INSULIN RESISTANCE IN OBESITY – An overview of fundamental alterations

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ABSTRACT

Obesity is a major health risk factor, and obesity-induced morbidity and complications account for huge costs for affected individuals, families, healthcare systems and society at large. In particular, obesity is strongly associated with the development of insulin resistance, which in turn plays a key role in the pathogenesis of obesity-associated cardiometabolic complications, including metabolic syndrome components, type 2 diabetes and cardiovascular diseases. Insulin sensitive tissues, including adipose tissue, skeletal muscle and liver are profoundly affected by obesity both at biomolecular and functional levels. Altered adipose organ function may play a fundamental pathogenetic role once fat accumulation has ensued. Modulation of insulin sensitivity appears to be, at least in part, related to changes in redox balance and oxidative stress as well as inflammation, with a relevant underlying role for mitochondrial dysfunction that may exacerbate these alterations. Nutrients and substrates as well as systems involved in host-nutrient interactions, including gut microbiota, have been also identified as modulators of metabolic pathways controlling insulin action. This review aims at providing an overview of these concepts and their potential inter-relationships in the development of insulin resistance, with particular regard to changes in adipose organ and skeletal muscle.

Keywords: obesity, insulin resistance, inflammation, oxidative stress

1. Definition of insulin resistance

Besides its pivotal role in the regulation of intermediate substrate metabolism, insulin also regulates a wide range of fundamental cell and organ functions that largely fall beyond the scope of this work [1-3]. The main physiological impact of insulin in the regulation of nutrient utilization and intermediate metabolism occurs in the post-prandial state, when variable rises in plasma glucose trigger insulin secretion [4,5]. This leads in turn to plasma glucose clearance by stimulating its uptake and utilization by skeletal muscle and adipose tissue, and by blunting hepatic glucose output through inhibition of liver gluconeogenesis and glycogenolysis. Major insulin actions also result in preservation of skeletal muscle mass through inhibition of protein breakdown and translation of specific protein groups [6,7], and in induction of lipid storage in adipose tissue [5]. Although any impairment of insulin effects on target tissues could be labelled as insulin resistance, in clinical practice the latter commonly identifies reduced insulin action on glucose metabolism. It should be conversely pointed out that individuals defined as insulin resistant for glucose metabolism may present less impaired or normal insulin action on other important biological targets. Indeed, the presence and time course of changes in insulin effects on protein turnover and lipid metabolic pathways in various tissues in obese insulin resistant individuals remains largely to be defined and represents a relevant question for basic and clinical research [8-10]. The current review will however focus on the commonly defined insulin resistance in terms of glucose metabolism and its consequences on glucose levels and major cardiometabolic risk factors.

2. Obesity and insulin resistance

Obesity is one of the most important risk factor for health and its cardiometabolic complications, including insulin resistance, metabolic syndrome components, type 2 diabetes and cardiovascular disease, represent a huge burden for affected individuals, healthcare systems and society at large

[11]. The American Medical Association (AMA), the largest physician organization in the United States has indeed recently issued a declaration characterizing obesity as a disease in its own right [12]. While the negative impact of obesity on human health is strongly established, it should be pointed out that development of metabolic and cardiovascular complications is not inevitable in obese individuals [13]. From both clinical and epidemiological points of view, it is therefore of pivotal importance to identify obese individuals at higher risk of obesity-associated diseases, since this would allow more effective utilization of limited resources for intensive therapeutic approaches. In recent years, the direct role of insulin resistance in the development of metabolic and cardiovascular complications even beyond type 2 diabetes has become increasingly clear, as exemplified by its major pathogenetic impact on the onset of metabolic syndrome [14]. Although clinical features contributing to the definition of metabolic syndrome may vary, there is indeed a general agreement on the involvement of abdominal obesity and insulin resistance in the development of lipid abnormalities and high blood pressure that commonly identify the syndrome and contribute to its negative impact on cardiometabolic disease along with high blood glucose [14]. In the present review, we will aim at providing an overview of current knowledge on major causes linking obesity to the onset of insulin resistance.

