antioxidants

MDPI

Review

Redox Regulation of Lipid Mobilization in Adipose Tissues

Ursula Abou-Rjeileh and G. Andres Contreras *

Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824, USA; abourje2@msu.edu
* Correspondence: contre28@msu.edu; Tel.: +1-517-353-9610

Abstract: Lipid mobilization in adipose tissues, which includes lipogenesis and lipolysis, is a paramount process in regulating systemic energy metabolism. Reactive oxygen and nitrogen species (ROS and RNS) are byproducts of cellular metabolism that exert signaling functions in several cellular processes, including lipolysis and lipogenesis. During lipolysis, the adipose tissue generates ROS and RNS and thus requires a robust antioxidant response to maintain tight regulation of redox signaling. This review will discuss the production of ROS and RNS within the adipose tissue, their role in regulating lipolysis and lipogenesis, and the implications of antioxidants on lipid mobilization.

Keywords: lipolysis; lipogenesis; redox signaling; antioxidants; oxidative stress

Citation: Abou-Rjeileh, U.; Contreras, G.A. Redox Regulation of Lipid Mobilization in Adipose Tissues. *Antioxidants* **2021**, *10*, 1090. https://doi.org/10.3390/antiox10071090

Academic Editor: Giuseppina Barrera

Received: 31 May 2021
Accepted: 1 July 2021
Published: 7 July 2021

1. Introduction

The adipose tissue (AT) is a specialized connective tissue that functions as the primary energy storage depot in mammals. During periods of negative energy balance, lipolysis hydrolyzes triacylglycerol (TAG) reserves in AT to release fatty acid (FA) and thus meet human and animal energy needs. On the other hand, under anabolic conditions, the AT stores energy in the form of lipids, such as FA and TAG, in a process known as lipogenesis. The regulation of FA trafficking in and out of the adipocyte (i.e., lipolysis and lipogenesis) involves metabolic and endo-, para-, and autocrine pathways that depend partly on redox signaling.

Redox signaling is a term used to describe cell signaling pathways where free radicals, or related species, serve as chemical messengers [1]. It is a fundamental process for many cell and tissue functions. Free radicals include reactive oxygen and nitrogen species (ROS and RNS), which are potent cellular metabolism products. At low concentrations, ROS and RNS are the effectors of redox signaling, but at high concentrations harm living organisms. During lipolysis, both ROS and RNS are generated by the activation of mitochondrial and cytosolic processes in AT cellular components such as adipocytes and immune cells. To maintain redox balance, antioxidant defenses are activated. However, in conditions with intense and protracted lipolysis such as human diabetes, obesity, and metabolic stress in dairy cows, the production of ROS and RNS rapidly depletes antioxidant systems, and oxidative stress (OS) develops. OS is generally defined as an imbalance between oxidants and antioxidants [2]. More precisely, it refers to increased levels of free radicals that cause cell damage. Lipids (predominantly unsaturated FA), proteins, and DNA are targets for oxidation, nitration, halogenation, and deamination by ROS and RNS [3]. This review will discuss the role that redox signaling plays in the control of lipolysis and lipogenesis in AT and the effects of antioxidants during lipid mobilization.

2. ROS and RNS Sources in AT

ROS is a family of free radicals, including superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$). Nitrogen-containing species, referred to as RNS, include nitric oxide ($NO^{\bullet}$) and its derivatives peroxynitrite ($ONOO^-$), nitrous anhydride, and nitrogen dioxide ($NO_2^{\bullet}$) [4]. All cellular components of AT, including adipocytes,

fibroblasts, endothelial cells, and adipocyte progenitors, are sources of free radicals. Within each AT cell, these sources include the mitochondria, cytosol, endoplasmic reticulum, peroxisomes, plasma membrane, and phagosomes (Figure 1; for a detailed review, readers are referred to [5]).

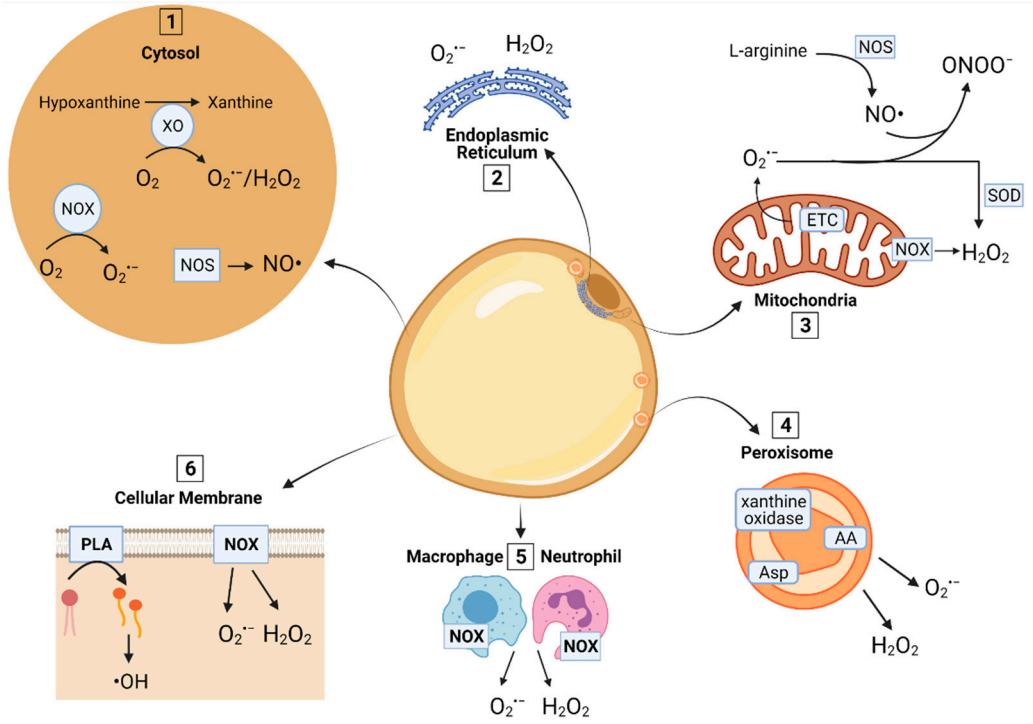


Figure 1. ROS and RNS sources in AT cells. (1) *Cytosol*: The oxidation of hypoxanthine to xanthine by xanthine oxidoreductase (XO) produces superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2). Nitric oxide synthase (NOS) produces nitric oxide ($NO^{\bullet}$). (2) *Endoplasmic reticulum*: Oxidative protein folding, carbohydrate addition, disulfide bond formation, and desaturation of FA generate $O_2^{\bullet-}$ and H_2O_2. (3) *Mitochondria*: $O_2^{\bullet-}$ is produced by complexes I and III of the electron transport chain (ETC). $O_2^{\bullet-}$ is then converted to H_2O_2 by superoxide dismutase (SOD), or to peroxynitrite ($ONOO^-$) in the presence of $NO^{\bullet}$. (4) *Peroxisomes*: $O_2^{\bullet-}$ and H_2O_2 are produced during FA oxidation by peroxisomal enzymes such as amino acids (AA), aspartate (Asp), and xanthine oxidases. (5) *Macrophages and neutrophils*: Generate $O_2^{\bullet-}$ and H_2O_2 by nicotinamide adenine dinucleotide phosphate oxidase (NOX) during the respiratory burst. NOX in the cytosol, cellular membrane, and mitochondria also produces $O_2^{\bullet-}$ and H_2O_2. (6) *Cellular membrane*: Phospholipases (PLA) hydrolyze phospholipids to produce free fatty acids, which are later oxidized by cyclooxygenases and lipoxygenases, releasing hydroxyl radicals ($^{\bullet}OH$).

2.1. Mitochondria

The production of ROS in the mitochondria is extensively reviewed [5,6]. In short, the mitochondrial electron transport chain generates $O_2^{\bullet-}$, which is the initial ROS formed, mainly at complexes I and III. Superoxide dismutase (SOD) catalyzes the dismutation (i.e., oxidation and reduction) of $O_2^{\bullet-}$ to molecular oxygen and the less harmful and reactive compound H_2O_2. During negative energy balance-induced lipolysis, mitochondrial FA oxidation is rapidly increased, and consequently, the electron transport chain activity is enhanced. Oxidation of FA generates more $O_2^{\bullet-}$ and H_2O_2 than that of amino acid or carbohydrate metabolites [7]. Therefore, AT is at a higher risk for developing OS during periods of negative energy balance.

2.2. Peroxisomes

After the mitochondria, peroxisomes are the most abundant source of $O_2^{\bullet-}$ and H_2O_2 in adipocytes [8]. This is because peroxisomes have relatively high FA oxidation activity (α and β) and contain active enzymes that generate free radicals such as amino acid, aspartate,

and xanthine oxidases. Like in the mitochondria, as lipolysis increases, the concentration of free FA available for oxidation rises, thus enhancing free radical production.

2.3. Cytosol

Several enzymatic and non-enzymatic reactions that occur in the cytosol release free radicals. (1) The metabolism of purines and other nitrogenous bases, especially the oxidation of hypoxanthine to xanthine by xanthine oxidoreductase, produces $O_2^{\bullet -}$ and H_2O_2 [9]. Diseases that induce hypoxia conditions in the AT, such as obesity, enhance the activity of xanthine oxidoreductase [10]. (2) Nicotinamide adenine dinucleotide phosphate oxidase (NOX) enzymes are another critical source of $O_2^{\bullet -}$ and H_2O_2 in the cytosol and mitochondria. In adipocytes, NOX4 is abundantly expressed, and its activity releases H_2O_2 [11]. In fact, silencing NOX4 in rat adipocytes inhibits ROS generation during metabolic stress induced by palmitate and glucose exposure [12]. In contrast, moderate NOX4 activation by non-steroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin and naproxen) reduces the production of cyclic adenosine monophosphate (cAMP), and the activation of protein kinase A leading to lipolysis inhibition [13].

2.4. Cellular Membrane

Major ROS generators in AT cellular membranes include enzymatic reactions by phospholipases (PLA), NOX, and non-enzymatic peroxidation of lipids. PLA are present in all AT cellular components. Different isoforms of PLA2 are abundantly expressed in adipocytes, including a specific adipose isoform AdPLA [14]. PLA hydrolyze phospholipids releasing FA. Among FA, polyunsaturated FA (PUFA) are the most abundant in cellular membranes. Once released by PLA2, PUFA are oxidized by cyclooxygenases and lipoxygenases to produce tyrosyl radicals, $^{\bullet}OH$, and oxylipids, including several peroxides [15,16]. Similar to $O_2^{\bullet -}$ and H_2O_2, $^{\bullet}OH$ damages intracellular proteins and lipids.

