FXR is an essential metabolic regulator in the context of bariatric weight loss surgery

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Summary

Obesity is currently the most prevalent disease according to the WHO and has been considered an epidemic for decades. To combat the increasing prevalence of excessive weight, health professionals frequently implement treatment plans such as lifestyle interventions and pharmacotherapy. However, patients are often nonresponsive, and these treatments often do not get the job done in the more extreme cases. For this group, there is the invasive treatment of bariatric surgery, which has shown incredible weight reduction and remission of related comorbidities, all much more durable than any other type of intervention. These effects seem not to only result from weight loss alone, and numerous beneficial effects are not explained by the primary malabsorption of macronutrients resulting from bariatric surgery. Numerous gut hormones have been investigated concerning their role in establishing these effects. However, not all effects can yet be explained, and it remains a goal to understand the hormonal and metabolic mechanisms behind bariatric surgery and if this can provide therapeutic targets.

The bile acid sensing farnesoid X receptor (FXR) is of much interest in this regard as it is still lesser known than other regulators in the gastrointestinal tract but has shown to have great metabolic regulating potentials such as lipid metabolism, bile acid, and glucose homeostasis. In this thesis, the known functions of FXR with bile acids as its primary ligand and FGF19 as one of its main effectors will be reviewed in the context of bariatric surgery. The roles FXR play in the metabolic changes observed post-bariatric surgery will be elucidated, and hypotheses will be summarized.

In conclusion, FXR seems to be an essential regulator in the context of bariatric surgery and can account for many of the beneficial effects observed. However, there are still some contradicting effects observed after stimulating this signaling pathway, and thus the window to target it as a therapeutic target is narrow. Furthermore, there are also some ill-researched correlations between major bariatric surgery complications like dumping syndrome/late hypoglycemic syndrome and possibly weight regain in the context of intestinal hyperplasia.

Table of contents

Introduction

Obesity is becoming more and more prevalent. In most of the westernized world, obesity is now considered an epidemic. Already in 1998, the WHO first classified obesity as an epidemic (World Health Organization, 2000) Unfortunately, the trend has not reversed, with currently more than 2 billion people being considered overweight or obese worldwide. Together with this, the prevalence of associated comorbidities of obesity like type 2 diabetes (T2D), cardiovascular disease, various cancers, and numerous inflammatory associated diseases like chronic kidney disease has increased dramatically. Especially in those with a BMI ≥ 30. (Ferrannini et al., 1997; GBD 2015 Obesity Collaborators, 2017; Owei et al., 2017; Soverini et al., 2010). The WHO stated that the prevalence of obesity in the adult European population, categorized by having a BMI exceeding 30 kg/m2, has gone from 9.9 % in 1975 to 23.3% in 2016, which is an increase of 135% (WHO, 2017).

Because of the immense impact obesity has on general health, it has become a vital spearpoint for health authorities to lower the prevalence of obesity. Obese patients are advised to take on a different lifestyle by promoting healthier nutrition and more exercise. These lifestyle interventions, however, show limited effects. In the Look AHEAD study, a large multicenter study examining the long-term impact of an intensive lifestyle intervention, better results were booked than in previous lifestyle interventions. However, it only remains to result in a mean 6.15% weight reduction, which is due to many patients not being able to adhere to the program resulting in no decreased weight or weight regain after adherence decreases (Wing et al., 2010). Pharmacotherapy is also becoming more effective and feasible. For example, the glucagon-like peptide-1 (GLP1) inhibitor semaglutide resulted in a weight decrease of 14.9% after 68 weeks (Wilding et al., 2021). However, not all patients respond to pharmacotherapy, and medication is not always effective enough to induce enough weight loss for the severely obese. Specifically in this group, bariatric surgery is an option to lower the patient's weight substantially. Following the most recent European clinical practice guideline, bariatric surgery is indicated in patients with a BMI ≥ 40, a BMI ≥ 35 with comorbidities, and in patients with a BMI ≥ 30 with refractory diabetes or poorly controlled hypertension (di Lorenzo et al., 2020).

Bariatric surgery has proven to be much more durable in causing weight loss than medical weight loss programs (Heymsfield et al., 2017; Lee & Shin, 2017). All the main types of bariatric surgery performed show superior effects on weight loss and associated comorbidities compared to other intervention types (Colquitt et al., 2014). A Systematic Review and Meta-analysis of long-term outcomes after bariatric surgery showed that all commonly used bariatric surgery techniques have an effect size three to four times that of optimal non-surgical therapy (O'Brien et al., 2019). The four most common types of surgery performed are Laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB),

sleeve gastrectomy (SG), Biliopancreatic diversion with a duodenal switch (BPD-DS) as can be seen in figure 1.

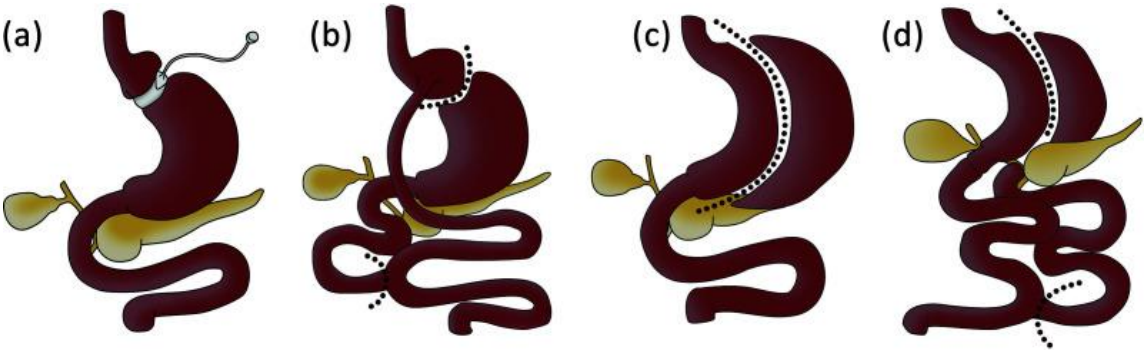

Figure 1: a schematic of common bariatric surgery techniques. (a) Adjustable gastric banding. (b) Roux-en-Y gastric bypass. (c) Sleeve gastrectomy. (d) Biliopancreatic diversion with a duodenal switch. Figure adapted from (Ruban et al., 2019).

While being very effective, also this invasive obesity treatment has its limitations. A systematic review carried out in 2019 found that 17.6% of patients that underwent either SG or RYGB experienced weight regain (WR), defined as regaining ≥ 10% of weight after successful weight loss following the surgery (Cooper et al., 2015). Furthermore, malabsorption of nutrients and drugs (primarily seen in RYGB and BPD-DS) and metabolic disorders are significant complications observed post-bariatric surgeries (Parrott et al., 2017). It has been argued that the alteration in absorption location and possibly altered composition of the absorbed nutrient disrupts normal gut hormone signaling, which gives rise to metabolic alterations or even malnourishment, as is visualized for RYGB in figure 2

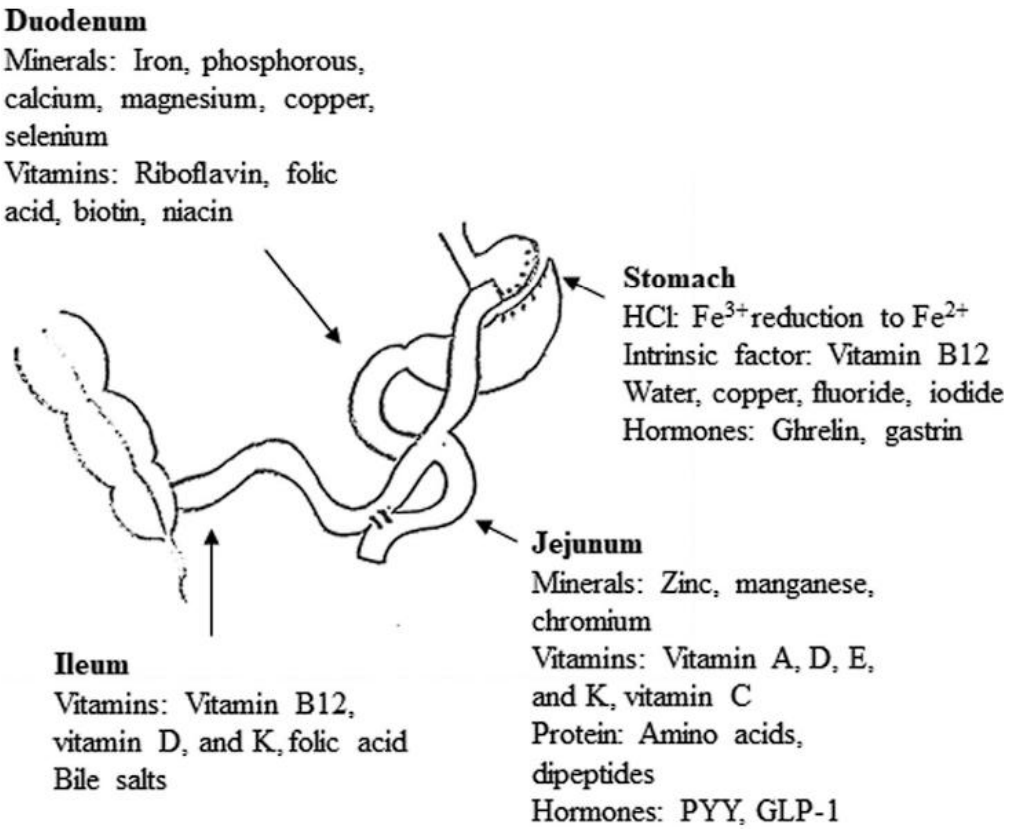

Figure 2: Sites of (micro)nutrients absorption and hormone production after RYGB. Figure adapted from (Mohapatra et al., 2020)

Multiple studies have now also been conducted investigating the roles of various gut hormones like leptin, ghrelin, and PYY play in bariatric surgery, next to the weight loss induced by malabsorption of macronutrients. Further investigation was necessary as not all positive effects observed after bariatric surgery can be related to weight loss alone (Dimitriadis et al., 2017). These studies have deepened our understanding of bariatric surgery's hormone-mediated effects on obese patients. However, not all observed effects and metabolic changes can be explained by these factors alone, and other factors may be involved (Steinert et al., 2017). Thus, more recently, researchers started investigating the effects that the bile acid (BA) sensing farnesoid X receptor (FXR) plays in metabolic regulation in the context of bariatric surgery. This proves to be an interesting subject as FXR is known to have extensive metabolic effects, and it is known that BA levels and composition are altered after bariatric surgery (Fang et al., 2015a; Kemper, 2011; Myronovych et al., 2014a; Patti et al., 2009; Zhang et al., 2006). With this metabolic regulation in mind and the possible altered hormonal signaling due to bariatric surgery, this thesis will investigate how FXR and its associated pathways mediate desired metabolic effects of bariatric surgery and which role it plays concerning complications of bariatric surgery.

Hormonal mediators in bariatric surgery

The surgical intervention in obesity has shown substantial and long-term weight loss in clinical practice. More recently, bariatric weight loss surgery is now also becoming known as metabolic surgery due to the substantive metabolic changes observed post bariatric surgery beyond body weight loss alone (Dimitriadis et al., 2017). Previous research into peripheral signals and hormones surrounding bariatric surgery has shown numerous hormonal effects of bariatric surgery on the patient's metabolism. These are mediated through hormones released by different parts of the gastrointestinal tract, which is in line with the gastrointestinal tract being regarded as the largest endocrine organ of the human body, with now more than thirty described peptides that are being secreted from enteroendocrine cells in response to food intake (Neary & Batterham, 2009).

It has been shown that bariatric surgery is very effective in targeting multiple aspects of T2D and other comorbidities commonly seen in obese patients. Remission of T2D has even been observed in 95-100% of adolescent diabetic patients undergoing bariatric surgery, with RYGB and SG mainly showing excellent results (Stefater & Inge, 2017). Some of the alleviations of comorbidities commonly observed in obese patients can be attributed to substantial weight loss; however, increasingly more evidence points towards underlying mechanisms of weight-independent factors. Such factors include the improved secretion of incretin, a recovering function of pancreatic islets, and restoring peripheral insulin sensitivity to regulate glucose homeostasis, which can contribute to more likelihood of insulin independence (Argyropoulos, 2015; Buchwald & Buchwald, 2019; Cerit, 2017; Guerrero-Pérez et al., 2020; Hankir et al., 2019; Ji et al., 2021a; Tangalakis et al., 2020; Torquati et al., 2019). Due to the metabolic nature of these changes, one study has indicated that even complications associated with type 1 diabetes, which is not weight-associated, can potentially be curbed by bariatric surgery, but the evidence is still limited (Samczuk et al., 2018).

Cardiovascular and cerebrovascular diseases are associated with obesity and T2D, so one would expect that bariatric surgery also may be able to attenuate this. Here again, numerous weight-independent effects related to vascular diseases are found, such as significantly lower blood triglyceride and glucose levels after bariatric surgery, and significant increases have been found in levels of postprandial adiponectin, glucagon-like peptide-1 (GLP-1), insulin, and serum insulin-like growth factor 1 (IGF-1) (Umeda et al., 2013). These effects combined facilitate a reduced incidence of sudden large vascular diseases and have a protective effect on the heart and vasculatures (Aminian et al., 2019; Domenech-Ximenos et al., 2020; Doumouras et al., 2021; D. P. Fisher et al., 2018; Osto et al., 2015; Umeda et al., 2013).

Next to this, nonalcoholic fatty liver disease (NAFLD) has been observed to significantly improve after bariatric surgery as well as the more advanced stages of nonalcoholic steatohepatitis (NASH) and liver fibrosis (Karcz et al., 2011; Mattar et al., 2005; Moretto et al., 2012; Mottin et al., 2005). Potential biomarkers that play a role here include Peptide YY (PYY), Fibroblast growth factors 19 and 21 (FGF19, FGF21), BAs, and GLP-1, which are all influenced by bariatric surgery (Arab et al., 2017; Armstrong et al., 2016; Chandarana et al., 2011; Chow et al., 2017; Crujeiras et al., 2017; Gómez-Ambrosi et al., 2017a; Harris et al., 2017a; Hutch & Sandoval, 2017; Ji et al., 2021b; Jiménez et al., 2013, 2014; Jørgensen et al., 2012; Kullman et al., 2016; Magouliotis et al., 2017; Manning et al., 2015; Martinez de la Escalera et al., 2017a; Nemati et al., 2018; Steinert et al., 2017; Zarei et al., 2018).

