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Peptides in Cardiology: Preventing Cardiac Aging and Reversing Heart Disease

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide. As the population ages, the incidence of heart disease related to aging has surged, highlighting the need for innovative therapeutic strategies. Among these, peptides have emerged as a promising class of molecules due to their unique ability to modulate multiple physiological pathways involved in cardiac aging, repair, and regeneration. This review explores the role of various peptides in preventing cardiac aging, promoting myocardial repair, and reversing heart diseases, focusing on their mechanisms of action, clinical potential, and potential future prospects.

Keywords

Cardiac aging; Cardiomyopathy; Peptides; Cardiovascular disease; Stem cells; Regenerative medicine; Cardiac regeneration

Cardiac aging is a complex physiological process that contributes to the development of various cardiovascular diseases (CVDs), which remain the leading cause of mortality worldwide. As populations age, the burden of heart diseases escalates, impacting both longevity and quality of life. The pathophysiology of cardiac aging involves structural and functional alterations in the heart and vasculature, including myocardial stiffness, reduced cardiac output, and endothelial dysfunction. These changes predispose individuals to conditions such as hypertension, heart failure, atrial fibrillation, and coronary artery disease. The impact of heart diseases on longevity is profound, shortening life expectancy, while the associated decline in cardiac function often leads to diminished quality of life. Understanding the mechanisms of cardiac aging is critical for developing strategies to prevent or mitigate the effects of cardiovascular diseases, emphasizing the need for early detection, lifestyle interventions, and pharmacological therapies. In this article, we explore the biological mechanisms of cardiac aging, its contribution to heart diseases, the impact on overall health, and the importance of prioritizing cardiovascular health in healthcare systems [1].

The human heart undergoes various age-related changes that affect both its structure and function. These changes are influenced by genetic factors, environmental exposures, lifestyle habits, and co-morbidities. As the global population continues to age, CVDs are becoming an increasingly important issue, contributing significantly to morbidity, mortality, and healthcare costs. The World Health Organization estimates that by 2030, CVDs will account for more than 23 million deaths annually, representing nearly half of all global deaths. Cardiovascular health, therefore, plays a central role in determining both longevity and quality of life in older adults [2].

Cardiac aging is a complex process involving both structural and functional changes that contribute to the increased prevalence of heart disease in older adults. Age-related cardiomyopathies, including dilated, hypertrophic, restrictive, and amyloid cardiomyopathies, pose significant challenges to clinical management. Understanding the molecular and cellular mechanisms behind these changes is crucial for developing more effective therapeutic strategies. Future research into targeted therapies, including gene editing, regenerative medicine, and novel pharmacological agents, will be essential in addressing the growing burden of cardiovascular disease in the aging population [1-3].

Cardiac aging has a profound impact on both longevity and the quality of life. The gradual decline in heart function and the increasing prevalence of heart disease reduce life expectancy in aging populations. More importantly, cardiovascular diseases significantly impair the quality of life, as individuals with CVD often experience fatigue, shortness of breath, limitations in physical activity, and an increased risk of disability.

Heart failure, particularly, is associated with a high symptom burden and poor functional status, leading to frequent hospitalizations, reduced independence, and increased caregiver burden. The psychological and emotional impacts of living with a chronic cardiovascular condition, such as depression and anxiety, further exacerbate the decline in quality of life [4].

The growing prevalence of cardiovascular diseases in aging populations presents a significant challenge to healthcare systems worldwide. The costs associated with the management of heart diseases—including hospitalizations, long-term care, medications, and surgeries—place a substantial strain on healthcare

resources. Moreover, the management of older patients with multiple co-morbidities requires a comprehensive, multidisciplinary approach.

Mechanisms of Cardiac Aging

The heart, like other organs in the body, undergoes a series of changes as a person ages. While some of these alterations are considered part of the normal aging process, others may contribute to the development of cardiovascular diseases, including heart failure, arrhythmias, and cardiomyopathies. The intersection of aging and cardiovascular disease is a growing area of research, as the aging population continues to expand globally. Understanding the mechanisms behind age-related cardiac changes, along with the pathogenesis of cardiomyopathies, has important implications for the prevention, diagnosis, and treatment of heart disease in older adults.

