

Gene-Activation Mechanisms in the Regression of Atherosclerosis, Elimination of Diabetes Type 2, and Prevention of Dementia

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Abstract: Atherosclerotic vascular disease, diabetes mellitus (DM) and dementia are major global health problems. Both endogenous and exogenous factors activate genes functioning in biological processes. This review article focuses on gene-activation mechanisms that regress atherosclerosis, eliminate DM type 2 (DM2), and prevent cognitive decline and dementia.

Gene-activating compounds upregulating functions of liver endoplasmic reticulum (ER) and affecting lipid and protein metabolism, increase ER size through membrane synthesis, and produce an antiatherogenic plasma lipoprotein profile. Numerous gene-activators regress atherosclerosis and reduce the occurrence of atherosclerotic disease. The gene-activators increase glucose disposal rate and insulin sensitivity and, by restoring normal glucose and insulin levels, remove metabolic syndrome and DM2. Patients with DM2 show an improvement of plasma lipoprotein profile and glucose tolerance together with increase in liver phospholipid (PL) and cytochrome (CYP) P450. The gene-activating compounds induce hepatic protein and PL synthesis, and upregulate enzymes including CYPs and glucokinase, nuclear receptors, apolipoproteins and ABC (ATP-binding cassette) transporters. They induce reparation of ER structures and eliminate consequences of ER stress. Healthy living habits activate mechanisms that maintain high levels of HDL and apolipoprotein AI, promote health, and prevent cognitive decline and dementia. Agonists of liver X receptor (LXR) reduce amyloid in brain plaques and improve cognitive performance in mouse models of Alzheimer's disease.

The gene activation increases the capacity to withstand cellular stress and to repair cellular damage and increases life span. Life free of major health problems and in good cognitive health promotes well-being and living a long and active life.

Keywords: Atherosclerosis, CYP, dementia, diabetes, endoplasmic reticulum, gene activation, HDL, LXR.

INTRODUCTION

Our survival depends upon the capacity to withstand cellular stress and repair molecular damage to maintain physiological functions. Both endogenous and exogenous factors influence the life maintaining activities. They influence the functions of genes that act as controllers of metabolic processes. Perturbations in lipid and protein metabolism are common in atherosclerotic cardiovascular diseases (CVDs) and metabolic disorders such as obesity, metabolic syndrome and type 2 diabetes (DM2) which are major health problems worldwide. Coronary heart disease (CHD) has been recognised as the most common cause of death in the world [1]. About nine out of ten patients with diagnosed DM in the U.S. have DM2 the prevalence of which has tripled in the last 30 years [2], and the prevalence of metabolic syndrome is rapidly increasing to epidemic proportions both in developed and developing countries [3]. The combination of obesity, elevated blood pressure and poor glucose tolerance often associates with elevated triglycerides and reduced HDL cholesterol (HDL-C) and together comprise the major components of the metabolic syndrome [4].

Clinical investigations performed in the 1970s revealed that drugs inducing protein synthesis and increasing liver proteins, in proportion to this effect produce plasma risk factor profile indicating a low probability of developing atherosclerotic disease [5, 6]. Studies in the 1980 including DM2 patients revealed that these gene-activating agents reduce both blood glucose and insulin [7, 8]. More recent studies have focused interest on gene-activation mechanisms affecting neuronal and cognitive function [9, 10]. A prospective study showed that removing modifiable risk factors of DM has a great reducing impact on the incidence of dementia, and suggested the elimination of DM as the principal target for health promotion programmes [11]. This review focuses on gene-activation mechanisms in the regression of atherosclerosis, elimination of DM2, and prevention of cognitive decline and dementia.

LIVER ENDOPLASMIC RETICULUM IN LIPID, PROTEIN AND GLUCOSE METABOLISM

The liver endoplasmic reticulum (ER) is the principal site for the synthesis and processing of lipids and proteins, and alterations in ER function influence plasma lipoprotein levels [12, 13]. Investigations performed in the 1960s revealed that induction of hepatic protein and lipid synthesis increases protein and phospholipid (PL) concentrations together with

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increase of ER membranes [14-16]. Phenobarbital (PB) has widely been used as a prototype for the evaluation of ER functions in protein, lipid, carbohydrate and xenobiotic metabolism. Studies performed in the 1970s and 1980s revealed that patients treated with PB-type gene-activating drugs show increase in liver protein and PL concentrations and P450 activity [5, 17] and decrease in hepatic triglycerides [18]. DM2 patients often have hepatic fatty degeneration together with increased triglyceride and reduced PL concentrations [19], and the gene-activating therapy reduces hepatic fat content as seen in light microscopy, and electron micrographs show reparation and increase in hepatocyte and ER membranes [7]. The therapy has similar effects also in obese mice with fatty liver [20]. The ER has a central role also in carbohydrate metabolism [21], and gene-activating compounds affect the fate of glucose. PB treatment reduces the activity of ER glucose-6-phosphatase [22] which is responsible for hepatic glucose production from glycogen breakdown or gluconeogenesis, and induces glucokinase [23], the major enzyme in the hepatic utilization of glucose.

