The role of bile acids in metabolic regulation

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Abstract

Bile acids (BA), long believed to only have lipid-digestive functions, have emerged as novel metabolic modulators. They have important endocrine effects through multiple cytoplasmic as well as nuclear receptors in various organs and tissues. BA affect multiple functions to control energy homeostasis, as well as glucose and lipid metabolism, predominantly by activating the nuclear farnesoid X receptor and the cytoplasmic G protein-coupled BA receptor TGR5 in a variety of tissues. However, BA also are aimed at many other cellular targets in a wide array of organs and cell compartments. Their role in the pathogenesis of diabetes, obesity and other 'diseases of civilization' becomes even more clear. They also interact with the gut microbiome, with important clinical implications, further extending the complexity of their biological functions. Therefore, it is not surprising that BA metabolism is substantially modulated by bariatric surgery, a phenomenon contributing favorably to the therapeutic effects of these surgical procedures. Based on these data, several therapeutic approaches to ameliorate obesity and diabetes have been proposed to affect the cellular targets of BA.

Key Words
- bile acids
- diabetes
- obesity
- energy homeostasis
- bariatric surgery

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Introduction

Bile acids (BA), which for decades were considered to only be involved in lipid digestion in the intestinal lumen and cholesterol solubilization in the bile, now seem to have pleiotropic effects: contributing to the homeostasis of lipids, glucose and other metabolic substrates (Li & Chiang 2014, Qi *et al.* 2015), affecting immune system functions (Sipka & Bruckner 2014) as well as gut microbiome composition (Ridlon *et al.* 2014). By binding to multiple cytoplasmic as well as nuclear receptors in various organs and tissues, they act as real hormones. Based on these facts, a paradigm for BA endocrine functions has recently been postulated (Houten *et al.* 2006).

Bile acid metabolism

BA are amphiphilic molecules derived from cholesterol in the hepatocytes. The principal metabolic changes are comprised of shortening of the cholesterol side chain plus hydroxylation of the core of the molecule at specific carbon atoms, forming the primary BA, cholic acid and chenodeoxycholic acid respectively (Hofmann 1984). These primary BA, after conjugation with glycine or taurine in the liver, are actively secreted into the bile via the bile salt export pump (BSEP, ABCB11, OMIM *603201). The BA pool in the human body is maintained by the efficient enterohepatic circulation (Hofmann 1984), preserving as much as 95% of conjugated BA. The active reabsorption of conjugated BA occurs in the distal ileum through the ASBT (also known as ISBT/IBAT/NTCP2, OMIM *601295) (Modica *et al.* 2010), and is profoundly deteriorated by inflammatory conditions affecting the ileal mucosa, such as in Crohn's disease (Lenicek *et al.* 2011, Vitek 2015). Unconjugated BA, formed after glycine/taurine hydrolysis by intestinal bacteria, can also

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be absorbed by passive diffusion from both the small and large intestine; however, their transport is much less effective via this route. The so-called 'BA gut–liver axis' is regulated by the farnesoid X receptor (FXR), the intracellular BA sensor. In the ileocytes, FXR controls for BA uptake, their intracellular trafficking as well as BA basolateral efflux (mediated by organic solute transporters α/β (OSTα/β)) (Zwicker & Agellon 2013). Simultaneously, ileal enterocytes, upon stimulation of FXR with BA, also secrete FGF19, which downregulates BA synthesis in the hepatocytes (Holt *et al.* 2003). However, FGF19 secreted from the small intestine in response to feeding also has insulin-like functions, whereas FGF21, a counterpart to FGF19, secreted from the liver in response to prolonged fasting, has glucagon-like effects (Potthoff *et al.* 2012). In fact, while insulin/glucagon serve as immediately acting fed-state and fasted-state hormones, FGF19 and FGF21 can be considered late-acting hormones (Potthoff *et al.* 2012). Interestingly, when administered in pharmacological doses, both FGF19 and FGF21 have insulin-sensitizing and hypolipidemic effects in rodent models of obesity and type 2 diabetes (T2DM) (Tomlinson *et al.* 2002, Kharitonenkov *et al.* 2005).

