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Heme-oxygenase and lipid mediators in obesity and associated cardiometabolic diseases: Therapeutic implications

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Abstract

Obesity-mediated metabolic syndrome remains the leading cause of death worldwide. Among many potential targets for pharmacological intervention, a promising strategy involves the heme oxygenase (HO) system, specifically its inducible form, HO-1. This review collects and updates much of the current knowledge relevant to pharmacology and clinical medicine concerning HO-1 in metabolic diseases and its effect on lipid metabolism. HO-1 has pleotropic effects that collectively reduce inflammation, while increasing vasodilation and insulin and leptin sensitivity. Recent reports indicate that HO-1 with its antioxidants via the effect of bilirubin increases formation of biologically active lipid metabolites such as epoxyeicosatrienoic acid (EET), omega-3 and other polyunsaturated fatty acids (PUFAs). Similarly, HO-1and bilirubin are potential therapeutic targets in the treatment of fat-induced liver diseases. HO-1-mediated upregulation of EET is capable not only of reversing endothelial dysfunction and hypertension, but also of reversing cardiac remodeling, a hallmark of the metabolic syndrome. This process involves browning of white fat tissue (i.e. formation of healthy adipocytes) and reduced lipotoxicity, which otherwise will be toxic to the heart. More importantly, this review examines the activity of EET in biological systems and a series of pathways that explain its mechanism of action and discusses how these might be exploited for potential therapeutic use. We also discuss the link between cardiac ectopic fat deposition and cardiac function in humans, which is similar to that described in obese mice and is regulated by HO-1-EET-PGC1α signaling, a potent negative regulator of the inflammatory adipokine NOV.

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Declaration of Competing Interest

The authors declare there are no conflicts of interest.

Keywords

Leptin resistance; Fatty liver; Pericardial fat; hypertension; Brown adipocyte; Diabetes; Stem cells

1. Introduction: obesity and the metabolic syndrome – the challenge

The occurrence of obesity is increasing in the U.S. (Lange et al., 2019) and adipogenesis has become an increasingly discussed topic in the field of obesity and diabetes. Globally, obesity rates have quadrupled between 1980 and 2014 (Ampofo & Boateng, 2020). The incidence of diabetes has nearly doubled in the same time period and is expected to further increase globally over the next 10 years (Ampofo & Boateng, 2020). When the BMI (body mass index) is 30 or more, an individual is identified as obese. A BMI between 25 and 30 denotes a diagnosis of overweight. According to the WHO, The United States has the highest prevalence of obesity, with 62% of adults classified as either obese or overweight. About 78.6 million people are affected by obesity in the U.S., and there is an expectation that this will rise to over 50% of the population by 2030 (Andolfi & Fisichella, 2018; James, 2008). Obesity increases risk of endothelial cell dysfunction, augments inflammatory cytokines, decreases adiponectin and leads to insulin resistance (Peterson et al., 2020; Peterson, Dave, & Kothari, 2020; Sasson et al., 2021). Obesity-mediated adipocyte dysfunction promotes adipocytokine release and this has systemic consequences, particularly in the vascular system, often due to mitochondrial dysfunction (Lee et al., 2019; Singh et al., 2016; Singh et al., 2016). Metabolic syndrome increases a patient's risk for diabetes and cardiovascular disease (CVD) (Drummond, Baum, Greenberg, Lewis, & Abraham, 2019). The hallmark criteria of the metabolic syndrome are increased waistline circumference (visceral fat), hyperglycemia, hypertension, low HDL cholesterol, insulin resistance and high serum levels of triglycerides. Obese individuals often have comorbidities, such as vascular dysfunction, diabetes secondary to insulin resistance, hypertension (Fontana, Eagon, Trujillo, Scherer, & Klein, 2007; Hall, 2003; Ogden et al., 2006), and high levels of proinflammatory cytokines (Marseglia et al., 2014){(Li et al., 2008) #15)}. Oxidative stress induced by the presence of reactive oxygen species (ROS) drives disease progression and has many negative effects (Drummond, et al., 2019; Holvoet, 2008; Qureshi & Abrams, 2007) It is imperative to develop novel pharmacological treatments that can attenuate the various negative effects of metabolic syndrome. This review examines the mechanisms behind the pathophysiology of the obese phenotype, gives particular attention to end-organ damage in both the liver and the heart, and explores the pharmacology of the heme oxygenase system and its attendant pathways as particularly important targets for therapeutic intervention.

2. Adipose tissue and adipocyte-mediated inflammation

2.1. Leptin resistance

In addition to its role in energy storage, adipose tissue is an active endocrine and paracrine organ. Among the most serious alterations in the pathophysiology of obesity, if not one of its prime movers, is leptin resistance. First described in 1994, leptin is an adipokine that functions primarily by binding to receptor sites that are most densely concentrated in the hypothalamus (Elmquist, Bjørbaek, Ahima, Flier, & Saper, 1998; Park & Ahima,

2015; Zhang et al., 1994). The leptin receptor is a single transmembrane protein which when bound to leptin activates Janus kinase 2 (JAK2) which in turn activates Signal transducer and activator of transcription 3 (STAT3), collectively known as the JAK2/STAT3 pathway (Banks, Davis, Bates, & Myers Jr., 2000). In the proopiomelanocortin (POMC) neuron of the arcuate nucleus (ARC), activation of the JAK/STAT pathway results in conversion of POMC into the neurotransmitter alpha-melanocyte-stimulating hormone (α-MSH) (Schwartz et al., 1997). α-MSH in turn binds to melanocortin receptors 3 and 4 (MC3R and MC4R) in the target neuron leading to central inhibition of food intake and increased thermogenesis (Balse-Srinivasan, Grieco, Cai, Trivedi, & Hruby, 2003). Concurrently, leptin antagonizes gene transcription in neurons expressing agouti-related protein (AgRP), further enhancing its anorexigenic effect (Mizuno & Mobbs, 1999; Ollmann et al., 1997).

Leptin resistance can be induced in at least two hypothalamic locations via at least two described mechanisms. Lipotoxic increase in ceramide concentration in the cytoplasm of cells in the ventromedial nucleus of the hypothalamus (VMH) has been shown to cause endoplasmic reticulum (ER) stress with resultant protein misfolding and secondary reduction in sympathetic nervous system (SNS) stimulation to brown adipose tissue (BAT) (Contreras et al., 2014). This, in turn, results in a decrease in elaboration of uncoupling protein (UCP)1, UCP3, and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) resulting in weight gain and decreases in mitochondrial biogenesis and thermogenesis. Similarly, ER stress in the POMC neuron of the arcuate nucleus has been shown to cause misfolding and inactivation of the α-MSH neurotransmitter and hence shutting down signaling to the target neuron resulting in weight gain and decreased thermogenesis (Ramírez & Claret, 2015) (Fig. 1).

ER stress itself is a result of the reduction in mitofusin proteins 1 and 2 (MFN1 and MFN2) caused by the presence of reactive oxygen species (ROS) and a reduction in the antioxidant cascade. In both hypothalamic mechanisms, plasma leptin levels are elevated while weight and obesity continue to increase.

By contrast, POMC AMPK enhances PGC-1α levels, while nuclear factor E2-related factor 2 (Nrf2) and its downstream product, HO1, suppress hypothalamic oxidative stress and improve leptin resistance, suggesting that improvement in leptin resistance is mediated by their salutary effect on mitochondrial function (Gill, Delezie, Santos, & Handschin, 2016; Yagishita et al., 2017). Also, HO-1 decreases body weight and increases metabolism in mice independent of central MC4R, suggesting that it may do this by increasing α-MSH binding to MC3r (Csongradi, Docarmo, Dubinion, Vera, & Stec, 2012). Leptin resistance appears to be a somewhat selective phenomenon in the hypothalamus. In the kidney, leptin induced activation of the phosphoinositide 3 kinase (PI3K) pathway continues unabated in the face of lipotoxic effects in the hypothalamus, leading to an increase in renal sympathetic activity and resultant hypertension (Rahmouni, Correia, Haynes, & Mark, 2005).

2.2. Types of adipose tissue

There are two main category types of adiposity: subcutaneous and visceral. Visceral adiposity has a better correlation with the complications of obesity which are affected by

both the location and the quality of adipose tissue (Peterson et al., 2019). Obesity-derived adipose tissue dysfunction has a crucial role in initiating the chronic, systemic inflammatory state that leads to insulin resistance, a required criterion for the metabolic syndrome, type 2 diabetes mellitus and increased risk of CVD (Alberti et al., 2009; Lakka et al., 2002). The pro-oxidant heme in conjunction with ROS leads to both adipocyte and vascular dysfunction (Peterson et al., 2016; Peterson et al., 2019a). There are two primary types of adipose tissue, the proinflammatory, white adipose tissue (WAT), and its healthy counterpart, brown AT (BAT). WAT is comprised of large adipocytes, produces pro-inflammatory molecules (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; Fontana et al., 2007; Kredel & Siegmund, 2014), has impaired mitochondrial thermogenesis (Singh et al., 2018; Singh, Bellner, et al., 2016; Singh, Schragenheim, et al., 2016), is the predominant component of visceral fat in obesity, and has severe systemic vascular consequences (Siriboon & Knodel, 1994). BAT, in contrast, contains smaller adipocytes, decreased cytokine production, increased mitochondrial thermogenesis and biogenesis, and a decrease in inflammation, metabolic disorders and cardiovascular risk (Cohen & Spiegelman, 2015).

Mitochondrial thermogenesis involves the production of heat via uncoupling protein 1 (UCP1) (Cohen & Spiegelman, 2015). UCP1 functions by allowing oxidation of glucose and fatty acids. The energy created during oxidative catabolism is released as heat (Cannon & Nedergaard, 2004). *In vivo* studies of UCP1 downregulation demonstrate an increased rate of diet-induced obesity (Feldmann, Golozoubova, Cannon, & Nedergaard, 2009). UCP1 overexpression reduces WAT and attenuates insulin resistance (Poher et al., 2015). A new form of adipose tissue named "beige" fat (an intermediate phenotype between WAT and BAT) is generated after the reprogramming of WAT (Singh et al., 2020).

Recent research has focused on improving the expression and the activity of BAT, since BAT has important beneficial effects on body weight, insulin sensitivity, glucose metabolism and energy homeostasis in rodents (Cannon & Nedergaard, 2004). Moreover, there is an inverse correlation between BAT and BMI (Halpern, Mancini, & Halpern, 2014).

2.3. inflammatory adipocytokines

Excess energy intake in the form of fatty acids and high glucose drives adipose tissue expansion and a preferential differentiation into inflammatory white adipocytes (Giske, 2019). Obesity-derived adipocyte dysfunction is characterized by critical changes in the AT microenvironment, due to the release of inflammatory adipocytokines such as IL-1, IL-6, TNF-α, and of 20-hydroxyeicosatetraenoic acid (20-HETE) and Angiotensin II (Ang II), as well as a decrease in expression/activity of HO-1, adiponectin, and epoxyeicosatrienoic acid (EET), all of which results in oxidative stress and decreased mitochondrial function and density (G. S. Drummond, et al., 2019) (Fig. 2). High glucose induces oxidative stress by inducing NADPH oxidases (Manea, 2010; Schiffer, Lundberg, Weitzberg, & Carlstrom, 2020) and impairs the mitochondrial respiratory chain (MRC) complex enzyme system (Rueckschloss, Quinn, Holtz, & Morawietz, 2002). Lastly, hyperglycemia induces xanthine oxidase, which generates oxidant species (Desco et al., 2002).

Adipose tissue inflammation involves different cell types including lymphocytes, macrophages, neutrophils and mast cells which are all increased in the adipose tissue of

obese mice (Thomas & Apovian, 2017). M1-like macrophage abundance correlates with insulin resistance and production of IL-6 and TNF-α. Also, in obesity, macrophages tend to surround lipid droplets of dead adipocytes, contributing to inflammation and insulin resistance (G. S. Drummond, et al., 2019). The pro-inflammatory environment activates the NF-κB pathway, perpetuating oxidative conditions that exacerbate insulin resistance (Bastard et al., 2006). Like other autoimmune diseases, chronic inflammation has been correlated with the onset of insulin resistant diabetes, which leads to activation of pro-apoptotic pathways in the pancreas. The chronic systemic inflammatory state causes insulin resistance, the metabolic syndrome, fatty liver and vascular damage (Peterson, Choudhary, et al., 2020).

2.4. Hypertension and the metabolic syndrome

Alterations of redox homeostasis and the production of adipocytokines by dysfunctional adipocytes can be in part responsible for the vascular dysfunction and hypertension that have been correlated with obesity and its associated chronic inflammation (Niskanen et al., 2004). Hypertension affects more than 600 million people worldwide, is estimated to continue to rise (Mittal & Singh, 2010), and represents an independent risk factor for most cardiovascular pathologies (Lacy, Kailasam, O'Connor, Schmid-Schonbein, & Parmer, 2000). High levels of ROS occur in hypertensive patients and in animal models of hypertension (Lacy et al., 2000; Stojiljkovic et al., 2002; Tanito et al., 2004; Touyz & Schiffrin, 2004). ROS play a pathophysiological role in the progression of endothelial dysfunction. This is due mainly to O_2^- excess and decreased NO in the vasculature and kidneys (Chabrashvili et al., 2002; Kishi et al., 2004; Touyz, 2003) (Fig. 3). Vascular endothelial cells serve as regulators in maintaining homeostasis by constantly releasing vasodilatory factors such as NO and producing vasoconstrictive factors such thromboxane and endothelin-1 (ET-1) (Feletou & Vanhoutte, 2006). Endothelial dysfunction-associated hypertension can result from unbalanced vasodilation related to mechanisms such as the natriuretic peptide system (Fig. 4). Ang II induces ROS production when introduced to arterial smooth muscle cells of hypertensive patients (Ahmad et al., 2017; Touyz & Schiffrin, 2001). ROS are produced in endothelial, adventitial, and smooth muscular cells of the vasculature, affecting vascular tone (Cines et al., 1998; Widlansky & Gutterman, 2011). In response, the endothelium attempts to produce vasorelaxation-inducing agents, such as NO, however NO is inactivated by ROS-generated peroxynitrate (Feletou, Kohler, & Vanhoutte, 2010). Excessive vasoconstriction of the smooth muscle layer results in hypertension (Fig. 4) (Busse et al., 2002).

3. The heme oxygenase system

Elevated heme levels increase adipogenesis (Raghuram et al., 2007), resulting in large dysfunctional adipocytes, dysregulation of adipocytokine production and mitochondrial dysfunction which further increases ROS production.

Heme is degraded to biliverdin by heme oxygenase (HO) which exists in two forms, HO-1 (inducible) and HO-2 (constitutive), with the simultaneous production of equimolar amounts of CO and iron, and in turn, biliverdin reductase rapidly reduces biliverdin to bilirubin

(Abraham, Junge, & Drummond, 2016) (Fig. 5). HO-1 and HO-2 are mechanistically similar, and both are susceptible to inhibition by metalloporphyrins (MMP's) (Abraham et al., 2016). In addition, HO-1 is induced by eicosanoids such as epoxyeicosatrienoic acid (EET), curcumin and resveratrol (Abraham et al., 2016). Alterations in the HO system contribute to a wide-variety of human diseases and are summarized in Table 1.

Carbon monoxide (CO), bilirubin and ferritin are all powerful antioxidant, anti-inflammatory and anti-apoptotic factors. CO is a signaling molecule that acts through both cGMP dependent and independent pathways to regulate blood pressure and mitochondrial function in mesenchymal stem cells (MSC), all of which has a beneficial impact on obesity and diabetes. Similarly, CO reduces vasoconstriction (Rodella et al., 2008), through inhibition of smooth muscle reactivity in the vasculature (Abraham et al., 2016).

Bilirubin is a ROS scavenger, recently shown to be a metabolic hormone acting through the peroxisome proliferator-activated receptor α (PPARα) to effect adipose tissue remodeling and quality (Gordon et al., 2020; Stec et al., 2016). Also, a moderate elevation of serum bilirubin concentration is linked with the amelioration of endothelial dysfunction. Patients with mild unconjugated hyperbilirubinemia without cardiovascular risk factors present with endothelium-dependent vasodilation and decreased oxidative stress level (Maruhashi et al., 2012).

