

Saturated Fatty Acid-Mediated Inflammation and Insulin Resistance in Adipose Tissue: Mechanisms of Action and Implications¹

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Abstract

This review highlights the inflammatory and insulin-antagonizing effects of saturated fatty acids (SFA), which contribute to the development of metabolic syndrome. Mechanisms responsible for these unhealthy effects of SFA include: 1) accumulation of diacylglycerol and ceramide; 2) activation of nuclear factor- κ B, protein kinase C- θ , and mitogen-activated protein kinases, and subsequent induction of inflammatory genes in white adipose tissue, immune cells, and myotubes; 3) decreased PPAR γ coactivator-1 α/β activation and adiponectin production, which decreases the oxidation of glucose and fatty acids (FA); and 4) recruitment of immune cells like macrophages, neutrophils, and bone marrow-derived dendritic cells to WAT and muscle. Several studies have demonstrated potential health benefits of substituting SFA with unsaturated FA, particularly oleic acid and (n-3) FA. Thus, reducing consumption of foods rich in SFA and increasing consumption of whole grains, fruits, vegetables, lean meats and poultry, fish, low-fat dairy products, and oils containing oleic acid or (n-3) FA is likely to reduce the incidence of metabolic disease.

SFA, obesity, and chronic disease

Obesity and metabolic disease. The WHO estimated that in 2005, 400 million people were obese (1). Furthermore, ~1.6 billion people were overweight and 20 million of them were children under the age of 5 y (1). Obesity is closely linked to insulin resistance or type 2 diabetes. About 80% of individuals with type 2 diabetes are classified as overweight or obese and 30% of obese children under the age of 12 y display insulin resistance (2). Along with type 2 diabetes, obesity is associated with hypertension and atherogenic dyslipidemia. Together, these disorders are referred to as metabolic syndrome and are closely linked to chronic inflammation.

SFA consumption. The average American diet is abundant in SFA, such as palmitate and stearate, and unsaturated fatty acids (FA), such as oleate and linoleate. Foods high in SFA include fast foods, processed foods, high-fat dairy products, red meats, and pork (3). The current consumption of total and saturated fat by Americans is substantially higher than the latest dietary recom-

mendations. The mean daily per capita consumption of fat in the US in 2003–2004 was 82.7 g, which exceeds the recommended amount by 16.0 g, based on a 8400-kJ diet. Mean SFA consumption was 27.7 g compared with the recommended 22 g (4). Consumption of diets rich in SFA is highly correlated with metabolic syndrome (5–7). Overconsumption of FA contributes to weight gain and inflammation (8), but SFA have a particularly strong effect on the inflammatory capacity of white adipose tissue (WAT)² [(9), reviewed in (10)].

Effects of SFA on WAT

WAT function. The role of WAT is more complex than just energy storage. WAT acts as an endocrine organ, secreting factors needed for glucose homeostasis, energy metabolism, food intake and body weight regulation, hemostasis, and immune function [reviewed in (11)]. As WAT expands, adipocytes increase in both size and number, leading to adipocyte dysfunction (12). Hypertrophied adipocytes secrete proinflammatory agents that promote systemic inflammation [reviewed in (13)]. Furthermore, lipid-engorged adipocytes die and release their contents, which recruit neutrophils (14) and macrophages (15). Consistent with this paradigm, adipocyte cell death may be as much as 300% higher in obese than in lean individuals (16,17). Thus, obesity-mediated macrophage recruitment to WAT is associated with excess consumption of fat, resulting in chronic, low-grade inflammation (Fig. 1).

