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TOPIC HIGHLIGHT

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Thyroid hormones and thyroid hormone receptors: Effects of thyromimetics on reverse cholesterol transport

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Abstract

Reverse cholesterol transport (RCT) is a complex process which transfers cholesterol from peripheral cells to the liver for subsequent elimination from the body *via* feces. Thyroid hormones (THs) affect growth, development, and metabolism in almost all tissues. THs exert their actions by binding to thyroid hormone receptors (TRs). There are two major subtypes of TRs, TRα and TRβ, and several isoforms (e.g. TRα1, TRα2, TRβ1, and TRβ2). Activation of TRα1 affects heart rate, whereas activation of TRβ1 has positive effects on lipid and lipoprotein metabolism. Consequently, particular interest has been focused on the development of thyromimetic compounds targeting TRβ1, not only because of their ability to lower plasma cholesterol but also due their ability to stimulate RCT, at least in pre-clinical models. In this review we focus on THs, TRs, and on the effects of TRβ1-modulating thyromimetics on RCT in various animal models and in humans.

Key words: Cardiovascular disease; Cholesterol; Lipoprotein metabolism; Reverse cholesterol transport; Thyroid hormones; Thyroid hormone receptors

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INTRODUCTION

Cardiovascular disease (CVD), resulting from the progression of atherosclerosis, is the leading cause of mortality and is no longer a disease limited to Western countries (for data and statistics visit the World Health Organization homepage at www.who.int). To date, the first treatment choice in the prevention and treatment of CVD are the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as statins[1]. These compounds lower hepatic cholesterol levels by activation of sterol regulatory element binding protein 2 (SREBP2). Activation of SREBP2 induces the expression of the low density lipoprotein (LDL) receptor (LDLR), which results in increased uptake of LDL-particles from plasma (see Figure 1 for a schematic representation of lipoprotein metabolism). Newer drugs such as ezetimibe, which acts by blocking intestinal cholesterol uptake, have recently been proposed as complements to statin therapy. Despite these new therapeutic approaches there is still a demand for improved treatment strategies, especially in light of the failure of some clinical trials[2]. A long debated approach is to promote reverse cholesterol transport (RCT)[3]. RCT is a complex process which transfers cholesterol from pe-

ripheral cells to the liver for subsequent elimination in the feces as bile acids and neutral steroids. RCT was originally proposed by Glomset[4] more than 40 years ago. Recently a non-biliary route for cholesterol elimination from the body has been described, named trans intestinal cholesterol excretion (TICE), in which cholesterol can be transported directly from blood across the enterocytes into the intestinal lumen[5].

THYROID HORMONES AND THYROID HORMONE METABOLITES

Thyroid hormones (THs) have prominent effects on growth, development, and metabolism in almost all tissues[6,7]. Thyroxine (T_4) and triiodothyronine (T_3) are synthesized by the thyroid gland and T_4 is the major secreted hormone. Yet, T_3 is classically considered as the active and more potent hormone since it binds to thyroid hormone receptors (TRs) with higher affinity than T_4. Selenoproteins known as deiodinases[8] convert T_4 to T_3 by 5' deiodination of the outer ring of molecules and regulate the local and systemic availability of T_3. Different types of deiodinases exist: type Ⅰ are present in peripheral tissues including the liver; type Ⅱ are mainly present in the pituitary gland, brain, and brown adipose tissue; and type Ⅲ are present in the placenta, brain, and skin. Whereas type Ⅰ deiodinases convert T_4 in the majority of circulating T_3, type Ⅱ deiodinases not only contribute to the circulating levels but also to the intracellular levels of T_3. Thus, type Ⅱ deiodinases confer to the tissues expressing this type of enzyme the ability to respond to circulating T_4 without being obligated to circulating T_3. Type Ⅲ deiodinases, together with type Ⅰ, convert T_4 into reverse T_3 (rT_3). rT_3 was regarded as an inactive metabolite, since no metabolic effects of rT_3 has been reported, however, the discovery of non-genomic actions of rT_3 on actin polymerization and microfilament organization in astrocytes and in the cerebellum[6,9] has shown that this molecule is active. In addition to deiodination, THs are metabolized by sulfation and glucuronidation[10]. These processes primarily occur in the liver, and to a lesser extent in the kidney, and results in relatively inactive metabolites with increased water solubility, which facilitate biliary and urinary secretion. When the activity of type Ⅰ deiodinases is low (e.g. in the fetus), T_3 sulfate may serve as a reservoir of inactive T_3 from which the active hormone can be generated by the action of tissue and intestinal bacterial sulfatases[11]. Similarly, iodothyronine glucuronides once excreted *via* the bile into the intestine can be substrates for the bacterial β-glucuronidases and the unconjugated THs generated can be reabsorbed into the body. Thus, THs undergo enterohepatic recirculation[12].