3. Causes of insulin resistance in obese individuals

Although obesity is not invariably associated with insulin resistance, a large majority of insulin resistant individuals is obese or overweight [13,11]. Obesity is therefore a fundamental risk factor for the onset and development of insulin resistance. Among possible causes of obesity-induced metabolic derangements, adipose organ dysfunction and altered adipose metabolic processes clearly play a fundamental role [15,16]. Oxidative stress resulting from imbalanced reactive oxygen species (ROS) generation and antioxidant defences as well as chronic inflammation in non-adipose

tissues are also major regulators of insulin sensitivity [1,17-24]; in particular, elevated pro-inflammatory stimuli may be enhanced by excess ROS and directly impair insulin signalling in insulin target tissues [1,17,18,25-27]. Complex systemic networks including responses to nutrients and substrates, the gut and its microbiota are also key players acting by regulating substrate utilization and balance, thereby modulating oxidizing and inflammatory stimuli [28,29].

3.1 Adipose organ dysfunction

Adipokines and adipose endocrine function

It is largely demonstrated that adipocytes secrete several hormones (collectively defined as adipokines or adipocytokines) with a large array of biological effects on metabolism, inflammation and haemostasis, thereby modifying the classical and currently obsolete view of adipose tissue as an inert fat storage tissue [15,30,16]. Describing the complexity of adipose endocrine functions is beyond the scope of this work; among better-characterized hormones with well-established clinical associations with insulin action, adiponectin is positively associated with insulin sensitivity and lower risk for metabolic syndrome and cardiometabolic diseases and it very well exemplifies adipose-derived metabolically beneficial hormones [30,16]. In particular, adiponectin has been shown to increase lean tissue lipid oxidation and mitochondrial function [31] by means of activation of AMP-activated protein kinase (AMPK), one major stimulator of substrate utilization and metabolism [32,31]. On the other hand, adipocytes secrete pro-inflammatory cytokines including TNF-alpha and IL-6, that may activate inflammatory responses both locally and systemically with negative systemic metabolic impact [33]. Caloric restriction and obesity importantly elicit opposite changes in adipocytokine secretion levels and patterns [34,33]. While obesity is characterized by low adiponectin levels and high adipose organ secretion of TNF-alpha and other proinflammatory cytokines, caloric restriction and fat loss may at least partly reverse

this alteration [34,33]. Although mechanisms controlling adipokine secretion have not been completely elucidated, adipose oxidative stress and organ plasticity are proposed to play key regulatory roles.

Oxidative stress – Adipocyte oxidative stress has been demonstrated both in vivo and in vitro to lead to secretion of metabolically harmful adipocytokine patterns [35]. Of note, in classic studies adiponectin expression was lower and IL-6 expression was increased in adipocytes after induction of oxidative stress; antioxidant treatment notably reversed these changes [35]. Plasma adiponectin levels have been also found to be negatively associated with circulating lipid peroxidation markers in humans with chronic kidney disease [36]. Primary stimuli leading to adipose and systemic oxidative stress in obesity remain incompletely defined but may include excess lipid as well as glucose substrate availability from dietary and non-dietary sources [37]. Similar to non-adipose tissues and organs that will be discussed below, emerging evidence indicates that mitochondrial dysfunction may also characterize dysfunctional adipocytes in obesity and may play a key role in ROS overproduction [38]. Additional systems have been however identified to contribute to oxidative stress, including NADPH oxidase [39,35].

