Molecular and Cellular Neuroscience 43 (2010) 33–42

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

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

Review

Cholesterol involvement in the pathogenesis of neurodegenerative diseases

Jun-Ping Liu [a,*], Ying Tang [a], Shufeng Zhou [b], Ban Hock Toh [c], Catriona McLean [d], He Li [a]

[a] Molecular Signaling Laboratory, Monash University Central Clinical School, Department of Immunology, AMREP, Commercial Road, Melbourne, Victoria 3004, Australia
[b] School of Health Sciences, RMIT University, Melbourne, Australia
[c] Centre for Inflammatory Diseases, Department of Medicine, Southern Clinical School, Clayton, Australia
[d] Department of Pathology, Alfred Hospital, Melbourne, Australia

ARTICLE INFO

Article history:
Received 26 March 2009
Revised 29 July 2009
Accepted 29 July 2009
Available online 4 August 2009

Keywords:
Cholesterol transport
Cholesterol binding protein
Niemann–Pick disease
NPC1
NPC2

ABSTRACT

Cholesterol, an essential component of cell membranes, plays an important role in the maintenance of cellular homeostasis and transmembrane communication within and between cellular compartments. In the brain that contains the highest levels of cholesterol in the body, cholesterol traffic occurs between nerve cells and between intracellular organelles in neurons to subserve normal brain function. Whereas glial cells produce the largest quantities of cholesterol, neurons also acquire cholesterol synthesized by astrocytes. The intracellular organelle endosomes and lysosomes receive and distribute cholesterol through the endocytic and retrograde transport pathways. However, deregulated cholesterol trafficking appears to be involved in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD) and Niemann–Pick disease type C (NPC) diseases. Under the pathological conditions of these neurodegenerative diseases, aberrant molecular interactions or particular depositions of cholesterol have been observed as critical causes to precipitate neuronal cell death. Here, we review the recent advances in terms of the role of cholesterol in healthy brain and molecular mechanisms of cholesterol involvement in AD, PD and NPC diseases. We discuss the different lines of evidence supporting different models of anomalous intracellular cholesterol trafficking with emphasis on cholesterol interactions with α-synuclein, NPC1 and NPC2 in AD, PD and NPC.

Contents

Introduction

Cholesterol plays integral roles in cell structure and function. It is an essential component of the cell membranes required for membrane lipid organization. Different concentrations of cholesterol regulate membrane fluidity, and thereby structural integrity and functional specificity at various cellular locations. However, cholesterol moves within and between different membranes and intracellular organelles. Cytoplasmic cholesterol is also a source of bioactive molecules such as steroid hormones, vitamin D and bile acids. Thus, cholesterol is implicated in regulating diverse cellular metabolisms, compartmental homeostasis, and molecular interactions in extracellular and intracellular communication. As a polar lipid cholesterol is also toxic to its host cell, and when accumulated, it causes cell death. It is thus important that while cholesterol is required, it must be harnessed in certain forms, locations and concentrations. Extensive studies on cholesterol

* Corresponding author. Fax: +61 3 99030120.
E-mail address: jun-ping.liu@med.monash.edu.au (J.-P. Liu).

1044-7431/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.mcn.2009.07.013

synthesis have been carried out in liver and vascular endothelial cells. In contrast, much remains to be understood about the role of cholesterol in normal brain function, and how the brain cells deal with high levels of cholesterol under various conditions including aging. Recently considerable evidence implicates cholesterol in the loss of nerve cells e.g. as demonstrated in the cholesterol transport disorder of Niemann–Pick disease type C (NPC). In this review, we discuss the general aspect of cholesterol distribution and function in the brain, and recent advances in our understanding of cholesterol involvement in Alzheimer's disease (AD), Parkinson's disease (PD) and NPC.