Apart from the FGF19 signaling pathway, hepatic BA synthesis is also controlled by another FXR-dependent mechanism, which is the small heterodimer partner (SHP, another orphan nuclear receptor) mediated downregulation of the *CYP7A1* gene, coding for cholesterol 7α-hydroxylase, the rate-limiting enzyme in BA synthesis from cholesterol (Chiang 2009). In addition to this important function, SHP serves as a versatile corepressor of gene expression by inhibiting numerous transcriptional factors in diverse metabolic, proliferative and inflammatory pathways (Seok *et al.* 2013).

Cellular targets of BA

The emerging role of BA in various metabolic processes is mediated through several membrane and nuclear receptors (Zhou & Hylemon 2014). These involve specific nuclear receptors. Apart from FXR, there are also vitamin D receptor (VDR), constitutive androstane receptor (CAR), pregnane X receptor (PXR) as well as the cytoplasmic receptors TGR5, muscarinic receptors and sphingosine 1-phosphate receptor 2 (S1PR2) (Table 1).

FXR, in addition to its essential role in cholesterol/BA metabolism, also contributes to triacylglycerol (Fuchs *et al.* 2013) and glucose metabolism. In fact, BA, via activation of FXR present in pancreatic β cells, are capable of stimulating insulin production (Schittenhelm *et al.* 2015). Furthermore, FXR is also involved in the control of glucose homeostasis via its direct interaction with carbohydrate-responsive element-binding protein (ChREBP) acting as an important transcription factor of glycolytic genes (Benhamed *et al.* 2014). Surprisingly, FXR is also expressed in cardiovascular organs such as the heart and arterial system including coronary arteries, aorta as well as atherosclerotic arteries (Bishop-Bailey *et al.* 2004). The same is also true for the expression of VDR (Mathew *et al.* 2008) and PXR (Wang *et al.* 2013), pointing to the complexity of BA action on various organs and systems.

Although the role of PXR (another intracellular BA sensor in the pathogenesis of obesity and other metabolic disorders) awaits definite clarification, its effect on energy metabolism has been proven (Gao & Xie 2012). Interestingly, PXR is also involved in the modulation of the innate immunity system. This is demonstrated even in vascular cells, protecting them against the harmful effects of xenobiotics (Wang *et al.* 2014).

CAR, originally reported as a nuclear receptor regulating the response to xenobiotics, is another nuclear receptor activated by BA (Zhang *et al.* 2004, Huang *et al.* 2006, Sipka & Bruckner 2014). It is interesting to note that CAR has been marked as an anti-obesity nuclear receptor improving insulin sensitivity (Gao *et al.* 2009) as well as lipid metabolism (Maglich *et al.* 2009) and thyroid functions (Maglich *et al.* 2004).

TGR5 (*GPBAR1*), a member of the rhodopsin-like subfamily of G protein-coupled receptors, is expressed in the enteroendocrine small-intestinal cells as well as in the thyroid gland, brown adipose tissue (Zhou & Hylemon 2014), macrophages (Perino *et al.* 2014) and in many other organs (Duboc *et al.* 2014). An increasing body of evidence shows TGR5's important role in energy homeostasis, glucose metabolism (Thomas *et al.* 2009) and the modulation of immune functions (Perino *et al.* 2014). In addition, recently published data also demonstrated TGR5 expression in pancreatic β cells, with a direct effect on insulin secretion (Kumar *et al.* 2012) (in a similar manner as described above for FXR) and also in cardiomyocytes (Desai *et al.* 2010).

BA have also been reported to activate specific muscarinic receptors (Raufman *et al.* 2003). Although this phenomenon has primarily been discussed in relationship to possible gastrointestinal pathologies (Zhou & Hylemon 2014), stimulation of muscarinic receptors in endothelial cells has been shown to attenuate atherosclerosis in an experimental animal model (Zhou *et al.* 2014). Furthermore, muscarinic M3 receptors are also expressed in the adipose tissue (Yang *et al.* 2009) as well as

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Table 1 Cellular targets of bile acids

