

REVIEW

Saturated fatty acids and insulin resistance

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Abstract : Insulin resistance is one of the pathophysiological features of obesity and type 2 diabetes. Recent findings have linked insulin resistance to chronic low-grade inflammation in white adipose tissue. Excess storage of saturated fat in white adipose tissue due to a modern life style causes hypertrophy and hyperplasia of adipocytes, which exhibit attenuated insulin signaling due to their production and release of saturated fatty acids. These adipocytes recruit macrophages to white adipose tissue and, together with them, initiate a proinflammatory response. Proinflammatory factors and saturated fatty acids secreted into the bloodstream from white adipose tissue impair insulin signaling in non-adipose tissues, which causes whole-body insulin resistance. *J. Med. Invest.* 56 : 88-92, August, 2009

Keywords : saturated fatty acid, insulin resistance, inflammation, white adipose tissue, adipocyte

PHYSIOLOGICAL ROLE OF ADIPOSE TISSUE IN ENERGY BALANCE

Evolutionally, humans have developed the ability to store excess calorie intake in adipose tissue as fat, which can be used in times of famine (1). Dietary fat absorbed into epithelial cells of the intestines is assembled into one type of lipoprotein, chylomicrons, enters the bloodstream, and is transported to peripheral tissues. Lipoprotein lipase (LPL) in adipocytes, one of the main destinations of chylomicrons, hydrolyses triglyceride (TG) in chylomicrons into free fatty acids (FFAs) and glycerol. Adipocyte LPL also hydrolyses TG in VLDL (very low density lipoprotein), supplied from the liver and in remnants of both chylomicrons and VLDL, into FFAs and glycerol. Adipocytes take up FFAs and glycerol and reassemble them into TG and store it in lipid

droplets (2). When necessary, stored TG in adipocytes can be hydrolysed by their adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) (3), and used as energy, which may help individuals in situations where the caloric intake falls short of its demand. Due to a robust food supply and sedentary life style in industrialized nations, the amount of caloric intake exceeds that of calorie demand in many individuals. Thus, white adipose tissue (WAT) in these individuals keep accumulating TG and growing both in size and in number, resulting in obesity and even type 2 diabetes through the development of insulin resistance (4).

PHYSIOLOGICAL ROLE OF ADIPOSE TISSUE IN ENDOCRINE SYSTEM

Recent studies have revealed that adipose tissue not only serves as a storage site for fat but also functions as an endocrine organ by secreting a wide range of hormones and cytokines (2, 5). For instance, leptin production by adipocytes, which is upregulated in large adipocytes (6), regulates food

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intake and fat mass through its action in the hypothalamus, resulting in decreased hunger and stimulated energy expenditure (7, 8). Leptin also increases lipid oxidation in the liver and lipolysis in skeletal muscle and adipocytes to control whole-body energy balance (9, 10). Adiponectin is exclusively produced by adipocytes and secreted into the bloodstream, where it self assembles into larger structures (trimer, hexamer and high-molecular weight forms). A proteolytic cleavage product of adiponectin, known as globular adiponectin, also circulates in human plasma (11). Although the biological activities of these isoforms are controversial, it appears that high-molecular weight adiponectin has a mainly beneficial role in humans and rodents (12, 13). In these studies, high-molecular weight adiponectin improved insulin sensitivity by inhibiting hepatic glucose production and enhancing glucose uptake into skeletal muscle. It also increased lipid oxidation in both the liver and skeletal muscle (14).

ADIPOSE TISSUE DYSFUNCTION IN OBESITY

A negative impact of excess plasma free fatty acids or triglycerides, including cellular dysfunction and programmed cell death, has been reported in a number of non-adipose tissues (15, 16). Thus, hypertrophy (increased cell size) and hyperplasia (increased cell number) of WAT to store more TG in their intracellular lipid droplets is a protective mechanism against calorie overload. However, the capacity of WAT to synthesize TG from FFAs is not infinite. Challenging adipocytes with an excess amount of FFAs saturates the biosynthetic pathway of TG in adipocytes, and FFAs start to accumulate in adipocytes. FFAs accumulated in adipocytes pose endoplasmic reticulum stress (ER stress) and oxidative stress at the level of the mitochondrion, both of which cause dysfunction in adipocytes (17). Affected adipocytes have decreased TG synthesis and increased lipolysis, which results in the systemic release of FFAs. In addition, hormones and cytokines produced and released by these adipocytes are different from those by healthy adipocytes. Secretion of adiponectin is attenuated, whereas that of proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor α (TNF α) and monocyte chemoattractant protein-1 (MCP-1) is elevated, which recruits macrophages into WAT, causing chronic low-grade inflammatory responses (18). Dysfunctional

adipocytes due to overloading of FFAs die and release their contents, which recruits neutrophils and macrophages into WAT and promotes a chronic low-grade inflammatory response in WAT (19, 20). As a result, the plasma level of inflammatory cytokines goes up and affects other tissues as well, such as liver, skeletal muscle, cardiac muscle and blood vessels, which eventually leads to insulin resistance and atherosclerosis (17).

