to acknowledge the efforts of the contributors who enthusiastically accepted to participate in this project and for their understanding and willing cooperation during the preparation of this book. I must also thank Morey Haymond for readily agreeing to write the introduction. I am deeply grateful to Maurice Arnal, without whose initial efforts and foresight, this book would never have gotten off the ground. His help and support throughout my career and up to his death in 2000 was invaluable. I am greatly indebted to Bernard Beaufrère who believed in me and gave me the confidence to take up research. My thanks go to Philip Calder, a firm supporter who was instrumental in turning my thoughts on glutamine metabolism into a book. I would like to thank Kevin Brindle for critically reading the manuscript and providing valuable comments to improve the relevance of the chapter on the use of hyperpolarized ^{15}N glutamine as a new therapeutic target in cancer. I would like also to thank Marc Ferrara, director of the Human Nutrition Unit to which I belong, who allowed me to embark on this project. I am grateful to Blandine Tamboise, for secretarial assistance in the preparation of this book. Finally, I would like to thank my husband, Christian, and my daughters, Audrey-Marie and Marie-Anaïs, for their total support and their patience during the hours I spent at my computer and not with them.

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Editor

Dominique Meynial-Denis studied biochemistry and molecular biology at the University Paul Sabatier of Toulouse, France and earned her PhD on intermolecular interactions between drug and plasma proteins using magnetic resonance spectroscopy (MRS) at the same University in 1985. Since 1986, she has worked as a scientist at the National Institute of Agricultural Research (INRA) in Clermont-Ferrand in the Department of Human Nutrition. She began specialist research into sarcopenia and aging in 1994. She applied MRS in work on metabolic pathways of amino acids in muscle during aging. Meynial-Denis earned a second PhD in 1998 on amino acid fluxes throughout skeletal muscle during aging. More recently, her main interest has been the effect of glutamine supplementation in advanced age. She is a member of the Société de Gérontologie et de Gériatrie (SFGG), of the International Association of Gerontology and Geriatrics (IAGG), of the Société Française de Nutrition Entérale et Parentérale (SFNEP), of the Société Européenne de Nutrition Clinique et Métabolisme (ESPEN), and of the Société Française de Nutrition (SFN). She is a regular referee for different international nutrition journals. As an editor of books that give an overview of latest scientific findings from recognized international experts she aims to enhance the status of research in the field.

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Introduction: The Magic of a Marvelous Amino Acid—Glutamine

Morey W. Haymond

This book is a truly unique contribution to the science of amino acid metabolism and particularly the role of glutamine in a wide variety of processes within the human body. Dominique Meynial-Denis is to be congratulated for her identifying this as an important need in the scientific literature at this time. She has gathered the collective experience and wisdom of some of the most prominent investigators from all over the broad scientific world today. Each of these individuals has made unique and important contributions to our understanding of the role of glutamine in human and animal physiology. These authors collectively provide the reader with the current state of knowledge of the clinical science and medicine today. This is both a superb and timely compendium of glutamine's role and effects as well as identifying future avenues for exploration.

Glutamine holds a distinct position in our understanding of physiologic and pathophysiological processes. As a 4 carbon molecule containing both an amino and an amide nitrogen, glutamine is a very unique nonessential amino acid. It serves in much the same way as other nonessential amino acids in providing substrate for protein synthesis. However, in contrast to most other amino acids, glutamine is pivotally involved in a variety of biological systems and is central to a number of specific regulatory homeostatic mechanisms in mammals and most likely other life forms. In this introduction, I have attempted to highlight a number of these effects. None are treated with the depth that each of the contributing authors have in their chapters. By reviewing a little of the history and the variety of research surrounding the role of glutamine in mammalian metabolism, you will be equally intrigued as to the importance and uniqueness of this single structure.

Glutamine is the most abundant free amino acid circulating in the human body. Its plasma concentrations are 3–200 times those of any other amino acid (Stein et al. 1954). As you will read, this amino acid serves as an important intermediary in a large number of vital functions in the human body. The history of glutamine and the discovery of its multiple roles in mammals traverse over 130 years of scientific investigation. Schulze and Boshard first identified glutamine in 1883 when they isolated it from beet juice (Meister 1956). This was a unique observation and discovery considering the analytical techniques available to scientists of that time. As glutamine spontaneously deaminates to glutamate *in vitro*, it has been one of the most difficult amino acids to quantitate accurately. It was not until 1935 that Krebs (Krebs 1935) reported the enzymatic synthesis of glutamine from glutamate and ammonia using guinea pig and the rat kidney, thus establishing that glutamine was most likely ubiquitously present in mammalian tissues. As you will read, there is ongoing and tremendous interest in glutamine and its potential therapeutic utility to this day.