Mechanism of action	Specific target[a]	Organ/tissue[a]	Function	References
Nuclear receptors	FXR	Liver	Bile acid, lipid and glucose metabolism	Mazuy *et al*. (2015)
		Intestine	Bile acid metabolism	Mazuy *et al*. (2015)
		Pancreatic β cells	Insulin secretion	Schittenhelm *et al*. (2015)
		Cardiovascular system	Cardiovascular system protection	Bishop-Bailey *et al*. (2004)
	VDR	Liver	Lipid metabolism	Chow *et al*. (2014)
		Cardiovascular system	Vasoprotection	Mathew *et al*. (2008)
	PXR	Liver	Lipid and glucose metabolism	Gao & Xie (2012)
		Vascular system	Regulation of innate immunity system	Wang *et al*. (2014)
		Immune system	Regulation of innate immunity system	Wang *et al*. (2014)
	CAR	Liver	Lipid and glucose metabolism	Maglich *et al*. (2009) and Gao *et al*. (2009)
Cytoplasmic receptors	TGR5	Intestine	Induction of GLP-1 secretion	Parker *et al*. (2012)
		Brown adipose tissue/ skeletal muscles	Energy expenditure via activation of triiodothyronine	Watanabe *et al*. (2006)
		Pancreatic β cells	Glucose metabolism	Kumar *et al*. (2012)
		Cardiac cells	Cardiac functions	Desai *et al*. (2010)
		Immune system	Anti-inflammatory action	Perino *et al*. (2014)
		Intestine	GI physiology	Zhou & Hylemon (2014)
	Muscarinic receptors	Endothelium	Anti-atherogenic effects	Zhou *et al*. (2014)
		Adipose tissue	Obesity control	Yang *et al*. (2009)
		Pancreas	Glucose metabolism	Hauge-Evans *et al*. (2014)
		Liver	Lipid metabolism	Zhou & Hylemon (2014)
	S1PR2	Vascular system	Vasorelaxation	Dopico *et al*. (2002)
Non-receptor-driven mechanisms	Large conductance Ca^{2+}-activated K^+ channels	Primarily liver	Various effects	Hylemon *et al*. (2009)
	Modulation of signalization cascades and enzymes regulating posttranslational modifications	Primarily liver	Multiple effects	Hylemon *et al*. (2009)

CAR, constitutive androstane receptor; EGFR, epidermal growth factor receptor; FXR, farnesoid X receptor; M3R, muscarinic M3 receptor, PXR, pregnane X receptor; S1PR2, sphingosine 1-phosphate receptor 2; TGR5, G protein-coupled bile acid receptor; VDR, vitamin D receptor.
[a]Only targets, organs and tissues believed to affect energy homeostasis are described.

the pancreas (Hauge-Evans *et al.* 2014), contributing significantly to glucose homeostasis.

Interestingly, BA also activate S1PR2 in liver cells, a mechanism believed to significantly regulate hepatic lipid metabolism (Zhou & Hylemon 2014). Sphingosine-1 phosphate, another natural ligand of S1PR2, also binds to apolipoprotein M, whose expression is under the influence of FXR, and it plays an important role in the pathogenesis of atherosclerosis and diabetes (Ren *et al.* 2015). Finally, deoxycholic acid, a secondary BA, has been surprisingly demonstrated to activate the epidermal growth factor receptor (EGFR) in hepatocytes (Qiao *et al.* 2001). EGFR is a factor known to be associated with the progression of vascular dysfunction in diabetes (Benter *et al.* 2015).

Apart from receptor-mediated actions, BA exert multiple functions through additional non-receptor-driven mechanisms involving the activation of large conductance Ca^{2+}-activated K^+ channels that regulate arterial tone (Dopico *et al.* 2002), as well as many other less well-defined effects, including apoptosis, angiogenesis/neovascularization, NO metabolism and/or inflammatory processes (for a review, see Khurana *et al.* (2011)). This suggests the complexity of the totality of possible biological functions of BA.

This wide array of BA-mediated functions results in the modulation of multiple signaling pathways including JNK1/2, ERK1/2 or AKT1/2, with many possible biochemical, pathophysiological and clinical consequences (Hylemon *et al.* 2009). BA (particularly UDCA) have been reported to even modulate the miR-34a/sirtuin1/p53 pro-apoptotic pathway in non-alcoholic fatty liver disease (NAFLD; Castro *et al.* 2013). It also modulates sirtuin 1, a histone deacetylase, which is an important sensor in regulating energy homeostasis (Li 2013) as well as in diabetes pathophysiology (Kitada & Koya 2013). Indeed, BA, via multiple transcriptional cofactors such sirtuin 1 or SHP, have been suggested to behave as epigenomic cofactors affecting the posttranslational modification of histones (Kemper 2011, Smith *et al.* 2013), with deep impacts on the possible pathophysiological consequences. Indeed, BA-induced phosphorylation of SHP has been demonstrated to posttranslationally regulate hepatic metabolic genes (Seok *et al.* 2013). BA also inhibit lysine-specific histone demethylase 1 (LD1) (Kim *et al.* 2015), an enzyme playing an important role in adipogenesis (Musri *et al.* 2010) as well as in the development of diabetes (Brasacchio *et al.* 2009). Furthermore, BA have been shown to be involved in the posttranscriptional modification of HMG-CoA reductase, a rate-limiting gene in cholesterol biosynthesis (Duckworth *et al.* 1991).