Effect of SFA on WAT function. WAT expansion is one of the ways in which SFA causes WAT dysregulation (18). Excess palmitate not only expands WAT, but it increases inflammation and apoptosis through oxidative or endoplasmic reticulum stress, generation of ceramide and reactive oxygen species (ROS), and protein kinase C (PKC) signaling (Fig. 2). In adipocytes, palmitate induced endoplasmic reticulum stress by increasing C/EBP homologous protein and glucose regulatory protein 78 and splicing of X box binding protein-1 mRNA, as well as altering phosphorylation of eIF2 α and increasing phosphorylation of c-jun-NH₂-terminal kinase (JNK) and extracellular receptor kinase (19). Palmitate activated PKC, nuclear factor- κ B (NF κ B), and mitogen-activated protein kinase (MAPK) signaling, leading to cytokine production in 3T3-L1 adipocytes (20). Furthermore, palmitate robustly increased the expression and secretion of tumor necrosis factor

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² Abbreviations used: BMDC, bone marrow-derived dendritic cell; DAG, diacylglycerol; DHA, decosahexanoic acid; FA, fatty acid; IL, interleukin; JNK, c-Jun-NH₂-terminal kinase; MAPK, mitogen-activated protein kinases; NF κ B, nuclear factor- κ B; PGC-1, PPAR γ coactivator 1; PKC, protein kinase C; TLR, toll-like receptor; TNF, tumor necrosis factor; WAT, white adipose tissue.

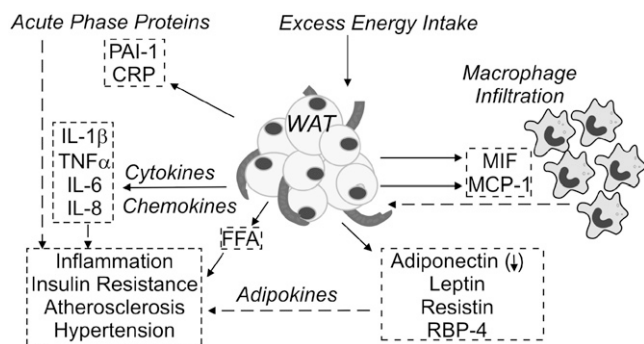


FIGURE 1 Excess energy intake enhances WAT inflammation and contributes to the development of metabolic syndrome.

(TNF) α and interleukin (IL)-10 in murine adipocytes compared with oleic acid and docosahexanoic acid (DHA) (21). SFA activated Toll-like receptor (TLR) signaling in murine adipocytes (22–24) and macrophages (22,23,25,26), leading to NF κ B and JNK activation and cytokine production. Consistent with these data, TLR4 knockout mice were protected against the adverse effects of feeding a high-fat diet rich in palmitate (27).

In vivo (28) and in vitro (29) studies have shown that palmitate inhibits the activation of insulin receptor substrate 1, phosphatidylinositol-3-kinase, or Akt, causing insulin resistance. Adiponectin, an insulin-sensitizing protein produced by adipocytes, is expressed at low levels in obese, insulin-resistant individuals (30,31). Reducing the levels of adiponectin appears to be the mechanism by which palmitate caused insulin resistance in isolated rat adipocytes (32). Furthermore, overexpression of adiponectin decreased insulin resistance in mice fed a high-fat diet (33). Thus, SFA impair insulin sensitivity by reducing adiponectin secretion and impairing insulin signaling pathways required for glucose uptake.

SFA promote cross-talk among adipocytes, macrophages, and myotubes

SFA-mediated macrophage recruitment and activation in WAT. Activated macrophages cause inflammation and insulin resistance in insulin-sensitive cells like WAT, muscle, heart, and liver [Fig. 3; reviewed in (12)]. Supplementation with palmitate, one of the major FA released from WAT, caused recruitment of

