Molecular and Cellular Endocrinology 368 (2013) 1–16

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

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

Review

Regulation of cholesterol homeostasis

Mariëtte Y.M. van der Wulp, Henkjan J. Verkade, Albert K. Groen *

Top Institute Food and Nutrition, Wageningen, The Netherlands
Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Beatrix Children's Hospital, Groningen University Institute for Drug Exploration, Center for Liver, Digestive and Metabolic Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

ARTICLE INFO

Article history:
Available online 19 June 2012

Keywords:
Cholesterol synthesis
Cholesterol absorption
Cholesterol excretion
Transintestinal cholesterol excretion
Reverse cholesterol transport

ABSTRACT

Hypercholesterolemia is an important risk factor for cardiovascular disease. It is caused by a disturbed balance between cholesterol secretion into the blood versus uptake. The pathways involved are regulated via a complex interplay of enzymes, transport proteins, transcription factors and non-coding RNA's. The last two decades insight into underlying mechanisms has increased vastly but there are still a lot of unknowns, particularly regarding intracellular cholesterol transport. After decades of concentration on the liver, in recent years the intestine has come into focus as an important control point in cholesterol homeostasis. This review will discuss current knowledge of cholesterol physiology, with emphasis on cholesterol absorption, cholesterol synthesis and fecal excretion, and new (possible) therapeutic options for hypercholesterolemia.

Contents

* Corresponding author at: Center for Liver, Digestive and Metabolic Diseases, Department of Pediatrics and Laboratory Medicine, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands, Tel.: +31 50 3632879; fax: +31 50 3611746.
E-mail address: a.k.groen@umcg.nl (A.K. Groen).

0303-7207/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mce.2012.06.007

1. Introduction

Cholesterol is of vital importance for vertebrate cell membrane structure and function (Maxfield and Tabas, 2005). Metabolites of cholesterol, such as bile salts (BS), steroid hormones and oxysterols, fulfill important biological functions (Rezen et al., 2011). It is obvious that adequate regulation of cholesterol homeostasis is essential. Hypercholesterolemia promotes atherosclerosis and thereby represents a major risk factor for cardiovascular disease (Kannel et al., 1979; Liu et al., 2006). The liver has been considered the major site of control in maintenance of cholesterol homeostasis (Dietschy et al., 1993). The liver facilitates clearance of (very) low density lipoprotein ((V)LDL) particles and cholesterol-containing chylomicron (CM) remnants, synthesizes cholesterol, synthesizes and secretes (nascent) high density lipoprotein (HDL) particles, secretes cholesterol and BS to bile and is involved in reverse cholesterol transport (RCT) (Glomset, 1970). RCT is classically defined as the process by which cholesterol from peripheral tissues is transported to the liver, followed by excretion via bile to feces in the form of neutral sterols and BS. In recent years, however, the importance of the intestine in many aspects of cholesterol physiology is increasingly recognized. The intestine has a major impact on cholesterol homeostasis at the level of cholesterol (re-)absorption, fecal excretion and *de novo* synthesis (Kruit et al., 2006). It has become apparent that, at least in mice, direct secretion of cholesterol from the blood compartment into the intestine, or transintestinal cholesterol excretion (TICE), plays a major role in disposal of cholesterol via the feces (van der Velde et al., 2010a). This review focuses on recent developments in research on the physiology of cholesterol homeostasis. In Section 1, we will summarize the transport of cholesterol through plasma in its different forms. Sections 2 and 3 will cover the process, measurement and inhibition of cholesterol synthesis and absorption, respectively.

Section 4 will discuss pathways of reverse cholesterol transport and finally section 5 will shortly describe the attempts that have been made to develop computational models of the complex processes involved in cholesterol homeostasis.

