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Review

Do flavanols-rich natural products relieve obesity-related insulin resistance?

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ABSTRACT

Growing evidence support that insulin resistance may occur as a severe problem due to chronic energetic overfeeding and subsequent obesity. When an abundance of glucose and saturated fat enter the cell, impaired blood flow, hypoxia, inflammation and macrophage infiltration in obese adipose tissue may induce oxidative stress and insulin resistance. Excessive circulating saturated fatty acids ectopically accumulate in insulin-sensitive tissues and impair insulin action. In this context, excessive hepatic lipid accumulation may play a central, pathogenic role in insulin resistance. It is thought that dietary polyphenols may ameliorate obesity-related insulin resistance by attenuating inflammatory responses and oxidative stress. The most often occurring natural polyphenolic compounds are flavonoids. In this review, the possible mechanistic effect of flavonoid-rich natural products on insulin resistance-related metabolic pathways is discussed. Polyphenol intake can prevent high-fat-diet-induced insulin resistance via cell surface G protein-coupled estrogen receptors by upregulating the expression of related genes, and their pathways, which are responsible for the insulin sensitivity.

1. Introduction

Overweight and obesity are expected to raise up to 89% and 85% in males and females, respectively by the year 2030. As a result, the obesity-related prevalence of coronary heart diseases will increase by 97%, while cancers will elevate by 61% and type 2 diabetes will raise by 21%. Thereby, total healthcare costs for major obesity-related conditions will increase from 2.55 billion Euro to 5.4 billion by 2030 (Engin, 2017; Keaver et al., 2013). As a consequence, worldwide increased prevalence of obesity and diabetes results in a significant economic impact which constitutes a remarkable portion of healthcare expenditure (Shamseddeen et al., 2011). Genome-wide studies found 97 body mass index (BMI)-associated loci, 56 of which are novel and suggest a role of the central nervous system in developing obesity. These findings suggest that synaptic function, glutamate signaling, insulin secretion, energy metabolism, and adipogenesis may be genetically determined (Locke et al., 2015). Additionally, due to the profound effects of insulin in the pathogenesis of cognitive impairment and neurodegeneration, there is growing evidence suggesting that insulin is a key player in cognitive functions. Impaired brain insulin signaling in the advancement of cognitive dysfunction is relevant to the pathophysiologic mechanisms of cognitive impairment and the risk of developing dementia (Kalmijn et al., 2000; Ma et al., 2015). High glucose is an independent risk factor for insulin resistance in human cortical neurons. Both mitochondrial dysfunction and impaired insulin signaling are the critical biochemical features in the high glucose-related neuronal dysfunction (Peng et al., 2016). In this context, insulin resistance is the result of a long-term process that is encountered by chronic energetic overfeeding, when an abundance of glucose and saturated fat enter the cell. Impaired blood flow, hypoxia, inflammation and macrophage infiltration are interrelated in obese adipose tissue. They altogether may induce oxidative stress and insulin resistance (Goossens, 2008; Roberts et al., 2013).

2. Obesity-related insulin resistance

Hypertrophic adipocytes secrete low levels of tumor necrosis factor-alpha (TNF-alpha), which stimulate preadipocytes and endothelial cells to produce Monocyte Chemoattractant Protein-1 (MCP-1), in turn, responsible for attracting macrophages to the adipose tissue, thus developing a state of chronic low-grade inflammation which is causally linked to insulin resistance. Eventually, the excess of circulating free fatty acids, TNF-alpha and other factors induce insulin resistance (Capurso and Capurso, 2012) (Fig. 1). The inappropriately excessive dietary fat intake that is accompanied by peripheral insulin resistance promotes triglycerides hydrolysis, and these contribute to the increase

