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Sphingolipids and Metabolic Disease

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SPHINGOLIPIDS AND METABOLIC DISEASE
L. Ashley Cowart

Sphingolipids and Metabolic Disease

Edited by

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PREFACE

Recent years have witnessed an explosion in the incidence of obesity and its sequelae including Type 2 diabetes and the metabolic syndrome. While originally confined to developed countries, increasing prosperity in developing countries has broadened the worldwide incidence of these disorders. Moreover, while diagnoses of Type 2 diabetes were originally almost exclusively confined to adult populations, the rise in childhood obesity has precipitated a marked increase of this disorder in children. Thus, it is crucial to explore all possible therapeutic and preventive methods to attenuate pathological processes associated with these disorders.

Current thinking holds that obesity derives primarily from overnutrition (though compelling arguments for other mechanisms, for example, endocrine disruption by environmental pollutants, also gain support from the literature). In animals, overnutrition is initially handled by adipose tissue expansion; however, exhaustion of this route of lipid sequestering results in oversupply of lipid to other tissues including skeletal muscle, heart, liver, and others. Failure of these tissues to clear excess lipids through either metabolism or sequestration into putatively inert triacylglycerols results in perturbation of bioactive lipid metabolism in cells. In particular, aberrant generation of bioactive sphingolipids is implicated in a multitude of pathological outcomes of metabolic disease including insulin resistance, inflammation, cardiomyopathy, and others. This volume addresses not only the fundamentals of sphingolipid metabolism and analysis, but also the roles of sphingolipids in these disease processes.

Chapter 1: *Sphingolipid Metabolism and Analysis in Metabolic Disease*, by Sarah E. Brice and L. Ashley Cowart. This chapter presents an overview of sphingolipid metabolism and its regulation, followed by caveats and technical considerations for sphingolipid measurement.

Chapter 2: *Sphingolipids and Cardiovascular Diseases,* by Xian-Cheng Jiang, Ira J. Goldberg, and Tae-Sik Park. This chapter addresses current knowledge of the roles of sphingolipids in dysfunction of the cardiovascular system including lipoprotein metabolism, atherosclerosis, and cardiomyopathy.

Chapter 3: *Heart Sphingolipids in Health and Disease,* by Marcin Baranowski and Jan Górski. This chapter continues the cardiovascular theme by addressing novel

mechanisms of regulating sphingolipid biosynthesis in the heart in diabetes as well as the protective role of sphingolipids in ischemia/reperfusion injury.

Chapter 4: *Blood Sphingolipids in Homeostasis and Pathobiology,* by Samar M. Hammad. This chapter addresses the clinical assessment of blood sphingolipids for diagnostic purposes.

Chapter 5: *Adipose Tissue and Ceramide Biosynthesis in the Pathogenesis of Obesity*, by Fahumiya Samad, Leylla Badeanlou, Charmi Shah, and Guang Yang. This chapter discusses changes in sphingolipids that occur as a result of obesity and how these changes mediate inflammation and cardiovascular risk.

Chapter 6: *Sphinoglipids and Hepatic Steatosis,* by Benjamin T. Bikman and Scott A. Summers. This chapter discusses how manipulation of sphingolipid metabolism influences triacylgylerol metabolism in the context of fatty liver.

Chapter 7: *Glycosphingolipids and Insulin Resistance,* by Johannes M. Aerts and colleagues. This chapter discusses the roles of glycosphinoglipids in insulin signaling and how pharmacological reduction of glycosphinoglipid synthesis ameliorates symptoms of the metabolic syndrome.

Chapter 8: *Glycosphingolipids and Kidney Disease*, by Andrew R. Mather and Leah J. Siskind. This chapter continues a focus on glycosphingolipids in the context of kidney pathology. Although the implication of glycosphingolipids in kidney disease associated with diabetes is still conjectural, the role these lipids play in a spectrum of kidney disorders, as discussed in this chapter, justifies further investigation in this highly novel and underexplored area.

Chapter 9: *Sphingolipid Synthetic Pathways are Major Regulators of Lipid Homeostasis*, by Tilla S. Worgall. This final chapter presents compelling findings that sphingolipids may regulate cholesterol homeostasis through SREBP and lipid efflux. The cross-talk between sphingolipids and lipoprotein metabolism presents rich opportunities for therapeutics aimed at ameliorating dyslipidemia associated with metabolic syndrome that promotes atherosclerosis.

Our goal in this volume was to compile chapters presenting broad overviews of tissue-specific effects of sphingolipids, while emphasizing interrelatedness of cellular processes and cross-talk between organs.

We hope you enjoy the volume.

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ABOUT THE EDITOR...

L. ASHLEY COWART obtained her BS in Biology in 1995 from Furman University in Greenville, South Carolina, and her PhD in Biochemistry in 2001 from Vanderbilt University in Nashville, Tennesee. After postdoctoral work in the laboratory of Dr. Yusuf Hannun, she joined the faculty at the Medical University of South Carolina in Charleston, South Carolina, where she currently holds the position of Assistant Professor of Biochemistry and Molecular Biology. Dr. Cowart's main research focus is the regulation of sphingolipid metabolism in diabetes and obesity and the roles of sphingolipids in pathological outcomes associated with these disorders. In addition to research, she is involved with graduate admissions and education.

