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Mini Review

Lipid-induced cardiovascular diseases

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Abstract

Cardiovascular diseases are the leading cause of death worldwide. There are many evidences that the dysfunctioning lipotoxicity is the one of major factors of cardiovascular diseases such as, atherosclerosis, hypertension, and coronary heart disease. Obesity and diabetes increase circulating lipids that are likely with more generation of toxic intermediates, which leading to the complications associated with cardiovascular diseases. Indeed, lipotoxicity is a metabolic syndrome caused by abnormal lipid accumulation, which leads to cellular dysfunction and necrosis. Here we review the factors that induced pathogenesis of cardiovascular diseases by lipid accumulation and the mechanisms underlying the lipotoxicity.

Introduction

Lipids are the essential component to maintain the cellular structure and provide energy, and are involved in the various cell signaling [1]. However, an abnormal lipid accumulation is a metabolic syndrome, which causes cellular toxicity called lipotoxicity leading to cellular dysfunction and necrosis [2]. This metabolic syndrome has various risk factors like high triglycerides, hypertension, low HDL cholesterol concentrations and glucose intolerance [3,4], which is closely associated with other abnormalities like obesity and diabetes [5,6].

In fact, there are many evidences that lipotoxicity might be a cause of lot of pathogenesis. Infused lipid into skeletal muscle elevated the level of caspase 3, which later resulted in increased level of fatty acid that activates pro-apoptotic pathways [7]. In case of pancreatic cells, secretion of insulin is malfunctioned by the over accumulation of free fatty acids, lipotoxicity [8], which can also lead to apoptosis [9-11]. In addition, the destruction in cells were observed in lipid over-loaded pancreas [12]. Lipid accumulation results in oxidative and ER stress, cell death and inflammation in hepatocytes, and ultimately induced cirrhosis by the activation of fibrogenic response in hepatic cells [13]. According to an animal experiments, failure in gluconeogenesis is caused by an accumulated lipid [14]. In addition, there is a report that excess lipid result in renal dysfunctioning and injury [15]. And most of cardiovascular diseases (CVD) like atherosclerosis, hypertension and coronary heart disease are also well known to be caused by lipotoxicity [16]. In this paper, we review about the brief introduction about the lipid toxicity, various factors that induced pathogenesis heart diseases and also the various pathways causing lipotoxicity.

Lipotoxicity in pathogenesis of heart

Cardiovascular disease (CVD) account for approximately one third of all deaths globally [17]. Indeed, lipid accumulation in non-adipose tissues is the major factor for obesity, and diabetes mellitus and cardiovascular disease may be its co-morbidities [18]. People suffering from obesity are likely to be at higher risk of cardiac diseases

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compare to the average weight people [19]. Various results like cell death, mitochondrial dysfunction, endoplasmic reticulum (ER) stress etc. is cause to the excess lipid intake [20]. In addition, insulin resistance is also developed due to the accumulation of increases in fat in cardiomyocyte [21]. Recently there have been some report that in heart failure condition there is an impaired fatty acid oxidation in diabetes and obesity which are responsible for lipid overload in intramyocardial [22].

This shows a firm establishment of the relationship between cardiomyopathy and lipid abnormalities in diabetic and obese human [23]. This means that these obesity and diabetes relation to the cardiac complication will be the important goal for understanding for the treatment of lipotoxicity in myocytes. For the cardiomyocyte metabolism, fatty acid plays an important role however detrimental effect is induced due to the imbalance of cellular uptake and usage results in lipid accumulation [23,24]. Indeed, the main cause of lipotoxicity in heart is known due to ceramide metabolized from free fatty acid (FFA) [25]. In addition, high cholesterol increased the incidence of coronary heart disease compared to the polyunsaturated fatty acid [26-29]. Therefore, attention should be made by the people on their diet to prevent from these pathological conditions. Lipotoxicity leads to various pathogenesis of heart diseases and some of them are listed below.

Atherosclerosis

Coronary artery disease (CAD) can be defined as development of athermanous plaques in the vessel of heart and block the flow of blood to the myocardium. And where lipotoxicity works as an elevating ectopic fat aggregation which cause worsen the condition local fat depots of CAD [30,31]. Indeed, the incidence of atherosclerosis is found to be elevated in patient showing insulin resistance with suffering from diabetes 2 mellitus [32], lipotoxicity is the major factor for insulin resistance [21].

