Progress in Lipid Research 50 (2011) 357–371

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Cholesterol metabolism in neurons and astrocytes

Frank W. Pfrieger *, Nicole Ungerer

CNRS UPR 3212, University of Strasbourg, Institute of Cellular and Integrative Neurosciences (INCI), 67084 Strasbourg Cedex, France

ARTICLE INFO

Article history:
Received 17 March 2011
Received in revised form 11 June 2011
Accepted 22 June 2011
Available online 1 July 2011

Keywords:
Neuroglia
Membrane lipids
Steroids
Apolipoproteins
Lipoproteins
Neurodegenerative diseases

ABSTRACT

Cells in the mammalian body must accurately maintain their content of cholesterol, which is an essential membrane component and precursor for vital signalling molecules. Outside the brain, cholesterol homeostasis is guaranteed by a lipoprotein shuttle between the liver, intestine and other organs via the blood circulation. Cells inside the brain are cut off from this circuit by the blood–brain barrier and must regulate their cholesterol content in a different manner. Here, we review how this is accomplished by neurons and astrocytes, two cell types of the central nervous system, whose cooperation is essential for normal brain development and function. The key observation is a remarkable cell-specific distribution of proteins that mediate different steps of cholesterol metabolism. This form of metabolic compartmentalization identifies astrocytes as net producers of cholesterol and neurons as consumers with unique means to prevent cholesterol overload. The idea that cholesterol turnover in neurons depends on close cooperation with astrocytes raises new questions that need to be addressed by new experimental approaches to monitor and manipulate cholesterol homeostasis in a cell-specific manner. We conclude that an understanding of cholesterol metabolism in the brain and its role in disease requires a close look at individual cell types.

Contents

Abbreviations: 24OHC, 24S-hydroxycholesterol; ABC, ATP binding cassette; CSF, cerebrospinal fluid; CNS, central nervous system; DRG, dorsal root ganglion; ER, endoplasmic reticulum; LXR, liver x receptor; RGCs, retinal ganglion cells; VLDL, very low density lipoproteins.

* Corresponding author. Address: CNRS UPR 3212, University of Strasbourg, Institute of Cellular and Integrative Neurosciences (INCI), 5, rue Blaise Pascal, 67084 Strasbourg Cedex, France. Tel.: +33 388456645; fax: +33 388601664.

E-mail addresses: fw-pfrieger@gmx.de, pfrieger@neurochem.u-strasbg.fr (F.W. Pfrieger).

0163-7827/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.plipres.2011.06.002

1. Introduction

Cholesterol is an indispensible component of biological membranes and precursor to numerous signalling molecules including steroid hormones. Its provision and disposal in all organs of the mammalian body – except for the brain – relies on dietary uptake by the intestine, on *de novo* synthesis in every organ, and on lipoprotein-mediated transport via the blood circulation. Cells in the brain are cut off from this elaborate system by the blood–brain barrier, which prevents lipoprotein exchange [1,2]. Therefore, cells in the brain have implemented their specific way to handle cholesterol turnover. Here, we summarize current knowledge of cholesterol metabolism in the central nervous system (CNS) with a focus on two cell types, namely neurons and astrocytes (Fig. 1). Their cooperation is essential for normal brain function, and a disturbance of their interactions can provoke pathologic changes. Complementary overviews focus on cholesterol metabolism in the nervous system [3–8] and possible links to brain injury and diseases [4,9–18].

2. Neurons and astrocytes: some background

The brain consists of neurons and glial cells. Neurons specialize in the generation and transmission of electrical signals that represent the basis of all brain functions. To accomplish this, they form elaborate processes called axons and dendrites and complex intercellular connections called synapses (Fig. 2). Glial cells, which comprise astrocytes, oligodendrocytes, ephendymal and microglial cells, provide structural and logistic support to neurons, which allows them to develop and function properly [19,20]. Among the glial cells, we focus on astrocytes, which form a complex fabric that enwraps neurons (Fig. 2) and ensure that neurons can generate and transmit electrical signals [21]. To this end, astrocytes regulate the extracellular potassium concentration [22], maintain the neuronal transmitter pool of glutamate by the glutamine–glutamate cycle [23], provide neurons with energy substrates and antioxidative substances [24,25] and mediate the activity-dependent regulation of cerebral blood flow [26,27]. Moreover, astrocytes promote the formation of synapses [28] and sense or even influence their activity [29–34]. Last but not least, there is evidence that astrocytes play a role in neurodegeneration [21,35–38].

