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Biogenic Aldehydes as Therapeutic Targets for Cardiovascular Disease

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Abstract

Aldehydes are continuously formed in biological systems through enzyme-dependent and spontaneous oxidation of lipids, glucose, and primary amines. These highly reactive, biogenic electrophiles can become toxic via covalent modification of proteins, lipids and DNA. Thus, agents that scavenge aldehydes through conjugation have therapeutic value for a number of major cardiovascular diseases. Several commonly-prescribed drugs (*e.g.*, hydralazine) have been shown to have potent aldehyde-conjugating properties which may contribute to their beneficial effects. Herein, we briefly describe the major sources and toxicities of biogenic aldehydes in cardiovascular system, and provide an overview of drugs that are known to have aldehyde-conjugating effects. Some compounds of phytochemical origin, and histidyl-dipeptides with emerging therapeutic value in this area are also discussed.

Introduction

As a consequence of the environment in which they exist, cells in highly oxidative tissues must continuously manage the burden of electrophilic aldehydes. Biogenic aldehydes are defined as those that are formed endogenously via spontaneous and enzyme-dependent oxidation of glucose, unsaturated lipids, primary amines, and other less-abundant substrates. If not metabolized by detoxification enzymes in the cell, biogenic aldehydes can become toxic due to excessive covalent modification of proteins (typically on Cys, Lys and His residues), DNA, and phospholipids. It is presumed that this reaction is irreversible, since at the present time, no enzymes capable of reversing this modification have been identified.

Because of the vast differences in chemical structure and site of formation, aldehydes differ in their reactivity and overall signaling effects in cells. This topic has a rich history and remains a very active area of research in biochemistry. Biogenic aldehydes are increasingly

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being recognized as major factors underlying cardiovascular disease, although the precise sources, reactivity, and pathological mechanisms by which they act remain obscure. A concise overview of the major deleterious effects of biogenic aldehydes in the cardiovascular system is provided in Figure 1. Probably the most convincing evidence in support of a pathological role is that pharmaceutical agents that blunt aldehyde formation, buffer/scavenge aldehydes directly via conjugation, or increase aldehyde metabolism have demonstrated beneficial effects for numerous cardiovascular diseases.

Since much of the biochemistry of biogenic aldehyde formation, cellular toxicity, and signaling effects in cells have been extensively reviewed in recent years [1,2*,3*], this review will focus specifically on the major known sources of biogenic aldehydes that have been described in cardiovascular pathophysiology. A brief summary of the drugs and nutraceutical compounds known to have aldehyde-trapping and therapeutic effect in cardiovascular diseases will follow.

Sources of biogenic aldehydes within the cardiovascular system

In most biological systems, the prominent source of biogenic aldehydes is the oxidation of sugars and lipids. When glucose undergoes autooxidation, the formation of Schiff base and subsequent Amadori product rearrangement generates glyoxal, methylglyoxal, and 3-deoxyglucosone [4-6]. Rearrangement and fragmentation of oxidized polyunsaturated fatty acids (PUFAs) also generates these aldehydes, in addition to α,β -unsaturated aldehydes, such as 4-hydroxynonenal (HNE) and 4-hydroxyhexenal (HHE), malondialdehyde, and keto-aldehydes [7,8***]. Since many phospholipids within cellular membranes contain PUFAs, it is the membranes that initially are the source of lipid peroxidation, typically initiated by the superoxide radical ($O_2^{\bullet-}$). Because of their proximity to blood, cells and tissues within the cardiovascular system are continuously exposed to some of the highest O_2 concentrations within the body. Consequently, since the rate of $O_2^{\bullet-}$ production and subsequent reactive oxygen species (ROS) formation is directly proportional to O_2 concentration [9***], cardiovascular tissues are susceptible to very high levels of spontaneous lipid and glucose oxidation.

Enzymatic oxidation of lipids and sugars is another pathway of biogenic aldehyde formation. Methylglyoxal (MGO) can be formed through methylglyoxal synthase, myeloperoxidase, and members of the cytochrome P450 superfamily [5]. Although beyond the scope of this review, there are numerous oxygenases within the prostaglandin pathway that catalyze the oxidation of PUFAs [10]. The products of these oxygenase-dependent reactions are typically more stable than the lipid peroxides formed via ROS, but are still capable of rearrangement and breakdown, thus making them sources of biogenic aldehydes.

Another endogenous source of biogenic aldehydes within the cardiovascular system comes from enzymatic metabolism of primary amines. Oxidative deamination of norepinephrine (NE) and dopamine (DA) by monoamine oxidase (MAO) produces the catecholaldehydes 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) and 3,4-dihydroxyphenylacetaldehyde (DOPAL), respectively, and H_2O_2 [11]. Both DOPEGAL and DOPAL have been demonstrated to be far more cytotoxic and reactive than the parent catecholamines or any

downstream metabolites. The surprisingly high reactivity and toxicity appears to stem from the reactivity of both catechol and aldehyde groups [12***]. Although a direct link between catecholaldehydes and cardiovascular disease remains to be elucidated, work in clinical and experimental models have documented a pathological role for MAO in cardiac injury from ischemia, diabetes, and hypertension [13-15].

