Multiple Sclerosis and Related Disorders 5 (2016) 53–65

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Review article

Cholesterol and markers of cholesterol turnover in multiple sclerosis: relationship with disease outcomes

Simon Zhornitsky [a,b], Kyla A. McKay [c], Luanne M. Metz [a,b], Charlotte E. Teunissen [d], Manu Rangachari [e,f,*]

[a] Department of Clinical Neurosciences, University of Calgary, Calgary, Canada
[b] Hotchkiss Brain Institute, University of Calgary, Calgary, Canada
[c] Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, Canada
[d] Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[e] Department of Neuroscience, Centre de recherche du CHU de Québec – Université Laval, Québec, Canada
[f] Department of Molecular Medicine, Faculty of Medicine, Université Laval, Québec, Canada

ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form
8 October 2015
Accepted 19 October 2015

Keywords:
Cholesterol
Biomarker
Multiple sclerosis
Clinically isolated syndrome
Apolipoprotein
ApoA
ApoB
ApoD
ApoE
Lipoprotein
LDL
HDL
Oxysterol
24-hydroxycholesterol

ABSTRACT

Multiple sclerosis (MS) is a chronic central nervous system disease that is associated with progressive loss of myelin and subsequent axonal degeneration. Cholesterol is an essential component of mammalian cellular and myelin membranes. In this systematic review, we examined the relationship between levels of cholesterol and markers of cholesterol turnover in circulation and/or cerebrospinal fluid (CSF) and disease outcomes in adults with clinically isolated syndrome (CIS) or confirmed MS. Studies suggest that elevated levels of circulating low density lipoprotein cholesterol (LDL), total cholesterol, and particularly, apolipoprotein B and oxidized LDL are associated with adverse clinical and MRI outcomes in MS. These relationships were observed as early as CIS. The studies also suggest that oxysterols, cholesterol precursors, and apolipoprotein E may be markers of specific disease processes in MS, but more research is required to elucidate these processes and relationships. Taken together, the data indicate that cholesterol and markers of cholesterol turnover have potential to be used clinically as biomarkers of disease activity and may even be implicated in the pathogenesis of MS.

Contents

* Correspondence to: Centre de recherche du CHU de Québec – Université Laval, Pavillon CHUL, 2705 boul Laurier, Québec, Canada G1V 4G2. manu.rangachari@crchudequebec.ulaval.ca
E-mail address: manu.rangachari@crchudequebec.ulaval.ca (M. Rangachari).

http://dx.doi.org/10.1016/j.msard.2015.10.005
2211-0348/

1. Introduction

Multiple sclerosis (MS) is a chronic central nervous system (CNS) disease characterized pathologically by inflammation, loss of myelin, and axonal loss. These pathological features translate into significant clinical disability and a highly variable and unpredictable disease course. There is therefore a need to develop readily accessible biomarkers that relate to disease evolution and outcomes and that enhance our understanding of specific disease processes in MS (Comabella and Montalban, 2014; Teunissen et al., 2005).

Cholesterol is as an essential component of cellular and myelin membranes, a cofactor for signalling molecules, and a precursor of steroid hormones, bile acids and vitamin D (Berg et al., 2002). Cholesterol homeostasis is compartmentalized, with only limited interaction between brain/CSF and circulation (Di Paolo and Kim, 2011). The first investigation into the role of cholesterol in the pathophysiology of MS was performed in 1926 (Poynder and Russell, 1926) – at a time when its presence in CSF was believed to reflect the "wasting of nerve structures" (Mott, 1910; reviewed in Plum, 1960). Subsequently, post-mortem data showed that esterification of free cholesterol is a characteristic of demyelination in MS white matter and spinal cord (Cumings, 1953, 1955; Shah and Johnson, 1980; Yu et al., 1982). Early research also showed a positive association between esterified cholesterol in CSF and greater disability in MS (Pedersen, 1974). More recently, the discovery of new forms of cholesterol and of markers of cholesterol turnover has opened up new avenues for research. For instance, associations between MS disease outcomes and levels of cholesterol precursors, oxysterols, and apolipoprotein (Apo) E in circulation and CSF have been reported (van de Kraats et al., 2014; Vuletic et al., 2014). Similarly, there are reports of associations between circulating lipoprotein-bound cholesterol and MS disease outcomes in MS, as well as correlation with risk factors for disease progression such as vitamin D deficiency and humoral responses to Epstein–Barr virus (Palavra et al., 2013; Weinstock-Guttman et al., 2011a, 2013a). This line of research is ever more pertinent with the recent publication of the MS-STAT study: a randomized, placebo-controlled trial (RCT) which showed that a high dose of the cholesterol-reducing medication simvastatin attenuated brain atrophy and disease progression among 140 patients with secondary progressive MS (SPMS) over 2 years (Chataway et al., 2014). Altogether, these data suggest that cholesterol and related molecules have the potential to be used clinically as biomarkers of treatment and disease outcomes in MS, and that they may represent potential new therapeutic targets. In order to further explore these putative associations, we conducted a systematic review of studies (dated 1983–2015) that examined cholesterol and markers of cholesterol turnover in circulation and/or CSF in relation to disease outcomes in MS.