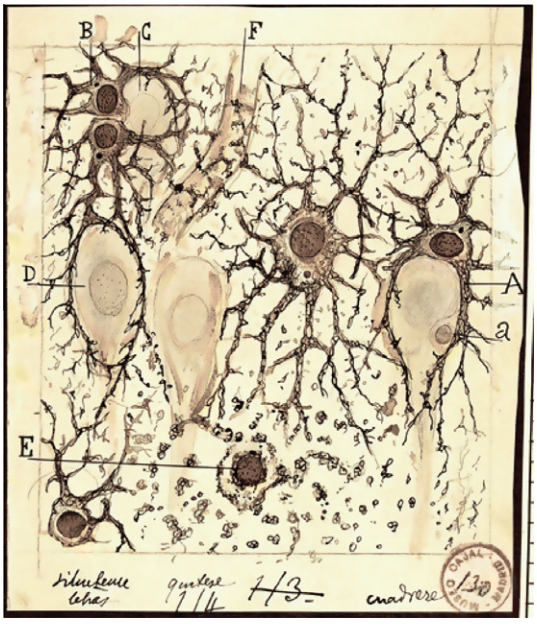

Fig. 1. Neurons and astrocytes. The drawing by the Spanish neuroscientist and Nobel prize winner Santiago Ramón y Cajal illustrates human hippocampal protoplasmic astrocytes (A and B) that embrace cell bodies and dendrites of pyramidal neurons (C and D). The drawing was made after light microscopic study of an autopsy sample subjected to histologic gold chloride-sublimate staining. Reprinted with permission from [336].

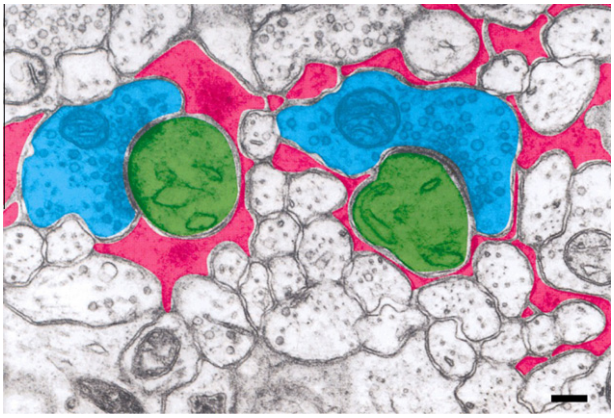

Fig. 2. Spatial arrangement of astrocytic processes and chemical synapses. The electron micrograph of the molecular layer of the monkey cerebellum shows astrocytic processes (red) and synaptic connections between a presynaptic neuron that forms vesicle-filled terminals (blue) and a postsynaptic neuron with receptor-bearing spines (green). Scale bar, 200 nm. Reprinted with permission from [337].

Neurons and astrocytes have a very high demand for cholesterol. Neurons need to build the enormous membrane surface of their axons, dendrites and synapses [39,40]. For example, the membrane area of cerebellar Purkinje cells, namely their dendrites, reaches up to 150,000 μm^2 [41], whereas myocyte membranes comprise only 5000 μm^2 [42]. Synapses contain large amounts of membrane in postsynaptic spines and presynaptic vesicles, which have a particularly high cholesterol content (40 mol%) [43]. Individual astrocytes require large amounts of membrane, as they occupy immense non-overlapping volumes and touch up to 100,000 synapses through fine, micrometer sized processes [44–48].

The demand of neurons and astrocytes for cholesterol in the adult brain cannot be measured directly. Previous studies indicated that the half-life of cholesterol in the brain lasts between two to six months [49,50], which indicated that there is little turnover of cholesterol in the brain. However, the bulk of cholesterol in the brain is contained in myelin, and therefore estimates of the metabolic stability of cholesterol in whole brain samples are largely determined by this pool [2]. The turnover of cholesterol in individual neurons and astrocytes may in fact be very high and reach an estimated 20% per day depending on the brain area and the neuronal cell type [2]. Support for this conclusion comes from the fact that the turnover of cholesterol is proportional to the metabolic rate across different tissues and animal species [2]. Since neurons have an intense