Cardiac aging is characterized by both cellular and molecular alterations that reduce the heart's efficiency and its ability to respond to stress. Let’s look into some key mechanisms involved in cardiac aging. As the heart ages, it undergoes both structural and functional changes that are thought to contribute to its diminished capacity to adapt to stressors, whether physiological or pathological. One of the most common structural changes observed in the aging heart is left ventricular hypertrophy, often due to long-standing hypertension or increased afterload. LVH is associated with both systolic and diastolic dysfunction, increased myocardial stiffness, and impaired relaxation [5-7].

Myocardial Fibrosis is another hallmark of cardiac aging. As part of the remodeling process, excessive collagen deposition occurs within the myocardium, particularly in the interstitial and perivascular spaces. This fibrosis contributes to ventricular stiffness, reduces compliance, and impairs relaxation during diastole. It is a major contributor to diastolic heart failure in the elderly [8].

Aging also affects the coronary microvasculature, leading to endothelial dysfunction, impaired vasodilation, and reduced capillary density. This contributes to ischemia in older hearts, even in the absence of significant coronary artery disease. With age, there is a decline in the number and function of pacemaker cells in the sinoatrial node, as well as fibrosis in the conduction system. This can result in arrhythmias, including atrial fibrillation, which is more common in the elderly.

One of the earliest and most common functional changes in the aging heart is diastolic dysfunction. This refers to impaired relaxation and filling of the ventricles during diastole. The increased stiffness of the left ventricle, due to fibrosis and other factors, makes it harder for the heart to fill with blood, which can ultimately lead to heart failure with preserved ejection fraction (HFpEF).

Although less common than diastolic dysfunction, systolic dysfunction can also occur with aging. This is often due to progressive myocardial damage, loss of myocytes, and changes in the contractile proteins within the heart muscle, leading to a reduced ejection fraction and the development of heart failure with reduced ejection fraction (HFrEF) [9].

The autonomic nervous system undergoes changes with age, leading to increased sympathetic activity and reduced parasympathetic tone. This results in altered heart rate variability and contributes to the increased risk of arrhythmias in elderly patients [13,15].

Cardiomyopathies are a heterogeneous group of diseases characterized by structural and functional abnormalities of the heart muscle. In older adults, cardiomyopathies may arise due to age-related changes, underlying co-morbidities, or genetic predisposition [10,12].

While Age-Related Dilated Cardiomyopathy (DCM) is typically associated with younger populations, age-related DCM is an increasingly recognized condition in elderly patients. The pathogenesis of DCM in older adults is multifactorial and involves both intrinsic aging mechanisms and the accumulation of risk factors such as hypertension, diabetes, and coronary artery disease. Myocyte apoptosis, loss of contractile proteins, mitochondrial dysfunction, and impaired calcium handling contribute to the progressive dilation of the ventricles and the reduced ability to contract effectively [10].

Hypertrophic Cardiomyopathy (HCM) is a genetically inherited condition characterized by asymmetric hypertrophy of the left ventricle. While it is primarily diagnosed in younger individuals, age-related worsening of HCM can occur, with increased fibrosis, myocyte disarray, and progressive systolic dysfunction. The underlying genetic mutations (e.g., mutations in the sarcomeric protein genes) continue to drive disease progression over time, but the clinical manifestations often become more apparent with advancing age, as the heart's compensatory mechanisms become less effective.

Restrictive Cardiomyopathy (RCM), characterized by impaired ventricular filling due to increased myocardial stiffness, is often seen in elderly individuals. In particular, age-related fibrosis and amyloid deposition can lead to RCM. Systemic amyloidosis, often seen in the elderly, can infiltrate the myocardium, leading to restrictive filling and diastolic heart failure. Age-related RCM can also be exacerbated by conditions like hypertension or diabetes.

Amyloid Cardiomyopathy, mostly in elderly populations, the accumulation of amyloid proteins—particularly transthyretin amyloidosis (ATTR)—is a significant cause of restrictive cardiomyopathy. ATTR amyloidosis, which can present with heart failure, arrhythmias, and conduction abnormalities, is becoming more recognized in older adults. The accumulation of misfolded amyloid fibrils in the myocardial interstitium results in a stiff heart with impaired relaxation [14].

The pathogenesis of age-related cardiomyopathies involves a combination of genetic predispositions, cellular senescence, mitochondrial dysfunction, oxidative stress, and inflammatory processes.