Membrane-bound NOX enzymes are the primary source of ROS from cellular membranes. Adipocyte-specific NOX4 knockout (KO) protects the carrier mice against insulin signaling dysregulation, which is one of the pathological changes leading to AT inflammation and impaired insulin sensitivity [11]. Within the AT, both macrophages and neutrophils use NOX enzymes to generate $O_2^{\bullet -}$ and H_2O_2 from oxygen to fuel the respiratory burst reaction that is essential for their phagocytic activity [17]. Obesity and metabolic syndrome in humans are associated with infiltration and M1 phenotype polarization of macrophages. M1 macrophages have a more effective respiratory burst than M2 cells that facilitates their phagocytic activity ([18] and reviewed in [19]). However, chronic infiltration of M1 macrophages exacerbates ROS production in AT, leading to OS. In veterinary species, similar to humans, changes in macrophage phenotype polarization are associated with ROS production and OS. We demonstrated that in cows with periparturient metabolic stress that develop hyperketonemia and displaced abomasum, AT macrophages become polarized to the M1 phenotype [20]. Cows challenged with these adverse health events exhibit OS in AT [21].

2.5. Endoplasmic Reticulum (ER)

The ER in adipocytes synthesizes adipokines such as leptin and adiponectin. The structure of the latter is particularly complex as it is secreted in the form of multimers. To produce these types of proteins, adipocytes' ER relies on oxidative protein folding and other post-translational structural modifications (e.g., carbohydrate addition and disulfide bond formation) that generate $O_2^{\bullet -}$ and H_2O_2 [22]. The level of H_2O_2 is rapidly reduced by adiporedoxin, an adipocyte-specific peroxiredoxin (Prx) [23]. The adipocyte ER is very sensitive to changes in its redox status, and when ER stress develops due to OS, secretion of adiponectin and other adipokines is suppressed. An additional source of ROS in the ER is the desaturation of FA. This process involves the action of desaturases (e.g., stearoyl-CoA desaturase-1) and cytochrome b_5 that generate $O_2^{\bullet -}$ as a byproduct (reviewed extensively

in [24]). During lipolysis, increased availability of saturated FA, substrates for desaturation reactions, may drive ROS production by desaturases.

2.6. Production of RNS

Nitric oxide synthases (NOS) convert L-arginine to $NO^{\bullet}$ and L-citrulline [5]. There are three known isoforms of NOS, endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). Studies performed using subcutaneous human AT [25] and rat adipocytes [26] show that both eNOS and iNOS, but not nNOS, are expressed in AT and fat cells. Hence, eNOS and iNOS are responsible for the production of $NO^{\bullet}$ within AT. Mechanistic evidence provided by eNOS KO mice demonstrates that the absence of eNOS activity, and consequently $NO^{\bullet}$, limits the development of redox signaling dysregulation related disorders [27]. RNS can also interact with ROS to produce other reactive species. For example, $NO^{\bullet}$ reacts with $O_2^{\bullet -}$ to produce $ONOO^-$ [4]. Most studies evaluating the effect of $NO^{\bullet}$ on lipolysis and lipogenesis have used an indirect approach through $NO^{\bullet}$ donors, scavengers, and NOS inhibitors. This is because the interaction between $NO^{\bullet}$ and oxygen makes it difficult to study its isolated function. The direct effect of $NO^{\bullet}$ on lipid mobilization, independent of its interaction with oxygen, remains to be explored.

3. Redox Signaling and Lipolysis

Within adipocytes, the process of lipolysis involves sequential hydrolysis of triglycerides (TAG). First, adipose tissue triglyceride lipase (ATGL) hydrolyses TAG into diacylglycerol (DAG) and releases a FA molecule. Hormone-sensitive lipase (HSL) hydrolyzes DAG to monoacylglycerol, which is then further broken down into FA and glycerol by monoacylglycerol lipase (reviewed in detail by [28]). The activation of ATGL and HSL is triggered by two major lipolytic pathways, classic and inflammatory, that involve several redox signaling mechanisms at different steps during the process, including cellular membrane receptors, protein kinases, and cytoplasmic enzymes.

The classic lipolytic pathway initiates by the activation of cell membrane β-adrenergic and growth hormone receptors, which in turn trigger the activity of adenylyl cyclase (AC), an enzyme that generates cAMP. The latter is a second messenger that starts intracellular signaling cascades through protein kinases. In contrast, the inflammatory lipolytic pathway is triggered through toll-like receptor 4 [29] and IL-6 cytokine receptors [30]. Lipolytic signals reach the neutral lipases (ATGL, HSL) through a series of protein phosphorylations involving protein kinases (PKA, PKC, PKG). The phosphorylation of ATGL co-activator CGI-58, perilipin 1 (PLIN1; lipid droplet coating), and HSL by protein kinases ultimately trigger lipolysis. ROS and RNS can alter the lipolytic pathways at various control points ranging from cellular membrane receptors to neutral lipase activation. However, the effect depends on the concentration, reactivity, and source of the reactive species. Below we summarize the impact of different ROS and RNS on the components of the lipolytic pathways (Figure 2).

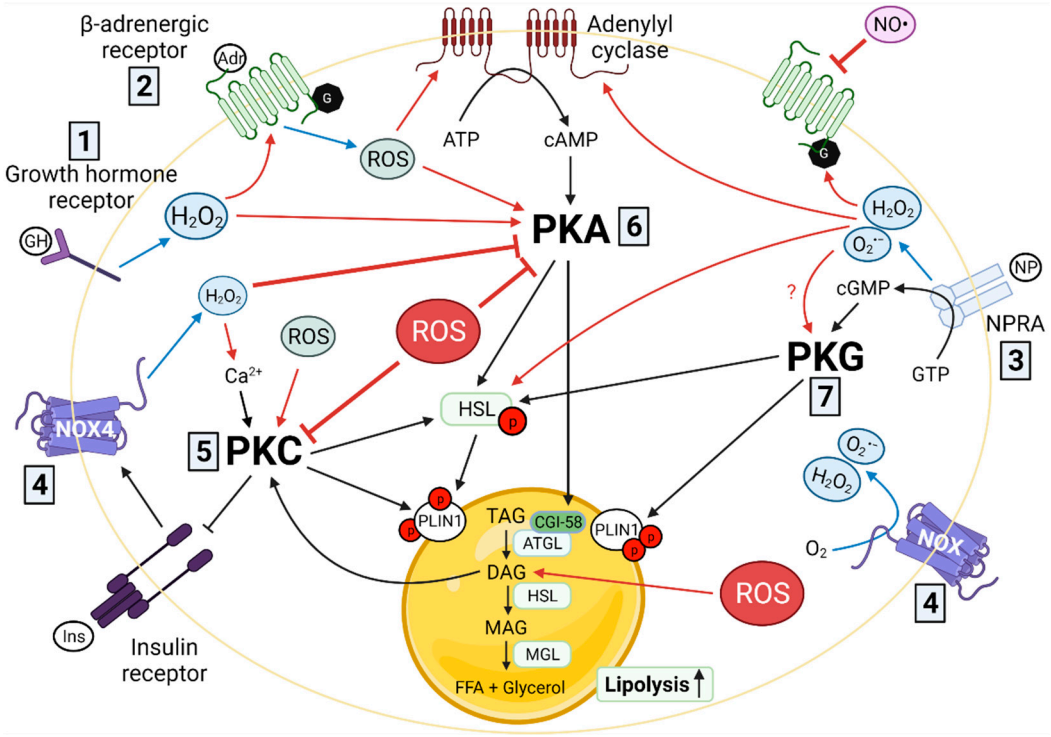


Figure 2. Redox signaling and lipolysis. ROS and RNS alter lipolytic pathways at different points. (1) *Growth hormone receptor*: ROS, especially H_2O_2, production increases upon growth hormone (GH) binding to the growth hormone receptor, consequently activating β-adrenergic receptor (βAR), adenylyl cyclase (AC), and protein kinases downstream, increasing lipolysis. (2) *β-adrenergic receptor*: Adrenalin (Adr) binds to βAR and increases the production of ROS. $O_2^{\bullet-}$ and H_2O_2 also oxidize βAR, increasing adipocyte sensitivity to lipolysis. On the other hand, NO• suppresses βAR activation. (3) *Natriuretic peptide receptor*: $O_2^{\bullet-}$ and H_2O_2 produced upon activation of NPRA enhance the activation of βAR, AC, and cAMP synthesis, increasing lipolysis. (4) *Nicotinamide adenine dinucleotide phosphate oxidase*: NOX converts O_2 to $O_2^{\bullet-}$ and H_2O_2. Moreover, insulin, through the production H_2O_2 by NOX4, inhibits PKA activation, reducing adrenergic stimulated lipolysis. (5) *Protein kinase C (PKC)*: at high concentration, $O_2^{\bullet-}$ and H_2O_2 activate PKC through the release of diacylglycerol (DAG) or may inactivate it by impairing its substrate-binding affinity. At low concentrations, ROS activate PKC by oxidizing its structural cysteine residues. H_2O_2 activates PKC by increasing Ca^{2+} concentrations. (6) *Protein kinase A (PKA)*: at high concentration, ROS inhibit cAMP-dependent PKA, but at low concentration, ROS prolong the activation of PKA by inhibiting the phosphatase that suppresses it. (7) *Protein kinase G (PKG)*: it is currently unknown how ROS affect PKG activity in adipocytes. Black arrows represent the classic lipolytic pathway, blue arrows represent the production of ROS/RNS, and red arrows represent the effect (activation or inhibition) of ROS/RNS.

3.1. Cell Membrane Receptors

3.1.1. β-Adrenergic Receptors

G protein-coupled β-adrenergic receptors (βAR) are an integral part of the plasma membrane that bind to adrenaline and other vasoactive amines. Adipocytes express the three types of β-adrenergic receptors (β1AR, β2AR, and β3AR), and their activation induces lipolysis through PKA mediated signaling [31]. βAR signaling regulates and is regulated by redox signaling. Upon binding to adrenalin, βAR increase ROS production in a NOX and time-dependent manner [32]. At the same time, $O_2^{\bullet-}$ and H_2O_2 can oxidize βAR by sulfenation [33]. This structural change increases the number of ligand binding sites on the βAR receptor, possibly increasing the sensitivity of adipocytes to lipolysis induced by vasoactive amines [32].

On the other hand, RNS, such as NO• and related species, affect the lipolytic pathway by suppressing the activation of the βAR. For example, nitroglycerine, a NO• donor, reduces βAR-stimulated lipolysis [34]. Likewise, *S*-nitroso-*N*-acetyl-D,L-penicillamine (SNAP), another NO• donor, decreases βAR-stimulated lipolysis and cAMP production.

SNAP does not affect dibutyryl cAMP (protein kinase activator), IBMX (phosphodiesterase activator), or forskolin (AC activator) stimulated lipolysis [35]. Moreover, inhibition of $NO^{\bullet}$ enhances βAR-stimulated lipolysis [36].

3.1.2. Growth Hormone Receptor

This class 1 cytokine receptor family member induces lipolysis in adipocytes upon binding to growth hormone (GH). Lipolysis induced by GH is particularly intense during prolonged fasting or states of negative energy balance, such as early lactation in dairy cows [37,38]. The mechanism of action for GH-induced lipolysis involves the activation of βAR 1 and 3 [39] and AC [40]. This increases ROS, including H_2O_2, generation at the growth hormone receptor-GH peptide interface within the cellular membrane. These ROS are ultimately responsible for the activation of the βAR, AC, and protein kinases, leading to lipolysis [41].

