Colesevelam a bile acid sequestrant use in type 2 diabetes mellitus as glucose and lipid lowering agent

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ABSTRACT

The bile acid sequestrants are the group of medications utilized to bind certain components of bile in the gastrointestinal tract. Enterohepatic circulation of bile acids is disrupted by sequestering bile acids and preventing their reabsorption from the gut. They are generally considered as hypolipidemic agents, although may be used for purposes other than cholesterol lowering. In diabetes lipid abnormality occur leading to various other cardiovascular complications. Studies have demonstrated that changes in enterohepatic circulation modulate FXR- and TGR5-mediated pathways may regulate glucose homeostasis. This review discusses the major findings of clinical studies which have investigated the glucose and lipid lowering effects of Colesevelam for the treatment of Type 2 Diabetes Mellitus (Type 2 DM) and the mechanism involved in regulating lipid and glucose metabolism through bile acid mediated activation of FXR and TGR 5 signaling pathways.

Keywords: Colesevelam, Type 2 DM, FXR, TGR5

INTRODUCTION

Bile acids are the potent digestive surfactants that promote/boost the lipid absorption including fat soluble vitamins and act as emulsifiers.[1,2] They form the primary pathway for the catabolism of cholesterol and account for 50% of the daily cholesterol turnover[1]. The synthesis of bile acid occurs exclusively in liver. In a series of enzymatic reactions, the hepatocytes convert the hydrophobic cholesterol into more water-soluble amphiphatic compounds.[2] The production of bile acids is localized primarily in the perivenous hepatocytes which are the cells surrounding the central hepatic vein.[3] The primary bile acids, the cholic and chenodeoxycholic acids are the immediate products of the bile acid synthetic pathways in humans. The action of intestinal bacterial flora on primary bile acids forms the secondary bile acid species, the deoxycholic and lithocholic acids which are the derivatives of cholic and chenodeoxycholic acids.[4]

Recently, in-vitro and in-vivo data showed that bile acids also modulate gluconeogenesis by regulating the expression of the rate-controlling enzyme of the lyase family, the phosphoenolpyruvate carboxykinase (PEPCK) employed in the metabolic pathway of gluconeogenesis, glucose-6-phosphatase (G6Pase) and that of the Fructose-1, 6-bisphophatase (FBP1).[4,5]

Colesevelam hydrochloride is a bile acid sequestrant that has been approved by the United States Food and Drug Administration (FDA) in January 18, 2008. It improves glycemic control (measured as hemoglobin A1C) in adults with type 2 diabetes mellitus (Type 2 DM). It is given in combination with metformin, sulfonylureas, or insulin either alone or in combination with other anti-diabetic agents.[6]

Mechanism of action

Primary hyperlipidemia:

Bile acid sequestrants (cholestyramine, colestipol, colestimide, and colesevelam) are positively charged non-digestible resins that become attached to the bile acids in the intestine and form an insoluble complex that is excreted in the feces. This decreases the level of bile acids in liver and increases bile acid synthesis from cholesterol and thus decreases hepatic cholesterol levels.[7]

Farnesoid X receptor (FXR) and Synthesis of bile acid:

FXR is member of the nuclear receptor super family of ligand-activated transcription factors. It occurs in the liver and intestine and gets activated under the influence of primary bile acid chenodeoxycholic acid.[8] In response to increase in size of the bile acid pool in liver, bile acid activation of FXR

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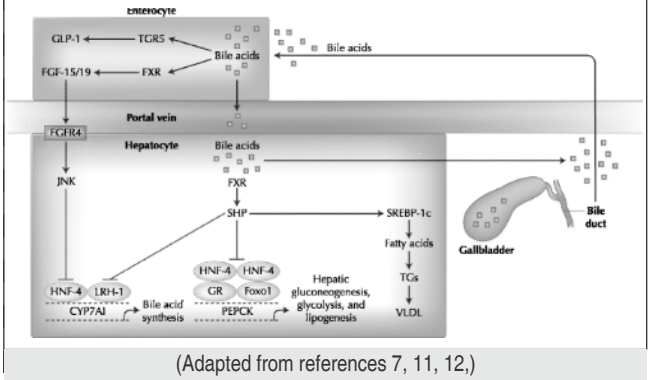
up-regulates expression of the gene encoding the inhibitory nuclear receptor's small heterodimer partner (SHP)[8]. Activation of several transcription factors including liver X receptor, liver receptor homologue-1 (LRH-1) and the hepatocyte nuclear factor-4α (HNF-4α) is repressed by SHP, subsequently suppressing the LRH-1 mediated activation of cytochrome P450 7A1 (CYP7A1) in humans, thereby inhibiting the first step in cholesterol catabolism (Fig. 1). Bile acid-mediated repression of HNF-4α inhibits the transcription of CYP7A1 as well.[9] FXR-mediated initiation of fibroblast growth factor-19 (FGF-19; [FGF-15 in mice]) in the intestine is a second pathway of bile acid-mediated repression of its own synthesis. In response to the presence of meal in the intestine, trans-intestinal transport of bile acids is done in the intestine inducing the activation of intestinal FXR thus resulting in the expression of FGF-19.[10] Binding of FGF-19 to surface hepatocyte fibroblast growth factor receptor 4 results in a c-Jun N-terminal kinase-mediated repression of CYP7A1 transcription which is a potent SHP-independent alternative pathway of CYP7A1 repression (Fig. 1).[10]