2. Cholesterol synthesis and metabolism

The synthesis, transport and metabolism of cholesterol are complex, multi-step processes (outlined in Fig. 1) that give rise to a plethora of potential biomarkers. Cholesterol synthesis is initiated by the conversion of acetyl-coenzyme A (CoA) to mevalonate by HMG-CoA-reductase. Mevalonate is subsequently converted to lanosterol and then to cholesterol itself (Ginsberg, 1998). As it is largely water-insoluble, cholesterol is carried in the bloodstream bound to lipid transporters (lipoproteins), which require apolipoproteins (e.g. ApoA1, A2, B, D, and E) for their formation. ApoB is a major component of low density lipoprotein (LDL), intermediate density cholesterol (IDL) and very low density cholesterol (VLDL), and composes 95%, 60%, and 30% of their protein content, respectively (Ginsberg, 1998). LDL, IDL, and VLDL and ApoB are synthesized exclusively in the periphery and cannot pass through an intact blood-brain barrier (BBB; Carlsson et al., 1991; Di Paolo and Kim, 2011). ApoA1 and ApoA2 are major components of high-density lipoprotein (HDL), consisting of 70–80% and 10–15% of its protein mass, respectively (Ginsberg, 1998). Other minor components of HDL include ApoE and ApoD (Ferretti and Bachetti, 2011). HDL and its component apolipoproteins can be synthesized in the periphery, as well as in the brain, and small amounts of HDL can cross the BBB (Di Paolo and Kim, 2011; Ferretti and Bacchetti, 2011; Harr et al., 1996; Poirier et al., 1991).

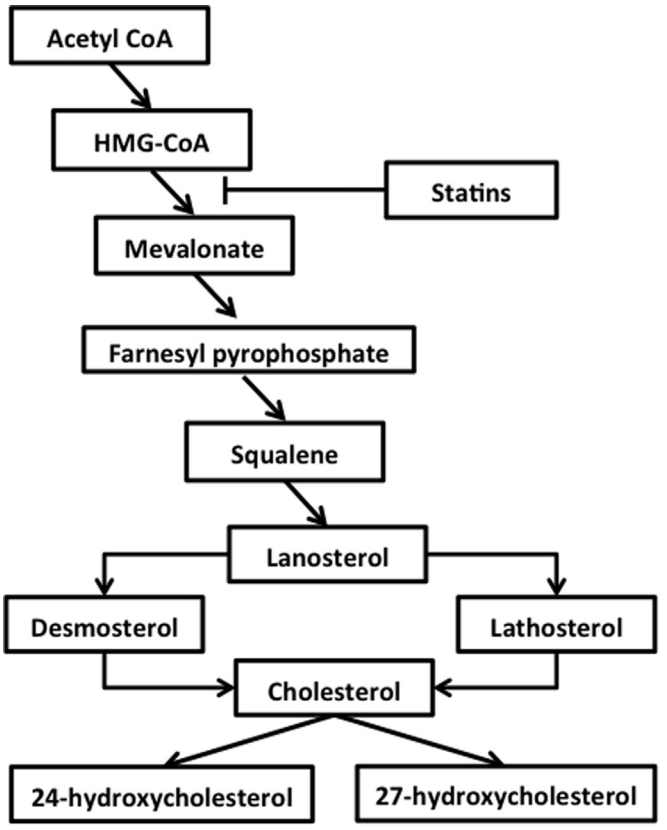

Fig. 1. Pathway of cholesterol synthesis and its metabolites. Cholesterol is the most prevalent steroid in mammals. Acetyl coenzyme A (Acetyl CoA) is converted to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) which is then converted to mevalonate. The latter reaction is inhibited by the statin class of drugs. Farnesyl pyrophosphate gives rise to several ubiquinone precursors, one of which is the cholesterol precursor squalene, which is cyclized to form lanosterol. The direct precursors of cholesterol are desmosterol and lathosterol. Oxidation of cholesterol leads to creation of the byproducts 24- and 27-hydroxycholesterol, amongst others. Multiple steps and enzymes are omitted for clarity.