HDL AND LDL RISK FACTORS AND ANTI-ATHEROGENIC MECHANISMS

HDL is known as the antiatherogenic lipoprotein acting in the reverse transport of cholesterol, and low density lipoprotein, LDL, as the atherogenic lipoprotein transporting cholesterol to tissues, including arteries. Apo AI and AII are major apolipoproteins of HDL and apo B the apolipoprotein of LDL. Two main subclasses, HDL2 and HDL3, can be separated in HDL density range. HDL2 is a large lipoprotein with high apo AI and PL content [24]. Phosphatidylcholine (PC) is the main PL (over 70%) of HDL [25], and the PC- and apo AI-rich HDL2 is known as the lipoprotein responsible for the antiatherogenic effect of HDL [26]. High HDL2-C level, HDL2-C/HDL3-C and apo AI/AII ratio, and low LDL-C level, and LDL-C/ HDL-C and apo B/apo AI ratio indicate a low risk of atherosclerotic disease.

Sophisticated regulatory systems maintain cholesterol homeostasis (reviewed in [27-29]). They include cytochrome (CYP) P450-monooxygenases, physiological factors in the catabolism of cholesterol to oxysterols and bile acids and activation of cholesterol-lowering mechanisms [30, 31]. Oxysterols are endogenous ligands for liver X receptors (LXR α and LXR β), and suppressors of hydroxyl-methylglutaryl CoA reductase (HMGCoAR), the rate-limiting enzyme in cholesterol synthesis, and their secretion from cells represents a form of cholesterol elimination. The LXRs mediate the expression of multiple genes in the regulation of cholesterol balance in the body, i.e. its cellular efflux, transport, excretion and absorption. LXRs upregulate ABC transporters including ABCA1, ABCG1, ABCG4, ABCG5 and ABCG8 that shuttle intracellular cholesterol for the efflux out of cells, and several apolipoproteins including apo AI and E. ABCA1 is a key playmaker in cholesterol efflux, and a major

determinant of plasma HDL level [29]. An increased ABCA1 and ABCG1 expression stimulates cellular cholesterol efflux to lipid poor apo AI and HDL, respectively [28].

LDL particles accumulated in the arterial wall can undergo oxidative modification [32]. Oxidized LDL contains products of lipid peroxidation including lipid hydroperoxides and oxidized phospholipids which are key factors in the initiation and progression of atherosclerotic lesions [32, 33]. Apart from the key role in cholesterol efflux, LXR activation is important in protecting cells from the atherogenic effects of lipid peroxides and inflammation [34]. HDL, apo AI, and apo AI-mimetic peptides prevent LDL oxidation and decrease atherosclerotic lesions, and improve vascular reactivity in animal models and in humans [32]. Apo AI in HDL [35] and plasma glutathione peroxidase [36] reduce PC hydroperoxides, and an infusion of apo AI-PC discs raising low HDL is effective in restoring the endothelial function [37].

EFFECTS OF GENE-ACTIVATING COMPOUNDS ON LIVER ER, RISK FACTORS, ATHERO-SCLEROSIS AND SURVIVAL

Healthy young nonobese subjects show high plasma HDL-C and HDL2-C and high HDL-C/ total cholesterol (T-C) and HDL2-C/HDL3-C ratio together with high plasma antipyrine (AP) clearance rate [38], which has been used as a measure of hepatic P450-activity *in vivo*. Functional crosstalk of common regulatory factors links lipid and xenobiotic metabolism and P450 activity [31, 39, 40]. A prospective, double-blind, placebo-controlled trial including nonepileptic subjects showed that phenytoin therapy raises plasma HDL-C, and particularly HDL2-C, and has no significant effect on HDL3-C, LDL-C, T-C and triglycerides [41].

Plasma HDL-C and apo A-I raise with increasing protein, PL (Fig. 1) [17], and P450 in the liver, and they are high in subjects undergoing gene-activating drug therapy [6, 42]. The subjects also show low LDL-C and LDL-C/HDL-C ratio [40] and high HDL2-C and HDL-C/ T-C ratio [38] together with high AP clearance rate. Plasma HDL-C, apo AI and HDL-C/ T-C ratio raise and triglycerides decrease with decreasing hepatic triglycerides [17], and fat content as determined microscopically [43]. These original studies linking gene activation, upregulation of hepatic ER functions, proteins, PL and P450 activity, with beneficial changes in key risk factors presented novel mechanisms to prevent and treat atherosclerotic vascular disease [5, 31].