BA have also been shown to have potent immunosuppressive effects (Sipka & Bruckner 2014). Obesity is associated with a chronic, low-grade inflammation (termed metabolic inflammation), which is an important contributor to the initiation and progression of NAFLD, insulin resistance, T2DM and atherosclerosis (Gregor & Hotamisligil 2011). Thus, BA may also exert their potential anti-obesity actions via these anti-inflammatory mechanisms.

BA, gut microbiota and diabetes

Recently published data strongly suggests an important role of the gut microbiota in the development of obesity and NAFLD (Park *et al.* 2013). Gut microbiota cover more than 2000 species of commensal bacteria (Neish 2009), but only the recent progress in molecular techniques has revealed the vast diversity of gut microbiota, with Firmicutes and Bacteroidetes being the predominant bacterial phyla (Neish 2009).

Animal studies have proven that colonization of lean germ-free mice with the cecal microbiota of obese counterparts increases hepatic triacylglycerol accumulation, most likely through an increase in short-chain fatty acid (SCFA) fermentation in the intestinal lumen, leading to the stimulation of *de novo* synthesis of hepatic triacylglycerols (Backhed *et al.* 2004). Indeed, the gut microbiota of obese humans have a higher proportion of energy-harvesting Firmicutes bacteria, which is believed to increase the energy yield from the intestinal contents and accelerate fat accumulation in the human body (Turnbaugh *et al.* 2006). In fact, the ratio between the Firmicutes and Bacteroidetes phyla is important for SCFA production and is linked to obesity (Fernandes *et al.* 2014). These recent observations are also the rationale for several clinical trials recently initiated to treat obesity, NAFLD and/or diabetes with fecal bacterial transplantation ((Vrieze *et al.* 2012); and www.clinicaltrials.gov, accessed Oct 31, 2015). Further support for these data is reinforced by the results of gastric bypass studies, which have shown marked changes in the gut microbiota, correlating with weight loss (Zhang *et al.* 2009, Furet *et al.* 2010, Li *et al.* 2011).

Besides obesity, the pathogenesis of diabetes also seems to be closely linked with gut microbiota. Based on metagenome-wide association studies, an increase in sulfate-reducing bacteria and a decrease in butyrate-producing species have been detected in T2DM (for a

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review, see Tilg & Moschen (2014)). It should be mentioned that sulfate-reducing bacteria utilize taurine for sulfur reduction. Taurine-conjugated BA are closely associated with a Western type of diet, contrasted to glycine-conjugated BA predominance (e.g. in native African populations), which are also devoid of 'diseases of civilization' (McGarr *et al*. 2005). Indeed, the Western diet has been reported to induce the taurine-conjugated BA pool, with important changes to the gut microbiome (Devkota *et al*. 2012). In addition, expansion of the Firmicutes phyla in the gut lumen is related to the intestinal BA pool (Islam *et al*. 2011). The relationship between BA metabolism and the intestinal microbiome is mutual. It is not only gut bacteria that are capable of metabolizing BA, but BA also importantly influence the gut's microbiota composition. This influence is mediated through direct antimicrobial effects on gut microbes (Begley *et al*. 2005), via production of antimicrobial peptides mediated by activated FXR in ileocytes (Inagaki *et al*. 2006), or by inhibiting intestinal absorption of bacterial endotoxins (Kocsar *et al*. 1969, Parlesak *et al*. 2007). However, these potential antimicrobial effects are still poorly understood (Hofmann & Eckmann 2006).