In the liver, oxidative deamination and decarboxylation of the alanine chain of T_3 and T_4 form triiodothyroacetic acid (Triac) and tetraiodothyroacetic acid (Tetrac), respectively. These so-called acetic acid analogues of THs are metabolically active. Tetrac has been evaluated in patients with myxedema and no major differences in efficacy were reported compared to T_4, except for the need for higher doses of Tetrac[13]. Also for Triac, the therapeutic doses to treat thyroid disorders are higher than those needed for T_4 in order to reach similar thyroid-stimulating hormone suppression[14]. Interestingly, Triac had bigger hepatic metabolic actions without enhanced thyromimetic activity specific to the pituitary gland[14]. The organ-selective effects of Triac are possibly explained by the higher affinity of this acetic acid analogue to TRβ (3.5-fold) and to TRα (1.5-fold) than T_3[15].

THYROID HORMONE RECEPTORS

TRs are members of the large superfamily of nuclear receptors (NRs) and can bind DNA as monomers, homodimers, or heterodimers mainly with the retinoic-X receptor α[16-18]. TRs are ligand-activated transcription factors and bind both THs and TH-response elements (TREs) classically located in the promoter regions of their target genes. TRs have the typical NR structure with a central DNA-binding domain containing two "zinc fingers" motifs which interact with the nucleotide of the TRE-sequences. The ligand-binding domain (LBD) is composed of twelve amphipathic helices, some of which specifically interact with co-activators and co-repressors[19-21]. Upon ligand-activation, TRs modify the conformation of their LBD region; a process that mainly involves helix 12 and results in release of co-repressors (e.g. NCoR and SMRT) and recruitment of co-activators (the steroid receptor co-activator complex[22] and the vitamin D receptor-interacting protein/TR associated protein complex[23]). Due to the interaction with co-repressors, TRs can decrease the transcriptional activity of the target genes, when not ligand-activated by THs. The interpretation of data generated in animal models in which TRs have been genetically depleted require caution when compared to conditions with low levels of circulating THs (e.g. after thyroidectomy, hypophysectomy, or in hypothyroidism). Under these conditions TRs are not ligand-activated and, being still present, may repress transcription. Apart from the genomic effect, which classically are mediated by activation of TRs bound to the promoter region of the target genes, THs may also regulate cells by non-transcriptional mechanisms[7].

The human TRs are encoded by the THRA and THRB genes, located on chromosome 17 and 3, respectively; the two TRα isoforms [TRα1, TRα2 (or c-erbAα2)] are generated by alternative splicing of the TRα mRNA whereas the two TRβ isoforms (TRβ1 and TRβ2) are generated by alternative promoter choice[16,24]. Both TRα1 and TRβ1 are expressed in almost all tissues[25], but the latter is the predominant TR isoform in the liver, brain, and kidney, whereas the former is predominantly expressed in muscle and brown adipose fat. TRβ2 is expressed in the hypothalamus, in the anterior pituitary gland, and in the developing brain[25-27].

