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Fatty acids and chronic low grade inflammation associated with obesity and the metabolic syndrome

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ABSTRACT

The metabolic syndrome is a group of obesity associated metabolic conditions that result in increased risk of cardiovascular disease and type 2 diabetes. Global increases in obesity rates have led to an increase in metabolic syndrome resulting in a demand for increased understanding of the mechanisms involved. This review examines the relationship between adipose tissue biology, lipid metabolism and chronic low grade inflammation relating to obesity and insulin resistance.

1. Introduction

First described in the 1920s as a combination of metabolic disturbances, the scientific community has somewhat struggled to define the Metabolic Syndrome (MetS) (Kylin, 1923). In the 1940s it was recognised that upper body adiposity was the type most often associated with metabolic abnormalities including type 2 diabetes (T2D) and cardiovascular disease (CVD) (Vague, 1947). In 1988 Gerald Reaven used the term Syndrome X to describe a collection of symptoms including resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very-low-density lipoprotein triglyceride or triacylglycerol (TAG), decreased high-density lipoprotein (HDL) cholesterol and hypertension. However, obesity was notably absent from this list (Reaven, 1988). The most recent formal definition for MetS available identifies raised blood pressure, elevated TAG, lowered HDL cholesterol, raised fasting glucose, and central obesity as its criteria (Alberti et al., 2009). Individuals with MetS experience at least a fivefold increased risk of developing T2D and a twofold increased risk of CVD, with profound implications for morbidity and quality of life (Eckel et al., 2010, 2005).

The global increase in obesity rates is of grave concern. As of 2011, the number of individuals classified as overweight is greater than those classified as undernourished, with more than 1.7 billion overweight individuals worldwide (Chawla et al., 2011). Increasing obesity rates are closely linked to greater prevalence of the MetS, non-alcoholic fatty liver disease (NAFLD), T2D and CVD (Hong et al., 2015; Sung et al., 2012; Targher and Arcaro, 2007; Targher, 2007; Targher et al., 2006). These statistics represent an enormous stress on global health services. It is imperative then that the mechanisms behind obesity and MetS are understood, in order to improve both preventative measures and outcomes. This review will focus on the inter-relationship between fatty acids and chronic low-grade inflammation in adipose tissue, which in turn

Abbreviations: AMPK, 5′ Adenosine Monophosphate-Activated Protein Kinase; ATGL, Adipose Triacylglycerol Lipase; BAT, Brown Adipose Tissue; BMI, Body Mass Index; CVD, Cardiovascular Disease; DAG, Diacylglycerol; DHA, Docosahexaenoic Acid; DIO, Diet Induced Obesity; EPA, Eicosapentaenoic Acid; ERK, Extra-Cellular Signal Related Kinase; GLUT-4, Glucose Transporter Type −4; HDL, High-Density Lipoprotein; HFD, High Fat Diet; HSL, Hormone Sensitive Lipase; Ig, Immunoglobulin; IKK-β, Inhibitor of Nuclear Factor Kappa-B Kinase Subunit –Beta; IL, Interleukin; IL-1R-1, Interleukin-1 Receptor-1; IRS, Insulin Receptor Substrate; IκBα, Nuclear Factor Kappa Light Polypeptide Chain Gene Enhancer in B-Cells Inhibitor, Alpha; JAK, Janus Kinase; JNK, c-Jun-N-Terminal Protein Kinase; LPL, Lipoprotein Lipase; MAPK, Mitogen Activated Protein Kinase; MCP-1, Monocyte Chemoattractant Protein −1; MetS, Metabolic Syndrome; MUFA, Monounsaturated Fatty Acid; (n−3 LCPUFA), n−3 Long Chain Polyunsaturated Fatty Acid; NAFLD, Non-Alcoholic Fatty Liver Disease; NFκB, Nuclear Factor Kappa Light Chain Enhancer of β-Cells; PKC, Protein Kinase C; PKC-θ, Protein Kinase C-θ; PKR, Protein Kinase R; PPAR-γ, Peroxisome Proliferator Activated Receptor γ; PUFA, Polyunsaturated Fatty Acid; SAT, Subcutaneous Adipose Tissue; SFA, Saturated Fatty Acid; SOCS-3, Suppressor of Cytokine Signalling-3; STAT-3, Signal Transducer and Activator of Transcription-3; SVF, Stromal Vascular Fraction; T2D, Type 2 Diabetes; TAG, Triacylglycerol; Th-1, T Helper −1; TLR-4, Toll like Receptor-4; TNFR-1, Tumour Necrosis Factor Receptor – 1; TNF-α, Tumour Necrosis Factor – α; Treg, T-Regulatory; VAT, Vascular Adipose Tissue; WAT, White Adipose Tissue