Finally, like every invasive treatment, certain complications may arise. As mentioned before, the malabsorptive effect of the surgery may lead to certain nutrient deficiencies and malnourishment. Dumping syndrome is also a frequent complication that can be categorized as either early or late dumping syndrome. Various symptoms within the first hour mainly characterize early dumping syndrome after a meal. Often observed are vasomotor symptoms such as fatigue, perspiration, flushing, palpitations, hypotension, and gastrointestinal symptoms such as abdominal pain, nausea, and diarrhea (Scarpellini et al., 2020; Tack et al., 2009; Tack & Deloose, 2014). Late dumping syndrome is mainly characterized by hypoglycemia, and symptoms usually can be seen between 1 and 3 hours after a meal (Scarpellini et al., 2020). It is generally accepted that dumping syndrome is caused by the increased amount and speed of undigested solid food being delivered to the small intestine resulting from the reduced gastric volume capacity (Mainly in early dumping syndrome). The effects are mediated by rapid fluid shifts from the plasma compartment to the intestinal lumen, but are also associated with various gastrointestinal hormones such as neurotensin, vasoactive intestinal peptide, GLP1, PYY, gastric inhibitory polypeptide, insulin, and glucagon (Adrian et al., 1985; Blackburn et al., 1980; Bloom et al., 1972; Ito et al., 1981; Lawaetz et al., 1983; Sagor et al., 1981; Scarpellini et al., 2020; Sirinek et al., 1985; Tack et al., 2009; van Beek et al., 2017). It has now also been observed that the FXR-related hormone FGF19 is upregulated in patients with post-bariatric hypoglycemia/late dumping syndrome together with an increase in postprandial BA levels and might be a potential contributor to insulin-independent pathways causing late dumping syndrome post bariatric surgery (Mulla et al., 2019). While all these hormones are essential components of the metabolic changes surrounding bariatric surgery, the remainder of this thesis will focus on FXR with its associated hormones and pathways.

FXR, bile acids, and FGF: mechanisms and pathways

FXR is a bile acid-activated receptor (BAR) and is a major regulator of BA synthesis, lipid metabolism, and glucose homeostasis (Fu et al., 2019; Kemper, 2011). The receptor was first discovered in 1995 as a nuclear receptor activated by farnesol metabolites, hence the name farnesoid X receptor (Forman et al., 1995). The FXR is translated from the FXRα gene, which encodes four isoforms expressed in a tissue-dependent manner (Boesjes et al., 2014; Zhang et al., 2003). In the gastrointestinal tract, all four isoforms can be found. FXR resides mainly in the ileum, where FXRα1 and FXRα2 are expressed moderately, and FXRα3 and FXRα4 are found to be abundantly expressed here. Furthermore, FXRα1 and FXRα2 are also expressed moderately in the adrenal glands, and FXRα3 and FXRα4 are moderately expressed in the kidney (Zhang et al., 2003). This tissue-dependent isoform expression may contribute to the vast array of metabolic effects observed and the fine-tuning of the signaling (van Zutphen et al., 2019).

To understand the FXR signaling, it is also important to know how its endogenous ligand functions. BAs are essential for the absorption of dietary fat as they are potent detergents stored in the gallbladder and secreted into bile. They are released into the proximal duodenum through the common bile duct in response to fatty food ingestion due to contraction of the gallbladder (Bozadjieva et al., 2018b). Only a tiny amount of the BA is excreted, 5 % via the stool, and 95% of BA is reabsorbed into the portal circulation using specific transport proteins (Fig. 3). BAs are categorized as atypical steroids, and in humans, we consider two main families. First, the primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in the liver from cholesterol. Next to those, there are the secondary BAs which are generated by bacteria in the gut from CA and CDCA and are named lithocholic acid (LCA) and deoxycholic acid (DCA), respectively (Fiorucci et al., 2020). Besides the role in fat uptake, it seems that BAs are self-regulating by functioning as the signaling molecules for their own synthesis. Furthermore, it has been shown that BA signaling is involved in diverse biological and pathophysiological processes, such as liver regeneration and proinflammatory and proapoptotic actions (Chiang, 2013; van Zutphen et al., 2019). The discovery of FXR as a BAR and later the discovery of other bile sensing receptors has led to BAs being now regarded as hormones and not only a factor in lipid absorption anymore.

Through an SHP-dependent mechanism, FXR also inhibits sodium taurocholate co-transporting polypeptide (NTCP). NTCP is responsible for the uptake of conjugated bile acids, and inhibiting this receptor will decrease BA uptake by the liver, which in turn will further affect BA homeostasis (Hoeke et al., 2009). Furthermore, FXR upregulates the gene expression of other BA transporters like the bile salt export pump (BSEP), the multidrug resistance protein-3 (MDR3), and the organic solute transporter alpha/beta (OSTα/β). The upregulation of these transporters increases the BA efflux from the liver to the canalicular lumen and portal vein, respectively (Ananthanarayanan et al., 2001; Dash et al., 2017; Ijssennagger et al., 2016). Finally, FXR also regulates key enzymes involved in BA conjugation and detoxification (Ijssennagger et al., 2016). An overview of this is presented in figure 4.

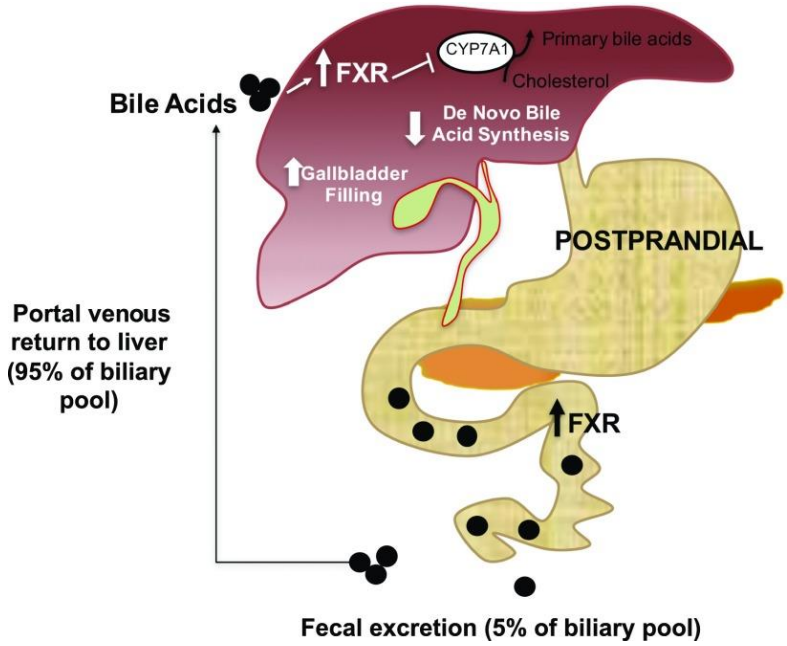

Figure 3: general overview of BA and FXR signaling. Food ingestion causes BA stored in the gallbladder to be released through the common bile duct into the duodenum. BA aid lipids absorption in the small intestine and activates FXR. The resulting signaling pathways regulate BA synthesis or gallbladder filling through the repression of CYP7A1 involved in converting cholesterol to BAs. BA is 95% reabsorbed and recycled back into the portal circulation using specific transport proteins in the ileum; the remaining 5% is excreted through the stool. Figure adapted from (Bozadjieva et al., 2018b)

FXR can regulate gene expression by binding DNA as a monomer or as a heterodimer with RXR (Claudel et al., 2002; Zhan et al., 2014). When FXR binds heterodimerically with RXR, it induces the expression of many genes, including the small heterodimer partner (SHP) gene. SHP causes transcriptional repression of the rate-limiting enzymes cholesterol 7α-monooxygenase (CYP7A1), sterol 12α hydroxylase (CYP8B1), and liver receptor homolog 1 (LRH-1), also shown in figure 4 (Chiang et al., 2000; Goodwin et al., 2000). SHP functions by recruiting repressive co-factors and binds to the respective genes inhibiting transcription (Miao et al., 2011). CYP7A1 is responsible for the de novo synthesis of primary BAs, meaning FXR stimulation by BA causes negative feedback to BA production (H. Wang et al., 1999). Next to direct signaling, intestinal BA-activated FXR can exert its effects using the hormones FGF19 (FGF15 in mice) and FGF21. This type of FXR signaling occurs mainly in the ileum as the ileal enterocytes of the small intestine specifically express FGF15/19 and release FGF 15/19 postprandially in response to bile acid absorption (Potthoff et al., 2011). The FGF15/19 originating from the ileum is released in the portal venous circulation and is transported to the liver, where it activates the fibroblast growth factor receptor 4 (FGFR4). FGFR4 is, as far we know, exclusively activated by FGF15/19 and is highly expressed in the gallbladder and liver. This signaling again represses de novo BA synthesis through suppression of CYP7A1 and CYP8B1 but also suppresses gluconeogenesis and lipogenesis and increases glycogen synthesis (Al-Aqil et al., 2018; Bozadjieva et al., 2018a; Inagaki et al., 2005; Shapiro et al., 2018).

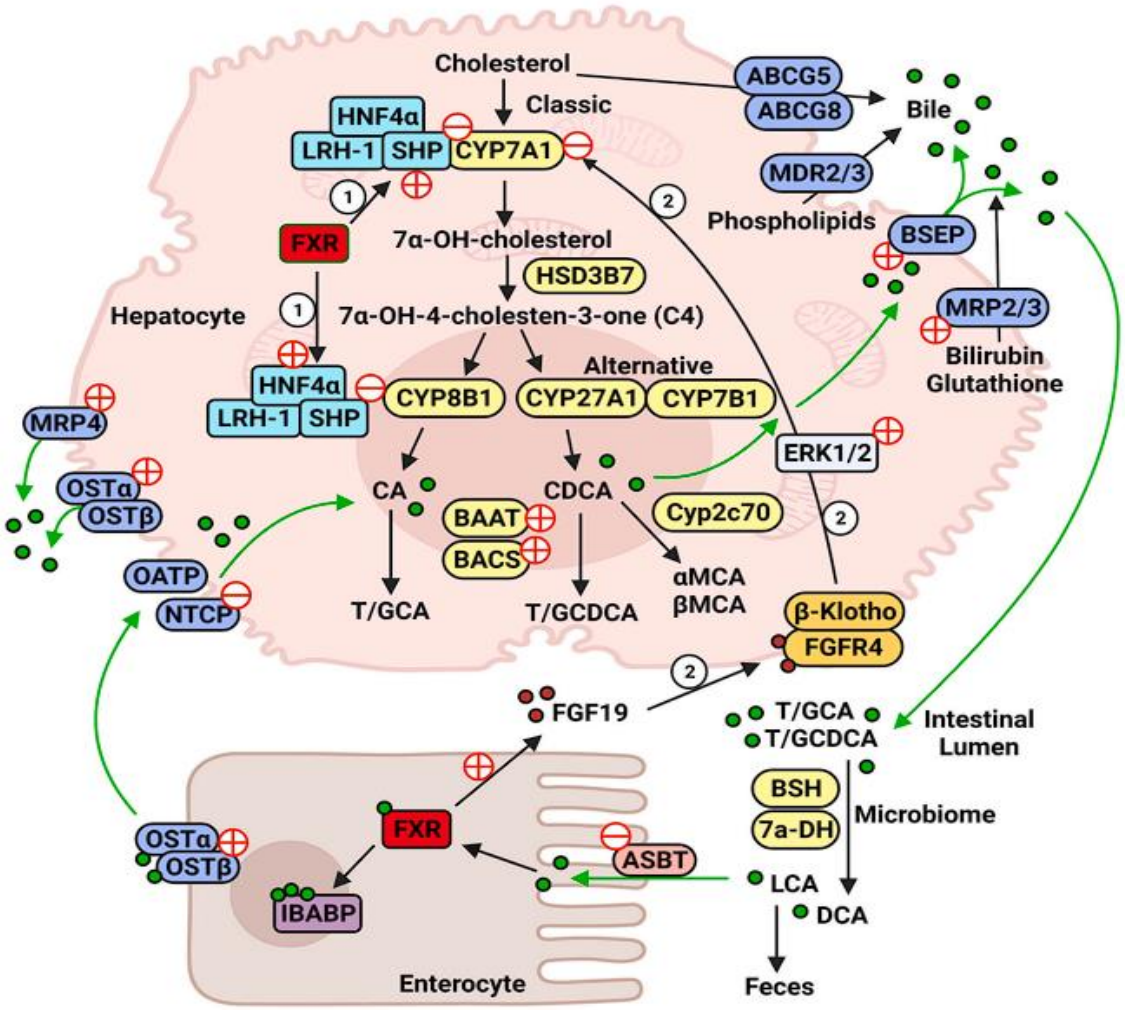

Figure 3 The role of FXR in the regulation of bile acid synthesis in hepatocytes and in the enterohepatic circulation of bile acids. Cholesterol is converted to cholic acid (CA) and chenodeoxycholic acid (CDCA) in human liver. The classic pathway is initiated by cholesterol 7α-hydroxylase (CYP7A1), while the alternative pathway is initiated by sterol 27-hydroxylase (CYP27A1) followed by oxysterol 7α-hydroxylase (CYP7B1). Sterol 12α-hydroxylase (CYP8B1) catalyzes cholic acid (CA) synthesis. In mouse liver, CDCA is converted to α- and β-muricholic acids (αMCA and βMCA) by Cyp2c70 as primary bile acids. Details of bile acid synthesis pathway and enzymes are described in the text. Major regulatory enzymes are shown. CA and CDCA are conjugated to taurine (T) or glycine (G) and are secreted into bile. Bile acids are reabsorbed in the ileum. In the colon, gut bacterial bile salt hydrolase (BSH) de-conjugates bile acids and 7α-dehydroxylase (7α-DH) converts CA and CDCA to deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. Bile acids activate FXR, which plays a critical role in the regulation of bile acid synthesis. Activation of FXR inhibits CYP7A1 and CYP8B1 through two pathways. In the liver, FXR induces short heterodimer partner (SHP) to inhibit CYP7A1 and CYP8B1 gene transactivation by HNF4α and LRH-1 (Pathway 1). In the intestine, FXR induces fibroblast growth factor 19 (FGF19), which activates hepatic FGF receptor 4 (FGFR4)/β-Klotho signaling mainly via ERK1/2 to inhibit CYP7A1 gene transcription (Pathway 2). FXR induces bile salt export pump (BSEP) to efflux bile acids into bile. ATP binding cassette G5 and G8 (ABCG5/G8) effluxes cholesterol and multidrug resistant protein 2/3 (MDR2/3) effluxes phospholipids into bile to form mixed micelles with bile acids. MDR related protein 2/3 (MRP2/3) effluxes bilirubin and glutathione-conjugated bile acids. In the enterocytes of the ileum, bile acids are reabsorbed via apical sodium-dependent bile acid transporter (ASBT), which is inhibited by bile acids and FXR. FXR induces intestine bile acid binding protein (IBABP), which binds and transports bile acids across the enterocyte to the sinusoidal membrane to be secreted to portal blood via the organic solute transporter α/β (OSTα/OSTβ) dimer, which is induced by FXR. Bile acids circulated to the liver are taken up by hepatic sodium-dependent taurocholate co-transporting peptide (NTCP), which is inhibited by bile acids via SHP. Organic anion transporting peptides (OATPs) and MRP4 uptake bile acids to hepatocytes independent of sodium. At the sinusoidal membrane, FXR induces OSTα/OSTβ or MRP4 (induced in cholestasis) to efflux bile acids into systemic blood circulation. (+) indicates stimulation, (−) indicates inhibition. Adapted from (Chiang & Ferrell, 2022)

The FXR/SHP pathway in the liver and the FXR/FGF15/19/FGFR4 pathway in the intestines are the primary regulators of BA synthesis (L. Jiang et al., 2021). BA's and FGF15/19 facilitate communication between the liver and small intestine. FGF15/19 can resemble insulin in reducing gluconeogenesis and stimulating protein and glycogen synthesis (DePaoli et al., 2019). In contrast to insulin, however, FGF15/19 can decrease hepatic triglycerides, which makes FGF19 an attractive therapeutic target as it can mimic or support the actions of insulin while avoiding some of the pitfalls (Bozadjieva et al., 2018b; Harrison et al., 2018). FGF15/19 can target the membrane-bound FGF receptor FGFR4. However, there are more FGF receptors with varying expression and activation by FGF15/19 between tissues. There are four FGF receptors, and for FGFR1, there are two known splice variants (FGFR1b and FGFR1c) (Kohli et al., 2010a; le Roux & Bueter, 2014; Myronovych et al., 2014b; Schauer et al., 2017). FGFR1 is highly expressed in the brain and adipose tissue but is generally expressed in most tissues (Lan et al., 2017a).