LESSONS FROM STUDIES IN RODENTS

The generation of TR specific knock-out mice revealed that the T_3-induced cardiovascular liability is mediated by

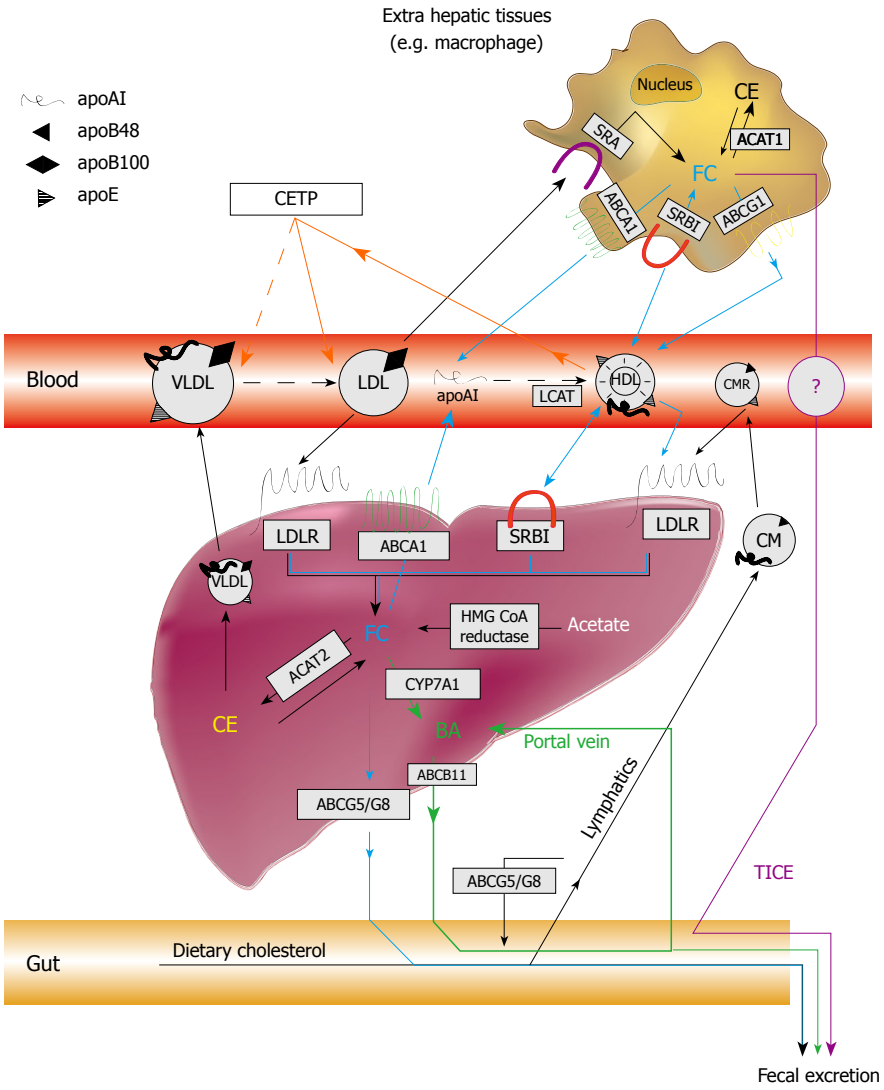

Figure 1 Schematic overview of cholesterol, bile acid, and lipoprotein metabolism. CE: Cholesteryl esters; FC: Free cholesterol; BA: Bile acids; CM: Chylomicrons; CMR: Chylomicron remnants; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; HDL: High density lipoprotein; apoAI: Apolipoprotein AI; apoB48: Apolipoprotein B48; apoB100: Apolipoprotein B100; apoE: Apolipoprotein E; CETP: Cholesterol ester transfer protein; LCAT: Lecithin cholesterol acyltransferase; LDLR: LDL receptor; ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; ABCG5: ATP-binding cassette transporter G5; ABCG8: ATP-binding cassette transporter G8; ABCB11: ATP-binding cassette transporter B11; SRA: Scavenger receptor type A; SRBI: Scavenger receptor type BI; ACAT1: Acyl-coenzyme A cholesterol acyltransferase 1; ACAT2: Acyl-coenzyme A cholesterol acyltransferase 2; HMGCoA reductase: 3-hydroxy-3-methylglutaryl coenzyme A reductase; CYP7A1: Cholesterol 7α-hydroxylase. Blue lines and arrows represent reverse cholesterol transport. Green lines and arrows represent enterohepatic bile acid circulation. Purple line and arrows represent transintestinal cholesterol excretion (TICE). Red lines and arrows represent the CETP mediated transfer of CE from HDL to LDL and to VLDL.