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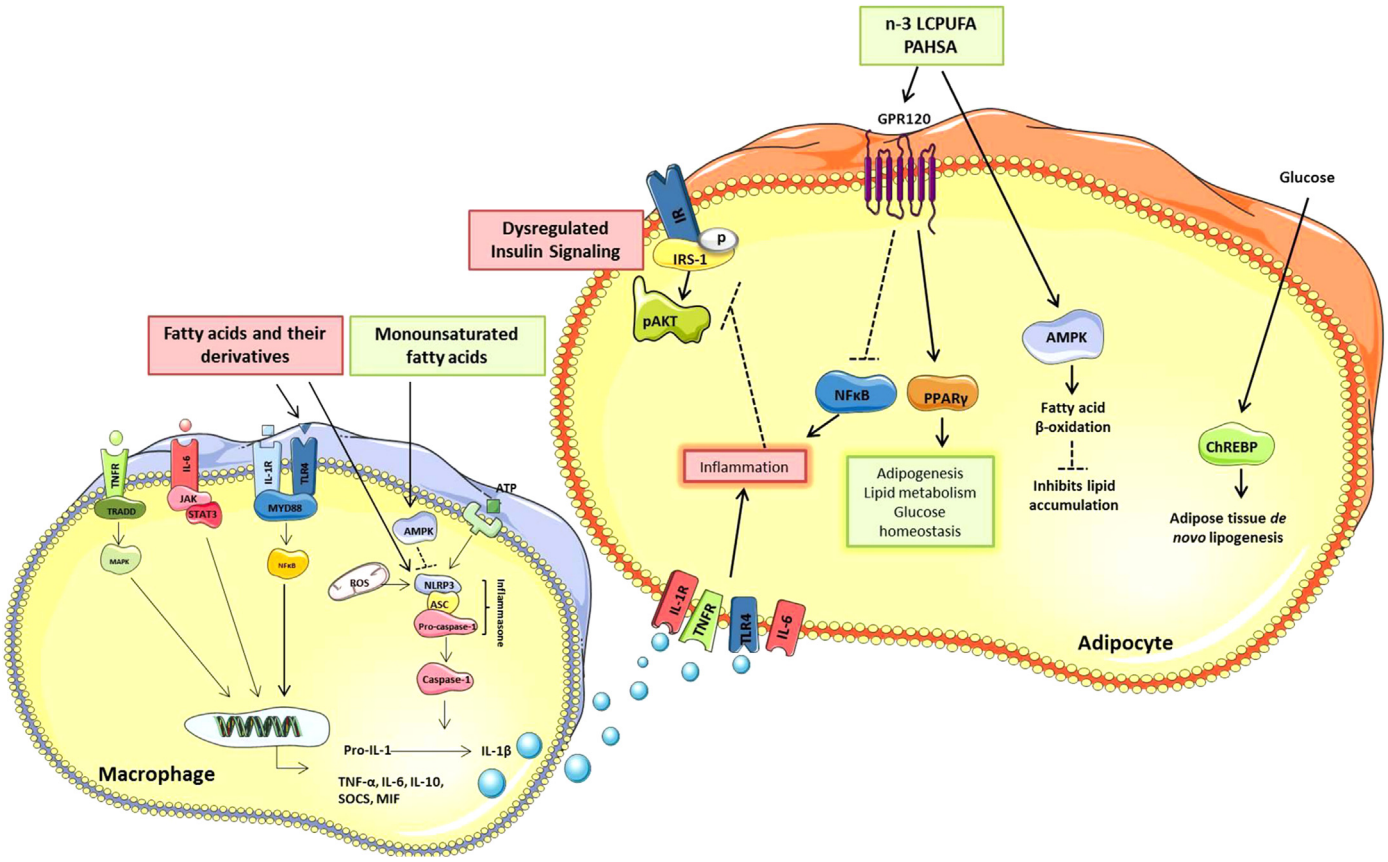

