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Lipid-Induced Insulin Resistance Mechanisms: The Link to Inflammation and Type 2 Diabetes

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1. Abstract

Insulin Resistance is the leading cause of Type 2 diabetes mellitus [T2DM] onset. It occurs as a result of disturbances in lipid metabolism and increased levels of circulating free fatty acids [FFAs]. FFAs accumulate within the insulin sensitive tissues such as muscle, liver and adipose tissues exacerbating different molecular mechanisms. Increased fatty acid flux has been documented to be strongly associated with insulin resistant states and obesity causing inflammation that eventually causes type 2-diabetes development. FFAs appear to cause this defect in glucose transport by inhibiting insulin –stimulated tyrosine phosphorylation of insulin receptor substrate-1 [IRS-1] and IRS-1 associated phosphatidyl-inositol 3-kinase activity. A number of different metabolic abnormalities may increase intramyocellular or intrahepatic fatty acid metabolites that induce insulin resistance through different cellular mechanisms. The current review point out the link between enhanced FFAs flux and activation of PKC and how it impacts on both the insulin signaling in muscle and liver as shown from our laboratory data and highlighting the involvement of the inflammatory pathways importance. This embarks the importance of measuring the inflammatory biomarkers in clinical settings.

2. Keywords: Clinical Biochemistry; Molecular, Diagnostic; Endocrinology; Insulin resistance; Free Fatty Acids [FFAs] and type 2 Diabetes Mellitus [T2DM]

3. Introduction

Type 2 diabetes mellitus is one of the defining medical challenges worldwide in the 21st century. Overconsumption of inexpensive and high caloric food has led to unprecedented increases in obesity. In 2017, more than 693 million people were affected by diabetes worldwide and projections point to a sustained rise in its prevalence in the next decades [1] In the United States, the combined prevalence of diabetes and prediabetes is over 50% [2]. Diabetes is a chronic metabolic disorder affecting ~ 5% of the population in the industrialized nations as it is becoming a huge concern. In Canada about ~1.3 million (~4.9 - 5.8% of the total Canadian population) aged greater than or equal to 12 years have diabetes [3-5]. The predicted 10-year risk of developing diabetes for the Canadian population in 2011/12 was 9.98%, corresponding to 2.16 million new cases [6]. In another part of the world, it is estimated that Diabetes Mellitus is a major emerging clinical and public problem in a country such as Egypt among others that creates a global epidemic concern [7].

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Severe reduction in insulin secretion due to autoimmune destruction of β-cell is responsible for type I diabetes mellitus onset. However, the more prevalent form is type 2 diabetes, it represents more than 85% - 90% of the cases globally [8]. The pathogenesis of type 2 diabetes is complex, involving progressive development of insulin resistance and a relative deficiency in insulin secretion that is the leading cause of the onset of hyperglycemia. This review outlines and focuses on the specific role of FFAs that contributed to the development of muscle and hepatic insulin resistance in vitro and in vivo models. Insulin Resistance Syndrome occurs as a result of disturbances in lipid metabolism due to increased availability of circulating FFAs that accumulate within the insulin sensitive tissues. Further knowledge and exploration of the molecular mechanisms involved are of substantial interest for future therapeutic interventions as well as in determining the high risk individuals through the discovery of novel diagnostic biomarkers.

About ~85% - 90% of diabetic subjects have type 2 diabetes mellitus [4-6], that is characterized by increased hepatic glucose production (HGP), the inability of insulin to increase the uptake of glucose (peripheral insulin resistance) and suppress HGP (hepatic insulin resistance), and impairment of insulin secretion [9-11].

Obesity is associated with insulin resistance that was clearly manifested in the 21st century. It is one of the key features of type 2 diabetes, mainly due to the release of FFAs [13-18] and secondary the release of inflammatory cytokines [18] from the expanded adipose tissue mass [13-19]. Studies conducted in our laboratory and others (i.e., Drs. Defronzo and Reaven) laboratories have clearly shown that individuals with obesity [20-24], type 2 diabetes [25] and obesity-associated type 2 diabetes [21-25] have elevated plasma FFAs levels.

The elevated plasma FFAs levels obese patients leading to an increased FFAs flux. The increased FFAs flux is mainly due to increased lipolysis from the expanded adipose tissue stores, to resist the insulin's antilipolytic action by increasing lipolytic`s hormones sensitivity [26]. Many studies have shown that FFAs are an important causative link between obesity, insulin resistance and type 2 diabetes mellitus [9,13,17-19]. Elevation of plasma FFAs has been shown to impair insulin action as a risk factor for type 2- diabetes development [27].