3.1.3. Natriuretic Peptide Receptors

Subtypes expressed in AT include type A (NPRA), a transmembrane protein, and NPRC, a G protein-linked receptor. These two receptors bind to natriuretic peptides (NP) and cause lipolytic effects in adipocytes [42]. The NP family includes the atrial-, brain-, and C-type NPs. Upon binding to NPRA, NPs activate guanylyl-cyclase, leading to the production of cyclic guanosine monophosphate (cGMP), which triggers the action of protein kinase G [43]. The latter phosphorylates HSL and PLIN1, leading to lipolysis activation. As with the GH receptor, activation of NPRA increases the generation of $O_2^{\bullet -}$ and H_2O_2 in a dose and NOX2 dependent manner, possibly leading to the stimulation of βAR [44].

3.2. Adenylyl and Guanylyl Cyclases and Their Cyclic Nucleotide Products (cAMP, cGMP)

The adenylyl cyclase/cAMP system is the target of many cell membrane receptors upon activation (e.g., βAR, NPRA). cAMP, a primary second messenger in cellular signaling, is synthesized by AC from ATP. There are at least nine subtypes of membrane-bound AC, and of those, II, IV, V, and VI are detectable in adipocytes [45]. These enzymes have 12 transmembrane domains and 2 cytoplasmic domains. Both $O_2^{\bullet -}$ and H_2O_2 enhance the activation of membrane-bound AC and the synthesis of cAMP, triggering lipolysis [46,47]. The reduction of cAMP protects against OS by upregulating the expression of the antioxidant MnSOD. Particularly, AC5 KO mice model protects against obesity and diabetes by reducing OS in AT. This finding highlights AC's as a critical target of ROS activity [48–50].

Guanylyl cyclase (GC) synthesizes cGMP from guanosine triphosphate. There are seven cell membrane-bound GCs. Of these, GC-A is specific for the lipolytic agent atrial NP (reviewed extensively in [51]). It is currently unknown if ROS or RNS modulate the activity of cell membrane-bound GCs. In contrast, soluble GC is activated by $NO^{\bullet}$ [52]. However, the lipolytic effect of soluble GC is unknown as the activity of this enzyme is compartmentalized intracellularly [53].

3.3. Protein Kinases

3.3.1. cAMP-Dependent Protein Kinase A (PKA)

The binding of cAMP to PKA releases its catalytic subunit initiating the phosphorylation of targets including HSL, PLIN1, and CGI-58 that activate lipolysis [54]. ROS generated by the oxidizing agent diamide at high concentrations (0.5 mM) can directly inhibit PKA activity by oxidizing a highly reactive cysteine in its catalytic subunits [55]. However, at low concentrations (100 μM), diamide can inactivate the phosphatases that inhibit PKA and thus prolong the lipolytic stimulus [54]. On the other hand, low concentrations (nano to micromolar) of intracellular H_2O_2 inactivate PKA, and this is the mechanism by which insulin reduces adrenergic stimulated lipolysis [56]. This signaling mechanism, also termed the redox paradox, is mediated by NOX4 production of H_2O_2 upon insulin binding to its receptor [57].

3.3.2. Protein Kinase C (PKC)

This family of enzymes includes at least ten isoforms (α, β1, β2, γ, δ, ε, η, θ, D1, D2, D3). The conventional subfamily (α, β1, β2) requires DAG and Ca^{2+} for activation while the novel group (ε, η, θ) only requires DAG [58]. PKC activation induces lipolysis as this enzyme can phosphorylate HSL, perilipin, and possibly CGI-58 [59]. PKC-induced lipolysis is triggered by toll-like receptor activation, making it one of the kinases involved in the inflammatory lipolytic pathway [60]. ROS enhance or reduce PKC activity by different mechanisms. First, high concentrations of $O_2^{\bullet -}$ and H_2O_2 can activate phospholipase C, releasing DAG from cellular membranes and activating PKC [61]. Second, H_2O_2 can increase intracellular concentrations of Ca^{2+} and therefore favor PKC activation [62]. Finally, $O_2^{\bullet -}$ and H_2O_2 at low concentrations can oxidize structural cysteine residues of PKC, leading to its activation. On the other hand, at high concentrations, $O_2^{\bullet -}$ and H_2O_2 inactivate PKC by impairing its substrate-binding affinity in a mechanism similar to the inactivation of PKA by ROS [63].

3.3.3. cGMP-Dependent Protein Kinase G (PKG)

There are two types of PKG, I and II. In adipocytes, PKG-I phosphorylates HSL and PLIN1 when cells are stimulated with atrial-NP [64]. Although it is currently unknown how ROS and RNS may modulate PKG-I activity in adipocytes, research in smooth muscle cells indicates that ROS and RNS activate the enzyme by oxidant-induced disulfide formation [65]. It is unclear whether or not high concentrations of ROS can inactivate PKG-I.

3.4. Lipases

3.4.1. Hormone-Sensitive Lipase

HSL is considered the rate-limiting enzyme for demand lipolysis. High and low ROS concentrations modulate the lipolytic activity of this neutral lipase. Reducing ROS concentrations with the antioxidants diphenyl iodonium (DPI), N-acetyl cysteine (NAC) and resveratrol inhibited lipolysis in human adipocytes [66]. DPI decreased both basal and forskolin (AC activator)-stimulated lipolysis. This effect is mediated by reducing the phosphorylation of an essential serine residue, Ser522, in HSL. It should be noted that all three antioxidants prevent the translocation of HSL from the cytosol to the lipid droplet under forskolin-stimulated lipolysis. Interestingly, scavenging ROS does not alter the expression of cAMP and PKA, suggesting that DPI inhibits lipolysis through direct action on HSL [66]. Aligning with this observation, Zhou, et al. [67] demonstrated that $O_2^{\bullet -}$ and H_2O_2 can induce phosphorylation of HSL; however, their experiments did not evaluate if the mechanisms of action involved changes in the active sites of HSL.

3.4.2. Adipose Tissue Triglyceride Lipase

ATGL is the rate-limiting enzyme of basal lipolysis in adipocytes and intracellular lipolysis in other cells. ATGL activation is dependent upon the phosphorylation of its co-activator CGI-58 [68]. It is currently unknown if ROS or RNS directly modify the structures or binding properties of ATGL or CGI-58.

3.5. Redox Signaling Dysregulation and Lipolysis

A common pathological change in metabolic diseases is excessive and protracted lipolysis that is accompanied by AT immune cell infiltration and inflammation, cellular proliferation, and extracellular matrix changes [69,70]. Macrophages and neutrophils are the primary cells infiltrating AT. Upon activation, the respiratory burst in these cells releases ROS through a NOX-dependent process. Excessive NOX3 and NOX4 stimulation during AT inflammation enhances ROS concentrations and impairs insulin signaling in adipocytes, further intensifying lipolysis [11,71]. As AT's free radical content increases, the organ becomes dysfunctional. For example, in obesity, a state of chronic inflammation leads to the overproduction of proinflammatory cytokines, including TNF-α, IL-1, and IL-6 in adipocytes [72]. These cytokines promote lipolysis and decrease insulin sensitivity,

resulting in AT dysfunction and systemic metabolic disturbances. On the other hand, in obese mice, apocynin, a NOX inhibitor, reduces AT ROS levels, restores dysregulated adipokine secretion, and improves hyperlipidemia and diabetes [73]. Hence, excessive production of free radicals is likely a critical mechanism for enhanced and dysregulated lipolysis in metabolic diseases.

4. Antioxidants and Lipolysis

As described above, ROS and RNS can enhance or limit lipolysis in adipocytes. However, dysregulated redox signaling can lead to OS when the production of oxidants exceeds the antioxidant system's capacity (readers refer to reviews on OS in AT [74–77]). To prevent OS, antioxidant mechanisms become active during lipolysis. For instance, in dairy cows, during periods of negative energy balance, the transcription networks related to antioxidants are activated to reduce pro-lipolytic effects and OS inducers [78]. Increasing evidence shows that antioxidants play a crucial role in regulating lipid mobilization during inflammatory diseases by scavenging free radicals. The AT antioxidant system consists of enzymatic antioxidants, including catalase (CAT), peroxiredoxins (Prxs), and glutathione peroxidase (GPx). The antioxidant activity in AT is regulated at the transcription level by different cell signaling proteins and transcription factors. Non-enzymatic antioxidants such as exogenous antioxidants commonly derived from dietary sources can also enhance AT's antioxidant capacity. We will further explain the contributions of enzymatic and non-enzymatic antioxidants to lipid mobilization in AT in the next section (summarized in Figure 3).

4.1. Catalase

CAT, an antioxidant enzyme produced by peroxisomes, catalyzes the breakdown of H_2O_2 into O_2 and water. In mammals, CAT is expressed in the liver, kidney, and AT. The antioxidant capacity of CAT is severely diminished in diseases that involve AT inflammation, such as human obesity [73]. In rodent models of obesity, CAT inhibits lipolysis and prevents non-alcoholic fatty liver disease (NAFLD) by scavenging peroxisomal H_2O_2. The capacity of CAT to reduce lipolysis was demonstrated in CAT KO mice (CKO). These animals have heightened plasma TAG, Free FA, and insulin when fed a high-fat diet (HFD) [79]. Although not demonstrated in AT, HSL activity in the liver was enhanced while ATGL expression decreased [80]. Moreover, CAT deficient cells have more pronounced lipogenesis compared with those derived from wild-type animals [81]. Using the catalase inhibitor 3-amino-1,2,4-triazole, Nunes-Souza and colleagues [82] demonstrated that reduced CAT activity enhances lipolysis in an HSL-dependent manner. On the other hand, exogenous CAT administration eliminates the antilipolytic effect of H_2O_2 in the presence of epinephrine [83].

4.2. Peroxiredoxins

Prxs are a family of antioxidant enzymes that catalyze the reduction of organic hydroperoxides, H_2O_2, and $ONOO^-$ [84]. PRDX6, an enzyme belonging to the Prxs family, plays a crucial role in decreasing ROS following OS during inflammatory diseases [85]. PRDX6 KO mice fed a HFD exhibited a higher lipolysis rate reflected by increased ATGL expression and serum Free FA compared with wild-type animals. Moreover, in these mice, insulin failed to suppress AT lipolysis [86]. Likewise, PRDX3 KO murine adipocytes display greater HSL and lipoprotein lipase gene expression [87]. Taken together, these results demonstrate that the peroxiredoxins inhibit lipolysis in AT.

4.3. Glutathione Peroxidase

GPx is a family of enzymatic antioxidants that reduce H_2O_2 to water, protecting against lipid peroxidation. It is well established that GPx serum concentration and AT expression are dysregulated during human obesity and metabolic disorders [88–90]. GPx alters lipid metabolism; however, its direct role on the lipolytic pathway is unknown.

Some evidence suggests that GPx activity may inhibit lipolysis. The mRNA expression of GPx3 in AT is higher in lean and insulin-sensitive individuals than in those obese and insulin-resistant [91]. Overexpression of GPx1 in mice increases body weight compared with wild-type littermates [92]. This phenotype could be related to a reduction in lipolysis. Alloxan, a toxic glucose analog that generates ROS, increases lipolysis by decreasing glutathione content in adipocytes. This response is accompanied by the impairment of the redox state of the glutathione system [93].