Adipose organ plasticity – Expansion of adipose mass is the hallmark of obesity. Paradoxically, recent reports however show that the ability to increase adipose mass during excess energy intake and positive energy balance actually leads to more favourable metabolic outcomes [40]. More effective lipid storage in adipocytes could at least in part explain this apparently counterintuitive observation; higher adipocytes lipid uptake would indeed prevent ectopic lipid deposition in non-adipose tissues, which could instead result in derangement of insulin action and cell metabolism [15]. Least harmful metabolic patterns are indeed associated with adipose organ growth in

response to excess energy intake through enhanced adipocytes differentiation and proliferation [40]. Conversely and importantly, inability to stimulate proliferation may result in adipocyte hypertrophy leading to cell damage, death through apoptosis and pyroptosis [41] and increased local and systemic inflammation due to macrophage recruitment and activation [42]. Although adipocytes proliferation, number and size are difficult to routinely measure in vivo in clinical studies, available evidence strongly supports the concept that these parameters contribute to define metabolic phenotypes including insulin resistance in obese individuals [43,44]. As a clinically relevant and well-established example, the well-known insulin sensitizing effect of antidiabetic drugs thiazolidinediones appears to involve at least in part their ability to stimulate adipocyte differentiation through PPARgamma activity [45]. Investigation of mechanisms regulating adipocyte differentiation and proliferation during adipose mass expansion are therefore undoubtedly of potential great interest and clinical impact. In particular, uncovering hormonal and nutritional regulatory mechanisms will enhance potential for effective therapeutic strategies aimed at preventing obesity-associated metabolic complications.

Adipose organ thermogenesis

Enhancing energy expenditure through increased metabolic inefficiency and heat production from mitochondrial uncoupling during substrate oxidation is also an emerging promising strategy in both prevention and treatment of obesity and metabolic syndrome, following the discovery that brown adipose tissue (BAT) deposits exist and their metabolic activity could be modulated in adult humans [46,47]. Both cold exposure and physical exercise, two classical mediators of increased energy expenditure, have been indeed shown to promote conversion of white into brown adipocytes; browning is also notably and accordingly reported to be increased by thyroid hormone and may be blunted by cortisol, although with possible species-specific differences [48-51].

PRDM16 has been identified as one major transcription factor involved in these processes in experimental models; relevant to the topic of this review, PRDM16 manipulation also results in enhanced glucose tolerance and improved metabolic phenotype [46]. Additional reports have shown that irisin, a myokine secreted following exercise, could have a browning effect [46], and potential transition from muscle cells into brown adipocytes has been also described [46,47]. Most intriguingly and importantly, reports of impaired BAT activation in obesity are available [52,53] and this potential fundamental alteration could therefore primarily contribute to both positive energy balance and metabolic complications including insulin resistance. Potential differential mechanisms regulating adipocyte thermogenesis in rodent experimental models and humans will require further investigation.

3.2 Substrate availability

Excess lipid substrates and lipotoxicity

Excess caloric intake, as commonly induced by high-fat/high-calorie western diets may directly trigger both oxidative stress and inflammation at tissue and systemic levels [25,54,55]; lipid substrates have been notably more extensively studied compared to glucose and will therefore represent the main focus of this section. Triglyceride i.v. infusion leading to high circulating fatty acids comparable to those observed following a high-fat meal directly causes systemic insulin resistance in humans and experimental models [56-60], and elevated plasma free fatty acids are common in obese individuals (40,41) due to both potential elevated dietary intake and enhanced lipolysis from adipocytes. Fatty acids levels importantly cause inflammation and oxidative stress in vitro in muscle cell cultures [61-63]; inflammation and oxidative stress along with additional mechanisms including endoplasmic reticulum stress are accordingly among proposed pathogenetic derangements linking excess fatty acid availability with insulin resistance

[1,57,58,61,60,64,65]. Under conditions of chronic excess fat availability with development of overweight or obesity, lipotoxicity and insulin resistance may chronically result through different mechanisms from lipid deposition in non-adipose insulin target tissues [59]. Intracellular triglyceride accumulation in both skeletal muscle and liver has indeed been long recognized to be associated with tissue and systemic insulin resistance [66,67]. Dyacyl-glycerol has been specifically shown to promote muscle insulin resistance by further impairing subsequent fat oxidation through negative feedback mechanisms [65]. Further clarification on how intracellular lipids impair insulin signalling came from more recent reports indicating excess saturated fatty acid availability as a source of excess ceramide and sphingolipids in skeletal muscle [68,69], in turn leading to impaired insulin signalling and insulin resistance. The process was further reported to be enhanced by pro-inflammatory changes, thereby unveiling potential vicious cycles linking fat, inflammation and metabolic dysfunction [68] (Figure 1).