Cholesterol distribution and function in the brain

Brain contains the highest levels of cholesterol in mammalian bodies. The human brain contains as much as 25% of total body cholesterol and cholesterol derivatives (~20 mg/g), although the human brain accounts for ~2% of total body weight (Dietschy and Turley, 2004; Vaya and Schipper, 2007). In the mouse, the brain contains about 15% of total cholesterol (15 mg/g), from ~8 mg/g in the grey matter to ~40 mg/g in the spinal cord (Xie et al., 2003). The five-fold more cholesterol in the spinal cord is consistent with the estimation of ~20% of total brain cholesterol to be intracellular. So, cholesterol export and import may be an important mechanism in the maintenance of cholesterol homeostasis. Cholesterol in the brain is mainly synthesized by oligodendrocytes and astrocytes, without significant contribution from the blood circulation as cholesterol in lipoprotein particles does not pass through the established blood–brain barrier (BBB) in adults. Whereas oligodendrocytes produce cholesterol to form the myelin sheaths, astrocytes also produce cholesterol 2–3 times more than that produced from neurons (Bjorkhem and Meaney, 2004). In contrast with oligodendrocytes that produce cholesterol to be immobilized into myelin for myelination, astrocytes may supply cholesterol to neurons by exporting cholesterol in mechanisms involving ATP-binding cassette A1 (ABCA1) and ABCG1 transporters (Hayashi et al., 2004; Karten et al., 2006; Wahrle et al., 2004) (Fig. 1). The ATP-binding cassette transporters are a family of 49 proteins that are grouped into 7 subclasses (from A through G). These proteins have a channel-like topology that transports various solutes including ions, drugs, peptides, proteins, sugars and lipids across cell membranes (Annilo et al., 2006; Dean et al., 2001; Oram and Heinecke, 2005). The transporters have two nucleotide-binding folds with characteristic Walker A and B motifs (90–120 amino acids apart) exposed to the cytoplasm, and two transmembrane domains each of which contains 6–11 membrane-spanning α-helices. Expressed in neurons, astrocytes and microglia, and required to maintain normal apolipoprotein E (ApoE) levels and for production of lipoproteins secreted by astrocytes and microglia (Hirsch-Reinshagen et al., 2004; Kim et al., 2007; Wahrle et al., 2004), ABCA1 has a broad substrate specificity, transporting diverse lipids including cholesterol and phospholipids, probably by flipping lipids from the inner to outer membrane leaflet through its channel-like structure (Oram and Heinecke, 2005). Currently, it remains to be learnt why and to what extent astrocytes contribute cholesterol in the neurons. It is thought that during development, neurons synthesize most of the cholesterol needed for growth and synaptogenesis, whereas mature neurons show reduced synthesis and become dependent on exogenous cholesterol from astrocytes (Quan et al., 2003). Reduced neuronal cholesterol synthesis in the adult may reflect a reduced general requirement for cholesterol in the brain, with a local need of cholesterol for synaptogenesis being achieved with regulation by astrocytes. The supply of cholesterol by astrocytes is also energy saving to neurons, as more than 100 ATP molecules are needed to synthesize one molecule of cholesterol in a lengthy process of more than 20 reactions and intermediates (Shobab et al., 2005).

Cholesterol synthesized and transported together with ApoE as a complex from astrocytes may enter neurons by receptor-mediated endocytosis (Hayashi et al., 2004). This uptake of cholesterol and ApoE complex is presumably followed by its transport from endosomes to lysosomes, endoplasmic reticulum (ER), Golgi apparatus and plasma membranes, and by cholesterol efflux out of neurons, to maintain a continuous equilibrium of balanced cholesterol transport. Whereas vesicular membrane transport of cholesterol represents a fraction of cholesterol movement from the Golgi, little is known of how cholesterol is transported across endosomal and lysosomal membranes, to axons, dendrites, plasma membrane and synaptosomes (Sarkanen et al., 2007; Vetrivel et al., 2004). It has been

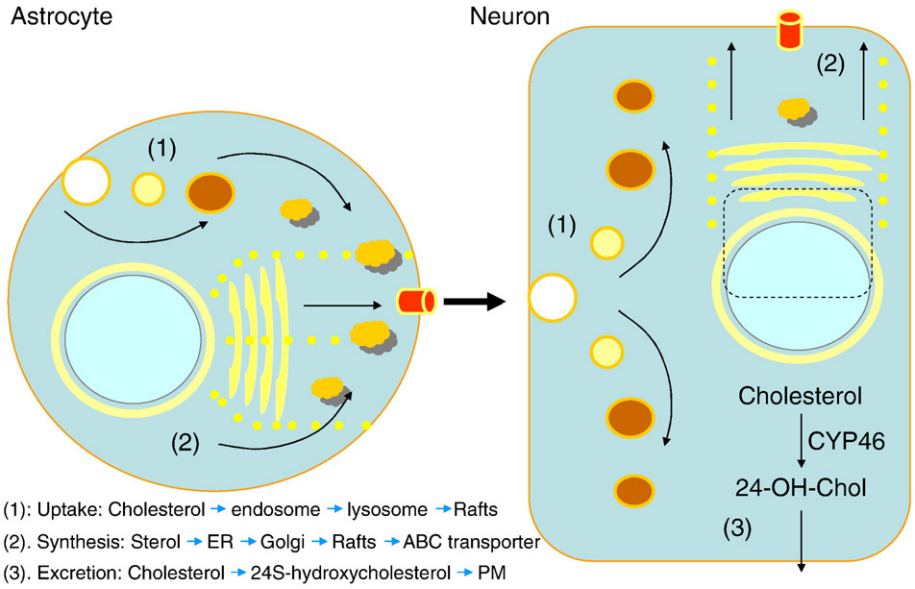

Fig. 1. Schematic pathways of cholesterol trafficking within and between astrocyte and neuron. Cholesterol biosynthesis is largely in astrocyte (left) whereas uptake is the major source for mature neuron (right). Cholesterol precursors are first synthesized in the cytosol with the final steps completed in the ER; it is then transported out of ER to the Golgi apparatus by unknown mechanisms, and reaches the plasma membrane through lipid rafts and in smaller part by vesicular traffic. Cholesterol taken up by receptor-mediated endocytosis is cleavage of cholesteryl esters to liberate cholesterol for transport from lysosomes. Oxidized cholesterol catalyzed by cholesterol 24-hydroxylase (CYP46) diffuses out from the cytosol through the plasma membrane; cholesterol may also be exported by the ATP-binding cassette transporter.