HO-1 induction is rapid in response to metal containing compounds like cobalt protoporphyrin IX dichloride (CoPP) due to CoPP binding to the metal-response element in the HO-1 promoter (Burgess et al., 2010). Induction of HO-1 has the therapeutic potential to restore insulin sensitivity and improve diabetes and the metabolic syndrome. It blocks the ROS-induced pancreatic β-cell destruction, induces critical agents (i.e., AMPK, cGMP, adiponectin and GLUT4) involved in insulin sensitization, and reduces inflammatory cytokines through the activation of both sGC and p38 MAPK. Importantly, HO-1 can supress adipocyte recruitment pathways and increase adiponectin-pAMPK signaling (Burgess, Vanella, Bellner, Schwartzman, & Abraham, 2012; Sacerdoti et al., 2007).

Induction of HO-1 by CoPP causes a maximal increase in HO activity at 3 days, lasting for up to 2 weeks (Drummond & Kappas, 1981). The HO-1 related antiadipogenic effect is also mediated by CO, Bilirubin and ferritin, while HO-1 also exerts its beneficial effect by degrading pro-oxidant heme which is elevated in obesity.

Unfortunately, increased ROS production does not activate the expression of the endogenous HO-1, therefore, the progression of obesity proceeds unimpeded (Roberts et al., 2006). Hence, increased ROS production results in downregulation of HO-1, which increases the risk of development of obesity induced metabolic syndrome (Ndisang, 2010; Peterson, Dave, & Kothari, 2020). Similarly, obesity-mediated insulin resistance results in hyperglycemia that suppresses HO-1 levels, CO, and bilirubin (Drummond, et al., 2019, while its inactivation by peroxynitrite, a product of the action of inducible nitric oxide synthetase (iNOS) on superoxides, increases cellular heme levels (Abraham et al., 2016) which, together with ROS, induces vascular and adipocyte dysfunction (Abraham & Kappas, 2008).

HO-1 expression is activated and repressed by several signaling pathways which regulate transcription factors known to activate or repress HO-1 gene expression (Fig 6)

HO-2 deficiencies have been linked to increased oxygen toxicity and increased iron in the lung (Dennery et al., 1998), diabetes-induced renal injury (Goodman et al., 2006), increased adiposity, increased systolic blood pressure (Sodhi et al., 2009), and impaired vasodilation (Roberts et al., 2006). Due to its inducible nature, HO-1 is the preferred pharmacological target of the two.

3.1. HO-1 and Adipogenesis

A better understanding of normal adipose tissue function is required in order to determine how it is converted to the pro-inflammatory phenotype in obesity. Pluripotent MSCs have been isolated from adipose tissue that can differentiate into different cell types, including adipocytes, osteoblasts, chondrocytes and myocytes (Vanella et al., 2010). Although the mechanism leading from MSC to preadipocyte is not known, some phases of this process are now better understood. MSC-derived pre-adipocytes go through at least 4 stages before becoming a mature adipocyte, whose phenotype is characterized by expression of the insulin receptor gene, GLUT4, fatty acid synthase (FAS) and the ability to secrete TNF-α, IL-6, adiponectin and leptin, among others. The first stage of differentiation ends with pre-adipocyte growth arrest, followed by the second stage of clonal expansion. During the third phase, growth arrest occurs that leads to the terminal differentiation of the last stage (Gesta, Tseng, & Kahn, 2007) (Fig. 7). HO-1 is involved in early stages of pre-adipocyte proliferation and clonal expansion and is downregulated in the later stages of maturation. Induction of HO-1 in MSCs increases adiponectin, PGC-1α, and leptin levels and decreases TNF-α, IL-6,and IL-1 whereas ROS and oxidative stress decrease HO-1 and increase inflammatory adipocytokines and dysfunctional adipocytes (Vanella et al., 2010) (Fig. 7).

Increases in ROS, in combination with pro-oxidant heme, contribute to the differentiation of pre-adipocytes to adipocytes (Peterson, Vanella, Bialczak, et al., 2016). Dysfunctional adipogenesis activates NADPH oxidase and the angiotensin II system (Ang II) resulting in diabetes, hypertension and CVD.

The differentiation of MSC to osteoblast or other cell lines is delicate and complex. In diabetes, for example, patients are often affected by osteopenia and osteoporosis, suggesting that hyperglycemia, insulin resistance and other diabetes-related factors can drive bone marrow-derived MSC differentiation toward adipogenesis rather than osteoblastogenesis (Barbagallo et al., 2010). High glucose decreases HO-1, whose upregulation mediated by osteogenic growth factor (OGF) and/or cobalt protoporphyrin (CoPP) shifts MSC differentiation toward osteoblast cell lineages. Furthermore, elevated HO-1 upregulates the expression of WNT signaling cascade factors such as Pref-1, Wnt10b and (β-catenin, which abrogates expression of adipogenic genes like Peg-1/Mest, C/EBP and PPARγ resulting in healthier adipocytes, increased adiponectin levels and decreased pro-inflammatory protein levels (Vanella et al., 2013).

The exogenous use of CoPP leads to a sustained rise in HO-1 levels and HO activity preventing weight gain and reducing visceral and subcutaneous fat content. Thus, HO-1 is

able to positively influence the MSC environment and stimulate pre-adipocyte growth arrest leading to healthy adipocytes and small lipid droplets through degradation of heme, and increased levels of CO/Bilirubin/Ferritin.

3.2. HO and the browning of white adipose tissue

Decreased HO-1 expression/activity increases adipogenesis and inflammation, resulting in ROS generation and mitochondrial dysfunction, while the opposite is true when HO-1 levels/activity increase (Singh, Bellner, et al., 2016; Singh, Schragenheim, et al., 2016). As noted above, brown adipocytes produce heat through the dissipation of chemical energy, mostly due to increased expression of UCP1, a key factor for non-shivering thermogenesis (Raffaele et al., 2020; Shen et al., 2020). Beige adipocytes also express UCP1 and are interspersed within WAT under certain conditions (Feldmann et al., 2009). Beige and brown adipocytes are small, insulin sensitive, generate heat energy, burn calories and are essential to weight loss (Abraham et al., 2016). PPAR γ and C/EBPs are key transcriptional factors in both WAT and BAT, and are essential for the development of adipose tissue (Cederberg et al., 2001). PRDM16 is required for adipose tissue propagation and binds directly to PGC-1α and PGC-1β, increasing their transcription and the development of BAT (Hardy, Kitamura, Harris-Stansil, Dai, & Phipps, 1997). Ablation of PRDM16 in mice results in a significant reduction of thermogenic gene expression and O_2 consumption in subcutaneous adipose tissue (but not in BAT) and a subcutaneous to visceral fat switch (Cohen et al., 2014) (Fig. 8).

HO-1 induced browning of WAT is in part facilitated by wingless integration site (Wnt)1 inhibition of glycogen synthase kinase 3 beta (gsk3β) phosphorylation with the consequent induction of the beta catenin transcription pathway leading to inhibition of PPARγ, adipocyte protein 2(aP2), CCAAT/enhancer binding protein (C/EBP) alpha, and platelet glycoprotein 4 (CD36), all of which inhibit the production of lipid-rich large white adipocytes (Vanella et al., 2013) (Fig. 9).

Inhibition of Wnt1 prevents HO-1 from increasing beta-catenin and the expression of Wnt1 responsive genes, which counters the beneficial effects of HO-1 (Cao et al., 2012; Cao et al., 2015). Concurrently, increased levels of HO-1 in diabetic rats increases serum adiponectin and cardiac expression of NO (L'Abbate et al., 2007). Moreover, enhanced HO-1 levels increase PGC-1α translocation into the adipocyte nucleus rendering it transcriptionally active (vide infra) (Singh et al., 2020). With the enlargement of lipid droplets in BAT cells (due to excess energy intake), capillary density lowers with a concomitant down regulation of vascular endothelial growth factor A (VEGF-A): this hypoxic state activates inflammatory pathways, causing adipose tissue dysfunction and whitening of BAT (Guo, Wang, Li, Wang, & Chen, 2017).

3.3. HO-1 and cytochrome P450 metabolites

Cytochrome P450 (CYP) is a super family of enzymes that metabolize different compounds via monooxygenase activity (Fig. 10). The actions of CYP are associated with the heme-HO degradation pathway, with heme being an essential prosthetic group necessary for CYP function (Maines & Kappas, 1974). As noted above, increased HO-1 activity depletes heme

levels, forming biliverdin, Fe and CO (Nath, 2006). The heme-dependent metabolism of omega-3 and omega-6 polyunsaturated fatty acids (ω-3 PUFAs and ω-6 PUFAs) occurs through the action of CYP enzymes and these PUFA metabolites can attenuate the metabolic syndrome and have cardioprotective effects. Arachidonic acid (AA) is a ω-6 PUFA (Vile, Basu-Modak, Waltner, & Tyrrell, 1994), and is metabolized from linoleic acid (LA) (Salem Jr., Pawlosky, Wegher, & Hibbeln, 1999). Essential ω-6 PUFAs are obtained from the diet, primarily from meat, fish, poultry, seafood, and eggs (Abedi & Sahari, 2014; Komprda, Zelenka, Fajmonova, Fialova, & Kladroba, 2005; Li, Ng, Mann, & Sinclair, 1998; Taber, Chiu, & Whelan, 1998), and are later stored in cellular membranes in their esterified forms (Schwartzman, Abraham, Carroll, Levere, & McGiff, 1986). Once released from the membrane, AA is quickly metabolized through the cyclooxygenase, lipoxygenase, and monooxygenase pathways (Schwartzman et al., 1986). Through the CYP monooxygenase pathway, AA is metabolized to form 20-hydroxyeicosatetraenoic acid (20-HETE) (via CYP ω-hydroxylase), multiple EETs (5,6-, 8,9-, 11,12-, and 14,15-EETs) via CYP epoxygenases (Capdevila, Harris, & Falck, 2002; Muller et al., 2004; Roman, 2002), and alcohol metabolites (Capdevila, Falck, & Estabrook, 1992; Laniado-Schwartzman & Abraham, 1992).

20-HETE is a prominent vasoconstrictive eicosanoid (Zou et al., 1996). *In vivo* anti-sense therapy that decreases 20-HETE levels decreases blood pressure in spontaneously hypertensive rats (Wang et al., 2001). It is suggested that the antihypertensive effects of HO-1 may in part be attributable to the decreased activity of CYP and therefore decreased production of 20-HETE (Escalante, Sessa, Falck, Yadagiri, & Schwartzman, 1989; Zou et al., 1996; Zou et al., 1994). Besides promoting vasoconstriction, 20-HETE induces superoxide and pro-inflammatory cytokines such as IL-6, thus promoting oxidative stress (Cheng et al., 2008; Ishizuka et al., 2008; Singh et al., 2007). The ratio of Ox-HDL/Total HDL strongly predicts cardiovascular risk (Morgantini et al., 2011). Ox-HDL and 20-HETE both upregulate ANG II via NF-kB but Ox-HDL also upregulates 20-HETE (Peterson, Shapiro, et al., 2019; Peterson, Vanella, Bialczak, et al., 2016). The inflammation and oxidative stress that results from Ox-HDL, 20-HETE and ANG II, combined with less adiponectin, is responsible for both mitochondrial dysfunction and destruction as well as endothelial cell dysfunction. The induction of 20-HETE counteracts elevation of HO-1 expression, suggesting a role for HO-1 in reducing vasoconstrictor pathways (Gupte et al., 2012; Haugen, Croatt, & Nath, 2000) (Fig. 11).

EETs are quickly hydrolyzed to form dihydroxyepoxytrienoic acids (DHET) via the action of soluble epoxide hydrolase (sEH) (Arnold et al., 2010). EETs inhibit inflammatory responses (Node et al., 1999), exert anti-apoptotic effects (Geng et al., 2017), and promote vasodilation, salt excretion and epithelial cell growth (Imig, 2005; Roman, 2002; Spector & Norris, 2007). EETs have a vasoprotective role via the induction of the CYP epoxygenase responsible for 11,12-EET formation (CYP2C23) (Muller et al., 2004) and the inhibition of sEH (Imig, 2005; Spector & Norris, 2007).

EET induced HO-1 expression leads to reduced adipocyte differentiation (Burgess et al., 2012; Burgess, Vanella, Bellner, Schwartzman, & Abraham, 2012; Kim et al., 2010; Vanella et al., 2010) and hypertrophy (Abraham et al., 2016). *In vivo* studies showed that EETs

and sEH inhibition reduce visceral subcutaneous adipose tissue and insulin resistance (Burgess et al., 2010; Ndisang, 2010; Nicolai et al., 2009; Peterson et al., 2008). EET levels are also suppressed in obesity (Zha et al., 2014). EETs increase HO-1 thus promoting depletion of heme, exerting a negative feedback loop on CYP function. 12,13-dihydroxy-9Z-octadecenoic acid (12,13-DiHOME), another prominent ω-6 PUFA metabolite (Hildreth, Kodani, Hammock, & Zhao, 2020) increases fatty acid uptake into BAT, normalizing hypertriglyceridemia.

3.4. Linoleic acid, eicosapentaenoic acid and HO-1

Eicosapentaenoic acid (EPA) is an anti-inflammatory ω-3 PUFA derived from alpha-linoleic acid (aLA). These compounds are anti-atherogenic, anti-arrhythmic, antihypertensive, anti-inflammatory and antithrombotic (Bargut, Frantz, Mandarim-de-Lacerda, & Aguila, 2014). ω-3 PUFAs are obtained from the diet including flax seeds, a good source of α-LA (Parikh et al., 2019; Parikh, Netticadan, & Pierce, 2018), while EPA can be obtained from the skin of some fish, flax, hemp, poppy and sesame seeds (Bargut et al., 2014). EPA is metabolized via CYPs to form epoxyeicosatetraenoic acids (EEQs) (Fleming, 2014), which are metabolized to form dihydroxyeicosatetraenoic acid (DHEQ) via sEH (Fleming, 2014; Karara, Dishman, Falck, & Capdevila, 1991).

EPA may attenuate some symptoms of obesity through its antioxidant properties and cardioprotective effects, but there is conflicting research on its ability to decrease visceral fat volume in humans. In an animal study combining a high fat diet (HFD) alongside ω-3 PUFA supplementation, those receiving ω-3 PUFA showed reduced ratio of oxidized to reduced glutathione in the liver, indicating decreased oxidative stress (Bautista et al., 2001). A direct decrease in pro-inflammatory molecules TNF-α and IL-6, with EPA supplementation, has been reported (Engstrom et al., 2002). Rats administered a chronic EPA enriched diet had more robust antioxidant properties across the heart indicating a cardioprotective effect (Leger et al., 2019; Macartney, Peoples, & McLennan, 2020). The cardioprotective effect of EPA has clinical implications for a variety of cardiovascular diseases including myocardial infarction and congestive heart failure. In fact, rodents given chronic EPA-ethyl ester treatment before beginning a HFD had improved cardiac function, no congestive heart failure, and improved fatty acid profile (Yamanushi et al., 2014). A number of clinical trials with heart failure patients demonstrated a correlation between ω-3 PUFA supplement and improved outcome (Jiang et al., 2018; Kalstad et al., 2021; Marchioli & Levantesi, 2013; Moertl et al., 2011). EPA reduced mortality after myocardial infarction influencing cardiac remodeling and reducing pro-inflammatory M1 macrophage recruitment (Takamura et al., 2017). EPA may provide these cardioprotective effects through its anti-inflammatory properties and its ability to decrease hypertriglyceridemia (Mori & Beilin, 2004; Zambon, Pirillo, Zambon, Norata, & Catapano, 2020). This triglyceride stabilizing effect of EPA has allowed icosapent ethyl, a highly purified EPA ethyl ester; to obtain FDA approval for the treatment of dyslipidemia (Fares, Lavie, DiNicolantonio, O'Keefe, & Milani, 2014).

The effect of HO-1 and EPA on adipose tissue is well studied. Fish oil derived ω-3 PUFAs attenuate adipose tissue hypertrophy and hyperplasia (Ruzickova et al., 2004), suggesting reprogramming from WAT to BAT. Other studies found beneficial effects on mitochondrial

function in adipose tissue treated with ω-3 PUFAs and reduced hypertriglyceridemia (Flachs et al., 2005). HO-1 is responsible for adipose phenotype reprogramming and promotes healthy mitochondrial function (Singh et al., 2020). The antioxidant properties of EPA have been attributed to the induction of HO-1 (Kusunoki et al., 2013). A dose-dependent increase in HO-1 mRNA and protein levels was found with increasing doses of EPA. Similar findings have been reported in a different cell line (Tatsumi et al., 2019). While many studies find the beneficial effects of fish oil derived ω-3 PUFAs, results are not consistent (Hilleman, Wiggins, & Bottorff, 2020; Shahidi & Ambigaipalan, 2018; Sherratt, Lero, & Mason, 2020).