A majority of in vitro studies demonstrating metabolically harmful effects of fatty acids in muscle cells utilized the saturated fatty acid palmitate; saturated fat has been consistently proposed to play a key role in deleterious metabolic effects of lipids [61-63]. Differential and potentially beneficial activities of unsaturated fatty acids, with particular regard to polyunsaturated n-3 moieties, have been conversely proposed also in terms of impact on insulin resistance and metabolic disease [70,71,63]. Direct relationships between chronic or acute elevation of both total and saturated fatty acids and oxidative stress, inflammation and insulin resistance has been reported in human studies [72,64,65,71,70,60], whereas protective effects of polyunsaturated n-3 fatty acids have emerged [70,71]. Recent evidence however also indicated that acute increments in saturated and monounsaturated circulating fatty acids through i.v. infusion in the presence of physiological hyperinsulinemia directly caused skeletal muscle and systemic insulin resistance

through enhanced mitochondrial ROS production and IKB-NF-kB pathway activation in rodents [1]. These observations directly suggest that at least under the above acute experimental conditions, saturated fatty acids may not be solely responsible of fat-induced metabolic derangements in vivo [1]. Albeit less investigated, the involvement of glucose metabolism in inflammation and oxidative stress particularly at skeletal muscle level is supported by both clinical observations in patients with diabetes mellitus and by experimental models. These reports indicate a pro-oxidant and pro-inflammatory role for glucose elevation [73], and moderate glucose fluctuations potentially reaching hyperglycaemic levels at least during post-prandial conditions could therefore contribute to the onset of obesity-induced insulin resistance.

Mitochondrial dysfunction

Over the last decades, associations between obesity, insulin resistance and low skeletal muscle mitochondrial function and ATP production capacity have been reported [74,75,19,76,77]. In humans, lower expression of the key regulator of muscle mitochondrial biogenesis PGC1α as well as reduced mitochondrial function have been described in progeny and first degree relatives of diabetic and insulin resistant patients [78,74]. Mitochondrial dynamics including balanced organelle fission and fusion may also be affected by excess fat, which may enhance mitochondrial fission and fragmentation with consequent organelle dysfunction [79]. Importantly, mitochondrial dysfunction may be a direct consequence of pro-inflammatory signalling and oxidative stress, both characterizing metabolically complicated obesity [80,81]. Altered mitochondrial dynamics and function in skeletal muscle may therefore represent relatively late and not primary-causal alterations in obese individuals [82-86]; once established, mitochondrial derangements have however substantial potential to synergistically worsen oxidative stress, inflammation and insulin resistance by promoting further increments in ROS production. In addition, impaired

mitochondrial fatty acid oxidative metabolism may worsen fatty acid accumulation and lipotoxicity [74,17,18] (Figure 2). More recently, an impairment of the process of autophagy, the quality control mechanism promoting renewal of intracellular damaged proteins and organelles, including mitochondria (i.e. mitophagy) has been reported in rodent models of obesity, diabetes and insulin resistance [18,87,17]; these alterations have been tissue-specifically reported at skeletal muscle level and could directly contribute to accumulation of dysfunctional mitochondria. Although these hypotheses require further confirmation, enhancing or restoring defective autophagy could become an additional promising approach for improvement of mitochondrial quality and activity, with potential positive impact on oxidative stress and insulin action at least in skeletal muscle tissue. It should indeed be pointed out that differential changes in energy metabolism gene expression have been conversely intriguingly reported in the liver in obese insulin resistant individuals [88,89]; such observations further underscore the complex interplay between obesity, energy metabolism and mechanisms underlying metabolic complications, whose tissue-specificity will require systematic investigation.