As a protective mechanism, cells maintain an array of detoxification enzymes that are tasked with metabolism and removal of biogenic aldehydes. These enzymes include aldehyde dehydrogenase, aldose reductase, carbonyl reductase, aldehyde reductase, and enzymes in the glutathione-dependent family [16]. However, this network of enzymes can be overwhelmed during periods of acute (*e.g.*, ischemia, sepsis) and chronic cardio-metabolic stress (*e.g.*, hypertension, diabetes) [2*]. Because of their high reactivity and potential for covalent modification of proteins and DNA, particularly cross-linking aldehydes such as glyoxal and catecholaldehyde, it has become evident that therapeutic strategies are needed that can buffer endogenous levels of biogenic aldehydes via conjugation.

Clinically approved agents with aldehyde scavenging capacities

The focus of this review includes drugs that have been approved for treatment of metabolic or cardiovascular diseases that have also been found to possess auxiliary aldehyde-conjugating properties. Such drugs are of great interest since the safety profile and pharmacodynamics/kinetics have already been established and, moreover, these agents are potentially included in regimens of patients diagnosed with cardiovascular diseases (Table 1).

Metformin

Metformin is approved and recommended as a first-line agent to treat type 2 diabetes [17]. Similar in structure to aminoguanidine, the guanidino group of metformin putatively confers anti-glycating and aldehyde-conjugating abilities [18]. In a clinical study of recently diagnosed type 2 diabetes-mellitus (T2DM) patients, metformin treatment was found to not only decrease advance oxidation protein products within plasma, but proved more beneficial in reducing circulating advanced glycation end-products (AGEs) compared to lifestyle modification alone [19]. In a smaller subset of T2DM patients, metformin therapy protected ApoB100 of LDL cholesterol against oxidative and glycated damage caused by AGEs [20]. Parallel findings were obtained in a T2DM rat model of diabetes, wherein metformin treatment decreased vascular AGE deposition and reversed diabetes-induced endothelial dysfunction within aortic sections [21]. In a recent study, Kinsky *et al.* examined urine samples from 92 metformin-treated T2DM patients and reported a strong positive correlation between oral metformin concentration and metformin-MGO conjugate levels in urine [22], suggesting that metformin scavenges and enhances renal excretion of MGO. In addition to its known mechanism of actions, such studies suggest a secondary therapeutic effect of metformin as an AGE scavenger.

Hydralazine

Hydralazine is approved for use as an anti-hypertensive medication and, since its discovery, has also been investigated as a scavenger of carbonyl species. Hydralazine contains a nucleophilic hydrazine moiety which binds with free and protein-bound aldehydes to form stable hydrazones [23,24**]. In animal models of atherosclerosis, hydralazine administration was found to reduce atherosclerotic lesion size and decrease carbonyl protein adducts within aortic sinuses, suggesting hydralazine possesses anti-atherogenic properties. [25,26]. Similar findings were observed within a streptozotocin mouse model of type 1 diabetes (T1DM) where hydralazine inhibited both formation and protein adduction of AGEs in plasma and kidney proteins. Within the same study, hydralazine decreased renal expression of receptor for AGE (rAGE) and NADPH oxidase (NOX), an interesting finding as these protein targets are upregulated via AGE activation and involved in AGE-rAGE mediated ROS production [27*]. Although translational studies investigating the aldehyde-scavenging abilities of hydralazine are limited, results from animal studies provide strong evidence that hydralazine is beneficial in sequestering biogenic aldehydes, thereby preventing downstream oxidative stress and vascular damage.

Edaravone

In 2001, Japan approved the use of Edaravone (3-methyl- 1-phenyl-2-pyrazolin-5-one, MCI-186) as a free radical scavenger for the treatment of acute ischemic stroke. The effectiveness of edaravone as an antioxidant is in its ability to quench hydroxyl radicals and inhibit hydroxyl- dependent lipid peroxidation [28,29]. More recently, the focus of edaravone research has shifted to mitigating the pathogenic activity of biogenic aldehydes within cardiovascular diseases.