4.4. Apelin

The adipokine apelin, secreted by adipocytes in both mice and human cells, is known for its anti-obesity and anti-diabetic properties. Its levels increase in obese patients, especially in hyperinsulinemia-associated obesity [94]. Apelin binds to its G-protein coupled receptor and suppresses the production and release of ROS by promoting the expression of antioxidant enzymes (SOD, CAT, and GPx) through the ERK/AMPK pathway. Moreover, it suppresses the expression of pro-oxidant enzymes such as NOX [95]. In rat adipocytes, apelin inhibits basal lipolysis through AMPK-dependent increases in perilipin expression. At the same time, this adipokine reduces βAR-induced lipolysis by abrogating the phosphorylation of HSL at Ser-563 [96,97]. These effects are also observed in vivo, where apelin-KO mice have significantly higher serum FA and glycerol compared to wild-type mice, yet this effect is abrogated after apelin infusions [97]. To summarize, apelin decreases lipolysis by stimulating antioxidant expression.

4.5. Nuclear Factor E2-Related Factor 2 (Nrf2)

Nrf2 is a basic leucine zipper (bZIP) protein associated with the cytoplasm. When cytoplasmic ROS levels increase, Nrf2 translocates to the nucleus and initiates the transcription of various antioxidant genes [98]. Nrf2 activation appears to reduce lipolysis in AT. In 3T3-L1 adipocytes, Nrf2 knockdown reduces H_2O_2-induced lipid accumulation. Nrf2 KO mice also have reduced transcription of lipogenic genes and increased ATGL and HSL activity when fed chow and HFDs [99]. Nrf2 activation in mice reduced HFD-induced lipid accumulation in white AT and HFD-induced obesity [100].

4.6. Antioxidant Supplementation

Under physiological conditions, endogenous antioxidants can prevent excessive ROS/RNS production. However, there is a continuous demand for exogenous sources such as selenium (Se) and vitamin E. These antioxidants are known to be effective in reducing OS in many human [101–103] and cattle [104] diseases. Se supplementation promotes adipocyte differentiation in AT; however, during obesity, it promotes lipolysis by activating the classic lipolytic pathway (PKA/HSL) in a dose-dependent manner [105]. Vitamin E supplementation improves insulin sensitivity in obese mice models and reduces plasma TAG levels [106]. Lastly, resveratrol, a naturally occurring phenolic compound, enhances lipid mobilization upon βAR activation but has no effect on basal lipolysis. At concentrations of10 μM, resveratrol increases βAR-stimulated lipolysis and impairs insulin's antilipolytic response [107]. Similar results are observed in rat adipocytes [108] and human AT explants [109] stimulated by epinephrine. It is important to note that ROS levels were not directly measured under these conditions.

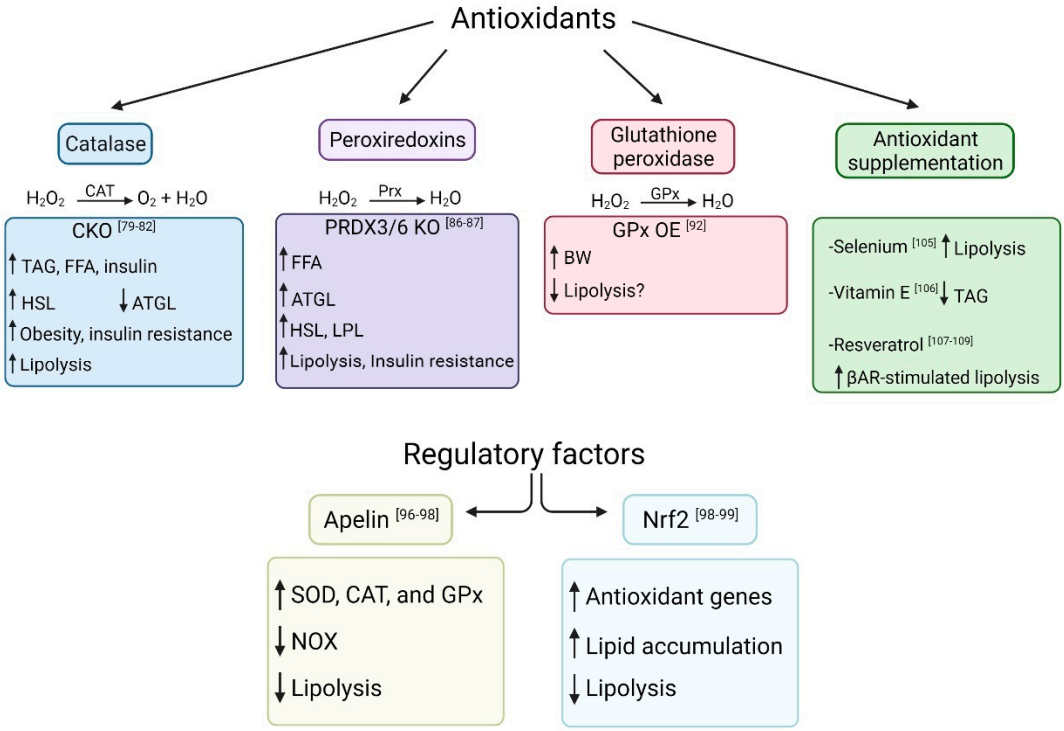
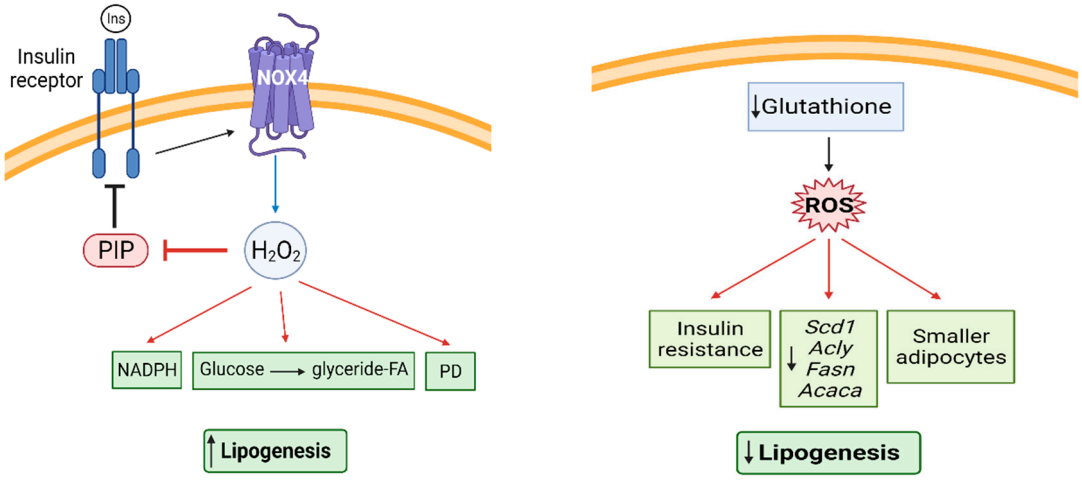


Figure 3. Antioxidant effect on lipolysis. *Catalase (CAT)*, an enzyme produced by peroxisomes, catalyzes the breakdown of H_2O_2 into O_2 and H_2O. CAT knockout models (CKO) fed a high-fat diet (HFD) have a higher lipolysis rate and are more susceptible to obesity and insulin resistance compared to wild-type littermates. *Peroxiredoxins (Prx)* catalyze the reduction of H_2O_2. Prx3/6 knockout mice (PRDX3/6 KO) have increased lipolysis and insulin resistance. *Glutathione peroxidase (GPx)* catalyzes the breakdown of H_2O_2 to water. GPx overexpression results in an increase in body weight (BW) possibly by decreasing lipolysis. *Selenium* promotes lipolysis during obesity. *Vitamin E* decreases plasma triacylglycerol (TAG). *Resveratrol* increases β-adrenergic receptor (βAR)-stimulated lipolysis and impairs insulin's antilipolytic effect. *Apelin* decreases lipolysis by promoting the expression of antioxidant enzymes (superoxide dismutase (SOD), CAT, and GPx) and suppressing the expression of nicotinamide adenine dinucleotide phosphate oxidase (NOX). *Nuclear factor E2-related factor 2 (Nrf2)* increases lipid accumulation and decreases lipolysis.

5. Redox Signaling and Lipogenesis

Reactive species can also modulate the lipogenic pathway. Lipogenesis refers to FA and TAG synthesis, which takes place in both the liver and AT. Within AT, TAG can be hydrolyzed to release FA by lipoprotein lipase (LPL) [110]. FA then enter adipocytes through fatty acid transporters such as CD36 and fatty acid transport protein-1 (FATP1) [108]. These FA can be esterified to form TAG and stored in the lipid droplet. Alternatively, in *de novo* lipogenesis, circulating carbohydrates are converted into FA that are then used for synthesizing TAG or other lipid molecules. This process can be stimulated by insulin through *GLUT4*, which triggers glucose uptake by adipocytes [111]. Some of the rate-limiting enzymes in lipogenesis include fatty acid synthase (*Fasn*), diacylglycerol O-acyltransferase 1 (*Dgat1*), stearoyl-CoA desaturase-1 (*Scd1*), and acetyl-CoA carboxylase (*Acaca*). Many studies have shown that redox signaling modulates lipogenesis mainly through H_2O_2 (Figure 4).



(**a**) (**b**)

Figure 4. Redox signaling and lipogenesis. (**a**) H_2O_2 acts as a secondary messenger of insulin in adipocytes by suppressing the oxidation of protein tyrosine phosphatases (PIP), thus facilitating insulin signaling. H_2O_2 also increases lipogenesis by increasing NADPH and glucose incorporation into glyceride-FA, and stimulating pyruvate dehydrogenase (PD); (**b**) enhanced Fat ROS, through the depletion of glutathione in adipocytes, decreases insulin sensitivity, reduces lipogenic gene expression, and display smaller adipocytes.

5.1. H_2O_2 and Lipogenesis

For decades, H_2O_2 has been suggested to play an essential role in cellular events, including glucose transport and uptake. More specifically, it is the second messenger of insulin in adipocytes [112]. At low concentrations, it inhibits the oxidation of protein tyrosine phosphatases, thus facilitating insulin signaling [57]. In rat adipocytes, H_2O_2 (0.15–0.5 mM) was shown to stimulate glucose carbon incorporation into glyceride-FA [113]. H_2O_2 increases lipogenesis by enhancing substrate transport and NADPH along with stimulating pyruvate dehydrogenase. This effect is abolished in the presence of CAT [83]. The concentration of H_2O_2 is a major factor in determining whether it enhances or suppresses lipogenesis in AT since OS has been shown to cause insulin resistance and impair lipolysis inhibition [114,115].

5.2. FA and TAG Synthesis

ROS increase lipid synthesis by promoting glucose use to synthesize lipids. Increasing ROS production with acetoacetate (Acoc, 20 mM) activates *de novo* lipogenesis in human adipocytes by enhancing glucose conversion to FA. Acoc also induces lipolysis, but the lipolytic rate does not exceed the rate of lipogenesis [116]. Treatment of mature 3T3-L1 adipocytes with the natural antioxidant in lyophilized cranberries decreases ROS levels by 29.3% and lipid accumulation in a dose-dependent manner. This is also accompanied by an increase in basal lipolysis [117].