The effects of EPA ingestion on epicardial and abdominal fat were studied in humans with coronary artery disease (CAD) (Sato, Kameyama, Ohori, Matsuki, & Inoue, 2014). Subjects with chronic EPA supplementation, in addition to conventional therapy, showed increased serum EPA levels and EPA/AA ratios, suggesting reduced systemic inflammation and reduced volume of epicardial and abdominal visceral fat compared to those receiving only conventional therapy. However, other clinical trials failed to replicate this EPA “anti-obesity” effect (de Luis et al., 2016; Lang et al., 2019). Overall, the mechanisms underlying the anti-inflammatory and cardioprotective effects of EPA remain unclear and do not occur alone, but when combined with lifestyle modifications.

Western diets are high in ω-6 PUFAs and have a predominance of pro-inflammatory AA metabolites. Increased consumption of EPA/DHA in rodents increases the ratio of anti-inflammatory ω-3 PUFA metabolites to AA-metabolites (Schunck, Konkel, Fischer, & Weylandt, 2018). This was confirmed in human volunteers with EPA/DHA dietary supplements (Fischer et al., 2014). In a study conducted with overweight and obese children it was found that those with higher endogenous levels of EPA had lower BP and healthier vasculature than other groups (Bonafini et al., 2018).

HO-1 levels are increased by nuclear factor E2-related factor 2 (Nrf2), which itself is induced by the metabolism of ω-3 PUFAs to 4-hydroxy-2E-hexenal (4-HHE) (Bu, Dou, Tian, Wang, & Chen, 2016; Kusunoki et al., 2013; Tatsumi et al., 2019; Singh, Vrishni, Singh, Rahman, & Kakkar, 2010). ω-3 PUFAs are CYP 450 mediated metabolic products of αLA which is ingested from seeds. Hence, increased levels of HO-1 can result from the activity of CYP 450 on both ω-6 and ω-3 PUFAs (Fischer et al., 2014).

ω-3 PUFA supplementation to a HFD mouse decreases systemic oxidative stress (Shang et al., 2017). A reduction in proinflammatory molecules occurs with n-3 FFA supplementation, particularly TNF-α, IL-1, IL-2, IL-6, and NfkB signaling (Endo & Arita, 2016; Kim et al., 2010). Rats kept on an EPA enriched diet possess more robust antioxidant properties in the heart resulting in cardioprotective effects (Zeghichi-Hamri et al., 2010). ω-3 PUFAs serve as an alternate substrate for cyclooxygenase and lipoxygenase, thereby inhibiting the conversion of AA into pro-inflammatory eicosanoids (Calder, 2013; Endo & Arita, 2016). In human trials, the addition of ω-3 PUFAs to statin therapy stabilized vulnerable coronary plaque, reduced plaque macrophage accumulation, total atheroma volume and decreased MCP-1 in monocytes (Baumann et al., 1999; Nishio et al., 2014; Watanabe et al., 2017; Yaqoob & Calder, 2003).

ω-3 PUFAs attenuate the hypertrophy and hyperplasia of adipose tissue, improve adipose tissue mitochondrial function, contribute to browning of WAT, and attenuate hypertriglyceridemia (Flachs et al., 2005; Ruzickova et al., 2004). Most importantly, the beneficial effects of ω-3 PUFAs on adipose tissue and mitochondrial function are attributed to their role in increasing HO-1 expression (Kusunoki et al., 2013; Nakagawa et al., 2014).

3.5. HO-1 and natural herbals

Induction of HO-1 can be achieved with Pomegranate seed oil (Raffaele et al., 2020) and a combination of Thymoquinone with omega 3 oils (ω3) (Shen et al., 2020) Fig. 12). HO-1 upregulation by either of these means results in improved adipocyte function and reverses metabolic syndrome phenotypes in a murine model of dietary-induced obesity (Shen et al., 2020). Importantly, improved HO-1 levels are known to alleviate diabetic cardiomyopathy (Waldman et al., 2019), improve vascular and renal function in type 1 DM (Kruger et al., 2006; Rodella et al., 2008) and demonstrate antiapoptotic and antioxidant effects (Kruger et al., 2006).

HO-1 upregulation can be achieved pharmacologically, although this induction is short-term compared to genetic overexpression (Peterson, Rubinstein, et al., 2019a). In mice, adipocyte-specific expression of HO-1 reduced adipose tissue mass and improved vascular function in mice (Cao, Peterson, et al., 2012). Since pharmacological approaches have not been successful in treating obesity and its related diseases, gene targeted therapy provides an attractive potential alternative. Targeting the HO-1 gene system in endothelial cells and adipocyte tissue has the advantage of re-programming white adipocyte stem cells to brown adipocyte stem cells, or browning of white fat, that prevents inflammation in adipose tissue, the liver, and the vascular system. This is achieved mostly through an increase in mitochondrial number and function, a decrease in ROS, Ox-HDL and adipocytokines, and an increase in adiponectin, insulin sensitivity and HO-1/activity. (Peterson, Choudhary, et al., 2020; Sasson et al., 2021). In obese patients HO-1 upregulation decreases the levels of the inflammatory multifunctional matrix protein nephroblastoma overexpressed CCN3 (NOV/CCN3) (Martinerie et al., 2016; Pakradouni et al., 2013; Paradis, Lazar, Antinozzi, Perbal, & Buteau, 2013; Shen et al., 2020) and reduces obstructive sleep apnea (OSA) (Weingarten et al., 2017).

4. Obesity and steatohepatitis – a therapeutic role for HO-1

The therapeutic role for HO-1 in preclinical models of cardiovascular and metabolic disease is summarized in Table 2. Obesity and the consequent heme-iron mediated oxidative stress, fatty acid accumulation and lipotoxicity contribute to the development of nonalcoholic steatohepatitis (NASH). Reduced HO-1 levels correlate with increased NOV levels, a proinflammatory adipokine produced by inflamed adipose tissue and this is responsible for most of NASH metabolic abnormalities (Sacerdoti et al., 2018). Adipose tissue dysfunction is also significantly increased by non-alcoholic fatty liver disease (NAFLD) (Luna-Luna et al., 2015). Any increase in HO-1, reduces the heme-mediated inhibition of the transcription factors PGC1α and FGF21, that regulate liver homeostasis and metabolism. HO-1 restores lipid metabolism and adipogenesis in the liver by acting on these factors and ameliorates

insulin resistance and increases adiponectin production through the antioxidant effects of CO/Bilirubin and upregulation of pAMPK and pAKT pathways (Martin et al., 1991; Regula, Ens, & Kirshenbaum, 2003). EET administration to db/db mice fed a HFD results in reduced fatty acid accumulation, improved NAFLD, and mitochondrial function because of the upregulation of PGC1α-HO-1 mitochondrial signaling (Raffaele et al., 2019). Hepatic steatosis is further complicated by upregulation of the endocannabinoid receptor-1 (CB1) and the resultant increase in synthesis of fatty acids, further increasing insulin resistance. L4F and EET decrease CB-1 expression in both visceral and subcutaneous fat, reduce fat cell size and hepatic lipid content, and reverse fatty liver by upregulation of HO-1 levels (Peterson et al., 2009). The CB-1 receptor, linked to PPARα and CB-1 blockade, reverses hepatic steatosis in wild-type mice, but not in PPARα null or in liver sirtuin-1 (SIRT1) deficient mice (Azar et al., 2020). Importantly, HO-1 upregulates SIRT-1 and PPARα, alleviating oxidative stress and reversing the adipocyte phenotype and hepatic steatosis (Azar et al., 2020; Lakhani et al., 2019). Therapeutic strategies for HO-1 as well as its metabolites are summarized in Table 3.

4.1. The role of bilirubin and biliverdin reductase (BVRA) in the metabolic syndrome – therapeutic implications

Bilirubin is the final product of the heme degradation pathway. HO breaks down heme to biliverdin, which is then reduced to bilirubin via biliverdin reductase-A (BVR-A). BVR-A is a ubiquitous protein that also has functions as transcription factor, signaling molecule and some of its peptide fragments are also endowed with biological activity (Gibbs, Tudor, & Maines, 2012; Kravets, Hu, Miralem, Torno, & Maines, 2004; Maines, 2007; O'Brien, Hosick, John, Stec, & Hinds Jr., 2015). Bilirubin mediates many protective effects (Clark et al., 2000; Liu et al., 2015; Yamaguchi et al., 1996). Plasma levels of bilirubin correlate with protection against cardiovascular and metabolic diseases and are predictive of risk of obesity and diabetes (Jenko-Praznikar, Petelin, Jurdana, & Ziberna, 2013; Kwon, Lee, & Lee, 2018; Seyed Khoei et al., 2018; Wang et al., 2017; Wu et al., 2011) or its complications (Bulum, Tomic, & Duvnjak, 2018; Hamamoto et al., 2015; Riphagen et al., 2014). Also, an inverse relationship between plasma bilirubin levels and NAFLD development exists in both adults and children (Hjelkrem, Morales, Williams, & Harrison, 2012; Kumar, Rastogi, Maras, & Sarin, 2012; Kwak et al., 2012; Puri et al., 2013).

Bilirubin is a potent antioxidant (Stocker & Peterhans, 1989; Stocker, Yamamoto, McDonagh, Glazer, & Ames, 1987). Bilirubin treatment of leptin receptor-deficient, db/db, and dietary-induced obese mice decreases ER stress and inflammation, improving insulin sensitivity (Dong et al., 2014). Bilirubin also acts as a ligand for PPARα and activates target genes (Stec et al., 2016). This was confirmed by competitive ligand-bind assays and chromatin immunoprecipitation (ChiP) assays for PPARα enrichment at gene promoters (Gordon et al., 2020; Stec et al., 2016). Bilirubin was found to remodel WAT through alterations in coregulator recruitment in the promotor of PPARα, promoting positive coregulators' binding and decreasing the binding of negative coregulators in the PPARα promotor (Gordon et al., 2020) Bilirubin activates the transcription of a number of genes in the presence of PPARα as opposed to when PPARα is absent (~400 vs. 23 genes) (Gordon et al., 2019). One of the PPARα targets induced by bilirubin is Cytochrome

P450 4A proteins (Vera et al., 2005), which are important in the hydroxylation of AA to 20-HETE (Rocic & Schwartzman, 2018; Roman, 2002). Thus, it appears that bilirubin is a novel hormonal regulator of obesity and metabolism (Hinds Jr. & Stec, 2018; Hinds Jr. & Stec, 2019). Gilbert's syndromeis a condition of moderate hyperbilirubinemia due to mutations in the promotor of the UDP glucuronosyltransferase 1A (UGT1A1) (Chen et al., 2012; van der Wegen et al., 2006). Mutations in UGT1A1, including the Gilbert's associated *28 allele are protective against the development of cardiovascular disease and metabolic syndrome (Schwertner & Vitek, 2008; Seyed Khoei et al., 2018). Additional studies in Gilbert's patients have demonstrated increased levels of PPARα target genes and reduced protein expression of the ATP-binding cassette transporter A1 (ABCA1) and decreased cholesterol transport in these individuals (Molzer et al., 2016; Wang et al., 2017). Likewise, humanized *28 transgenic mice are protected from HFD-induced obesity, hyperglycemia, and hyperinsulinemia (Hinds Jr. et al., 2017). PPARα is regulated by phosphorylation at serine 73[(Ser(P)(73)], which decreases its activity by reducing its protein levels via enhanced proteasomal degradation through the ubiquitin pathway (Hinds Jr. et al., 2016). Humanized *28 transgenic mice have decreased levels of Ser(P)(73) PPARα and increased levels of PPARα-target gene expression, suggesting a protective role of moderate hyperbilirubinemia via enhanced PPARα activity (Hinds Jr. et al., 2017).

Low levels of BVR-A expression in human VAT are associated with increased adipocyte size and enhanced expression of inflammatory cytokines resulting in VAT dysfunction (Ceccarelli et al., 2020). BVRA expression is reduced in peripheral blood mononuclear cells from obese patients altering insulin signaling pathways and contributing to insulin resistance (Cimini et al., 2019). Mice with adipose-specific knockout of the *Blvra* gene exhibit increased deposition of visceral fat, adipocyte hypertrophy, decreased adipocyte mitochondria, and increased adipose inflammation (Stec et al., 2020). Similar to humans with reduced levels of adipocyte BVR-A, adipose-specific *Blvra* knockout mice are insulin resistant and exhibit alterations in insulin signaling (Stec et al., 2020). Not only does the whole BVR-A protein regulate adipocyte function and insulin signaling, but the c-terminal peptide of human BVR-A increased glucose uptake in hepatocytes and improved glucose clearance and hyperglycemia in obese leptin-deficient *ob/ob* mice (Gibbs, Lerner-Marmarosh, Poulin, Farah, & Maines, 2014; Gibbs, Miralem, Lerner-Marmarosh, & Maines, 2016). Taken together, the results from studies in both obese humans as well as mice lacking BVR-A in adipocytes demonstrate the critical role of BVR-A in the regulation of adipocyte function, inflammation, and insulin action and suggests that treatment with the c-terminal peptide fragment could be a novel treatment for type II diabetes.

Numerous studies have examined the relationship between plasma levels of bilirubin and NAFLD incidence in several patient populations. Population studies from China, Korea, and India found that NAFLD incidence correlated negatively with plasma bilirubin levels (Kumar et al., 2012; Kwak et al., 2012; Tian et al., 2016). Higher plasma bilirubin levels also decreased NAFLD progression to the more severe condition, NASH (Hjelkrem et al., 2012). The protective effect of bilirubin against NAFLD progression to NASH was also observed in children (Puri et al., 2013). Bilirubin acts as a ligand for PPARα increasing its target gene expression as well as increasing its activity via decreasing Ser(P)(73) to reduce turnover (Fig. 13A). PPARα is an important gene that protects against NAFLD, and hepatocyte-

specific deletion of *Ppara* gene results in enhanced hepatic lipid accumulation (Seo et al., 2008; Stec et al., 2019). Cultured hepatocytes, with a CRISPR/Cas9 mediated deletion of *Blvra*, also exhibit enhanced lipid accumulation and increases in oxidative stress, reduced mitochondria number and mitochondrial biogenesis markers, and reduced mitochondrial oxygen consumption (Gordon et al., 2019) (Fig. 13B). All of this evidence suggests that bilirubin could be a potential treatment for NAFLD (Hinds Jr., Adeosun, Alamodi, & Stec, 2016). However, given its low solubility, direct treatment with bilirubin is not viable. Formulations of more soluble forms of bilirubin coupled to pegylated nanoparticles (PEG-BR) have been developed to circumvent the limited water solubility of bilirubin (Kim et al., 2017; Lee et al., 2016). A recent study used PEG-BR in a model of dietary obesity-induced NAFLD. Dietary-induced obese mice were treated with PEG-BR for 6 weeks, and several indices of hepatic steatosis and insulin resistance were measured (Hinds Jr. et al., 2020). PEG-BR decreases hepatic fat content as measured by Echo-MRI as well as Oil Red O staining and decreased hepatic triglyceride levels (Hinds Jr. et al., 2020). PEG-BR treatment lowered fasting blood glucose levels and improved insulin sensitivity in the dietary-induced obese mice while only resulting in a moderate (50%) increase in plasma bilirubin levels (Hinds Jr. et al., 2020). Moreover, PEG-BR treatment decreased *de novo* lipogenesis and increased fat-burning β-oxidation, providing metabolites for enhanced ketone production (Hinds Jr. et al., 2020). These results demonstrate the therapeutic potential of moderate hyperbilirubinemia for the treatment of NAFLD (see also Table 3).

5. The interface Of Ho-1 with adipose tissue and heart failure

Heart failure (HF) currently affects more than 37 million persons worldwide (Braunwald, 2015). It is characterized by a progressive decline in the ability of the heart to maintain an adequate cardiac output to meet body requirements (Ziaeian & Fonarow, 2016). The heart has a high energy demand, and in pathological conditions such as HF, it is the altered regulation of cardiac fatty acid and glucose metabolism that contributes to cardiac dysfunction (Neely & Morgan, 1974; Neubauer, 2007). Obesity is associated with inflammation of the heart, often leading to myocardial infarction (MI), reduction in left ventricular (LV) function, and reduced ejection fraction (Lutton, Schwartzman, & Abraham, 1989). For each incremental increase of 1 point in BMI, the heart failure risk increases by greater than 5% in both sexes (Sciomer et al., 2020). The link between obesity and heart disease is such that it was recently the subject of an extensive scientific statement by the American Heart Association (Powell-Wiley et al., 2021).

