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Interactions between differential fatty acids and inflammatory stressors—impact on metabolic health

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ABSTRACT

Current interest in obesity has established a clear link between diets high in fat and metabolic complications such as Type 2 Diabetes. Dietary fats and their metabolites act as stressors to induce a pro-inflammatory immune response which dysregulates many essential metabolic functions. Recent research suggests that different dietary fats may have varying inflammatory potentials. However the molecular mechanisms involved in the cross talk between dietary fat composition and the 'immuno-metabolism' remain enigmatic. It is probable that lipids, and their derivatives, differentially regulate IL-1β activation and inflammatory signaling via the NLRP3 inflammasome complex. Also from the translational perspective, certain nutrient sensitive genotypes and potential gene nutrient interactions offer the possibility to reduce inflammation through personalized nutrition approaches.

1. Obesity, inflammation & insulin resistance—an overview

The heightened prevalence of obesity and associated co-morbidities is cause for concern, doubling since 1980 [1] and over 347 million people worldwide have diabetes [2]. Diets high in saturated fats have been attributed as a leading cause for the rise in obesity and related metabolic complications, thus there has been considerable interest in their immuno-modulatory effects on metabolic health. Dietary fats and their metabolites act as metabolic stressors to induce inflammation, which can dysregulate adipose tissue functionality and promote insulin resistance (IR) [3]. There is evidence to suggest that differential dietary fats have varying inflammatory potential, wherein monounsaturated fatty acids (MUFA) and certain polyunsaturated fatty acids (PUFA) may induce a less profound inflammatory response compared to saturated fatty acids (SFA). This subsequently may impact upon metabolism, in particular insulin sensitivity [4–8]. The concept of nutrient sensitive genotypes has attracted a lot of attention in recent years and has potential to translate therapeutically through a personalized nutrition approach. However, the precise mechanisms involved in the cross talk between dietary fat and 'immuno-metabolism' in obesity and insulin resistance remain enigmatic. The purpose of this review is to evaluate according to current knowledge, the inflammatory impact of fatty acids on metabolic health with particular focus on NLRP3 inflammasome/interleukin-1 beta (IL-1β) mediated inflammation and potential gene-nutrient interactions.

Abbreviations: NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; IR, insulin resistance; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; IL-1β, interleukin-1 beta; MetS, metabolic syndrome; T2D, Type 2 Diabetes; AT, Adipose tissue; TAG, triacylglyceride; MCP-1, monocyte-chemotactic protein-1; LTB4, leukotriene B4; MIF-1, macrophage inhibitory factor-1; SAA, serum amyloid A; TNF-α, tumour necrosis factor; IL-6, interleukin 6; IFN-γ, interferon gamma; FFA, free fatty acids; AGE, advanced glycation end products; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; RAGE, receptor for advanced glycation end products; SVF, stromal vascular fraction; TH2, T helper 2 cells; Treg, regulatory T cells; Th1, T helper 1 cells; CD4+, cluster of differentiation 4 positive; CD8+, cluster of differentiation 8 positive; ATM, adipose tissue macrophages; BMI, body mass index; TLR4, toll like receptor 4; HFD, high fat diet; GLUT4, glucose transporter type 4; IL-10, interleukin 10; STAT3, Signal transducer and activator of transcription 3; AKT, protein kinase B; IL-1α, interleukin 1 alpha; IL-1Ra, interleukin-1 receptor antagonist; IL-18, interleukin 18; IL-33, interleukin 33; IL-1F5, interleukin 36 receptor antagonist; IL-1F10, interleukin 38; IRS-1, insulin receptor substrate-1; mRNA, messenger ribonucleic acid; IL-1R1$^{-/-}$, interleukin-1 receptor 1 knockout; NALP3, (NLRP3) nod like receptor pyrin domain 3; ASC, apoptosis-associated speck-like protein containing a CARD; TLR2, toll like receptor 2; LC n-3 PUFA, long chain n-3 polyunsaturated acids; PPARγ, peroxisome proliferator activated receptor gamma; AA, arachidonic acid; EPA, eicosapentaenoic acid; COX, cyclooxygenase; LOX, lipooxygenase; DHA, docosahexaenoic acid; LF, low fat; C3, complement component 3; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance; LTA, lymphotoxin-alpha; SNP, single nucleotide polymorphism; ADIPOQ, single nucleotide polymorphism on the adiponectin gene; ADIPOR1, single nucleotide polymorphism on the adiponectin receptor gene; LPS, lipopolysaccharide; IL-4, interleukin 4; IL-13, interleukin 13; AMPK, AMP-activated protein kinase; miRNAs, micro ribonucleic acids; CPT-1, carnitine palmitoyltransferase