The generation of mice with genetically manipulated ROS in adipocytes allows us to understand better the role of ROS in lipid synthesis. Through the overexpression of CAT and SOD1, Fat ROS-eliminated mice display enhanced insulin sensitivity and AT expansion. *De novo* lipogenesis in WAT from these mice is enhanced and is associated with increased expression of FA-synthesizing genes (*Acly*, *Scd1*, *Fasn*, and *Acaca*). On the contrary, mice with enhanced content of ROS in adipose depots, through the depletion of adipocyte glutathione, exhibit smaller-sized adipocytes with decreased expression of lipogenic genes (*Acly*, *Scd1*, *Fasn*, *Acaca*, and *Srebf1*). ROS-induced downregulation of lipogenic genes appears to be mediated through the suppression of sterol-regulatory element-binding transcription factor 1 transcriptional activity in rat adipocytes [116]. Similarly, octanoate,

a medium-chain FA, inhibits lipogenesis through the decrease of key lipogenic genes including *LPL, Fasn*, and diacylglycerol acyltransferase 2 in rat adipocytes [118]. This response may be mediated through the generation of ROS. These results suggest that ROS production in adipocytes might directly inhibit *de novo* lipogenesis.

6. Redox Signaling and Dairy Cows' Lipid Mobilization

Similar to humans and other animal models, alterations in redox signaling, and the consequent development of OS, act as a determining factor in abnormal inflammatory responses in the AT of dairy cows, especially during the periparturient period [119–121]. This segment of the lactation cycle, spanning from 3 weeks before calving until 3 weeks postpartum, is characterized by intense lipolysis and limited lipogenesis. As a consequence, the AT generates vast amounts of ROS. Significant sources of ROS in periparturient cows' AT include mitochondrial activity and the production of oxidized fatty acids, termed oxylipids. We demonstrated that lipolysis is determinant in the biosynthesis of oxylipids as it provides abundant substrates (unsaturated FA) for their biogenesis by enzymatic and non-enzymatic reactions [122]. Higher maternal ROS metabolites in blood, especially in cows with high body condition scores, are associated with greater lipolysis [123]. Moreover, enhanced energy needs for fetal growth and lactogenesis, increase mitochondrial respiration that in turn enhances $O_2^{\bullet -}$ and H_2O_2 production. More research is needed on the activity of other major sources of ROS, such as peroxisomes and ER, and RNS in AT of periparturient cows to better direct nutritional or pharmacological interventions aimed at minimizing OS.

As AT lipolysis intensity increases postpartum, the antioxidant defenses of AT become active. The transcription of GPx system components, including glutathione peroxidase 1 and transaldolase 1, is upregulated as well as the protein abundance of glutathione S-transferase mu 1 [124]. Other physiological conditions associated with an intense lipolytic response also trigger antioxidant defenses in dairy cows. For example, a proteomics analysis performed in dairy cows with heat stress identified the Nrf2 OS response components as one of the top canonical pathways upregulated compared to control cows [78]. A comprehensive characterization of OS during the periparturient period or health events in AT of dairy cows is currently lacking. However, there is evidence for the presence of OS in AT of these cows as we detected isoprostanes, the gold standard OS biomarker, in AT during the first three weeks after calving [125].

7. Conclusions and Future Prospective

To summarize, ROS/RNS regulate lipid mobilization in AT by modulating different lipolysis and lipogenic signaling pathways. Uncontrolled production of ROS favors lipolysis. However, one should not generalize about the direct effect of ROS and RNS on lipid mobilization since each species is unique in its function. Free radical actions will depend on the reactive species, its origin/source, concentration, and length of exposure. Likewise, AT antioxidant mechanisms function differently as they act on distinct ROS/RNS. More research is needed to determine the effect of specific antioxidants to optimize their clinical use and as nutritional supplements. Moreover, direct measurement of particular ROS or RNS, such as $O_2^{\bullet -}$ and $NO^{\bullet}$, is limited and complex. Therefore improving the sensitivity and specificity of ROS/RNS detection in AT is essential to expand our understanding of redox signaling and OS development.

Author Contributions: Conceptualization, U.A.-R. and G.A.C.; literature search, U.A.-R. and G.A.C.; writing—original draft preparation, U.A.-R. and G.A.C.; figures preparation U.A.-R.; writing—review and editing, U.A.-R. and G.A.C.; funding acquisition, G.A.C. Both authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Institute of Food and Agriculture, US Department of Agriculture, grant numbers 2019-67015-29443 and 2021-67015-34563. And the College of Veterinary Medicine Graduate Office Fellowship Fund, Summer 2020.

Acknowledgments: The authors thank Adam Lock, Miguel Chirivi, Madison N. Myers, C. Javier Rendon, and Kim Giessler for their comments and suggestions. All figures were created with BioRender.com, accessed on 31 May 2021.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ROS	Reactive oxygen species
RNS	Reactive nitrogen species
AT	Adipose tissue
TAG	Triacylglycerol
FA	Fatty acid
OS	Oxidative stress
$O_2^{\bullet -}$	Superoxide anion
H_2O_2	Hydrogen peroxide
$^{\bullet}OH$	Hydroxyl radical
$NO^{\bullet}$	Nitric oxide
$ONOO^-$	Peroxynitrite
$NO_2^{\bullet}$	Nitrogen dioxide
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
NOS	Nitric oxide synthases
ATGL	Adipose tissue triglyceride lipase
HSL	Hormone sensitive lipase
DAG	Diacylglycerol
AC	Adenylyl cyclase
βAR	β-adrenergic receptor
PKA	Protein kinase A
PKC	Protein kinase C
PKG	Protein kinase G
Prx	Peroxiredoxin
CAT	Catalase
GPx	Glutathione peroxidase
SOD	Superoxide dismutase
LPL	Lipoprotein lipase

References

1. Halliwell, B. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol.* **2006**, *141*, 312–322. [CrossRef]
2. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 8416763. [CrossRef]
3. Lykkesfeldt, J.; Svendsen, O. Oxidants and antioxidants in disease: Oxidative stress in farm animals. *Vet. J.* **2007**, *173*, 502–511. [CrossRef]
4. Radi, R. Peroxynitrite, a Stealthy Biological Oxidant*. *J. Biol. Chem.* **2013**, *288*, 26464–26472. [CrossRef]
5. Di Meo, S.; Reed, T.T.; Venditti, P.; Victor, V.M. Role of ROS and RNS Sources in Physiological and Pathological Conditions. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 1245049. [CrossRef]
6. Murphy, M.P. How mitochondria produce reactive oxygen species. *Biochem. J.* **2009**, *417*, 1–13. [CrossRef] [PubMed]
7. Perevoshchikova, I.V.; Quinlan, C.L.; Orr, A.L.; Gerencser, A.A.; Brand, M.D. Sites of superoxide and hydrogen peroxide production during fatty acid oxidation in rat skeletal muscle mitochondria. *Free Radic. Biol. Med.* **2013**, *61*, 298–309. [CrossRef] [PubMed]
8. Liu, J.; Lu, W.; Shi, B.; Klein, S.; Su, X. Peroxisomal regulation of redox homeostasis and adipocyte metabolism. *Redox Biol.* **2019**, *24*, 101167. [CrossRef] [PubMed]
9. Kelley, E.E.; Khoo, N.K.; Hundley, N.J.; Malik, U.Z.; Freeman, B.A.; Tarpey, M.M. Hydrogen peroxide is the major oxidant product of xanthine oxidase. *Free Radic. Biol. Med.* **2010**, *48*, 493–498. [CrossRef]
10. Nagao, H.; Nishizawa, H.; Tanaka, Y.; Fukata, T.; Mizushima, T.; Furuno, M.; Bamba, T.; Tsushima, Y.; Fujishima, Y.; Kita, S.; et al. Hypoxanthine Secretion from Human Adipose Tissue and its Increase in Hypoxia. *Obesity* **2018**, *26*, 1168–1178. [CrossRef]
11. Den Hartigh, L.J.; Omer, M.; Goodspeed, L.; Wang, S.; Wietecha, T.; O'Brien, K.D.; Han, C.Y. Adipocyte-Specific Deficiency of NADPH Oxidase 4 Delays the Onset of Insulin Resistance and Attenuates Adipose Tissue Inflammation in Obesity. *Arter. Thromb. Vasc. Biol.* **2017**, *37*, 466–475. [CrossRef]

