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Hormonal Regulation of Cholesterol Homeostasis

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Abstract

Cholesterol homeostasis is tightly regulated by a group of endocrine hormones under physiological conditions. Hormonal dysregulation is often associated with disturbed cholesterol homeostasis, resulting in many clinical disorders including atherosclerosis, fatty liver and metabolic syndrome. Circulating hormones regulate cholesterol metabolism by altering levels of relative genes either through their interactions with nuclear receptors or by interfering with bile acid signaling pathways. A better understanding of hormonal regulation of cholesterol metabolism would improve our likelihood of identifying effective and selective targets for the intervention of disturbed cholesterol. In this review, we discuss selected hormones critical for the cholesterol balance, including thyroid hormone, sex hormones, growth hormone, glucagon and irisin. We focus our discussion on the most recent advance in clinical epidemiology, animal mechanistic studies and the clinical application.

Keywords: cholesterol, thyroid hormone, sex hormones, growth hormone, glucagon and irisin

1. Introduction

Cholesterol is mainly composed of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL). It plays a critical role in membrane biogenesis and steroid hormone biosynthesis. The disturbed plasma cholesterol is associated with many diseases, such as cardiovascular disease, diabetes and hepatic steatosis. Cholesterol is either uptaken exogenously from the diet or synthesized endogenously within cells. The liver is the major organ for cholesterol de novo synthesis which involves 19-step complex biochemical process. The rate-limiting enzyme is 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase. Sterol regulatory element-binding protein 1c (SREBP-1c) is the master regulator

of cholesterol by stimulating the transcription of LDL and HMG-CoA. LDL receptor (LDLr) is responsible for importing LDL from extracellular to intracellular environment for metabolism. Cholesterol is the primary source for biogenesis of steroid hormones. In turn, many hormones exert critical effects on cholesterol synthesis or metabolism. This occurs through the direct effect of these hormones on regulation of the expression or activity of HMG-CoA reductase, SREBP-1c or LDLr. In this chapter, we will discuss the regulatory role of several interesting hormones in cholesterol metabolism.

2. Thyroid hormone

2.1. Thyroid hormone and thyroid hormone receptors

Thyroid hormones (THs) include thyroxine (T4) and triiodothyronine (T3). They are synthesized and secreted by the thyroid gland. T4 is the major secreted hormone, while T3 has a higher affinity for TH receptors (TRs). T3 is considered as the active and more potent TH. T4 could be converted to T3 through a deiodination process catalyzed by deiodinases. TH regulates a number of biological functions including growth, development and metabolism in almost all tissues [1]. TH exerts these effects through binding to TRs which are expressed on different cells and tissues. TRs have two isoforms, TR α and TR β , which are encoded by the THRA and THRB genes, respectively, in humans. Each TR isoform has several splice products, TR α 1 (α 2) and TR β 1 (β 2). TR α 1 and TR β 1 are ubiquitously expressed, while TR β 1 is the major TR existed in the liver. TR β 2 is expressed in the hypothalamus, the pituitary gland and the developing brain [2]. TRs are ligand-activated transcription factors, belonging to the family of nuclear receptors (NRs). It can bind to DNA sequences called TH-responsive elements (TREs) together with the retinoid X receptor alpha (RXR- α). In the absence of TH, TRs bind with corepressors, e.g., nuclear receptor corepressor and silencing mediator for retinoid and thyroid hormone receptor (NCOR2), suppressing the transcriptional activity. In the presence of TH, the binding induces a conformational change of TRs, releasing the corepressors and recruiting several co-activators to enhance the transcriptional activity. Since TRs associate with corepressors without ligand binding, it could decrease the transcriptional activity of the target genes. Therefore, it should be cautious to compare the data from animal models in which TRs are genetically deleted with the models with low levels of circulating THs, such as hypothyroidism or thyroidectomy [3].