Studies in both animal and human showed that non-esterified fatty acids (NEFA) increased by lipid infusion also elevated diacylglycerol which has an inhibitory effect in insulin secretion [33]. The insulin resistance has a close bonding with the people with type 2 diabetic mellitus and obese which are elevated by increased in ceramide level in both muscle and plasma. In addition except, this circulating NEFA has inflammatory effect which activates toll-like receptor 4. Normally, the elevation of NEFA in people with normal glucose resistance increases the connective tissue growth factor which has a characteristic feature of atherogenesis plaque deposition [21]. In addition, overexpression of platelet-derived growth factor receptor (PDGFR) and malfunctioning activation of PDGFR signaling was seen due to the inactivation of lipoprotein receptor-related protein 1 (LRP1) in vascular smooth muscle cells (VSMCs) of mice which resulted in the deterioration of elastic layer and pointed sensitivity to cholesterol induced atherosclerosis [34].

Hyperlipidemia and hypertension, both causes oxidative stress and oxygen free radical production by the arterial wall. In the presence of hyperlipidemia, there is the occurrence of atherosclerosis and formation of foam cell. These both hyperlipidemia and hypertension have synergistic effects on the arthrosclerosis [35].

Pathogenesis in hypertension

There is a positive correlation of patient with heritable pulmonary arterial hypertension (PAH) and lipotoxicity. A rodent model with expression of mutation of bone morphogenic protein receptor 2 (BMPR2), a gene that cause the heritable PAH, showed the lipid over-deposition in right ventricle [36]. Studies have shown that there is the alteration of lipid metabolism with high intake of fat diet, sequentially leading to lipid accumulation in renal, elevation in oxidative stress and renal injury, including glomerulosclerosis, interstitial fibrosis and albuminuria. In addition, filtered albumin bound to FFA leads to tubule-interstitial damage later causing pro-inflammatory phenotype, then can lead to the hypertension [37].

Pathogenesis of ventricular dysfunction and cardiac hypertrophy

Malfunctioning in the lipid storage in the cardiac in systemic metabolism leads to cardiomyopathy. Mitochondrial fatty acid oxidation, caused by cardiac lipid overload is linked with the heart failure and sudden death [38]. This aggregation of lipid also has shown the triggering effect of arrhythmias in the cardiomyocyte from mice. In addition, the progression of increase of serum FFA and triglycerides has been revealed due to the functional loss of leptin receptor, which also showed that deposition of fat induced death and deprivation in systolic function in cardiomyocytes [39]. In this model, the lipid accumulation shows the various cardiac myopathy with initial effect with hypertrophic condition in heart, subsequently malfunctioning of left-ventricular and premature death, which was coincided with another report that lipid accumulation showed cardiac hypertrophy, contractility function impaired and increased mortality [24]. These reports demonstrated that lipid accumulation leads to cardiac hypertrophy and systemic ventricular dysfunction.

Lipid signaling pathways

Accumulation of the lipid in the cardiomyocyte due to the deterioration of lipid metabolism is caused by fatty acids and fatty acyl coA, acylcarnitine, unesterified cholesterol, lysolecithin, diacylglycerol and ceramide [40]. Apoptosis, inflammation, mitochondrial dysfunction, and/or defective intracellular signaling plays an important role of these toxic lipids. The various signaling pathways that lead to lipid accumulation are explained below and the associated mechanisms in circulatory systems are also shown in table 1.

Apoptotic pathways

Obesity and diabetes is associated with cardiac lipid overload and this is induced by apoptotic cascade. Some reports have shown that palmitic acid causes cardiolipin loss cytochrome *c* release, mitochondrial swelling, and DNA laddering with the change in mitochondrial swelling in isolated neonatal rat myocytes [41,42]. In addition, ceramide can participate in a variety of cellular signaling, including the regulating differentiation, proliferation, and apoptosis of cells. Several studies have shown that ceramide accumulation followed by the treatment of apoptotic agents including ionizing radiation [43], UV light [44], TNF-alpha [45], and chemotherapeutic agents, resulting to cellular apoptosis via mitochondrial dysfunction [46,47]. Ceramide is synthesized by two ways. In the first, serine palmitoyltransferase catalyzes patmitoyl-coA serine, generating 3 ketosphingonine which later produce ceramide [48-50]. And sphingomyelinase hydrolyzes sphingomyelin and ceramide is released in other pathway [51]. Thus, obesity increases intracellular lipid leading to diabetes.