Both FGF21 and FGF15/19 can target FGFR1c, and this has led researchers to explore the tissue-specific mechanism of FGF19 and FGF21 in reducing body weight, blood glucose, insulin, and hepatic triglycerides. FGF21 is a key hepatokine that exerts pleiotropic metabolic actions on various organs, such as adipose tissue and skeletal muscles, to antagonize obesity and diabetes (F. M. Fisher & Maratos-Flier, 2016). The hepatic gene expression of FGF21 is transcriptionally regulated by peroxisome proliferator-activated receptor a (PPARa), a transcription factor activated by free fatty acid mediating the fasting response (Lundåsen et al., 2007). FGF21 can act directly on the central nervous system, which induces sympathetic outflow towards white and brown adipose tissue, increasing energy expenditure (Douris et al., 2015; Owen et al., 2014). FGFRs also form cell surface receptor complexes together with the single-pass transmembrane protein providing tyrosine kinase activity to the complex (Kuro-O, 2012). When β-Klotho was explicitly ablated in hepatocytes, adipose tissue, or neurons, the researchers found that FGF also targets the brain. In the absence of β-Klotho in neurons, the weight-loss effects of FGF15/19 and FGF21 were absent. However, this was not the case in adipose or liver tissue (Lan et al., 2017b) This is reinforced by numerous other studies that elaborate on the effects of FGF15/19 in the central nervous system and discuss FGF15/19 signaling in reducing food intake and improving glucose homeostasis (Lan et al., 2017b; Morton et al., 2013; Perry et al., 2015; Ryan et al., 2013). However, some of the more acute FGF15/19 effects may also partly depend on the increased insulin sensitivity mediated by adipose tissue and altered whole-body glucose uptake. Recently, also muscle was identified as a target of FGF15/19, as it has been shown that skeletal muscle mass and strength can be increased by FGF15/19. Recommendations have been made to study the increase in FGF15/19 as an adaptive mechanism to prevent muscle loss after weight-loss surgery (Benoit et al., 2017). It is also possible that additional FGFRs are present and other tissues are involved in FGF15/19 signaling in glucose homeostasis and body weight. Furthermore, our current understanding of FGF15/19 signaling in pancreatic α- and β-cells is still lacking concerning insulin and glucagon levels post-bariatric surgery, and only limited data is present on the possible role of FGF15/19 in pancreatic islet function and cell mass (Bozadjieva et al., 2018a) In conclusion, our understanding of the pathways has greatly increased over the past few years, but the complete picture of some essential elements are still missing.

FXR modulation

As FXR signaling proves to be extremely important surrounding metabolic disease, numerous studies have been conducted on possible modulators and agonistic drugs. Research into various endogenous and (semi)synthetic compounds has resulted in our current understanding of how FXR can be modulated. FXR was initially an orphan NR as the receptor was discovered before the ligand. FXR was named farnesoid X-activated receptor following the identification of the ligand farnesol and its related metabolites (Forman et al., 1995). Also, cafestol was an early discovered agonist of FXR. Cafestol has been known for a long time as one of the most potent cholesterol-elevating compounds, and the research into cafestol has led to a better understanding of FXR signaling. Several genes involved in cholesterol homeostasis regulated by cafestol, including CYP7A1, were shown to be FXR related, leading to later studies demonstrating that cafestol is an agonist of FXR in mice. It has been demonstrated that cafestol increases IBABP and FGF15/19 expression in the intestine. However, cafestol does not affect FXR target genes in the liver, which indicates that cafestol behaves as an intestine-restricted FXR agonist (Ricketts et al., 2007).

The potency varies of the various endogenous BA species to activate FXR and is ranked as CDCA > DCA > LCA > CA, which served as a baseline for designing steroidal FXR agonists (H. Wang et al., 1999). Using the structures-activity relationship (SAR) analysis of the different BAs has shown that for FXR agonism, amino acid placement in positions 3 and 7 of the BA skeleton, as well as the side chain is crucial for its function (H. Wang et al., 1999). With an EC50 of 50 µM in mice and 10 µM in humans on FXR, CDCA was the most potent natural activator. Thus CDCA was used to generate a panel of semisynthetic derivatives, which was used to clarify further the SAR and made it possible to create highly potent agonists (Gioiello et al., 2014; Pellicciari et al., 2006). On top of the BAs themselves, a biotransformation intermediate of the primary BA synthesis, 22(R)-hydroxycholesterol, has also been identified as an FXR agonist (Deng et al., 2006). Expanding on FXR agonists, several steroidal compounds such as etiocholanolone, MFA-1, and androsterone have shown FXR activation next to the BA-related compounds (Soisson et al., 2008; S. Wang et al., 2006).

To test the direct effects of BAs and if they were a possible suitable drug, exogenous BA administration has been done in the context of clinical studies. These have shown that exogenous BA can have numerous metabolic effects such as improved glucose homeostasis due to increased insulin and GLP-1 levels, decreased appetite, and increased energy expenditure and activity of brown adipose tissue (Adrian et al., 2012; Bray & Gallagher, 1968; Broeders et al., 2015; Wu et al., 2013). This has been reinforced by mice studies where total body FXR knockout mice were used, which resulted in increased serum triglyceride and cholesterol levels and excessive fat accumulation in the liver, as BAs were unable to initiate (Cariou et al., 2006; Sinal et al., 2000). These FXR-lacking mice also show signs of insulin resistance and have reduced glucose disposal characterized by decreased liver and adipose tissue insulin signaling when mice are maintained on standard chow (Cariou et al., 2006; Zhang et al., 2006). On top of this, FXR overexpression in db/db mice (an animal model for T2D combined with obesity) or treatment with the FXR agonist GW4064 (both a hepatic and intestinal FXR activator) in both db/db and ob/ob mice (an animal model also focused on obesity and T2D) showed positive metabolic effects. Being an effective treatment in both groups, FXR stimulation proves to be a potential therapeutic strategy for metabolic disease. A fundamental limitation of these results is that FXR knockout mice are resistant to

high-fat diet-induced obesity and glucose intolerance which means that successfully targeting to achieve the desired effect can be challenging (Prawitt et al., 2011). The main argument for the ambiguous results surrounding FXR is that its role in metabolic regulation differs between various tissues, which may be crucial for the beneficial effects of BA metabolism post-bariatric surgery.

Next to steroidal agents, numerous FXR agonists containing isoxazoles have been published over the last 20 years. The first selective agonist of FXR, GW4064, was a full agonist without activity on other NRs at concentrations up to 1 μM and was patented in 1998 and published in 2000 (Maloney et al., 2000). GW4064 exhibits a high affinity for FXR. However, poor bioavailability and potential hepatobiliary toxicity limited its clinical application, but it remained the structural template for the development of numerous patentable and druggable FXR agonists (Akwabi-Ameyaw et al., 2008; Bass et al., 2011). Modifications had to be implemented to enhance the drug properties, such as the implementation of an oxymethylene or amino-methylene replacing the stilbene olefin or linking the middle and the terminal aryl rings using a hydroxyl-bearing ring replacement (Abel et al., 2010; Kinzel et al., 2016) Next to these implementations, several heterocyclic analogs were synthesized as the isoxazole ring is crucial for FXR activation, and great agonist activity was observed with triazoles, oxazolidinones, and pyrazoles (Smalley et al., 2015).

Fexaramine (Fex) is also an agonist from a different class than GW4064 and steroidal ligands. Fex is developed using combinatorial chemistry and has a 100 times higher affinity than CDCA. It was observed that co-activator SRC-1 peptide recruitment to FXR caused by Fex is functionally and biologically similar to that of GW4064, and Fex was able to achieve induction of target genes at a comparable concentration to GW4064 (Downes et al., 2003). Also, Fex behaved as an intestine-restricted FXR agonist with minimal effect elsewhere (Fang et al., 2015a). Furthermore, the FXR agonist GW4064 and FXR ligand taurochenodeoxycholic acid were tested in treating primary cultured islets. Here it was found that FXR stimulation resulted in increased calcium concentrations and electrical activity, leading to increased insulin secretion which the authors attributed to FXR-induced inhibition of KATP channel activity and not the regulation of insulin synthesis (Düfer et al., 2012).

Finally, what is interesting about FXR is the diverse effects it has on metabolism varying per tissue in the context of stimulation or inhibition. For example, most research has ruled in favor of FXR stimulation, and most research has been conducted on FXR agonists. However, multiple less hydrophobic BA have been observed as FXR antagonists. Such BAs are, for example, Tauro-β-murocholic acid(T-β-MCA) and Glycine-murocholic acid (G-MCA), which have also been proved to decrease obesity and improve metabolic parameters in high-fat diet-induced and genetic obesity (C. Jiang, Xie, Lv, et al., 2015; F. Li et al., 2013). This makes the interpretation of mechanisms and the expected effects challenging to predict.

FXR signaling surrounding bariatric surgery

When patients undergo bariatric surgery, their enterohepatic circulation is altered. These procedures have demonstrated changes to numerous traditional gut hormones levels, and, more importantly, bariatric surgery also alters both the levels and composition of BA in rodents and humans (Kohli et al., 2010a; Myronovych et al., 2014b; Patti et al., 2009; Pournaras et al., 2012). All different procedures induce considerable changes in the internal environment of the gastrointestinal lumen giving rise to changes in nutrient intake, gastric emptying, and gastric acid production. However, specifically, in both VSG and RYGB, the gut microbiota is shown to be affected and, consequently, the BA composition (Aron-Wisnewsky & Clement, 2014). Recalling from earlier, gut biota is responsible for synthesizing secondary BAs from primary BAs, which has been previously proven by germ-free mice having a much lower BA diversity than those with normal gut microbiota. Fecal transplantation from regular gut biota-containing mice successfully restored diversity (Sayin et al., 2013a). Concluding from this, the altered BA composition can be acquitted to the altered microbiota composition due to the bariatric surgery. Also, surgical bile diversion into the ileum creates interesting enough comparable effects as seen in RYGB and leads to weight loss and improved glucose tolerance in rodents without gastric restriction; however, when BAs were diverted more proximally in the small intestine, the effects disappeared (Albaugh et al., 2019; Flynn et al., 2015).

Next, after obese mice underwent VSG, a study reported an increase in circulating CA and additionally found an increase in taurine-conjugated DCA. These increases correlate to the VSG group's maximum weight loss and previously observed improvements upon liver steatosis (Sayin et al., 2013b). Two other studies showed that VSG was more successful in improving liver lipids than calorie restrictive-related weight loss, underlining that bariatric surgery's metabolic impact on the liver goes beyond its impact on weight loss (Kohli et al., 2015; Myronovych et al., 2014a). Similar results have also been obtained in humans, pigs, and rats when another study compared changes in circulating BAs after RYGB. Differences were observed between the three species concerning the BA composition alterations, however, they showed an overall BA increase after surgery. More specifically, secondary taurine-conjugated BAs were most increased, which suggests that bariatric surgery changes BA composition as a direct effect of alterations by the bariatric surgery in the microbiome (Spinelli et al., 2016).

Next to DCA and LCA, there is a bacterial-derived T-β-MCA that has been discussed before. Interestingly, T-β-MCA inhibits the negative feedback on primary BA synthesis. T-β-MCA inhibits FXR and FGF15/19 signaling resulting in an increase in primary BA synthesis and, consequently, a more diverse composition of BA due to the bacterial hydrolyzation of host-derived primary BAs (Sayin et al., 2013b). This increase in T-β-MCA mediated FXR modulation is in line with the observations of an increased primary BA synthesis after VSG surgery (Myronovych et al., 2014a). With the enterohepatic circulation of BAs altered post-bariatric surgery, it has been hypothesized that BAs mediate observed effects on weight and glucose homeostasis post-bariatric surgery through their associated receptors. This hypothesis has been reinforced by FXR-deficient mice showing diminished effects of VSG, such as diminished weight loss and less improved glucose tolerance, whereas TGR5-deficient mice show expected weight loss but have only a marginal improvement of glucose regulation in response to VSG (McGavigan et al., 2017; Ryan et al., 2014). TGR5 is also a BAR and is now becoming better known as a BA sensing metabolic regulator like FXR. It has been found, for example, that the TGR5 activation leads to a stimulatory effect

on GLP-1 secretion (Thomas et al., 2008). TGR5 possibly is also responsible for BA mediated effect but unfortunately lies beyond the scope of this thesis.

Furthermore, resulting from the increase in BA, one would expect an increase in FXR stimulation post-bariatric surgery. Moreover, the increased FXR stimulation can indeed be observed due to increases in FGF levels post-bariatric surgery, such as increased FGF15/19 levels, and several studies claim it is inevitable and necessary for catalyzing weight loss in obese as well as nonobese patients (Nemati et al., 2018). Interestingly, numerous other studies indicate a surgery-specific effect on in vivo FGF levels. FGF15/19/21 are associated with macronutrient ingestion and fast glucose delivery rates to the liver and thus may be affected, but not the effector. However, FGF levels still may be helpful as a potential biomarker for indicating weight loss after bariatric surgery (Bozadjieva et al., 2018c; DePaoli et al., 2019; Gómez-Ambrosi et al., 2017b; Harris et al., 2017b; Ji et al., 2021c; Martinez de la Escalera et al., 2017b; Sandhu et al., 2014; Werner, 1998). In another study, plasma levels of FGF19 and FGF21 were analyzed in 28 patients who underwent RYGB or LAGB, and in both procedures, an increase in postprandial plasma FGF19 concentrations was observed (Harris et al., 2017b).