2.2. Role of TH in cholesterol metabolism

There is substantial evidence linking TH status with cholesterol or lipid metabolism. Thyroid dysfunction exerts an important effect on the cholesterol level. Hypothyroidism patients typically have elevated plasma cholesterol and increased lipid accumulation in the liver. TH supplement can normalize this lipid dysregulation. THs promote cholesterol synthesis through inducing HMG-CoA reductase and farnesyl pyrophosphate gene expression [1]. THs markedly decrease the expression of apoB-100, the major protein of LDL, while increasing the expression of apo A-I, the major protein of HDL. In addition, THs increase LDLr gene expression. LDLr mediates the uptake of LDL from blood to the liver. Rat LDLr promoter contains two functional TREs. THs could directly bind to the TRE and upregulate

the LDLr gene expression [4]. THs may also regulate the clearance of circulating remnant lipoproteins. Hepatic low-density lipoprotein receptor-related protein 1 (LRP1) is a receptor for remnant lipoproteins. Hepatic LRP1 protein expression and function are reduced in the hypothyroidism mouse model. T3 supplement partially normalizes its protein expression level [5]. THs also promote the cholesterol elimination by increasing conversion and secretion of cholesterol into bile acids. In this process, cholesterol 7 α -hydroxylase (Cyp7A1), the enzyme in the cytochrome P450 family, is responsible for catalyzing the rate-limiting reaction in the degradation of cholesterol. Cyp7A1 is a direct TR target gene with TREs in its promoter region [6]. ATP-binding cassette (ABC) transporters G5 (ABCG5) and G8 (ABCG8) form a heterodimer that limits intestinal absorption and facilitates biliary secretion of cholesterol. Mice homozygous for disruption of *Abcg5* demonstrate a significant reduction in basal biliary cholesterol secretion. T3 treatment does not increase the cholesterol secretion in *Abcg5*^{-/-} mice as in the wild-type control mice. This observation suggests that THs induce secretion of cholesterol, largely dependent on the ABCG5/G8 transporter complex [7]. THs also modulate gene expression via micro-RNAs. In a human hepatic cell line, THs decrease sterol O-acyltransferase 2 (SOAT2 or ACAT2), the enzyme crucial for the hepatic secretion of cholesterol esters, via miR-181d [8].

T3 also upregulates LDLr gene expression by activating the expression of the sterol regulatory element-binding protein-2 (SREBP-2) and scavenger receptor class B1 (SR-B1) [9]. Cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl esters from HDL to the VLDL and from total triglyceride (TG) to the opposite direction. THs could increase the activity of CETP to influence HDL metabolism [10]. In addition, THs stimulate the lipoprotein lipase (LPL) and hepatic lipase (HL) levels, catabolizing the TG-rich lipoproteins.

2.3. Interaction with other transcription factors

In addition to the direct action on the cholesterol-related genes, TRs also cross talk with many nuclear receptors to regulate their transcriptions. It shares the same DNA-binding site (direct repeat 4) with liver X receptor (LXR). Activation of TR β 1 by T3 upregulates mouse LXR α , but not LXR β , mRNA expression in the liver at the transcriptional level [11]. TR β 1 is the major TR mediating the TH effects on plasma cholesterol. ATP-binding cassette transporter A1 (ABCA1) is important for HDL assembly and transporting cholesterol back to the liver for excretion. TR forms a heterodimer with retinoid X receptor (RXR) and binds to the DR-4 element of ABCA1 promoter, suppressing its transcription [12]. The apolipoprotein AV gene (APOA5) is a key determinant of the plasma triglyceride level. It affects the plasma TG level through promoting lipolysis of TG-rich lipoproteins and removal of their remnants [13]. TR- β mediates the effects of THs on the activation of APOA5 gene. Administration of TR- β -selective agonist increases apoAV and diminishes triglyceride levels [14]. In addition, TR- β may compete with LXR/RXR heterodimers for binding to the DR-4 element in the CYP7A1 promoter [15]. TR- β but not TR- α KO mice completely lost the induction effects of T3 on Cyp7a1 gene, confirming the critical role of TR- β in mediating the TH effect on cholesterol metabolism [16].

Taken together, TH regulates the serum cholesterol level in multiple crucial steps including stimulating its hepatic synthesis, serum uptake and the intrahepatic conversion to bile acids. The physiological level of TH is essential for maintaining the cholesterol homeostasis.