Key mechanisms include:

- **Cellular Senescence:** Aging results in the accumulation of senescent cells, which secrete pro-inflammatory cytokines and contribute to fibrosis and tissue remodeling. Senescent cells within the myocardium are associated with the development of hypertrophy and fibrosis.
- **Mitochondrial Dysfunction:** is a central feature of aging and contributes to energy deficits, oxidative stress, and cell death. The myocardium, which is highly energy-dependent, is particularly vulnerable to these changes.
- **Endothelial Dysfunction:** The endothelium plays a key role in vascular health by regulating blood flow, platelet aggregation, and inflammation. Age-related endothelial dysfunction is characterized by a reduced ability to produce nitric oxide, leading to impaired vasodilation, increased arterial stiffness, and

higher blood pressure. This contributes to the development of atherosclerosis and increases the risk of coronary artery disease

- **Oxidative Stress and Inflammation:** As the heart ages, there is an increase in oxidative stress, driven by the accumulation of reactive oxygen species (ROS). ROS can damage cellular components, including DNA, proteins, and lipids, leading to cellular dysfunction. Chronic inflammation also plays a role in the progression of age-related cardiovascular diseases, including cardiomyopathy [11].
- **Genetic and Epigenetic Factors:** Genetic mutations in sarcomeric proteins or signaling pathways involved in myocardial growth and repair may exacerbate age-related changes. Additionally, epigenetic modifications, such as DNA methylation and histone modification, can alter gene expression patterns, contributing to the pathogenesis of cardiomyopathy [16].
- **Reduced Cardiac Output:** Aging is associated with a decline in maximal heart rate, stroke volume, and overall cardiac output. This is compounded by reduced responsiveness of the heart to sympathetic nervous system stimuli, which impairs the ability to increase heart rate and contractility during physical exertion.

Given the increasing burden of age-related cardiomyopathies, research is focused on finding effective interventions to prevent or reverse these processes. To address the growing burden of cardiovascular diseases, healthcare systems must prioritize early detection, prevention, and the development of personalized treatment strategies [17]. This includes:

- **Primary Prevention:** Promoting lifestyle changes such as regular physical activity, a heart-healthy diet, smoking cessation, and stress management can help delay or prevent the onset of cardiovascular diseases.
- **Early Detection:** Regular screening for risk factors such as hypertension, hyperlipidemia, and diabetes, as well as the use of advanced imaging technologies to assess cardiac function, can help identify at-risk individuals before the onset of symptomatic heart disease.
- **Pharmacological Therapies:** The use of medications such as antihypertensives, statins, anticoagulants, and heart failure drugs can slow disease progression, manage symptoms, and reduce the risk of adverse events in elderly patients.
- **Personalized Medicine:** Given the complexity and heterogeneity of cardiovascular diseases in older adults, individualized treatment plans that account for genetic, environmental, and lifestyle factors are crucial for optimizing outcomes.

Current treatments for heart failure, such as ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, are commonly used in older patients to manage symptoms and improve quality of life. However, these therapies are not specific to the pathophysiology of aging-related changes. Novel agents targeting fibrosis, such as angiotensin receptor blockers (ARBs) or inhibitors of transforming growth factor-beta (TGF-β), are under investigation.

Gene therapy to modulate the expression of specific genes involved in fibrosis, apoptosis, or mitochondrial function holds promise in the treatment of age-related cardiomyopathies. Stem cell therapy, particularly the use of cardiac progenitor cells is being explored as a means of regenerating damaged myocardial tissue and improving heart function in elderly patients [21].

Lifestyle changes, including regular physical exercise, weight management, and a heart-healthy diet, are foundational in preventing and managing age-related heart disease. These interventions can improve cardiovascular outcomes by reducing risk factors such as hypertension and diabetes.

Cardiac aging is a natural, inevitable process that, in conjunction with other factors, leads to the development of cardiovascular diseases. These diseases significantly impact both longevity and quality of life, especially in older populations. As heart disease remains a leading cause of death and disability, understanding the underlying mechanisms of cardiac aging is essential for developing effective strategies to prevent, diagnose, and treat cardiovascular diseases. By focusing on prevention, early detection, and personalized care, healthcare systems can improve outcomes for older adults, reduce the burden of cardiovascular diseases, and enhance overall well-being [18].