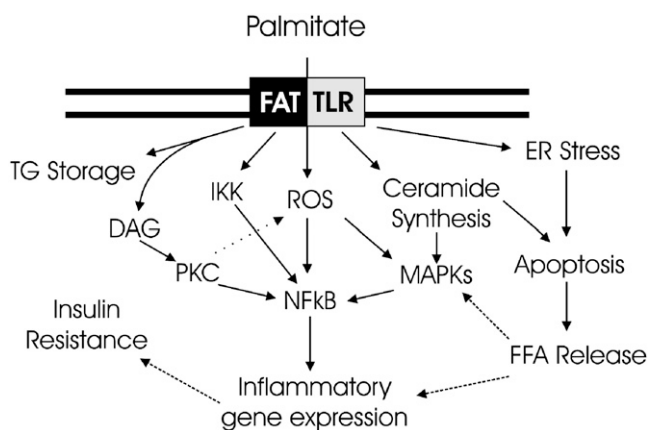


FIGURE 2 Proposed mechanisms by which palmitate mediates inflammation in cultures of human adipocytes.

monocytes to hypertrophied murine adipocytes by inducing monocyte chemoattractant protein-1 production via JNK and NF κ B activation (18). Similarly, palmitate increased inflammatory gene expression in human macrophages (U937) by an NF κ B-dependent mechanism (34). Consistent with these data, lauric acid, but not DHA, activated costimulatory molecules (e.g. CD40, CD80, CD86) and cytokines in bone marrow-derived dendritic cells (BMDC) (35). FFA were reported to trigger JNK signaling via TLR2/4 activation in murine macrophages (RAW264.7) and BMDC (36). Furthermore, feeding a high-fat diet rich in SFA increased the number and inflammatory activity of resident macrophages or BMDC in WAT (37). Taken together, these data show that SFA are particularly potent in recruiting and activating immune cells in WAT, thereby increasing inflammation.

Macrophage-adipocyte interactions. WAT regularly releases FA, activating resident macrophages or recruiting new ones. In a reciprocal manner, activated macrophages influence adipocyte function by increasing inflammation and insulin resistance. Using direct contact or transwell cocultures of murine macrophages (RAW264) and adipocytes (3T3-L1), Suganami et al. (38) demonstrated that each cell type had the capacity to induce inflammation in the other. SFA increased TNF α mRNA levels in cocultures of adipocytes and macrophages, whereas unsaturated FA had no effect. Moreover, TNF α expression was higher and adiponectin expression was lower in cocultures containing hypertrophied adipocytes compared with cocultures containing adipocytes with smaller lipid droplets. These data show that lipid-filled adipocytes containing SFA have the ability to activate macrophages to a greater extent than smaller adipocytes, especially when compared with adipocytes enriched in unsaturated FA. SFA increased inflammatory gene expression in both cell types by TLR4/NF κ B signaling (23). Consistent with these data, high-fat feeding in mice increased TLR4 signaling in macrophages and adipocytes and impaired insulin signaling, whereas mice lacking TLR4 were resistant to these effects (26). Clearly, factors secreted from macrophages increase adipocyte inflammation and insulin resistance (39,40). Lastly, FA-binding proteins play an important role in cross-talk between adipocytes and macrophages, as mice lacking FA-binding proteins in these tissues have reduced inflammatory signaling and improved insulin sensitivity when fed a high-fat diet (41).

SFA cause inflammation and insulin resistance in muscle. SFA can directly cause inflammation and insulin resistance in muscle. For example, palmitate-mediated lipid accumulation in rat muscle caused insulin resistance via PKC signaling (28). Mice fed a high-fat diet rich in SFA expressed increased levels of CD11c, indicating infiltration of muscle by inflammatory BMDC,

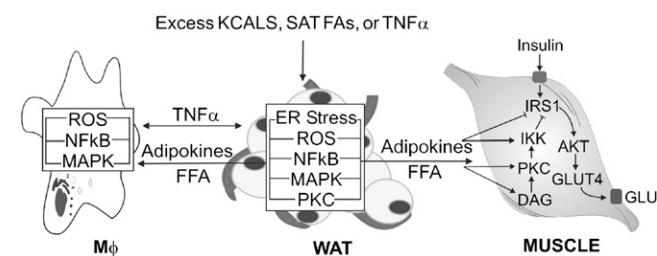


FIGURE 3 Cross-talk between inflamed WAT, macrophages (M Φ), and muscle, leading to insulin resistance.