3. Sex hormones

It is well recognized that premenopausal females have better lipid profiles than males and are more protected from hypercholesterolemia-related diseases, such as cardiovascular diseases. Lipid screening has found that premenopausal women are associated with a lower level of LDL cholesterol and a higher level of HDL cholesterol. After menopause, the gender difference of lipid profiles disappears, and women even have higher-level LDL compared to age-matched men [17]. Estrogen replacement therapy would improve lipoprotein profiles in postmenopausal women [18]. Sex hormones, especially estrogen, account for the gender difference of cholesterol profiles.

3.1. Estrogen and estrogen receptors

The predominant and most important biologically relevant form of estrogen is 17 β -estradiol (E2). Both women and men produce E2 through aromatization of androgen. In premenopausal women, estrogen is mainly synthesized in the ovaries. While in postmenopausal women and men, it is primarily converted from testosterone by aromatase (encoded by CYP19 gene) in extragonadal tissues such as adipose tissue, adrenal glands, bones, etc. [19]. There are at least three types of estrogen receptors, ER- α , ER- β and membrane-bound receptor G protein-coupled ER (GPER, also known as GPR 30). ER- α and ER- β are the classic estrogen receptors and are mainly expressed in the cytosol. Upon estrogen binding, ER- α and ER- β form homo- or heterodimers and bind to estrogen response element (ERE) in the downstream target genes, to initiate or suppress the transcriptional activity. The GPER and membrane-associated ER- α and ER- β variants are expressed in the plasma membrane. They mainly exert actions via non-genomic signaling. This membrane-initiated signaling involves protein kinase A (PKA), protein kinase C (PKC) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase (ERK) signaling pathways [20–22].

3.2. Role of estrogens in cholesterol homeostasis

The influence and mechanism of estrogens on cholesterol metabolism have been investigated for a long time. Studies by Cypriani et al. in 1988 demonstrated that estrogens induced HMG-CoA reductase and subsequent cholesterol synthesis in breast cancer cell line [4]. Later, it was found that HMG-CoA reductase gene promoter contains an estrogen-responsive element-like sequence at position-93 (termed Red-ERE). And, estrogen induction of HMG-CoA reductase gene is dependent on the Red-ERE. The induction activity of estrogens occurs in the breast cancer cells but not in hepatic cells, indicating differential regulation of HMG-CoA reductase by estrogens in a tissue-specific manner [23]. Aromatase is an enzyme responsible for the key step in the biosynthesis of estrogens. Aromatase knockout (ArKO) mice display increased intra-abdominal adipose tissue and lipid droplet accumulation in the liver. Total cholesterol and LDL are also elevated in these transgenes [24]. Supplement of estrogens in both ArKO mice and rats with ovariectomy (OVX) normalizes LDL and total cholesterol levels, confirming the important role of estrogens in the lipid homeostasis in both males and females [25]. Hormone replacement therapy (HRT) increases the expression of leucocyte ABCA1 gene,

which mediates the efflux of cholesterol to the HDL particles, leading to the subsequent increase in the HDL cholesterol level [26]. Estrogens thus play an important role in the modulation of the total cholesterol level by reducing LDL and concurrently increasing HDL.

The beneficial role of estrogens on cholesterol metabolism is mediated through nuclear and extra-nuclear ER- α and ER- β , as well as GPER. Genetic deletion of ER- α in mice results in upregulation of the genes involved in hepatic lipid biosynthesis and downregulation of the genes involved in lipid transport, indicating that estrogens act via ER- α to regulate lipid metabolism [27]. ER- α KO and ER- α/β double KO mice showed increased serum cholesterol and smaller LDL particles, but not in ER- β single KO mice [28]. Therefore, ER- α plays a more prominent role than ER- β . The roles of GPER in the regulation of metabolism are only beginning to emerge, which gains more attentions. GPER knockout mice exhibit impaired cholesterol homeostasis manifesting significantly a higher LDL level but a normal HDL level, suggesting that GPER mainly regulates LDL metabolism [29]. And, human individuals with a hypofunctional GPER P16L allele are associated with elevated plasma LDL. In vitro study shows that activation of GPER by the agonist upregulates hepatic LDLr expression [30]. The role of GPER signaling in cholesterol or metabolic control remains unclear and needs more further investigations [31]. In summary, estrogens protect against increases in the plasma cholesterol level mainly by activating ER- α and GPER.