Next to all the positive effects the increased levels and altered composition of the BA seem to have with the resulting FXR stimulation and FGF15/19 release, some complications can result from the same changes. In patients with late dumping syndrome/post-bariatric hypoglycemia, FGF19 is increased and is the top-ranking differentially abundant protein at 120 minutes after a mixed meal (Mulla et al., 2019). FGF19 levels were 2.4-fold higher in late dumping syndrome/post-bariatric hypoglycemia vs. asymptomatic post-RYGB, which possibly indicates that FXR/FGF signaling also inherits some unwanted side effects of bariatric surgery.

Discussion

In conclusion, FXR signaling seems to contribute significantly to the metabolic changes observed post-bariatric surgery in both weight-independent metabolic alterations and the weight loss itself. All bariatric surgery procedures showed FXR-mediated effects, with RYGB showing the most convincing results. It can be speculated that this effect is mainly seen here in the duodenum, as it is exposed to undiluted bile as nutrients bypass the duodenum. The delayed mixing of BA and ingested food possibly give rise to a more concentrated bile solution in the ileum and could also facilitate the bacterial conversion of primary to secondary BAs, which can alter the FXR signaling pathway.

Furthermore, surgical bariatric interventions appear to alter the levels and composition of BAs significantly, and these BAs are important molecular mediators of effects on energy and glucose homeostasis. An important future directive is, therefore, to obtain a deeper understanding of how and to what extent the changes in microbiota account for the altered enterohepatic BA circulation and what role the gut microbiota plays in both BA composition and the general health of the host (Arora & Bäckhed, 2016; Fernandes et al., 2016; Peat et al., 2015). It would be interesting, for example, to observe the effects that the pre and postoperative diet have on the patient's gut microbiota and how that affects the BA composition.

Furthermore, it is well known that FXR signaling and its effectors are tissue-specific and can have opposing effects. It has been observed that mice selectively lacking intestinal expression of FXR have decreased insulin resistance and fatty livers in response to a high-fat diet (C. Jiang, Xie, Li, et al., 2015; C. Jiang, Xie, Lv, et al., 2015). They have also proven that the selective high-affinity intestinal FXR inhibitor G-MCA can prevent and even reverse obesity, glucose intolerance, insulin resistance, and hepatic steatosis in genetically and high-fat diet-induced obese mice (Fang et al., 2015b). Next, it was also found that in ileum biopsies from obese patients, FXR expression levels showed a positive correlation with BMI (C. Jiang, Xie, Lv, et al., 2015). From these results, it could be concluded that an increase in FXR signaling in the ileum negatively impacts body weight and glucose homeostasis. In contrast, however, treatment with the gut-specific FXR agonist Fex improved hepatic glucose and lipid metabolism, reduced body weight, improved glucose homeostasis, decreased insulin resistance, promoted adipose tissue browning, and increased energy expenditure (Fang et al., 2015a; Pathak et al., 2018). The hepatic FXR signaling has also been tested using liver-specific FXR knockout mice, which showed increased plasma triglycerides. Next, these mice were not protected from high-fat diet-induced obesity and insulin resistance (Prawitt et al., 2011). In contrast, another study on hepatic FXR using a constitutively active FXR resulted in lower plasma glucose levels in nondiabetic mice and reduced hyperglycemia in db/db mice (Zhang et al., 2006). In summary, FXR is intimately involved in the entire metabolic process of bile acid synthesis, transport, and reabsorption (Cao et al., 2019; Ovadia et al., 2019). However, due to the tissue-specific and context-dependent nature of FXR signaling, closely monitored trials are necessary for determining the conditions for each effect. This, in combination with the use of SBARMs, may hopefully lead to effective pharmacotherapeutic alternatives for surgery.

What also may be of interest is induced intestinal hypertrophy, mainly in RYGB. The cause for the transformation of the intestinal lining is unclear but presumably depends on an adaptive response to handle the new composition of luminal content and could rely on increased BAs, changed microbiota, or different macronutrient composition (Bäckhed et al., 2005; Korner et al., 2009; le Roux et al., 2010a;

Saeidi et al., 2012). This physical change of the GI mucosa is prominent after RYGB surgery but not after VSG (Mumphrey et al., 2013, 2015). It has been speculated that this physical adaption of the gut may underpin the beneficial effects of these procedures as nutrient absorption increases again (Evers et al., 2017) Other types of bariatric surgeries that reroute the intestine also cause hypertrophy. Duodenal jejunal bypass surgery in rats, a procedure where the placement of a duodenal-endoluminal sleeve prohibits nutrient-to-tissue interaction, causes atrophy in the bypassed limb but induces increased villus length throughout the small intestine and hyperplasia in the portion of jejunum exposed to nutrients that, under normal circumstances, are alien to these intestinal sites (Habegger et al., 2014; B. Li et al., 2013). In an alternative surgical intervention, the interposition of a piece of ileum within the jejunum leads to a "jejunization" of the transposed ileal section at the level of villi length and GATA4/ILBP mRNA expression (Kohli et al., 2010b). Lastly, RYGB in rats is associated with increased bowel width, villus height, crypt depth, and cell proliferation in the alimentary and common intestinal limbs but not in the biliopancreatic limb (le Roux et al., 2010b; Taqi et al., 2010). This hypertrophy could be linked to FXR signaling as related circulating growth factors, such as IGF-1, glucagon-like peptide-2 (GLP-2), FGF, and epidermal growth factor (EGF), all increase in rats and mice following RYGB and play a role in intestinal growth and proliferation (Brubaker et al., 1997). Considering the timeline at which this hyperplasia occurs with increased ability for nutrient absorption, one could also argue that weight regains, as observed in a significant portion of post-bariatric surgery patients, is a result of this. If this is true, better knowledge of the exact mediators of this hyperplasia might become a therapeutic target to attenuate this complication and produce even better results. Furthermore, it is recommended to investigate further possible FXR-regulated micronutrient metabolisms. An example would be investigating vitamin D and bone metabolism as it is one of the downstream targets of FXR which can possibly tie into the widespread vitamin D deficiency seen post bariatric surgery(Massafra et al., 2018; Tack & Deloose, 2014).

Overall, FXR proves to be an essential mediator in mainly the positive effects of bariatric surgery but still might be implicated in the common complications seen with this treatment. FXR has been targeted for two decades, and the increasing knowledge still opens up more avenues for new therapeutic options and better treatment of metabolic conditions. However, as it, unfortunately, goes for all newly found targets, it is not the cure for all. There are still contradictions, and where some effects can be beneficial, some also result in unwanted side effects. The FXR remains an attractive therapeutic target, but as always, new targets have to keep being discovered, and mechanisms have to be further elucidated.

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References

Abel, U., Schlüter, T., Schulz, A., Hambruch, E., Steeneck, C., Hornberger, M., Hoffmann, T., Perović-Ottstadt, S., Kinzel, O., Burnet, M., Deuschle, U., & Kremoser, C. (2010). Synthesis and pharmacological validation of a novel series of non-steroidal FXR agonists. *Bioorganic & Medicinal Chemistry Letters*, *20*(16), 4911–4917. https://doi.org/10.1016/J.BMCL.2010.06.084

Adrian, T. E., Gariballa, S., Parekh, K. A., Thomas, S. A., Saadi, H., al Kaabi, J., Nagelkerke, N., Gedulin, B., & Young, A. A. (2012). Rectal taurocholate increases L cell and insulin secretion, and decreases blood glucose and food intake in obese type 2 diabetic volunteers. *Diabetologia*, *55*(9), 2343–2347. https://doi.org/10.1007/S00125-012-2593-2

Adrian, T. E., Long, R. G., Fuessl, H. S., & Bloom, S. R. (1985). Plasma peptide YY (PYY) in dumping syndrome. *Digestive Diseases and Sciences*, *30*(12), 1145–1148. https://doi.org/10.1007/BF01314048

Akwabi-Ameyaw, A., Bass, J. Y., Caldwell, R. D., Caravella, J. A., Chen, L., Creech, K. L., Deaton, D. N., Jones, S. A., Kaldor, I., Liu, Y., Madauss, K. P., Marr, H. B., McFadyen, R. B., Miller, A. B., III, F. N., Parks, D. J., Spearing, P. K., Todd, D., Williams, S. P., & Wisely, G. B. (2008). Conformationally constrained farnesoid X receptor (FXR) agonists: Naphthoic acid-based analogs of GW 4064. *Bioorganic & Medicinal Chemistry Letters*, *18*(15), 4339–4343. https://doi.org/10.1016/J.BMCL.2008.06.073

Al-Aqil, F. A., Monte, M. J., Peleteiro-Vigil, A., Briz, O., Rosales, R., González, R., Aranda, C. J., Ocón, B., Uriarte, I., de Medina, F. S., Martinez-Augustín, O., Avila, M. A., Marín, J. J. G., & Romero, M. R. (2018). Interaction of glucocorticoids with FXR/FGF19/FGF21-mediated ileum-liver crosstalk. *Biochimica et Biophysica Acta. Molecular Basis of Disease*, *1864*(9 Pt B), 2927–2937. https://doi.org/10.1016/J.BBADIS.2018.06.003

Albaugh, V. L., Banan, B., Antoun, J., Xiong, Y., Guo, Y., Ping, J., Alikhan, M., Clements, B. A., Abumrad, N. N., & Flynn, C. R. (2019). Role of Bile Acids and GLP-1 in Mediating the Metabolic Improvements of Bariatric Surgery. *Gastroenterology*, *156*(4), 1041. https://doi.org/10.1053/J.GASTRO.2018.11.017

Aminian, A., Aleassa, E. M., Bhatt, D. L., Tu, C., Khorgami, Z., Schauer, P. R., Brethauer, S. A., & Daigle, C. R. (2019). Bariatric surgery is associated with a lower rate of death after myocardial infarction and stroke: A nationwide study. *Diabetes, Obesity and Metabolism*, *21*(9), 2058–2067. https://doi.org/10.1111/DOM.13765

Ananthanarayanan, M., Balasubramanian, N., Makishima, M., Mangelsdorf, D. J., & Suchy, F. J. (2001). Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. *The Journal of Biological Chemistry*, *276*(31), 28857–28865. https://doi.org/10.1074/JBC.M011610200

Arab, J. P., Karpen, S. J., Dawson, P. A., Arrese, M., & Trauner, M. (2017). Bile acids and nonalcoholic fatty liver disease: Molecular insights and therapeutic perspectives. *Hepatology (Baltimore, Md.)*, *65*(1), 350. https://doi.org/10.1002/HEP.28709

Argyropoulos, G. (2015). Bariatric Surgery: Prevalence, Predictors, and Mechanisms of Diabetes Remission. *Current Diabetes Reports*, *15*(4). https://doi.org/10.1007/S11892-015-0590-9

Armstrong, M. J., Hull, D., Guo, K., Barton, D., Hazlehurst, J. M., Gathercole, L. L., Nasiri, M., Yu, J., Gough, S. C., Newsome, P. N., & Tomlinson, J. W. (2016). Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *Journal of Hepatology*, *64*(2), 399–408. https://doi.org/10.1016/J.JHEP.2015.08.038

Aron-Wisnewsky, J., & Clement, K. (2014). The effects of gastrointestinal surgery on gut microbiota: potential contribution to improved insulin sensitivity. *Current Atherosclerosis Reports*, *16*(11), 1–11. https://doi.org/10.1007/S11883-014-0454-9

Arora, T., & Bäckhed, F. (2016). The gut microbiota and metabolic disease: current understanding and future perspectives. *Journal of Internal Medicine*, *280*(4), 339–349. https://doi.org/10.1111/JOIM.12508

Bäckhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A., & Gordon, J. I. (2005). Host-bacterial mutualism in the human intestine. *Science (New York, N.Y.)*, *307*(5717), 1915–1920. https://doi.org/10.1126/SCIENCE.1104816

Bass, J. Y., Caravella, J. A., Chen, L., Creech, K. L., Deaton, D. N., Madauss, K. P., Marr, H. B., McFadyen, R. B., Miller, A. B., Mills, W. Y., Navas, F., Parks, D. J., Smalley, T. L., Spearing, P. K., Todd, D., Williams, S. P., & Wisely, G. B. (2011). Conformationally constrained farnesoid X receptor (FXR) agonists: heteroaryl replacements of the naphthalene. *Bioorganic & Medicinal Chemistry Letters*, *21*(4), 1206–1213. https://doi.org/10.1016/J.BMCL.2010.12.089

Benoit, B., Meugnier, E., Castelli, M., Chanon, S., Vieille-Marchiset, A., Durand, C., Bendridi, N., Pesenti, S., Monternier, P. A., Durieux, A. C., Freyssenet, D., Rieusset, J., Lefai, E., Vidal, H., & Ruzzin, J. (2017). Fibroblast growth factor 19 regulates skeletal muscle mass and ameliorates muscle wasting in mice. *Nature Medicine*, *23*(8), 990–996. https://doi.org/10.1038/NM.4363

Blackburn, A. M., Christofides, N. D., Ghatei, M. A., Sarson, D. L., Ebeid, F. H., Ralphs, D. N., & Bloom, S. R. (1980). Elevation of plasma neurotensin in the dumping syndrome. *Clinical Science (London, England : 1979)*, *59*(4), 237–243. https://doi.org/10.1042/CS0590237

Bloom, S. R., Royston, C. M. S., & Thomson, J. P. S. (1972). Enteroglucagon release in the dumping syndrome. *Lancet (London, England)*, *2*(7781), 789–791. https://doi.org/10.1016/S0140-6736(72)92147-2

Boesjes, M., Bloks, V. W., Hageman, J., Bos, T., van Dijk, T. H., Havinga, R., Wolters, H., Jonker, J. W., Kuipers, F., & Groen, A. K. (2014). Hepatic Farnesoid X-Receptor Isoforms α2 and α4 Differentially Modulate Bile Salt and Lipoprotein Metabolism in Mice. *PLoS ONE*, *9*(12). https://doi.org/10.1371/JOURNAL.PONE.0115028

Bozadjieva, N., Heppner, K. M., & Seeley, R. J. (2018a). Targeting FXR and FGF19 to Treat Metabolic Diseases—Lessons Learned From Bariatric Surgery. *Diabetes*, *67*(9). https://doi.org/10.2337/DBI17-0007

Bozadjieva, N., Heppner, K. M., & Seeley, R. J. (2018b). Targeting FXR and FGF19 to Treat Metabolic Diseases—Lessons Learned From Bariatric Surgery. *Diabetes*, *67*(9), 1720. https://doi.org/10.2337/DBI17-0007

Bozadjieva, N., Heppner, K. M., & Seeley, R. J. (2018c). Targeting FXR and FGF19 to treat metabolic diseases-lessons learned from bariatric surgery. *Diabetes*, *67*(9), 1720–1728. https://doi.org/10.2337/DBI17-0007

Bray, G. A., & Gallagher, T. F. (1968). Suppression of appetite by bile acids. *Lancet (London, England)*, *1*(7551), 1066–1067. https://doi.org/10.1016/S0140-6736(68)91415-3

