Molecular Aspects of Medicine 56 (2017) 90–100

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

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

Bile acids and gestation

Saraid McIlvride, Peter H. Dixon, Catherine Williamson*

Division of Women's Health, King's College London, Guy's Campus, Hodgkin Building, SE1 1UL, London, United Kingdom

ARTICLE INFO

Article history:
Received 16 January 2017
Received in revised form
27 March 2017
Accepted 8 May 2017
Available online 18 May 2017

Keywords:
Bile acids
Pregnancy
Fetus
Placenta
Metabolism
Intrahepatic cholestasis of pregnancy

ABSTRACT

There are numerous profound maternal physiological changes that occur from conception onwards and adapt throughout gestation in order to support a healthy pregnancy. By the time of late gestation, when circulating pregnancy hormones are at their highest concentrations, maternal adaptations include relative hyperlipidemia, hypercholanemia and insulin resistance. Bile acids have now been established as key regulators of metabolism, and their role in gestational changes in metabolism is becoming apparent. Bile acid homeostasis is tightly regulated by the nuclear receptor FXR, which has been shown to have reduced activity during pregnancy. This review focuses on the gestational alterations in bile acid homeostasis that occur in normal pregnancy, which in some women can become pathological, leading to the development of intrahepatic cholestasis of pregnancy. As well as their important role in maternal metabolic health, we will review bile acid metabolism in the feto-placental unit.

1. Physiological changes during pregnancy

During pregnancy, the mother's body undergoes dramatic anatomical and physiological changes. Every organ system in the body needs to adapt in order to support a healthy pregnancy. For example, maternal plasma volume increases by 50%, the normal ranges for many haematological and biochemical indices change, and there is an increased requirement for iron, folate and vitamin B12. From early in pregnancy there are changes in the cardiovascular system, such as increased cardiac output and decreased systemic vascular resistance. There are also significant increases in basal metabolic rate and oxygen consumption (Soma-Pillay et al., 2016).

Maternal metabolism adapts as pregnancy progresses to accommodate the changing needs of the growing fetus, a key feature of which is altered glucose metabolism. Throughout gestation there are alterations in insulin sensitivity, pancreatic beta cell function and hepatic gluconeogenesis which facilitate shunting of glucose and nutrients towards the developing fetus. In early pregnancy, fasting blood glucose levels are unchanged or slightly lower than outside of pregnancy (Angueira et al., 2015). During the third trimester, there is an increased demand for glucose by the feto-placental unit and fasting blood glucose levels are reduced slightly further (Angueira et al., 2015). This fall in blood glucose is accompanied by enhanced insulin sensitivity in early pregnancy; however during the second and third trimesters there is marked insulin resistance (Newbern and Freemark, 2011). These changes in glucose homeostasis support the diversion of glucose towards the fetus. Progressively increasing levels of several hormones, in particular progesterone, cortisol and placentally-derived human growth hormone, lead to peripheral insulin resistance in muscle and adipose tissue by interfering with insulin receptor signalling (Newbern and Freemark, 2011). At the same time, it is necessary to maintain adequate maternal nutrition, and therefore maternal free fatty acid levels and hepatic gluconeogenesis are increased (Angueira et al., 2015).

Lipid metabolism is also affected, due in part to the changes in insulin sensitivity, and the progressive rise in estrogen and placental hormones. During early pregnancy (i.e. the first trimester), there is an accumulation of body fat due to hyperphagia, enhanced lipogenesis and increased lipoprotein lipase (LPL) activity, which promotes the uptake of fatty acids and glycerol into adipose tissue (Herrera et al., 2006). In the second and third trimesters, when insulin resistance has developed, there is enhanced lipolysis to utilise stored lipid and promote transfer of nutrients to the feto-placental unit (Butte, 2000).