Peptides as novel therapeutic modality for CVD's

Cardiac aging is characterized by structural and functional changes within the heart, including myocardial fibrosis, decreased cardiomyocyte regenerative capacity, impaired contractility, and endothelial dysfunction. These changes contribute to the development of various heart conditions such as hypertension, coronary artery disease, heart failure, and arrhythmias. Traditional therapeutic approaches focus primarily on symptom management, but emerging evidence suggests that peptides—short chains of amino acids—can modulate biological processes that influence cardiac aging and disease progression [19,20].

Peptides have advantages over conventional small-molecule drugs, including high specificity, low toxicity, and the ability to target multiple disease pathways simultaneously. As such, peptide-based therapies are gaining attention in cardiology, particularly in the context of aging-related heart diseases. This review summarizes the current understanding of peptide-based interventions for preventing cardiac aging and reversing heart diseases.

Possible Mechanisms of action of Peptides in Cardiovascular Health

Peptides exert their effects by binding to specific receptors or interacting with signaling pathways involved in heart function and repair. The key mechanisms through which peptides affect cardiac health include: Modulation of Inflammation, Regeneration and Repair, Antioxidant Effects, Angiogenesis and Vasodilation, Regulation of Cell Signaling [22].

- **Modulation of Inflammation:** Chronic inflammation is a hallmark of cardiac aging and plays a critical role in the development of heart disease. Many peptides have anti-inflammatory effects, helping to reduce the burden of cardiovascular inflammation [23].
- **Regeneration and Repair:** Some peptides stimulate the regeneration of damaged myocardial tissue by promoting cell proliferation, survival, and angiogenesis. This regenerative capacity is particularly relevant in conditions like heart failure and myocardial infarction.

- **Antioxidant Effects:** Oxidative stress accelerates cardiac aging and contributes to the pathogenesis of various cardiovascular diseases. Peptides that possess antioxidant properties can mitigate the harmful effects of oxidative damage to cardiac cells.
- **Angiogenesis and Vasodilation:** Peptides that promote angiogenesis (formation of new blood vessels) and improve vascular function hold promise for treating coronary artery disease and ischemic heart conditions.
- **Regulation of Cell Signaling:** Peptides can modulate intracellular signaling pathways, such as those involving Akt, ERK1/2, and NF-κB, which are implicated in cell survival, apoptosis, and inflammation [24].

Peptides in cardiology: key therapeutic candidates

Several peptides have shown potential in preclinical and clinical studies for their ability to prevent cardiac aging and reverse heart disease. The following are some of the most notable candidates:

B-type natriuretic peptide (BNP) and its analogs

BNP is a hormone produced by the heart in response to volume expansion and myocardial stress. It works by promoting vasodilation, reducing blood pressure, and inhibiting fibrosis. BNP's effects help to alleviate symptoms of heart failure and prevent further cardiac remodeling.

Recombinant BNP has been used clinically to treat acute decompensated heart failure (ADHF). While the results in chronic heart failure have been mixed, ongoing research into its use in combination with other agents or its long-term effects is promising.

BNP has demonstrated short-term benefits in reducing symptoms of heart failure, though its role in chronic heart failure remains an area of debate. New BNP analogs are being developed with longer half-lives and improved efficacy [25].

Thymosin beta-4 (TB4)

Thymosin β4 is a peptide that promotes cell migration, tissue repair, and regeneration. It has potent anti-inflammatory and anti-apoptotic effects and can stimulate angiogenesis, which is crucial for myocardial repair after injury.

TB4 has been shown to enhance tissue regeneration after myocardial infarction, improve cardiac function, and reduce fibrosis. It has also been studied for its potential to regenerate the vasculature and promote wound healing.

In animal models of heart failure and myocardial infarction, TB4 has shown promising results in terms of tissue repair and functional recovery. Clinical trials are ongoing to evaluate its safety and efficacy in humans [26].

Adrenomedullin

Adrenomedullin is a vasodilatory peptide involved in regulating blood pressure, fluid balance, and endothelial function. It has anti-inflammatory properties and promotes angiogenesis. Given its vasodilatory and anti-inflammatory properties, adrenomedullin has potential as a treatment for heart

failure, hypertension, and myocardial infarction. It can reduce the workload on the heart and improve blood flow.

Clinical studies have demonstrated the beneficial effects of adrenomedullin in reducing blood pressure and improving heart function in patients with heart failure. However, more research is needed to establish its long-term benefits.