ROLE OF GLUTAMINE IN MUSCLE

Since the early studies of Cahill, G.F., Jr. and coworkers, it is recognized that muscle releases alanine and glutamine in excess to their content in the muscle itself (Pozefsky et al. 1969; Marliss et al. 1971). It continues to be thought that these amino acids provide a nontoxic form to transport ammonia from one tissue to another for subsequent reuse or disposal. Although no absolutes can be stated, it has been stated that alanine is transported for the disposal of the nitrogen as urea in the liver and glutamine to the kidney where the nitrogen is disposed of as ammonium. However, it is clear that both substrates are catabolized in both liver and kidney. In both organs, the carbon skeletons of

alanine and glutamine serve as potential gluconeogenic substrates with one entering as pyruvate and the other as α-ketoglutarate. Although it has been speculated that glutamine may provide some direct or indirect stimulation of muscle protein synthesis, this may not be the case (Wilkinson et al. 2006). Although there is evidence that glutamine may affect mTOR and protein synthesis in tumor cells (see below), there is no evidence of this in muscle. Thus, glutamine's primary role is muscle is as an amino acid for protein synthesis and as a vehicle to transport carbon and nitrogen for other organ functions.

GUT METABOLISM

Glutamine has been investigated extensively as a potential nutrient source and/or growth factor for the human gut. The classic papers of Windmueller and Spaeth provide the first description of the uptake of glutamine by the gut with the release of a number of urea-cycle intermediates (Windmueller and Spaeth 1974; Windmueller and Spaeth 1975). This led to speculation about the role of this amino acid in gut nutrition and nitrogen flux, at least in the rat gut. Glutamine has been subsequently tested in a number of well-designed clinical trials as an agent that might stimulate gut growth. In subjects with short-gut syndrome, glutamine enteral treatment (with or without growth hormone) demonstrated no clear beneficial effect. Additional studies continue to explore the utility of glutamine supplementation in situations of gut injury such as radiation-induced intestinal damage. In this condition, it has been demonstrated to decrease gut permeability and inflammation but was not superior to standard nutrition in maintaining weight (Yao et al. 2015). Finally it appears that glutamine supplementation reverses the effect of aging on the gut mucosa in a rodent model (Beaufrère et al. 2014).

CANCER AND GLUTAMINE

In certain neoplasms, glutamine appears to affect the proliferation of these tumors (Chen and Cui 2015). A potential mechanism for this appears to be through mTOR. As tumor growth involves protein anabolism, it is not clear why this effect appears to be restricted to these specific neoplastic tissues as there is no clear evidence of a protein anabolic effect of glutamine in other tissues (Marwood and Bowtell 2008). This does not mean that glutamine may not be having an effect(s) but that other mechanisms may be offsetting any anabolic effect on mTOR (Yuan et al. 2015). This is clearly an area in need of and receiving new investigative scrutiny in both normal and neoplastic tissues as you will find in the chapters by Dr. Bode and Dr. Meynial-Denis in this monograph.

RENAL ACID–BASE METABOLISM AND GLUCONEOGENESIS

One of the well-established roles of glutamine in daily physiology is its central role in the maintenance of pH homeostasis via its metabolism in the kidney. Under conditions of acidosis (whether metabolic or respiratory), the kidney plays a primary counter-regulatory role, which has been referred to as the acid or pH switch (Goodman et al. 1966). Glutamine is taken up by the kidney and ammonia released from both the amide and amino nitrogens. This ammonia is secreted into the lumen of the renal tubule and combines with filtered H^+ ions forming ammonium, which is excreted in the urine, and thus removing a mole for mole of H^+ with each mole of ammonia secreted. Several of the more common physiologic causes of mild and severe metabolic acidosis are fasting ketosis and diabetic ketoacidosis, respectively. The kidney is one of three tissues that contain all of the enzymatic capability to produce glucose via gluconeogenesis, the others being the gastrointestinal tract and the liver. The role of this enzyme in the gut is unclear in humans and in other animal models (Newsholme and Carrié 1994; Kim et al. 2015). As the nitrogen groups in glutamine are utilized for hydrogen excretion, the carbon from the glutamine is directed to renal gluconeogenesis.