Table 1: Lipid-associated mechanisms in circulatory systems

Mechanism	Observation	References
AMPK	Activation protects against FA-induced cell death	[77,78]
Autophagy	Enhanced by FA-induced activation of PKC	[79]
	Enhanced by WD via *O*-GlcNAcylation of autophagy proteins	[80]
	Inhibition protects against FA-induced cell death in endothelium	[81]
Ceramide	Enhances PP2A-eNOS mediated endothelial dysfunction	[82]
	Inhibition protects against FA-induced cell death	[25,83]
ER stress	Enhanced by FA-induced activation of Ca^{2+}-mediated activation of BCL-2, BAX, and BAK	[22]
Leptin	Treatment protects against cardiac dysfunction by reducing lipid accumulation and restoring PPAR signaling	[84]
Lipid (TG) storage	Feeding unsaturated FA, protects against saturated FA-induced cell death by sequestering lipids in intracellular droplets	[85,86]
	Perlipins regulate FA-storage to regulate and maintain normal oxidative balance	[87,88]
MicroRNA	FA-induced changes in miR regulation results in insulin resistance	[89]
Mitochondrial function	FA-induced mitochondrial fragmentation and increased reactive oxygen species (ROS)	[90]

* FA: fatty acid; TAG: triacylglycerol; WD: western diet

To show the effect of ceramide on lipotoxicity in heart, blocking of ceramide formation by myriocin, inhibitor of serine palmitoyltransferase (SPT), or deletion of long chain base biosynthesis protein 1 (LCB1), a part of SPT, showed the increased survival rate [48]. In addition, declining of fatty acid and elevation of glucose oxidation in lipoprotein lipase (LpL)-overexpressed heart by blocking of SPT reduced the cardiac sphingomyelin and ceramide and then finally improved systolic function and survival was prolonged [25]. Therefore, reduction of the ceramide might be the selective target of the drug for the treatment of lipid-induced heart disease in obese and diabetic patients.

AMP activated protein kinase

AMP activated protein kinase (AMPK) has an important role in the energy homeostasis in cellular level. ATP activates AMPK which has been correlated to FA transport and oxidation [52]. The effect of palpitate on myocyte is blocked by the activation of AMPK with a cell permeable AMPK activator, AICAR. That causes to reduce malonyl-coA level which results in the decrease of FA transportation and oxidation in mitochondria and ultimately decreases the toxicity in cells. In addition, AMPK is also an activator for expression of fatty acid transport proteins, FAT/CD36 and plasma membrane fatty acid-binding protein (FABPpm), in a time dependent and dose dependent, which were not overexpressed when the AMPK phosphorylation was blocked [41,53,54]. Thus, AMPK is an essential 'master regulator' of the metabolism of sugar and FA for the normal functioning of heart. Therefore AMPK signaling pathway will be an important target in the treatment of cardiovascular disease induced by lipid accumulation.

Peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPARs) are known as nuclear receptors, all three members PPARα, PPARδ, and PPARγ. PPARα has been directly related to elevate the oxidation of fatty acid in heart [55]. In addition, PPARα is a ligand activating transcription of mitochondrion fatty acid oxidation enzymes involved in cellular fatty acid intake [56]. Indeed, there was an increase in fatty acid metabolism and expression of genes of lipid uptake in myocardium by the overexpression of PPAR [55]. And the decreased PPARα gene expression causes to decrease the metabolic rate of fatty acid in both in cardiac hypertrophy and infracted myocardium [57-59], which was likely due to the hypoxic condition by some evidences. In fact, PPARα expression level in human heart was decreased by 54% in patient with hypertrophy and also in MI rat heart. Furthermore, PPARα generates the peroxisomal and mitochondrial enzymes such as acyl CoA oxidase (AOX) and carnitine palmitoyltransferase which controls the fatty acid metabolism in hearts [60,61]. In addition, PPAR has the capability to decrease the plasma triglyceride and elevate HDL cholesterol level, which was effective in the treatment of abnormal in lipid level [62]. Decreasing the levels of circulating triglycerides responsible for triglycerides inducing adipose cell hypertrophy and hyperplasia is reduced by PPARα activators [63]. In conclusion, PPARs has important role in the maintenance of lipid level which has direct relationship with the atherosclerosis, inflammation, and the reduced foam cell formation.

