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REVIEW ARTICLE

RESOLVINS: LIPID MEDIATORS IN RELATION WITH INFLAMMATION AND INSULIN RESISTANCE

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ABSTRACT : The inflammation process exerts a critical role in the pathophysiology of insulin resistance (IR) as the reason behind of the chronic disease including diabetes, cancer and cardiovscular diseases. In this regard recently described n-3 fattyacids-derived mediators such as resolvins series D and E (from DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), respectively) and protectins affect the inflammatory process and immune system through blocking the inflammatory mediator production in result of diminishing the accumulation of leukocytes at the site of inflammation. In this article, we aimed to discuss resolvin as a marker which involves in inflammation and insulin resistance.
***Keywords*:** Insulin resistance; lipid mediators; Resolvin; Inflammation disease.

CHRONIC INFLAMMATION

Inflammation, the physiological host immune response against the pathogens is characterized by heat, swelling, redness and pain. Also infiltration of polymorphonuclear neutrophils (PMNs) and the production of inflammatory cytokines, eicosanoids and release of mediators from leukocytes at the site of inflammation are other hallmarks of inflammatory process (1, 2). In order to prevent the progression of acute inflammation to chronic inflammation compromising arthritis, periodontal disease and cardiovascular diseases, the concentration of leukocytes and PMNs must be strictly controlled. (2, 3, 4).
TNF-α, the marker of chronic inflammation, is secreted by adipocytes, stromavascular cells, and macrophages while, its secretion correlated with the amount of adipose tissue (5). On the other hands, it plays an important role in insulin-resistance induction via suppression of the insulin receptor-signaling pathway. Therefore elevation of circulating TNF-α level occurs in consequent of adipose tissue expansion, and development of insulin-resistance (6). Inflammations in adipose tissue intensify the release of the proinflammatory cytokines such as IL-1β and IL-18 by induction of the macrophages activation. (7)

INSULIN RESISTANCE

Insulin, a polypeptide hormone, which is produced by beta cells of the Langerhans islets in the pancreas, has important impacts in the metabolism of carbohydrate, glucose homeostasis and other nutrients (8).
Insulin resistance (IR) defined as the state of high insulin concentration in blood, occurs in result of inadequate response of peripheral tissues to glucose and causes the alleviation of normal insulin activity. These conditions are characterized by hyperglycemia and hyperinsulinemia. (8-9)
Genetics and environmental factors are the main etiological parameters which exert roles in IR. IR reduced glucose uptake in skeletal muscles by decreasing the GLUT4 (glucose transporter type4) expression. Consequently, the synthesis of glucose increases in the liver. Moreover, the plasma levels of fatty acids elevates in IR which affects the insulin signaling by IRS-1 (insulin receptor substrate-1) inhibition (8-10).
Insulin resistance risk factors are T2D, dyslipidemia, hyperglycemia, hypertension, atherosclerosis, polycystic ovarian disease and the metabolic syndrome. (11)
Several factors participates in the development of insulin resistance containing lipopolysaccharides (LPSs), environmental stress, nutrients, increased free fatty acid level, mitochondrial dysfunction, pro inflammatory cytokine secretion including tumor necrosis factor-α, interleukin (IL)-6, and IL-1β, retinol binding protein-4 (RBP4) and oxidative stress.(12, 13)

THE ROLE OF CHRONIC INFLAMMATION IN IR

Inflammation associated with chronic diseases such as cardiovascular diseases, obesity, type 2 diabetes mellitus, metabolic syndrome, and cancer. (14)

The systemic inflammation has impaled serum levels of inflammatory cytokines and the blood lymphocytes proliferation. These conditions link the inflammation to the development of insulin resistance and T2DM (15). The inflammation is involved in insulin signaling by releasing inflammatory factors such as cytokines TNF-*α*, IL-1 and IL-6 in a way that immune system over response causes disruption of insulin signaling and glucose homeostasis. (16-17)

Tomor necrosis factor α (TNF-*α)* impairs insulin signaling by stimulating IRS-1 serine phosphorylation and inhibiting activation of AKT (a protein kinase B), therefore blocks insulin activity (18). Besides, the pro inflammatory mediators and cytokines activate TLR2 (Toll-like receptor 2) and TLR4 (Toll-like receptor 4), then activate IKK (inhibitor of kappa B kinase) and JNK (c-Jun N-terminal kinase). JNK phosphorylates serine kinases like IRS-1 or IRS-2 (**Figure 1)**. These pathways cause transcription of inflammatory genes and results in decreasing insulin sensitivity.