TRα1[28,29], while the effect of T_3 on plasma cholesterol levels is mediated through TRβ1[30]. These findings raised interest in the development of thyromimetic compounds that specifically modulate TRβ1, either by selective hepatic uptake and/or by higher binding affinity to TRβ1, rather than TRα1. The first thyromimetic compound to be described was SK&F L-94901, which does not preferentially bind to either TRα or TRβ; instead the TRβ1 selective action is achieved by its liver-specific uptake[31]. L-94901 reduced plasma cholesterol levels, mainly in the LDL fraction, in cholesterol-fed hypothyroid and euthyroid rats[32]. Likewise, GC-1 (sobetirome) and KB-141 reduced plasma cholesterol levels in normal and hypothyroid mice and rats[33,34]. T-0681 decreased plasma apoB-containing lipoproteins and reduced atherosclerosis in cholesterol-fed rabbits[35], while MB07811 elicited a similar lipid-lowering effect in rats, as well as in obese mice[36].

The ability of thyromimetic compounds to reduce LDL-cholesterol can partly be explained by increased clearance through increased hepatic LDLR expression. KB-141, MB07811, and T-0681 induced hepatic LDLR expression in several mouse models[35,36], and T-0681 increased hepatic LDLR levels (approximate 2.5-fold) in hypercholesterolemic rabbits[35]. In accordance, LDLR expression was suggested to be crucial for the thyromimetic effect on lipid metabolism, since mice deficient in LDLR do not respond to treatment with either MB07811[36] or T-0681[35]. However, T_3 and sobetirome failed to induce hepatic LDLR mRNA expression and activity, despite reduced circulating levels of LDL-cholesterol in hyper-

cholesterolemic euthyroid mice[34]. Similarly, T-0681 had no effect on the hepatic LDLR protein expression in either C57BL/6 or apoE$^{-/-}$ mice[35]. Thus, the stimulation of LDLR by thyromimetics is not an obligatory finding.

In all animal models, the lipid-lowering effects were achieved at doses that did not affect the heart rate. For sobetirome and KB-141, the concentrations that produced tachycardia were almost 30-fold higher than the therapeutic concentrations in rats and even greater in non-human primates[33].

EFFECTS OF THYROID HORMONES AND THYROMIMETICS ON RCT IN RODENTS

Evidence from animal studies suggested that THs and thyromimetics have the capacity to promote RCT. Despite its complexity, the RCT pathway can be summarized in four major steps: (1) synthesis and lipidation of apolipoprotein AI (apoAI) to generate nascent high density lipoprotein (HDL); (2) efflux of excess cholesterol from peripheral cells (e.g. macrophages) to plasma HDL; (3) hepatic uptake of cholesterol from HDL *via* scavenger receptor class B type I (SRBI) and LDL *via* LDLR - the latter especially in the presence of cholesterol ester transfer protein (CETP); and (4) biliary secretion of cholesterol, as such, or after its conversion to bile acids, for final excretion from the body in feces.

Studies in rodents showed that T_3 and the thyromimetic compound CGS-23425 increased the levels of plasma apoAI[37,38], suggesting that TR stimulation may promote the synthesis of HDL and thus affect the initial step of RCT. Whether thyromimetic compounds stimulate cholesterol efflux to HDL by a direct action on peripheral cells (e.g. macrophages) is still unclear. Studies in rodents show that the ability of THs and thyromimetics to increase RCT is related to their capacity to stimulate the hepatic and final steps of this process by increasing the expression and activity of: (1) SRBI, responsible for the uptake of cholesterol-enriched HDL; (2) cholesterol 7α-hydroxylase (CYP7A1), which converts cholesterol into bile acids in the liver; and (3) ATP-binding cassette transporter G5 (ABCG5) and G8 (ABCG8), which promote biliary cholesterol excretion[30,34-36].