Broeders, E. P. M., Nascimento, E. B. M., Havekes, B., Brans, B., Roumans, K. H. M., Tailleux, A., Schaart, G., Kouach, M., Charton, J., Deprez, B., Bouvy, N. D., Mottaghy, F., Staels, B., van Marken Lichtenbelt, W. D., & Schrauwen, P. (2015). The Bile Acid Chenodeoxycholic Acid Increases Human Brown Adipose Tissue Activity. *Cell Metabolism*, *22*(3), 418–426. https://doi.org/10.1016/J.CMET.2015.07.002

Brubaker, P. L., Izzo, A., Hill, M., & Drucker, D. J. (1997). Intestinal function in mice with small bowel growth induced by glucagon-like peptide-2. *The American Journal of Physiology*, *272*(6 Pt 1). https://doi.org/10.1152/AJPENDO.1997.272.6.E1050

Buchwald, H., & Buchwald, J. N. (2019). Metabolic (bariatric and nonbariatric) surgery for type 2 diabetes: A personal perspective review. *Diabetes Care*, *42*(2), 331–340. https://doi.org/10.2337/DC17-2654

Cao, Y., Xiao, Y., Zhou, K., Yan, J., Wang, P., Yan, W., & Cai, W. (2019). FXR agonist GW4064 improves liver and intestinal pathology and alters bile acid metabolism in rats undergoing small intestinal resection. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *317*(2), G108–G115. https://doi.org/10.1152/AJPGI.00356.2017

Cariou, B., van Harmelen, K., Duran-Sandoval, D., van Dijk, T. H., Grefhorst, A., Abdelkarim, M., Caron, S., Torpier, G., Fruchart, J. C., Gonzalez, F. J., Kuipers, F., & Staels, B. (2006). The farnesoid X receptor modulates adiposity and peripheral insulin sensitivity in mice. *The Journal of Biological Chemistry*, *281*(16), 11039–11049. https://doi.org/10.1074/JBC.M510258200

Cerit, Z. (2017). Bariatric surgery, diabetes mellitus, and epicardial adipose tissue. *Nutrition, Metabolism and Cardiovascular Diseases*, *27*(6), 581. https://doi.org/10.1016/J.NUMECD.2017.03.007

Chandarana, K., Gelegen, C., Karra, E., Choudhury, A. I., Drew, M. E., Fauveau, V., Viollet, B., Andreelli, F., Withers, D. J., & Batterham, R. L. (2011). Diet and gastrointestinal bypass-induced weight loss: The roles of ghrelin and peptide YY. *Diabetes*, *60*(3), 810–818. https://doi.org/10.2337/DB10-0566

Chiang, J. Y. L. (2013). Bile Acid Metabolism and Signaling. *Comprehensive Physiology*, *3*(3), 1191. https://doi.org/10.1002/CPHY.C120023

Chiang, J. Y. L., & Ferrell, J. M. (2022). Discovery of farnesoid X receptor and its role in bile acid metabolism. *Molecular and Cellular Endocrinology*, *548*. https://doi.org/10.1016/j.mce.2022.111618

Chiang, J. Y. L., Kimmel, R., Weinberger, C., & Stroup, D. (2000). Farnesoid X receptor responds to bile acids and represses cholesterol 7alpha-hydroxylase gene (CYP7A1) transcription. *The Journal of Biological Chemistry*, *275*(15), 10918–10924. https://doi.org/10.1074/JBC.275.15.10918

Chow, M. D., Lee, Y. H., & Guo, G. L. (2017). The Role of Bile Acids in Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Molecular Aspects of Medicine*, *56*, 34. https://doi.org/10.1016/J.MAM.2017.04.004

Claudel, T., Sturm, E., Duez, H., Torra, I. P., Sirvent, A., Kosykh, V., Fruchart, J.-C., Dallongeville, J., Hum, D. W., Kuipers, F., & Staels, B. (2002). Bile acid-activated nuclear receptor FXR suppresses apolipoprotein A-I transcription via a negative FXR response element. *The Journal of Clinical Investigation*, *109*(7), 961. https://doi.org/10.1172/JCI14505

Colquitt, J. L., Pickett, K., Loveman, E., & Frampton, G. K. (2014). Surgery for weight loss in adults. *The Cochrane Database of Systematic Reviews*, *2014*(8). https://doi.org/10.1002/14651858.CD003641.PUB4

Cooper, T. C., Simmons, E. B., Webb, K., Burns, J. L., & Kushner, R. F. (2015). Trends in Weight Regain Following Roux-en-Y Gastric Bypass (RYGB) Bariatric Surgery. *Obesity Surgery*, *25*(8), 1474–1481. https://doi.org/10.1007/S11695-014-1560-Z

Crujeiras, A. B., Gomez-Arbelaez, D., Zulet, M. A., Carreira, M. C., Sajoux, I., de Luis, D., Castro, A. I., Baltar, J., Baamonde, I., Sueiro, A., Maclas-Gonzalez, M., Bellido, D., Tinahones, F. J., Martinez, J. A., & Casanueva, F. F. (2017). Plasma FGF21 levels in obese patients undergoing energy-restricted diets or bariatric surgery: A marker of metabolic stress? *International Journal of Obesity*, *41*(10), 1570–1578. https://doi.org/10.1038/IJO.2017.138

Dash, A., Figler, R. A., Blackman, B. R., Marukian, S., Collado, M. S., Lawson, M. J., Hoang, S. A., Mackey, A. J., Manka, D., Cole, B. K., Feaver, R. E., Sanyal, A. J., & Wamhoff, B. R. (2017). Pharmacotoxicology of Clinically-Relevant Concentrations of Obeticholic Acid in an Organotypic Human Hepatocyte System. *Toxicology in Vitro : An International Journal Published in Association with BIBRA*, *39*, 93. https://doi.org/10.1016/J.TIV.2016.11.014

Deng, R., Yang, D., Yang, J., & Yan, B. (2006). Oxysterol 22(R)-hydroxycholesterol induces the expression of the bile salt export pump through nuclear receptor farsenoid X receptor but not liver X receptor. *The Journal of Pharmacology and Experimental Therapeutics*, *317*(1), 317–325. https://doi.org/10.1124/JPET.105.097758

DePaoli, A. M., Zhou, M., Kaplan, D. D., Hunt, S. C., Adams, T. D., Marc Learned, R., Tian, H., & Ling, L. (2019). FGF19 analog as a surgical factor mimetic that contributes to metabolic effects beyond glucose homeostasis. *Diabetes*, *68*(6), 1315–1328. https://doi.org/10.2337/DB18-1305

di Lorenzo, N., Antoniou, S. A., Batterham, R. L., Busetto, L., Godoroja, D., Iossa, A., Carrano, F. M., Agresta, F., Alarçon, I., Azran, C., Bouvy, N., Balaguè Ponz, C., Buza, M., Copaescu, C., de Luca, M., Dicker, D., di Vincenzo, A., Felsenreich, D. M., Francis, N. K., … Silecchia, G. (2020). Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. *Surgical Endoscopy*, *34*(6), 2332. https://doi.org/10.1007/S00464-020-07555-Y

Dimitriadis, G. K., Randeva, M. S., & Miras, A. D. (2017). Potential Hormone Mechanisms of Bariatric Surgery. *Current Obesity Reports*, *6*(3), 253. https://doi.org/10.1007/S13679-017-0276-5

Domenech-Ximenos, B., Cuba, V., Daunis-i-Estadella, P., Thió-Henestrosa, S., Jaldo, F., Biarnes, C., Molina, X., Xifra, G., Ricart, W., Bardera, A., Boada, I., Essig, M., Pedraza, S., Federici, M., Fernández-Real, J. M., & Puig, J. (2020). Bariatric Surgery-Induced Changes in Intima-Media Thickness and Cardiovascular Risk Factors in Class 3 Obesity: A 3-Year Follow-Up Study. *Obesity*, *28*(9), 1663–1670. https://doi.org/10.1002/OBY.22905

Doumouras, A. G., Wong, J. A., Paterson, J. M., Lee, Y., Sivapathasundaram, B., Tarride, J. E., Thabane, L., Hong, D., Yusuf, S., & Anvari, M. (2021). Bariatric Surgery and Cardiovascular Outcomes in Patients with Obesity and Cardiovascular Disease: A Population-Based Retrospective Cohort Study. *Circulation*, *143*(15), 1468–1480. https://doi.org/10.1161/CIRCULATIONAHA.120.052386

Douris, N., Stevanovic, D. M., Fisher, F. M., Cisu, T. I., Chee, M. J., Nguyen, N. L., Zarebidaki, E., Adams, A. C., Kharitonenkov, A., Flier, J. S., Bartness, T. J., & Maratos-Flier, E. (2015). Central Fibroblast Growth Factor 21 Browns White Fat via Sympathetic Action in Male Mice. *Endocrinology*, *156*(7), 2470–2481. https://doi.org/10.1210/EN.2014-2001

Downes, M., Verdecia, M. A., Roecker, A. J., Hughes, R., Hogenesch, J. B., Kast-Woelbern, H. R., Bowman, M. E., Ferrer, J. L., Anisfeld, A. M., Edwards, P. A., Rosenfeld, J. M., Alvarez, J. G. A., Noel, J. P., Nicolaou, K. C., & Evans, R. M. (2003). A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR. *Molecular Cell*, *11*(4), 1079–1092. https://doi.org/10.1016/S1097-2765(03)00104-7

Düfer, M., Hörth, K., Wagner, R., Schittenhelm, B., Prowald, S., Wagner, T. F. J., Oberwinkler, J., Lukowski, R., Gonzalez, F. J., Krippeit-Drews, P., & Drews, G. (2012). Bile acids acutely stimulate insulin secretion of mouse β-cells via farnesoid X receptor activation and K ATP channel inhibition. *Diabetes*, *61*(6), 1479–1489. https://doi.org/10.2337/DB11-0815/-/DC1

Evers, S. S., Sandoval, D. A., & Seeley, R. J. (2017). The Physiology and Molecular Underpinnings of the Effects of Bariatric Surgery on Obesity and Diabetes. *The Annual Review of Physiology Is Online At*, *79*, 313–347. https://doi.org/10.1146/annurev-physiol-022516-034423

Fang, S., Suh, J. M., Reilly, S. M., Yu, E., Osborn, O., Lackey, D., Yoshihara, E., Perino, A., Jacinto, S., Lukasheva, Y., Atkins, A. R., Khvat, A., Schnabl, B., Yu, R. T., Brenner, D. A., Coulter, S., Liddle, C., Schoonjans, K., Olefsky, J. M., … Evans, R. M. (2015a). Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nature Medicine*, *21*(2), 159. https://doi.org/10.1038/NM.3760

Fang, S., Suh, J. M., Reilly, S. M., Yu, E., Osborn, O., Lackey, D., Yoshihara, E., Perino, A., Jacinto, S., Lukasheva, Y., Atkins, A. R., Khvat, A., Schnabl, B., Yu, R. T., Brenner, D. A., Coulter, S., Liddle, C., Schoonjans, K., Olefsky, J. M., … Evans, R. M. (2015b). Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nature Medicine*, *21*(2), 159. https://doi.org/10.1038/NM.3760

Fernandes, R., Beserra, B. T. S., Mocellin, M. C., Kuntz, M. G. F., da Rosa, J. S., de Miranda, R. C. D., Schreiber, C. S. O., Fröde, T. S., Nunes, E. A., & Trindade, E. B. S. M. (2016). Effects of Prebiotic and

Synbiotic Supplementation on Inflammatory Markers and Anthropometric Indices After Roux-en-Y Gastric Bypass: A Randomized, Triple-blind, Placebo-controlled Pilot Study. *Journal of Clinical Gastroenterology*, *50*(3), 208–217. https://doi.org/10.1097/MCG.0000000000000328

Ferrannini, E., Natali, A., Bell, P., Cavallo-Perin, P., Lalic, N., & Mingrone, G. (1997). Insulin resistance and hypersecretion in obesity. *Journal of Clinical Investigation*, *100*(5), 1166–1173. https://doi.org/10.1172/JCI119628

Fiorucci, S., Biagioli, M., Sepe, V., Zampella, A., & Distrutti, E. (2020). Bile acid modulators for the treatment of nonalcoholic steatohepatitis (NASH). *Expert Opinion on Investigational Drugs*, *29*(6), 623–632. https://doi.org/10.1080/13543784.2020.1763302

Fisher, D. P., Johnson, E., Haneuse, S., Arterburn, D., Coleman, K. J., O'Connor, P. J., O'Brien, R., Bogart, A., Theis, M. K., Anau, J., Schroeder, E. B., & Sidney, S. (2018). Association between Bariatric Surgery and Macrovascular Disease Outcomes in Patients with Type 2 Diabetes and Severe Obesity. *JAMA - Journal of the American Medical Association*, *320*(15), 1570–1582. https://doi.org/10.1001/JAMA.2018.14619

Fisher, F. M., & Maratos-Flier, E. (2016). Understanding the Physiology of FGF21. *Annual Review of Physiology*, *78*, 223–241. https://doi.org/10.1146/ANNUREV-PHYSIOL-021115-105339

Flynn, C. R., Albaugh, V. L., Cai, S., Cheung-Flynn, J., Williams, P. E., Brucker, R. M., Bordenstein, S. R., Guo, Y., Wasserman, D. H., & Abumrad, N. N. (2015). Bile diversion to the distal small intestine has comparable metabolic benefits to bariatric surgery. *Nature Communications*, *6*. https://doi.org/10.1038/NCOMMS8715

Forman, B. M., Goode, E., Chen, J., Oro, A. E., Bradley, D. J., Perlmann, T., Noonan, D. J., Burka, L. T., McMorris, T., Lamph, W. W., Evans, R. M., & Weinberger, C. (1995). Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell*, *81*(5), 687–693. https://doi.org/10.1016/0092-8674(95)90530-8

Fu, T., Coulter, S., Yoshihara, E., Oh, T. G., Fang, S., Cayabyab, F., Zhu, Q., Zhang, T., Leblanc, M., Liu, S., He, M., Waizenegger, W., Gasser, E., Schnabl, B., Atkins, A. R., Yu, R. T., Knight, R., Liddle, C., Downes, M., & Evans, R. M. (2019). FXR regulates intestinal cancer stem cell proliferation. *Cell*, *176*(5), 1098. https://doi.org/10.1016/J.CELL.2019.01.036

GBD 2015 Obesity Collaborators. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *The New England Journal of Medicine*, *377*(1), 13. https://doi.org/10.1056/NEJMOA1614362

Gioiello, A., Cerra, B., Mostarda, S., Guercini, C., Pellicciari, R., & Macchiarulo, A. (2014). Bile acid derivatives as ligands of the farnesoid x receptor: molecular determinants for bile acid binding and receptor modulation. *Current Topics in Medicinal Chemistry*, *14*(19), 2159–2174. https://doi.org/10.2174/1568026614666141112100208