The omega-3 fatty acids alter this process by activating GPR120 (G-protein coupled receptor 120) receptors; the subsequent of receptors inhibits TAK (transforming growth factor-b activated kinase1) which causes suppress of inflammatory signaling. (19, 20)

INSULIN RESISTANCE AND INFLAMMATION IN ADIPOSE TISSUE

The chronic inflammation in visceral adipose tissue induces insulin resistance .Adipocytes from adipose tissue increase secretion of pro inflammatory cytokines such as tumor necrosis factor, interleukin 6, resistin and angiotensinogen. Therefore the inhibition of adipose tissue macrophages (ATMs) reduces obesity induced insulin resistance (21).

It was shown in previous murine studies that, 45-60% of adipocytes in obese mice expressed the macrophage marker F4/80+. In contrary, in lean ones 10-15% of cells expressed the macrophage marker F4/80+. (22) In addition, a macrophage inflammatory reaction in the lean mice is less severe than obese mice and it might be associated with insulin resistance. In adipose tissue of lean animals less inflammatory macrophage phenotype (M2) is activated, whereas in adipose tissue of obese mice, a pro-inflammatory phenotype of macrophages (M1) is activated. Macrophages which are activated in adipose tissue of the lean mice including CD301+, CD206+ and Arginase-1+, secret IL-10 that has important roles in insulin signaling and insulin sensitivity. In contrast, in obese adipose tissue the TNFα+ and Nos2+ has expressed which can stimulate insulin resistance by JNK, IKK, ERK (extracellular-signal-regulated kinases), PKC (Protein kinase C). Such results show elevated inflammation and insulin resistance in adipose tissue in result of adiposity. (23, 24)

RESOLUTION OF INFLAMMATION

Resolution of inflammation is a physiological process which involves molecular and cellular pathways. This process is conducted by adjusting factors cooperating in inflammation. Neutrophils are first line of defense and play an important role in inflammatory processes. Hence, neutrophil apoptosis is an essential element in abbreviating inflammation and cytokine production. Macrophages and lactoferrin has impact on apoptosis and clearance of neutrophils. Lactoferrin reduces neutrophil migration and chemotaxis. Neutrophil signals such as lysophosphatidylcholine (LPC), the nucleotides ATP and UTP attracts macrophages (find me signals). Another effect of macrophages is releasesing anti-inflammatory mediators including TGF-β1 (Transforming growth factor beta 1) and IL-10; these cytokines are also involved in phagocytosis and apoptosis. (25, 26)

RESOLVIN (NOVEL FAMILIES OF LIPID-DERIVED MEDIATORS)

The inflammation resolving lipid mediators are some novel mediators, including protectins, lipoxin and resolvin. (27) These mediators have important roles in controlling inflammation, stimulating apoptosis of PMNs and controlling the duration and severity of inflammation (28, 29).

The E-series resolvins are emerged from eicosapentaenoic acid (EPA) including resolvin E1 (RvE1) and resolvin E2 (RvE2). Transcellular formation of RvE1 occurs when endothelial cells contact with leukocytes (30). D-series resolvins are derived from DHA. Firstly, DHA transformed to 17S-hydroperoxy-DHA (17S-H (p) DHA) by 15-lipoxygenase (ALOX15). This substance can be

converted to bioactive materials including resolvin D1, RvD2, RvD3 and RvD (31). ChemR23, the receptor of RvE1, is expressed on monocytes, macrophages and dendritic cells (DCs) (32).
Resolvins (resolution phase interaction products) are lipid mediators derived from omega-3 polyunsaturated fatty acids which have anti-inflammatory properties. Resolvin as a regulating factor of the immune system can blocks PMN migration and regulates production of pro-inflammatory cytokine and mediators. The action of RV D1 has been studied in several inflammatory diseases and it was shown that it has protective effect against asthma (allergic inflammation), heart diseases, cancer and cystic fibrosis. (33- 34-35)
It is also important to notice the roles of lipid mediators as novel therapeutic method of pain reduction. Indeed, inflammation is associated with pain when body is exposed to injury. Evidence shows that resolvins, such as RvE1, RvD1 exert a role in reducing pain which is accompanied by the inflammatory process. (36)

