Biochimica et Biophysica Acta 1851 (2015) 51–60

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Lipids in the nervous system: From biochemistry and molecular biology to patho-physiology ☆

Gaia Cermenati, Nico Mitro, Matteo Audano, Roberto C. Melcangi, Maurizio Crestani, Emma De Fabiani *, Donatella Caruso

DiSFeB, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, via Balzaretti 9, 20133 Milan, Italy

ARTICLE INFO

Article history:
Received 23 June 2014
Received in revised form 8 August 2014
Accepted 12 August 2014
Available online 20 August 2014

Keywords:
Myelin lipids
Myelin proteins
Nervous system
Transgenic models
Neuroprotection

ABSTRACT

Lipids in the nervous system accomplish a great number of key functions, from synaptogenesis to impulse conduction, and more. Most of the lipids of the nervous system are localized in myelin sheaths. It has long been known that myelin structure and brain homeostasis rely on specific lipid–protein interactions and on specific cell-to-cell signaling. In more recent years, the growing advances in large-scale technologies and genetically modified animal models have provided valuable insights into the role of lipids in the nervous system. Key findings recently emerged in these areas are here summarized. In addition, we briefly discuss how this new knowledge can open novel approaches for the treatment of diseases associated with alteration of lipid metabolism/homeostasis in the nervous system. This article is part of a Special Issue entitled Linking transcription to physiology in lipidomics.

1. Introduction

Lipids play important roles as structural and signaling molecules in the brain. This is witnessed by the enormous number of publications in the field dealing with their functions in the central and peripheral nervous system. The current understanding of the many roles of lipids in the nervous system stems from multidisciplinary work at the intersection of biochemistry, molecular biology, (patho)-physiology. In this short review, we will summarize key knowledge and recent advances in the biology and biochemistry of lipids in the nervous system, focusing especially on myelin. More emphasis will be given to studies in animal models that have provided valuable insights into the contribution of lipids in brain homeostasis, also in relation to human pathologies. We will also discuss studies highlighting how the intimate relationship between lipids and proteins is fundamental for myelin biogenesis and maintenance.

2. Brief overview of lipid species in the nervous system

The nervous system is highly enriched in lipids that are necessary for a number of key functions (synaptogenesis, neuritogenesis, insulation, rapid saltatory nerve impulse conduction, etc.). A panel of the most abundant lipid species that are present in the nervous system is reported in Fig. 1.

In addition to lipids present at high concentration, central and peripheral nervous system also contain less abundant lipid species, localized in myelin, in the plasma membranes of neurons and glial cells, or intracellularly, where they exhibit signaling and regulatory functions. Among these, we mention derivatives of cholesterol such as oxysterols and neuroactive steroids, derivatives of long chain fatty acids such as prostaglandins, endocannabinoids, neuroprotectins and resolvins.

Myelin sheaths represent a highly specialized form of plasma membrane present exclusively in the central and peripheral nervous system (CNS and PNS, respectively). A hallmark of these membranes is their unusual enrichment in lipids. Given its importance in both architecture and function of CNS and PNS, the lipid composition of myelin has been

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ApoA-1, apolipoprotein A-1; ApoE, apolipoprotein E; CNS, central nervous system; COX, cyclooxygenase; COX-2, cyclooxygenase-2; Cyp46a1, cholesterol 24-hydroxylase; Dhcr24, 24-dehydrocholesterol reductase; Dhcr7, 7-dehydrocholesterol reductase; DM-20, splicing variant of proteolipid protein; HDL, high density lipoprotein; LXRs, liver X receptors; LXRα, liver X receptor alpha; LXRβ, liver X receptor beta; M6b, glycoprotein M6b; Mbp, myelin basic protein; Mpz, myelin protein zero; Npc1, Niemann–Pick disease type C1; Npc2, Niemann–Pick disease type C2; PGs, prostaglandins; Plp, proteolipid protein; Pmp2 or Fabp8, peripheral myelin protein 2 or fatty acid binding protein 8; PMP22, peripheral myelin protein 22; PNS, peripheral nervous system; PUFAs, polyunsaturated fatty acids; SCAP, SREBP cleavage activating protein; Sf-1, steroidogenic factor 1; SLOS, Smith–Lemli–Opitz syndrome; SREBPs, sterol regulatory element binding proteins; StAR, steroidogenic acute regulatory protein; TGR5/Gpbar-1, G protein-coupled bile acid receptor 1; TSPO, translocator protein 18 kDa

☆ This article is part of a Special Issue entitled Linking transcription to physiology in lipidomics.

* Corresponding author at: Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, via Balzaretti 9, 20133 Milan, Italy. Tel.: +39 02 50318329; fax: +39 02 50318391.