Hepatic CTP:phosphocholine cytidyltransferase- α (CCT α), the regulatory enzyme for the synthesis of PC, is a key player in maintaining plasma HDL-C level [44]. Elevation of cellular cholesterol induces generation of oxysterols that upregulate CCT α and PC synthesis [45]. PC is the most important PL in reverse cholesterol transport because it is the essential cholesterol-binding component of lipoproteins and the acyl donor in the

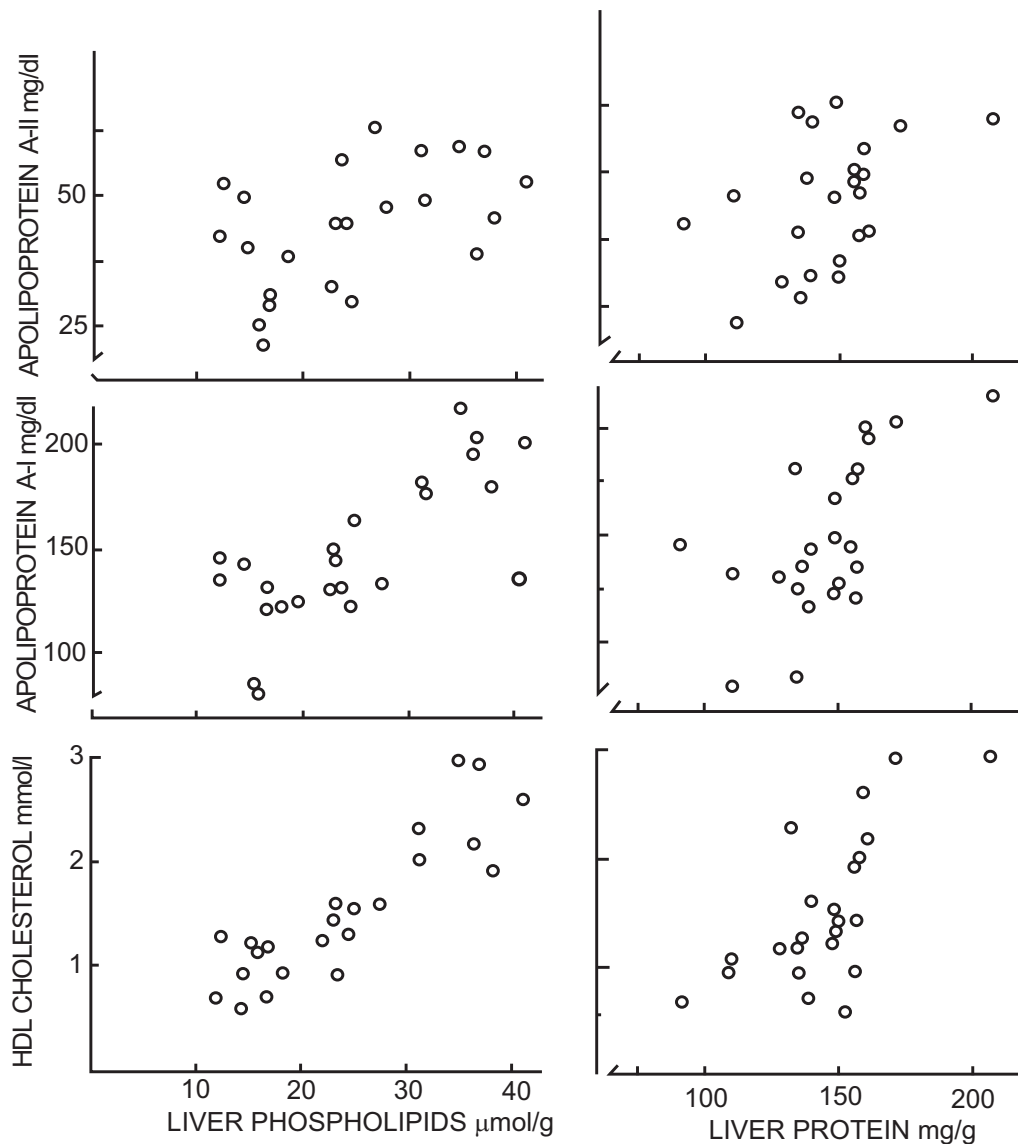


Fig. (1). Relation of liver phospholipid and protein concentrations to plasma HDL cholesterol ($r=0.878$ and $r=0.670$, respectively), apolipoprotein A-I ($r=0.812$ and $r=0.614$) and A-II ($r=0.433$ and $r=0.408$) levels in 23 subjects. Reproduced from: Luoma PV, *et al.* *Acta Med Scand.*, 1983; 214: 103-109 [17].

esterification of free cholesterol by lecithin:cholesterol acyltransferase (LCAT) [26]. In agreement with these studies, high PL content in HDL2 particles has been found to be an efficient driving factor for cholesterol removal from peripheral cells [46, 47], an intravenous infusion of apo A/PC discs to stimulate reverse cholesterol transport in humans [48], and plasma HDL-PL levels to inversely correlate to the extent of atherosclerosis in coronary arteries [49].