12. Han, C.Y.; Umemoto, T.; Omer, M.; Den Hartigh, L.J.; Chiba, T.; LeBoeuf, R.; Buller, C.L.; Sweet, I.R.; Pennathur, S.; Abel, E.D.; et al. NADPH Oxidase-derived Reactive Oxygen Species Increases Expression of Monocyte Chemotactic Factor Genes in Cultured Adipocytes*. *J. Biol. Chem.* **2012**, *287*, 10379–10393. [CrossRef]
13. Vázquez-Meza, H.; de Piña, M.Z.; Pardo, J.P.; Riveros-Rosas, H.; Villalobos-Molina, R.; Piña, E. Non-steroidal anti-inflammatory drugs activate NADPH oxidase in adipocytes and raise the H_2O_2 pool to prevent cAMP-stimulated protein kinase a activation and inhibit lipolysis. *BMC Biochem.* **2013**, *14*, 13. [CrossRef]
14. Duncan, R.E.; Sarkadi-Nagy, E.; Jaworski, K.; Ahmadian, M.; Sul, H.S. Identification and functional characterization of adipose-specific phospholipase A2 (AdPLA). *J. Biol. Chem.* **2008**, *283*, 25428–25436. [CrossRef]
15. Muralikrishna Adibhatla, R.; Hatcher, J.F. Phospholipase A2, reactive oxygen species, and lipid peroxidation in cerebral ischemia. *Free Radic. Biol. Med.* **2006**, *40*, 376–387. [CrossRef] [PubMed]
16. Yin, H.; Xu, L.; Porter, N.A. Free Radical Lipid Peroxidation: Mechanisms and Analysis. *Chem. Rev.* **2011**, *111*, 5944–5972. [CrossRef]
17. Robinson, J.M. Reactive oxygen species in phagocytic leukocytes. *Histochem. Cell Biol.* **2008**, *130*, 281–297. [CrossRef] [PubMed]
18. Lam, R.S.; O'Brien-Simpson, N.M.; Holden, J.A.; Lenzo, J.C.; Fong, S.B.; Reynolds, E.C. Unprimed, M1 and M2 Macrophages Differentially Interact with Porphyromonas gingivalis. *PLoS ONE* **2016**, *11*, e0158629. [CrossRef] [PubMed]
19. Tan, H.Y.; Wang, N.; Li, S.; Hong, M.; Wang, X.; Feng, Y. The Reactive Oxygen Species in Macrophage Polarization: Reflecting Its Dual Role in Progression and Treatment of Human Diseases. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 2795090. [CrossRef] [PubMed]
20. Contreras, G.A.; Kabara, E.; Brester, J.; Neuder, L.; Kiupel, M. Macrophage infiltration in the omental and subcutaneous adipose tissues of dairy cows with displaced abomasum. *J. Dairy Sci.* **2015**, *98*, 6176–6187. [CrossRef]
21. Sun, X.; Li, X.; Jia, H.; Loor, J.J.; Bucktrout, R.; Xu, Q.; Wang, Y.; Shu, X.; Dong, J.; Zuo, R.; et al. Effect of heat-shock protein B7 on oxidative stress in adipocytes from preruminant calves. *J. Dairy Sci.* **2019**, *102*, 5673–5685. [CrossRef] [PubMed]
22. Ozgur, R.; Turkan, I.; Uzilday, B.; Sekmen, A.H. Endoplasmic reticulum stress triggers ROS signalling, changes the redox state, and regulates the antioxidant defence of Arabidopsis thaliana. *J. Exp. Bot.* **2014**, *65*, 1377–1390. [CrossRef] [PubMed]
23. Jedrychowski, M.P.; Liu, L.; Laflamme, C.J.; Karastergiou, K.; Meshulam, T.; Ding, S.-Y.; Wu, Y.; Lee, M.-J.; Gygi, S.P.; Fried, S.K.; et al. Adiporedoxin, an upstream regulator of ER oxidative folding and protein secretion in adipocytes. *Mol. Metab.* **2015**, *4*, 758–770. [CrossRef]
24. Napier, J.A.; Michaelson, L.V.; Sayanova, O. The role of cytochrome b5 fusion desaturases in the synthesis of polyunsaturated fatty acids. *Prostaglandins Leukot. Essent. Fat. Acids* **2003**, *68*, 135–143. [CrossRef]
25. Elizalde, M.; Rydén, M.; van Harmelen, V.; Eneroth, P.; Gyllenhammar, H.; Holm, C.; Ramel, S.; Olund, A.; Arner, P.; Andersson, K. Expression of nitric oxide synthases in subcutaneous adipose tissue of nonobese and obese humans. *J. Lipid Res.* **2000**, *41*, 1244–1251. [CrossRef]
26. Ribiere, C.; Jaubert, A.M.; Gaudiot, N.; Sabourault, D.; Marcus, M.L.; Boucher, J.L.; Denis-Henriot, D.; Giudicelli, Y. White Adipose Tissue Nitric Oxide Synthase: A Potential Source for NO Production. *Biochem. Biophys. Res. Commun.* **1996**, *222*, 706–712. [CrossRef] [PubMed]
27. Shankar, R.R.; Wu, Y.; Shen, H.Q.; Zhu, J.S.; Baron, A.D. Mice with gene disruption of both endothelial and neuronal nitric oxide synthase exhibit insulin resistance. *Diabetes* **2000**, *49*, 684–687. [CrossRef]
28. Lafontan, M.; Langin, D. Lipolysis and lipid mobilization in human adipose tissue. *Prog. Lipid Res.* **2009**, *48*, 275–297. [CrossRef]
29. Zu, L.; He, J.; Jiang, H.; Xu, C.; Pu, S.; Xu, G. Bacterial endotoxin stimulates adipose lipolysis via toll-like receptor 4 and extracellular signal-regulated kinase pathway. *J. Biol. Chem.* **2009**, *284*, 5915–5926. [CrossRef] [PubMed]
30. Han, M.S.; White, A.; Perry, R.J.; Camporez, J.-P.; Hidalgo, J.; Shulman, G.I.; Davis, R.J. Regulation of adipose tissue inflammation by interleukin 6. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 2751–2760. [CrossRef]
31. Collins, S. β-Adrenoceptor Signaling Networks in Adipocytes for Recruiting Stored Fat and Energy Expenditure. *Front. Endocrinol.* **2012**, *2*. [CrossRef]
32. Rambacher, K.M.; Moniri, N.H. The β2-adrenergic receptor-ROS signaling axis: An overlooked component of β2AR function? *Biochem. Pharmacol.* **2020**, *171*, 113690. [CrossRef]
33. Burns, R.N.; Moniri, N.H. Agonist- and hydrogen peroxide-mediated oxidation of the β2 adrenergic receptor: Evidence of receptor s-sulfenation as detected by a modified biotin-switch assay. *J. Pharmacol. Exp. Ther.* **2011**, *339*, 914–921. [CrossRef]
34. Andersson, K.; Gaudiot, N.; Ribiere, C.; Elizalde, M.; Giudicelli, Y.; Arner, P. A nitric oxide-mediated mechanism regulates lipolysis in human adipose tissue in vivo. *Br. J. Pharmacol.* **1999**, *126*, 1639–1645. [CrossRef]
35. Gaudiot, N.; Jaubert, A.M.; Charbonnier, E.; Sabourault, D.; Lacasa, D.; Giudicelli, Y.; Ribière, C. Modulation of white adipose tissue lipolysis by nitric oxide. *J. Biol. Chem.* **1998**, *273*, 13475–13481. [CrossRef]
36. Jordan, J.; Tank, J.; Stoffels, M.; Franke, G.; Christensen, N.J.; Luft, F.C.; Boschmann, M. Interaction between beta-adrenergic receptor stimulation and nitric oxide release on tissue perfusion and metabolism. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 2803–2810. [CrossRef] [PubMed]
37. Sakharova, A.A.; Horowitz, J.F.; Surya, S.; Goldenberg, N.; Harber, M.P.; Symons, K.; Barkan, A. Role of growth hormone in regulating lipolysis, proteolysis, and hepatic glucose production during fasting. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 2755–2759. [CrossRef] [PubMed]
38. Contreras, G.A.; Strieder-Barboza, C.; Raphael, W. Adipose tissue lipolysis and remodeling during the transition period of dairy cows. *J. Anim. Sci. Biotechnol.* **2017**, *8*, 41. [CrossRef] [PubMed]

39. Yang, S.; Mulder, H.; Holm, C.; Edén, S. Effects of Growth Hormone on the Function of β-Adrenoceptor Subtypes in Rat Adipocytes. *Obes. Res.* **2004**, *12*, 330–339. [CrossRef] [PubMed]
40. Yip, R.G.; Goodman, H.M. Growth hormone and dexamethasone stimulate lipolysis and activate adenylyl cyclase in rat adipocytes by selectively shifting Gi alpha2 to lower density membrane fractions. *Endocrinology* **1999**, *140*, 1219–1227. [CrossRef] [PubMed]
41. DeYulia, G.J., Jr.; Cárcamo, J.M.; Bórquez-Ojeda, O.; Shelton, C.C.; Golde, D.W. Hydrogen peroxide generated extracellularly by receptor-ligand interaction facilitates cell signaling. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 5044–5049. [CrossRef] [PubMed]
42. Kovacova, Z.; Tharp, W.G.; Liu, D.; Wei, W.; Xie, H.; Collins, S.; Pratley, R.E. Adipose tissue natriuretic peptide receptor expression is related to insulin sensitivity in obesity and diabetes. *Obesity* **2016**, *24*, 820–828. [CrossRef] [PubMed]
43. Sengenès, C.; Berlan, M.; de Glisezinski, I.; Lafontan, M.; Galitzky, J. Natriuretic peptides: A new lipolytic pathway in human adipocytes. *FASEB J.* **2000**, *14*, 1345–1351. [CrossRef] [PubMed]
44. Fürst, R.; Brueckl, C.; Kuebler, W.M.; Zahler, S.; Krötz, F.; Görlach, A.; Vollmar, A.M.; Kiemer, A.K. Atrial Natriuretic Peptide Induces Mitogen-Activated Protein Kinase Phosphatase-1 in Human Endothelial Cells via Rac1 and NAD(P)H Oxidase/Nox2-Activation. *Circ. Res.* **2005**, *96*, 43–53. [CrossRef]
45. Serazin-Leroy, V.; Morot, M.; de Mazancourt, P.; Giudicelli, Y. Differences in type II, IV, V and VI adenylyl cyclase isoform expression between rat preadipocytes and adipocytes. *Biochim. Biophys. Acta (BBA) Protein Struct. Mol. Enzymol.* **2001**, *1550*, 37–51. [CrossRef]
46. Tan, C.M.; Xenoyannis, S.; Feldman, R.D. Oxidant Stress Enhances Adenylyl Cyclase Activation. *Circ. Res.* **1995**, *77*, 710–717. [CrossRef] [PubMed]
47. Raimondi, L.; Banchelli, G.; Sgromo, L.; Pirisino, R.; Ner, M.; Parini, A.; Cambon, C. Hydrogen peroxide generation by monoamine oxidases in rat white adipocytes: Role on cAMP production. *Eur. J. Pharmacol.* **2000**, *395*, 177–182. [CrossRef]
48. Vatner, S.F.; Pachon, R.E.; Vatner, D.E. Inhibition of Adenylyl Cyclase Type 5 Increases Longevity and Healthful Aging through Oxidative Stress Protection. *Oxidative Med. Cell. Longev.* **2015**, *2015*, 250310. [CrossRef]
49. Guers, J.J.; Zhang, J.; Campbell, S.C.; Oydanich, M.; Vatner, D.E.; Vatner, S.F. Disruption of adenylyl cyclase type 5 mimics exercise training. *Basic Res. Cardiol.* **2017**, *112*, 59. [CrossRef]
50. Vatner, S.F.; Park, M.; Yan, L.; Lee, G.J.; Lai, L.; Iwatsubo, K.; Ishikawa, Y.; Pessin, J.; Vatner, D.E. Adenylyl cyclase type 5 in cardiac disease, metabolism, and aging. *Am. J. Physiol. Heart Circ. Physiol.* **2013**, *305*, H1–H8. [CrossRef]
51. Lafontan, M.; Moro, C.; Sengenes, C.; Galitzky, J.; Crampes, F.; Berlan, M. An Unsuspected Metabolic Role for Atrial Natriuretic Peptides. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 2032–2042. [CrossRef]
52. Potter, L.R. Guanylyl cyclase structure, function and regulation. *Cell Signal.* **2011**, *23*, 1921–1926. [CrossRef] [PubMed]
53. Friebe, A.; Sandner, P.; Schmidtko, A. cGMP: A unique 2nd messenger molecule—Recent developments in cGMP research and development. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2020**, *393*, 287–302. [CrossRef] [PubMed]
54. Humphries, K.M.; Pennypacker, J.K.; Taylor, S.S. Redox Regulation of cAMP-dependent Protein Kinase Signaling: Kinase versus phosphatase inactivation. *J. Biol. Chem.* **2007**, *282*, 22072–22079. [CrossRef] [PubMed]
55. Humphries, K.M.; Juliano, C.; Taylor, S.S. Regulation of cAMP-dependent Protein Kinase Activity by Glutathionylation. *J. Biol. Chem.* **2002**, *277*, 43505–43511. [CrossRef]
56. de Pina, M.Z.; Vazquez-Meza, H.; Pardo, J.P.; Rendon, J.L.; Villalobos-Molina, R.; Riveros-Rosas, H.; Pina, E. Signaling the signal, cyclic AMP-dependent protein kinase inhibition by insulin-formed H_2O_2 and reactivation by thioredoxin. *J. Biol. Chem.* **2008**, *283*, 12373–12386. [CrossRef] [PubMed]
57. Goldstein, B.J.; Mahadev, K.; Wu, X. Redox paradox: Insulin action is facilitated by insulin-stimulated reactive oxygen species with multiple potential signaling targets. *Diabetes* **2005**, *54*, 311–321. [CrossRef]
58. Steinberg, S.F. Mechanisms for redox-regulation of protein kinase C. *Front. Pharm.* **2015**, *6*, 128. [CrossRef]
59. Fricke, K.; Heitland, A.; Maronde, E. Cooperative activation of lipolysis by protein kinase A and protein kinase C pathways in 3T3-L1 adipocytes. *Endocrinology* **2004**, *145*, 4940–4947. [CrossRef]
60. Loegering, D.J.; Lennartz, M.R. Protein kinase C and toll-like receptor signaling. *Enzym. Res* **2011**, *2011*, 537821. [CrossRef]
61. Wang, X.T.; McCullough, K.D.; Wang, X.J.; Carpenter, G.; Holbrook, N.J. Oxidative stress-induced phospholipase C-gamma 1 activation enhances cell survival. *J. Biol. Chem.* **2001**, *276*, 28364–28371. [CrossRef]
62. Al-Anazi, A.; Parhar, R.; Saleh, S.; Al-Hijailan, R.; Inglis, A.; Al-Jufan, M.; Bazzi, M.; Hashmi, S.; Conca, W.; Collison, K.; et al. Intracellular calcium and NF-kB regulate hypoxia-induced leptin, VEGF, IL-6 and adiponectin secretion in human adipocytes. *Life Sci.* **2018**, *212*, 275–284. [CrossRef] [PubMed]
63. Humphries, K.M.; Deal, M.S.; Taylor, S.S. Enhanced dephosphorylation of cAMP-dependent protein kinase by oxidation and thiol modification. *J. Biol. Chem.* **2005**, *280*, 2750–2758. [CrossRef] [PubMed]
64. Sengenes, C.; Bouloumie, A.; Hauner, H.; Berlan, M.; Busse, R.; Lafontan, M.; Galitzky, J. Involvement of a cGMP-dependent pathway in the natriuretic peptide-mediated hormone-sensitive lipase phosphorylation in human adipocytes. *J. Biol. Chem.* **2003**, *278*, 48617–48626. [CrossRef] [PubMed]
65. Burgoyne, J.R.; Prysyazhna, O.; Rudyk, O.; Eaton, P. cGMP-dependent activation of protein kinase G precludes disulfide activation: Implications for blood pressure control. *Hypertension* **2012**, *60*, 1301–1308. [CrossRef] [PubMed]
66. Krawczyk, S.A.; Haller, J.F.; Ferrante, T.; Zoeller, R.A.; Corkey, B.E. Reactive oxygen species facilitate translocation of hormone sensitive lipase to the lipid droplet during lipolysis in human differentiated adipocytes. *PLoS ONE* **2012**, *7*. [CrossRef]

