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Editorial

Carbonyl Stress as a Therapeutic Target for Cardiac Remodeling in Obesity/Diabetes

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Editorial

As cardiometabolic diseases associated with obesity (i.e. hyperglycemia/ insulin resistance, hypertension and dyslipidemia) become increasingly pervasive in the modern world [1], it is evident that the demand for novel therapeutic agents will increase in the coming years. One avenue that continues to show promise is targeted disruption of reactive oxygen species (ROS) production and its consequent deleterious effects. Numerous studies have reported increased oxidative damage in muscle [2-4], adipose [5-7] and livers [8] with obesity, the collective implication being that there is likely to be a causal link between ROS and cardiometabolic diseases associated with obesity. Lipid peroxidation of polyunsaturated fatty acids (PUFAs) is a well-documented consequence of oxidative stress, particularly in the cardiovascular system [9-14]. Formation of α, β unsaturated aldehydes occurs as PUFA-derived lipid peroxides accumulate during periods of persistent oxidative stress. The biochemistry of this reaction is well described in the literature and lipid peroxidation end products such as Thiobarbituric acid reactive substances (TBARS), 4-hydroxy-2-nonenal (HNE) and Malondialdehyde (MDA) are common biomarkers of cellular stress and toxicity [15,16].

However, the biological significance of these species as physiological signaling molecules, or their role in etiology of cardiomyopathy is unclear [17-20]. Here, we shall discuss the potential pathways that link carbonyl stress to the cardiac remodeling known to occur with obesity and its associated pathologies (i.e., Type II diabetes). A brief outline of prototypical and novel therapeutic compounds that mitigate carbonyl stress is also included.

Carbonyl stress, chronic Inflammation and profibrotic signaling in the obese/diabetic heart

The most prominent histopathologic finding in the hearts of obese/diabetic patients is fibrosis, as damaged myocardium is infiltrated by fibroblasts [21-23]. Myocyte death, collagen deposition and development of fibrotic lesions are visible even before decreased cardiac performance is observed [24,25]. Upon initial onset, fibrosis is a compensatory response that adds increased tensile strength to counteract pressure overload in the heart. The transition to maladaptation occurs gradually as muscle fibers are encased in extracellular matrix, leading to ventricular wall stiffening and ultimately decompensation which manifests as diastolic dysfunction [26]. Over-production of extracellular matrix has physical effects on the microstructure as well as changes in physiological environment through the release of factors such as transforming growth factor-β(TGF-β) [27]. The most notable change in cellular physiology is the transformation of fibroblasts to myofibroblasts. Myofibroblasts are crucial in the normal response to injury and there is evidence to suggest the processes that trigger this transformation are tissue dependent [28,29]. Myofibroblasts are highly specialized for the secretion of extracellular matrix. Furthermore, they are more responsive to stimulation by factors such cytokines [30]. In certain patients this transition in phenotype to a myofibroblast- predominant population of cells may increase risk of adverse cardiac events [31-33]. For example, since fibrotic tissue lacks electrical conductivity it has been proposed that this change in phenotype may directly account for increased risk of ventricular arrhythmias. Studies show that hyperglycemia/ insulin resistance promotes fibroblast - myofibroblasts transformation [29]. Furthermore in the context of lipid peroxidation it is intriguing that *in vitro* treatment of human fibroblasts with carbonyl modified proteins produces a similar phenotype transition [24]. This effect may be mitigated by carbonyl scavengers such as carnosine (Box 1) and it is postulated that inhibition of the TGF-β pathway may serve as a potential mechanism [34]. These observations are not confined to patients with metabolic syndrome, in fact in a subset of 'healthy' obese patients with a relatively normal cardiometabolic profile (normotensive, euglycemic), the early stages of irreversible fibrotic cardiac remodeling have been observed [35].

Advanced Glycation End-products, a unique type of carbonyl stress with therapeutic potential

The receptor for advanced glycation end-products (RAGE) is a 35KDa receptor that belongs to the immunoglobulin G family of receptors [36,37]. RAGE does not recognize a primary amino acid sequence nor arrangement. It is essentially a pattern recognition receptor (PRR) that displays affinity to a wide variety of glycated proteins [38]. Since in many cases lipid peroxidation end-products (LPPs) and Advanced Glycation End Products (AGE) often share structural homology, proteins modified with LPPs (e.g., HNE, MDA) may serve as candidate ligands for RAGE. The importance of RAGE in diabetic pathologies (retinopathy, neuropathy) is an established and active area of study. In the context of carbonyl stress, RAGE may serve as a key mediator of carbonyl stress in cardiometabolic disease. Formation of AGE occurs through the Maillard reaction. PUFA-derived aldehydes contribute in the conversion of the unstable Schiff Base intermediate in an irreversible rearrangement reaction to a stable Amadori product [39-41]. Therefore in conditions of elevated carbonyl stress, it is plausible that increased cross-linking of Amadori products would shift the dynamic equilibrium even more in favor of

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Box 1: Drugs Targeting Carbonyl Species.