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CHAPTER 1

SPHINGOLIPID METABOLISM AND ANALYSIS IN METABOLIC DISEASE

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Abstract: Sphingolipids are an important class of structural and signaling molecules within the cell. As sphingolipids have been implicated in the development and pathogenesis of insulin resistance and the metabolic syndrome, it is important to understand their regulation and metabolism. Although these lipids are initially produced through a common pathway, there is no "generic" sphingolipid. Indeed, the biophysical and signaling properties of lipids may be manipulated by the subunit composition or isoform of their synthetic enzymes, via regulation of substrate integration. Functionally distinct pools of chemically-equivalent lipids may also be generated by de novo synthesis and recycling of existing complex sphingolipids. The highly integrated metabolism of the many bioactive sphingolipids means that manipulation of one enzyme or metabolite can result in a ripple effect, causing unforeseen changes in metabolite levels, enzyme activities, and cellular programmes. Fortunately, a suite of techniques, ranging from thin-layer chromatography to liquid chromatography-mass spectrometry approaches, allows investigators to undertake a functional characterization of all or part of the sphingolipidome in their systems of interest.

INTRODUCTION

Mammalian sphingolipid metabolism consists of a complex network of interlocking pathways (Fig. 1). The basic currency of sphingolipid metabolism is the sphingoid base (1,3-dihydroxy-2-amino-alkane and its derivatives); this base may be subject to the addition of a fatty acid, head group, or phosphate moiety (reviewed in refs. 1-3). This intricate

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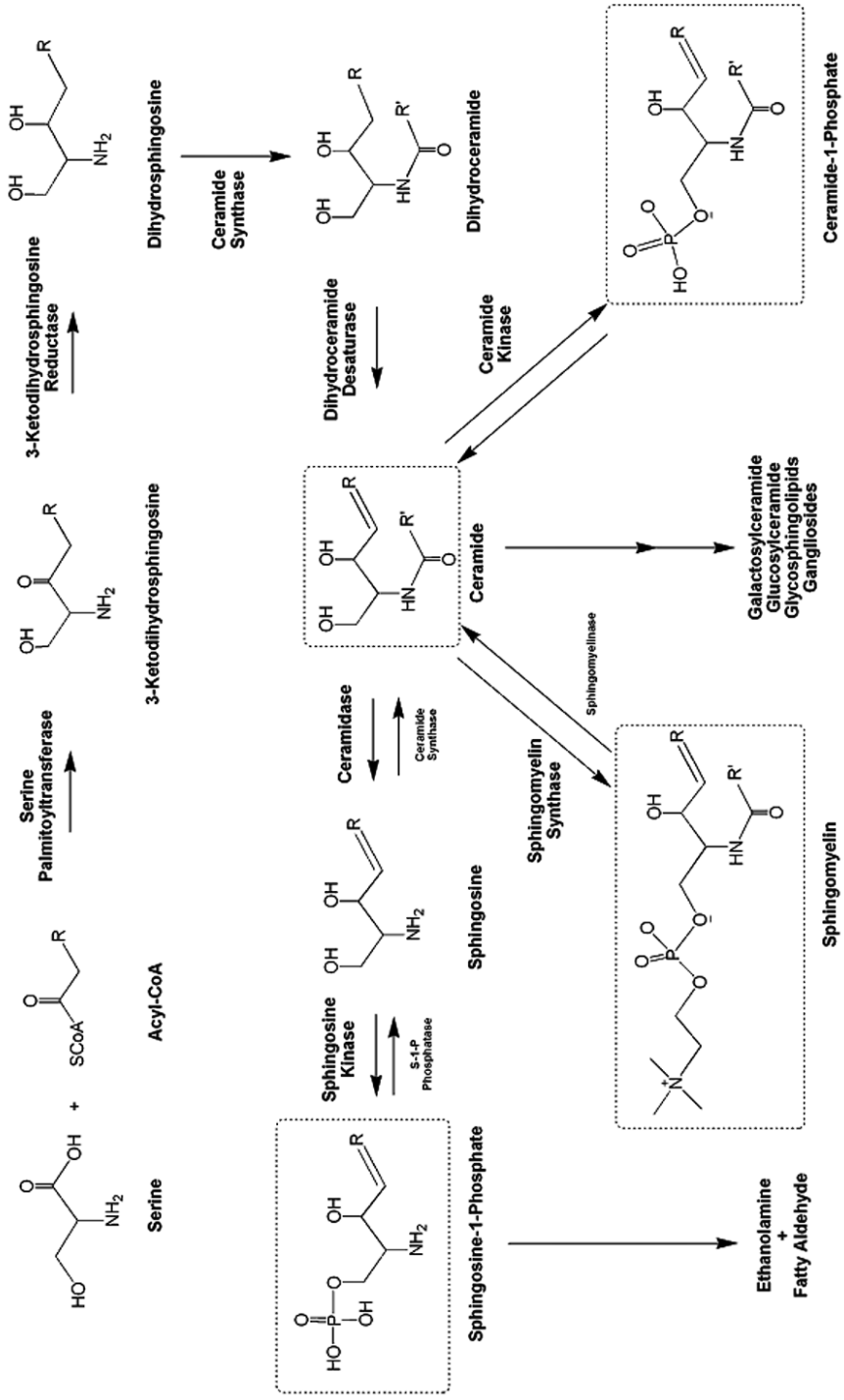

Figure 1. Metabolism of simple sphingolipids.