4. Insulin Resistance

Insulin resistance is defined as the decreased ability of insulin to regulate glucose metabolism. It is an important target of medical research and in clinical practice as it represents a common disorder/disease in a range of metabolic diseases that are termed as Metabolic Syndrome (MS). MS includes type 2 diabetes, glucose intolerance, dyslipidemia, hypertension and cardiovascular diseases. The skeletal muscle is responsible for about 80% of whole-body insulin stimulated glucose uptake [28]. The specific cause of reduced insulin action in skeletal muscle cells is unclear. It is aberrant that the dysregulated lipid metabolism and the increased FFAs have a strong implication that affects insulin signaling.

4.1. The link between increased lipid availability and insulin resistance

In the year, 1963, Randle et. al. was the first scientist to suggest a primary role for elevated FFAs effect on the development of insulin resistance. His speculation was based on the observation that high plasma concentration of FFAs is one of the common characteristics in patients with either diabetes or other carbohydrate disorders [29,30]. Randle’s hypothesis was supported by different studies, it manifested that insulin resistance can be induced within hours through lipid infusion or weeks through a high fat feeding regimen. In addition, studies of a number of genetic experimental models of insulin resistance also implicate the role of increased lipid availability in the pathogenesis of the disease.

4.2. The glucose fatty acid cycle

Randle's hypothesis is scientifically based on the increased FFAs oxidation. As a result, the mitochondrial acetyl-CoA/CoA ratio increases that causes a reduction in the supply of acetyl –CoA from pyruvate. This leads to the increase of citrate concentration that would cause an accumulation of glucose 6-phosphate resulting in an inhibition of hexokinase and the uptake of glucose by the cell [29,30].

Although lipid infusion results in an inhibition of glucose oxidation, the insulin stimulated glucose uptake appears with no effect for hours. Apparently, the impairment effect is implicated on the glycogen synthesis instead. In addition, the reduction in glycogen synthesis occurs with a decreased level of glucose 6-phosphate rather than the accumulation and increase in its level. The current consensus has been attributed to the reduction of glucose transport and phosphorylation in association with a reduction in the activity of the insulin signaling cascade [31,32]. These are the main reasons that shed a light for the involvement of the other mechanisms for the development of insulin resistance.

Early studies have pointed out that high fat feeding result in an accumulation of intracellular triglyceride as a major factor involved in insulin resistance. This is now looked as one of most consistent markers of whole-body insulin resistance. Other major contributors for causing the onset of insulin resistance are the lipid intermediates such as long-chain fatty acyl CoAs (LCACoAs), diacylglycerol (DAG) and ceramides.

4.3. LCACoAs: It representing the activated form of intracellular FFAs [33]. LCACoAs are seen as signaling molecules that affect a variety of cellular processes for example, LCACoA inhibits the hexokinase activity in muscle in vitro. LCACoAs are known to interfere with the muscle glucose utilization through the activation of Protein Kinase C (PKC) [34]. In addition, LCACoAs can modulate gene transcription such as the hepatic nuclear factor 4α [35].

4.4. DAG: It is an intermediate of both triglyceride and phospholipid metabolism that accumulates in the muscle insulin resistant as documented in rat model following high fat feeding [36]. DAG can be generated by de novo synthesis following the esterification of LCACoAs to glycerol-3-phosphate or through the breakdown of phospholipids such as phosphatidylinositol-4, 5-bisphosphate and phospatidylcholine by phospholipases C and D. DAG acts as important second messenger involved in intracellular signaling in addition to its effect on insulin action through PKC activation [37].

4.5. Ceramide: It is a derivative of sphingomyelin, the phospholipid component for cell membranes that is synthesized through the action of sphingomyelinase from the palmitoyl CoA. Ceramide acts as second messenger that can alter the activity of kinases, phosphatases and transcription factors that regulate a number of processes such as proliferation, differentiation and apoptosis. Our own data and others have demonstrated that palmitate induce insulin resistance in muscle model through the reduction of IRS-1 and PKB phosphorylation as a result of activation of protein phosphatase 2A (PP2A) [38]. Other reports have shown that ceramide can mediate the inhibition of insulin signaling through the tumor necrosis factor- α (TNF-α), an activator of sphingomylinase [39]. TNF-α is among many other inflammatory markers that triggers inflammation and type 2 diabetes processes as discussed below.