Numerous xenobiotic compounds upregulate antiatherogenic mechanisms (reviewed in [50]). The compounds include drugs for dyslipidemias such as statins, niacin, fibrates, resins, as well as compounds for other purposes, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers, glitazones and anticonvulsants, and alcohol. A number of xenobiotic gene-activators raise HDL2-C [50] and produce plasma

lipoprotein pattern which is typical of low risk of atherosclerotic disease and exceptional longevity [51, 52], regress atherosclerosis, and reduce mortality and/or morbidity from CHD, cerebrovascular disease, and also death from any cause [50].

EFFECTS OF GENE-ACTIVATORS ON LIVER ER AND GLUCOSE AND INSULIN

Clinical investigations performed in the 1980s evaluated the effects of gene-activating agents on glucose and insulin. The studies including DM2 patients revealed that the therapy induces plasma membrane reparation and increases the surface density in ER membranes of hepatocytes together with an elimination of liver fat, a decrease both in blood glucose and plasma IRI levels and enhancement of P450-mediated AP clearance [7]. These original

observations linking upregulation of ER membranes and functions and lowering of glucose and IRI levels presented a novel approach for the prevention and treatment of DM2 [7]. Subsequent studies clarified, by using the euglycemic clamp technique, the effects of gene-activating compounds on glucose- insulin homeostasis both in healthy volunteers and patients with DM2 [8, 53]. The results revealed that a short-term PB treatment of healthy volunteers increases glucose disposal rate by approximately 30% and also the metabolic clearance rate of glucose, with concomitant enhancement of AP elimination [53]. PB therapy also reduced fasting IRI, while fasting blood glucose in healthy subjects remained unaltered. In contrast to PB effects, cimetidine, an inhibitor of P450, reduced glucose disposal rate and glucose metabolic clearance rate, and AP elimination [53].

In subjects with liver disease glucose disposal rate varies proportionately to the amount of unaltered hepatic parenchyma as evaluated morphometrically, and to hepatic P450-mediated AP kinetics [54]. The glucose disposal rate was lowest among patients with fatty liver and those with liver cirrhosis. PB treatment of DM2 patients reduced both fasting blood glucose and IRI [8]. In addition, glucose disposal rate, metabolic clearance rate of glucose, and insulin sensitivity index, determined by using the euglycemic clamp technique, increased during therapy (Fig. 2) [8].

Glucose has recently been identified as a natural LXR agonist [21]. It activates LXR at physiological concentrations expected in the liver and induces expression of LXR target genes with efficacy similar to that of oxysterol and determines its own fate [21]. Glucose binds and stimulates the transcriptional activity of LXR and coordinates hepatic lipid metabolism. Hepatic LXR activation suppresses gluconeogenic genes, and induces glucokinase in the liver that promotes hepatic glucose utilization [55].

COGNITIVE IMPAIRMENT – MECHANISMS AND RISK FACTORS

Mild Cognitive Impairment (MCI) has been used to describe the transitional state between normal cognitive function and Alzheimer's disease (AD). AD is the most common cause of dementia [56], the prevalence of which doubles every five years between 65 and 85 years of age [57]. The accumulation of amyloid β ($A\beta$) in the brain has been considered as the main culprit in the pathogenesis of AD, resulting in synapse disruption and neuronal destruction. Cognitive processes require gene expression modification to consolidate information, and transcriptional dysregulation could perturb neuronal function and cognitive performance [58].

Recent studies in the AD context have focused attention on LXRs [9, 59] and the so-called LXR-ABCA1- apo E axis [10, 60]. LXRs have an important function in lipid homeostasis in the brain, and the loss of the receptors leads to neurodegenerative processes

[59]. ABCA1 has been shown to influence brain levels and lipidation of apo E in mice. A poor lipidation of apo E increases amyloid burden in mouse models of AD and, conversely, an overexpression of ABCA1 in the brain promotes apo E lipidation and reduces the formation of mature amyloid plaques [60]. LXR activating compounds reducing amyloid load also improve cognitive performance in mouse models of AD [61]. An activation of pregnane X receptor (PXR) may also improve cognitive function. Pregnenolone-16 α -carbonitrile (PCN), a PXR agonist, has been shown to induce the expression of blood-brain barrier protein known as P-glycoprotein, and to reduce brain $A\beta$ levels in a mouse model of AD [62]. This protein specifically mediates the efflux transport of $A\beta$ from mouse brain capillaries into vascular space, a critical component of the $A\beta$ brain efflux mechanism [69]. A recent study using a mouse model of AD and analyzing the effects of phenylbutyrate, revealed that the drug reduces AD linked tau protein and ameliorates cognitive deficit [58]. The drug is already approved for clinical use, and it may provide a novel approach for the treatment of AD [58].