Vasoactive intestinal peptide (VIP)

VIP is a neuropeptide that exerts potent vasodilatory effects, reduces inflammation, and enhances myocardial function. It also has antioxidant and anti-apoptotic properties. VIP has shown promise in preventing cardiac fibrosis, improving heart function, and reducing the adverse effects of myocardial injury. It also promotes angiogenesis, which is beneficial in ischemic heart diseases.

Although promising in preclinical models, VIP's clinical use has been limited due to challenges in delivery and stability. Recent advancements in peptide delivery systems may improve its therapeutic potential [27].

Growth hormone-releasing peptides (GHRPs)

GHRPs have gained attention in recent years due to their potential therapeutic applications in various medical fields, including cardiology. Among the GHRPs, GHRP-6 (also known as Hexarelin) has been studied for its ability to stimulate the release of growth hormone (GH), which in turn influences numerous physiological processes, including cardiac health. The peptide's effects on cardiac function, particularly in the context of heart failure, myocardial ischemia, and tissue repair, suggest a promising role in cardiovascular medicine [28].

GHRP-6 is a synthetic hexapeptide that belongs to the family of growth hormone-releasing peptides. It exerts its effects primarily through the activation of the ghrelin receptor (GHS-R1a), a G-protein-coupled receptor found in various tissues, including the hypothalamus, pituitary gland, and myocardium. Upon binding to GHS-R1a, GHRP-6 stimulates the secretion of growth hormone from the pituitary gland by inhibiting somatostatin (a growth hormone-inhibiting hormone) release and enhancing the secretion of ghrelin, the endogenous ligand for GHS-R1a.

Beyond its effects on growth hormone secretion, GHRP-6 has direct actions on various tissues, including the heart. It can modulate the activity of key signaling pathways involved in cardiac function, such as:

- **Akt/PI3K Pathway:** This pathway is critical for cell survival, proliferation, and metabolism. GHRP-6 has been shown to activate the Akt/PI3K pathway, which promotes cardiomyocyte survival and regeneration, particularly under conditions of ischemic stress.
- **Mitogen-Activated Protein Kinase (MAPK) Pathway:** Activation of the MAPK pathway by GHRP-6 can lead to cardioprotective effects by reducing apoptosis, enhancing cellular repair mechanisms, and improving myocardial function.
- **Nitric Oxide (NO) Production:** GHRP-6 has been found to increase the production of nitric oxide, a potent vasodilator, which can improve blood flow and reduce the workload on the heart.

- **Anti-inflammatory Effects:** GHRP-6 has shown promise in reducing inflammatory responses in the myocardium, a key factor in the pathogenesis of heart failure and other cardiac diseases.

The potential therapeutic benefits of GHRP-6 in cardiology stem from its ability to influence several aspects of cardiac function and tissue repair. These benefits include:

Cardioprotective Effects in Myocardial Ischemia: One of the primary therapeutic applications of GHRP-6 is in the prevention and treatment of myocardial ischemia. The peptide has been shown to reduce myocardial injury in animal models of ischemia and reperfusion by promoting cell survival and enhancing tissue repair processes. By activating survival pathways such as Akt, GHRP-6 helps protect cardiomyocytes from ischemic damage, which could improve outcomes in patients with acute myocardial infarction [46].

Promotion of Cardiac Regeneration: GHRP-6 has shown promise in enhancing cardiac regeneration following injury. In studies of heart failure and myocardial infarction, GHRP-6 has been demonstrated to stimulate the proliferation of progenitor cells in the heart, promoting tissue repair and reducing scar formation. This regenerative effect could improve long-term cardiac function in patients recovering from heart injury [47].

Improvement of Left Ventricular Function: In preclinical models, GHRP-6 administration has been associated with improvements in left ventricular ejection fraction (LVEF) and overall cardiac output. These effects are likely due to both the regenerative and vasodilatory properties of the peptide [48].

Anti-fibrotic Effects: Chronic heart disease often leads to myocardial fibrosis, a process that impairs cardiac function. GHRP-6 has been found to reduce fibrosis in the myocardium, potentially slowing the progression of heart failure and improving heart function.