Data from our laboratory has clearly demonstrated the effect of FFAs induced insulin resistance in two insulin sensitive tissues, muscle and liver.

The key findings are summarized as follow:

1- Free fatty acids (FFAs) - induced PKC and NFκB activation, two key events in two different models for insulin resistance, the skeletal muscle and liver [40,42].

2- In the C2C12 muscle insulin resistant model,

different FFAs – induced serine 307 phosphorylation for IRS-1 as a mechanism for skeletal muscle insulin resistance [40]. The inhibitory effects of PKC on insulin signaling may at least in part be explained by the serine/threonine phosphorylation of IRS-1. Both oleate and palmitate treatment were able to increase the serine 307 phosphorylation of IRS-1. IRS-1 serine 307 phosphorylation is inducible which causes the inhibition of IRS-1 tyrosine phosphorylation by either IκB-kinase (IKK) or c-jun N-terminal kinase (JNK) [40, 41].

3- In the fructose fed hamster model of hepatic insulin resistance, free fatty acids - induced PKC and NFκB activation as a mechanism for both insulin resistance and dyslipidemia [42].

Our in vitro and in vivo key findings support the relevance and highlight the importance of elucidating the human insulin resistance scenario. Strong body of evidences and data from our laboratory have pointed out the involvement of the IKK-beta/IKappa B/NFKappa B pathway in insulin resistance in the two models of muscle and liver [40, 42].

Furthermore, our laboratory has manifested a direct effect for FFAs induced insulin resistance through the serine phosphorylation of IRS-1 in C2C12 skeletal muscle cell model. The finding requires further attention as it represents a therapeutic target for the disease intervention. On the other hand, we also reported that increased FFAs influx to the liver and the resulting PKC activation in the fructose-fed model are important events that contribute to hepatic apoB-100 overproduction commonly observed in insulin resistant states [42]. These current data point to FFAs-induced PKC activation and its impact on dyslipidemia as a potential therapeutic target in the treatment of diabetes and insulin resistance.

4.6. The link between increased lipid availability and Inflammation

Many prospective studies in different human populations have identified pro-inflammatory cytokines, acute phase proteins and several indirect markers of inflammation as predictors of type 2 diabetes and glucose disorders in relation to FFA elevation [43]. Interestingly, interleukin-6 (IL-6) levels have been reported to be elevated in subjects with type 2 diabetes [44] and correlate with the direct and indirect measures of insulin resistance [45]. The leading hypothesis linking cytokines such as TNF-α to insulin resistance has long been reported that cytokine receptor activation in insulin target cells activates signaling pathways that directly or indirectly impair insulin action. Efforts to understand the close mechanistic circuit linking cytokine receptor activation and impaired insulin signaling have largely converged on a pleiotropic effector of both cytokine signaling and ER stress: JNK. JNK induces a complex pro-inflammatory transcriptional program but also directly phosphorylates IRS1. JNK activity is increased in obese insulin-resistant liver and skeletal muscle [45]. The inflammatory markers IL-6 and TNFα are playing a major role in the pathophysiology of metabolic syndrome and type 2 diabetes development [46-50]. This highlights the importance of testing the inflammatory proteins in the clinical setting as a diagnostic strategy for early prevention and intervention.

5. Summary

Fatty acid homeostasis reflects on a state of balance between processes that generate or deliver FFAs and processes that utilize these molecules. FFAs are generated through the de-novo synthetic pathway that are liberated when triglycerides and phospholipids are hydrolyzed by cellular lipases [51]. High plasma FFAs and triglyceride levels lead to increased import of FFAs into non-adipose tissues, contributing to intracellular lipid accumulation. Non-adipose tissues such as liver and skeletal muscle [52] have a limited capacity for lipid storage leading to cellular dysfunction that is termed lipotoxicity. Studies have documented that primary hyperlipidemia, serum triglycerides [53, 54] and FFAs [55, 56] are elevated in type 1 and type 2 diabetes and plasma FFAs are

elevated in obese individuals [57]. Insulin resistance is believed to be the primary cause of type 2 diabetes. Studies have shown that elevated plasma levels of FFAs is shown to increase insulin resistance in muscle and liver. Lowering of FFAs levels is therefore postulated to be a potential therapeutic strategy for handling type 2 diabetes.