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2. Excess dietary energy triggers an immune response

At the simplest level excess dietary energy intake over time leads to obesity. Obesity is associated with increased adiposity and chronic, low grade inflammation which has been attributed to the development of insulin resistance, the metabolic syndrome (MetS) and Type 2 Diabetes (T2D). Adipose tissue (AT) is a highly diverse metabolically active organ with dual functionality. Classically it is an energy storage reservoir while also having a more understated role as an endocrine organ. Obese adipose tissue becomes hypertrophic as it attempts to store the excess energy as lipid in triacylglycerides (TAG) [9,10]. Hypertrophic adipocytes secrete a plethora of proteins which are collectively known as 'adipokines'. Adiponectin, leptin, monocyte-chemotactic protein-1 (MCP-1), leukotriene B4 (LTB4), macrophage inhibitory factor-1 (MIF-1), serum amyloid A (SAA) are examples. Adipokines attract immune cells, primarily macrophages preceded by T-cells [11], into the adipose tissue, where they produce cytokines tumour necrosis factor (TNF-α), interleukin 6 (IL-6), interferon gamma (IFN-γ) and interleukin 1 beta (IL-1β). These cytokines initiate a pro-inflammatory cascade which transcends systemically [10]. Considerable metabolic stress ensues which dysregulates many of the body's essential functions particularly insulin signalling [10]. Disruptions to the insulin signalling pathway result in reduced cellular glucose uptake, promoting enhanced insulin production to compensate. This leads to hyperinsulinemia, insulin resistance and glucose intolerance which can drive pancreatic beta cell failure and progress to T2D [12]. Hyperglycemia, lipotoxicity and increased circulating free fatty acids (FFA) are further consequences of disturbed metabolism and insulin resistance, each of which can be considered as metabolic stressors themselves.

Other metabolic stressors include ceramides, advanced glycation end products (AGE) and reactive oxygen species (ROS), and each of these can mimic a pathogen induced immune response. Ceramides are a class of sphingolipid and their synthesis *in vivo* is dependent on the quantity of long chain saturated fats in the diet [13]. Ceramides are linked to insulin resistance and lipotoxicity [14]. They accumulate in insulin sensitive tissues particularly skeletal muscle, where they antagonise insulin action through manipulation of various components of the insulin signalling pathway [14]. AGE are glycated endogenous lipids or proteins which have been exposed to excess circulating sugars, hence, they are dominant in T2D [15]. AGE cause the up-regulation of pro-inflammatory transcription factor nuclear factor kappa B (NF-κB) and inhibits nitric oxide production in endothelium, increasing ROS production [15]. ROS production during obesity, leads to increased oxidative stress and can affect the regulation of adipokines, glucose and lipid metabolism, as well directly impairing insulin signalling [16]. The presence of ROS can also result in the downstream activation of the receptor for AGE (RAGE) and release of pro-inflammatory RAGE ligands [17], thus displaying a cross-talk between metabolic stressors.