It is also interesting to note that gut microbiome diversity is an important factor, capable to differentiate between lean and obese human subjects (Le Chatelier *et al*. 2013). The gut microbiome gene richness efficiently responds to dietary interventions (Cotillard *et al*. 2013), suggesting promising therapeutic approaches for obese patients.

BA, besides their 'classical' lipid digestive and respective TGR5-mediated metabolic functions, may also exert many other effects within the intestinal lumen. These, in turn, affect the susceptibility to obesity, the metabolic syndrome and/or diabetes.

One of these additional mechanisms may involve BA-mediated modulation of innate intestinal immunity. It has been demonstrated that activation of FXR modulated TLR4 of the intestinal myeloid cells results in anti-inflammatory effects in murine models of colitis (Vavassori *et al*. 2009). Also, *vice versa*, activation of TLR4/9 on monocytes has potent modulating effects on FXR, indicating a close interplay between FXR and effectors of innate immunity (Renga *et al*. 2013). Although it has been proposed that these mechanisms are implicated in intestinal inflammatory diseases, it is highly likely that they can also affect energy homeostasis as well as the risks of obesity, NAFLD and diabetes. These are all conditions where TLRs are believed to play an important pathogenic role (Jia *et al*. 2014, Ferreira *et al*. 2015).

As mentioned above, both *TGR5* and *FXR* (*NR1H4*) are also functionally expressed in pancreatic β-cells, where they regulate insulin secretion (Renga *et al*. 2010, Seyer *et al*. 2013). In fact, *Fxr*-deficient mice develop insulin resistance (Zhang *et al*. 2006); on the other hand, activation of FXR reverses this phenomenon in various animal models (Zhang *et al*. 2006, Cipriani *et al*. 2010). Based on these observations, FXR activation has been proposed as a promising therapeutic target for diabetic patients (Zhang *et al*. 2006). Indeed, treatment of patients having NAFLD and T2DM with obeticholic acid (a potent FXR agonist) has been demonstrated to increase insulin sensitivity in a recent human trial (Mudaliar *et al*. 2013); however, this was not confirmed in another study (Neuschwander-Tetri *et al*. 2015).

Furthermore, GLUT4, the main insulin-responsive glucose transporter, playing a critical role in maintaining systemic glucose homeostasis and contributing to insulin resistance, can be induced in hepatocyte- and adipocyte-like cells by chenodeoxycholic acid, which is a natural FXR agonist (Shen *et al*. 2008). Nevertheless, BA might also exert protective effects via FXR-independent action by the suppression of hepatic fatty acid and triacylglycerol gene expression (Wu *et al*. 2014).

However, not all recent data are fully supportive of the concept of the beneficial effects of FXR activation on energy homeostasis. It has recently been reported that selective disruption of intestinal FXR mediates gut microbiota-associated NAFLD development via the ceramide axis, pointing out the complexity of the entirety of FXR-mediated actions (Jiang *et al*. 2015). Additionally, in a mouse model, it has been demonstrated that alteration of the gut microbiota can antagonize the intestinal FXR via increased production of taurine-conjugated muricholic acid (Li *et al*. 2013, Sayin *et al*. 2013). It remains to be confirmed whether human BA conjugates may also exert the same inhibitory action on intestinal FXR.

BA metabolism in constipation and possible link to metabolic diseases

The interrelationship between BA homeostasis and metabolic diseases is far more complex. For example, it is known that patients with chronic constipation have a higher risk for cardiovascular disease (Shakir *et al*. 2007, Salmoirago-Blotcher *et al*. 2011) and T2DM (Talley *et al*. 2003, Salmoirago-Blotcher *et al*. 2011). In fact, decreased fecal BA output, a phenomenon associated with chronic constipation (Abrahamsson *et al*. 2008, Hofmann *et al*. 2008), has been reported in patients with coronary

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atherosclerosis (Charach *et al*. 1998, 2011). Constipation not only seems to be a consequence of autonomic diabetic neuropathy (Vinik *et al*. 2003), but, based on the evidence discussed above, is instead a contributing factor, via impaired intestinal and hepatic BA metabolism.

