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Review

Sphingolipids and glycerophospholipids – The "ying and yang" of lipotoxicity in metabolic diseases

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ABSTRACT

Sphingolipids in general and ceramides in particular, contribute to pathophysiological mechanisms by modifying signalling and metabolic pathways. Here, we present the available evidence for a bidirectional homeostatic crosstalk between sphingolipids and glycerophospholipids, whose dysregulation contributes to lipotoxicity induced metabolic stress. The initial evidence for this crosstalk originates from simulated models designed to investigate the biophysical properties of sphingolipids in plasma membrane representations. In this review, we reinterpret some of the original findings and conceptualise them as a sort of "*ying/yang*" interaction model of opposed/complementary forces, which is consistent with the current knowledge of lipid homeostasis and pathophysiology. We also propose that the dysregulation of the balance between sphingolipids and glycerophospholipids results in a lipotoxic insult relevant in the pathophysiology of common metabolic diseases, typically characterised by their increased ceramide/sphingosine pools.

Contents

Abbreviations: AA, arachidonic acid; AKT, RAC-alpha serine/threonine-protein kinase; CCTα, choline-phosphate cytidylyltransferase A; CERK, Ceramide Kinase; C1P, ceramide-1-phosphate; CerS, ceramide synthase; CERT, ceramide transport protein; HDL, high-density lipoproteins; PAF, platelet activating factor; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PH, pleckstrin homology domain; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PLA2, phospholipase A2; PLC, phospholipase C; PLD, phospholipase D; PS, phosphatidylserine; S1P, sphingosine-1-phosphate; SM, Sphingomyelin; SMase, sphingomyelinase; SMS, sphingomyelin synthase; Sphk1, sphingosine kinase 1; SPTLC, serine palmitoyltransferase; SRE, sterol regulatory element; SREBP1, sterol regulatory element-binding protein 1; TG, triglyceride.

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1. Introduction

In the context of common metabolic diseases such as obesity, diabetes or non-alcoholic fatty liver disease (NAFLD), the concept of *"lipotoxicity"* refers to the inappropriate ectopic accumulation of lipids in non-adipose organs causing metabolic stress and dysfunction. Lipotoxicity in liver, skeletal muscle, heart, pancreas or brain has been identified as an important pathogenic contributor to their metabolic dysfunction. Lipotoxicity can operate at multiple levels spanning from cellular to organ levels and involves a repertoire of characteristic biochemical mediators. The severity of the lipotoxic insult is modulated by the specific cellular genetic vulnerability to the toxicity induced by lipids. When at physiological concentrations, most of these lipid species exert important physiological functions that contribute to structural, signalling or cellular homeostasis. Hence, these lipids per se only become toxic when: a) they accumulate in excessive quantities as a result of exacerbated biosynthesis and/or impaired turnover; b) they exhibit distorted qualitative properties (e.g. both biologically or chemically induced) and/or c) when their spatio-temporal location in the cell is atypical (*being in the wrong place at the wrong time*).

When in excess, sphingolipids behave as lipotoxic lipid species. Among them, ceramides and sphingosines are considered the *"usual pathogenic suspects"*. The biochemical processes of biosynthesis and remodelling of ceramides/sphingolipids are undoubtedly complex involving at least three well-characterised pathways described in detail elsewhere [1,2]. These biosynthetic pathways are highly compartmentalised within the cell, which leads to the formation of discrete organelle lipid pools accumulating specific ceramide and other sphingolipids species (Fig. 1). Their topographic localisation within the cell determines their supplied/targeted structures and also affects

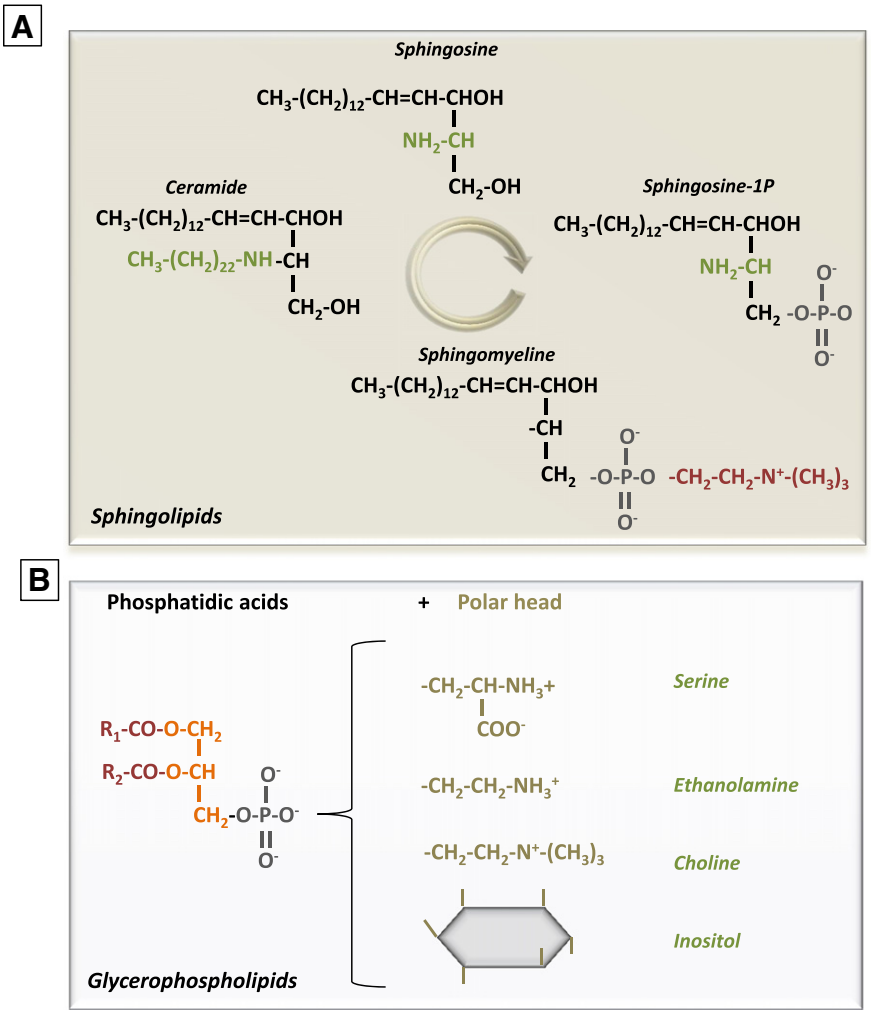

Fig. 1. Structure of the major sphingolipids [A] and glycerophospholipids [B].