The regulation of bile acid synthesis by TRs and THs has been widely demonstrated in rodents[39-41]. In mice, TRβ has been identified as the primary mediator of the effect of T_3 on the stimulation of CYP7A1 expression and activity[30]. Also thyromimetic compounds such as MB07811, KB-141, T-0681, or sobetirome have been shown to increase the expression of hepatic CYP7A1[34-36]. In addition to the stimulation of bile acid synthesis, we were able to show that sobetirome increases the hepatic SRBI protein expression in normal and hypercholesterolemic euthyroid mice, leading to lower HDL-cholesterol levels and higher fecal bile acid excretion[34]. A limitation of our study was that a direct quantification of the *in vivo* RCT was not performed. RCT can be quantified *in vivo* by assessing the transport of [^{3}H]cholesterol from intraperitoneally injected macrophages to plasma, liver, and feces (called the macrophage-to-feces RCT)[42,43]. Recently, T-0681 was shown to stimulate the *in vivo* RCT in C57BL/6 mice[35] resulting in elevated fecal excretion of radiolabeled cholesterol, both as neutral sterols and as bile acids. This was paralleled by an increase in the hepatic expression of SRBI, CYP7A1, and ABCG5/G8[35].

Mice and rats have no plasma activity of CETP, which transfers cholesteryl esters from HDL to LDL. Thus, the RCT pathway in these rodent models does not properly resemble the human RCT, in which part of the cholesterol originally carried by HDL is delivered to the liver by LDL. Overexpression of human CETP in mice stimulates the *in vivo* RCT and, as expected, a considerable amount of the radiolabeled cholesterol effluxed from the macrophages was transferred from HDL to LDL for subsequent uptake by hepatic LDLR[44]. Surprisingly, T-0681 failed to stimulate *in vivo* RCT in mice overexpressing human CETP[35], despite the stimulation of hepatic SRBI and LDLR. In this mouse model, T-0681 did not affect hepatic ABCG5/G8 and CYP7A1 expression, as observed in wild-type mice[35]. Plasma CETP-mass was reduced and the authors suggested this was a possible cause of disturbed delivery of cholesterol to the liver[35]. Nevertheless, it is evident that it is difficult to draw any definite conclusions relevant to humans by studying mice overexpressing human CETP. In apoE knockout mice, treatment with T-0681 for 8 wk decreased plasma cholesterol levels and reduced the development of atherosclerosis, whereas treatment for 4 wk slightly increased small fatty streak lesions[35]. In line with the above observation, up-regulation of both hepatic ABCG5/G8 and CYP7A1 were only observed after 8 wk of treatment[35]. Recently, we treated (up to 25 wk) apoE-deficient mice with the new thyromimetic compound KB3495 (KaroBio AB). Reduced atherosclerosis and increased fecal excretion of neutral and acidic sterols were observed independently of the circulating levels of cholesterol in apoB-containing lipoproteins. This suggests that stimulation of RCT was *per se* sufficient to achieve the antiatherogenic effects[45]. Furthermore, no major effects on the hepatic expression of ABCG5/G8 mRNA were seen suggesting that TRβ1 modulation may increase RCT possibly by stimulation of TICE[5].

LESSONS FROM STUDIES IN HUMAN AND PRIMATES

It has been known since 1930 that hyperthyroidism is associated with reduced plasma cholesterol levels[46]. Also, studies have shown that hyperthyroid women have lower HDL-cholesterol and apoAI levels compared to healthy controls[47,48]. In addition, treatment with 1-thyroxine in patients with severe primary hypothyroidism significantly increased apoAI but modestly decreased HDL-cholesterol levels[49]. Interestingly, subjects with resistance to thyroid hormone, defined genetically by mutations in TRβ, have lower HDL-cholesterol levels compared to controls[50].

So far, no human or non-human primate studies that specifically aimed to investigate the role of thyromimetics in RCT have been performed. Rodents, unlike humans,

transport plasma cholesterol mainly in HDL-particles, lack CETP activity in plasma, and do not develop atherosclerosis. Also, the feed-forward response on Cyp7A1 activity by dietary cholesterol, which is mediated by activation of liver X receptor α (LXRα) in mice, is absent in humans, because functional LXRα response elements are not present within the human CYP7A1 promoter[51]. Hence, caution is required when extrapolating mechanisms in RCT from rodent studies to humans.