SATURATED FATTY ACID CONSUMPTION

Among dietary fat constituents, saturated fat, which contains saturated fatty acids (SFA), is drawing particular attention these days, since a strong correlation between SFA intake and the metabolic syndrome, which exhibits insulin resistance, has been reported (21-23). Foods that contain a high level of SFA are dairy products, fatty meats, palm oil, coconut oil and some processed foods (24). Although overconsumption of FFAs generally leads to chronic low-grade inflammation in WAT, as described above, SFAs exhibit a particularly strong effect to induce WAT inflammation (25).

SFA-INDUCED INSULIN RESISTANCE AND INFLAMMATORY RESPONSE IN WAT

Overloading of adipocytes with SFAs, transported from the bloodstream presumably by CD36/FAT, results in accumulation of diacylglycerol (DAG), which in turn activates protein kinase C (PKC) θ and desensitizes adipocytes to insulin stimulation (26, 27). PKC θ activates the I-kappa-B kinase (IKK) and c-Jun N-terminal kinase (JNK) pathways, which induces serine phosphorylation and degradation of IRS-1 and stimulates production and secretion of proinflammatory cytokines (28). Overloading SFAs also results in accumulation of ceramide in adipocytes, which is reported to activate IKK and JNK, as well (29, 30). Accelerated β -oxidation of SFAs causes excess electron flux in the mitochondrial respiratory chain, resulting in increased production of reactive oxygen species (ROS), which was reported to cause insulin resistance and an inflammatory response in adipocytes (31). Furthermore, SFAs activate Toll-like receptor 4 (TLR4) on the surface of adipocytes, which activates the NF κ B pathway and JNK pathway (32, 33). Thus, SFAs both transported into adipocytes and bound to TLR4 impair insulin

signaling and stimulate secretion of proinflammatory factors from adipocytes.

CROSSTALK BETWEEN ADIPOCYTES AND MACROPHAGES IN SFA-INDUCED INSULIN RESISTANCE

In obesity, hypertrophied adipocytes in WAT secrete proinflammatory cytokines (called adipokines, as they are produced in and released from adipocytes), such as MCP-1, which recruit macrophages into WAT. SFAs released from hypertrophied adipocytes bind to TLR4 on the surface of macrophages, and together with adipokines, activate macrophages. As a result, active macrophages in WAT stimulate the NF κ B pathway to produce and secrete cytokines that impair the insulin signaling and further potentiate inflammation in adipocytes (33). In fact, TLR4 knockout mice failed to develop high fat diet-induced insulin resistance, due to a lack of NF κ B activation, both in adipocytes and macrophages (34). Thus, infiltration of macrophages into WAT and crosstalk between adipocytes and macrophages through their SFA-TLR4-NF κ B pathways are crucial for the development of SFA-induced chronic low-grade inflammation and insulin resistance in WAT.

SFA-INDUCED CHRONIC LOW-GRADE INFLAMMATION IN WAT CAUSES INSULIN RESISTANCE IN NON-ADIPOSE TISSUES

SFA-induced chronic low-grade inflammation and insulin resistance in WAT affects other tissues and impairs their sensitivity to insulin, as well. SFA overflow from WAT is taken up by myotubes and hepatocytes, and accumulates in them. Similar to adipocytes, SFAs in myotubes activate signal transduction pathways through IKK and JNK, which causes serine phosphorylation and degradation of IRS-1 and desensitizes myotubes to insulin stimulation (35-38). NF κ B activation by binding of SFA to TLR4 is also reported in myotubes (39). Since skeletal muscle accounts for the majority of insulin-stimulated whole body glucose uptake, impaired insulin signaling in skeletal muscle causes marked insulin resistance (40).

SFA-induced serine phosphorylation and degradation of IRS-1 are also observed in hepatocytes, which lead to less insulin-regulated inhibition of

hepatic glucose production and increased fasting glycemia (41). SFA is also reported to induce apoptosis of hepatocytes through the JNK pathway (42).

CONCLUSION

Cellular dysfunction of adipocytes in WAT due to overloading of SFAs into them, designated 'lipotoxicity', is a chronic low-grade inflammation of WAT. It not only impairs insulin signaling in WAT, but also affects insulin signaling in remote tissues, resulting in whole body insulin resistance. Lipotoxicity by SFAs is one of the underlying pathophysiological mechanisms of obesity and type 2 diabetes.

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