ABSTRACT

The aim of the theses is to characterize the mechanism that participate in the regulation of activity of cholesterol 7α-hydroxylase (CYP7A1) – the key enzyme of classical pathway of bile acids synthesis.

The function and metabolism of cholesterol and bile acid is described at the beginning. Cholesterol is a substrate for CYP7A1 and bile acids are produced in the reaction catalyzed by the enzyme.

The other parth of theses is dedicated to feedback inhibition of CYP7A1 by bile acids and describes particular regulatory pathways involved. The crucial factors for *CYP7A1* expression are bile acids response elements (BARE) in the promoter of CYP7A1 gene. Central role is played by farnesoid X receptor activated by bile salts that induces expression of protein called small heterodimer partner (SHP) in the liver. SHP interacts with trancription factors in BARE and inhibits *CYP7A1* transcription. In the instestine FXR induces fibroblast growth factor 19 (FGF19) that activates signalling pathways leading to inhibition of CYP7A1 in the liver. The activity of CYP7A1 can be regulated independently of FXR – there is a role for hormones (insulin, glucagon), glucose, activation of proinflammatory cytokines and other nuclear receptors (pregnane X receptor and vitamin D receptor), that participate in protection of the liver against toxic properties of bile salts.

The CYP7A1 activity plays a role in maintaining cholesterolemia. In mice and rats, *CYP7A1* expression is induced by intermediary products of cholesterol metabolism (oxysterols) that activate liver X receptor (LXRα) and excess cholesterol is metabolized into BA. In humans, such a mechanism is not employed but the promoter polymorphism of the *CYP7A1*, that affects the cholesterol concentration response to dietary cholesterol, was identified.

Key words:

Cholesterol 7α-hydroxylase, liver, cholesterol, bile acids, nuclear receptors, cytokines, farnesoid X receptor, liver X receptor, polymorphism