Adipose tissue serves as a powerful regulator of cardiovascular function via multiple mechanisms. In addition to direct myocardial lipotoxicity, adipose tissue has profound endocrine and paracrine effects that alter cardiovascular activity both directly and indirectly. In the process, adipose tissue elaborates a multiplicity of signaling factors that influence cardiac function both positively and negatively through a variety of complementary pathways. In particular, the axis comprising adiponectin, cytochrome P450 metabolites of AA and αLA, HO-1, EET, and PGC-1α plays a powerful role in both the endocrine and the paracrine regulation of myocardial function. In so doing, this axis has the capability to antagonize leptin resistance, reduce the activity of multiple inflammatory mediators, enhance mitochondrial bioenergetics, assist in the browning of WAT, and improve LV

ejection fraction (LVEF). Most importantly, evidence is emerging that adipose tissue located proximal to the heart itself plays a prominent role in myocardial function in both a positive and negative manner. The following sections review these pathways in detail and their effect on both the cause and potential treatment of the failing heart.

5.1. Cardiac lipotoxicity: how fat can directly damage the heart

Lipotoxicity has a negative effect on myocardial function at multiple intracellular sites. Increased delivery of saturated FFA to the myocyte enhances triglyceride accumulation and resultant ceramide biosynthesis (Summers, Chaurasia, & Holland, 2019). The accumulation of ceramide drives apoptosis and myocardial hypertrophy (Drosatos, 2016; Rodríguez-Calvo et al., 2007; Yaguchi, Nagashima, Izumi, & Okamoto, 2003; Zhou et al., 2000). Cardiomyocyte ceramide is markedly elevated in the failing right ventricles of humans with pulmonary hypertension, and plasma ceramide levels correlate with both severity and mortality in patients with heart failure (Brittain et al., 2016; Yu et al., 2015). Ceramides derived from adipose tissue have also been shown to be modifiable regulators of vascular redox state in obese humans, and are tied to an increase in cardiac mortality in patients with advanced atherosclerosis (Akawi et al., 2021). A further complicating factor noted in the failing human ventricle is impairment of mitochondrial beta-oxidation resulting from a decrease in the intracellular acylcarnitine concentration (Neubauer, 2007). Downregulation of mitochondrial beta-oxidation is induced by a decrease in expression of PGC-1α (Finck & Kelly, 2006; Lopaschuk, Folmes, & Stanley, 2007). Other potential mediators of cardiac lipotoxicity include microRNAs (miRNA) which are either induced or repressed by lipid overload in cell culture (Kuwabara et al., 2015).

5.2. Role of adiponectin – a connection to the HO-1 axis

Adiponectin is the most abundant of the circulating adipokines but is also found secreted in small amounts by multiple organs including the myocardium (Achari & Jain, 2017; Sharma & Abraham, 2016; Vaiopoulos, Marinou, Christodoulides, & Koutsilieris, 2012). It circulates as a trimer, a hexamer, and a high molecular weight multimer which exert the majority of their effects by binding to two receptor sites, adiponectin receptor 1 and 2 (adipoR1 and adipoR2) (Yamauchi et al., 2003). In the vascular endothelium, hexameric adiponectin is primarily bound to T-cadherin (Parker-Duffen et al., 2013). AdipoR1 binding results in an influx of calcium into the cell resulting in activation of calcium/calmodulin-dependent protein kinase kinase beta (CaMKKβ) with secondary activation of AMPK and SIRT1 (Iwabu et al., 2010). In the adipocyte, SIRT1 deacetylates PPARγ in WAT promoting conversion to BAT with a resultant increase in thermogenesis (Qiang et al., 2012). In the adipocyte nucleus, SIRT1 deacetylates nuclear factor kB (NfkB), inhibiting its transcriptional activity and reducing inflammation (Yeung et al., 2004).

In the cardiomyocyte, circulating adiponectin primarily binds to adipoR1 resulting in activation of SIRT1 which deacetylates PGC-1α and increases its expression (Nemoto, Fergusson, & Finkel, 2005). As described earlier, PGC1α increases Cyp-450-derived EET and HO-1 levels. This, in turn, results in enhanced mitochondrial biogenesis, improved bioenergetics, and thermogenesis. Biologically active endogenous adiponectin is synthesized by the cardiomyocyte, however the precise mode of action remains unknown (Wang et al.,

2010). One of the key pathways through which PGC-1α functions in both the target myocyte and the adipocyte is via mediation of EET induced increase in HO-1 levels and HO activity (Singh, Bellner, et al., 2016; Singh, Schragenheim, et al., 2016; Waldman et al., 2016). Enhanced HO-1 levels increased EET as well as further activation of SIRT1 both of which attenuate adipocyte dysfunction and increase PGC-1α expression (Burgess, Vanella, Bellner, Schwartzman, & Abraham, 2012; Lakhani et al., 2019; Li et al., 2008). This sets in motion a feedback loop wherein PGC-1α increases HO-1 synthesis, which in turn increases EET synthesis, further enhancing PGC-1α activity (Bellner et al., 2020). In a similar feedback mechanism, enhanced HO-1 levels increase adiponectin and reduce its oxidation resulting in reduced adipogenesis and a reduction in inflammatory cytokines (Kim et al., 2008; L'Abbate et al., 2007).

5.3. Role of endotrophin in fat-mediated inflammation

Endotrophin is a proinflammatory and profibrotic adipokine elaborated by WAT. Local overexpression of endotrophin increases several collagens in WAT resulting in local fibrosis and dysfunction of BAT (Sun et al., 2014). Collagen deposition in adipose tissue is associated with local attraction of macrophages which, in turn, secrete proinflammatory factors including IL-1β, TNFα, and MCP-1 (Halberg et al., 2009; Xu et al., 2003). The resulting local stress leads to secondary adipocyte death and both local and systemic inflammation (Sun, Kusminski, & Scherer, 2011).

6. The HO-1-EET-PGC-1α axis and cardiac function

6.1. The role of EET

Among other things, EET augments the phosphoinositide 3 kinase (PI3K) pathway with secondary increase in protein kinase B (Akt) resulting in both an increase in myocardial angiogenesis and inhibition of apoptosis (Dhanasekaran et al., 2008; Spector & Norris, 2007). Treatment with an EET agonist increases serum adiponectin and vascular and adipose tissue levels of EET and HO-1 in rats fed a HFD, while decreasing blood pressure, subcutaneous and visceral adipose tissue, TNFα and IL-6 (Kim, Vanella, et al., 2010). Concurrently, EET upregulation increases eNOS expression with a resultant improvement in aortic endothelial function, and restores levels of AMPK, Akt, SIRT1, and FAS. In the adipocyte, EET attenuated adipose tissue expansion and enhanced metabolic efficiency (Zha et al., 2014). This is accomplished by the induction of HO-1, which results in increased levels of HO-1, improved adipocyte function, conversion of large white adipocytes to smaller brown or beige adipocytes, and a reduction in inflammation (Burgess et al., 2010; Vanella et al., 2011).

In the diabetic myocardium, EET provides protection from cardiomyopathy and cardiac hypertrophy in mice with streptozotocin-induced diabetes mellitus (Ma et al., 2013). EET decreases myocardial fibrosis and inflammation, reduces hypertrophy, and improves diastolic function in a mouse model of the metabolic syndrome (Roche et al., 2015). Increased EET levels restored microvascular function in the hearts of diabetic mice (Kusmic et al., 2010; Roche et al., 2015). EET decreases myocardial fibrosis, inflammation, and diastolic dysfunction in a mouse model of the metabolic syndrome (Roche et al., 2015).

It also reverses myocardial mitochondrial dysfunction resulting from Ischemia/reperfusion injury (Katragadda et al., 2009). Also, EET increases glucose sensitization both directly and via its activation of HO-1, providing protection to the cardiomyocyte from lipotoxicity by reducing its dependence on FFA for fuel (Burgess, Vanella, Bellner, Schwartzman, & Abraham, 2012).

Ischemic cardiomyopathy is characterized by an increase in ROS during reperfusion of the ischemic zone as well as in sites remote from the infarct (Grieve, Byrne, Cave, & Shah, 2004; Kim et al., 1998). Similar to diabetic cardiomyopathy, plasma, adipose tissue, and cardiac adiponectin levels are lower in this population and are accompanied by a concomitant increase in ROS leading to myocardial fibrosis and heart failure (Kalisz et al., 2015; Sovari, Shroff, & Kocheril, 2012). EET improves LV function and decreases myocardial fibrosis acutely and for as long as a week after infarction in murine models (Di et al., 2011; Merabet et al., 2012). The EET-induced decrease in fibrosis is blocked by inhibition of HO activity demonstrating a dependence upon HO activity (Cao et al., 2015).

EET is metabolized by sEH to the less active DHET (Imig, 2012). Inhibition of sEH results in EET accumulation and retention in target tissues, thus, an sEH inhibitor as therapy for cardiovascular diseases, particularly atherosclerosis and cardiomyopathy, has been considered (He, Wang, Zhu, & Ai, 2015; Imig, 2006; Imig & Hammock, 2009). At least two sEH inhibitors have completed phase 1 safety trials in humans, however more robust evaluation of these compounds remains to be performed (Tripathi et al., 2018).

6.2. The role of HO-1

Enhanced HO-1 expression decreases fat deposition, adipocyte terminal differentiation, and hypertrophy with a concomitant reduction in TNF-α, IL-6, and MCP-1 levels (Cao, Peterson, et al., 2012; Waldman et al., 2016). HO-1 plays a central role in promoting and maintaining beige adipose tissue and improves cardiovascular function, as a result of which, HO-1 upregulation has been investigated as a therapeutic approach for the treatment of obesity and its associated metabolic and cardiovascular complications (Abraham et al., 2016; Abraham & Kappas, 2008; Drummond, Mitchell, Abraham, & Stec, 2019). HO-1 inhibits formation of inflamed large WAT and enhances browning of WAT.

In the myocardium, HO-1 enhances mitochondrial quality control and limits myocyte death (Piantadosi, Carraway, Babiker, & Suliman, 2008; Suliman, Keenan, & Piantadosi, 2017). In a mouse model of diabetic cardiomyopathy, L-4F increases cardiac expression of HO-1, AMPK, and eNOS, provides protection from diabetic cardiomyopathy and coronary dysfunction, reduces subcutaneous and total fat, increases insulin sensitivity and adiponectin levels, and decreases inflammatory cytokine levels, thereby improving cardiac function (Peterson et al., 2009). Similarly, L4-F reduces coronary resistance in an isolated heart (Vecoli et al., 2011). HO-1 induction improves cardiac function, enhances coronary flow, blunts oxidative stress, and reverses LV systolic and diastolic dysfunction in diabetic rats (Cao et al., 2012). In rat and mouse models of ischemic cardiomyopathy, increased HO-1 levels are associated with an antioxidant related increase in survival (Collino et al., 2013b; Issan et al., 2014b). Enhanced HO-1 levels reduce heart to body weight ratio, peri-infarct hypertrophy, and chronic inflammation in a rat model of MI (Chen et al., 2013). Increased

HO-1 levels and HO activity are associated with an increase in cardiac allograft survival in a murine model (Evans et al., 2012).

Recently, SGLT2 inhibitors have demonstrated efficacy in enhancing LV function in patients with heart failure with and without diabetes (McMurray et al., 2019; Packer et al., 2020). One of the mechanisms by which this occurs is the ability of empagliflozin and canagliflozin to stimulate the Nrf2/HO-1 pathway leading to an increase in HO-1 levels in the heart and vasculature (Behnammanesh, Durante, Khanna, Peyton, & Durante, 2020; Li et al., 2019). HO-1 expression is increased by EET-mediated downregulation of Bach-1 (a negative regulator of HO-1) (Sodhi et al., 2012). EET-agonists have indeed been used to increase EET levels and downregulate stem cell differentiation of adipocytes by augmenting the Wnt signaling pathway and downregulating PPARγ and C/EBPα (Kawai et al., 2007). Importantly, EET induced HO-1 expression and activity improves insulin sensitivity and reduces inflammatory cytokines which has important potential therapeutic potential in obesity and the metabolic syndrome (Vanella et al., 2011).

6.3. The role of PGC-1α

PGC-1α is a coactivator of PPAR-γ which enhances expression of UCP-1 and promotes thermogenesis and browning of WAT (Bostrom et al., 2012; Puigserver et al., 1998). In addition, PGC-1α promotes mitochondrial biogenesis and enhances oxidative metabolism in adipose tissue, skelet al muscle, and the myocardium (Mitra et al., 2012; Puigserver & Spiegelman, 2003). Conversely, the absence of PGC-1α results in a decrease in mitochondrial biogenesis and an increase in fatty acid oxidation and insulin resistance (Kleiner et al., 2012) in mouse adipose tissue.

In the mitochondrion, PGC-1α is responsible for the detoxification of ROS (St-Pierre et al., 2003; Valle, Alvarez-Barrientos, Arza, Lamas, & Monsalve, 2005). In addition to enhancing bioenergetics, PGC-1α prevents the buildup of by-products of oxidative metabolism (Austin & St-Pierre, 2012). Overexpression of PGC-1α in endothelial cells reduced ROS levels of, rescued ROS-mediated mitochondrial toxicity and cellular apoptosis, and increased levels of AMPK, preventing oxidative cell injury (Schulz et al., 2008; Won et al., 2010).

PGC-1α is a required intermediate in the beneficial effect of EET and HO-1 on adipocyte differentiation (Waldman et al., 2016). PGC-1α is essential for the positive effects of EET and HO-1 on mitochondrial bioenergetics to occur (Singh, Bellner, et al., 2016; Singh, Schragenheim, et al., 2016). Moreover, elimination of HO-1 in adipose tissue results in a reduction in PGC-1α and loss of mitochondrial integrity (Singh et al., 2017). Hence, EET, PGC-1α, and HO-1 comprise a positive feedback loop that enhances mitochondrial biogenesis and oxidative function during adipogenesis.

In the myocardium PGC-1α is required for FFA beta oxidation in the cardiomyocyte mitochondrion (Vega, Huss, & Kelly, 2000). In addition, PGC-1α is critically involved in mitochondrial biogenesis via activation of estrogen-related receptors and coactivation of nuclear respiratory factor 1 (NRF-1) (Huss et al., 2007; Lehman et al., 2000; Mitra et al., 2012). Hearts of PGC-1α knockout mice have reduced levels of ATP and an inability to increase work output in response to stimuli (Arany et al., 2005). Similarly, PGC-1α

deficiency is associated with LV dilatation and poor cardiac contractility (Arany et al., 2005). Conversely, an EET-induced increase in myocardial PGC-1α restores normal cardiac contractility (Cao et al., 2017).

6.4. A role for NOV/CCN3 in adipose tissue and the myocardium

NOV is a multifunctional matricellular protein that is synthesized and secreted by adipose tissue, with plasma levels highly correlated to BMI (Pakradouni et al., 2013). It is involved in many pathophysiological processes including tissue repair, fibrotic and inflammatory diseases, and cancer (Chen & Lau, 2009; Kular, Pakradouni, Kitabgi, Laurent, & Martinerie, 2011; Marchal et al., 2015) and the pathogenesis of inflammation and insulin resistance (Le et al., 2010; Martinerie et al., 2016). Induction of NOV results in increased adipose tissue deposition and enhanced cholesterol and plasma triglyceride levels in human cardiometabolic patients, and it has recently been implicated in the pathogenesis of obstructive sleep apnea (OSA) (Pakradouni, Le, et al., 2013; Weingarten et al., 2017). Moreover, NOV is increased in the adipose tissue of obese mice, resulting in mitochondrial dysfunction (Sacerdoti et al., 2018). NOV is increased in the cardiac tissue of obese mice with marked LV dysfunction. An EET agonist has been shown effective in reducing NOV expression and normalizing cardiac function (Cao et al., 2017).

