ABSTRACT

This thesis summarizes current data about cholesterol metabolism and its regulation in the liver.

First part describes cholesterol transport among tissues by lipoproteins.

Second part of this work deals with description of metabolic pathways of cholesterol conversion – how the cells obtain and metabolise cholesterol. Almost all cells can synthesize cholesterol or take it up from the circulation. The cells dispose of abundant cholesterol by several mechanisms – they convert cholesterol to cholesteryl esters that can be stored in lipid droplets; they turn cholesterol into oxysterols that can escape easier from the cell; or they export cholesterol through ATP-binding cassette (ABC) transporters. Specialized tissues (adrenal, gonads) transform cholesterol to steroid hormones. However, only the liver can remove cholesterol from the body in physiologically significant amount – it secretes cholesterol into the bile either directly or after conversion to bile acids.

Third section deals with regulation of cholesterol metabolism in hepatocyte. Three transcription factors – sterol regulatory element binding protein (SREBP), liver X receptor (LXR), and farnesoid X receptor (FXR) – play the main role in regulation. Their activities are determined by concentration of cellular cholesterol or its metabolites – oxysterols and bile acids. Inactive SREBP resides in the endoplasmic reticulum; if cholesterol concentration in the cell decreases, SREBP is released and regulates transcription of genes involved in cholesterol uptake and biosynthesis. If cholesterol is abundant, oxysterols are produced in mitochondria and serve as the ligands for LXR that activates the expression of genes which induce cholesterol eflux (ABC). FXR responds to the increase of bile acid concentration by inhibition of their synthesis and thus influences the metabolic conversion of cholesterol.

Keywords:

Cholesterol, hepatocyte, active cholesterol, oxysterol, bile acid, SREBP, LXR, FXR