67. Zhou, C.; Zaman, N.; Li, Y.; Martinez-Arguelles, D.B.; Papadopoulos, V.; Zirkin, B.; Traore, K. Redox regulation of hormone sensitive lipase: Potential role in the mechanism of MEHP-induced stimulation of basal steroid synthesis in MA-10 Leydig cells. *Reprod. Toxicol.* **2019**, *85*, 19–25. [CrossRef]
68. Sahu-Osen, A.; Montero-Moran, G.; Schittmayer, M.; Fritz, K.; Dinh, A.; Chang, Y.-F.; McMahon, D.; Boeszoermenyi, A.; Cornaciu, I.; Russell, D.; et al. CGI-58/ABHD5 is phosphorylated on Ser239 by protein kinase A: Control of subcellular localization. *J. Lipid Res.* **2015**, *56*, 109–121. [CrossRef]
69. Kosteli, A.; Sugaru, E.; Haemmerle, G.; Martin, J.F.; Lei, J.; Zechner, R.; Ferrante, A.W., Jr. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. *J. Clin. Investig.* **2010**, *120*, 3466–3479. [CrossRef]
70. Sun, K.; Kusminski, C.M.; Scherer, P.E. Adipose tissue remodeling and obesity. *J. Clin. Investig.* **2011**, *121*, 2094–2101. [CrossRef]
71. Issa, N.; Lachance, G.; Bellmann, K.; Laplante, M.; Stadler, K.; Marette, A. Cytokines promote lipolysis in 3T3-L1 adipocytes through induction of NADPH oxidase 3 expression and superoxide production. *J. Lipid Res.* **2018**, *59*, 2321–2328. [CrossRef]
72. Fernández-Sánchez, A.; Madrigal-Santillán, E.; Bautista, M.; Esquivel-Soto, J.; Morales-González, A.; Esquivel-Chirino, C.; Durante-Montiel, I.; Sánchez-Rivera, G.; Valadez-Vega, C.; Morales-González, J.A. Inflammation, oxidative stress, and obesity. *Int. J. Mol. Sci.* **2011**, *12*, 3117–3132. [CrossRef] [PubMed]
73. Furukawa, S.; Fujita, T.; Shimabukuro, M.; Iwaki, M.; Yamada, Y.; Nakajima, Y.; Nakayama, O.; Makishima, M.; Matsuda, M.; Shimomura, I. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J. Clin. Investig.* **2004**, *114*, 1752–1761. [CrossRef] [PubMed]
74. Marseglia, L.; Manti, S.; D'Angelo, G.; Nicotera, A.; Parisi, E.; Di Rosa, G.; Gitto, E.; Arrigo, T. Oxidative stress in obesity: A critical component in human diseases. *Int. J. Mol. Sci.* **2014**, *16*, 378–400. [CrossRef]
75. Le Lay, S.; Simard, G.; Martinez, M.C.; Andriantsitohaina, R. Oxidative stress and metabolic pathologies: From an adipocentric point of view. *Oxidative Med. Cell. Longev.* **2014**, *2014*. [CrossRef] [PubMed]
76. Masschelin, P.M.; Cox, A.R.; Chernis, N.; Hartig, S.M. The Impact of Oxidative Stress on Adipose Tissue Energy Balance. *Front. Physiol.* **2020**, *10*, 1–8. [CrossRef] [PubMed]
77. Ruskovska, T.; Bernlohr, D.A. Oxidative stress and protein carbonylation in adipose tissue — Implications for insulin resistance and diabetes mellitus. *J. Proteom.* **2013**, *92*, 323–334. [CrossRef] [PubMed]
78. Salcedo-Tacuma, D.; Parales-Giron, J.; Prom, C.; Chirivi, M.; Laguna, J.; Lock, A.L.; Contreras, G.A. Transcriptomic profiling of adipose tissue inflammation, remodeling, and lipid metabolism in periparturient dairy cows (Bos taurus). *BMC Genom.* **2020**, *21*, 824. [CrossRef] [PubMed]
79. Hwang, I.; Uddin, M.J.; Pak, E.S.; Kang, H.; Jin, E.-J.; Jo, S.; Kang, D.; Lee, H.; Ha, H. The impaired redox balance in peroxisomes of catalase knockout mice accelerates nonalcoholic fatty liver disease through endoplasmic reticulum stress. *Free Radic. Biol. Med.* **2020**, *148*, 22–32. [CrossRef]
80. Shin, S.-K.; Cho, H.-W.; Song, S.-E.; Bae, J.-H.; Im, S.-S.; Hwang, I.; Ha, H.; Song, D.-K. Ablation of catalase promotes non-alcoholic fatty liver via oxidative stress and mitochondrial dysfunction in diet-induced obese mice. *Pflügers Arch. Eur. J. Physiol.* **2019**, *471*, 829–843. [CrossRef]
81. Shin, S.-K.; Cho, H.-W.; Song, S.-E.; Im, S.-S.; Bae, J.-H.; Song, D.-K. Oxidative stress resulting from the removal of endogenous catalase induces obesity by promoting hyperplasia and hypertrophy of white adipocytes. *Redox Biol.* **2020**, *37*, 101749. [CrossRef] [PubMed]
82. Nunes-Souza, V.; Dias-Júnior, N.M.; Eleutério-Silva, M.A.; Ferreira-Neves, V.P.; Moura, F.A.; Alenina, N.; Bader, M.; Rabelo, L.A. 3-Amino-1,2,4-Triazole Induces Quick and Strong Fat Loss in Mice with High Fat-Induced Metabolic Syndrome. *Oxid Med. Cell. Longev.* **2020**, *2020*, 3025361. [CrossRef] [PubMed]
83. Prasad Mukherjee, S. Mediation of the antilipolytic and lipogenic effects of insulin in adipocytes by intracellular accumulation of hydrogen peroxide. *Biochem. Pharmacol.* **1980**, *29*, 1239–1246. [CrossRef]
84. Abbas, K.; Riquier, S.; Drapier, J.-C. Chapter Six—Peroxiredoxins and Sulfiredoxin at the Crossroads of the NO and H2O2 Signaling Pathways. In *Methods in Enzymology*; Cadenas, E., Packer, L., Eds.; Academic Press: Cambridge, MA, USA, 2013; Volume 527, pp. 113–128.
85. Arevalo, J.A.; Vázquez-Medina, J.P. The Role of Peroxiredoxin 6 in Cell Signaling. *Antioxidants* **2018**, *7*, 172. [CrossRef] [PubMed]
86. Arriga, R.; Pacifici, F.; Capuani, B.; Coppola, A.; Orlandi, A.; Scioli, M.G.; Pastore, D.; Andreadi, A.; Sbraccia, P.; Tesauro, M.; et al. Peroxiredoxin 6 Is a Key Antioxidant Enzyme in Modulating the Link between Glycemic and Lipogenic Metabolism. *Oxid Med. Cell. Longev.* **2019**, *2019*, 9685607. [CrossRef]
87. Huh, J.Y.; Kim, Y.; Jeong, J.; Park, J.; Kim, I.; Huh, K.H.; Kim, Y.S.; Woo, H.A.; Rhee, S.G.; Lee, K.J.; et al. Peroxiredoxin 3 is a key molecule regulating adipocyte oxidative stress, mitochondrial biogenesis, and adipokine expression. *Antioxid. Redox Signal.* **2012**, *16*, 229–243. [CrossRef]
88. Baez-Duarte, B.G.; Zamora-Ginez, I.; Mendoza-Carrera, F.; Ruiz-Vivanco, G.; Torres-Rasgado, E.; Gonzalez-Mejia, M.E.; Garcia-Zapien, A.; Flores-Martinez, S.E.; Perez-Fuentes, R. Serum levels of glutathione peroxidase 3 in overweight and obese subjects from central Mexico. *Arch. Med. Res.* **2012**, *43*, 541–547. [CrossRef] [PubMed]
89. Baez-Duarte, B.G.; Mendoza-Carrera, F.; García-Zapién, A.; Flores-Martínez, S.E.; Sánchez-Corona, J.; Zamora-Ginez, I.; Torres-Rasgado, E.; León-Chávez, B.A.; Pérez-Fuentes, R. Glutathione peroxidase 3 serum levels and GPX3 gene polymorphisms in subjects with metabolic syndrome. *Arch. Med. Res.* **2014**, *45*, 375–382. [CrossRef]