Fig. 1. **The inter-relationship between fatty acids, inflammation and insulin signalling - Cellular cross talk between macrophages and adipocytes**. Fatty acids and their derivatives have been shown to modulate inflammatory pathways in immune cells. This results in increased pro-inflammatory cytokine secretion from immune cells such as macrophages and T cells which in turn act on adipocytes to disrupt insulin signalling. (This figure was prepared using the Servier medical art website http:// www.servier.fr/servier-medical-art.).

modulates insulin signalling (Fig. 1). Given the importance of lipid metabolism in this paradigm, our perspective will focus on whether different fatty acids may mediate differential effects on adipose tissue inflammation and insulin resistance, within the broader context of the MetS and T2D risk.

2. Adipose tissue

Obesity is characterised by excess adipose tissue, which itself can be categorised into two types: brown adipose tissue (BAT) and white adipose tissue (WAT) (Rosenwald and Wolfrum, 2014). BAT is known to play a role in thermogenic processes (Nedergaard et al., 2007). Until recently, BAT was thought to be present only in new-born humans. However, recent work has suggested a role for BAT in thermoregulatory processes in adults (Nedergaard et al., 2007). In contrast, WAT plays a significant role in regulating energy metabolism and storing excess energy as TAG (Schweiger and Schreiber, 2006).

Adipocytes represent the primary cellular component of WAT. The lipid stored within adipocytes is in constant flux and readily adapts to fluctuating nutritional demand (Lafontan and Langin, 2009). In the postprandial state, lipoprotein lipase (LPL), located within the endothelial lining of blood vessels hydrolyses circulating TAG. This process releases free fatty acids which are taken up by adipocytes and re-esterified to generate TAG for storage. In contrast, in times of energy deficit or increased energy requirements, TAG undergoes lipolysis, wherein it is hydrolysed by adipose triacylglycerol lipase (ATGL) and hormone sensitive lipase (HSL) to release free fatty acids for β-oxidation (Lafontan and Langin, 2009).

During persistent positive energy balance, WAT is forced to expand to facilitate increased TAG storage (Virtue and Vidal-Puig, 2010). Depending on its location, increased adipose tissue expansion can result in considerable adipose tissue dysfunction, which is characterised by decreased insulin sensitivity (Hotamisligil et al., 1993), increased immune cell infiltration (Hotamisligil, 2006), fibrosis (Sun et al., 2013), hypoxia (Sun et al., 2013) and increased intracellular and systemic free fatty acid flux (Yu and Ginsberg, 2005). Expansion of WAT is peroxisome proliferator- activated receptor-γ (PPAR-γ) dependent and occurs via an increase in adipocyte cell size (hypertrophy), cell number (hyperplasia) or both (Jo et al., 2009). It is now known that increased hyperplasia is linked to a more favourable phenotype, which likely reflects less adipose tissue inflammation (Lundgren et al., 2007).

In addition to cell morphology, distribution of excess adipose tissue has a significant impact on pathology, wherein increased visceral adipose tissue (VAT) to a greater extent than subcutaneous adipose tissue (SAT) is associated with MetS development (Després and Lemieux, 2006). Additionally, SAT is rich in preadipocytes prone to rapid replication, which increases its buffering capacity (Tchkonia et al., 2005). Vidal-Puig and colleagues hypothesised that individuals reach a limit of SAT expansion, after which excess TAG can no longer be facilitated within the subcutaneous region (Virtue and Vidal-Puig, 2008). This inability of SAT to buffer macronutrient surplus promotes lipotoxicity, wherein excess energy is directed towards the VAT depot as well as to non-adipose locations, such as skeletal muscle, the liver and