RESOLVIN AFFECTS INFLAMMATION

The inflammatory response is a physiologically protective response to injury or infection. Increasing inflammatory responses can lead to chronic disorders. Neutrophil can aggravate this process by producing pro-inflammatory mediators, including leukotrienes and prostaglandins. DHA and EPA have anti-inflammatory effect in some o inflammatory diseases. (37, 38)
Eicosanoids, 20- carbon polyunsaturated fatty acids (PUFAs), considered as the regulatory mediators of inflammation and the link between inflammation and PUFAs are generated from. The membrane of inflammatory cells contains high proportion of n_6 PUFA arachidonic acid and low proportions of other 20-carbon PUFAs and eicosanoids high consumption of long-chain n_3 PUFAs (EPA, DHA), may change proportions of fatty acids and induce elevation of long-chain n_3 PUFAs on immune cells membrane surface. This incorporation alters eicosanoids generation and produces a novel group of mediators such as resolvins. (39-40).
The resolvin involved in regulation of inflammation and inflammatory diseases by below mechanisms:
- RvE1 blocks PMN migration and PMN induces stimulation of inflammatory pathways, such as NF-κB pathway. In addition, RvE1 increases PMN removal of mucosal epithelial cells by macrophage phagocytosis.
-RvE1 regulates the production of pro-inflammatory mediators by inhibiting chemotaxis properties of IL-8 and blocking of leukotriene B4 (LTB4), that stimulated by neutrophils.
- n-3 fatty acids and its derived-mediators 3 such as resolvin have protective effects against asthma, cystic fibrosis, heart diseases and cancer, by reducing the number of inflammatory cells including T helper (Th1/Th17) cells, inhibiting the production of pro-inflammatory mediators (TNF and IL-1) and increasing production of the anti-inflammatory cytokine IL-10.
Furthermore, -Studies have indicated that disorder in resolvin signaling pathways cause progression of the acute inflammatory responses to chronic pathologic inflammation. (5-36-41)
The required dose of n-3 PUFAs to decrease different inflammatory conditions has not yet found, since it depends on type of inflammation and resolving system condition.(shape1) (42)

CORRELATION BETWEEN RESOLVIN AND INSULIN RESISTANCE

Previous studies demonstrated that the n-3-PUFAs have declined insulin resistance by up-regulating the expression of important genes involved in insulin sensitivity, such as insulin signaling pathway, insulin receptors (IRS-1 and IRS-2) and glucose transport in liver and adipose tissue. In addition, n-3-PUFAs are engage in modulating glucose homeostasis and insulin secretion via adipokine increment and the impact on AMPK (AMP-activated protein). (43, 44)
The resolvin E1 receptor, which namely chemerin receptor, ChemR23 or CMKLR1 (chemokine-like receptor 1), is more expressed in mouse and human adipose tissues, cardiovascular system, gastrointestinal tissues, kidney, brain, and bone marrow. Chemerin is an adipokine that can effect on inflammatory process, glucose and lipid homeostasis in adipocytes and is elevated in adipose tissue of diabetic patients. (45-46-47)
These receptors have two different effects. Chemerin ligands of ChemR23, was negatively correlated with insulin sensitivity, insulin function and glucose uptake in skeletal muscle cells. When resolvin joined to ChemR23 resulting in inhibition of tumor necrosis-α (TNF-α)-stimulation of NF-κB activation and inhibition of leukocyte infiltration and pro inflammatory gene expression. The expression of these receptors increases in adipose

tissue. Functional interactions between RvE1 and ChemR23 remain to elucidate. (32-47)

-The accruement of inflammatory response leads to chronic disorders such as insulin resistance. Some inflammatory mediators impair insulin signaling pathway such as TNF-α which inhibits GLUT4. (44)

-Pro-resolving lipid mediators are novel endogenous chemical mediators, including lipoxin, resolvins and protectins that are involved in inflammation.