90. Lee, Y.S.; Kim, A.Y.; Choi, J.W.; Kim, M.; Yasue, S.; Son, H.J.; Masuzaki, H.; Park, K.S.; Kim, J.B. Dysregulation of adipose glutathione peroxidase 3 in obesity contributes to local and systemic oxidative stress. *Mol. Endocrinol.* **2008**, *22*, 2176–2189. [CrossRef]
91. Langhardt, J.; Flehmig, G.; Klöting, N.; Lehmann, S.; Ebert, T.; Kern, M.; Schön, M.R.; Gärtner, D.; Lohmann, T.; Dressler, M.; et al. Effects of Weight Loss on Glutathione Peroxidase 3 Serum Concentrations and Adipose Tissue Expression in Human Obesity. *Obes. Facts* **2018**, *11*, 475–490. [CrossRef]
92. McClung, J.P.; Roneker, C.A.; Mu, W.; Lisk, D.J.; Langlais, P.; Liu, F.; Lei, X.G. Development of insulin resistance and obesity in mice overexpressing cellular glutathione peroxidase. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 8852–8857. [CrossRef] [PubMed]
93. Ivanov, V.V.; Shakhristova, E.V.; Stepovaya, E.A.; Zhavoronok, T.V.; Novitsky, V.V. Effect of alloxan on spontaneous lipolysis and glutathione system in isolated rat adipocytes. *Bull. Exp. Biol. Med.* **2011**, *151*, 314–317. [CrossRef] [PubMed]
94. Boucher, J.; Masri, B.; Daviaud, D.; Gesta, S.; Guigné, C.; Mazzucotelli, A.; Castan-Laurell, I.; Tack, I.; Knibiehler, B.; Carpéné, C.; et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology* **2005**, *146*, 1764–1771. [CrossRef] [PubMed]
95. Than, A.; Zhang, X.; Leow, M.K.; Poh, C.L.; Chong, S.K.; Chen, P. Apelin attenuates oxidative stress in human adipocytes. *J. Biol. Chem.* **2014**, *289*, 3763–3774. [CrossRef]
96. Than, A.; Cheng, Y.; Foh, L.C.; Leow, M.K.; Lim, S.C.; Chuah, Y.J.; Kang, Y.; Chen, P. Apelin inhibits adipogenesis and lipolysis through distinct molecular pathways. *Mol. Cell. Endocrinol.* **2012**, *362*, 227–241. [CrossRef]
97. Yue, P.; Jin, H.; Xu, S.; Aillaud, M.; Deng, A.C.; Azuma, J.; Kundu, R.K.; Reaven, G.M.; Quertermous, T.; Tsao, P.S. Apelin Decreases Lipolysis via Gq, Gi, and AMPK-Dependent Mechanisms. *Endocrinology* **2011**, *152*, 59–68. [CrossRef]
98. Nguyen, T.; Nioi, P.; Pickett, C.B. The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. *J. Biol. Chem.* **2009**, *284*, 13291–13295. [CrossRef]
99. Sun, X.; Li, X.; Jia, H.; Wang, H.; Shui, G.; Qin, Y.; Shu, X.; Wang, Y.; Dong, J.; Liu, G.; et al. Nuclear Factor E2-Related Factor 2 Mediates Oxidative Stress-Induced Lipid Accumulation in Adipocytes by Increasing Adipogenesis and Decreasing Lipolysis. *Antioxid. Redox Signal.* **2020**, *32*, 173–192. [CrossRef]
100. Xu, J.; Kulkarni, S.R.; Donepudi, A.C.; More, V.R.; Slitt, A.L. Enhanced Nrf2 activity worsens insulin resistance, impairs lipid accumulation in adipose tissue, and increases hepatic steatosis in leptin-deficient mice. *Diabetes* **2012**, *61*, 3208–3218. [CrossRef]
101. Koushki, M.; Amiri-Dashatan, N.; Ahmadi, N.; Abbaszadeh, H.-A.; Rezaei-Tavirani, M. Resveratrol: A miraculous natural compound for diseases treatment. *Food Sci. Nutr.* **2018**, *6*, 2473–2490. [CrossRef]
102. Kieliszek, M.; Błażejak, S. Selenium: Significance, and outlook for supplementation. *Nutrition* **2013**, *29*, 713–718. [CrossRef] [PubMed]
103. Clarke, M.W.; Burnett, J.R.; Croft, K.D. Vitamin E in human health and disease. *Crit. Rev. Clin. Lab. Sci.* **2008**, *45*, 417–450. [CrossRef]
104. Abuelo, A.; Hernández, J.; Benedito, J.L.; Castillo, C. The importance of the oxidative status of dairy cattle in the periparturient period: Revisiting antioxidant supplementation. *J. Anim. Physiol. Anim. Nutr.* **2015**, *99*, 1003–1016. [CrossRef]
105. Wang, X.; Wu, H.; Long, Z.; Sun, Q.; Liu, J.; Liu, Y.; Hai, C. Differential effect of Se on insulin resistance: Regulation of adipogenesis and lipolysis. *Mol. Cell. Biochem.* **2016**, *415*, 89–102. [CrossRef] [PubMed]
106. Alcalá, M.; Sánchez-Vera, I.; Sevillano, J.; Herrero, L.; Serra, D.; Ramos, M.P.; Viana, M. Vitamin E reduces adipose tissue fibrosis, inflammation, and oxidative stress and improves metabolic profile in obesity. *Obesity* **2015**, *23*, 1598–1606. [CrossRef] [PubMed]
107. Gomez-Zorita, S.; Treguer, K.; Mercader, J.; Carpene, C. Resveratrol directly affects in vitro lipolysis and glucose transport in human fat cells. *J. Physiol. Biochem.* **2013**, *69*, 585–593. [CrossRef]
108. Szkudelska, K.; Nogowski, L.; Szkudelski, T. Resveratrol, a naturally occurring diphenolic compound, affects lipogenesis, lipolysis and the antilipolytic action of insulin in isolated rat adipocytes. *J. Steroid Biochem. Mol. Biol.* **2009**, *113*, 17–24. [CrossRef] [PubMed]
109. Pedersen, S.B.; Ølholm, J.; Paulsen, S.K.; Bennetzen, M.F.; Richelsen, B. Low Sirt1 expression, which is upregulated by fasting, in human adipose tissue from obese women. *Int. J. Obes.* **2008**, *32*, 1250–1255. [CrossRef]
110. Merkel, M.; Eckel, R.H.; Goldberg, I.J. Lipoprotein lipase. *J. Lipid Res.* **2002**, *43*, 1997–2006. [CrossRef]
111. Shepherd, P.R.; Kahn, B.B. Glucose Transporters and Insulin Action—Implications for Insulin Resistance and Diabetes Mellitus. *N. Engl. J. Med.* **1999**, *341*, 248–257. [CrossRef] [PubMed]
112. Ciaraldi, T.P.; Olefsky, J.M. Comparison of the effects of insulin and H2O2 on adipocyte glucose transport. *J. Cell. Physiol.* **1982**, *110*, 323–328. [CrossRef]
113. May, J.M.; de Haën, C. The insulin-like effect of hydrogen peroxide on pathways of lipid synthesis in rat adipocytes. *J. Biol. Chem.* **1979**, *254*, 9017–9021. [CrossRef]
114. Hoehn, K.L.; Salmon, A.B.; Hohnen-Behrens, C.; Turner, N.; Hoy, A.J.; Maghzal, G.J.; Stocker, R.; Van Remmen, H.; Kraegen, E.W.; Cooney, G.J. Insulin resistance is a cellular antioxidant defense mechanism. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 17787–17792. [CrossRef]
115. Houstis, N.; Rosen, E.D.; Lander, E.S. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* **2006**, *440*, 944–948. [CrossRef]
116. Okuno, Y.; Fukuhara, A.; Hashimoto, E.; Kobayashi, H.; Kobayashi, S.; Otsuki, M.; Shimomura, I. Oxidative Stress Inhibits Healthy Adipose Expansion Through Suppression of SREBF1-Mediated Lipogenic Pathway. *Diabetes* **2018**, *67*, 1113–1127. [CrossRef]

117. Kowalska, K.; Olejnik, A.; Rychlik, J.; Grajek, W. Cranberries (Oxycoccus quadripetalus) inhibit adipogenesis and lipogenesis in 3T3-L1 cells. *Food Chem.* **2014**, *148*, 246–252. [CrossRef]
118. Guo, W.; Xie, W.; Han, J. Modulation of adipocyte lipogenesis by octanoate: Involvement of reactive oxygen species. *Nutr. Metab.* **2006**, *3*, 30. [CrossRef] [PubMed]
119. Sordillo, L.M.; Aitken, S.L. Impact of oxidative stress on the health and immune function of dairy cattle. *Vet. Immunol. Immunopathol.* **2009**, *128*, 104–109. [CrossRef] [PubMed]
120. Sordillo, L.M.; Contreras, G.A.; Aitken, S.L. Metabolic factors affecting the inflammatory response of periparturient dairy cows. *Anim. Health Res. Rev.* **2009**, *10*, 53–63. [CrossRef]
121. Contreras, G.A.; Sordillo, L.M. Lipid mobilization and inflammatory responses during the transition period of dairy cows. *Comp. Immunol. Microbiol. Infect. Dis.* **2011**, *34*, 281–289. [CrossRef] [PubMed]
122. Contreras, G.A.; Strieder-Barboza, C.; de Souza, J.; Gandy, J.; Mavangira, V.; Lock, A.L.; Sordillo, L.M. Periparturient lipolysis and oxylipid biosynthesis in bovine adipose tissues. *PLoS ONE* **2017**, *12*, e0188621. [CrossRef] [PubMed]
123. Bernabucci, U.; Ronchi, B.; Lacetera, N.; Nardone, A. Influence of Body Condition Score on Relationships Between Metabolic Status and Oxidative Stress in Periparturient Dairy Cows. *J. Dairy Sci.* **2005**, *88*, 2017–2026. [CrossRef]
124. Liang, Y.; Alharthi, A.S.; Bucktrout, R.; Elolimy, A.A.; Lopreiato, V.; Martinez-Cortés, I.; Xu, C.; Fernandez, C.; Trevisi, E.; Loor, J.J. Body condition alters glutathione and nuclear factor erythroid 2-like 2 (NFE2L2)-related antioxidant network abundance in subcutaneous adipose tissue of periparturient Holstein cows. *J. Dairy Sci.* **2020**, *103*, 6439–6453. [CrossRef] [PubMed]
125. Andres Contreras, G.; De Koster, J.; de Souza, J.; Laguna, J.; Mavangira, V.; Nelli, R.K.; Gandy, J.; Lock, A.L.; Sordillo, L.M. Lipolysis modulates the biosynthesis of inflammatory lipid mediators derived from linoleic acid in adipose tissue of periparturient dairy cows. *J. Dairy Sci.* **2020**, *103*, 1944–1955. [CrossRef]