6.5. The special role of epicardial and pericardial fat in CVD

Along with VAT, EAT shares a common embryologic origin with cardiomyocytes (Marchington, Mattacks, & Pond, 1989). Epicardial fat is anatomically directly adjacent to the epicardium and is not separated by a fascial layer (Iacobellis, Corradi, & Sharma, 2005). The lack of a barrier between EAT and the myocardium facilitates the transport of adipokines into the heart with relative ease by several mechanisms, including a concentration gradient. This is confirmed by greater expression of NOV in the adipose tissue proximal to the heart than in the myocardium of obese mice (Cao et al., 2017). EAT secretes a remarkably large number of inflammatory mediators compared to subcutaneous fat (Mazurek et al., 2003). Adipose tissue accumulation and coincident inflammation adjacent to the epicardium and pericardium is associated with a local decrease in HO-1 levels and an increase in ROS resulting in altered cardiac structure and decreased function (Liu et al., 2011; Pucci et al., 2014). EAT and pericardial adipose tissue (PAT) in humans is associated with cardiac remodeling and cardiomyopathy, which increases the likelihood of further obesity, insulin resistance, and LV dysfunction (Fuster, Ouchi, Gokce, & Walsh, 2016; Graner et al., 2014). Similarly, adiponectin expression in human EAT is lower in patients with coronary disease than in other fat depots of normal controls (Baker et al., 2006; Iacobellis et al., 2005).

In humans, the quality of the fat in EAT and PAT and its associated paracrine signaling pathways seems to be of greater importance than its volume. In an obese mouse model, EET augmentation in pericardial fat increases levels of HO-1 via enhancement of PGC-1α expression, resulting in an increase in the Wnt1/beta catenin axis, mitochondrial function, adiponectin secretion, and normalized LV fractional shortening, with concurrent decreases in NOV, TNFα, IL-6, aP2, and mesoderm-specific transcript (MEST) (Cao et al., 2017). Of greater importance, Wnt1 and beta catenin levels, in response to EET, are higher in

the pericardial fat than in the myocardium, again suggesting that localized adipose tissue regulates myocardial signaling. Moreover, NOV expression in the PAT of obese mice is greater than that found in VAT and the same phenomenon has been observed in the EAT of humans with coronary disease (Singh et al., 2019; Xie et al., 2020). Consequently, epicardial fat appears to play a critical role in the pathogenesis of heart failure and therefore constitutes a novel target for the treatment of both obesity and its related cardiomyopathic syndromes.

6.6. Epicardial fat and COVID cardiomyopathy

The observation that EAT volume was greater in young patients with severe COVID-19 when compared to subcutaneous adipose tissue volume led to speculation on the role played by EAT in the pathogenesis of this virus (Deng et al., 2020). This speculation has been bolstered by the observation that angiotensin-converting enzyme 2 (ACE-2) is the entry ligand receptor of COVID-19 and a decrease in ACE-2 is associated with EAT inflammation (Patel et al., 2016). Adipose tissue attenuation on CT scanning has been associated with inflammation and the severity of EAT attenuation is correlated with the clinical severity of COVID-19 (Iacobellis et al., 2020; Iacobellis & Mahabadi, 2019). COVID-19 not only binds ACE-2 receptors but also porphyrin molecules and removes iron and oxygen to form a COVID-19-Porphyrin complex, hence behaving as a metalloporphyrin and inhibiting HO activity (Hooper, 2020; Liu & H., 2020). Dexamethasone, which has induced a favorable response in particularly severe cases, is an inducer of HO-1 thus increasing bilirubin production (Vallelian et al., 2010). This, along with the observation that HO-1 is inhibited by the virus, has led to the hypothesis that increased levels of HO-1 may be a suitable therapeutic target for amelioration of the cytokine storm associated with COVID-19 (Fakhouri et al., 2020; Wagener et al., 2020).

6.7. The cardiac pathways summarized

In summary, adipose tissue signaling and particularly that of PAT and EAT involves key pathways that control myocardial function. Products of CYP 450 activity appear to be master regulators of adipose tissue signaling and cardiac function, and CYP 450 activity promotes the metabolism of both ω-6 and ω-3 FFA into a series of positive feedback loops that includes EET, PGC-1α, HO-1, and adiponectin.

All these pathways inhibit the activity of NOV, TNFα, IL6, IL1β, MEST, and aP2, products of inflamed WAT. Reduction in NOV production itself appears to lead to enhanced EET-PGC-1α-HO-1-Wnt1 signaling that, in turn, improves cardiac mitochondrial function, energy metabolism, and LV function in the failing heart (Cao et al., 2017).

There are therefore at least three interconnected positive feedback loops that function in EAT. The first begins with EET, augmentation of which increases production of PGC1α which in turn increases HO-1 and further enhances EET activity. The second begins with HO-1 which increases secretion of adiponectin which binds to adipoR1, increasing SIRT1 which deacetylates PGC-1α and leads to further increases in HO-1. The third involves the activation of SIRT1 by adiponectin binding to adipoR1 binding which promotes browning of WAT leading to increased adiponectin secretion. All these feedback loops can enhance mitochondrial function, inhibit the negative effects of NOV and other inflammatory

mediators, enhance the Wnt1/beta catenin pathway, and restore LVEF in the failing heart. These interconnected pathways provide multiple targets for pharmacologic intervention in the treatment and prevention of cardiomyopathy, however the one entity that is common to all three is HO-1 (see diagram in Fig. 14).

7. Conclusion

The targeting of HO-1 and its biologically associated signaling pathways offers a unique opportunity for the treatment of obesity related illness, particularly the metabolic syndrome, NAFLD and heart failure. HO-1 levels can be enhanced through either pharmacological or natural product inducers, with a consequent increase in CO and bilirubin, the metabolically active products of heme degradation, and a concurrent increase in levels of key mediators such as EET, PGC1α, and adiponectin. These pathways have the potential to reverse leptin resistance, promote browning of WAT, improve glucose homeostasis, enhance endothelial function, and improve LV function. Strategies to accomplish this can potentially offer significant protection from and treatment for end-organ injury due to diabetes, hypertension, obesity, and its attendant inflammation.

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Abbreviations:

AA	Arachidonic acid
AdipoR1	Adiponectin Receptor-1
AdipoR2	Adiponectin Receptor-2
AgRP	Agouti-related protein
Akt	Protein kinase B (PKB)
AMPK	AMP-activated protein kinase
AngII	Angiotensin II
AP-1	Activator protein *1*
ARC	Arcuate Nucleus
ATP	Adenosine Triphosphate
BACH1	BTB Domain And CNC Homolog 1
BMI	Body Mass Index
BAT	Brown Adipose Tissue
BVR-A	Biliverdin Reductase-A

CO	Carbon Monoxide
CoPP	cobalt protoporphyrin
CVD	Cardiovascular Disease
CYP	Cytochrome P450
EAT	Epicardial Adipose Tissue
ET-1	Endothelin-1
EET	Epoxyeicosatrienoic acid
EPA	Eicosapentaenoic acid
ER	Endoplasmic Reticulum
FGF21	Fibroblast Growth Factor-21
GSK3β	Glycogen Synthase Kinase 3 beta
HF	Heart Failure
HO	heme oxygenase
HO-1	heme oxygenase isozyme 1, inducible form
HFD	High Fat Diet
IL-1	Interleukin-1
IL-6	Interleukin-6
IR	insulin receptor
IRS	Insulin receptor substrate
IRS-1	Insulin receptor substrate type 1
JAK2	Janus kinase 2
LV	Left Ventricle
MCP-1	*Monocyte Chemoattractant Protein-1*
MFN-1	Mitofusin 1
MFN-2	Mitofusin 2
MSC	Mesenchymal Stem Cells
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steato-hepatitis

NO	Nitric Oxide
NOV	Nephroblastoma overexpressed
Nrf2	Nuclear factor E2-related factor 2
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OGF	Osteogenic Growth Factor
Ox-HDL	Oxidized High-Density Lipoproteins
PAT	Pericardial adipose tissue
PI3K	Phosphoinositide 3 kinase
PRDM16	PR domain containing 16
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator type 1 alpha
POMC	Proopiomelanocortin
PPARα	Peroxisome proliferator-activated receptor α
PPAR γ	Peroxisome proliferator-activated receptor γ
PUFA	Polyunsaturated Fatty Acids
ROS	Reactive oxygen species
sEH	Soluble epoxide hydrolase
SGLT2	Sodium-glucose transport protein 2
SIRT1	Sirtuin-1
STAT3	Signal transducer and activator of transcription 3
SNS	Sympathetic Nervous System
TNF-α	Tumor necrosis factor-alpha
UCP	uncoupling protein
UGT1A1	UDP glucuronosyltransferase 1A
VAT	Visceral Adipose Tissue
VMH	Ventromedial nucleus of the hypothalamus
WAT	White Adipose Tissue
Wnt1	Wingless/Integrated-1
20-HETE	20-Hydroxyeicosatetraenoic acid

α-MSH	alpha-melanocyte-stimulating hormone

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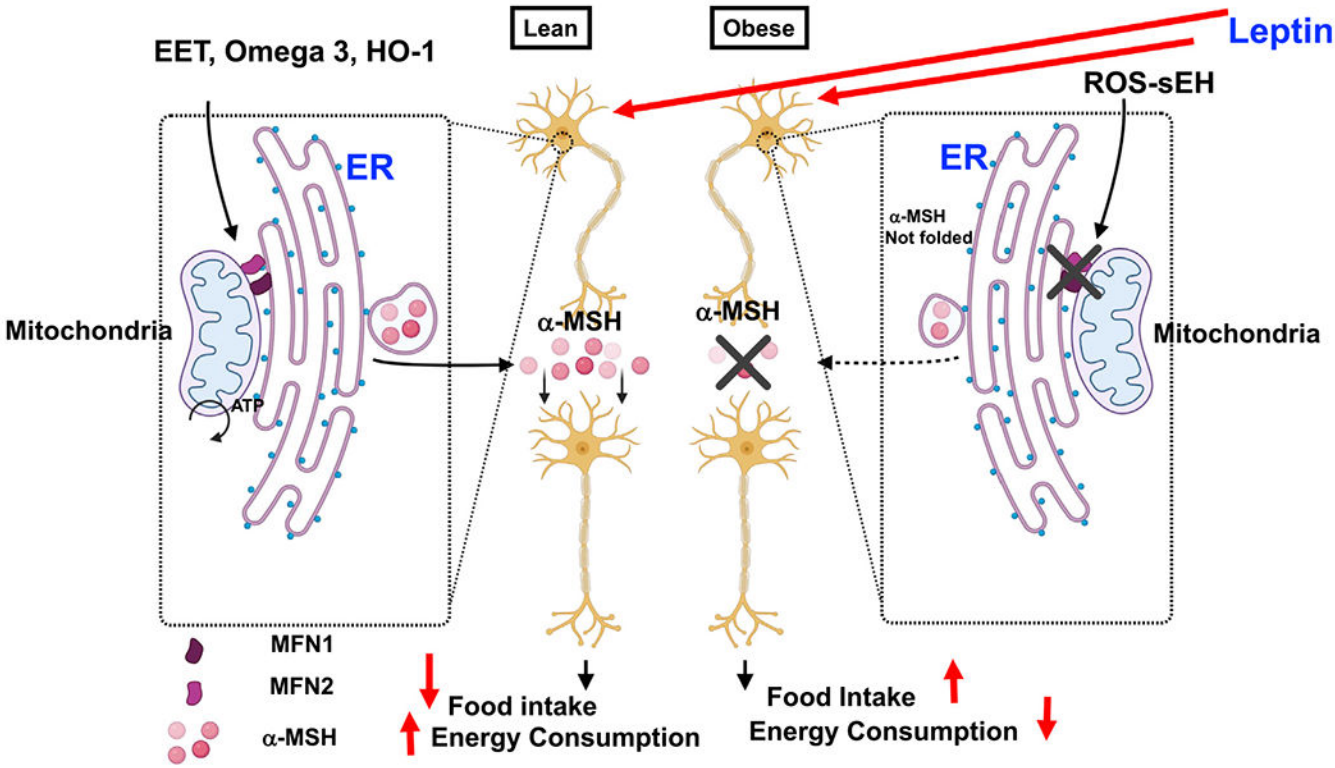

Fig. 1.

Mechanism of Leptin Resistance. Under physiologic conditions, leptin binding to POMC neuron leads to synthesis of the neurotransmitter α-MSH from the ER which, when bound to the target neuron inhibits appetite resulting in diminished food intake and increased energy consumption. This is enhanced by epoxyeicosatrienoic acid (EET) and omega 3 free fatty acid derived HO-1. In the obese subject, inhibition of the fusion proteins Mfn1 and Mfn2 by ROS results in reduced mitochondrial bioenergetics leading to misfolding of α-MSH protein and reduction in neurotransmitter. Leptin levels subsequently climb while food intake rises, and energy consumption drops. EET epoxyeicosatriennoic acid; Omega 3 ω-3 FFA; HO-1 heme oxygenase-1; ROS reactive oxygen species; sEH soluble epoxide hydrolase; ER endoplasmic reticulum; α-MSH alpha melanocyte stimulating hormone; Mfn1 mitofusin 1; Mfn2 mitofusin 2.

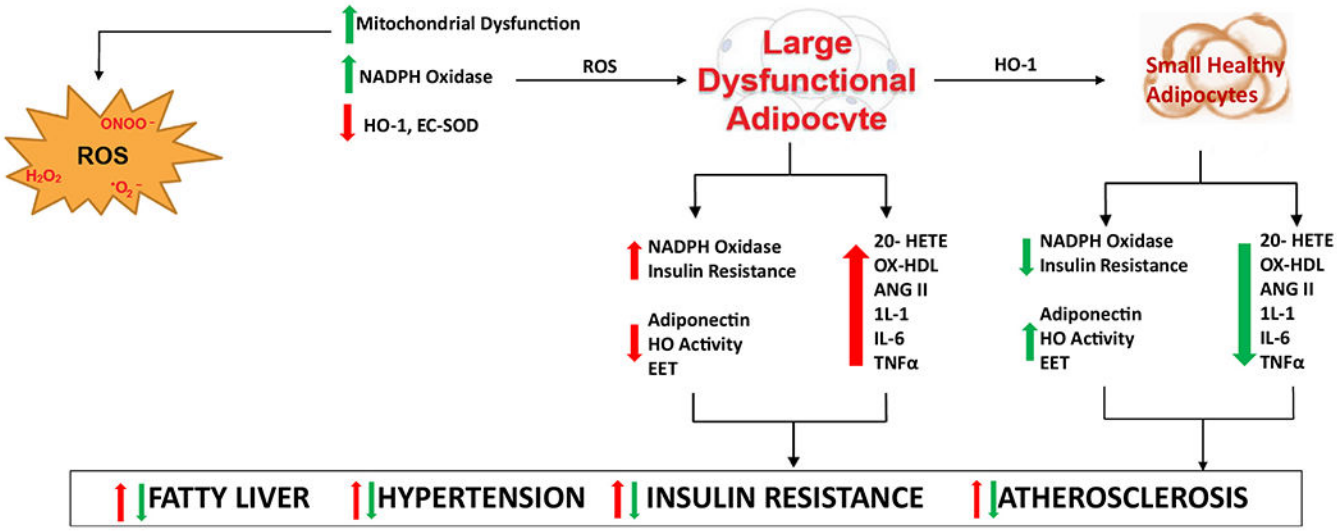

Fig. 2.

ROS, Adipocytes, and Cardiovascular Disease. ROS include peroxynitrite ($ONOO^-$), hydrogen peroxide (H_2O_2) and superoxides (O^-). Obesity and the chronic inflammatory state create ROS with the subsequent release of inflammatory adipocytokines. HO-1 upregulation reverses this process and improves mitochondrial function, and reducing 20-HETE, Ox-HDL, ANG II, IL-6, IL-1 and TNFα. It also increases levels of bilirubin (antioxidant) and CO (antiapoptotic).