Several clinical studies have reported benefits of edaravone administration in patients with acute coronary infarct. When given 10 min before reperfusion, edaravone therapy chronically improved left ventricle ejection fraction (LVEF), decreased infarct size and reduced occurrence of reperfusion-associated ventricular tachyarrhythmias. In addition, plasma biomarkers measured after edaravone administration revealed a decrease in plasma creatine kinase (CK-MB), serum thioredoxin levels, and levels of monocyte chemoattractant protein-1 (MCP-1), a major chemokine involved in the vascular inflammatory response [30]. Although biogenic aldehydes were not measured in these studies, when used in a mouse model of atherosclerosis, edaravone treatment decreased circulating plasma isoprostane levels and decreased levels of 4-HNE within aortic atherosclerotic lesions [32] proposing that the sequestering of aldehydes by edaravone attenuates mechanical and oxidative damage associated with myocardial ischemia.

Pyridoxamine

As a derivative of vitamin B₆, pyridoxamine is critically involved in both the early and late stages of AGE formation [33]. Within several rat models of T1DM, pyridoxamine decreased circulating levels of triglycerides, total cholesterol, and AGEs and advanced lipoxidation end-products (ALEs) [34]. In a similar study investigating the cardiac effects of diabetes, diastolic dysfunction, aberrant Ca²⁺ concentrations, and carbonyl modifications of SERCA, were observed within diabetic rat hearts. Importantly, diabetic rats treated with

pyridoxamine retained diastolic function and SERCA activity and showed decreased levels of AGEs and ALEs within ventricular sections [35]. A study by Jain *et al.* investigated the effect of isolated human erythrocytes in high glucose medium co-incubated with pyridoxamine and observed reduced hydroxyl radical production, glycated hemoglobin, and lipid peroxidation, and furthermore sustained Na⁺/K⁺-ATPase activity compared to non-pyridoxamine treated cells [36]. Collectively, these studies support pyridoxamine as an exploratory treatment to attenuate cardiac dysfunction and hyperlipidemia observed within diabetes. Although clinical trials investigating pyridoxamine as a treatment for diabetic nephropathy were terminated after phase II [37], current trials are ongoing to determine the efficacy of pyridoxamine on insulin sensitivity and microvasculature function in obese patients.

Nutraceuticals as biogenic aldehyde scavengers

Polyphenols

Several epidemiological studies suggested that consumption of polyphenol rich diet reduces the incidence of cardiovascular diseases [38,39]. Polyphenols are plant metabolites that are present in fruits and vegetables, of which flavonoids are an important class. Flavonoids are polycyclic antioxidants composed of C₆-C₃-C₆ ring. The phenolic hydroxyl group of these compounds donates active hydrogen atoms and thus prevents formation of lipid peroxidation products.

Although *in-vitro* and intervention studies in rat models of hypertension suggest that flavonoids prevents oxidative stress and reduces left ventricular hypertrophy [40,41] clinical studies in humans failed to show effectiveness in preventing cardiovascular diseases [42]. In a randomized, double-blind placebo-controlled trial (RCT) with grade 1 hypertension, consumption of red wine (280 ml or 560 ml/day for 4 weeks) did not show any effects on ambulatory blood pressure and pulse wave reflection indexes [43]. In a second RCT with 69 treated hypertensive subjects, supplementation with Vitamin C (500 mg/ day) and grape seed extract (1000 mg/day) for 6 weeks [44**] had no effect on blood pressure. Similarly, supplementation of freeze-dried strawberry extract (50 g/day for 8 weeks) to subjects with metabolic syndrome showed no effects on serum glucose, blood pressure or waist circumference [45]. From these studies, it seems that the cardiovascular disease goes beyond oxidative stress, and anti-oxidative properties of polyphenols are not enough to circumvent these effects.

Carnosine

Reactive aldehydes are also removed by endogenous nucleophiles such as glutathione and histidyl dipeptides such as carnosine and anserine [46,47]. Carnosine (β-alanine + histidine) is abundantly present in the skeletal muscle, heart and brain, and is synthesized by the ATP grasp enzyme carnosine synthase (ATPGD1) [48,49]. The homeostasis of this dipeptide in the skeletal muscle is maintained by transporters PHT1, PEPT₂ and Taut [50-52]. In addition to its ability to react with HNE and acrolein, carnosine chelates transition metals, for example, Cu²⁺ and Fe²⁺, and buffers intracellular pH [53].

Dietary supplementation of carnosine has been shown to play a neuroprotective role in focal cerebral ischemia, attenuate development of dyslipidemia, hypertension and carbonyl stress in obese Zucker rats [54], and decrease atherosclerotic lesion formation and accumulation of HNE, acrolein protein adducts in the lesions of *apoE*^{-/-} mice [55]. Studies from our laboratory and others have shown that carnosine imparts cardio-protection in isolated rat and mice hearts during ischemia/reperfusion (I/R) injury [46,56]. Similarly, cardio-specific overexpression of ATPGD1 enhances carnosine levels in cardiac tissue and decreases infarct size during I/R injury (unpublished results). Recent clinical studies with human heart failure patients have suggested that supplementation of carnosine for 6 months improves exercise performance and quality of life in these subjects [57] and administration of carnosine to obese individuals improves glucose uptake [58^{***}] and increases the extrusion of urinary carnosine-acrolein conjugates in these subjects [59]. Accumulated mechanistic data suggests that the potential of carnosine in treating metabolic and cardiovascular diseases is due to conjugation of reactive carbonyl species. In addition to their synthesis and abundance *in vivo*, the fact that these histidyl-dipeptides are food constituents with medicinal value makes them ideal candidates for the prevention and treatment of cardiovascular diseases.