3. Immune cell infiltration, adipose tissue inflammation & metabolic health

Obesity is classically characterized by an excess of adipose tissue, which is both the source and target of inflammation. It is important to appreciate that the inflammatory profile of obese AT contributes to metabolic dysfunction, which results in a homeostatic imbalance that precipitates IR and T2D. Adipose tissue is comprised of two distinct compartments, the adipocytes which store triacylglycerides (TAG) and the stromal vascular fraction (SVF) which contains immune cells, particularly T cells and macrophages [18]. In the lean insulin sensitive state the SVF contains T helper 2 cells (TH2) and regulatory T cells (Treg), which secrete anti-inflammatory cytokines IL-10, IL-4 and attract anti-inflammatory M2 macrophages [10]. During obesity, chronic inflammation causes the homeostatic balance within the AT to become disrupted and augmented macrophage infiltration occurs [19] which hinders insulin sensitivity. Obese SVF contains an alternate immune milieu; CD4+ T helper 1 cells (TH1) and CD8+ effector T cells are in abundance [11,20]. TH1 derived cytokines, TNF-α and IL-1β, enhance an already inflamed environment within the tissue, to attract macrophages [11,20]. These cytokines in conjunction with adipokines/chemokines are thought to polarize the resident M2 macrophages towards a pro-inflammatory M1 phenotype [10,21], however AT macrophages (ATM) are likely present as part of a spectrum rather than crudely categorized as M1 or M2 populations [22].

ATM content is positively correlated with adiposity, body mass index (BMI) and average adipocytes cross-sectional area [19]. Accumulated ATM, aggregate and cluster around necrotic adipocytes, forming crown like structures [19,23,24]. Consequently, initial ATM infiltration may be a protective mechanism to deal with the deleterious effects of AT hypertrophy [23]. Free fatty acids promote ATM accumulation through activation of the TLR4 receptor [25] following high fat diet (HFD) [26] and contribute to the release of pro-inflammatory cytokines. It was demonstrated that mice lacking TLR4 had increased activation of M2 macrophages within AT [25,26]. Increasing adiposity and enhanced inflammatory gene expression occurs 3 weeks following HFD before the onset of hyperinsulinemia [23]. TNF-α expression is enhanced in multiple models of obesity [27]. TNF-α decreases adipocyte GLUT4 expression [27,28] and also inhibits insulin action by impeding insulin receptor tyrosine phosphorylation [29]. M1 macrophages are the prominent source of TNF-α within adipose [19,30]. During obesity a phenotypic switch occurs from anti-inflammatory M2 macrophages to pro-inflammatory M1 macrophages [21]. M2 macrophage derived IL-10 maintains insulin sensitivity in 3T3-L1 pre-adipocytes via tyrosine phosphorylation of transcription factor STAT3 and phosphorylated AKT activation [21]. Furthermore IL-10 pre-treatment of adipocytes prevents TNF-α induced inhibition of insulin-stimulated glucose uptake [21]. Release of pro-inflammatory cytokines, such as TNF-α and IL-1β, in conjunction with adipokines/chemokines are thought to polarize the M2 macrophages towards pro-inflammatory M1 macrophages [10,21]. Mice with a deletion of the receptor for the pro-inflammatory cytokine IL-1 (IL-1RI-/-) on HFD, have a skewed ATM phenotype despite equivalent M1 infiltration [31]. IL-1 is considered as an important mediator of the fatty acid induced inflammation and insulin resistance.

3.1. *Interleukin-1β; functional consequences on adipose biology and insulin resistance*

Interleukin-1 (IL-1) is a potent pro-inflammatory cytokine secreted by monocytes, macrophages and dendritic cells. The IL-1 super family, represents 11 members to date, IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-18, IL-33, and IL-1F5 to IL-1F10 (inclusive) [32]. IL-1α, IL-1β and IL-1Ra all signal though IL-1 receptor 1 (IL-1R1). IL-1α and IL-1β initiate a pro-inflammatory response through inflammatory transcription factor NFκB, while IL-1Ra antagonizes the receptor preventing the initiation of inflammatory pathways and thus has an anti-inflammatory effect. IL-1α is biologically active upon production whereas IL-1β needs to be matured.

IL-1β has detrimental effects on pancreatic beta cells causing cell death, an effect opposed by IL-1Ra [33,34]. IL-1β also promotes insulin resistance through inhibition of AKT phosphorylation coincident with serine phosphorylation of IRS-1 [35]. Interestingly IL-1β mediates inter organ cross talk between adipocytes and the liver, accentuating systemic inflammation and lipotoxicity [36]. *in vitro* IL-1β reduces GLUT4, IRS-1 mRNA expression which impairs insulin signaling, while elevating the expression of the pro-inflammatory