Protein kinase C

Protein kinase C (PKC) is an enzyme which regulates function of protein through phosphorylation of amino acids and performs various cellular activities. These are widely expressed in myocardium and have function for the regulating some pathways in heart. There are evidences that PKCβ has an effect to cause myocardial necrosis and to thicken ventricular walls [64]. Furthermore, lipotoxicity is increased in heart during the activation of PKCβ2 by the high intake of fat diet, resulting into cardiac hypertrophy [65].

Low-density lipoprotein receptors

Low-density lipoprotein receptor-related protein 1 (LPR1) has a function over the storage of lipid in the liver through canonical Wnt5a signaling pathway [34]. The

study showed that there was pathological accumulation of lipid in the liver during the silencing of LRP1 gene in animal experiment. In this condition, there was an indirect accumulation of lipid in liver via white adipocytes. In addition, wnt5a corrected the malfunctioning of the cholesterol and cholestryl ester accumulation during silencing of LRP1 in mouse embryonic fibroblasts (MEFs) [34]. Low-density lipoprotein receptor-related protein 5 (LRP5) have been also shown as an important part for maintaining the level of cholesterol, and there was a downfall in the hepatic clearance of chylomicron in LRP5 deficient mice fed with high fat diet [66]. CD36, also known as platelet glycoprotein 4, fatty acid translocase (FAT), is a multifunctional membrane protein found on the surfaces of various cell types including cardiomyocytes. Kim, et al have reported that the saturated fatty acid, palmitate, significantly induced lipotoxic cell death in RAW264.7 macrophages, which was antagonized by the monounsaturated fatty acid, oleate, through the down-regulation of CD36 expression [67]. In addition, the treatment of high density lipoprotein (HDL) reversed palmatic acid-induced lipotoxicity and energy metabolism imbalance in H9c2 cardiomyoblast cells and in neonatal rat cardiomyocytes [68].

Lipid-induced defective insulin signaling

Insulin signaling mediated by activation of eNOS in hearts such as increasing the carbohydrate oxidation during ischemia and direct activation of AKT have shown anti-apoptotic function and cardiac protecting effect [69]. Insulin resistance is caused due to the improper metabolism of lipid in heart which leads to the improper management of insulin and decreases cardiac efficiency in cardiomyocytes [30,70-73]. Further, insulin has effects on maintaining of the intracellular Ca^{2+} and survival of cardiomyocytes. In fact, deficiency of insulin signaling caused to exacerbate cardio-lipotoxicty [69,70], which are caused by ceramide and diacyl glycerol (DAG).

MAPK

Mitogen activated protein kinases (MAPKs) represent an essential group of kinases which is involved in cell signaling and regulation pathways. Erk1, Erk2, JNK1, JNK2, and P38 are members of MAPK which involves in oxidative stress in cardiomyocytes and are identified to regulate insulin signaling [74,75]. Treatment of Erk and JNK antagonist showed the blocking of dilation of left ventricular end systole and elevation of fraction and the decrease of myocardial fibrosis [76]. Addition, JNK has shown an apoptotic effect on rat cardiomyocytes induced by oleate combined with palmitate. From these reports, MAPKs might be a mediator for protection of lipid mediated apoptosis.

Conclusion

As from various studies, it has shown that alteration in the lipid metabolism has concomitant effect in the normal functioning of the heart with development of various cardiovascular diseases and similarly affecting other organs too. And there are various signaling pathways for the accumulation of lipid and eventually causing lipotoxicity. Therefore, main focus for the research should be taken on the signaling pathways of lipid accumulation and the development of therapeutic drugs for the adjustment of lipid level. In addition, the earlier prediction of lipotoxicity should be needed to prevent the late complication of lipotoxicity.

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