Conclusion

Although the clear benefit and need for aldehyde-conjugating therapies exists for cardiovascular disease, many compounds fail during clinical trials due to inefficacy or unforeseeable safety concerns. Translational studies and clinical trials have documented that commonly prescribed cardiovascular drugs such as metformin and hydralazine are capable of mitigating aldehyde-adduct formation and promote aldehyde conjugation. While the therapeutic benefits of these drugs are unquestionable, newer aldehyde-conjugating therapies such as edaravone, pyridoxamine and nutraceutical compounds (*e.g.*, carno sine) require further study and evaluation.

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- of special interest
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Figure 1.

Pathogenic role and therapeutic targeting of biogenic aldehydes in cardiovascular disease. MGO, MDA, and DOPAL are formed through the oxidation of reducing sugars, lipids, and primary amines, respectively. Under conditions of compromised aldehyde detoxification and increased aldehyde production, termed aldehydic stress, alterations to cardiovascular structure and function develop. Aldehydes have been found to play a role in the pathophysiology of cardiac fibrosis, atherosclerosis, cardiac hypertrophy, and systolic/diastolic dysfunction. Pharmaceutical agents approved (or currently within clinical trials) to manage complications of hyperglycemia and hypertension have been found to possess aldehyde scavenging properties. Translational studies have shown these agents to inhibit the formation of reactive aldehydes, prevent the formation of aldehyde adducts and increase the removal of aldehyde conjugates, thereby attenuating cardiovascular complications. Dihydroxyphenylacetaldehyde (DOPAL), extracellular matrix (ECM), endothelial nitric oxide synthase (eNOS) left ventricle (LV), malondialdehyde (MDA), methylglyoxal (MGO), nitric oxide (NO), ryanodine receptor 2 (RyR2).

Table 1

Summary of human studies investigating aldehyde scavenging ability of approved or currently investigated agents

Drug	Subjects	Treatment groups	Key findings	Ref.
Metformin (1 g/day for 12 weeks)	T2DM individuals	Lifestyle consultation (n = 49) Metformin + lifestyle consultation (n = 50)	Plasma AGE levels and advanced oxidation protein products were significantly lowered in metformin + lifestyle consultation group compared to lifestyle consultation alone group	[19]
Metformin (median dose: 1.5 g/day)	T2DM individuals	Control group (n = 21) T2DM patients not receiving metformin (n = 19) T2DM patients receiving metformin (n = 13)	Arginine-derived AGE and protein modified methionine residue levels of apolipoprotein B100 of LDL were reduced in diabetic patients receiving metformin compared to diabetic patients not receiving metformin	[20]
Edaravone (30 mg IV before reperfusion)	Patients with AMI	Placebo group (n = 20) Edaravone group (n = 25)	Edaravone group had decreased plasma levels of CK-MB and MCP-1 3 days after reperfusion. After 12 month follow up, edaravone group had significantly higher LVEF compared to control group	[30]
Edaravone (30 mg IV before reperfusion)	Patients with initial AMI	Placebo group (n = 51) Edaravone group (n = 50)	The edaravone group showed decrease infarct size and lower incidences of reperfusion arrhythmia. Post-reperfusion plasma thioredoxin levels were significantly reduced in the edaravone treated group	[31]
Pyridoxamine (100 mg/day for 24 weeks OR 500 mg/day for 20 weeks)	T1DM and T2DM individuals with mild/moderate diabetic nephropathy	Placebo (n = 63) 100 mg/day pyridoxamine (n = 65) OR Placebo (n = 27) 500 mg/day pyridoxamine (n = 57)	Pooled data from both phase II studies showed pyridoxamine treatment lowered plasma AGE levels and improved creatinine clearance	[37]
Carnosine (2 g/day for 12 weeks)	Nondiabetic overweight and obese individuals	Placebo group (n = 15) 2 g/day carnosine (n = 15)	Insulin secretion and sensitivity improved in carnosine treatment group, even in individuals with impaired glucose tolerance	[58***]
L-Carnosine (500 mg/day for 6 months)	Patients with Class II or III HF on medical therapy	Placebo group (n = 25) L-Carnosine (n = 25)	Patients who received L-carnosine showed an improved peak VO ₂ and increased cardiac functional capacity	[57]