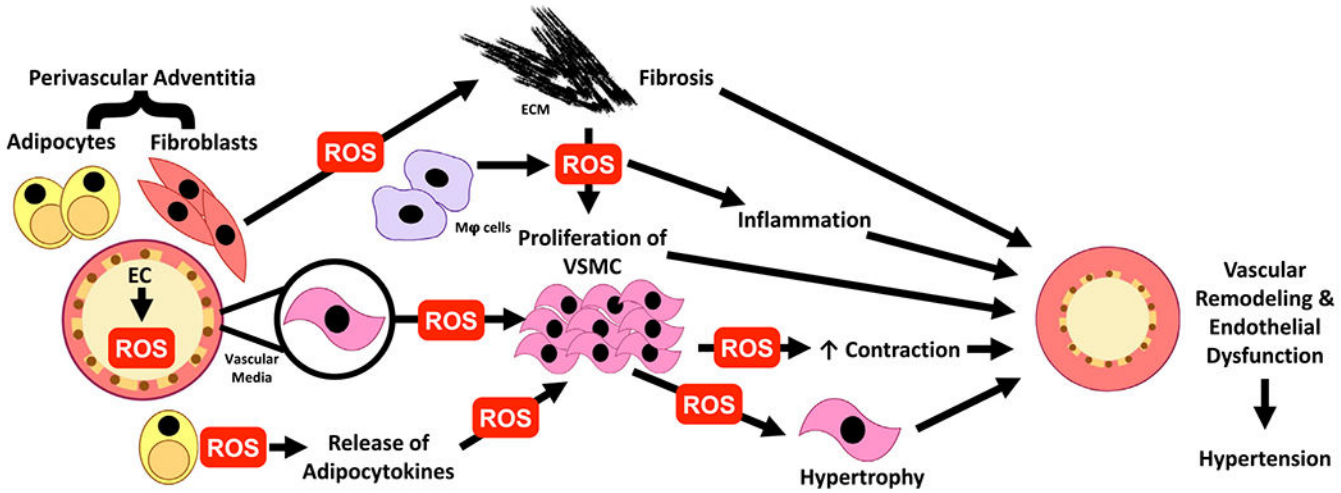

Fig. 3.

Mechanisms of ROS-induced endothelial dysfunction and hypertension. Vascular damage results from increased ROS and decreased NO bioavailability in the endothelium. Endothelial dysfunction also presents with activation of a proinflammatory response, proliferation of vascular smooth muscle cells (VSMC), elevated secretion of adipocytokines, collagen deposition leading to fibrosis. This leads to vascular remodeling, vasoconstriction, and hypertension.

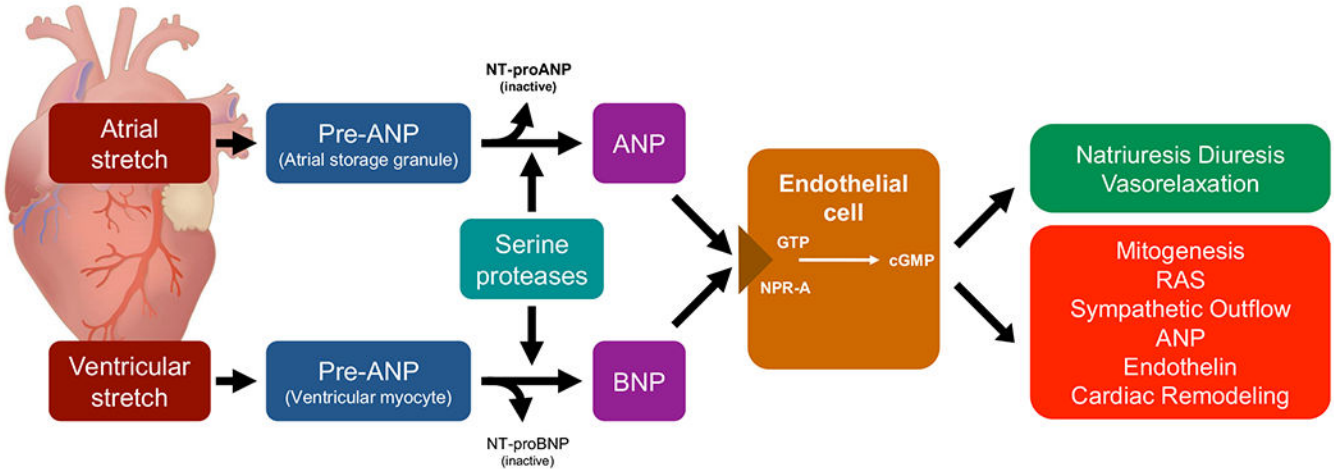

Fig. 4.

The natriuretic peptide system. The precursors are released in response to atrial stretch. Guanosine 5'-triphosphate (GTP) is converted to cyclic guanosine monophosphate (cGMP) leading to vasorelaxation. ANP: atrial natriuretic peptide; NT-proANP: N-terminal pro-ANP; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; NPR-A: natriuretic peptide receptor A; RAS: renin-angiotensin system.

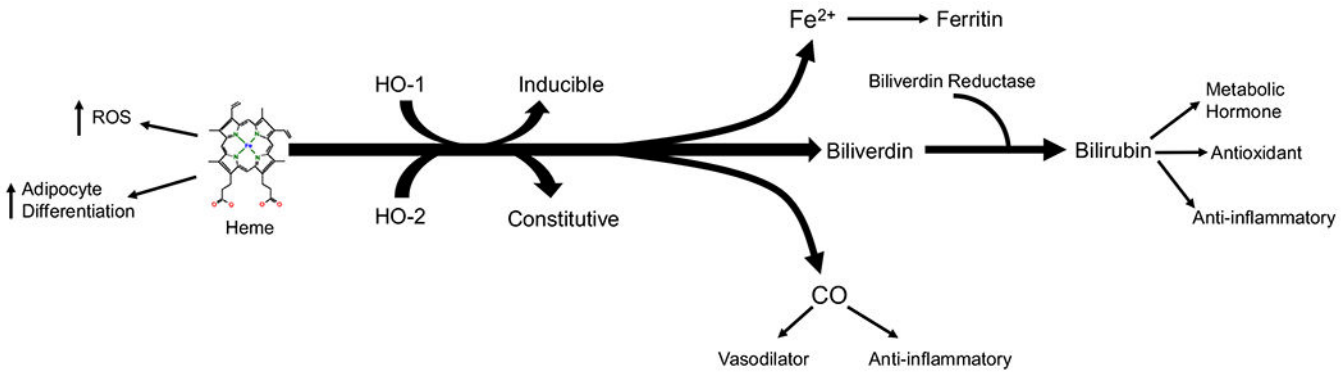

Fig. 5.

Heme degradation pathway; HO-1 and HO-2 initiates the majority of pro-oxidant heme degradation. The critical step of biliverdin reductase requires NADPH as the reducing agent. CO and Bilirubin have major anti-inflammatory properties.

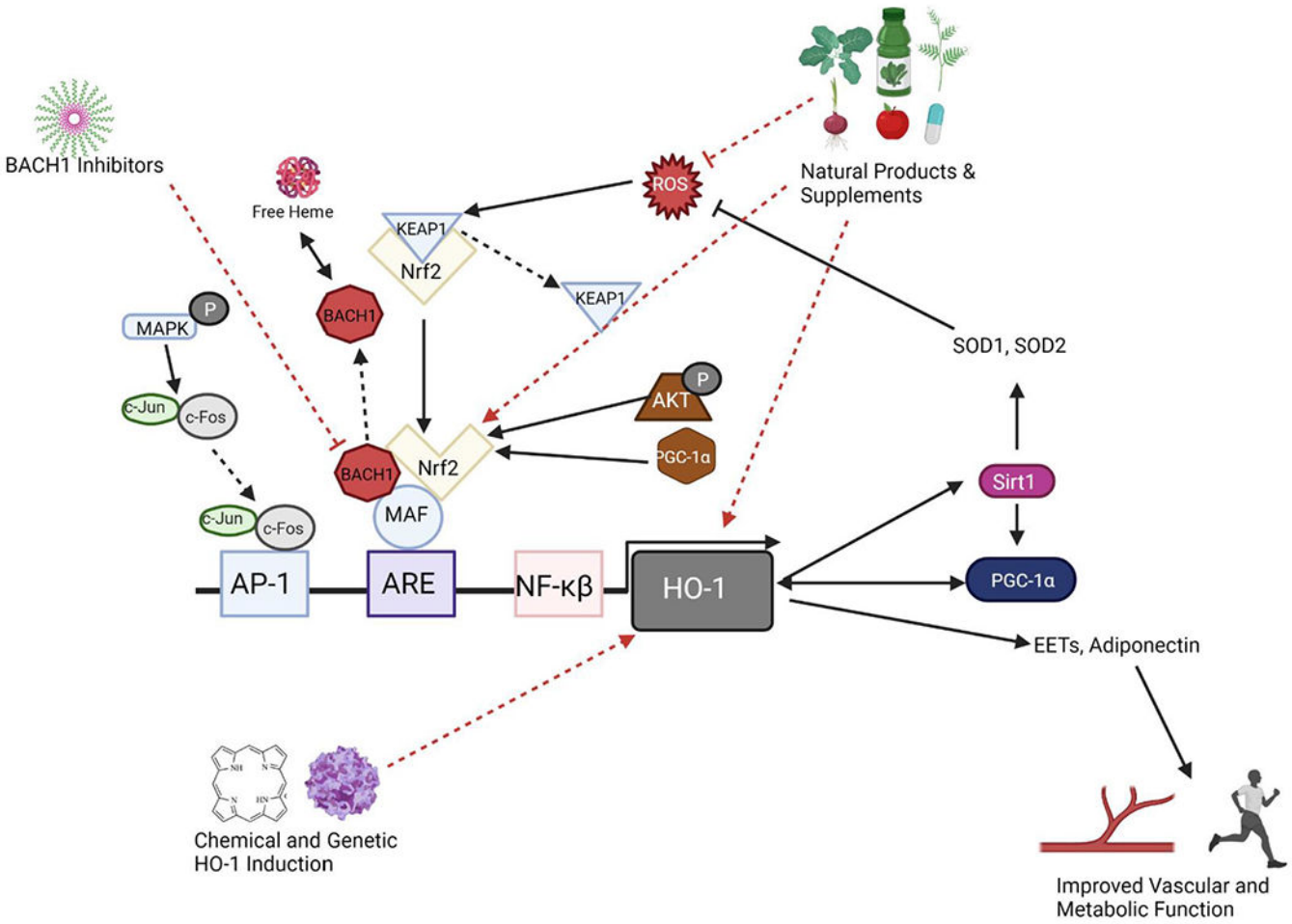

Fig. 6.

Regulation of HO-1 transcription. HO-1 is under the transcriptional control of activator protein-1 (AP-1), antioxidant regulatory element (ARE), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Mitogen activated protein kinase (MAPK) regulates transcription factors that bind to the AP-1 site to increase HO-1 transcription. BTB Domain and CNC Homolog 1(BACH1) and Nuclear factor E2-related factor 2 (Nrf2) bind to the ARE to regulate HO-1 transcription. BACH1 is a negative regulator that binds heme to increase HO-1 gene expression. Nrf2 is regulated by Kelch-like ECH-associated protein 1 (KEAP1). Stimuli such as reactive oxygen species (ROS) as well as natural products can interact with KEAP1 to disassociate it from Nrf2. Signaling proteins like Akt and PGC-1α can also active Nrf2 to bind MAF associated with the ARE on the HO-1 gene promoter. BioRender.com created the image.

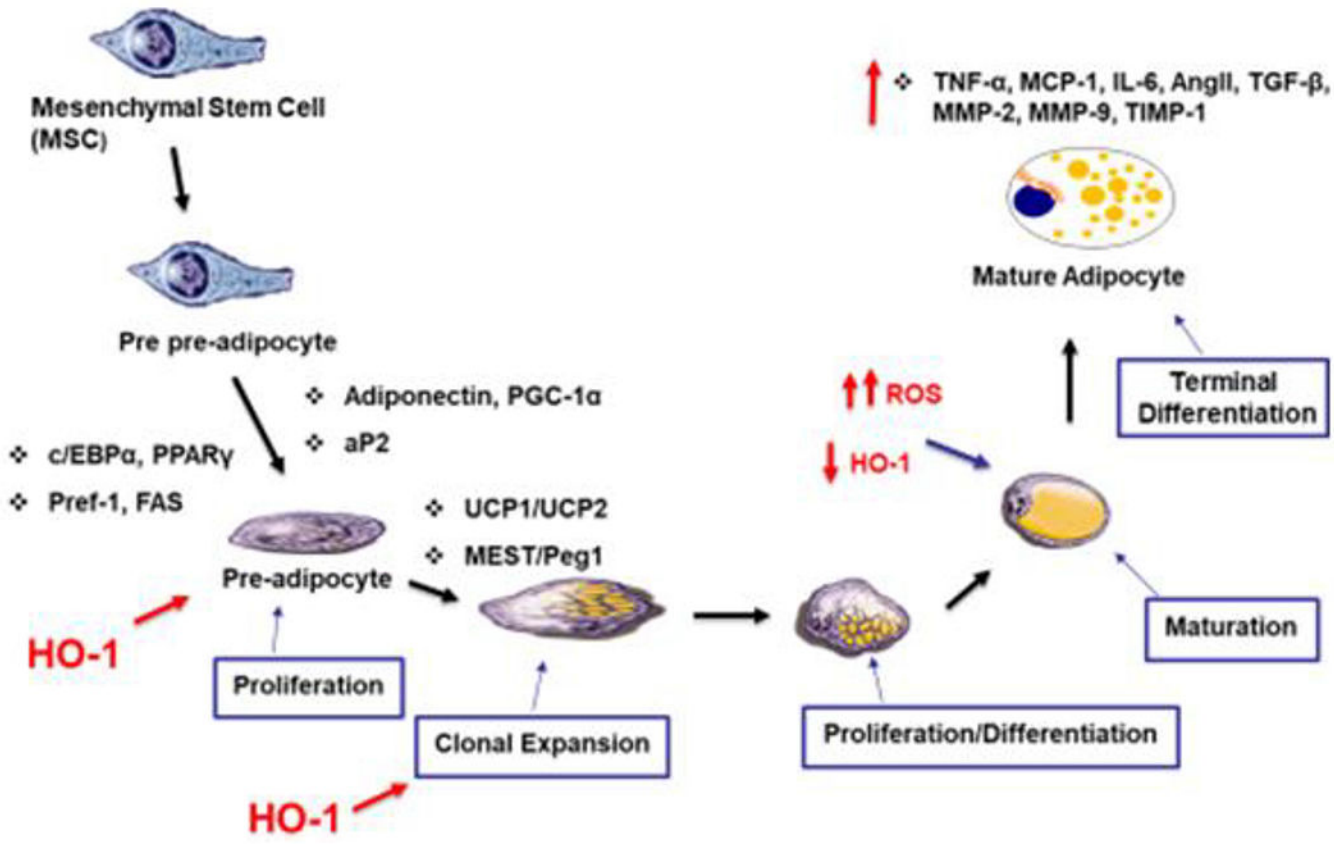

Fig. 7.

HO-1 acts on adipocyte differentiation during the early stages of proliferation and clonal expansion, by increasing PGC-1α and adiponectin, which are essential for the development of small healthy adipocytes. In contrast, increased ROS, and oxidative stress, decreases HO-1, favoring mature adipocytes. These dysfunctional adipocytes produce inflammatory adipocytokines (TNFα, IL-1, Ang II and MCP-1), that create the vascular complications of obesity and the metabolic syndrome.