3.3. Androgens

The human androgens include dehydroepiandrosterone, androstenedione, testosterone and dihydrotestosterone (DHT). Testosterone can be converted to DHT via 5 α -reductase. Testosterones and DHT are active androgens, because they are the only androgens capable of binding to androgen receptors (ARs) to exert biological functions. AR is mainly expressed in the prostate, skeletal muscle, liver and central nervous system (CNS). Like ERs, AR is a member of the steroid and nuclear receptor superfamily. Ligand binding induces a conformation change of AR, leading to recruitment of cofactor proteins and transcriptional machinery and subsequent regulation of the target genes' transcription.

The effect of androgen on cholesterol is still not conclusive. Clinical studies show that androgen deficiency, such as in old men, is associated with increased risks of dyslipidemia, higher serum cholesterol and LDL levels [32]. Another study has found that AR antagonists might be useful in the treatment of obesity in men [33]. In the animal studies, dihydrotestosterone (DHT) treatment in castrated obese mice decreases LDL secretion and increases the expression of hepatic scavenger receptor class B member 1 (SR-1B) which is important in regulating cholesterol uptake from HDL. It also decreases the enzyme cholesterol 7 α -hydroxylase which participates in bile formation and cholesterol removal. In another study using an orchidectomized Sprague–Dawley (SD) rat model, DHT treatment causes decreased lipid accumulation and cholesterol synthesis by increasing expression of carnitine palmitoyl transferase 1 and phosphorylation of HMG-CoA reductase via an AR-mediated pathway [34]. However, this finding in animals contradicts a clinical study showing that a single dose of testosterone injection increases the total cholesterol level by 15% through stimulating the hepatic expression of HMG-CoA reductase [35]. These contradictory results indicate a complex role of androgen on the cholesterol homeostasis in the liver.

4. Growth hormone

4.1. Growth hormone and growth hormone receptors

Growth hormone (GH) is secreted by the somatotroph cells of the anterior pituitary gland under neural, hormonal and metabolic control. GH regulates postnatal growth, as well as lipid, glucose and energy metabolism. The molecular mechanism of GH action is relatively complicated. It affects metabolism through direct or indirect action via insulin-like growth factor-1 (IGF-1) or antagonism of insulin action. GH receptor (GHR) is a member of the cytokine receptor superfamily. Upon binding to GH, GHR activates the cytoplasmic tyrosine kinase Janus kinase 2 (Jak2) and then recruits members of the signal transducer and activator of transcription (STAT) family of transcription factors. Phosphorylated STATs translocate into the nucleus and modulate the transcription of multiple target genes, including IGF-1, ALS and suppressor of cytokine signaling (SOCS) [36]. In addition to the Jak2/STAT signaling pathway, GHR can activate the Src tyrosine kinase signaling pathway and cross talk with insulin and IGF-1 signaling pathways.

4.2. Role of GH in cholesterol and lipid metabolism

There exists a negative relationship between obesity and GH. Enormous evidence supports that GH alters lipid metabolism. Clinical studies have shown a significant association between lower serum GH levels and non-alcoholic fatty liver disease (NAFLD). Hypopituitary patients with GH deficiency are more prone to NAFLD than control subjects [37–39]. GH supplementation has been shown to improve the NAFLD and the metabolic dysfunction [40, 41]. In rodent studies, high-fat diet feeding and obesity suppress pulsatile GH secretion [42]. In turn, chronic GH treatment ameliorates hepatic lipid peroxidation and improves lipid metabolism in high-fat diet-fed rats [43].