BA, thyroid functions and energy expenditure

Apart from in the small intestine, TGR5 is expressed in numerous tissues and organs including the thyroid gland, brown adipose tissue, skeletal cardiac muscle, liver and pancreas (Duboc *et al*. 2014). This fact led to investigations of the effects of BA on these organs. Surprisingly, it turned out that BA-activated TGR5 in brown fat in mice (as well as in human myocytes) stimulated intracellular cAMP formation and activated type 2 iodothyronine deiodinase (D2), which is responsible for the conversion of T_4 to T_3, and mediated thermogenic effects of BA (Watanabe *et al*. 2006). This observation was also confirmed in an experimental study by da-Silva *et al*. (2011), who observed exactly the same effects on D2 activity and energy expenditure with tauroursodeoxycholic acid. However, these effects may be due to the modulation of intracellular pathways unrelated to TGR5 activation (Malisova *et al*. 2013). In fact, thermogenic effects of BA were also verified in a human study by Ockenga *et al*. (2012), who reported a positive association in subjects of venous BA concentrations with energy expenditure; however, this was not observed in obese subjects (Brufau *et al*. 2010). The effect of BA on thyroid function seems to be more complex. A negative association between BA and TSH levels has been reported in certain patients (Patti *et al*. 2009, Ockenga *et al*. 2012) as well as in healthy subjects (Song *et al*. 2015). This is most likely due to the effect of BA on TGR5 expressed in the pituitary gland (Doignon *et al*. 2011, Ockenga *et al*. 2012). Importantly, BA sequestrants have been shown to efficiently ameliorate hyperthyroidism (Shakir *et al*. 1993, Hagag *et al*. 1998, Kaykhaei *et al*. 2008), even in refractory patients (Sebastian-Ochoa *et al*. 2008, Alswat 2015, Yang *et al*. 2015). This effect is believed to be mediated by impaired reabsorption of thyroid hormones (de Luis *et al*. 2002), but is probably much more complex.

In this context, it is also interesting to note a feedback effect of TSH/thyroxine on BA production, primarily mediated by the modulation of CYP7A1 in the liver tissue (Ellis 2006, Song *et al*. 2015). However, not all data are conclusive, and the role of thyroid hormones in the BA biosynthetic pathway still awaits further elucidation.

BA, incretins and glucose homeostasis

Incretin hormones, specifically glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are intestine-derived hormones that increase insulin secretion and decrease glucagon secretion upon stimulation by food ingestion (Holst & Gromada 2004), thus significantly contributing to the regulation of glucose metabolism (Holst *et al*. 2008). A majority of patients with T2DM have a combination of reduced GLP-1 secretion and partial resistance to its effects (Nauck *et al*. 2011). Both of these defects contribute to impairments of glucose metabolism in T2DM. Pharmacological approaches, which either increase endogenous GLP-1 or use the analogues of GLP-1 with a longer half-life, are now routinely used in the treatment of T2DM (Martin *et al*. 2011). Glucagon-like peptide 2 (GLP-2) is another intestine-derived hormone, which, in contrast to GLP-1 and GIP, does not have incretin effects. It is an important regulator of gastric motility, gastric acid secretion and intestinal hexose transport, with enhancing effects on the barrier function of the gut epithelium (Yusta *et al*. 2012).

BA have been shown to directly promote GLP-1 and GLP-2 secretion in small-intestinal enteroendocrine cells through TGR5 (Parker *et al*. 2012). Furthermore, their effect appears to be synergistic to that of glucose (Parker *et al*. 2012). Studies have shown that increased BA concentrations after malabsorptive bariatric surgery procedures (details provided in the next section) correlate with peak GLP-1 levels and fasting GIP levels (Patti *et al*. 2009, Pournaras *et al*. 2012, Kohli *et al*. 2013*a*). Similar associations have also been found in some other types of surgical manipulations. Importantly, numerous experimental studies have also found a positive correlation between increased BA levels after bariatric surgery and improvements in glucose homeostasis (Penney *et al*. 2015).