Low HDL has been identified as a risk factor for deficit and decline in memory in midlife [63], and high HDL-C and apo AI concentrations correlate with cognitive function in advanced age [64]. Hyperinsulinemia associated with insulin resistance reduces insulin transport across the blood brain barrier, BBB, and subsequently lowers insulin levels and activity in the brain. The reduced brain insulin signaling associates with increased $A\beta$ levels in mouse model of diabetes [65], and hyperinsulinemia increases risk of AD in man [56]. CYP enzymes could also influence the development of AD [66]. Polymorphism of CYP46, the cholesterol metabolizing enzyme in the brain, has been shown to influence brain $A\beta$ - load, cerebrospinal fluid levels of $A\beta$ peptides, and the risk of late-onset AD in man [67].

DISTURBANCE AND RESTORATION OF ER FUNCTION AND METABOLIC DISEASE

Recent studies on the pathogenesis of metabolic diseases have clarified mechanisms that by disturbing ER homeostasis cause accumulation of unfolded or misfolded proteins and result in a state known as ER stress [68, 69]. During ER stress, these proteins are prevented from trafficking to their proper subcellular localizations and are usually rapidly regraded [70]. A disruption in the condition of this organelle affects the fate of lipids, proteins, glucose and insulin and associates with common ailments including atherosclerosis, DM, obesity and neurodegenerative disease [31, 70]. ER responds to the stress by triggering signalling cascade called unfolded protein response (UPR) for restoring the metabolic balance. A failure in this response can promote the disease process. The UPR maintains ER homeostasis by two connected mechanisms; by providing new ER-folding machinery and by providing ER expansion with

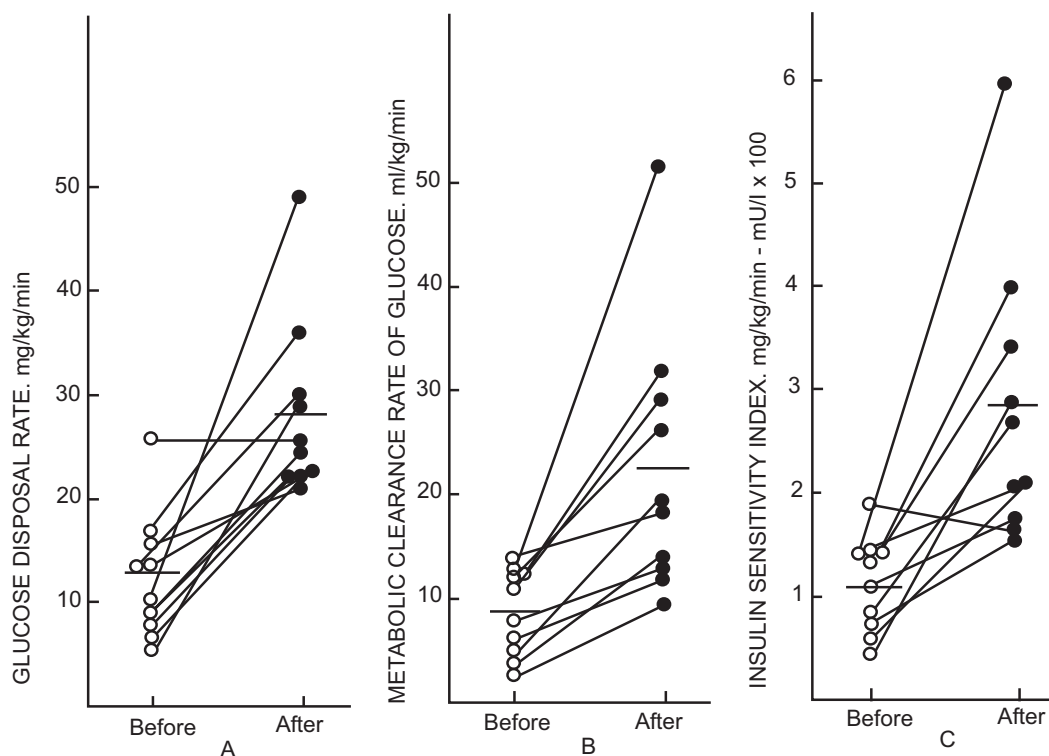


Fig. (2). Change in glucose disposal rate (**A**), in metabolic clearance rate of glucose (**B**) and insulin sensitivity index (**C**) for individual type 2 diabetic subjects during glucose clamp studies performed using an insulin infusion rate of 1 mU/ kg before and after Phenobarbital therapy. Reproduced from: Lahtela JT, *et al.* Diabetes, 1985; 34: 911-6 [8], with permission from American Diabetes Association.