Hypophysectomy is a surgery process in which the pituitary gland (hypophysis) is removed, leading to an impairment of GH secretion. This model is used for investigating the GH function in animals under pathophysiology conditions. Increase of hepatic LDLr and hypocholesterolemia induced by estrogens is completely attenuated in hypophysectomized rats. Only GH supplementation is able to restore this effect of hypophysectomy. Further, GH treatment on the gallstone patients stimulates the expression of hepatic LDLr by twofold, leading to subsequent decrease in serum cholesterol by 25%. This study indicates that GH secretion is critical for the control of plasma LDL levels in humans [44]. GH is also important for the synthesis of bile acids by maintaining the normal activity of cholesterol 7α -hydroxylase. Hypophysectomized rats show significantly reduced activities of HMG-CoA reductase and cholesterol 7α -hydroxylase and hence an inhibition of cholesterol and bile acid biosynthesis. GH substitution restores the enzymatic activity of 7α -hydroxylase and increases the fecal excretion of bile acids [45]. Treatment of LDLr-deficient mice with GH reduces their elevated plasma cholesterol and triglyceride levels by stimulating the activities of HMG-CoA reductase and cholesterol 7α -hydroxylase [46]. GH thus regulates plasma lipoprotein levels and bile acid metabolism by altering hepatic LDLr expression and the enzymatic activity of cholesterol 7α -hydroxylase, respectively.

GHR is present in the liver and critical for the hepatic lipid metabolism. Laron dwarfism is a disorder characterized by an insensitivity to GH due to a genetic mutation of GHR. These male patients manifest NAFLD in adults [47]. Liver-specific deletion of GHR in mice leads to increased circulating free fatty acids and fatty liver as a result of increased synthesis and decreased efflux of triglyceride [48]. Binding of GH to GHR activates JAK2-STAT5 signaling pathway and modulates a number of target genes. Among these, altered expression of CD36, PPAR γ and PGC1 α/β , along with fatty acid synthase, lipoprotein lipase and very-low-density lipoprotein receptor (VLDLr) contributes to the hepatic lipid metabolism process [49, 50]. All these findings suggest that hepatic GH signaling is essential for the regulation of intrahepatic lipid and cholesterol metabolism.

5. Glucagon

Glucagon is a 29-aa peptide hormone secreted from the pancreatic islet alpha cells in response to low glucose. It is a well-known counter-regulatory hormone to insulin, mainly stimulating hepatic glucose production by increasing glycogenolysis and gluconeogenesis and concurrently inhibiting glycogen synthesis. Glucagon also affects hepatic cholesterol metabolism. The relationship between glucagon and cholesterol has been investigated since the 1950s [51]. The portacaval shunt surgery in a 6-year-old girl with the homozygous form of familial hypercholesterolemia disorder has been reported to significantly reduce LDL and cholesterol synthesis 5 months after surgery. This alteration is associated with a marked elevation of bile acids and the glucagon level, indicating that glucagon may improve hepatic lipid metabolism [52]. In the animal study, infusion of glucagon into the hyperlipidemic rat reduces circulating VLDL apoprotein and serum TG levels. It is due to the inhibition of incorporating amino acid into the apoprotein by glucagon [53]. Chronic glucagon administration in rats significantly reduces serum cholesterol and triglyceride levels but not in the liver. The internal secretion of cholesterol and cholesterol transformation into bile acids measured by an isotope balance method are strikingly increased, suggesting that glucagon stimulates cholesterol turnover rate [54]. Studies by Rudling et al. have found that injection of glucagon increases LDL binding to the LDLr in a dose-dependent manner and concomitantly decreases cholesterol and apoB/E in LDL and large HDL particles in rats. Moreover, the induction of LDLr by glucagon is not due to increased mRNA levels, indicating a novel posttranscriptional regulatory mechanism present in the liver [55]. In humans, glucagon administration represses cholesterol 7 α -hydroxylase (CYP7A1) mRNA expression by increasing the PKA phosphorylation of HNF4a and reducing its ability to bind with the CYP7A1 gene, thus inhibiting bile acid synthesis [56].