Fig no. 1: FXR- and TGR5-mediated regulation of bile acid synthesis and lipid and glucose metabolism in the liver and intestine



(Adapted from references 7, 11, 12,)

{FXR- and TGR5-mediated regulation of bile acid synthesis and lipid and glucose metabolism in the liver and intestine. Bile acid synthesis and lipid and glucose metabolism are regulated in the liver and intestine via pathways involving the bile acid receptors FXR and TGR5. In the liver, bile acids activate FXR resulting in upregulation of SHP, an inhibitor of bile acid synthesis, gluconeogenesis, and fatty acid synthesis. In the intestine, bile acid activation of FXR upregulates FGF-15/19 and ultimately inhibits bile acid synthesis[7]}.

{CYP7A1—cytochrome P450 enzyme cholesterol 7 α-hydroxylase, FGF-15/19—fibroblast growth factor 15/19, FGFR4—fibroblast growth factor receptor 4,FXR—farnesoid X receptor,GLP-1—glucagon-like peptide-1, GR—glucocorticoid receptor, HNF-4—hepatocyte nuclear factor-4, JNK—c-jun N-terminal kinase; LRH-1—liver receptor homologue-1, PEPCK—phosphoenolpyruvate carboxykinase, SHP—small heterodimer partner, SREBP-1c—sterol regulatory element-binding protein-1c, TGs—triglycerides, VLDL—very low density lipoprotein.}.

Cholesterol 7 alpha-hydroxylase also known as cholesterol 7-alpha-monooxygenase or cytochrome P450 7A1 (CYP7A1):

Cholesterol 7 alpha-hydroxylase in humans is encoded by the CYP7A1 gene. During the bile synthesis from cholesterol this enzyme (Cholesterol 7 alpha-hydroxylase) functions as a rate-limiting enzyme. [13]

Fibroblast growth factor 15/19 (FGF-15/19), fibroblast growth factor receptor 4 (FGFR4):

FGFs are multifunctional proteins that act as a mitogens and also have various regulatory, morphological, and endocrine effects. It is synthesized in the intestinal cells but acts on FGFR4-expressing liver cells to down regulate key genes in the bile acid synthesis pathway. Its synthesis occurs in bone but acts on FGFR1-expressing kidney cells to regulate the synthesis of vitaminD and in turn affect calcium homeostasis. [14]

Farnesoid X receptor:

Farnesoid X receptor (FXR/bile acid receptor), occurs in the liver and intestine. Chenodeoxycholic acid and other bile acids are natural ligands for FXR. Similar other nuclear receptors, when activated, FXR translocates to the cell nucleus, forms a dimer (in this case a heterodimer with RXR) and binds to hormone response elements on DNA which up- or down-regulates the expression of certain genes. One of the primary functions of FXR are to beat down cholesterol 7 alphahydroxylase (CYP7A1), that is rate limiting in bile acid synthesis from cholesterol. FXR induces expression of small heterodimer partner (SHP) which then functions to inhibit transcription of the CYP7A1 gene. In this way a negative feedback pathway is established in which synthesis of bile acids is inhibited when cellular levels are already high. [15,16]

Glucagon-like peptide-1(GLP-1):

The incretins are peptide hormones. Peptides are short polymers formed by the linking, in a defined order, of α-amino acids. They are secreted into the circulation, in response to luminal nutrients, within minutes of eating. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide

(GIP). GLP-1 is secreted by the L cells in the ileum and colon whereas GIP is secreted by enteroendocrine cells (called K cells) in the duodenum.[17, 18, 19, 20, 21]

Glucocorticoid receptor (GR):

Glucocorticoids exert their physiological functions by the GR and have their important role in the regulation of carbohydrate, protein, and fat metabolism. Gluconeogenesis and glycogen synthesis is stimulated by the different mechanisms by glucocorticoids in fasting state. These include increase in the synthesis of essential enzymes for gluconeogenesis, increase in the secretion of amino acids from muscles, enhanced insulin resistance in the peripheral tissues, and inhibition of adipokines such as adiponectin. These processes defend glucose-dependent tissues (e.g. brain and heart) during starvation.[22, 23]

Hepatocyte nuclear factor-4:

Hepatocyte nuclear factor (HNF)-4a is a transcription factor which has critical role in the transcriptional regulation of genes involved in glucose metabolism in both hepatocytes and pancreatic b-cells. Recent evidence has implicated AMP-activated protein kinase (AMPK) in the modulation of both insulin secretion by pancreatic b-cells and the control of glucose-dependent gene expression in both hepatocytes and b-cells. [24]

C-Jun N-terminal kinases (JNKs):

JNK is the kinase that attaches and phosphorylates c-Jun on Ser63 and Ser 73 within its transcriptional activation domain.[25] Kinase is also known as a phosphotransferase. It is a type of that transfers phosphate groups from high-energy donor molecules, such as ATP to specific substrates. The process is known as phosphorylation and should not to be confused with phosphorolysis which takes place by phosphorylases. Phosphorylation is the transfer of a phosphate group to a molecule, not the reverse, i.e., phosphorolysis, the transfer of a molecular to a phosphate group. An enzyme that removes phosphate groups is known as a phosphatase.[26]

The c-Jun N-terminal kinases (JNKs) regulate the essential physiological and pathological processes which are involved in several diseases including diabetes, atherosclerosis, stroke, Parkinson's and Alzheimer's diseases. Inhibition of JNKs suppresses pathological features of these diseases but the many physiological functions of these enzymes argue against the use of sustained, systemic, nonspecific inhibition in the treatment of these diseases. For example, loss or absence of the gene that encodes JNK1 prevents insulin resistance, disrupts neuronal cytoarchitecture and initiates the pathology of Alzheimer's disease. Thus, it is not enough to inhibit selectively either JNKs or individual isoforms of JNK. Instead, the aim is to inhibit the damaging actions of JNK. This can be achieved using peptides that selectively block molecular domains of individual JNK signaling complexes (exclusively) that form under pathological conditions. Peptide inhibitors of JNK are useful in preventing ischemia-induced brain damage and insulin resistance following obesity.[27]

Liver receptor homolog-1:

LRH-1 is a member of the nuclear receptor family of intracellular transcription factors. Liver receptor homolog 1 (LRH-1), an orphan nuclear receptor, is abundant in liver and intestine, where it regulates the cholesterol, bile acid, and steroid hormone homeostasis. Among the proposed LRH-1 target genes in liver are those encoding cholesterol 7α-hydroxylase (CYP7A1) and sterol 12α-hydroxylase (CYP8B1), which catalyze key steps in bile acid synthesis. [28]

Phosphoenolpyruvate carboxykinase:

Phosphoenolpyruvate carboxykinase (PEPCK) of lyase family participates in metabolic pathway of gluconeogenesis converts oxaloacetate into phosphoenolpyruvate and carbon dioxide. When dietary carbohydrate is unavailable, glucose required to support metabolism in vital tissues is generated via gluconeogenesis in the liver. Expression of phosphoenolpyruvate carboxykinase (PEPCK), commonly considered the control point for liver gluconeogenesis, is normally regulated by circulating hormones to match systemic glucose demand. However, this regulation fails in diabetes.[29]

Small Heterodimer Partner:

Small heterodimer partner (SHP) is an atypical orphan nuclear receptor that prohibits transcriptional activation by several other nuclear receptors. It has been reported recently that mutations in the SHP gene are associated with insulin resistance. A reporter gene assay showed that a gene product of SHP increased the transcriptional activation of peroxisome proliferator-activated receptor (PPAR) gamma. [30, 31]

Sterol regulatory element-binding protein-1c:

Sterol Regulatory Element Binding Proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Mammalian SREBPs are

encoded by the genes SREBF1 and SREBF2. SREBP-1 expression produces two different isoforms, SREBP-1a and -1c.

Sterol regulatory element-binding protein 1 (SREBP-1) also known as sterol regulatory element-binding transcription factor 1 (SREBF1) is a protein that in humans is encoded by the SREBF1.

Sterol regulatory element-binding protein 2 (SREBP-2) also termed as sterol regulatory element binding transcription factor 2 (SREBF2) is a protein which is encoded by the SREBF2 gene in case of humans.[32]

Forkhead box protein O1 (FOXO1): a protein which is encoded by the FOXO1 gene in human. In rhabdomyosarcoma, it is recognized as forkhead. In pancreatic alpha-cells FOXO1 is important in regulating prepro-glucagon expression. In pancreatic beta cells it mediates glucagon-like peptide-1 effects on pancreatic beta-cell mass[33].

Type 2 Diabetes Mellitus:

The mechanism by which Colesevelam lowers glucose levels in patients with Type 2 DM is not yet clearly understood. However, evidences point towards the fact that the glycemic effects of bile acid sequestrants occur through farnesoid X receptor (FXR/bile acid receptor), liver X receptor, fibroblast growth factor-19 and TGR5-mediated effects on intestinal glucose absorption, and through hepatic glucose metabolism in addition to influences on peripheral insulin sensitivity, incretin effects and energy homeostasis[7,34].

