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Review

New insights into the molecular actions of plant sterols and stanols in cholesterol metabolism

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Abstract

Plant sterols and stanols (phytosterols/phytostanols) are known to reduce serum low-density lipoprotein (LDL)-cholesterol level, and food products containing these plant compounds are widely used as a therapeutic dietary option to reduce plasma cholesterol and atherosclerotic risk. The cholesterol-lowering action of phytosterols/phytostanols is thought to occur, at least in part, through competition with dietary and biliary cholesterol for intestinal absorption in mixed micelles. However, recent evidence suggests that phytosterols/phytostanols may regulate proteins implicated in cholesterol metabolism both in enterocytes and hepatocytes. Important advances in the understanding of intestinal sterol absorption have provided potential molecular targets of phytosterols. An increased activity of ATP-binding cassette transporter A1 (ABCA1) and ABCG5/G8 heterodimer has been proposed as a mechanism underlying the hypocholesterolaemic effect of phytosterols. Conclusive studies using ABCA1 and ABCG5/G8-deficient mice have demonstrated that the phytosterol-mediated inhibition of intestinal cholesterol absorption is independent of these ATP-binding cassette (ABC) transporters. Other reports have proposed a phytosterol/phytostanol action on cholesterol esterification and lipoprotein assembly, cholesterol synthesis and apolipoprotein (apo) B100-containing lipoprotein removal. The accumulation of phytosterols in ABCG5/G8-deficient mice, which develop features of human sitosterolaemia, disrupts cholesterol homeostasis by affecting sterol regulatory element-binding protein (SREBP)-2 processing and liver X receptor (LXR) regulatory pathways. This article reviews the progress to date in studying these effects of phytosterols/phytostanols and the molecular mechanisms involved.

Keywords: Intestine; Phytosterols; Phytostanols; Molecular mechanisms; Cholesterol absorption

Contents

Abbreviations: ACAT, acyl-CoA:cholesterol acyltransferase; ABC, adenosine triphosphate-binding cassette transporter; ANXA2–CAV1, annexin 2/caveolin 1; apo, apolipoprotein; CVD, cardiovascular disease; CYP7A1, cytochrome P450 family 7 subfamily A polypeptide 1; FPPS, farnesyl pyrophosphate synthase; FC, free cholesterol; HDL, high-density lipoprotein; HMG-CoA, hydroxymethylglutaryl coenzyme A; IDL, intermediate-density lipoprotein; LXR, liver X receptor; LDL, low-density lipoprotein; LDLr, LDL receptor; LRP, LDL-related protein; NPC1L1, Niemann-Pick C1-like 1; PPAR, peroxisome-proliferator-activated receptor; RXR, retinoid X receptor; SR-BI, scavenger receptor class-BI; SREBP, sterol regulatory element-binding protein; VLDL, very low-density lipoprotein.

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1. Introduction

Whole-body cholesterol homeostasis requires precise regulation of processes that control *de novo* cholesterogenesis, cholesterol absorption and cholesterol excretion. An imbalance of these processes may lead to elevated plasma cholesterol concentrations, cholesterol accumulation in different tissues and increased risk of cardiovascular diseases (CVD). Wide clinical and epidemiological evidence supports a direct link between high plasma cholesterol, particularly that of low-density lipoprotein (LDL), and atherosclerotic CVD risk [1]. The management of hypercholesterolaemia normally involves hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) [2]. However, other strategies, such as the inhibition of intestinal cholesterol absorption by ezetimibe, have been pursued [3]. Similarly, phytosterols/phytostanols have long been known to lower plasma LDL cholesterol levels by reducing intestinal cholesterol absorption, while not significantly altering high-density lipoprotein (HDL)-cholesterol or triglycerides [4,5]. Phytosterols are plant-specific phytochemicals that are essential components of cell membranes. Phytosterols and their saturated forms (saturation of the double bond at carbon-5), termed phytostanols, are structurally related to cholesterol, although they differ in the complexity of their side chain which is attached to the steroid ring [6]. These compounds cannot be synthesised by humans and, therefore, always originate from the diet. Lipid-rich plant foods such as nuts, legumes and seeds contain a relatively high amount of phytosterols [7]. Over 40 phytosterols have been identified; of these, campesterol, stigmasterol and β-sitosterol account for more than 95% of total phytosterol dietary intake (Fig. 1). Phytostanols are not abundant in nature. Minor sterols, including brassicasterols and avenasterols, can represent a small percent of sterols in particular foods such as pistachio and ginseng oils [7,8]. The presence of phytosterols in the Western diet is almost equal to that of cholesterol (∼400 mg/day) and increases in vegetarian diets. Phytosterols are poorly absorbed in the intestine (0.4–3.5%), while phytostanol absorption (0.02–0.3%) is even lower [9,10]. This contrasts with intestinal cholesterol absorption that ranges from 35 to 70% [9,11]. Sitosterolaemia is a rare autosomal recessively inherited disease caused by mutations affecting ABCG5 and ABCG8 and characterised by elevated plasma and tissue phytosterol concentrations (see Section 3) [12]. In contrast to healthy subjects in whom total plasma phytosterols are less than 1 mg/dL, patients with sitosterolaemia have plasma phytosterol levels ranging from 12 to 40 mg/dL [12]. Furthermore, phytosterol absorption and plasma phytosterol concentrations are strongly determined by genetic factors [13]. There is wide variability associated with apoE phenotypes, gender and ATP-binding cassette (ABC) transporter polymorphisms, among others [14]. Further details on the contribution of all these factors to plasma phytosterol absorption can be obtained from several recent reviews [13–15].

The cholesterol-lowering effect of phytosterols/phytostanols has been demonstrated in both humans and animals [5,16–19] and existing guidelines for cholesterol management of the National Cholesterol Education Program (NCEP) encouraged phytosterol/phytostanol consumption as a therapeutic dietary option to lower LDL cholesterol [20]. A daily intake of 2–2.5 g of this functional food results in an average reduction in LDL cholesterol of up to 14% [4,16].

This review analyses the results of recent studies addressing the molecular mechanisms by which phytosterols/phytostanols influence cholesterol homeostasis.

2. Cholesterol-lowering mechanism of action of phytosterols/phytostanols

Competition between phytosterols/phytostanols and intestinal cholesterol for incorporation into mixed micelles has been proposed as the mechanism underlying the hypocholesterolaemic effect of these plant compounds, taking into account that phytosterols/phytostanols are more hydrophobic and have higher affinity for micelles than cholesterol [21]. However, one of the potential explanations for this competition, the cocrystallisation of cholesterol and phytosterols/phytostanols in the intestinal lumen, has been shown to be unlikely [22]. Further, other studies have suggested that phytosterols/phytostanols may exert an unknown molecular action inside enterocytes and hepatocytes, since phytosterols/phytostanols do not need to be present in the intestinal lumen simultaneously with cholesterol to inhibit its absorption [5]. This reinforces the idea that the reduced insertion of cholesterol into micelles is not the only mechanism of phytosterol/phytostanol-induced cholesterol absorption inhibition [23]. In line with this, several studies have provided considerable evidence for a hypocholesterolaemic action of phytosterols/phytostanols other