The aim of current review article and the studies conducted in our laboratory and others was to further elucidate the hypothesis that "Increased lipid induces perturbations in key molecules of the insulin-signaling pathway leading to reduced insulin action in insulin sensitive tissues such as muscle and liver. FFAs induced insulin resistance is a key important underlying factor in the development of insulin resistance and eventually type 2 diabetes". We focused on elucidating the molecular mechanisms by which FFAs induce insulin resistance in two insulin sensitive tissues, muscle and liver as reported in our studies and others. The work conducted in our laboratory, we investigated in details the mechanisms and the effects of two FFAs. We studied the oleate, the monounsaturated FFA (18:1) and palmitate, the saturated FFA (16:00) as they are the most predominant two fatty acids in the circulation [58]. We investigated their effect on glucose metabolism and insulin action in two insulin sensitive tissues the muscle and the liver and studied how they can induce the insulin resistance at the molecular level in vitro and in vivo in two different experimental designs for insulin resistance.

A strong correlation between insulin resistance and the increased lipid availability in the muscle tissue has been manifested from the literature and our own data. Several mechanisms that affect insulin signal transduction have been identified. In our laboratory, we found that oleate does not affect the total protein level of PKB/Akt total but partially reduces the phosphorylation of PKB in oleate and dramatically in palmitate treated cells. On the other hand, our data suggest that the monounsaturated fatty acid; oleate muscle insulin resistance mainly via PKC. On the contrary, the saturated fatty acid, palmitate induces insulin resistance mechanistically through the PKB inhibition that is well documented through the ceramide formation and PP2A activation. In addition, the two FFAs are also to activate the NFκB and the stress kinases that contribute to the induction of serine-307 phosphorylation of IRS-1 and the development of insulin resistance in the C2C12 muscle model. The serine 307 phosphorylation of IRS-1 is considered as a potential therapeutic target for the early intervention with the onset of the disease. Wang C et al. have reported that palmitate specifically induced insulin resistance by PKC theta-dependent activation of mTOR/S6K pathway in C2C12 myotubes [59]. However, more studies are still required to further elucidate the exact consequences of PKC activation following other species of FFA(s) treatment.

Furthermore, our second set of data is to represent the experimental work that was conducted in the fructose fed hamster as a liver model for diet induced insulin resistance. The data points the FFAs - induced PKC activation and its impact on dyslipidemia seen in the liver model. The fructose fed hamster model as a model of diet induced model for studying insulin resistance in the liver, has revealed the importance of PKC activation for both insulin resistance and de novo lipogenesis. As reported Ragheb R, et al. have demonstrated that the antioxidant, Taurine was capable of reversing the oleate-induced insulin resistance in myocytes as manifested from the glucose uptake data [40]. Han. P. et.al have also reported that Taurine prevented FFAs-induced hepatic insulin resistance in association with inhibiting JNK1 activation and improving insulin signalling in vivo [60]. Taurine is considered as a potential therapeutic target in protecting from insulin resistance caused by elevated FFAs caused by different mechanisms of oxidative stress and inflammatory pathways. Further, we highlights the clinical importance for measuring

the inflammatory biomarkers. The inflammatory markers IL-6 and TNFα are among the key players manifesting a major role in the pathophysiology of insulin resistance syndrome and type 2 diabetes development.

6. Conclusion

This current review has outlined aspects of FFAs induced insulin resistance in insulin sensitive tissues. It is clear that the development of insulin resistance as a metabolic disease is marked by the disturbances of lipids in the body. Our research work data showed a direct evidence for the desensitization of muscle cells following FFAs exposure but no observable changes in hepatic insulin signaling at the insulin receptor level. Furthermore, the data have demonstrated the importance of PKC activation in two different models for FFAs induced insulin resistance, the muscle and liver. In 1997, the WHO has recognized the importance of insulin resistance and its link to type 2 diabetes, the growing problem that of great deal for the public health globally. Further insight to the field will be invaluable and of great impact on the treatment and the early intervention of the disease onset that is tightly linked to a number of other diseases such as lipid disorders, cardiovascular diseases and inflammation. In addition, the early measurement of the inflammatory biomarkers, IL-6 and TNFα and FFAs levels in plasma have clinical significance as a diagnostic tool that would benefit patients with insulin resistance syndrome through early intervention protocols used for prevention and early diagnosis of type 2- diabetes (Pre-diabetics). Further, the utilization of the current information discussed for therapy and diagnosis will have a great potential to control the growing epidemic of diabetes.

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