How BA contribute to the effect of bariatric surgery on energy homeostasis

Bariatric surgery not only substantially decreases body weight, but also markedly improves glucose metabolism, frequently leading to a complete remission of diabetes, as evidenced in both experimental and clinical studies (Ashrafian *et al*. 2010). Nevertheless, different types of operations clearly differ in their rates of diabetes remission as well as in the timing of metabolic improvements (Dixon *et al*. 2012). In general, bariatric operations can be classified as restrictive procedures such as gastric banding, gastric plication and sleeve gastrectomy (LSG) – or malabsorptive

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or combined procedures (e.g. gastric bypass, biliopancreatic diversion) (O'Brien 2010). In the former group, the decreased food intake and weight loss is achieved through the restriction of the stomach size without further modifications of digestive tract anatomy (Pories 2008). In the majority of malabsorptive procedures, the stomach size is also partially restricted, and a direct connection of the stomach and the lower part of the small intestine is created, thus bypassing a significant portion of the intestine. Studies have shown that restrictive procedures do not alter circulating BA concentrations, with a majority of the studies reporting either no change of BA after gastric banding (Kohli *et al*. 2013*a*) or inconsistent results after sleeve gastrectomy (Haluzikova *et al*. 2013, Myronovych *et al*. 2014). On the contrary, malabsorptive operations such as gastric bypass, which are usually more effective toward improvements of glucose metabolism, increase circulating BA levels (Kohli *et al*. 2013*a*). Plasma BA levels have also been found to increase after ileal interposition surgery, where the ileum is repositioned distal to the duodenum (Kohli *et al*. 2010). This manipulation is also associated with improvement of the components of the metabolic syndrome in rats with diet-induced obesity. Furthermore, the insertion of a duodenal–jejunal bypass liner (an endoscopically implanted device that eliminates the duodenum and proximal jejunum contact with digested food) has also been found to be associated with increased BA concentration in an experimental study