Another notable feature of metabolic adaptations during pregnancy is a gradual increase in serum bile acid levels. While in most women this increase is moderate enough to remain within normal

* Corresponding author. 2.33W Hodgkin Building, King's College London, Guy's Campus, London, SE1 1UL, United Kingdom.
E-mail address: catherine.williamson@kcl.ac.uk (C. Williamson).

http://dx.doi.org/10.1016/j.mam.2017.05.003
0098-2997/

reference ranges, a subset of women develop intrahepatic cholestasis of pregnancy (ICP), a pregnancy-specific disease which is associated with adverse fetal outcomes including stillbirth. Therefore, regulation of bile acid metabolism during gestation is of key importance in maintaining a healthy pregnancy.

2. Bile acids in pregnancy

2.1. Bile acid homeostasis

Bile acids are synthesized in the liver from cholesterol. A key function of bile acids is to promote excretion of hydrophobic compounds and to facilitate the absorption of fat. However, they also act as metabolic signalling molecules, acting through a number of specific pathways. Due to their detergent properties, high concentrations of bile acids are toxic to cells, and therefore bile acid levels must be tightly regulated. There are two main pathways for bile acid synthesis: the classical pathway and the alternative pathway. The classical pathway is the dominant pathway in adults and results in the production of the primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA). This pathway involves at least 17 separate steps, including cytochrome P450 enzymes, CYP7A1, (the rate-limiting enzyme), CYP8B1 and CYP27A1. In the alternative pathway, extrahepatic CYP27A1 converts cholesterol to 27-hydroxycholesterol, which is then taken up by the liver and primarily converted to CDCA. Prior to export from the liver, bile acids are conjugated with taurine or glycine (approximately 1:3) to become bile salts, thereby making them more hydrophilic, less cytotoxic.

Bile is composed of bile salts, phospholipids and cholesterol. Due to their hydrophilicity, bile salts require transmembrane transporters to cross the canalicular membrane of the hepatocyte and enter bile canaliculi. The majority of bile salts are secreted into the bile canaliculi by the bile salt export pump (BSEP; *ABCB11*) (Kullak-Ublick et al., 2000). BSEP activity is thought to be the rate-limiting step in the clearance of bile acids from the serum. Phosphatidylcholine is transported via the multidrug resistance 3 protein (MDR3; *ABCB4*) (Oude Elferink and Paulusma, 2007), allowing the formation of mixed micelles within the bile canaliculus. Cholesterol is transported into the canaliculi by the ATP-binding cassette (ABC) transporters G5/G8 heterodimer (Graf et al., 2003). Multidrug resistance-associated protein 2 (MRP2; *ABCC2*) and multidrug resistance protein 1 (MDR1; *ABCB1*) are additional key transporters present on the canalicular membrane (Nies and Keppler, 2007; Stieger and Meier, 2011). Alternative transporters multidrug resistance-associated protein 3 (MRP3; *ABCC3*) and 4 (MRP4; *ABCC4*) are expressed at very low levels on the basolateral membrane under normal conditions, but are upregulated in cholestasis (Denk et al., 2004; Donner and Keppler, 2001).

Upon ingestion of food, the peptide hormone cholecystokinin (CCK) is secreted from the enteroendocrine cells of the duodenum. CCK induces gallbladder contraction, causing bile to be released into the intestine, where bile salts facilitate the absorption of dietary fats and fat-soluble vitamins. The majority of bile salts are taken up in the distal ileum by the apical sodium-dependent bile acid transporter (ASBT; *SLC10A2*), also known as ileal bile acid transporter (IBAT; Stieger and Meier, 2011). Approximately 5% of bile salts are not reabsorbed and are instead deconjugated by gut flora, then converted into the secondary bile acids, deoxycholic acid (DCA) and lithocholic acid (LCA). Secondary bile acids are then passively reabsorbed in the colon or eliminated via feces. Reabsorbed primary and secondary bile acids are exported into the enterohepatic circulation by the heterodimeric organic solute transporter alpha-beta (OSTα/β; *SLC51A/B*) present on the basolateral membrane of ileal epithelial cells (Ballatori et al., 2009). The bile acids are transported back to the liver where they are taken up into the hepatocytes by the Na^+-taurocholate co-transporting polypeptide (NTCP; *SLC10A1*) or organic anion transporting polypeptides (OATPs, also known as SLCOs) (Meier and Stieger, 2002).