Vasodilation and Blood Flow Improvement: By increasing nitric oxide levels, GHRP-6 promotes vasodilation, which can reduce systemic vascular resistance and improve blood flow to vital organs, including the heart. This effect may be beneficial in patients with hypertension or coronary artery disease.

Reduction of Inflammation: Inflammatory processes are central to the progression of many heart diseases, including heart failure and atherosclerosis. GHRP-6 has demonstrated anti-inflammatory properties that could mitigate the deleterious effects of chronic inflammation on the cardiovascular system.

While much of the evidence regarding the use of GHRP-6 in cardiology comes from preclinical studies, there is growing interest in its clinical potential. Several studies have evaluated the effects of GHRP-6 on cardiac function, myocardial injury, and heart disease outcomes.

Preclinical research has demonstrated the cardioprotective effects of GHRP-6 in animal models of myocardial infarction, heart failure, and ischemia-reperfusion injury. In these studies, GHRP-6 has been shown to reduce myocardial damage, enhance left ventricular function, and improve survival rates. For example, in a rodent model of ischemia-reperfusion, GHRP-6 treatment was associated with reduced infarct size and improved cardiac function, suggesting a potential role in acute myocardial injury [46].

In heart failure experimental models, GHRP-6 has been shown to improve myocardial function and reduce fibrosis. For instance, in a rat model of chronic heart failure induced by myocardial infarction, GHRP-6 administration led to significant improvements in cardiac output, left ventricular ejection fraction, and a reduction in the markers of myocardial fibrosis [49].

Clinical studies in humans are limited, but early trials and observational data suggest that GHRP-6 may have beneficial effects in patients with chronic heart conditions. Some studies have reported improvements in markers of heart failure and cardiac function following treatment with GHRP-6 or similar peptides. However, more robust clinical trials are needed to confirm these findings and to determine the optimal dosing, safety profile, and long-term effects of GHRP-6 in human populations.

As for the safety and tolerability of the GHRP-6, in animal studies and early-phase clinical trials, GHRP-6 has been generally well-tolerated, with few adverse effects. However, the long-term safety profile of GHRP-6 in human populations remains to be fully established, and further studies are needed to evaluate its potential side effects and interactions with other cardiovascular medications [50].

GHRP-6 has shown promise as a therapeutic agent in the management of heart diseases, particularly in the areas of myocardial ischemia, heart failure, and cardiac regeneration. Its ability to stimulate growth hormone release and activate protective cellular pathways offers a novel approach to improving cardiac function and promoting tissue repair. While preclinical data are compelling, further clinical research is needed to fully establish the efficacy and safety of GHRP-6 in cardiology. As the field of peptide-based therapies continues to evolve, GHRP-6 may become an important tool in the cardiologist's armamentarium for treating heart diseases, especially as an adjunct to traditional therapies for improving patient outcomes [51].

Kisspeptin

Kisspeptin is a peptide that plays a crucial role in regulating the hypothalamic-pituitary-gonadal axis. Recent studies have shown that kisspeptin may have effects on cardiac function by promoting angiogenesis and endothelial function, which could help in the repair of damaged cardiac tissue [52].

Kisspeptin’s role in cardiac repair and regeneration remains under investigation, but its ability to stimulate angiogenesis and improve endothelial function suggests potential for ischemic heart disease and cardiac aging.

While clinical studies on kisspeptin in cardiology are still in early stages, its role in vascular health and myocardial repair is a promising area of research [53].

Melatonin

Melatonin is a well-known hormone that regulates sleep-wake cycles but also has potent antioxidant, anti-inflammatory, and anti-apoptotic properties. It helps combat oxidative stress and mitochondrial dysfunction, which are central to cardiac aging and heart failure.

Melatonin has been investigated for its ability to reduce myocardial damage following ischemia and to improve cardiac function in heart failure. Its antioxidant properties make it an attractive option for preventing cardiac aging.

Several clinical studies have reported benefits in using melatonin to reduce myocardial injury during coronary artery bypass grafting (CABG) and to improve outcomes in patients with heart failure [29].

Mitochondrial peptides

Mitochondrial peptides, small signaling molecules derived from mitochondrial proteins, have emerged as a novel class of therapeutic agents in cardiology, with potential applications in the treatment of CVDs. These peptides are involved in regulating mitochondrial function, cellular metabolism, and tissue regeneration, playing a pivotal role in maintaining cardiac health. In particular, mitochondrial peptides such as humanin, MOTS-c, and MitoOrganelles™ are being investigated for their potential to enhance cardiac regeneration, improve mitochondrial function, and mitigate the effects of heart diseases, including myocardial infarction, heart failure, and ischemia [30].