-Resolvins are derived from EPA and DHA. Resolvins are also produced by the COX-Two pathways have important roles in controlling inflammation and stimulating apoptotic PMNs. Resolvins resolve inflammation with changing the activity and counter-regulating of pro-inflammatory signals and abatement of pro-inflammatory cytokines production. In some studies also there was relationship between resolvin and levels of IL-10 (anti-inflammatory cytokine). Indeed, IL-10 inhibits TNF-α and can affect insulin sensitivity. In addition RvE1 regulates release of pro-inflammatory mediators such as IL-8 or TNF-α. (43-48)

CONCLUDING IDEA

According to an association between chronic inflammation and insulin resistance, this paper highlighted the role of n-3 fatty acids and lipid mediators in the pathogenesis of insulin resistance, inflammation and accentuates the effect of n-3 fatty acids on inflammation and insulin sensitivity processes.

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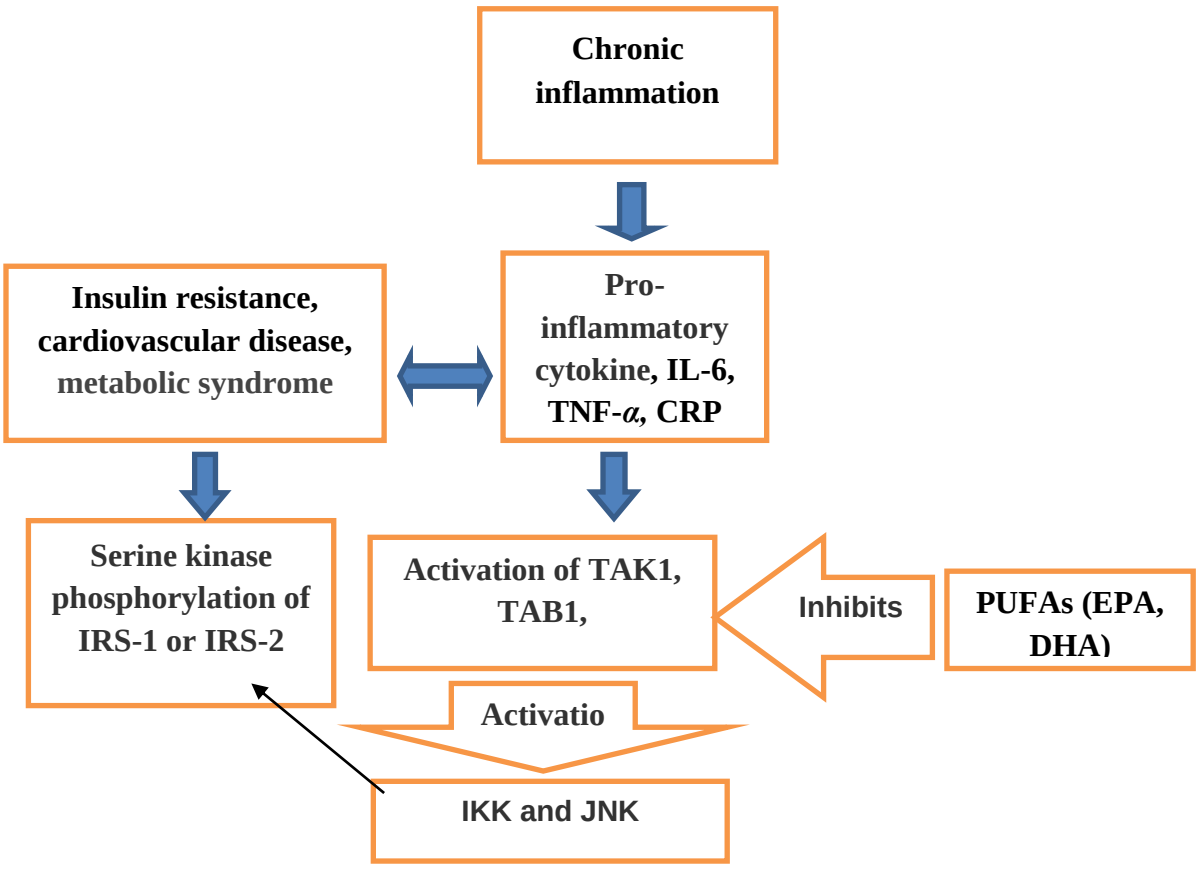

Figure 1: The role of inflammation and omega-3 fatty acids in insulin resistance pathways.

Shape1:the role of omega3 in inflammation genes