2. Transport of cholesterol through plasma

A plethora of epidemiological studies have unequivocally shown that increased plasma cholesterol levels are associated with cardiovascular disease risk. Interestingly this does not necessarily coincide with increased tissue cholesterol, but is probably caused by changes in rates of secretion and uptake of cholesterol (Osono et al., 1995). Cholesterol is a lipophilic molecule and is transported through blood in the form of lipoproteins. The type of lipoprotein is determined by its buoyant density and apoprotein composition, which act as emulsifying coating and target their metabolism. The physiology of lipoprotein metabolism has been reviewed extensively in the past and will therefore not be covered here (Tulenko and Sumner, 2002).

There are marked differences in lipoprotein metabolism between humans and rodents. For example, mice do not possess cholesterol-ester transport protein (CETP) and have an up to 40-

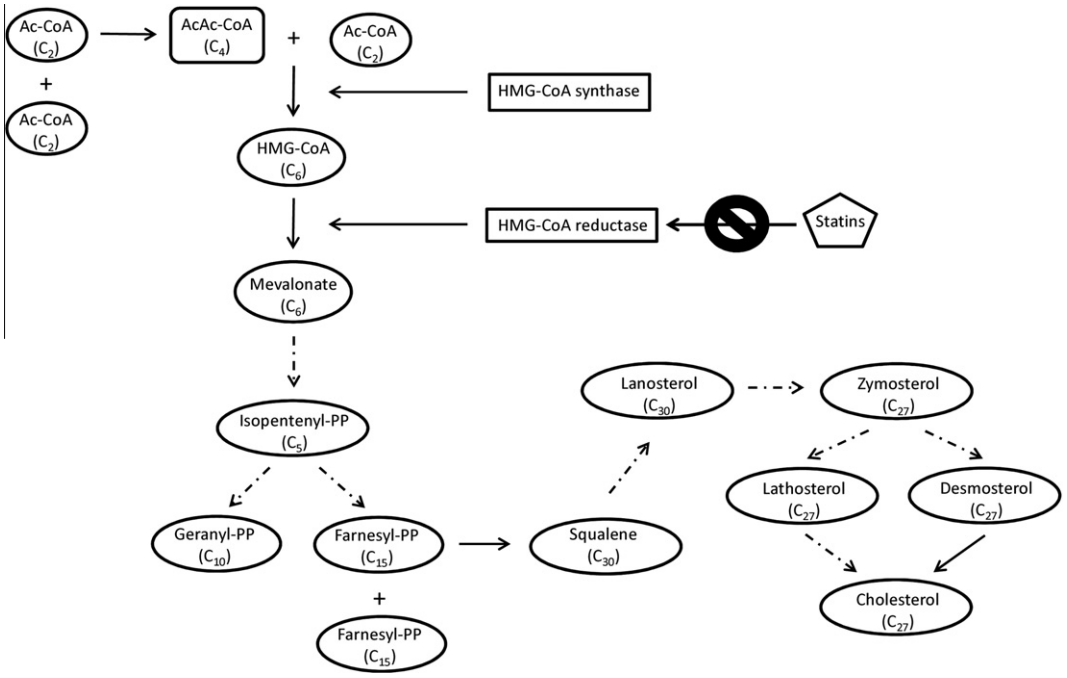

Fig. 1. Cholesterol biosynthesis pathway. Cholesterol is synthesized from its precursor unit acetyl-CoA (Ac-CoA). Two acetyl-CoAs are condensed, forming acetoacetyl-CoA (AcAc-CoA). AcAc-CoA and a third acetyl-CoA are converted to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) by the action of HMG-CoA synthase. HMG-CoA is converted to mevalonate by HMG-CoA reductase. Mevalonate is subsequently converted to an isoprenoid molecule, isopentenyl pyrophosphate (PP), with the concomitant loss of CO_2. Geranyl-PP and farnesyl-PP are produced from isopentenyl-PP. Two farnesyl-PP subunits are combined to form squalene. Squalene is converted to lanosterol and subsequently cholesterol via many intermediates, including zymosterol, desmosterol and lathosterol. Solid line: direct step. Dashed line: product is formed via intermediate steps.