STEROLS, ESPECIALLY CHOLESTEROL AND PHYTOSTEROLS, IN HUMAN METABOLISM

M. Vecka, A Žák, E. Tvrzická
4th Department of Medicine, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

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Contents

Summary

Sterols, important members of the metabolic pathways and structural motifs of the eucaryotic cells, are mostly referred to in the common sense as cholesterol and its metabolites. Apart from cholesterol, several other sterols can be found in human plasma. Many of these sterols are derived either from endogenous biosynthesis of cholesterol or they come from dietary sources and are mainly of plant origin, called phytosterols. Both green plants and vertebrates use acetyl-CoA for the synthesis of sterols via several reaction steps with a remarkable level of conservativeness. The striking feature of all sterols is the ability of the core tetracyclic system to resist all enzymatic activities. Plenty of derived compounds are used in the membrane structures or as signal molecules, which modulate the activities of biochemical pathways. Steroid hormones contribute to, for example, the regulation of gluconeogenesis (glucocorticoids), sodium-potassium balance (mineralo-corticoids) and reproductive functions and differentiation of the sexes (sex steroids) among several other functions. In animals, cholesterol is converted to bile acids to serve as emulsifying agents of lipids in their digestion. Such a broad abundance of compounds and several modes of action further emphasizes the importance of sophisticated systems regulating cholesterol homeodynamics, i.e. the integration of the absorption, intracellular uptake and endogenous synthesis which take place in parallel in humans and non-animals.

1. Introduction

The first sterol molecule appeared on the Earth more than 2.7 billion years ago, when oxygen molecules needed for squalene cyclization became available. Since then, many life forms have evolved, all of them taking advantage of sterol molecules. Biosynthetic pathways in vertebrates serve to produce mainly cholesterol, whereas the green plants also synthesize other sterols.

The most important biosynthetic precursors of cholesterol include lathosterol, desmosterol, 7-dehydrocholesterol and lanosterol, which is commonly used for the evaluation of cholesterol biosynthesis. In animal tissues, sterols (mainly cholesterol) are present in both free and esterified form. Cholesterol contributes to the structure of membranes. In the human brain, cholesterol is one of the most abundant lipids accounting for 10-20% of its dry weight. Cholesterol serves as the starting point and substrate in the biosynthesis of several hormones (like gluco- and mineralo-corticoids and sex steroids (see *Endocrinology*) as well as of the bile acids (see *Enzymes of Digestion*). The hormonal steroids contribute to the regulation of many functions. Bile acids are important cofactors in the digestion and absorption of lipids.

The pattern of phytosterols is much broader, but from the human nutritional point of view, only some of them are efficiently absorbed in the intestine and appear in plasma. Examples are β-sitosterol and campesterol. In higher plants, phytosterol molecules occur either on free or in ester form, β-D-glycosides (sterolins) and their 6-O´-esters. Glycosides normally comprise one tenth of total phytosterol content. Phytosterols serve important functions in the gut as reducing agents of cholesterol absorption.