Glucagon receptor, encoded by the GCGR gene, is a seven-transmembrane protein and belongs to the class II guanine nucleotide-binding protein (G protein)-coupled receptor superfamily. They are abundantly expressed in the liver and kidney. In the liver, glucagon receptors are mainly located in hepatocytes, with a small number expressed on the surface of Kupffer cells [57]. Mice with a null mutation of the glucagon receptor (*Gcgr*^{-/-}) display low blood glucose and markedly elevated the plasma LDL level. Serum total cholesterol and HDL are not significantly changed in *Gcgr*^{-/-} mice [58]. *Gcgr*^{-/-} mice are more prone to develop

hepatosteatosis following high-fat diet feeding [59]. Several glucagon receptor antagonists (GRA) have been developed to reduce hepatic glucose overproduction and improve the overall glycemic status. However, some GRAs including MK-0893 have been shown to dose-dependently increase LDL in T2DM patients. In the rodent preclinical trial, blockade of glucagon receptor using various GRAs elevates plasma LDL-c and total cholesterol. This is caused by increased cholesterol absorption instead of the change in cholesterol synthesis or secretion [60]. Taken together, these results suggest that glucagon plays a hypolipidemic effect through its glucagon receptors, making it an interesting and attractive pharmaceutical agent for the treatment of dyslipidemia and obesity.

6. Irisin

Irisin is a newly identified hormone encoded by the gene fibronectin type III domain-containing protein 5 (FNDC5). It is secreted into the circulation as a cleaved protein product and induced by exercise [61]. Irisin is proposed to mediate the metabolic benefits of exercising by promoting the browning of subcutaneous adipose tissue, reducing visceral obesity and improving glucose and cholesterol metabolism. Circulating the irisin level is negatively associated with fat mass, fasting glucose and dyslipidemia, as well as intrahepatic TG contents in humans [62, 63]. A higher baseline irisin level is associated with the metabolic benefits of diet-restricted treatment on human weight loss [64]. Lentivirus-mediated FNDC5 overexpression or subcutaneous perfusion of irisin promotes lipolysis and reduces hyperlipidemia in obese mice [65]. Irisin is negatively associated with HDL cholesterol and large HDL particles in adults with higher cardiovascular risk [66]. In addition, the serum irisin level is significantly higher in the NAFLD patients than in normal subjects [67]. Elevation of saliva irisin is positively related to total cholesterol [68]. Subcutaneous infusion of irisin decreases body weight, plasma total, VLDL, LDL, HDL cholesterol in diet-induced obese mice. The hepatic levels of total and esterified cholesterol are also reduced. These alterations are associated with significant reduction in the expression of the genes important for cholesterol synthesis, including *Srebp2*, HMG-CoA reductase (*Hmgcr*), the liver X receptor α (*Lxra*, *Nr1h3*) and HMG CoA synthase (*Hmgcs*) in the liver and primary hepatocytes. Further experiments demonstrate that irisin inhibits cholesterol synthesis in hepatocytes through the activation of AMPK and SREBP2 [69]. As a novel hormone, evidence supporting the critical role of irisin in the regulation of cholesterol or lipid metabolism is still limited. More studies are needed to clarify the role of FNDC5/irisin in the lipid homeostasis under physiological and pathological conditions.

7. Conclusion

Cholesterol balance is regulated at multiple steps, including the biosynthesis, uptake, intracellular transport and conversion to bile acids for excretion. Hormones affect cholesterol biosynthesis and uptake by altering the transcription of genes critical for these biological processes (Table 1). Novel identified hormones are constantly added into the list implicated

	Origin	Biosynthesis	Uptake	Secretion	Conversion to bile acid
Thyroid hormone	Thyroid	↑	↑		↑
Sex hormone					
Estrogen	Ovary	↑		↑	
Androgen	Testis		↑	↑	↑
Growth hormone	Pituitary	↑	↑		↑
Glucagon	Islet α cells			↑	↓
Irisin	Skeletal muscle	↓			

Table 1. Effect of hormones on cholesterol metabolism.

in cholesterol balance process. Identification of hormonal receptor agonist/antagonist and understanding the hormonal regulatory mechanisms would help to identify potential effective and selective targets for the control of cholesterol dysfunction.

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