Key genes which encode proteins involved in bile acid synthesis, metabolism and transport are under transcriptional regulation of the nuclear receptor, farnesoid X receptor (FXR; *NR1H4;* see Fig. 1). FXR is predominantly activated by primary bile acids, thereby regulating their own synthesis and metabolism. FXR is largely expressed in the liver, intestine, kidneys and adrenal glands. In the liver, bile acids activate FXR which then upregulates the expression of small heterodimer protein (SHP; *NR0B2*). SHP represses the expression of CYP7A1 and NTCP, thereby reducing hepatic uptake of bile acids. FXR also induces expression of BSEP and MDR3 to promote efflux of bile acids and phosphatidylcholine into the canaliculus (Kalaany and Mangelsdorf, 2006). Together these pathways work to protect the hepatocytes from toxic levels of bile acids. FXR also functions in the distal ileum, where its activation induces the expression of fibroblast growth factor 19 (FGF19/FGF15 in mice), SHP, the transporters OSTα/β and ileal bile acid binding protein (IBABP; *FABP6*). FGF19 is then released into the enterohepatic circulation where it feeds back to the liver and activates a cell surface receptor complex, consisting of a tyrosine kinase receptor FGF receptor 4 (FGFR4), and βKlotho (*KLB*), a single transmembrane protein (Lin et al., 2007). This causes repression of the transcription of CYP7A1, thereby downregulating bile acid synthesis (Kliewer and Mangelsdorf, 2015). As well as maintaining bile acid homeostasis, there is evidence that FXR is also involved in triglyceride and glucose metabolism (Kalaany and Mangelsdorf, 2006).

Bile acids are also ligands for the membrane Takeda G-protein receptor 5 (TGR5; *GPBAR1*). TGR5 is widely expressed, particularly in the gastrointestinal tract, and accordingly has a higher affinity for secondary bile acids (Kawamata et al., 2003). Although TGR5 protein has not been detected in hepatocytes, it has been localised to the biliary tree, gallbladder epithelia and cholangiocytes (Keitel and Haussinger, 2011; Keitel et al., 2010). In line with this, it is thought that TGR5 has a role in gallbladder relaxation and filling (Lavoie et al., 2010). Similar to FXR, TGR5 has been implicated in a diverse range of processes, including inflammation, energy expenditure and insulin secretion (Duboc et al., 2014).

2.2. Gestational changes in bile acid metabolism

2.2.1. Serum bile acid levels

Several studies provide evidence that during normal pregnancy, women develop sub-clinical cholestasis (Lunzer et al., 1986; Pascual et al., 2002). The majority of studies investigating bile acids during pregnancy show a progressive rise in serum bile acids with advancing gestation, with primary bile acids showing the highest increase. However, there is some disagreement over whether CA or CDCA is predominant in serum of pregnant women, with some studies reporting higher levels of CA (Carter, 1991; Fulton et al., 1983; Laatikainen and Hesso, 1975; Laatikainen et al., 1978; Lunzer et al., 1986; Sjovall and Sjovall, 1966) and others showing higher levels of CDCA (Heikkinen, 1983; Heikkinen et al., 1981). This inconsistency could arise from different measurement techniques or time-point of measurement in pregnancy. Several studies also report that conjugated bile acids are higher in serum of pregnant women (Brites, 2002; Castano et al., 2006; Fulton et al., 1983; Simcock and Forster, 1967), in particular there is an increase in taurine conjugates (Castano et al., 2006).

2.2.2. Gestational factors affecting bile acid homeostasis

The primary underlying factor responsible for the increase in