increase in ER surface area and luminal space [71]. Gene-activating agents including P450-inducers increase ER size through membrane synthesis [31] that is an integral yet distinct part of the cellular program to overcome ER stress [71]. Chaperones are specialized proteins with a key role in cellular homeostasis by assisting in protein folding, assembly of the macromolecular complexes, protein transport and cellular signalling [70].

A dysregulation of ER function causing fatty regeneration in the liver, unfavorably affects lipoprotein metabolism, while an activation of ER functions increases ER membranes, reduces hepatic lipid deposition [7, 18], and has beneficial effects on lipoprotein risk factors [6]. X box-binding protein 1 (XBP-1) is a transcription factor which directs cells to construct more ER membranes for maintaining ER function [72]. An activation of the factor enhances CCT α activity and the synthesis of protein and PC, which is the principal PL of ER membranes and plasma lipoproteins [44]. Gene-activating compounds induce protein and PC synthesis and increase PC-rich HDL2 [50]. The PCs are essential cholesterophilic components of HDL2 in the reverse transport and elimination of cholesterol [26].

An accumulation of cholesterol and other lipids in macrophages can cause ER stress and eventually lead to the death of the cells [68]. Macrophage death in advanced atherosclerotic lesions could have

deleterious consequences, such as exacerbated metabolic dysregulation and the rupture of vascular plaques. Phenylbutyrate, a chemical chaperone has been shown to mitigate macrophage ER stress and apoptosis in atherosclerotic lesions *in vivo*, indicating that the therapy improving ER chaperoning function can protect against the deleterious effects of toxic lipids in promoting atherosclerotic lesions [73].

Factors disturbing ER function affect the fate of glucose and promote hyperglycemia through insulin resistance, stimulation of hepatic glucose production and suppression of glucose disposal [8, 68], and gene-activating therapy can restore normal glucose-insulin homeostasis [7, 8]. Lipid, protein and glucose metabolism are linked and, correspondingly, DM2 patients show improvement of both glucose tolerance and plasma lipoprotein profile together with increase in liver PL and P450 [19]. An analysis of biopsies from obese subjects after weight loss and subsequently reduced adiposity after gastric bypass surgery showed reduced ER stress in liver and adipose tissue together with a 90 % decrease in liver triglyceride content and improvement of insulin sensitivity [74]. Tauroursodeoxycholic acid (TUDCA), a chemical chaperone used to treat cholelithiasis and cholestatic liver disease, has been shown to alleviate ER stress in obese and diabetic mouse models, normalize hyperglycemia, increase insulin sensitivity, resolve the fatty liver disease and enhance insulin action in liver, muscle and adipose tissues [75]. First studies testing

TUDCA in obese subjects with insulin resistance have also resulted in promising results, an increase in hepatic and muscle insulin sensitivity [76].

METABOLIC AND HEALTH EFFECTS OF LIFESTYLE FACTORS

Major lifestyle factors affecting health include poor dietary habits together with unhealthy composition of the diet with excess calories, physical inactivity, inadequate weight control, obesity, smoking, and excessive alcohol consumption.

Dietary factors have favorable metabolic effects. Weight control by a low calorie diet with adequate nutrition increases insulin sensitivity and reduces insulin secretion [77]. The effect of the diet on sirtuin 1 (SIRT1) could contribute to atheroprotection. The enzyme is an activator of LXR and cholesterol efflux *via* HDL formation. SIRT1 overexpression could also induce hepatic CYP7A1, decrease hepatic cholesterol and *via* upregulation of the LDLR pathway reduce plasma LDL-C [78, 79]. Diet constituents such as soy proteins and alcohol upregulate apo AI gene and raise HDL-C [80], and vitamin B3 or niacin increases apo AI production [81]. Natural mechanisms modify the effects of unhealthy diet. A278C polymorphism in hepatic CYP7A1 gene affects the effect of a high-cholesterol diet on plasma HDL-C and cholesterol [82]. The increase in plasma cholesterol in the subjects with CC (Cytosine – Cytosine) genotype was mainly due to the larger increase in HDL-C. The activation of nuclear receptors could also modify the effect of the diet. Recent studies revealed that activation of constitutive androstane receptor (CAR) which is highly expressed in the liver, prevents diet-induced obesity, reduces hepatic steatosis, improves insulin sensitivity [83], and ameliorates diabetes and fatty liver disease in mice [84].