3.3 Host-nutrient interactions – The case of gut microbiota

Growing evidence indicates gut microbiota as a key player in the regulation of host-substrates interactions, with particularly regard to metabolic responses to food intake [28,29,90-92]. It is indeed widely accepted that differential metabolic and energy balance-modulating responses to nutrient intake are affected by gut microbiota composition. Consistent with deleterious metabolic impact of specific bacterial phyla in metabolic regulation, germ-free animals are protected from diet-induced obesity [93,90]. High heterogeneity in human gut bacteria has been however found to be protective and associated to lower risk of obesity and related diseases, while higher risk to develop obesity was associated with less heterogeneous phyla [94]. Of note, as shown by gene

cluster analysis, dietary restriction is also able to modulate gut microbiota [95] and this process involves increasing abundance of bacterial phyla, that may be reversed upon restoration of normal-calorie diet [96]. Remarkably, diet-induced metabolic derangements that are directly involved in the onset of insulin resistance, also independently from obesity, have been reported to be directly modulated and at least in part mediated by gut bacterial metabolism in experimental models [97]. Strong evidence indeed indicates that excess consumption of diets enriched in saturated fat leads to increased bacterial production of proinflammatory lipopolysaccharide as well as gut permeability that allows for enhancement of systemic inflammation [97]. Overall, the concept of metabolic endotoxemia has emerged, representing a potential key diet-modulated contributor to obesity-associated metabolic derangements including insulin resistance [97]. From a mechanistic point of view, bacterial production levels of short chain fatty acids (SCFA) in response to nutrient-lipid intake appears to play a major role in the ability of gut microbiota to positively modulate energy balance and metabolism [93,98].

4. Conclusions

Insulin resistance, i.e. a lower that normally expected impact of insulin on glucose metabolism and plasma levels at any given insulin concentration, has increasing prevalence and incidence in humans mainly due to corresponding increments in obesity levels, with substantial impact on human disease. The pathophysiology of insulin resistance is complex and still incompletely understood. Fat accumulation with particular regard to visceral adiposity and ectopic lipid deposition in extra-adipose tissues may independently sustain metabolic abnormalities through chronically altered, pro-inflammatory and insulin-desensitizing signals from dysfunctional adipose organ. Tissue inflammation and oxidative stress may be sustained by the onset of metabolically-induced mitochondrial dysfunction, potentially resulting in metabolic vicious cycles. The latter may

be also directly triggered by acute and chronic exposure to high nutrients and substrates per se, at least partly independent of excess body fat mass. In particular, complex heterogeneous mechanisms underlying metabolically harmful effects of lipid substrates, that appear to include negative interaction with gut microbiota, play a central role in linking diet, obesity and insulin resistance. Increasing knowledge on metabolic and organ networks underlying and sustaining insulin resistance, the role of substrates and the key involvement of adipose organ dysfunction should be strongly pursued for its major potential to reduce the burden of obesity-associated metabolic and cardiovascular complications.

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FIGURE LEGEND

Fig. 1 Putative mechanisms contributing to negative effects of Free Fatty Acids (FFA), and their saturated fraction, on tissue and systemic insulin sensitivity. DAG: di-acyl glycerol; ER: endoplasmic reticulum.