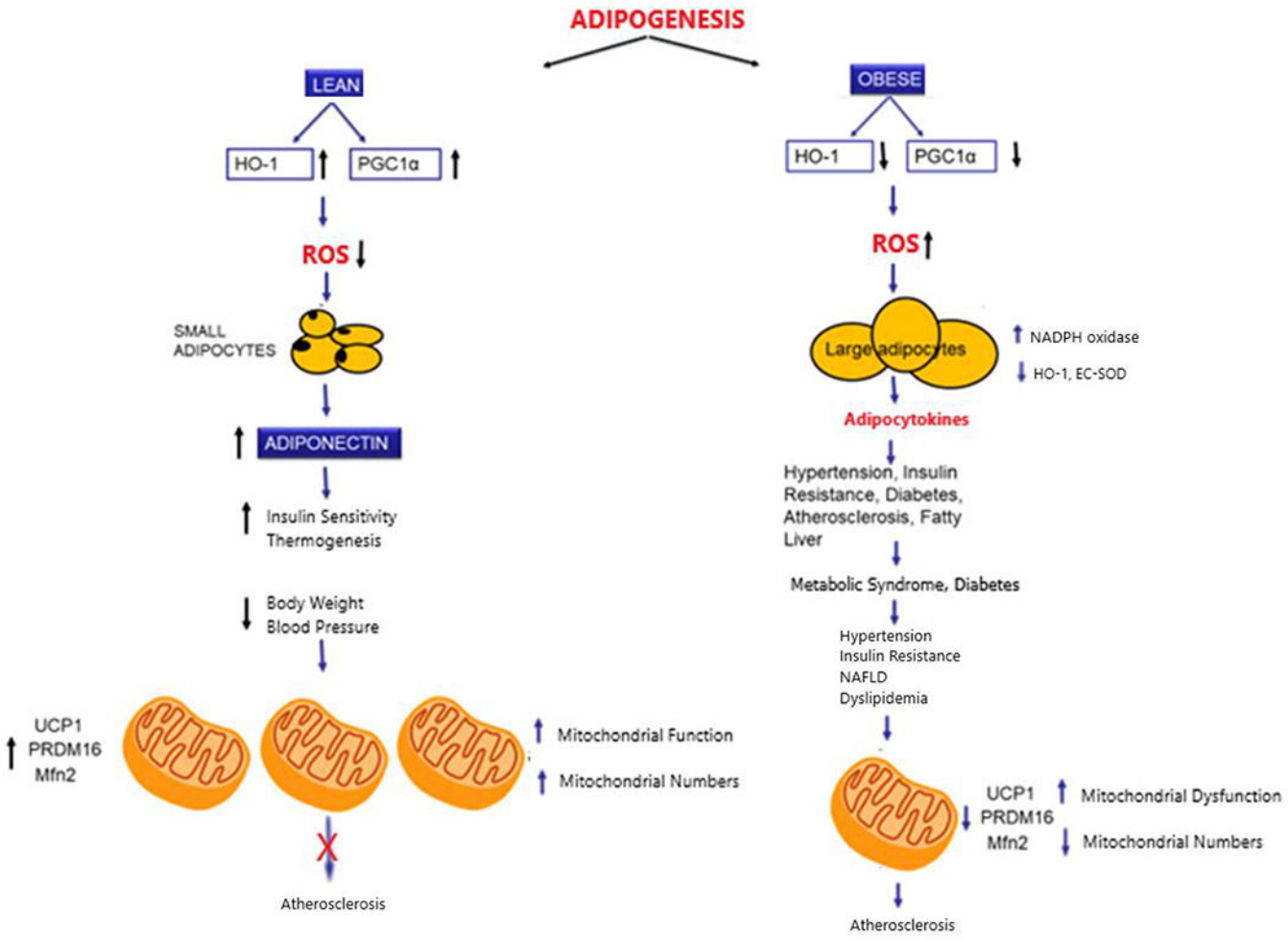

Fig. 8.

Improvement in obesity, metabolic syndrome, NAFLD, and cardiac dysfunction is dependent on the conversion of white to brown adipocyte phenotype which itself is regulated by HO-1 and PGC1-α. Conversion to a beige phenotype promotes improvement in thermogenesis and energy production in the form of ATP that is essential to cardiometabolic function and cardio-protection (Sasson et al., 2021).

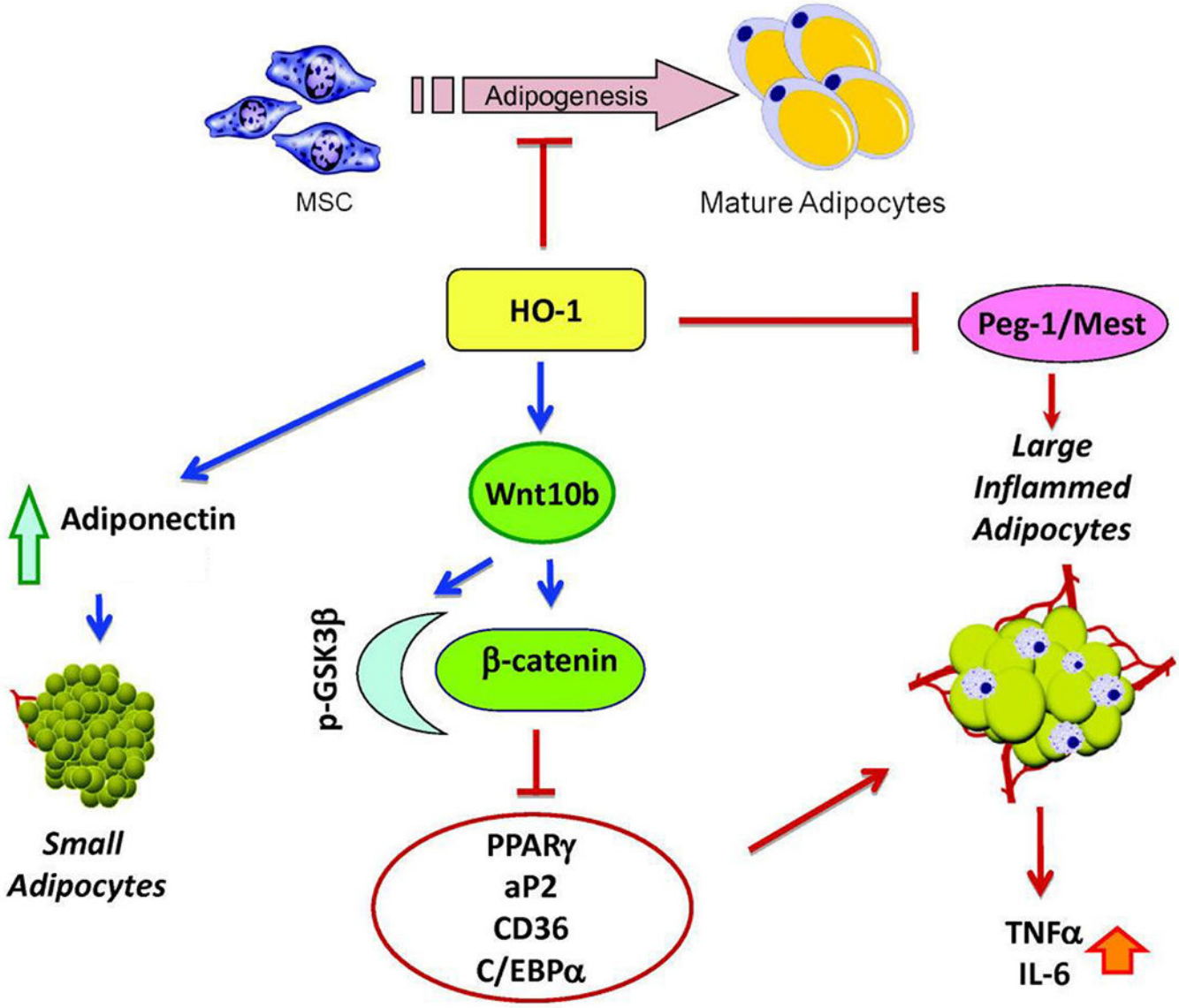

Fig. 9.

HO-1 and Wnt Signaling. HO-1 directly inhibits adipogenesis from mesenchymal stem cells. Concurrently, it inhibits paternally expressed 1 /mesoderm specific transcript (PEG1/MEST) which are also responsible for the generation of WAT. HO-1 increases expression of Wnt signaling which regulates glycogen synthase kinase (GSK)3 activity by physically displacing complexed GSK3 from its regulatory binding partners, and consequently preventing the phosphorylation and degradation of β-catenin. β-catenin in turn is translated into the nucleus where it inhibits expression of adipogenic transcription factors platelet glycoprotein 4 (CD36), CCAAT/enhancer binding protein alpha (CEBPα), peroxisome proliferator-activated receptor (PPAR)γ, and fatty-acid-binding protein (aP2). This in turn reduces expression of TNFα and IL6. Finally, HO-1 expression increases serum adiponectin levels leading to browning of WAT.

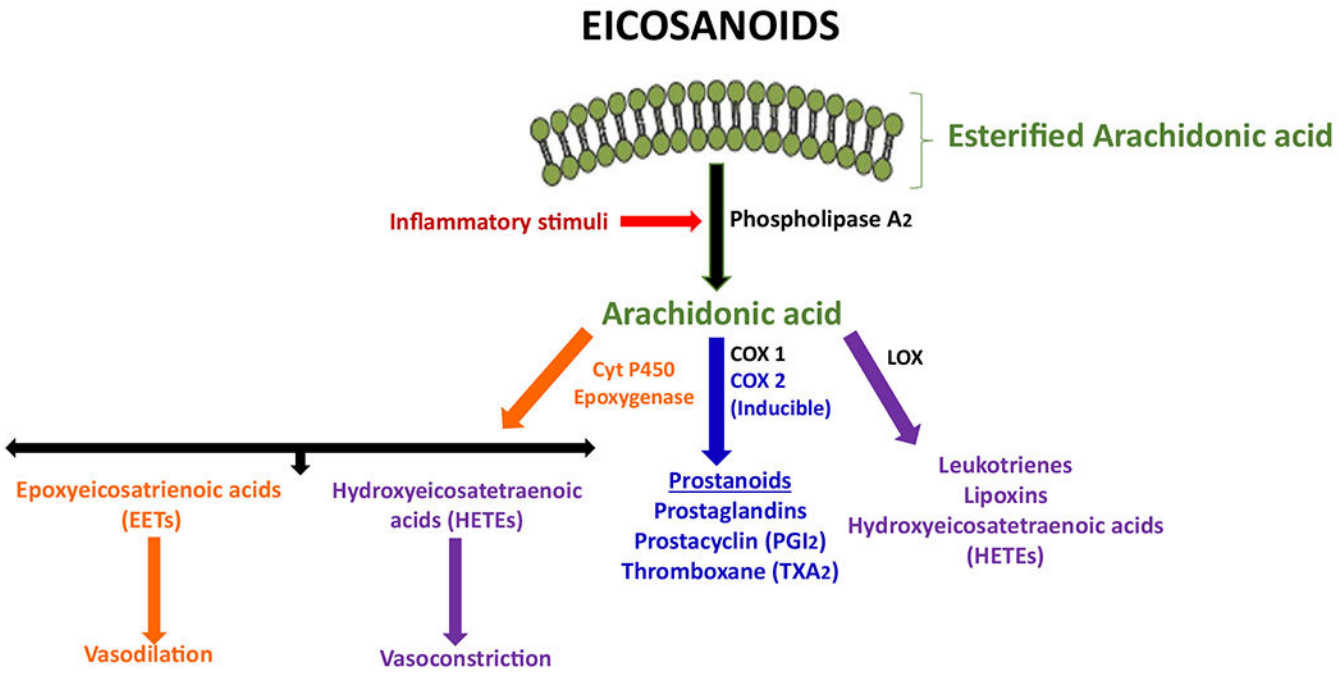

Fig. 10.

The Arachidonic Acid (AA) Pathway is a central regulator of the inflammatory response. Vasodilator EETs and vasoconstrictor HETEs are formed. EETs upregulate HO-1 and vice versa. 20-HETE is derived from two different pathways.

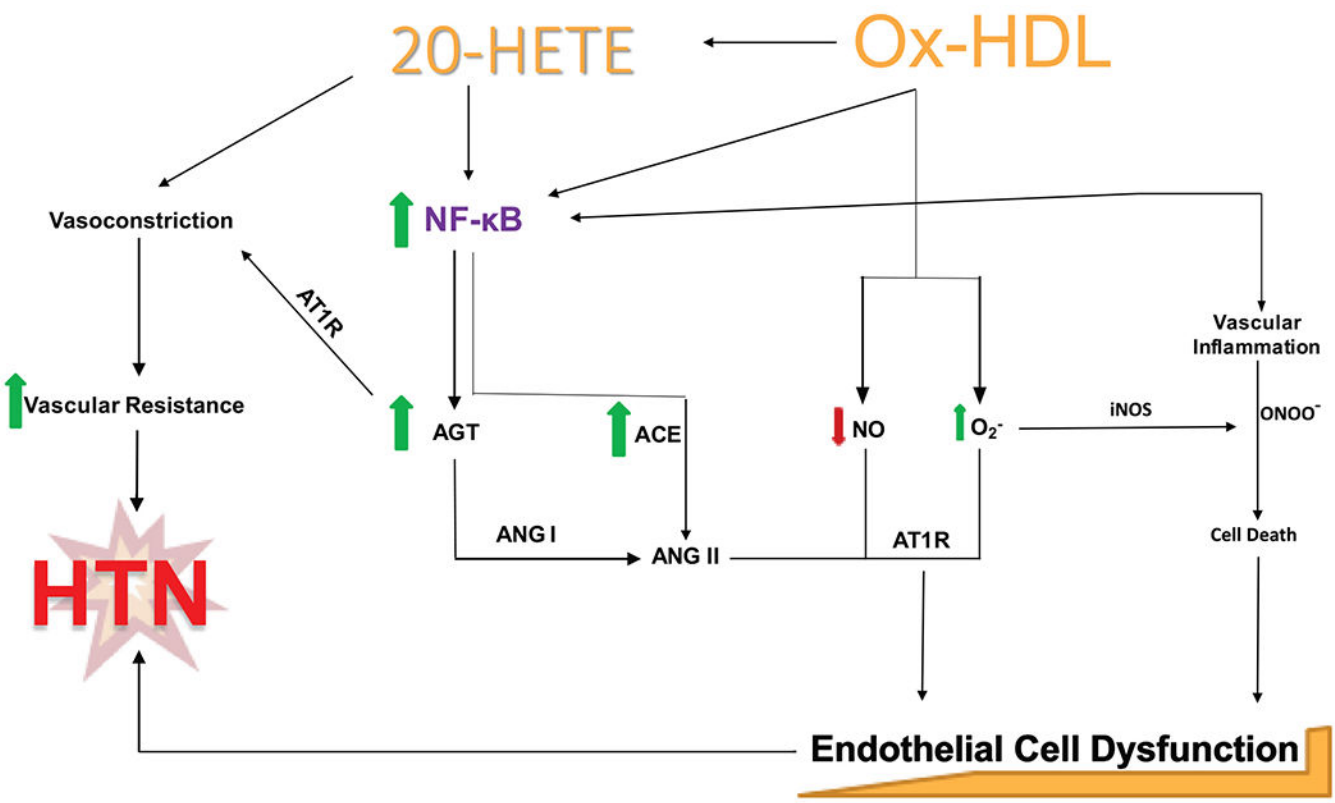

Fig. 11.

The effects of Ox-HDL and 20-HETE production from ROS on induction of adipogenesis. Both Ox-HDL and 20-HETE upregulate NF-kB which leads to generation of ANGII and activation of the RAS System. In addition, Ox-HDL upregulates 20-HETE, exacerbating inflammation and adipogenesis. The increase in ROS also reduces NO levels, augmenting cell death. HO-1 upregulation reverses these processes.

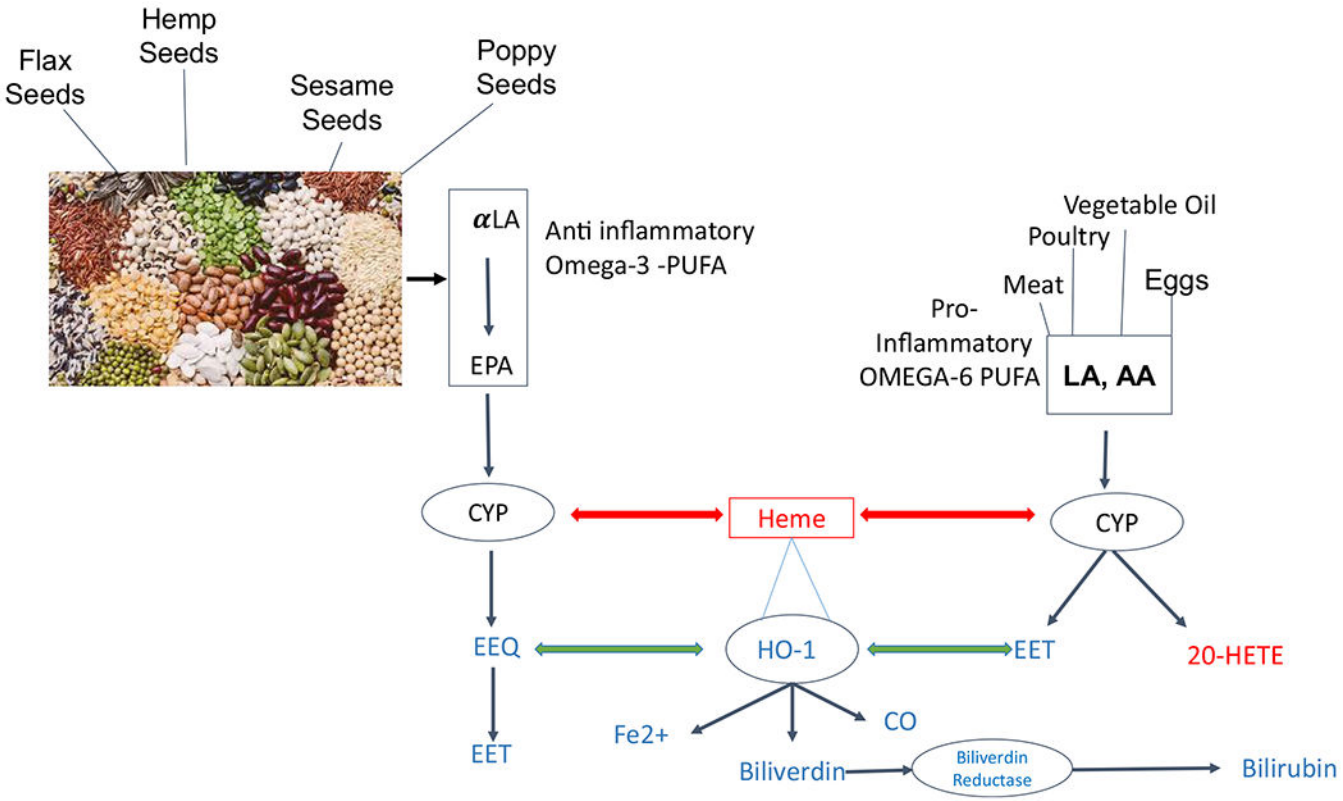

Fig. 12.