Gómez-Ambrosi, J., Gallego-Escuredo, J. M., Catalán, V., Rodríguez, A., Domingo, P., Moncada, R., Valentí, V., Salvador, J., Giralt, M., Villarroya, F., & Frühbeck, G. (2017a). FGF19 and FGF21 serum concentrations in human obesity and type 2 diabetes behave differently after diet- or surgically-

induced weight loss. *Clinical Nutrition*, *36*(3), 861–868. https://doi.org/10.1016/J.CLNU.2016.04.027

Gómez-Ambrosi, J., Gallego-Escuredo, J. M., Catalán, V., Rodríguez, A., Domingo, P., Moncada, R., Valentí, V., Salvador, J., Giralt, M., Villarroya, F., & Frühbeck, G. (2017b). FGF19 and FGF21 serum concentrations in human obesity and type 2 diabetes behave differently after diet- or surgically-induced weight loss. *Clinical Nutrition*, *36*(3), 861–868. https://doi.org/10.1016/J.CLNU.2016.04.027

Goodwin, B., Jones, S. A., Price, R. R., Watson, M. A., McKee, D. D., Moore, L. B., Galardi, C., Wilson, J. G., Lewis, M. C., Roth, M. E., Maloney, P. R., Willson, T. M., & Kliewer, S. A. (2000). A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. *Molecular Cell*, *6*(3), 517–526. https://doi.org/10.1016/S1097-2765(00)00051-4

Guerrero-Pérez, F., Casajoana, A., Gómez-Vaquero, C., Virgili, N., López-Urdiales, R., Hernández-Montoliu, L., Pujol-Gebelli, J., Osorio, J., Alves, C., Perez-Maraver, M., Pellitero, S., Vidal-Alabró, A., Fernández-Veledo, S., Vendrell, J., & Vilarrasa, N. (2020). Changes in Bone Mineral Density in Patients with Type 2 Diabetes After Different Bariatric Surgery Procedures and the Role of Gastrointestinal Hormones. *Obesity Surgery*, *30*(1), 180–188. https://doi.org/10.1007/S11695-019-04127-5

Habegger, K. M., Al-Massadi, O., Heppner, K. M., Myronovych, A., Holland, J., Berger, J., Yi, C. X., Gao, Y., Lehti, M., Ottaway, N., Amburgy, S., Raver, C., Müller, T. D., Pfluger, P. T., Kohli, R., Perez- Tilve, D., Seeley, R. J., & Tschöp, M. H. (2014). Duodenal nutrient exclusion improves metabolic syndrome and stimulates villus hyperplasia. *Gut*, *63*(8), 1238–1246. https://doi.org/10.1136/GUTJNL-2013-304583

Hankir, M. K., Rullmann, M., Seyfried, F., Preusser, S., Poppitz, S., Heba, S., Gousias, K., Hoyer, J., Schütz, T., Dietrich, A., Müller, K., & Pleger, B. (2019). Roux-en-Y gastric bypass surgery progressively alters radiologic measures of hypothalamic inflammation in obese patients. *JCI Insight*, *4*(19). https://doi.org/10.1172/JCI.INSIGHT.131329

Harris, L. A. L. S., Smith, G. I., Mittendorfer, B., Eagon, J. C., Okunade, A. L., Patterson, B. W., & Klein, S. (2017a). Roux-en-Y gastric bypass surgery has unique effects on postprandial FGF21 but not FGF19 secretion. *Journal of Clinical Endocrinology and Metabolism*, *102*(10), 3858–3864. https://doi.org/10.1210/JC.2017-01295

Harris, L. A. L. S., Smith, G. I., Mittendorfer, B., Eagon, J. C., Okunade, A. L., Patterson, B. W., & Klein, S. (2017b). Roux-en-Y gastric bypass surgery has unique effects on postprandial FGF21 but not FGF19 secretion. *Journal of Clinical Endocrinology and Metabolism*, *102*(10), 3858–3864. https://doi.org/10.1210/JC.2017-01295

Harrison, S. A., Rinella, M. E., Abdelmalek, M. F., Trotter, J. F., Paredes, A. H., Arnold, H. L., Kugelmas, M., Bashir, M. R., Jaros, M. J., Ling, L., Rossi, S. J., DePaoli, A. M., & Loomba, R. (2018). NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet (London, England)*, *391*(10126), 1174–1185. https://doi.org/10.1016/S0140-6736(18)30474-4

Heymsfield, S. B., Bourgeois, B., & Thomas, D. M. (2017). Why is it Difficult to Lose and Maintain Large Amounts of Weight with Lifestyle and Pharmacologic Treatments? *Obesity (Silver Spring, Md.)*, *25*(12), 2017. https://doi.org/10.1002/OBY.22045

Hoeke, M. O., Plass, J. R. M., Heegsma, J., Geuken, M., van Rijsbergen, D., Baller, J. F. W., Kuipers, F., Moshage, H., Jansen, P. L. M., & Faber, K. N. (2009). Low retinol levels differentially modulate bile salt-induced expression of human and mouse hepatic bile salt transporters. *Hepatology (Baltimore, Md.)*, *49*(1), 151–159. https://doi.org/10.1002/HEP.22661

Hutch, C. R., & Sandoval, D. (2017). The role of GLP-1 in the metabolic success of bariatric surgery. *Endocrinology*, *158*(12), 4139–4151. https://doi.org/10.1210/EN.2017-00564

Ijssennagger, N., Janssen, A. W. F., Milona, A., Ramos Pittol, J. M., Hollman, D. A. A., Mokry, M., Betzel, B., Berends, F. J., Janssen, I. M., van Mil, S. W. C., & Kersten, S. (2016). Gene expression profiling in human precision cut liver slices in response to the FXR agonist obeticholic acid. *Journal of Hepatology*, *64*(5), 1158–1166. https://doi.org/10.1016/J.JHEP.2016.01.016

Inagaki, T., Choi, M., Moschetta, A., Peng, L., Cummins, C. L., McDonald, J. G., Luo, G., Jones, S. A., Goodwin, B., Richardson, J. A., Gerard, R. D., Repa, J. J., Mangelsdorf, D. J., & Kliewer, S. A. (2005). Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metabolism*, *2*(4), 217–225. https://doi.org/10.1016/J.CMET.2005.09.001

Ito, S., Iwasaki, Y., Momotsu, T., Takai, K., Shibata, A., Matsubara, Y., & Muto, T. (1981). Neurotensin and substance P and dumping syndrome. *The Tohoku Journal of Experimental Medicine*, *135*(1), 11–21. https://doi.org/10.1620/TJEM.135.11

Ji, Y., Lee, H., Kaura, S., Yip, J., Sun, H., Guan, L., Han, W., & Ding, Y. (2021a). Effect of Bariatric Surgery on Metabolic Diseases and Underlying Mechanisms. *Biomolecules*, *11*(11). https://doi.org/10.3390/BIOM11111582

Ji, Y., Lee, H., Kaura, S., Yip, J., Sun, H., Guan, L., Han, W., & Ding, Y. (2021b). Effect of Bariatric Surgery on Metabolic Diseases and Underlying Mechanisms. *Biomolecules*, *11*(11). https://doi.org/10.3390/BIOM11111582

Ji, Y., Lee, H., Kaura, S., Yip, J., Sun, H., Guan, L., Han, W., & Ding, Y. (2021c). Effect of Bariatric Surgery on Metabolic Diseases and Underlying Mechanisms. *Biomolecules*, *11*(11). https://doi.org/10.3390/BIOM11111582

Jiang, C., Xie, C., Li, F., Zhang, L., Nichols, R. G., Krausz, K. W., Cai, J., Qi, Y., Fang, Z. Z., Takahashi, S., Tanaka, N., Desai, D., Amin, S. G., Albert, I., Patterson, A. D., & Gonzalez, F. J. (2015). Intestinal farnesoid X receptor signaling promotes nonalcoholic fatty liver disease. *The Journal of Clinical Investigation*, *125*(1), 386. https://doi.org/10.1172/JCI76738

Jiang, C., Xie, C., Lv, Y., Li, J., Krausz, K. W., Shi, J., Brocker, C. N., Desai, D., Amin, S. G., Bisson, W. H., Liu, Y., Gavrilova, O., Patterson, A. D., & Gonzalez, F. J. (2015). Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction. *Nature Communications*, *6*. https://doi.org/10.1038/NCOMMS10166

Jiang, L., Zhang, H., Xiao, D., Wei, H., & Chen, Y. (2021). Farnesoid X receptor (FXR): Structures and ligands. *Computational and Structural Biotechnology Journal*, *19*, 2148. https://doi.org/10.1016/J.CSBJ.2021.04.029

Jiménez, A., Casamitjana, R., Viaplana-Masclans, J., Lacy, A., & Vidal, J. (2013). GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. *Diabetes Care*, *36*(7), 2062–2069. https://doi.org/10.2337/DC12-1535

Jiménez, A., Mari, A., Casamitjana, R., Lacy, A., Ferrannini, E., & Vidal, J. (2014). GLP-1 and glucose tolerance after sleeve gastrectomy in morbidly obese subjects with type 2 diabetes. *Diabetes*, *63*(10), 3372–3377. https://doi.org/10.2337/DB14-0357

Jørgensen, N. B., Jacobsen, S. H., Dirksen, C., Bojsen-Møller, K. N., Naver, L., Hvolris, L., Clausen, T. R., Wulff, B. S., Worm, D., Lindqvist Hansen, D., Madsbad, S., & Holst, J. J. (2012). Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *American Journal of Physiology - Endocrinology and Metabolism*, *303*(1). https://doi.org/10.1152/AJPENDO.00073.2012

Karcz, W. K., Krawczykowski, D., Kuesters, S., Marjanovic, G., Kulemann, B., Grobe, H., Karcz-Socha, I., Hopt, U. T., Bukhari, W., & Grueneberger, J. M. (2011). Influence of sleeve gastrectomy on NASH and type 2 diabetes mellitus. *Journal of Obesity*, *2011*. https://doi.org/10.1155/2011/765473

Kemper, J. K. (2011). Regulation of FXR Transcriptional Activity in Health and Disease: Emerging Roles of FXR Cofactors and Post-Translational Modifications. *Biochimica et Biophysica Acta*, *1812*(8), 842. https://doi.org/10.1016/J.BBADIS.2010.11.011

Kinzel, O., Steeneck, C., Schlüter, T., Schulz, A., Gege, C., Hahn, U., Hambruch, E., Hornberger, M., Spalwisz, A., Frick, K., Perović-Ottstadt, S., Deuschle, U., Burnet, M., & Kremoser, C. (2016). Novel substituted isoxazole FXR agonists with cyclopropyl, hydroxycyclobutyl and hydroxyazetidinyl linkers: Understanding and improving key determinants of pharmacological properties. *Bioorganic & Medicinal Chemistry Letters*, *26*(15), 3746–3753. https://doi.org/10.1016/J.BMCL.2016.05.070

Kohli, R., Kirby, M., Setchell, K. D. R., Jha, P., Klustaitis, K., Woollett, L. A., Pfluger, P. T., Balistreri, W. F., Tso, P., Jandacek, R. J., Woods, S. C., Heubi, J. E., Tschoep, M. H., D'Alessio, D. A., Shroyer, N. F., & Seeley, R. J. (2010a). Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity-related comorbidities. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *299*(3), G652. https://doi.org/10.1152/AJPGI.00221.2010

Kohli, R., Kirby, M., Setchell, K. D. R., Jha, P., Klustaitis, K., Woollett, L. A., Pfluger, P. T., Balistreri, W. F., Tso, P., Jandacek, R. J., Woods, S. C., Heubi, J. E., Tschoep, M. H., D'Alessio, D. A., Shroyer, N. F., & Seeley, R. J. (2010b). Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity-related comorbidities. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *299*(3). https://doi.org/10.1152/AJPGI.00221.2010

Kohli, R., Myronovych, A., Tan, B. K., Salazar-Gonzalez, R. M., Miles, L., Zhang, W., Oehrle, M., Sandoval, D. A., Ryan, K. K., Seeley, R. J., & Setchell, K. D. R. (2015). Bile Acid Signaling: Mechanism for Bariatric Surgery, Cure for NASH? *Digestive Diseases (Basel, Switzerland)*, *33*(3), 440–446. https://doi.org/10.1159/000371699

Korner, J., Inabnet, W., Febres, G., Conwell, I. M., McMahon, D. J., Salas, R., Taveras, C., Schrope, B., & Bessler, M. (2009). Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. *International Journal of Obesity (2005)*, *33*(7), 786–795. https://doi.org/10.1038/IJO.2009.79

Kullman, E. L., Kelly, K. R., Haus, J. M., Fealy, C. E., Scelsi, A. R., Pagadala, M. R., Flask, C. A., McCullough, A. J., & Kirwan, J. P. (2016). Short-Term aerobic exercise training improves gut peptide regulation in nonalcoholic fatty liver disease. *Journal of Applied Physiology*, *120*(10), 1159–1164. https://doi.org/10.1152/JAPPLPHYSIOL.00693.2015

Kuro-O, M. (2012). Klotho and βKlotho. *Advances in Experimental Medicine and Biology*, *728*, 25–40. https://doi.org/10.1007/978-1-4614-0887-1_2

Lan, T., Morgan, D. A., Rahmouni, K., Sonoda, J., Fu, X., Burgess, S. C., Holland, W. L., Kliewer, S. A., & Mangelsdorf, D. J. (2017a). FGF19, FGF21 and an FGFR1/β-Klotho-activating Antibody Act on the Nervous System to Regulate Body Weight and Glycemia. *Cell Metabolism*, *26*(5), 709. https://doi.org/10.1016/J.CMET.2017.09.005

Lan, T., Morgan, D. A., Rahmouni, K., Sonoda, J., Fu, X., Burgess, S. C., Holland, W. L., Kliewer, S. A., & Mangelsdorf, D. J. (2017b). FGF19, FGF21 and an FGFR1/β-Klotho-activating Antibody Act on the Nervous System to Regulate Body Weight and Glycemia. *Cell Metabolism*, *26*(5), 709. https://doi.org/10.1016/J.CMET.2017.09.005

Lawaetz, O., Blackburn, A. M., Bloom, S. R., Aritas, Y., & Ralphs, D. N. L. (1983). Gut hormone profile and gastric emptying in the dumping syndrome. A hypothesis concerning the pathogenesis. *Scandinavian Journal of Gastroenterology*, *18*(1), 73–80. https://doi.org/10.3109/00365528309181562

le Roux, C. W., Borg, C., Wallis, K., Vincent, R. P., Bueter, M., Goodlad, R., Ghatei, M. A., Patel, A., Bloom, S. R., & Aylwin, S. J. B. (2010a). Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. *Annals of Surgery*, *252*(1), 50–56. https://doi.org/10.1097/SLA.0B013E3181D3D21F

le Roux, C. W., Borg, C., Wallis, K., Vincent, R. P., Bueter, M., Goodlad, R., Ghatei, M. A., Patel, A., Bloom, S. R., & Aylwin, S. J. B. (2010b). Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. *Annals of Surgery*, *252*(1), 50–56. https://doi.org/10.1097/SLA.0B013E3181D3D21F

le Roux, C. W., & Bueter, M. (2014). The physiology of altered eating behaviour after Roux-en-Y gastric bypass. *Experimental Physiology*, *99*(9), 1128–1132. https://doi.org/10.1113/EXPPHYSIOL.2014.078378