Dietary factors activating ER functions and stimulating cholesterol effluxing mechanisms, prevent and regress atherosclerosis. Moderate alcohol consumption protects from both atherosclerotic disease and dementia [85], and reduces CHD and all-cause mortality [31], and the Mediterranean-type of diet has multiple beneficial effects. The people on the diet have low blood pressure and fasting blood glucose and IRI levels, an antiatherogenic plasma risk factor profile [86], and low mortality rate from CHD, CVD, cancer, and also total mortality [50]. Adherence to the diet also associates with reduced risk of AD [87]. A healthy diet also reduces insulin secretion and increases insulin sensitivity and prevents the occurrence of metabolic syndrome [88], and also DM2 in people with impaired glucose tolerance [89], both of which impair cognitive performance [56].

Regular physical activity has beneficial metabolic effects (reviewed in [50]). It upregulates receptors such as LXR α , PPAR γ (peroxisome proliferator-activated receptor γ), scavenger receptor B1 (SRB1) and LDLR, enzymes such as CYPs, LCAT and paraoxonase 1,

and transporters such as ABCA1, ABCG1 and apo AI. It also raises plasma apo AI, HDL-C and HDL2-C, and decreases LDL-C, cholesterol and triglycerides, and promotes cellular cholesterol efflux. Regular exercise improves oxygen uptake and weight control, lowers blood pressure, upregulates mechanisms protecting arteries from atherosclerosis and also decreases CHD, cardiovascular, cancer, and also total mortality [50]. Moderate exercise performed in midlife or late life also associates with later reduced odds of having MCI [90], and reduces the risk for AD [87]. In addition, physical activity reduces insulin resistance and postprandial hyperglycemia, improves glucose tolerance and prevents the development of DM2 in cases with impaired glucose tolerance [89].

DISCUSSION

Both endogenous and exogenous factors including living habits activate functions of genes with favorable effects on major health problems. The gene-activators regress atherosclerosis, by normalization blood glucose – insulin homeostasis remove metabolic syndrome and DM2, and prevent cognitive decline and dementia. Moreover, preclinical animal studies show that the compounds eliminate amyloid from brain plaques and improve cognitive performance. The compounds induce reparation and expansion of ER membranes and normalize or improve ER functions that maintain cellular metabolic homeostasis. They protect cells from the effects of inflammation and immune response and eliminate fat in cases with hepatic fatty degeneration. The gene-activation mechanisms correcting disturbed ER functions eliminate ER stress that links atherosclerosis, obesity, insulin action and DM2.

Together with inducing protein synthesis and reparation of cellular structures, the gene-activators increase hepatic protein and PL and stimulate enzymes including CYPs and glucokinase. They also upregulate NRs, apolipoproteins and ABC transporters, and further produce antiatherogenic plasma lipoprotein profile and enhance glucose disposal rate and insulin sensitivity. Numerous gene-activators raise plasma HDL2 with high PC content [50], effective driving factor in key steps of the reverse cholesterol transport [26], and DM2 patients show improved glucose tolerance with increase in liver PL and P450 [19].

The liver has a key role in glycemic control. It produces more than 90% of endogenous glucose, and as much as 40% of alimentary glucose is taken up by the liver, and alterations in hepatic function influence glucose flux [91]. Gene-activating drug therapy reducing blood glucose induces hepatic glucokinase [23] which has been considered as a potential key target for glucose lowering therapy. A recent study showing that restoration of hepatic glucokinase expression beneficially corrects hepatic glucose flux and normalizes plasma glucose in diabetic fatty rats, supports this possibility [91].

Table 1. Orphan NRs and their Ligands with Effects on Metabolic Disorders/Diseases

Receptor	Endogenous ligand	Exogenous ligand	Disorder/Disease	References
LXR	Oxysterols, bile acids	TO901317	Dyslipidemia, atherosclerosis	[27, 92, 93]
LXR	Glucose	GW3965	Hyperglycemia	[21, 94]
PPAR α	Fatty acids	Fibrate	Dyslipidemia, atherosclerosis	[92]
PPAR γ	Fatty acids	Glitazone	DM, glucose intolerance, insulin resistance	[92]
PPAR $\alpha - \gamma$		Statin	Dyslipidemia, atherosclerosis	[95]
PPAR δ	Fatty acids	GW501516	Dyslipidemia, atherosclerosis	[92]
PXR	Bile acids	Rifampicin	Cholestasis, jaundice	[92, 96]
PXR-CAR		Phenobarbital	DM2, glucose intolerance, insulin resistance	[7, 8]
PXR-CAR		Phenobarbital	Hepatic steatosis	[7, 20]
PXR-CAR		Phenobarbital	Hyperbilirubinemia, cholestasis	[93]
CAR	Steroids, Bile acids	CITCO	Cholestasis, jaundice	[92, 93]
CAR		TCPOBOP	Glucose intolerance, insulin resistance, fatty liver	[83, 84]
FXR	Bile acids	Chenodeoxycholic acid	Cholestasis	[92]
FXR		GW4046	Dyslipidemia, hyperglycemia, insulin resistance	[97]