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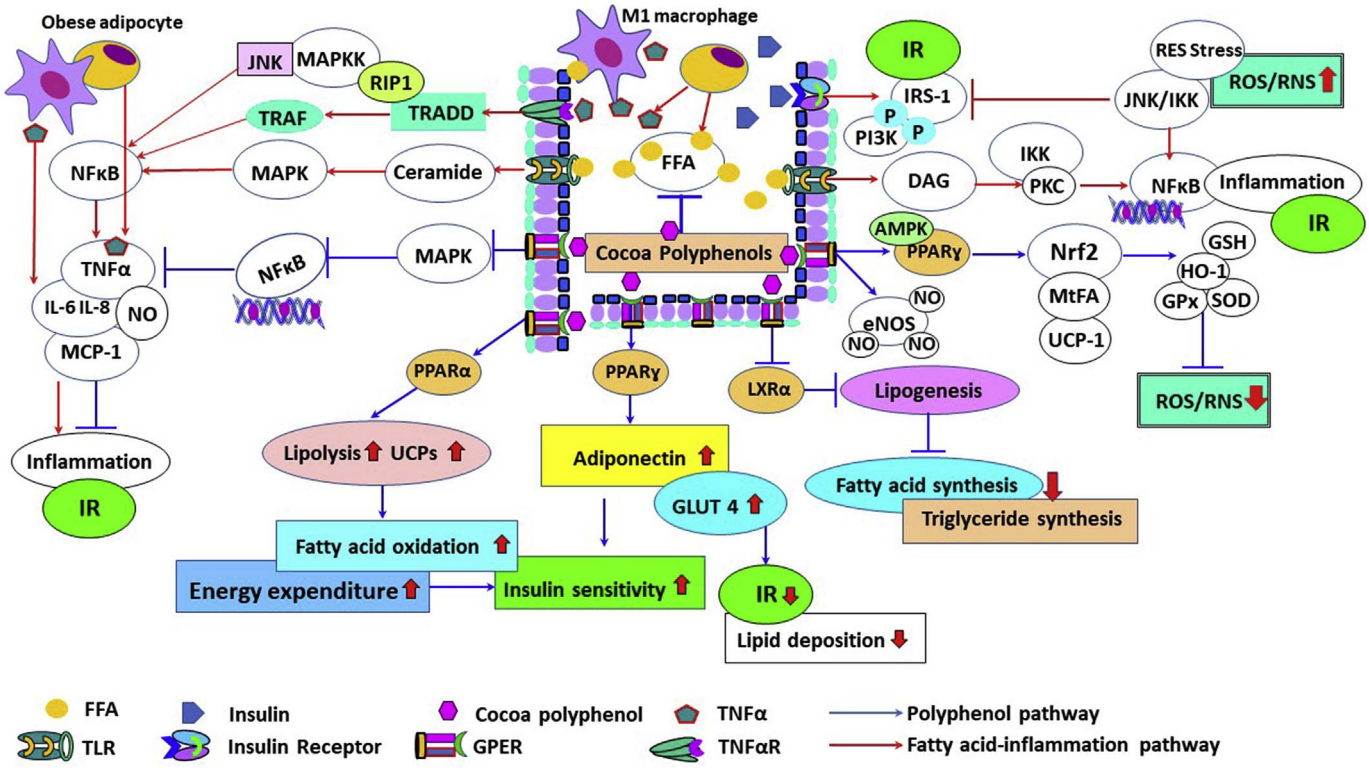

Fig. 1. Obesity is a state of chronic, low-grade adipose tissue inflammation and is associated with increased serum markers of inflammation and mitochondrial oxidative stress. Excessive circulating fatty acids ectopically accumulate in insulin-sensitive tissues and impair insulin action. Furthermore macrophage-mediated inflammation induces insulin resistance by causing decreased insulin signaling in target cells, as well. Elevated TNF-α and FFA levels in adipose tissue and blood lead to activation of serine kinases, proinflammatory cytokines, reactive oxygen and nitrogen species production and endoplasmic reticulum stress through TNF-αR and TLR4 pattern recognition receptors, respectively. Polyphenol intake attenuates high-fat diet-induced inflammatory responses and oxidative stress. Dietary polyphenols prevent insulin resistance through the decreased lipogenesis, and the simultaneous stimulation of fatty acid beta-oxidation due to increased lipolysis, in addition to accelerating adiponectin and GLUT4 expression. It has been thought that polyphenols achieve these effects by upregulating the expression of related genes via GPERs. Abbreviations: FFA, Free fatty acid; TNF-α, Tumor necrosis factor-alpha; TNF-αR, Tumor necrosis factor-alpha receptor; NF-κB, Nuclear factor-kappa B; IL-6, Interleukin-6; IL-8, Interleukin-8; MCP-1, Monocyte chemoattractant protein-1 (CCL2); IR, Insulin resistance; JNK, c-Jun N-terminal kinase; MAP kinase kinase (MAPKK), Mitogen-activated protein kinase kinases; RIP1, Receptor-interacting serine/threonine protein kinase 1; TRADD, tumor necrosis factor receptor type 1-associated death domain protein (adaptor protein); IKK, Inhibitor kappa B kinase; TRAF, TNF receptor associated factor; PPAR-α, Peroxisome proliferator-activated receptor-alpha; LXR, Liver X receptor alpha ligand-activated transcription factor; GLUT 4, glucose transporter-4; IRS, Insulin receptor substrate; ROS, Reactive oxygen radicals; TLR4, toll-like receptor-4; PI3K, Phosphoinositide-3 kinase; DAG, Diacylglycerol; RES, Reticuloendothelial system; PKC, Protein kinase C; Nrf2, Nuclear factor erythroid 2-related factor-2; GPER, G protein-coupled estrogen receptor; NO, Nitric oxide; eNOS, endothelial nitric oxide synthase; RNS, reactive nitrogen species; SOD, Superoxide dismutase; GPx, glutathione peroxidase; UCP, Uncoupling protein; GSH, Reduced glutathione; HO-1, heme oxygenase-1.