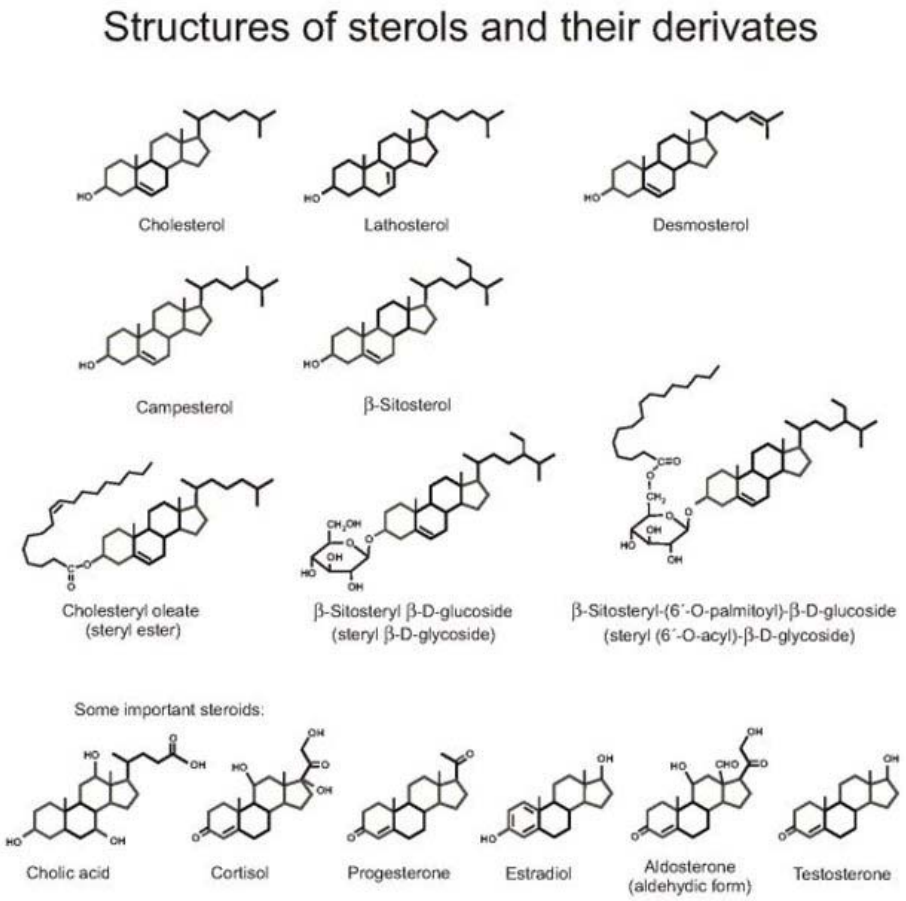

Figure 1. Structures of sterols and their derivatives.

In this chapter, the main emphasis has been given to cholesterol and to those phytosterols, which are found in human plasma. The hormone derivatives of cholesterol are only briefly mentioned, as are the bile acids (see Figure 1).

2. Nutrition and Digestion of Sterols

2.1. Sterols in the Diet

2.1.1. Cholesterol

The dietary intake and cellular demands of cholesterol vary widely both during development and in different nutritional states. Growing neuronal tissue has the highest cholesterol requirements. Almost one quarter of body cholesterol is hidden in our brain. The human newborn brain weighs 11-14% of body weight, but the brain tissue consumes some 75% of the total energy. A part of this energy is used for the synthesis

of brain cholesterol, which forms usually 20-30% of the lipid portion of brain tissue. Almost all sterol in brain is unesterified cholesterol, although small amount of desmosterol has been found in young humans. In newborns, the so-called Bloch (desmosterol) biosynthetic pathway predominates rather than the Kandutsch-Russel (lathosterol) pathway, which is used in adults (see Figure 2)

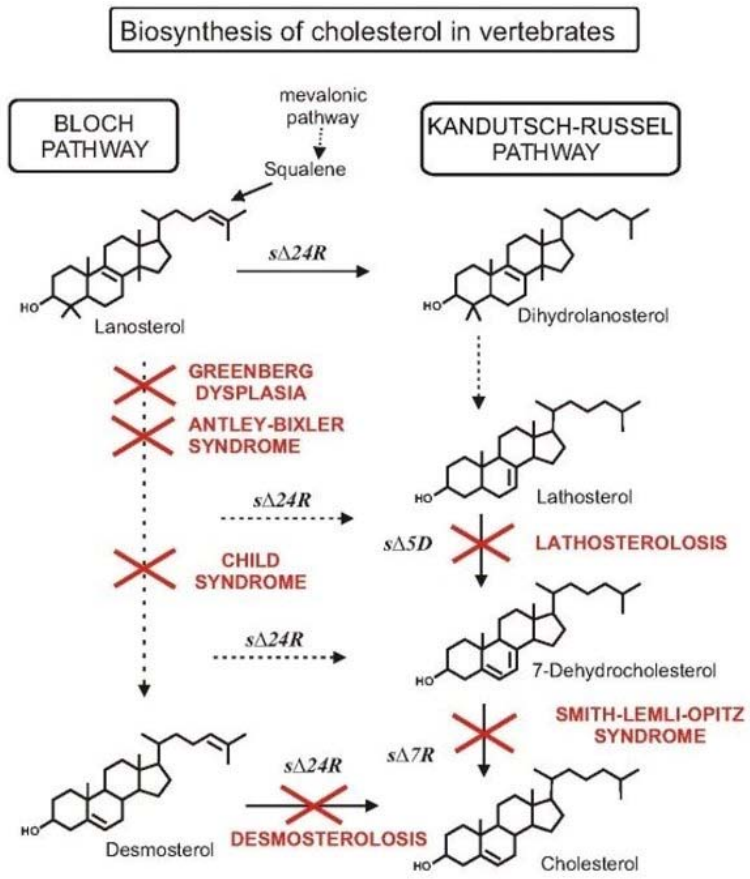

Figure 2. The pathways of cholesterol biosynthesis in vertebrates and the genetic disorders in these two different routes.

Evolution of humankind probably involved periods demanding rather vegetarian behavior, but in the long run man developed into a hunter-gatherer. With the invention of agriculture, the diet has changed and maybe 90% of food was derived from plants; this probably caused a decline in human stature. The industrial revolution and better food supply has again increased the stature. This development of industry has allowed an increase of living standards, which has also meant a greater availability of fat. That promoted the frying technique in the processing of the food, and offered chances to compose the food from nutrients at one's own will.