Schematic depicting PUFA metabolism, showing the existence of a negative feedback loop between heme, the heme-dependent CYPs and the metabolites that increase HO-1 levels.

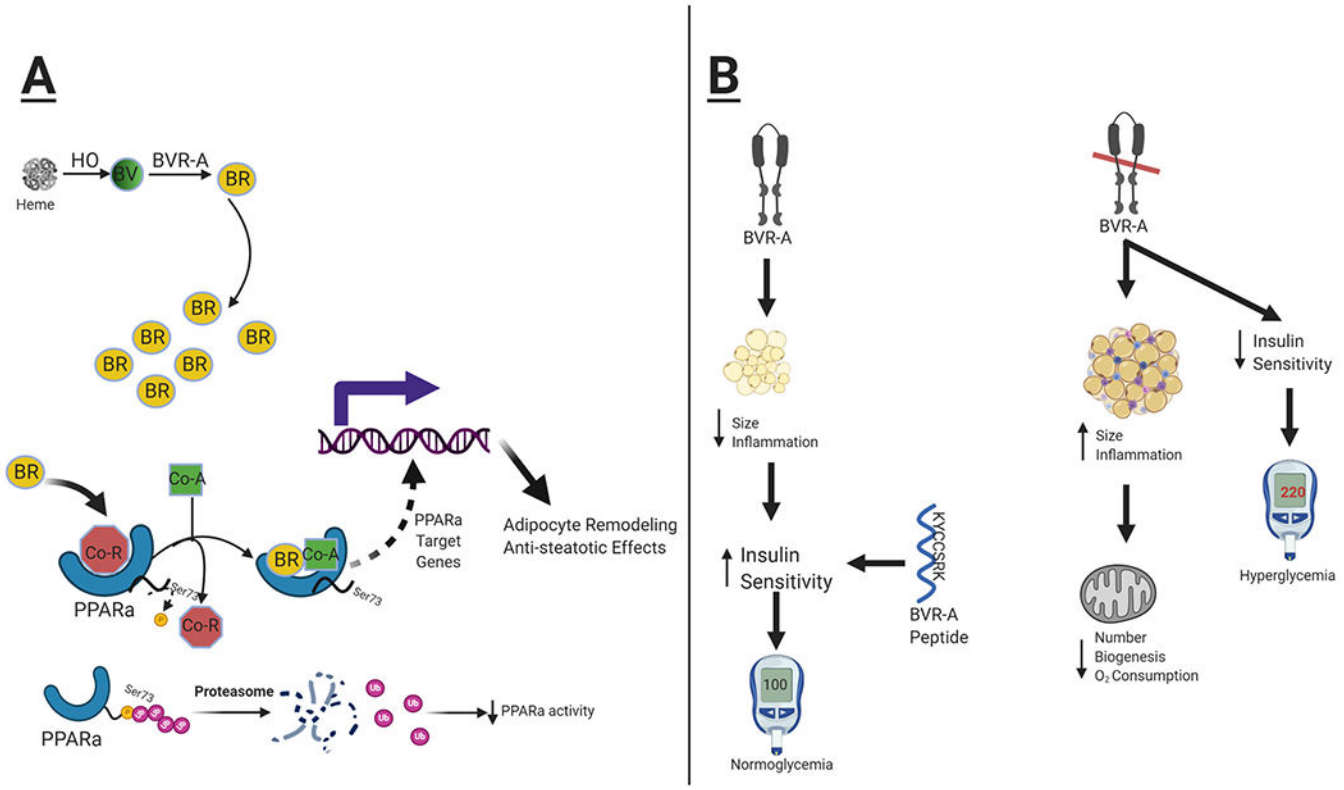

Fig. 13.

Schematic diagram of the actions of bilirubin (Panel A) and biliverdin reductase-A (BVR-A, Panel B). A) Bilirubin generated via the actions of HO and BVR-A binds to the *peroxisome proliferator-activated receptor-alpha (PPARα) promoter, which causes transcriptional co-repressors (Co-R) to disassociate at the same time allowing for the binding of transcriptional co-activators (Co-A), which activates transcription of PPARα target genes to remodel adipocytes and protects against steatosis. Bilirubin also lowers the levels of serine 73 (Ser73) phosphorylation which promotes binding of* ubiquitin (Ub) and increased proteasomal degradation of PPARα. B) BVR-A expression decreases adipocyte size and inflammation while promoting insulin sensitivity (left side). Similar effects on insulin sensitivity are observed with the c-terminal BVR-A peptide. Loss of BVR-A results in adipose tissue expansion and inflammation, decreased mitochondrial number, biogenesis, and oxygen consumption. Decreased BVR-A levels also results in decreased insulin sensitivity and promotes hyperglycemia. BioRender.com created the image.

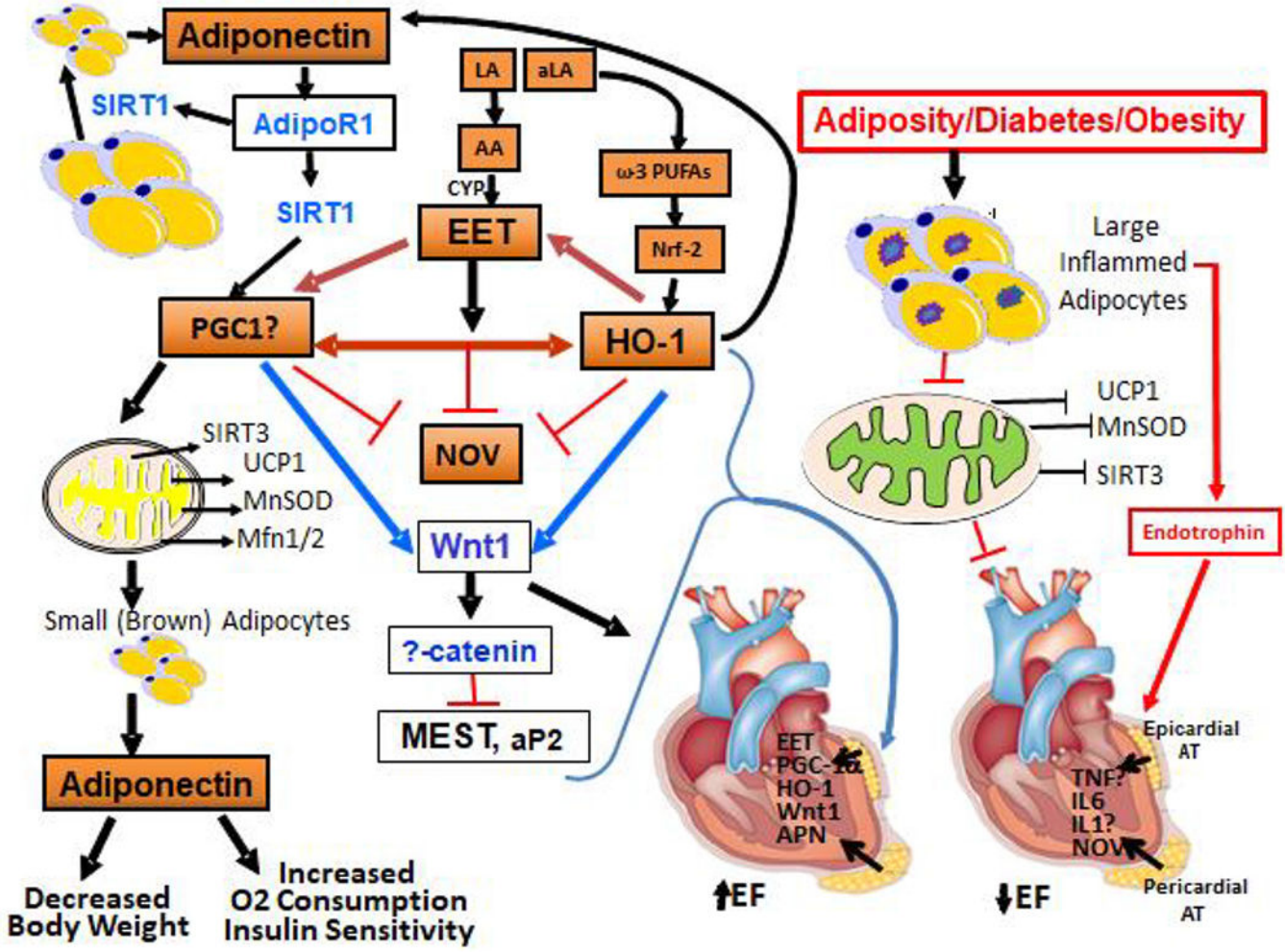

Fig. 14.

Interaction of CYP Derived Mediators and Adiponectin in Epicardial and Pericardial Fat of Healthy and Failing Hearts. Linoleic acid (LA) is metabolized to arachidonic acid (AA). AA and alpha linoleic acid (αLA) are metabolized to epoxyeicosatrienoic acids (EET) and n-3 polyunsaturated fatty acids (n-3 PUFAs) respectively via cytochrome P 450 (CYP). EET upregulates expression of peroxisome proliferator-activated receptor γ coactivator 1a (PGC-1α) which enhances mitochondrial bioenergetics by upregulating sirtuin 3 (SIRT3), uncoupling factor 1 (UCP1), superoxide dismutase (MnSOD), and mitofusin 1 and 2 (Mfn1/2). PGC-1α also upregulates expression of HO-1 which itself upregulates EET expression creating a positive feedback loop. HO-1 mobilizes the wingless integration site (Wnt) pathway which inhibits the expression of inflammatory mediators.

Table 1

Clinical evidence for HO-1 in human disease.

Condition	Phenotype	Reference
Complete Loss of HO-1	severe hemolysis, inflammation, nephritis	(Chau et al., 2020; Kawashima, Oda, Yachie, Koizumi, & Nakanishi, 2002; Radhakrishnan et al., 2011; Yachie & Koizumi, 2001)
Genetic Polymorphisms in HO-1 Promoter	Increased susceptibility to cardiovascular and renal disease	(Chen et al., 2012; Kaneda et al., 2002; Leaf et al., 2016; Pechlaner et al., 2015; Yun et al., 2009)
Genetic Polymorphisms in HO-1 Promoter	Increased susceptibility to diabetes and metabolic diseases	(Bao et al., 2010a; Lee et al., 2015; Martinez-Hernandez et al., 2015)
Plasma Levels of HO-1	Increased levels could be a biomarker in several diseases including diabetes, Atherosclerosis, renal failure	(Bao et al., 2010b; Kishimoto et al., 2018; Zager, Johnson, & Becker, 2012)
Gilbert's Polymorphism	Protection against cardiovascular and metabolic disease	(Bulmer, Blanchfield, Toth, Fassett, & Coombes, 2008; Molzer et al., 2016; Seyed Khoei et al., 2018; Wallner et al., 2013)
HO-1 Induction in Humans	Induction of HO-1 with Hemin and Heme Arginate	(Andreas et al., 2018; Bharucha et al., 2010)
HO-1 and COVID-19	COVID-19 inhibits HO, HO as a therapeutic target for COVID	(Hooper, 2020; Wagener, Pickkers, Peterson, Immenschuh, & Abraham, 2020)

Table 2

Preclinical studies of HO-1 in models of cardiovascular and metabolic disease.

Experimental Model	Intervention	Major Finding	Reference
Rodent (mice, rats) models of hypertension	Pharmacological induction/ inhibition of HO-1	Lowering of blood pressure with induction, hypertension with inhibition	(Botros et al., 2007; Csongradi, Storm, & Stec, 2012; Li, Yi, Dos Santos, Donley, & Li, 2007; Martasek et al., 1991; Ndisang, Zhao, & Wang, 2002; Sacerdoti et al., 1989; Vera, Kelsen, & Stec, 2008; Vera, Kelsen, Yanes, Reckelhoff, & Stec, 2007;Wang, Shamloul, Wang, Meng, & Wu, 2006)
Rodent (mice, rats) models of hypertension	Genetic induction or knockout of HO-1	Lowering of blood pressure with induction, hypertension with knockout	(Nath et al., 2007; Olszanecki et al., 2007; Sabaawy et al., 2001; Stec et al., 2012)
Rat model of preeclampsia	Pharmacological induction/ inhibition of HO-1	Lowering of blood pressure with induction, hypertension with inhibition	(George et al., 2011; George et al., 2011; George, Hosick, Stec, & Granger, 2013)
Rodent (mice, rats) Models of Myocardial Infarction	Pharmacological induction/ inhibition of HO-1	Improvement in heart function and reduced injury with induction, worsening with inhibition	(Collino et al., 2013a; Issan et al., 2014a; Monu et al., 2013; Zhao et al., 2013)
Rodent (mice, rats) Models of Myocardial Infarction	Genetic induction or knockout of HO-1	Improvement in heart function and reduced injury with induction, worsening with knockout	(Liu, Wei, Peng, Layne, & Yet, 2005; Tang et al., 2005; Yet et al., 2001; Yoshida, Maulik, Ho, Alam, & Das, 2001)
Rodent (mice, rats) Models of Obesity & Diabetes	Pharmacological induction/ inhibition of HO-1	Lowering of body weight and fasting blood glucose with induction, worsening with inhibition	(Burgess et al., 2010; Csongradi, Docarmo, et al., 2012; Li et al., 2008; Ndisang, Lane, & Jadhav, 2009 ; Nicolai et al., 2009)
Rodent (mice, rats) Models of Obesity & Diabetes	Genetic induction/inhibition of HO-1	Lowering of body weight and fasting blood glucose with induction, worsening with inhibition	(Abraham et al., 2004; Hosick, Weeks, Hankins, Moore, & Stec, 2017; Peterson et al., 2019b ; Singh, Grant, Meissner, Kappas, & Abraham, 2017)
Rodent (mice, rats) Models of Kidney Disease	Pharmacological induction/ inhibition of HO-1	Protection with HO-1 induction/worsening with inhibition	(Demirogullari et al., 2006; Goodman et al., 2007; Salom et al., 2007; Shimizu et al., 2000 ; Shiraishi et al., 2000; Toda et al., 2002; Wiesel et al., 2001)

Table 3

Therapeutic strategies for HO-1 induction and formulations of its bioactive products.

HO-1 Induction	Model	Reference
Hemin and Heme Arginate	Humans	(Andreas et al., 2018; Bharucha et al., 2010)
(apo)A-I mimetic peptide D-4F	Humans	(Dunbar et al., 2017)
Dimethyl Fumarate (DMF)	Humans	(Altmeyer et al., 1994; Bar-Or et al., 2013; Koulinska, Riester, Chalkias, & Edwards, 2018)
Bilirubin Formulations		
PEGylated Bilirubin	Mice	(Hinds Jr. et al., 2020; Kim, Lee, Jon, & Lee, 2017; Lee et al., 2016)
bilirubin-10-sulfonate	Rats	(Shiels et al., 2020; Shiels et al., 2021)
Carbon Monoxide		
Carbon Monoxide Inhalation	Humans	(Casanova et al., 2019; Fredenburgh et al., 2018; Rosas et al., 2018)
Carbon Monoxide Donors	Mice	(Braud et al., 2018; El Ali et al., 2020; Hosick et al., 2014; Motterlini et al., 2019)

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