{TGR5 is a G protein-coupled receptor found in brown adipose tissues and muscles where its activation by bile acids triggers an increase in energy expenditure and attenuates diet-induced obesity. Using a combination of pharmacological and genetic gain- and loss-of-function studies in vivo, TGR5 signaling activates intestinal glucagon-like peptide-1 (GLP-1) release, leading to improved liver and pancreatic function and enhanced glucose tolerance in obese mice. In addition, the induction of GLP-1 release in enteroendocrine cells by 6alpha-ethyl-23(S)-methyl-cholic acid (EMCA, INT-777), a specific TGR5 agonist, is linked to an increase of the intracellular ATP/ADP ratio and a subsequent rise in intracellular calcium mobilization[34]}.

It has been shown that the bile acid induced activation of FXR reduces expression of genes involved in gluconeogenesis including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. In addition, hepatic glucose production during fasting and postprandial hepatic glucose utilization may be modulated by FXR.[35,36] However, alterations in the bile acid pool in Type 2 DM and its subsequent effects on FXR activation are still under investigation. Emerging data suggest a partial regulatory role for FXR modulators in peripheral insulin sensitivity suggesting a future role for FXR for treating insulin resistance and Type 2 DM.[37,38] The incretin release and the induction of glucagon-like peptide-1 (GLP-1) secretion through activation of the G-protein coupled receptor TGR5 is also influenced by the bile acids.[39,40] Colestimide, a bile acid sequestrant causes an increased secretion of GLP-1 in patients with Type 2 DM, although the functional consequences are still unclear.[41] Bile acids have also been implicated in metabolic regulations through FXR-mediated regulation of energy substrate mobilization and storage.[42] These glycemic effects are unique to bile acid sequestrants and among these only colesevelam have been approved for improving glycemic control in adults with Type 2 DM. Cholesterol absorption inhibitor, the ezetimibe does not show these effects. Further study, however, is needed to determine the precise mechanism involved in the effect of bile acid sequestrants on glucose metabolism in patients with Type 2 DM.

FXR receptor and its role in hepatic Glucose Metabolism:

Liver asserts a balance between glucose production and utilization and thus plays a central role in controlling blood glucose homeostasis (Fig. 1). Moreover, various studies have emphasized the role of bile acids in glucose metabolism and have shown that the composition and pool size of the bile acid gets altered in diabetic animals and humans.[43,44] A link between FXR and glucose metabolism has been proved by the observation that hepatic expression of the gene encoding FXR was decreased following quantitative analysis of hepatic FXR mRNA expression in a rat model of type 1 diabetes. This was also accompanied by increased expression of CYP7A1 which contributes to the enlarged bile acid pool that is also characteristic of such diabetic animals.[44] Moreover, hepatic expression of FXR also decreased with age in a rat model of Type 2 DM[45]. When the hepatocytes from nondiabetic rats were incubated with glucose and insulin to assess the effects of these two on hepatic FXR expression, the groups of hepatocytes incubated with insulin repressed the expression of FXR, an effect that is reduced by glucose. These results suggested that diabetes impairs the normal regulation of FXR expression[45]. However, a precise mechanism of FXR regulation of glucose metabolism is unclear.

Pharmacodynamics:

The maximum therapeutic lipid-lowering response of colesevelam was achieved within 2-weeks and was maintained during long-term therapy. In the diabetes clinical studies, a therapeutic response to colesevelam, as reflected by a reduction in hemoglobin A1C was initially noted following 4-6 weeks of treatment and reached maximal or near-maximal effect after 12-18 weeks of treatment.[6,46]

Pharmacokinetics:

Absorption: Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed.

Distribution: Colesevelam hydrochloride is not absorbed and, therefore, its distribution is limited to the gastrointestinal tract.

Metabolism: Colesevelam hydrochloride is not metabolized systemically and hence does not interfere with systemic drug-metabolizing enzymes such as cytochrome P-450.

Excretion: In 16 healthy volunteers an average of 0.05% of administered radioactivity from a single 14C-labeled colesevelam hydrochloride dose was excreted in the urine.[6,46]

Pregnancy Category -Colesevelam is Pregnancy Category B.[6,46,47]

CONCLUSION

Bile acid sequestrants change the bile acid pools thus affecting lipid and glucose metabolism. Studies have demonstrated that changes in enterohepatic circulation modulate FXR- and TGR5-mediated pathways may regulate glucose homeostasis. However, further studies are required to assess the role of FXR- and TGR5-mediated signaling pathways on lipid and glucose metabolism in animal and human models of Type 2 DM and obesity. Studies are also required to understand how these signals become united to mediate the lipid- and glucose-lowering effects of bile acid sequestrants.

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