Fig. 2 Putative clustered metabolic derangements contributing to obesity-induced skeletal muscle insulin resistance

Figure 2

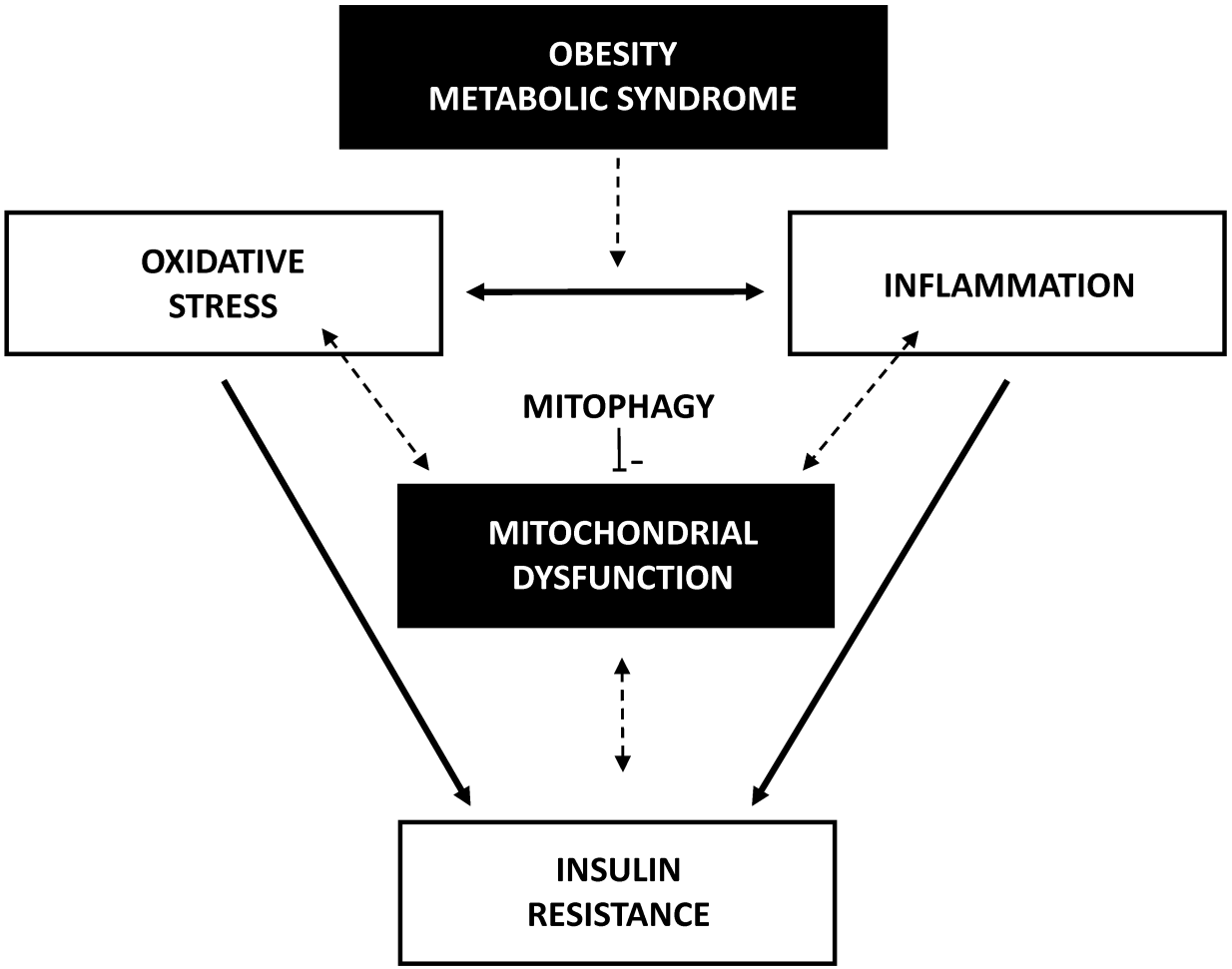
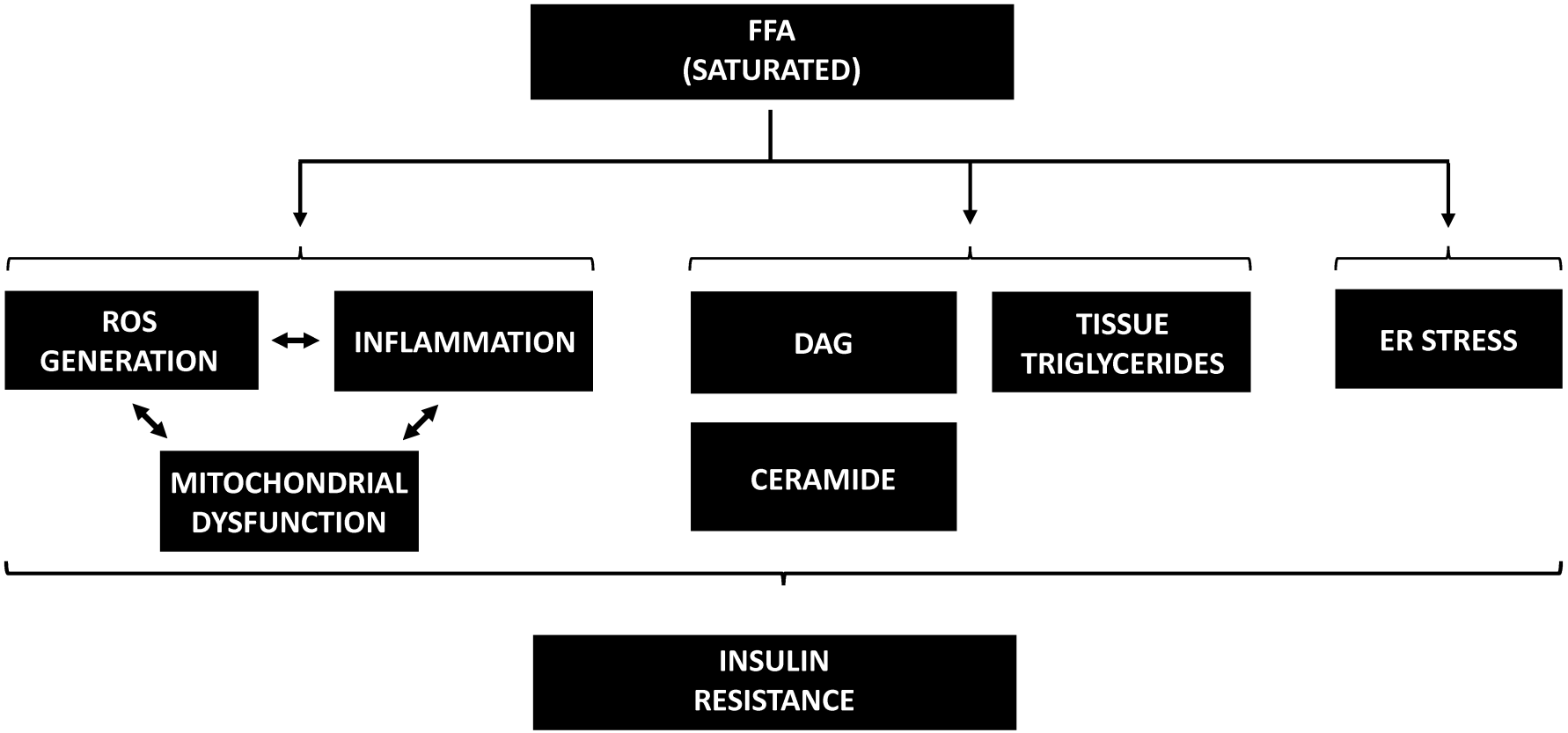

OBESITY
METABOLIC SYNDROME
OXIDATIVE
STRESS
INFLAMMATION
MITOPHAGY
MITOCHONDRIAL
DYSFUNCTION
INSULIN
RESISTANCE

Figure 1


FFA
(SATURATED)
ROS
GENERATION
INFLAMMATION
MITOCHONDRIAL
DYSFUNCTION
DAG
TISSUE
TRIGLYCERIDES
CERAMIDE
ER STRESS
INSULIN
RESISTANCE