E-mail addresses: gaia.cermenati@unimi.it (G. Cermenati), nico.mitro@unimi.it (N. Mitro), matteo.audano@unimi.it (M. Audano), roberto.melcangi@unimi.it (R.C. Melcangi), maurizio.crestani@unimi.it (M. Crestani), emma.defabiani@unimi.it (E. De Fabiani), donatella.caruso@unimi.it (D. Caruso).

http://dx.doi.org/10.1016/j.bbalip.2014.08.011
1388-1981/

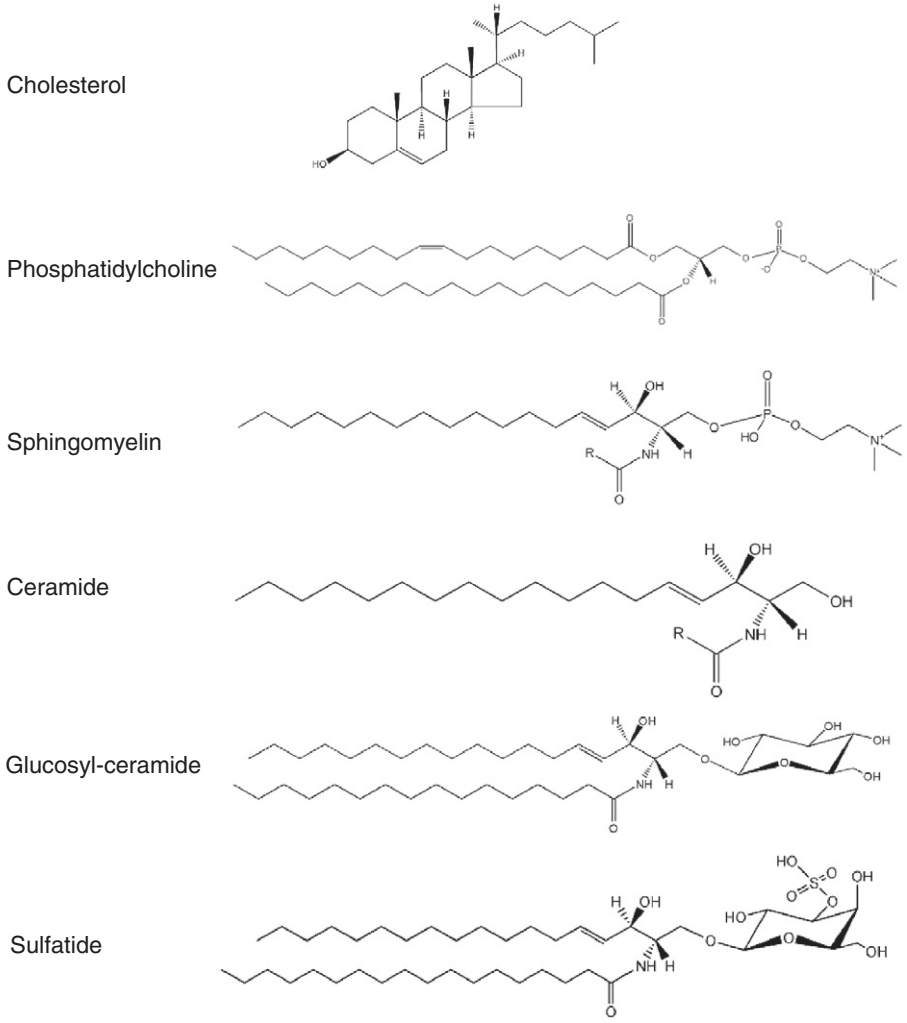

Fig. 1. Major lipid species of the nervous system. The chemical structure and common name of the most abundant lipid classes present in the nervous system are represented.

investigated in depth. CNS myelin mainly reflects the biosynthetic and assembling properties of oligodendrocytes, supported by adjacent astrocytes [1]. On the other hand, myelin of PNS results from components provided and structured by Schwann cells [2].

According to a recent report, the lipidome of human CNS myelin consists of about 700 different lipid moieties, partly already known and classified like phosphatidylcholines, phosphatidylethanolamines, sphingomyelins, cerebrosides, sulfatides and accounting for about 60%, while the remaining species have not been previously associated with myelin [3].

Notably, the major lipid constituents of myelin, cholesterol, glycerophospholipids and glycosphingolipids (particularly galactocerebrosides) are present at a fairly constant molar ratio (about 4:4:2). Similarly, the lipid to protein ratio is maintained at about 1:1 in CNS myelin and 5:1 in peripheral nerves. Qualitative and/or quantitative alterations of these ratios are always associated with myelin dysfunction.

From the qualitative point of view, the apparent strict homeostatic composition of myelin is rather flexible and related to the anatomic architecture of the sheath and the developmental stage. For example, in CNS galactosylceramide is more abundant in compact myelin while its sulfated derivative (sulfatide) is mainly located in noncompact myelin [4]. Moreover, the analysis of developmental and regional changes in lipid content in rat brain revealed a highly-ordered temporal–spatial distribution of phosphatidylcholines and sphyngomyelins, matched by expression gradients of myelin structural and regulatory genes [5].

Consequently, the high level of complexity of myelin relies on specific molecular determinants. Moreover, the pathways responsible for the synthesis, metabolism, uptake, ordered sorting/trafficking of myelin lipids and proteins must be coordinately regulated to maintain the key functions of this specialized membrane.

3. Functional and metabolic roles of lipid species in the nervous system

3.1. Cholesterol and its derivatives

Cholesterol is an integral and essential component of both CNS and PNS myelin. In addition, glia-derived cholesterol drives synaptogenesis in CNS neurons [6]. Since circulating lipoproteins do not cross the blood brain barrier under normal conditions, active de novo synthesis, efflux and uptake of cholesterol occur in glial cells and neurons. These processes are highly regulated and their importance for brain health is underlined by the fact that disturbances of cholesterol homeostasis, at various levels, are associated with neurological disorders [7].

Substitution of membrane-associated cholesterol with analogs or precursors, as it occurs in subjects carrying genetic defects in cholesterol biosynthesis, has obvious consequences on the topology, physicochemical properties and functions of all cell membranes. Furthermore, post-translational modification with cholesterol of members of the hedgehog family, a group of signaling proteins involved in development