The NRs are ligand-activated transcription factors that control a wide variety of metabolic processes by regulating the expression of genes encoding enzymes, transporters and other proteins involved in metabolic homeostasis [92]. NRs with known physiological ligands include endocrine receptors and adopted and enigmatic orphan receptors [92]. Ligands for endocrine NRs include glucocorticoid, mineralocorticoid, androgen, estrogen, thyroid hormone, retinoid acid and vitamin D. Table 1 presents ligands for orphan NRs with favorable metabolic effects.

Large population studies indicate that absence in middle age of modifiable risk factors such as overweight, hyperglycemia, dyslipidemia and hypertension, are positively related to exceptional survival in old age [98, 99]. The reviewed studies indicate that these risk factors typical of metabolic syndrome are linked with the disturbed hepatic ER function affecting the fate of lipids, proteins, glucose and insulin. The studies also show that gene-activating therapy can eliminate abnormalities in the syndrome. It eliminates liver fat and reduces elevated plasma triglycerides and raises low HDL-C. The therapy can also normalize glucose tolerance and insulin level, promote weight control and reduce blood pressure. Healthy lifestyle choices together with natural gene activation have an important role in normalization of

metabolic abnormalities, weight control and elimination of obesity, and decreasing blood pressure.

HDL has anti-inflammatory, antioxidant, antiapoptotic, neuroprotective, vasodilatory and anti-thrombotic effects that protect cells from the effects of aging process [51]. Plasma HDL levels decline with age in prospective studies but cross-sectionally, by contrast, they do not change much or even slightly increase with age suggesting that people with still high HDL levels survive [51, 52]. In very old people age correlates positively with HDL2, a low HDL is very rare among them [51], and high HDL-C and apo AI correlate with cognitive function in advanced age [64].

A number of factors and activities can prevent cognitive impairment in man. Elimination of modifiable reasons of obesity, DM, dyslipidemia, heart disease, stroke, and hypertension, delays cognitive decline and development of dementia [11, 100]. Active participation in stimulating cognitive, social, and physical activities, and healthy diet, also have a positive delaying effect on the onset of dementia [11, 100]. Studies showing that carotid intimal thickness predicts accelerated cognitive decline among adults without clinical vascular disease [101], and that atherosclerosis in intracerebral arteries is an independent risk factor for dementia [102], indicate that activities and therapies protecting arteries from atherosclerosis are central for maintaining cognitive health.

CONCLUSIONS

Both endogenous and exogenous factors including living habits influence life maintaining functions. They activate genes in the processes that beneficially affect the fate of lipids, proteins and glucose, and protect cells from the effects of aging process. Gene-activating compounds induce reparation of altered cellular structures consequent to ER stress, and normalize and improve metabolic functions. They prevent and regress atherosclerosis and, by restoring normal glucose-insulin homeostasis, remove metabolic syndrome and DM2. The gene-activation produces positive changes that eliminate major cardiovascular and metabolic diseases, prevent cognitive impairment and dementia, and promote well-being and active living in advanced age.

ACKNOWLEDGEMENTS

The author is grateful for excellent collaboration especially to Eero Sotaniemi [†], Olavi Pelkonen, Markku Savolainen and Vilho Myllylä from the University of Oulu, Finland; Christian Ehnholm from the National Institute of Health and Welfare, Helsinki; and Heikki Vapaatalo from the University of Helsinki. The studies have been supported by the Academy of Finland and the Paavo Nurmi Foundation, Finland.

ABBREVIATIONS

ABC	=	ATP-binding cassette
AD	=	Alzheimer`s disease
AP	=	antipyrene
apo	=	apolipoprotein
CAR	=	constitutive androstane receptor
CCT α	=	CTP:phosphocholine cytidyltransferase- α
CHD	=	coronary heart disease
CYP	=	cytochrome
ER	=	endoplasmic reticulum
FXR	=	farnesoid X receptor
HMGCoAR	=	hydroxymethylglutaryl-coenzyme A reductase
IRI	=	immunoreactive insulin
LCAT	=	lecithin:cholesterol acyltransferase
LDLR	=	low density lipoprotein receptor
LXR	=	liver X receptor
PB	=	phenobarbital
PC	=	phosphatidylcholine
PPAR	=	peroxisome proliferator-activated receptor
PXR	=	pregnane X receptor

SIRT1 = sirtuin 1

T-C = total cholesterol

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