Lee, S. J., & Shin, S. W. (2017). Mechanisms, Pathophysiology, and Management of Obesity. *The New England Journal of Medicine*, *376*(15), 1491–1492. https://doi.org/10.1056/NEJMc1701944

Li, B., Lu, Y., Srikant, C. B., Gao, Z. H., & Liu, J. L. (2013). Intestinal adaptation and Reg gene expression induced by antidiabetic duodenal-jejunal bypass surgery in Zucker fatty rats. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *304*(7). https://doi.org/10.1152/AJPGI.00275.2012

Li, F., Jiang, C., Krausz, K. W., Li, Y., Albert, I., Hao, H., Fabre, K. M., Mitchell, J. B., Patterson, A. D., & Gonzalez, F. J. (2013). Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nature Communications*, *4*. https://doi.org/10.1038/NCOMMS3384

Lundåsen, T., Hunt, M. C., Nilsson, L. M., Sanyal, S., Angelin, B., Alexson, S. E. H., & Rudling, M. (2007). PPARalpha is a key regulator of hepatic FGF21. *Biochemical and Biophysical Research Communications*, *360*(2), 437–440. https://doi.org/10.1016/J.BBRC.2007.06.068

Magouliotis, D. E., Tasiopoulou, V. S., Sioka, E., Chatedaki, C., & Zacharoulis, D. (2017). Impact of Bariatric Surgery on Metabolic and Gut Microbiota Profile: a Systematic Review and Meta-analysis. *Obesity Surgery*, *27*(5), 1345–1357. https://doi.org/10.1007/S11695-017-2595-8

Maloney, P. R., Parks, D. J., Haffner, C. D., Fivush, A. M., Chandra, G., Plunket, K. D., Creech, K. L., Moore, L. B., Wilson, J. G., Lewis, M. C., Jones, S. A., & Willson, T. M. (2000). Identification of a chemical tool for the orphan nuclear receptor FXR. *Journal of Medicinal Chemistry*, *43*(16), 2971–2974. https://doi.org/10.1021/JM0002127

Manning, S., Pucci, A., & Batterham, R. L. (2015). GLP-1: A mediator of the beneficial metabolic effects of bariatric surgery? *Physiology*, *30*(1), 50–62. https://doi.org/10.1152/PHYSIOL.00027.2014

Martinez de la Escalera, L., Kyrou, I., Vrbikova, J., Hainer, V., Sramkova, P., Fried, M., Piya, M. K., Kumar, S., Tripathi, G., & McTernan, P. G. (2017a). Impact of gut hormone FGF-19 on type-2 diabetes and mitochondrial recovery in a prospective study of obese diabetic women undergoing bariatric surgery. *BMC Medicine*, *15*(1). https://doi.org/10.1186/S12916-017-0797-5

Martinez de la Escalera, L., Kyrou, I., Vrbikova, J., Hainer, V., Sramkova, P., Fried, M., Piya, M. K., Kumar, S., Tripathi, G., & McTernan, P. G. (2017b). Impact of gut hormone FGF-19 on type-2 diabetes and mitochondrial recovery in a prospective study of obese diabetic women undergoing bariatric surgery. *BMC Medicine*, *15*(1). https://doi.org/10.1186/S12916-017-0797-5

Massafra, V., Pellicciari, R., Gioiello, A., & van Mil, S. W. C. (2018). Progress and challenges of selective Farnesoid X Receptor modulation. *Pharmacology & Therapeutics*, *191*, 162–177. https://doi.org/10.1016/J.PHARMTHERA.2018.06.009

Mattar, S. G., Velcu, L. M., Rabinovitz, M., Demetris, A. J., Krasinskas, A. M., Barinas-Mitchell, E., Eid, G. M., Ramanathan, R., Taylor, D. S., Schauer, P. R., Sugerman, H. J., Wolfe, B. M., Ascher, N. L., Sarr, M. G., & Pellegrini, C. A. (2005). Surgically-induced weight loss significantly improves nonalcoholic fatty liver disease and the metabolic syndrome. *Annals of Surgery*, *242*(4), 610–620. https://doi.org/10.1097/01.SLA.0000179652.07502.3F

McGavigan, A. K., Garibay, D., Henseler, Z. M., Chen, J., Bettaieb, A., Haj, F. G., Ley, R. E., Chouinard, M. L., & Cummings, B. P. (2017). TGR5 contributes to glucoregulatory improvements after vertical sleeve gastrectomy in mice. *Gut*, *66*(2), 226–234. https://doi.org/10.1136/GUTJNL-2015-309871

Miao, J., Choi, S. E., Seok, S. M., Yang, L., Zuercher, W. J., Xu, Y., Willson, T. M., Eric Xu, H., & Kemper, J. K. (2011). Ligand-dependent regulation of the activity of the orphan nuclear receptor, small heterodimer partner (SHP), in the repression of bile acid biosynthetic CYP7A1 and CYP8B1 genes.

Molecular Endocrinology (Baltimore, Md.), *25*(7), 1159–1169. https://doi.org/10.1210/ME.2011-0033

Mohapatra, S., Gangadharan, K., & Pitchumoni, C. S. (2020). Malnutrition in obesity before and after bariatric surgery. *Disease-a-Month : DM*, *66*(2). https://doi.org/10.1016/J.DISAMONTH.2019.06.008

Moretto, M., Kupski, C., da Silva, V. D., Padoin, A. v., & Mottin, C. C. (2012). Effect of bariatric surgery on liver fibrosis. *Obesity Surgery*, *22*(7), 1044–1049. https://doi.org/10.1007/S11695-011-0559-Y

Morton, G. J., Matsen, M. E., Bracy, D. P., Meek, T. H., Nguyen, H. T., Stefanovski, D., Bergman, R. N., Wasserman, D. H., & Schwartz, M. W. (2013). FGF19 action in the brain induces insulin-independent glucose lowering. *The Journal of Clinical Investigation*, *123*(11), 4799. https://doi.org/10.1172/JCI70710

Mottin, C. C., Moretto, M., Padoin, A. V., Kupski, C., Swarowsky, A. M., Glock, L., Duval, V., & Braga Da Silva, J. (2005). Histological behavior of hepatic steatosis in morbidly obese patients after weight loss induced by bariatric surgery. *Obesity Surgery*, *15*(6), 788–793. https://doi.org/10.1381/0960892054222830

Mulla, C. M., Goldfine, A. B., Dreyfuss, J. M., Houten, S., Pan, H., Pober, D. M., Wewer Albrechtsen, N. J., Svane, M. S., Schmidt, J. B., Holst, J. J., Craig, C. M., McLaughlin, T. L., & Patti, M. E. (2019). Plasma FGF-19 Levels are Increased in Patients with Post-Bariatric Hypoglycemia. *Obesity Surgery*, *29*(7), 2092. https://doi.org/10.1007/S11695-019-03845-0

Mumphrey, M. B., Hao, Z., Townsend, R. L., Patterson, L. M., & Berthoud, H. R. (2015). Sleeve Gastrectomy Does Not Cause Hypertrophy and Reprogramming of Intestinal Glucose Metabolism in Rats. *Obesity Surgery*, *25*(8), 1468–1473. https://doi.org/10.1007/S11695-014-1547-9

Mumphrey, M. B., Patterson, L. M., Zheng, H., & Berthoud, H. R. (2013). Roux-en-Y gastric bypass surgery increases number but not density of CCK-, GLP-1-, 5-HT-, and neurotensin-expressing enteroendocrine cells in rats. *Neurogastroenterology and Motility : The Official Journal of the European Gastrointestinal Motility Society*, *25*(1). https://doi.org/10.1111/NMO.12034

Myronovych, A., Kirby, M., Ryan, K. K., Zhang, W., Jha, P., Setchell, K. D., Dexheimer, P. J., Aronow, B., Seeley, R. J., & Kohli, R. (2014a). Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. *Obesity (Silver Spring, Md.)*, *22*(2), 390. https://doi.org/10.1002/OBY.20548

Myronovych, A., Kirby, M., Ryan, K. K., Zhang, W., Jha, P., Setchell, K. D., Dexheimer, P. J., Aronow, B., Seeley, R. J., & Kohli, R. (2014b). Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. *Obesity (Silver Spring, Md.)*, *22*(2), 390–400. https://doi.org/10.1002/OBY.20548

Neary, M. T., & Batterham, R. L. (2009). Gut hormones: Implications for the treatment of obesity. *Pharmacology and Therapeutics*, *124*, 44–56. https://doi.org/10.1016/j.pharmthera.2009.06.005

Nemati, R., Lu, J., Dokpuang, D., Booth, M., Plank, L. D., & Murphy, R. (2018). Increased Bile Acids and FGF19 After Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Correlate with Improvement in

Type 2 Diabetes in a Randomized Trial. *Obesity Surgery*, *28*(9), 2672–2686. https://doi.org/10.1007/S11695-018-3216-X

O'Brien, P. E., Hindle, A., Brennan, L., Skinner, S., Burton, P., Smith, A., Crosthwaite, G., & Brown, W. (2019). Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. *Obesity Surgery*, *29*(1), 3. https://doi.org/10.1007/S11695-018-3525-0

Osto, E., Doytcheva, P., Corteville, C., Bueter, M., Dörig, C., Stivala, S., Buhmann, H., Colin, S., Rohrer, L., Hasballa, R., Tailleux, A., Wolfrum, C., Tona, F., Manz, J., Vetter, D., Spliethoff, K., Vanhoutte, P. M., Landmesser, U., Pattou, F., … Lüscher, T. F. (2015). Rapid and body weight-independent improvement of endothelial and high-density lipoprotein function after Roux-en-Y gastric bypass role of glucagon-like peptide-1. *Circulation*, *131*(10), 871–881. https://doi.org/10.1161/CIRCULATIONAHA.114.011791

Ovadia, C., Perdones-Montero, A., Spagou, K., Smith, A., Sarafian, M. H., Gomez-Romero, M., Bellafante, E., Clarke, L. C. D., Sadiq, F., Nikolova, V., Mitchell, A., Dixon, P. H., Santa-Pinter, N., Wahlström, A., Abu-Hayyeh, S., Walters, J. R. F., Marschall, H. U., Holmes, E., Marchesi, J. R., & Williamson, C. (2019). Enhanced Microbial Bile Acid Deconjugation and Impaired Ileal Uptake in Pregnancy Repress Intestinal Regulation of Bile Acid Synthesis. *Hepatology (Baltimore, Md.)*, *70*(1), 276. https://doi.org/10.1002/HEP.30661

Owei, I., Umekwe, N., Provo, C., Wan, J., & Dagogo-Jack, S. (2017). Insulin-sensitive and insulin-resistant obese and non-obese phenotypes: role in prediction of incident pre-diabetes in a longitudinal biracial cohort. *BMJ Open Diabetes Research & Care*, *5*(1). https://doi.org/10.1136/BMJDRC-2017-000415

Owen, B. M., Ding, X., Morgan, D. A., Coate, K. C., Bookout, A. L., Rahmouni, K., Kliewer, S. A., & Mangelsdorf, D. J. (2014). FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metabolism*, *20*(4), 670–677. https://doi.org/10.1016/J.CMET.2014.07.012

Parrott, J., Frank, L., Rabena, R., Craggs-Dino, L., Isom, K. A., & Greiman, L. (2017). American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. *Surgery for Obesity and Related Diseases*, *13*(5), 727–741. https://doi.org/10.1016/J.SOARD.2016.12.018

Pathak, P., Xie, C., Nichols, R. G., Ferrell, J. M., Boehme, S., Krausz, K. W., Patterson, A. D., Gonzalez, F. J., & Chiang, J. Y. L. (2018). Intestine farnesoid X receptor agonist and the gut microbiota activate G-protein bile acid receptor-1 signaling to improve metabolism. *Hepatology (Baltimore, Md.)*, *68*(4), 1574. https://doi.org/10.1002/HEP.29857

Patti, M. E., Houten, S. M., Bianco, A. C., Bernier, R., Larsen, P. R., Holst, J. J., Badman, M. K., Maratos-Flier, E., Mun, E. C., Pihlajamaki, J., Auwerx, J., & Goldfine, A. B. (2009). Serum Bile Acids Are Higher in Humans With Prior Gastric Bypass: Potential Contribution to Improved Glucose and Lipid Metabolism. *Obesity (Silver Spring, Md.)*, *17*(9), 1671. https://doi.org/10.1038/OBY.2009.102

Peat, C. M., Kleiman, S. C., Bulik, C. M., & Carroll, I. M. (2015). The Intestinal Microbiome in Bariatric Surgery Patients. *European Eating Disorders Review : The Journal of the Eating Disorders Association*, *23*(6), 496–503. https://doi.org/10.1002/ERV.2400

Pellicciari, R., Gioiello, A., Costantino, G., Sadeghpour, B. M., Rizzo, G., Meyer, U., Parks, D. J., Entrena-Guadix, A., & Fiorucci, S. (2006). Back door modulation of the farnesoid X receptor: design, synthesis, and biological evaluation of a series of side chain modified chenodeoxycholic acid derivatives. *Journal of Medicinal Chemistry*, *49*(14), 4208–4215. https://doi.org/10.1021/JM060294K

Perry, R. J., Lee, S., Ma, L., Zhang, D., Schlessinger, J., & Shulman, G. I. (2015). FGF1 and FGF19 reverse diabetes by suppression of the hypothalamic–pituitary–adrenal axis. *Nature Communications*, *6*. https://doi.org/10.1038/NCOMMS7980

Potthoff, M. J., Boney-Montoya, J., Choi, M., He, T., Sunny, N. E., Satapati, S., Suino-Powell, K., Xu, H. E., Gerard, R. D., Finck, B. N., Burgess, S. C., Mangelsdorf, D. J., & Kliewer, S. A. (2011). FGF15/19 Regulates Hepatic Glucose Metabolism By Inhibiting the CREB-PGC-1α Pathway. *Cell Metabolism*, *13*(6), 729. https://doi.org/10.1016/J.CMET.2011.03.019

Pournaras, D. J., Glicksman, C., Vincent, R. P., Kuganolipava, S., Alaghband-Zadeh, J., Mahon, D., Bekker, J. H. R., Ghatei, M. A., Bloom, S. R., Walters, J. R. F., Welbourn, R., & le Roux, C. W. (2012). The Role of Bile After Roux-en-Y Gastric Bypass in Promoting Weight Loss and Improving Glycaemic Control. *Endocrinology*, *153*(8), 3613. https://doi.org/10.1210/EN.2011-2145