which impair insulin sensitivity (36). Additionally, palmitate increased the expression and secretion of inflammatory cytokines (e.g. IL-6 and TNF α) and impaired insulin sensitivity via an NF κ B/PKC θ pathway in muscle cells (C2C12) (42,43). Similarly, palmitate caused insulin resistance in murine L6 myotubes via NF κ B signaling (44). Cosupplementation with linoleate prevented palmitate-induced NF κ B activation and subsequent expression and secretion of IL-6 in human myotubes (45).

SFA can also induce insulin resistance by antagonizing PPAR γ coactivator (PGC)-1 α . PGC-1 α promotes oxidative phosphorylation, mitochondrial gene expression, and insulin-stimulated glucose uptake [reviewed in (46)]. Palmitate activated extracellular receptor kinase and NF κ B in C2C12 myotubes, decreasing PGC-1 α activity (47), which was restored by cosupplementation with oleate (48). Oleate cosupplementation blocked palmitate-mediated suppression of β -oxidation, insulin sensitivity, and diacylglycerol (DAG) accumulation in C2C12 myotubes. Consistent with these data, palmitate and stearate increased p38 MAPK signaling, thereby reducing PGC-1 α /1 β expression and activity, mitochondrial gene expression, and oxygen consumption in C2C12 myotubes (49). Thus, SFA-mediated reductions in PGC-1 α activation would lead to decreased oxidation of FA and glucose, thereby increasing their accumulation in tissues and blood.

Accumulation of DAG and ceramide is associated with insulin resistance in muscle via PKC θ , JNK, or I κ B α kinase signaling [reviewed in (50)]. Palmitate, but not oleate, caused the accumulation of DAG and ceramide in C2C12 myotubes (29). The resulting insulin resistance was blocked by overexpressing acid ceramidase (51). Similarly, palmitate, but not linoleate, increased the levels of DAG and ceramide and reduced insulin-stimulated glucose uptake in murine L6 myotubes (52). Rats fed a high-SFA diet had increased levels of DAG in muscle and were insulin resistant compared with rats fed a diet rich in unsaturated FA (52). Taken together, these data demonstrate the adverse effects of SFA on glucose uptake and utilization in muscle, i.e. increased inflammation due to increased DAG, ceramide, PKC, and NF κ B signaling and decreased PGC-1 α / β activation.

Adipocyte-myotube interactions. Eckel et al. (53) used human skeletal muscle cells treated with conditioned media from adipocytes, as well as cocultures of adipocytes and muscle cells. They demonstrated that adiponectin supplementation rescued decreased Akt and glycogen synthase phosphorylation and insulin-dependent glucose transporter 4 translocation in skeletal muscle cells induced by conditioned media from adipocytes (53). Monocyte chemoattractant protein-1 secretion from adipocytes was largely responsible for the impaired insulin signaling and glucose uptake in muscle (54). Mice fed a high-fat diet had reduced adiponectin levels and increased muscle FA, as well as reduced muscle mass, compared with controls (55). Moreover, FA increased protein degradation in C2C12 myotubes by downregulating insulin receptor substrate 1 and Akt signaling, thereby activating E3 ubiquitin ligases (55). Palmitate activation of the E3 ligases was prevented by adiponectin supplementation.

Collectively, these studies demonstrate the adverse effects of elevated FFA, especially SFA, on WAT function. Specifically, excess consumption of SFA enhances WAT expansion and adipocyte hypertrophy and subsequent death. These events increase inflammatory signaling and recruitment and activation of macrophages, neutrophils, and BMDC, leading to inflammation, impaired insulin signaling, and insulin resistance in multiple tissues, especially in WAT and muscle. Substituting

SFA with unsaturated FA, particularly oleic acid and DHA, ameliorates many of these adverse metabolic effects of SFA.

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