At present, one part of our diet is vegetable-derived with negligible cholesterol content, and the other part is cholesterol-rich animal food. The uncertain balance of these two types of diet is reflected in the fact that in most healthy individuals, endogenous synthesis of cholesterol adjusts in the liver to the level of dietary cholesterol intake. For example, the daily intake of cholesterol is low in populations consuming a vegetable rich diet, such as lacto-ovo-vegetarians (60 mg d^{-1}), whereas omnivores have an order of

magnitude more cholesterol in their food (perhaps 500 mg d^{-1}). It has been estimated that the Paleolithic diet contained perhaps the same amount of cholesterol as is consumed at present in the Western diet [480 mg a day (mg d^{-1})], but it was in connection with the high content of animal proteins and unsaturated fatty acids, with much less carbohydrate in the diet.

Not only dietary intakes of cholesterol, but also plasma levels are highly variable in various populations. Free-living non-human primates and ancient foraging societies have probably had similar mean serum cholesterol levels (perhaps 3.25 mmol L^{-1}). This is far below the present recommended limit (5.2 mmol L^{-1}). As many individuals even with serum cholesterol levels below this recommended limit develop coronary artery disease (CAD) and consequently get myocardial infarctions, this limit value continues to be discussed and probably will be re-evaluated. The relatively weak association between dietary cholesterol and CAD and the relatively strong association between the serum cholesterol and saturated and trans fatty acids has shifted the nutritionists' view from eggs to fatty acids. It is known that a change in intake of fatty acids (and dietary cholesterol) can predict a change in one's plasma cholesterol concentration.

2.1.2. Non-cholesterol Sterols

Dietary intake of phytosterols averages 200 to 500 mg d^{-1} depending on the type of diet. The most important sources include vegetable oils (corn, soya bean) and barley, cashew, peanuts, sunflower as well as sesame seeds, and whole meal. Herbivore mollusks and crabs are rich in phytosterols, too. The absorption of phytosterols is promoted by the presence of a double bond. This means that phytosterols are usually better absorbed than their saturated analogues, phytostanols. Furthermore, the nature of the side chain plays a role—the more complicated the side chain is, the less phytosterol passes into the enterocytes in the gut. The most easily absorbed phytosterol is thus campesterol, which is absorbed with some 5% efficiency, in contrast to β-sitosterol, which is absorbed only with 2% efficiency.

Possible dietary sources of cholesterol precursors include animal products with high content of cholesterol—eggs or sheep milk with approximately 1 mg of lathosterol in 100 mg cholesterol. Therefore studies using these precursors as markers of cholesterol biosynthesis should be controlled for cholesterol input. Moreover, sheep milk contains some 2 mg lanosterol and 0.1 mg desmosterol in 100 mg cholesterol.

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Biographical Sketches

Marek Vecka, MSc., was born in Domažlice, Czech Republic, in 1976. After obtaining his BSc. degree in chemistry (1997) and MSc. degree in biochemistry (1999) from the Faculty of Science in Charles University in Prague, he passed a doctoral examination (2001) in biochemistry and pathobiochemistry. He is currently a postgradual student of the 1st Faculty of Medicine in Charles University, Prague, with the position of research specialist. His major areas of interest include sterol and fatty acid metabolism. He is the author and co-author of 25 publications and more than 40 scientific presentations.

Aleš Žák, MD, DSc, Assoc. prof. finished his studies at the School of General Medicine (now the 1st School of Medicine), Charles University, Prague, in 1975. He was approved as an assistant professor (1982) and associate professor of medicine (1999), a PhD degree received in 1995 and a DSc in 2001 from the 1st School of Medicine, Prague. He has been on the staff of the 4th Department of Medicine, 1st School of Medicine, Charles University in Prague as an assistant registrar (1976 - 1982), registrar (1982 - 1985), head of the biochemical laboratory (1985 – 1998), head of ICU (1995), and a head of Department (2001 - present). His research projects and teaching activities cover studies on lipid transport disorders with respect to effects of essential fatty acids and with respect to atherosclerotic vascular disease, changes in cholesterol and fatty acid metabolism in protein-energetic malnutrition and teaching students of the 1st School of Medicine (internal medicine, pathobiochemistry). Assoc. prof. A. Žák is an author and co-author of 150 publications and more than 200 scientific presentations on various congresses and symposia.

RNDr. Eva Tvrzická, PhD, Assistant prof. After having finished studies on the Faculty of Science, Charles University, Prague (1966) and completing PhD studies (1974), Eva Tvrzická was employed as a chemist-specialist. At present, she occupies the position of senior research scientist, 1st Faculty of Medicine, Research Angiologic Laboratory, that is focused on the application of chromatographic methods in lipid and lipoprotein research, studies on lipid metabolism under different pathological

conditions, serum and tissue lipids under various pathological states, risk factors of atherosclerosis, and new methodologies for the studying of lipids as well as lipoproteins. She is the author and co-author of more than 120 publications and more than 150 scientific presentations.