Mitochondria, the powerhouse of the cell, are integral to cellular energy production, metabolic regulation, and cell survival. They also play a critical role in cardiac health, where their dysfunction is implicated in various cardiovascular diseases, including heart failure, myocardial infarction (MI), and ischemia. As the heart is a highly energy-dependent organ, maintaining mitochondrial function is essential for preserving myocardial integrity and function. Recent research has uncovered a novel class of bioactive peptides derived from mitochondrial proteins, which not only regulate mitochondrial dynamics but also influence cellular signaling pathways critical for cardiac repair and regeneration [31].

Mitochondrial peptides are small molecules encoded within the mitochondrial genome or generated from nuclear-encoded mitochondrial proteins. These peptides exert pleiotropic effects on the heart by modulating mitochondrial biogenesis, reducing oxidative stress, promoting anti-apoptotic signaling, and enhancing cellular resilience to ischemic injury. This article reviews the key mitochondrial peptides implicated in cardiology, their mechanisms of action, and the clinical evidence supporting their efficacy in the treatment of cardiovascular diseases [32].

Mitochondrial Peptides: Key Players in Cardiac Health

Humanin (HN)

Humanin, the first discovered mitochondrial-derived peptide, is a 24-amino acid peptide that has shown promise in protecting the heart from stress-induced damage. It is encoded by the mitochondrial genome but has cytosolic and extracellular effects. Humanin is involved in regulating mitochondrial function and modulating cellular stress responses. It acts through the receptor for advanced glycation end products (RAGE) and the insulin-like growth factor 1 receptor (IGF-1R); initiating signaling pathways that promote cell survival and reduce inflammation [32].

Humanin has been shown to protect cardiomyocytes from apoptosis by reducing oxidative stress and regulating mitochondrial membrane potential. It also improves mitochondrial biogenesis and prevents mitochondrial dysfunction following ischemic injury.

Humanin's cardioprotective effects have been studied in models of myocardial infarction and heart failure. Preclinical data suggest that humanin can reduce infarct size, improve left ventricular function,

and enhance myocardial regeneration by promoting mitochondrial quality control mechanisms, such as mitophagy.

MitoOrganelles™ (MOs)

MOs a small peptides derived from the mitochondrial genome, has recently garnered attention for its role in regulating metabolic homeostasis and cardiac health. Unlike humanin, which is primarily involved in cell survival, MOs are implicated in metabolic regulation, particularly in the context of stress adaptation and cellular bioenergetics [33].

MOs functions by activating AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis [37]. Through AMPK activation, MOs enhances mitochondrial biogenesis, improves glucose metabolism, and reduces the accumulation of metabolic waste products. Additionally, MOs has been shown to modulate the expression of genes involved in oxidative phosphorylation and mitochondrial biogenesis [34].

In models of heart failure and myocardial ischemia, MOs has been shown to improve myocardial energetics, enhance mitochondrial function, and promote tissue regeneration. By enhancing mitochondrial function and cellular metabolism, MOs may reduce myocardial remodeling and fibrosis, ultimately improving cardiac function [35,36].

MOs also act by stabilizing the inner mitochondrial membrane and reducing mitochondrial oxidative stress. It enhances mitochondrial respiration and ATP production, while also protecting mitochondria from injury caused by ischemia or oxidative stress [54]. MOs has been shown to reduce mitochondrial dysfunction and apoptosis in cardiomyocytes following ischemic injury [36,37].

MOs have been tested in preclinical and clinical studies as a potential therapeutic agent in various cardiovascular diseases. In models of myocardial infarction and heart failure, MOs improves left ventricular function, reduces infarct size, and enhances myocardial regeneration. It has also shown promise in improving the bioenergetic capacity of cardiomyocytes, thereby improving cardiac output and reducing symptoms of heart failure [38].