in the blood free fatty acid concentration (Sanyal et al., 2001). Eventually, in the insulin-sensitive tissues, the released excessive circulating fatty acids may ectopically accumulate and may impair the insulin action. This influence on the whole-body insulin sensitivity is related to the elevation in the basal lipolysis levels that alters the secretory profile of adipose tissue. Finally, the excessive fatty acid release may also worsen adipose tissue inflammation, which is a well-known parameter contributing to insulin resistance (Morigny et al., 2016). Accumulation of bioactive lipid species, diacylglycerol, and ceramides, have been demonstrated to play essential roles in the establishment of insulin resistance in insulin-sensitive tissues by activating proinflammatory signaling pathways and protein kinase C isoforms (PKC) (Turban and Hajduch, 2011). On the one hand, diacylglycerol-activated PKC inhibits insulin receptor substrate (IRS)-1 by increasing the phosphorylation on its Ser636/639 residues (Mack et al., 2008). On the other hand, ceramides induce the recruitment and retention of both PKC and protein kinase B (PKB/Akt) in caveolin-enriched microdomains of the plasma membrane. The accumulation of PKB significantly contributes to ceramide-induced inhibition of PKB-directed signaling (Fox et al., 2007; Hajduch et al., 2008). Consequently, ceramides repress insulin signaling through segregation of both PKB/PKC in these sub-microdomains of adipocytes and muscle cells (Turban and Hajduch, 2011). Ceramide-induced inactivation of PKB/Akt via activation of atypical PKC isoforms (aPKCs) is the second mechanism of insulin resistance (Hage Hassan et al., 2014). Many researchers agree that impaired insulin action occurs at the level of IRS-1 following stress kinases activation, such as c-Jun N-terminal kinase (JNK) and nuclear factor-kappaB (IkappaB) kinase (IKK)beta. Eventually phosphorylation of IRS-1 decreases (Aguirre et al., 2000, 2002; Rui et al., 2001). Reduced IRS-1 phosphorylation on critical tyrosine residues prevents binding with p85 of phosphoinositide 3-kinase (PI3K) and subsequently downstream signal transduction. Furthermore, alteration in phosphorylation of serine residues is shown to target IRS-1 for proteasomal degradation. Therefore, glucoregulatory tissues harvested from obese individuals express reduced levels of IRS-1 protein (Ahmad et al., 1997; Pederson et al., 2001; Potashnik et al., 2003; Wang et al., 2009).

Obesity is recognized as a state of chronic, low-grade inflammation and is associated with increased serum markers of inflammation and oxidative stress (Festa et al., 2000; Keaney et al., 2003). While individuals with a central obesity display elevated cardiovascular morbidity and mortality (Montague and O'Rahilly, 2000), abdominal obesity primarily contributes to acquired insulin resistance. In this case, insulin resistance is associated with a clustering of metabolic disorders, in which increasing adiposity is correlated with impaired insulin action (DeFronzo and Ferrannini, 1991). Indeed, insulin resistance both in nondiabetic and diabetic subjects is frequently associated with obesity, particularly with an excess of intraabdominal fat (Calabrò et al., 2009). In mammals, fat is classified by histological appearance as being either