Prawitt, J., Abdelkarim, M., Stroeve, J. H. M., Popescu, I., Duez, H., Velagapudi, V. R., Dumont, J., Bouchaert, E., van Dijk, T. H., Lucas, A., Dorchies, E., Daoudi, M., Lestavel, S., Gonzalez, F. J., Oresic, M., Cariou, B., Kuipers, F., Caron, S., & Staels, B. (2011). Farnesoid X receptor deficiency improves glucose homeostasis in mouse models of obesity. *Diabetes*, *60*(7), 1861–1871. https://doi.org/10.2337/DB11-0030/-/DC1

Ricketts, M. L., Boekschoten, M. v., Kreeft, A. J., Hooiveld, G. J. E. J., Moen, C. J. A., Müller, M., Frants, R. R., Kasanmoentalib, S., Post, S. M., Princen, H. M. G., Porter, J. G., Katan, M. B., Hofker, M. H., & Moore, D. D. (2007). The cholesterol-raising factor from coffee beans, cafestol, as an agonist ligand for the farnesoid and pregnane X receptors. *Molecular Endocrinology (Baltimore, Md.)*, *21*(7), 1603–1616. https://doi.org/10.1210/ME.2007-0133

Ruban, A., Stoenchev, K., Ashrafian, H., & Teare, J. (2019). Current treatments for obesity. *Clinical Medicine*, *19*(3), 205. https://doi.org/10.7861/CLINMEDICINE.19-3-205

Ryan, K. K., Kohli, R., Gutierrez-Aguilar, R., Gaitonde, S. G., Woods, S. C., & Seeley, R. J. (2013). Fibroblast Growth Factor-19 Action in the Brain Reduces Food Intake and Body Weight and Improves Glucose Tolerance in Male Rats. *Endocrinology*, *154*(1), 9. https://doi.org/10.1210/EN.2012-1891

Ryan, K. K., Tremaroli, V., Clemmensen, C., Kovatcheva-Datchary, P., Myronovych, A., Karns, R., Wilson-Pérez, H. E., Sandoval, D. A., Kohli, R., Bäckhed, F., & Seeley, R. J. (2014). FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*, *509*(7499), 183–188. https://doi.org/10.1038/NATURE13135

Saeidi, N., Nestoridi, E., Kucharczyk, J., Uygun, M. K., Yarmush, M. L., & Stylopoulos, N. (2012). Sleeve gastrectomy and Roux-en-Y gastric bypass exhibit differential effects on food preferences, nutrient absorption and energy expenditure in obese rats. *International Journal of Obesity (2005)*, *36*(11), 1396–1402. https://doi.org/10.1038/IJO.2012.167

Sagor, G. R., Bryant, M. G., Ghatei, M. A., & Bloom, S. R. (1981). Release of vasoactive intestinal peptide in the dumping syndrome. *British Medical Journal (Clinical Research Ed.)*, *282*(6263), 507–510. https://doi.org/10.1136/BMJ.282.6263.507

Samczuk, P., Hady, H. R., Adamska-Patruno, E., Citko, A., Dadan, J., Barbas, C., Kretowski, A., & Ciborowski, M. (2018). In-and-Out Molecular Changes Linked to the Type 2 Diabetes Remission after Bariatric Surgery: An Influence of Gut Microbes on Mitochondria Metabolism. *International Journal of Molecular Sciences*, *19*(12). https://doi.org/10.3390/IJMS19123744

Sandhu, D. S., Baichoo, E., & Roberts, L. R. (2014). Fibroblast growth factor signaling in liver carcinogenesis. *Hepatology*, *59*(3), 1166–1173. https://doi.org/10.1002/HEP.26679

Sayin, S. I., Wahlström, A., Felin, J., Jäntti, S., Marschall, H. U., Bamberg, K., Angelin, B., Hyötyläinen, T., Orešič, M., & Bäckhed, F. (2013a). Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metabolism*, *17*(2), 225–235. https://doi.org/10.1016/J.CMET.2013.01.003

Sayin, S. I., Wahlström, A., Felin, J., Jäntti, S., Marschall, H. U., Bamberg, K., Angelin, B., Hyötyläinen, T., Orešič, M., & Bäckhed, F. (2013b). Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metabolism*, *17*(2), 225–235. https://doi.org/10.1016/J.CMET.2013.01.003

Scarpellini, E., Arts, J., Karamanolis, G., Laurenius, A., Siquini, W., Suzuki, H., Ukleja, A., van Beek, A., Vanuytsel, T., Bor, S., Ceppa, E., di Lorenzo, C., Emous, M., Hammer, H., Hellström, P., Laville, M., Lundell, L., Masclee, A., Ritz, P., & Tack, J. (2020). International consensus on the diagnosis and management of dumping syndrome. *Nature Reviews. Endocrinology*, *16*(8), 448. https://doi.org/10.1038/S41574-020-0357-5

Schauer, P. R., Bhatt, D. L., Kirwan, J. P., Wolski, K., Aminian, A., Brethauer, S. A., Navaneethan, S. D., Singh, R. P., Pothier, C. E., Nissen, S. E., & Kashyap, S. R. (2017). Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes. *The New England Journal of Medicine*, *376*(7), 641. https://doi.org/10.1056/NEJMOA1600869

Shapiro, H., Kolodziejczyk, A. A., Halstuch, D., & Elinav, E. (2018). Bile acids in glucose metabolism in health and disease. *The Journal of Experimental Medicine*, *215*(2), 383. https://doi.org/10.1084/JEM.20171965

Sinal, C. J., Tohkin, M., Miyata, M., Ward, J. M., Lambert, G., & Gonzalez, F. J. (2000). Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell*, *102*(6), 731–744. https://doi.org/10.1016/S0092-8674(00)00062-3

Sirinek, K. R., O'dorisio, T. M., Howe, B., & Mcfee, A. S. (1985). Neurotensin, vasoactive intestinal peptide, and Roux-en-Y gastrojejunostomy. Their role in the dumping syndrome. *Archives of*

Surgery (Chicago, Ill. : 1960), *120*(5), 605–609. https://doi.org/10.1001/ARCHSURG.1985.01390290083014

Smalley, T. L., Boggs, S., Caravella, J. A., Chen, L., Creech, K. L., Deaton, D. N., Kaldor, I., & Parks, D. J. (2015). Novel heterocyclic scaffolds of GW4064 as farnesoid X receptor agonists. *Bioorganic & Medicinal Chemistry Letters*, *25*(2), 280–284. https://doi.org/10.1016/J.BMCL.2014.11.050

Soisson, S. M., Parthasarathy, G., Adams, A. D., Sahoo, S., Sitlani, A., Sparrow, C., Cui, J., & Becker, J. W. (2008). Identification of a potent synthetic FXR agonist with an unexpected mode of binding and activation. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(14), 5337–5342. https://doi.org/10.1073/PNAS.0710981105

Soverini, V., Moscatiello, S., Villanova, N., Ragni, E., di Domizio, S., & Marchesini, G. (2010). Metabolic syndrome and insulin resistance in subjects with morbid obesity. *Obesity Surgery*, *20*(3), 295–301. https://doi.org/10.1007/S11695-009-9999-Z

Spinelli, V., Lalloyer, F., Baud, G., Osto, E., Kouach, M., Daoudi, M., Vallez, E., Raverdy, V., Goossens, J. F., Descat, A., Doytcheva, P., Hubert, T., Lutz, T. A., Lestavel, S., Staels, B., Pattou, F., & Tailleux, A. (2016). Influence of Roux-en-Y gastric bypass on plasma bile acid profiles: a comparative study between rats, pigs and humans. *International Journal of Obesity (2005)*, *40*(8), 1260–1267. https://doi.org/10.1038/IJO.2016.46

Stefater, M. A., & Inge, T. H. (2017). Bariatric Surgery for Adolescents with Type 2 Diabetes: An Emerging Therapeutic Strategy. *Current Diabetes Reports*, *17*(8), 62. https://doi.org/10.1007/S11892-017-0887-Y

Steinert, R. E., Feinle-Bisset, C., Asarian, L., Horowitz, M., Beglinger, C., & Geary, N. (2017). Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. *Physiological Reviews*, *97*(1), 411–463. https://doi.org/10.1152/PHYSREV.00031.2014

Tack, J., Arts, J., Caenepeel, P., de Wulf, D., & Bisschops, R. (2009). Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nature Reviews. Gastroenterology & Hepatology*, *6*(10), 583–590. https://doi.org/10.1038/NRGASTRO.2009.148

Tack, J., & Deloose, E. (2014). Complications of bariatric surgery: dumping syndrome, reflux and vitamin deficiencies. *Best Practice & Research. Clinical Gastroenterology*, *28*(4), 741–749. https://doi.org/10.1016/J.BPG.2014.07.010

Tangalakis, L. L., Tabone, L., Spagnoli, A., Muehlbauer, M., Omotosho, P., & Torquati, A. (2020). Effects of Roux-en-Y Gastric Bypass on Osteoclast Activity and Bone Density in Morbidly Obese Patients with Type 2 Diabetes. *Obesity Surgery*, *30*(1), 290–295. https://doi.org/10.1007/S11695-019-04154-2

Taqi, E., Wallace, L. E., de Heuvel, E., Chelikani, P. K., Zheng, H., Berthoud, H. R., Holst, J. J., & Sigalet, D. L. (2010). The influence of nutrients, biliary-pancreatic secretions, and systemic trophic hormones on intestinal adaptation in a Roux-en-Y bypass model. *Journal of Pediatric Surgery*, *45*(5), 987–995. https://doi.org/10.1016/J.JPEDSURG.2010.02.036

Thomas, C., Auwerx, J., & Schoonjans, K. (2008). Bile acids and the membrane bile acid receptor TGR5--connecting nutrition and metabolism. *Thyroid : Official Journal of the American Thyroid Association*, *18*(2), 167–174. https://doi.org/10.1089/THY.2007.0255

Torquati, A., Shantavasinkul, P. C., Omotosho, P., Corsino, L., & Spagnoli, A. (2019). Perioperative changes in prouroguanylin hormone response in severely obese subjects after bariatric surgery. *Surgery (United States)*, *166*(4), 456–459. https://doi.org/10.1016/J.SURG.2019.06.037

Umeda, L. M., Pereira, A. Z., Carneiro, G., Arasaki, C. H., & Zanella, M. T. (2013). Postprandial adiponectin levels are associated with improvements in postprandial triglycerides after Roux-en-Y gastric bypass in type 2 diabetic patients. *Metabolic Syndrome and Related Disorders*, *11*(5), 343–348. https://doi.org/10.1089/MET.2012.0042

van Beek, A. P., Emous, M., Laville, M., & Tack, J. (2017). Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, *18*(1), 68–85. https://doi.org/10.1111/OBR.12467

van Zutphen, T., Bertolini, A., de Vries, H. D., Bloks, V. W., de Boer, J. F., Jonker, J. W., & Kuipers, F. (2019). Potential of Intestine-Selective FXR Modulation for Treatment of Metabolic Disease. *Handbook of Experimental Pharmacology*, *256*, 207–234. https://doi.org/10.1007/164_2019_233

Wang, H., Chen, J., Hollister, K., Sowers, L. C., & Forman, B. M. (1999). Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Molecular Cell*, *3*(5), 543–553. https://doi.org/10.1016/S1097-2765(00)80348-2

Wang, S., Lai, K. D., Moy, F. J., Bhat, A., Hartman, H. B., & Evans, M. J. (2006). The nuclear hormone receptor farnesoid X receptor (FXR) is activated by androsterone. *Endocrinology*, *147*(9), 4025–4033. https://doi.org/10.1210/EN.2005-1485

Werner, S. (1998). Keratinocyte growth factor: A unique player in epithelial repair processes. *Cytokine and Growth Factor Reviews*, *9*(2), 153–165. https://doi.org/10.1016/S1359-6101(98)00010-0

WHO. (2017). GHO | By category | Prevalence of obesity among adults, BMI ≥ 30, age-standardized - Estimates by WHO region. *WHO*. https://apps.who.int/gho/data/view.main.REGION2480A?lang=en

Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T. D., Wadden, T. A., Wharton, S., Yokote, K., Zeuthen, N., & Kushner, R. F. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. *The New England Journal of Medicine*, *384*(11), 989–1002. https://doi.org/10.1056/NEJMOA2032183

Wing, R. R., Bahnson, J. L., Bray, G. A., Clark, J. M., Coday, M., Egan, C., Espeland, M. A., Foreyt, J. P., Gregg, E. W., Goldman, V., Haffner, S. M., Hazuda, H., Hill, J. O., Horton, E. S., Hubbard, V. S., Jakicic, J., Jeffery, R. W., Johnson, K. C., Kahn, S., … Yanovski, S. Z. (2010). Long Term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes: Four Year Results of the Look AHEAD Trial. *Archives of Internal Medicine*, *170*(17), 1566. https://doi.org/10.1001/ARCHINTERNMED.2010.334

World Health Organization. (2000). *Obesity: preventing and managing the global epidemic. Report of a WHO consultation* . https://pubmed.ncbi.nlm.nih.gov/11234459/

Wu, T., Bound, M. J., Standfield, S. D., Gedulin, B., Jones, K. L., Horowitz, M., & Rayner, C. K. (2013). Effects of rectal administration of taurocholic acid on glucagon-like peptide-1 and peptide YY secretion in healthy humans. *Diabetes, Obesity & Metabolism*, *15*(5), 474–477. https://doi.org/10.1111/DOM.12043

Zarei, M., Barroso, E., Palomer, X., Dai, J., Rada, P., Quesada-López, T., Escolà-Gil, J. C., Cedó, L., Zali, M. R., Molaei, M., Dabiri, R., Vázquez, S., Pujol, E., Valverde, Á. M., Villarroya, F., Liu, Y., Wahli, W., & Vázquez-Carrera, M. (2018). Hepatic regulation of VLDL receptor by PPARβ/δ and FGF21 modulates non-alcoholic fatty liver disease. *Molecular Metabolism*, *8*, 117–131. https://doi.org/10.1016/J.MOLMET.2017.12.008

Zhan, L., Liu, H. X., Fang, Y., Kong, B., He, Y., Zhong, X. B., Fang, J., Wan, Y. J. Y., & Guo, G. L. (2014). Genome-Wide Binding and Transcriptome Analysis of Human Farnesoid X Receptor in Primary Human Hepatocytes. *PLoS ONE*, *9*(9). https://doi.org/10.1371/JOURNAL.PONE.0105930

Zhang, Y., Kast-Woelbern, H. R., & Edwards, P. A. (2003). Natural structural variants of the nuclear receptor farnesoid X receptor affect transcriptional activation. *The Journal of Biological Chemistry*, *278*(1), 104–110. https://doi.org/10.1074/JBC.M209505200

Zhang, Y., Lee, F. Y., Barrera, G., Lee, H., Vales, C., Gonzalez, F. J., Willson, T. M., & Edwards, P. A. (2006). Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(4), 1006–1011. https://doi.org/10.1073/PNAS.0506982103