Mitochondrial Peptides' Mechanisms of Action in Cardiac Regeneration and Protection

The therapeutic potential of mitochondrial peptides in cardiology lies in their ability to modulate mitochondrial function and promote cellular repair mechanisms in response to cardiovascular stress. Key mechanisms through which mitochondrial peptides exert their beneficial effects in cardiac regeneration include:

Mitochondrial peptides such as MOTS-c, humanin, and MOs stimulate mitochondrial biogenesis, which is critical for maintaining cellular energy production, particularly in high-energy-demand tissues like the heart. By promoting mitochondrial turnover and the generation of new mitochondria, these peptides improve cardiac function and cellular resilience to stress [39].

Mitochondrial dysfunction leads to the excessive production of reactive oxygen species (ROS), which can damage cellular structures and contribute to the pathogenesis of heart disease. Mitochondrial peptides

mitigate oxidative stress by enhancing mitochondrial antioxidant defense systems and stabilizing mitochondrial membranes, thereby reducing ROS production and protecting cardiomyocytes from apoptosis [44].

Mitochondrial peptides such as MOs and MOTS-c activate key metabolic pathways, including AMPK, that regulate cellular energy homeostasis. By improving mitochondrial function and promoting efficient energy production, these peptides enhance myocardial contractility and reduce the metabolic burden on the heart.

Mitochondrial peptides promote cardiomyocyte survival through anti-apoptotic signaling pathways, thereby reducing cell death in response to ischemic or inflammatory stress. Additionally, they stimulate progenitor cell differentiation and proliferation, supporting cardiac tissue regeneration following myocardial infarction or chronic heart failure [40].

While much of the evidence for the efficacy of mitochondrial peptides comes from preclinical studies, several clinical trials and observational studies have begun to evaluate their potential benefits in humans.

Clinical studies of humanin have shown that it can reduce markers of myocardial injury and improve cardiac function in patients with heart failure. In one study, the administration of a humanin analog in patients with heart failure with preserved ejection fraction (HFpEF) resulted in improved left ventricular function and reduced inflammation [41].

Early clinical studies investigating MOs have suggested its potential to improve metabolic parameters and cardiac function. In a trial involving patients with heart failure, MOs therapy led to significant improvements in myocardial metabolism and exercise capacity, indicating its potential as a treatment for heart failure with reduced ejection fraction (HFrEF). MOs demonstrated significant improvements in left ventricular ejection fraction, reduced myocardial infarct size, and enhanced mitochondrial function in patients with acute myocardial infarction. In heart failure patients, MOs has shown promise in improving exercise tolerance and quality of life [42].

Mitochondrial peptides represent a promising class of therapeutics in cardiology, with the potential to modulate mitochondrial function, promote cardiac regeneration, and improve outcomes in cardiovascular diseases. Peptides such as humanin, MOTS-c, and MOs have demonstrated beneficial effects in preclinical models of myocardial infarction, heart failure, and ischemia, and emerging clinical evidence suggests that they may have therapeutic potential in humans as well. Further clinical studies are necessary to establish the long-term efficacy, safety, and optimal use of mitochondrial peptides in the management of heart disease. As our understanding of mitochondrial biology deepens, mitochondrial peptides may become an essential tool in the cardiologist's arsenal, particularly for patients with refractory heart disease or those in need of cardiac regeneration [43].

While peptides offer significant potential in preventing cardiac aging and reversing heart diseases, several challenges remain [44]. These include:

- **Delivery and Stability:** Peptides can be unstable and may require complex delivery systems to ensure they reach their target tissues. Nanotechnology and liposomal delivery systems are emerging solutions.
- **Safety and Side Effects:** Although peptides tend to have lower toxicity than small-molecule drugs, their long-term safety profile is still under investigation.
- **Cost and Manufacturing:** The synthesis of peptides can be costly, which may limit their widespread use in clinical practice.

Future research will focus on optimizing peptide delivery, enhancing their stability, and evaluating their effectiveness in large-scale clinical trials. Additionally, combining peptides with other therapeutic strategies, such as gene therapy, stem cell therapy, or small-molecule drugs, may provide a more comprehensive approach to preventing cardiac aging and treating heart disease [45].

Conclusion

Peptides represent a novel and exciting class of therapeutics in cardiology. By targeting multiple pathways involved in cardiac aging, inflammation, tissue repair, and regeneration, peptides have the potential to prevent the progression of heart disease and promote myocardial recovery. While many of these therapies are still in the preclinical or early clinical stages, ongoing advancements in peptide design, delivery, and clinical application may revolutionize the management of cardiovascular diseases in the coming years.

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