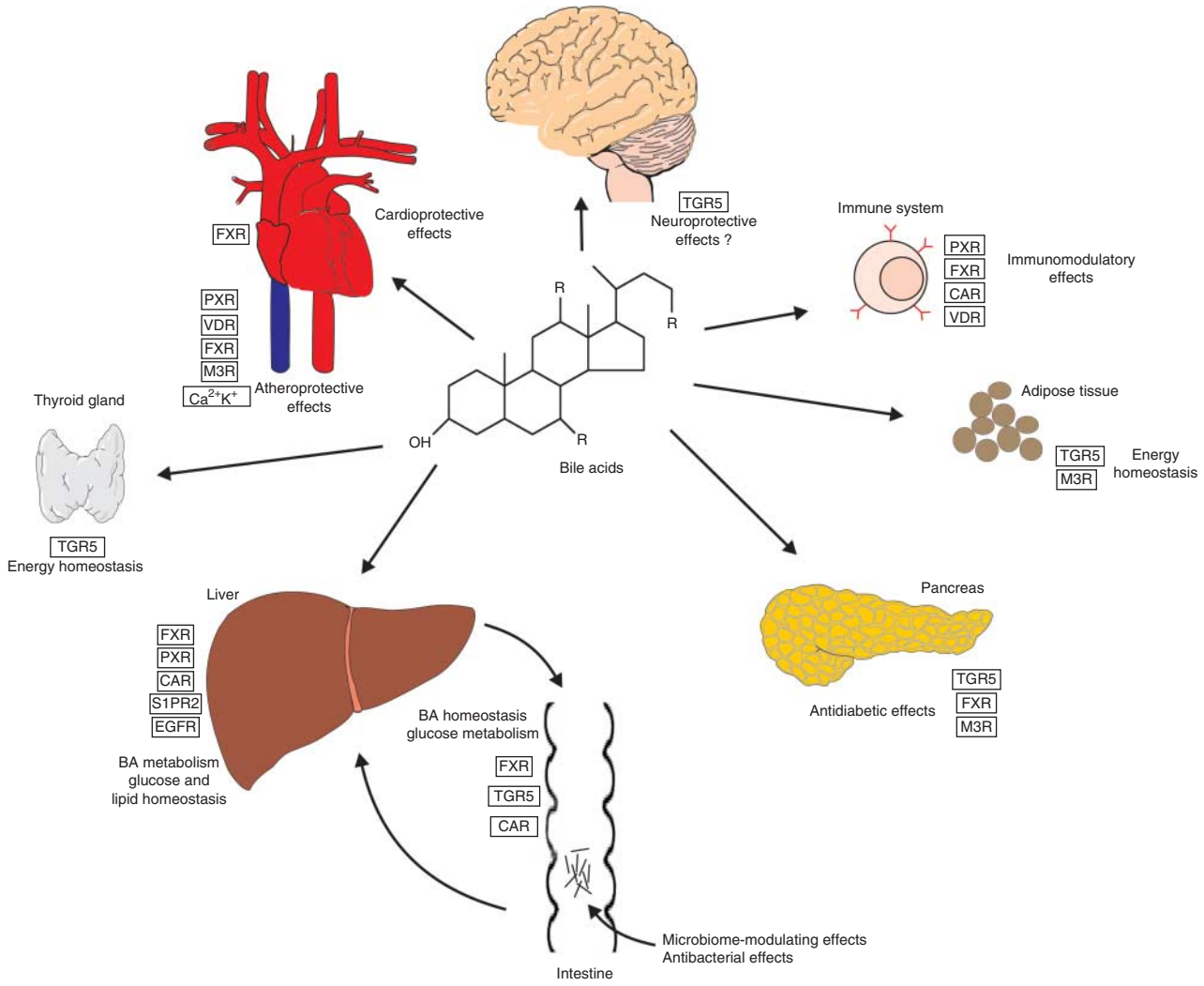

Figure 1
Receptor-mediated effects of bile acids on various tissues and organs involved in energy homeostasis. CAR, constitutive androstane receptor; EGFR, epidermal growth factor receptor; FXR, farnesoid X receptor; M3R, muscarinic M3 receptor, PXR, pregnane X receptor; S1PR2, sphingosine 1-phosphate receptor 2; TGR5, G protein-coupled bile acid receptor; VDR, vitamin D receptor.

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(Habegger *et al*. 2014). We recently observed a similar increase in patients with type 2 diabetes 6 months after the implantation of a duodenal–jejunal bypass liner (Kavalkova P, Mraz M, Trachta P, Haluzikova D, Lacinová Z, Benes M, Vlasakova Z, Petr T, Vitek L, Pelikanova T & Haluzik M, unpublished observations). Two experimental studies have directly demonstrated the importance of BA in post-bariatric surgery metabolic improvements by experimental diversion of bile to the distal gut, using either a catheter placed into the common bile duct of male obese rats to divert BA to the more distal jejunum (Kohli *et al*. 2013*b*) or a surgical manipulation to divert BA into the ileum (Pournaras *et al*. 2012) respectively. Both manipulations were associated with increased serum BA, postprandial GLP-1 secretion and improved glucose metabolism. Finally, *Fxr*-null mice have been shown to exhibit significantly blunted weight loss and improvements in glucose metabolism after bariatric surgery, suggesting an important role of FXR-mediated BA signaling after bariatric surgery (Ryan *et al*. 2014). Taken together, BA concentrations are significantly increased after malabsorptive bariatric surgery procedures. Multiple studies have shown that this increase significantly contributes to improvements in glucose homeostasis through modulations of GLP-1 secretion from the gut, changes of gut microbiota and endocrine effects of circulating BA in various organs and tissues (Fig. 1).

Conclusion

Our knowledge on the effects of BA on energy homeostasis and metabolism has dramatically expanded during the last decade. It is likely that further surprises are on the horizon, and BA will appear to have even more profound metabolic impacts. One example might be found in the observation that administration of BA sequestrants (a completely different approach from that described above) increases insulin sensitivity (Staels & Kuipers 2007, Suzuki *et al*. 2007*a*). This most likely takes place by delaying fatty acid absorption (Suzuki *et al*. 2007*b*) and increased production of secondary BA derived from sequestrant-trapped primary BA (Harach *et al*. 2012), thus leading to the stimulation of GLP-1 release. The same mechanism also seems to be in play for the ASBT inhibitor elobixibat, which may provide positive metabolic side effects (in addition to positive effects on the symptoms and signs of constipation mentioned above), reducing the risk for CVD and T2DM. Indeed, decreased LDL-cholesterol and increased GLP-1 levels have been reported in patients with dyslipidemia treated with elobixibat (Rudling *et al*. 2015). Interestingly, the hypoglycemic effect of metformin has been suggested to be at least partly accounted for by decreased intestinal BA absorption (Carter *et al*. 2003). Thus, it is not surprising that colesevelam, a potent BA sequestrant, has been approved by the FDA for the treatment of T2DM. An increasing body of evidence demonstrates the important therapeutic potential of BA metabolism modulation, either through the direct regulation of a wide array of their specific receptors or as a consequence of bariatric surgical procedures. BA interaction with the intestinal microbiome is also important, although in this respect, our knowledge is still far from complete.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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