Edaravone- Edaravone (Norphenazone) is a free radical scavenger developed by Mitsubishi Chemicals [53]. It was identified as a metabolite of Antipyrine biotransformation. Its mechanism of action is the inhibition of lipoperoxide 15-HPETE and it was shown to prevent membrane peroxidation [54,55]. It reacts non-selectively with carbonyls and is a particularly efficient scavenger of α, β- unsaturated aldehydes [56]. In a clinical pilot study of 80 patients, Edaravone reduced infarct size, improved ejection fraction and decreased rates of cardiovascular events in long term follow up studies [57,58] .
Aminoquanidine- Aminoguanidine is highly nucleophilic and is thought to prevent protein carbonylation by reacting with Amadori intermediates thus preventing the formation of the final end product [59]. Furthermore, aminoguanidine inhibits enzymes such as nitric oxide synthases [60]. Aminoguanidine has been shown to reduce lipid peroxidation in animal models.
Hydralazine-As a prototype of pthalazine drugs, hydralazine has a strongly nucleophilic properties of the terminal nitrogen. Relatively low amounts of hydralazine inhibit carbonylation of proteins [61].
Alagebrium (ALT-711) - Alagebrium belongs the class of Thiazolium compounds. These compounds break the covalent linkages formed between AGEs and proteins. In some experimental models it has been shown to reduce cardiac AGE deposition and stiffness [52,62,63].
Pyridoxamine and other vitamin B6 related compounds- the maintenance of the cellular glutathione pool is thought to be the main mechanism of action of the B6 related compounds in the prevention of lipid peroxidation [52].
Carnosine- Carnosine is an endogenous dipeptide present in high concentrations in muscle. It is a potent antioxidant and is often used as an over the counter supplement. It has no direct scavenging of peroxides or oxygen radicals, rather it reacts with carbonyl derivatives. However, *in vivo* it is rapidly hydrolyzed by serum carnosinase and this is a great hindrance to its therapeudic potential. D-carnosine (B-alanylhistidine) is the isomer of carnosine. In a pilot study in Zucker obese mice it reduced dyslipidaemia and improved renal function [64]. D-carnosine has low bio- availability and this has been a significant limitation to the progress with this compound. However, development of promising novel analogues is in advanced stages [56,61,65].

the formation AGE according to Le Chatelier's principle. This would, in theory, increase the concentration of RAGE ligand.

RAGE signaling activates two key pathways relevant to cardiac remodeling [42,43], and increased localized RAGE tissue expression and activation may be viewed as a form of localized 'metabolic memory' through which previous insults are sustained through lingering signals [36]. RAGE gene expression is regulated by the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) transcription factor [36]. Conversely, NFκB is also activated by RAGE signaling. The RAGE/ NFκB axis is unique in that it typically overwhelms endogenous auto- regulatory feedback inhibition loops. In other words, once RAGE switches NFκB on, it is difficult to switch off. Carbonyl stress may contribute to chronic low grade inflammation through this mechanism [44]. Chronic low grade inflammation is a mechanism that underlies many diseases associated with metabolic syndrome [45]. The cyclic pattern of RAGE/ NF-κB activation is consistent with these observations. This may explain, in part, why deterioration of cardiac function persists even after onset of anti-hyperglycemic therapy. Interestingly, treatment with the antioxidant selenium, which induces the expression of many glutathione-dependent antioxidant enzymes, has been shown to reduce both RAGE expression and NF-κB activation in diabetic rats [46].

RAGE is also a well-known activator of the TGF-β pathway [39,45,47-49]. The TGF-β proteins are pleiotropic and have been implicated in diverse mechanisms which include cell differentiation and proliferation. TGF-β receptors type I and II (TGFβRI and TGFβRII) are present in virtually all mammalian cells. TGF-β1, the major isoform in heart, is expressed in cardiac fibroblasts and cardiac myocytes (CMs) and stimulates transformation to myofibroblasts and proliferation, as well as ECM production. Active TGF-β1 binds membrane receptors that activate downstream signaling molecules $Smad_2$ and $Smad_3$, which are phosphorylated on the C-terminal serine residues. Phosphorylated $Smad_2$ and $Smad_3$ ($pSmad_2$ and $pSmad_3$) bind to $Smad_4$ and translocate to the nucleus. The Smad complex then binds to response elements in the promoter regions of the ECM genes and activates pro-fibrogenic factors by up-regulating gene transcription [50]. TGF-β increases the abundance of mRNA for collagen types I and III in the whole heart and enhances collagen type I. Models of TGFβ1 overexpression in mice suggest that $Smad_2$ is the isoform involved in cardiac remodeling involving hypertrophy and fibrosis [45,47,48]. In human fibroblasts, HNE suppresses the TGF-β mediated production of elastin which compromises ventricular elasticity [51].

Current pharmacologic therapies and future directions

Relatively few studies have tested compounds that target lipid peroxidation and or neutralize LPPs. From a pharmco-chemical standpoint, viable drugs need to be sufficiently lipophilic in order to enter cellular compartments, as well as nucleophilic enough for carbonyl species to preferentially react with it, or alternatively break the covalent bond formed. It is imperative that the drug is only moderately reactive (which would be selectively beneficial in obese/ diabetic patients) since many groups have demonstrated that 'over-scavenging' can potentially interrupt the normal redox cell signaling pathways and can be detrimental to health. A brief description of drugs that have been explored in this capacity is provided below in Box 1 with information pertinent to cardiometabolic disease included where available. In addition, other compounds relevant to this discussion but not included in this table include Angiotensin converting enzyme inhibitors, AT1 angiotensin receptor inhibitors, N-acetyl cysteine and antioxidants such as Tocopherol-α and resveratrol [52].

In conclusion, the available data on the role of carbonyl species in the type of cardiac remodeling known to occur with obesity/diabetes is limited but rapidly growing. An increase in knowledge of the underlying mechanisms of LPP formation and the consequences of increased protein carbonylation in the heart will be greatly beneficial to healthcare providers as this would lead to improvements in preventative and current treatment strategies for this condition, and accelerate the development of novel therapeutics.

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