Under more prolonged fasting or diabetic ketoacidosis, ketone bodies are produced from the partial oxidation of fatty acids in the liver. Both β-hydroxybutyrate and acetoacetate are produced as free acids. The ketone bodies, but not fatty acids, can cross the blood–brain barrier and be oxidized, thus displacing to a considerable proportion the dependence of the CNS on glucose per se. With progressive fasting, hepatic glycogen stores are depleted and glucose production decreases, as does the plasma glucose resulting in a decrease in insulin secretion in normal health, or in the absence of an effective plasma insulin concentration in diabetes, fasting promotes fatty acid mobilization and ketogenesis. In addition to decreasing brain glucose utilization, the acidosis induced by ketosis results in an increase in the net production of glucose from the kidney via gluconeogenesis. During prolonged fasting it has been estimated that as much as 40% of glucose production is derived via renal gluconeogenesis but other substrates such as lactate, alanine, pyruvate, and α-ketoglutarate also contribute (Owen et al. 1969). Thus, one can appreciate the interrelationships among brain glucose utilization, hepatic and renal gluconeogenesis, and maintenance of acid–base balance—all of which relate back to an important role of glutamine in this latter process. It is of interest that despite the central role of the kidney in glutamine catabolism the plasma glutamine concentrations are not recognized to be elevated in renal failure.

ANTIOXIDANT AND GLUTAMINE METABOLISM

Chapters by Drs. Jahoor, Abumrad, Smedberg, and Coeffier provide current and erudite discussion of the roles amino acid supplementation and glutamine may play in stress with aging, critical illness, obesity, and disease. A number of studies have reported lower glutamine concentrations in critically ill children, which is associated with a greater degree of organ failure (Elmark et al. 2015). Whether this is a cause and effect or an association is not clear, but studies are underway to determine whether glutamine supplementation will impact biomarkers or true outcomes (Wernerman 2014). As more evidence is accumulated in the pathophysiology of the metabolic syndrome, it is increasingly clear that the generation of intracellular free radical may play a significant part in the complications recognized with this disorder(s) (Elmark et al. 2015). In humans, the plasma and red blood cell glutathione are used as surrogate makers for abnormalities in the intracellular oxidative stress (Wernerman 2014). The potential of utilizing specific oral amino acids, one of which is glutamine, to alter this oxidative stress has been demonstrated in short-term studies that provide the impetuous for longer-term interventional trials to determine whether these have a therapeutic effect. This will be an important area to follow, and understanding the role that amino acid supplementation may have on oxidative stress may lead to new avenues of research and potentially simple therapeutic interventions in humans.

CENTRAL NERVOUS SYSTEM AND GLUTAMINE METABOLISM

Plasma glutamine concentrations are quite stable under both feeding and fasting conditions. Even under more prolonged fasting conditions, plasma glutamine concentrations may decrease by only 20%–30%. In contrast, in conditions such as urea cycle inborn errors of metabolism or in hepatic failure, the plasma concentrations of glutamine can be exceedingly elevated. These conditions are frequently associated with hyperammonemic encephalopathy. Under these conditions, one might speculate that the glutamine pool extensively expanded because of the increased availability of ammonia. The observation that glutamine supplementation in a subject with a previously unknown partial defect in the urea cycle led to transient encephalopathy is concerning but demonstrates the close relationship among glutamine, ammonia, the urea cycle, and brain function (Ramadan et al. 2013; Zielinska et al. 2014). The precise role of glutamine in brain metabolism remains to be clarified, but as glutamine is deamidated by glutaminase to glutamate and that glutamate is a potent neurotransmitter, it would not be surprising to find a clear link.

MICROBIOME

The role of the microbiome in human health and disease is currently under intense study in broad areas of medicine and health. Our symbiotic relationship with our individually larger biomass of bacteria is an interesting and potentially powerful new tool to be used in human disease identification, understanding a pathophysiology role, if any, and in disease prevention. It has been demonstrated that the administration of glutamine can alter the human microbiome (Van Zwol et al. 2010; de Souza et al. 2015). It remains to be determined whether changes in the human microbiome are a cause or an effect and will only be determined by research currently underway that may lead to new hypotheses to be tested. At this point in time it is unclear what beneficial role, if any, that glutamine may have in this exciting new area of clinical research.

SUMMARY

The above offering is only intended to entice the readers to delve deeply into this literature by promoting not only a deeper understanding of glutamine metabolism and its complexity and interactions with other systems and pathways but also to stimulate new thoughts and ideas about the importance and role of glutamine in human physiology.

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