EFFECTS OF THYROMIMETICS ON BILE ACID SYNTHESIS IN HUMANS

Bile acid synthesis serves as the major elimination route of excess cholesterol, participating in maintenance of cholesterol homeostasis and in the hepatic part of RCT. In the liver, cholesterol is converted to 7α-hydroxycholesterol by the microsomal enzyme CYP7A1, the rate-limiting enzyme of the classic pathway, which is then converted to 7α-hydroxy-4 cholesten-3-one (C4). In humans, the classic pathway is responsible for the main part of bile acid synthesis[52]. Thus, it has been shown that plasma levels of C4 reflect bile acid synthesis and that plasma levels of C4 correlate with the enzymatic activity of CYP7A1 assayed in human hepatic microsomes[53-56].

Studies in human hepatoma cells and in primary human hepatocytes suggest that human CYP7A1 expression and promoter activity is actively repressed in response to THs[57,58], suggesting that THs and thyromimetic compounds would decrease bile acid synthesis. Nevertheless, treatment of moderately overweight and hypercholesterolemic subjects with eprotirome (KB2115), administered at 100 and 200 μg orally once daily for 2 wk, increased bile acid synthesis (C4) by approximate 50% and 100%, respectively. Since no effect on cholesterol synthesis in the body (indirectly measured as the ratio of lathosterol to cholesterol in plasma)[59] was observed it seems that eprotirome may induce a net cholesterol efflux from the body[59].

EFFECTS OF THYROMIMETICS ON HDL, apoAI, apoB AND LIPOPROTEIN (a) IN HUMANS AND NON-HUMAN PRIMATES

Measurement of apoAI, the major apolipoprotein in HDL, is as important as the measurement of HDL-cholesterol and the balance between apoB and apoAI (i.e. the apoB/apoAI ratio) indicates cardiovascular risk[60]. In a study by Ladenson *et al*[61], patients with hypercholesterolemia, who were already receiving simvastatin or atorvastatin, were administered 25, 50 or 100 μg eprotirome (KB2115) or placebo daily for 12 wk in addition to continued statin-therapy[61]. Serum total-, LDL-, and HDL-cholesterol, as well as apoB, apoAI, apoB/apoAI ratio, TG, and lipoprotein (a) [Lp(a)] decreased in the eprotirome-treated subjects[61] without adverse effects on heart or bones. In the study by Berkenstam *et al*[59], treatment with eprotirome was found to reduce serum total- and LDL-cholesterol levels as well as the apoB/apoAI ratio without detectable effects on the heart[59]. No significant changes in HDL-cholesterol, TG, Lp(a), or body weight were observed[59]. The discrepancies between these two studies with regard to HDL-cholesterol and apoAI, and whether the combination-therapy with statins and eprotirome[61] affects this, needs to be further investigated by studying CETP and lecithin cholesterol:acyltransferase (LCAT) activities, C4, hepatic gene expression (e.g. SRBI, CYP7A1, ABCG5/G8, ABCA1), and by studies on sterol fecal excretion.

Intestinal and hepatic ABCA1 regulates HDL levels[62,63]. Co-transfection experiments, performed in human embryonal kidney cells (HEK293) with the human ABCA1 promoter and an expression vector for TRβ, showed suppression of the ABCA1 promoter activity in the presence of T_3[64]. Whether TRβ1-modulators suppress the hepatic and intestinal ABCA1 transcription and expression *in vivo* in humans remains to be elucidated.

Lp(a) may contribute to the development of atherosclerosis, and extreme levels have been shown to increase the risk for myocardial infarction[65]. Cynomolgus monkeys have a lipoprotein cholesterol profile that resembles the human profile and express Lp(a). Sobetirome and KB141 reduce plasma levels of Lp(a) in this non-human primate model[33]. Eprotirome in combination with statin-treatment reduced the levels of Lp(a)[61] which was not observed in patients treated with eprotirome only[59], suggesting again that a possible synergism between statins and eprotirome may exist.

CONCLUSION

Compounds that specifically target TRβ1 have consistently been shown to stimulate RCT and decrease atherosclerosis in animal models, and may hypothetically be useful as a complement to statin therapy in the prevention of CVD. However, future studies evaluating the effects of these compounds on RCT in humans need to be performed. Clarification of the primary effect of TRβ1 modulation on human RCT is of great scientific value and strategic interest. The attractiveness of drugs able to promote RCT and lower LDL-cholesterol in humans - especially if not only acting *via* stimulation of LDLR - is immense.

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