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Humanin and Cardiovascular Diseases

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SOUHRN

Peptidy produkované mitochondriemi (mitochondrial-derived peptides, MDPs) jsou kódovány mitochondriální DNA. Mezi MDP patří humanin, ribosomální ribonukleová kyselina typu c (ribosomal ribonucleic acid type c, MOTS-c) a malé humanin-like peptidy 1–6 (SHLP1-6). Ve stresových situacích MDP podporují aktivitu mitochondrií a napomáhají přežití buněk; kromě toho ovlivňují metabolismus, odpověď na stres i zánět jak *in vivo*, tak *in vitro*. Výzkum v poslední době prokázal, že MDP hrají významnou úlohu v rozvoji kardiovaskulárních onemocnění (KVO). Mezi další možné faktory patří ischemie, neúspěšná reperfuze, fibróza a dysfunkce koronární mikrocirkulace. Peptidy produkované mitochondriemi mohou sloužit jako markery KVO nebo se stát cílem léčby KVO. Do této skupiny peptidů patří humanin, MOTS-c a SHLP. Humanin snižuje oxidační stres cestou inhibice aktivity mitochondriálního komplexu 1. Je prokázáno, že MDP účinně pomáhají léčit metabolické poruchy včetně diabetu 2. typu. Humanin může sloužit jako marker aktivity mitochondrií v léčbě KVO nebo přímo v léčbě endoteliální dysfunkce. Tento přehled se zabývá novými možnostmi využití humaninu a jeho biologickým významem v léčbě KVO.

Keywords:
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ABSTRACT

Mitochondrial-derived peptides (MDPs) are encoded by mitochondrial DNA. MDPs include humanin, ribosomal ribonucleic acid type c (MOTS-c), and small humanin-like peptides 1–6 (SHLP1–6). In times of stress, they support mitochondrial activity and cell survival. MDPs influence cell survival, metabolism, stress response, and inflammation *in vivo* and *in vitro*. Recent research shows MDPs play a significant role in cardiovascular disease (CVD) development. In addition, possible pathogenic pathways include ischemia, reperfusion damage, fibrosis, and coronary microcirculatory dysfunction. CVD biomarkers or therapy targets, MDPs. This group of peptides includes humanin, MOTS-c, and SHLPs. Humanin reduces oxidative stress by inhibiting mitochondrial complex 1 activity. MDPs have been shown to help metabolic illnesses including type 2 diabetes. Humanin may be utilized as a marker for mitochondrial activity in cardiovascular illness or as an endothelial dysfunction treatment. This review will address humanin's novel roles and its biological relevance in cardiovascular diseases.

Introduction

Mitochondrial malfunction has been linked to ageing and age-related illnesses, highlighting their role in cell homeostasis. The mitochondria create peptides that translocate into the nucleus and interact with deoxyribonucleic acid (DNA). These mitochondrial-derived peptides (MDPs) regulate metabolism and have been found to have antioxidative, anti-inflammatory, and antiapoptotic properties.[1,2]

It is believed that mitochondrial DNA developed from the bacterial genome to coordinate metabolic and stress responses. Mitochondria may export and import peptides; the folding and assembly of freshly translated polypeptides maintains mitochondrial protein homeostasis. Reactive oxygen species (ROS) formed inside mitochondria provide a challenge to the mitochondrial protein-folding environment. Anterograde and retrograde signaling routes between mitochondria and nucleus are important in mitochondrial activity.[3–5]

The mitochondrial unfolded protein response regulates nuclear genes important in cellular homeostasis.[6] Unfolded protein response signaling promotes cell survival and adaptability to endoplasmic reticulum (ER) stress when the ER detects it.[7] Humanin and its variants, for example, are mtDNA-encoded peptides that have crucial physiological activities.[1] We want to elucidate humanin's unique functions and biological significance in cardiovascular disorders.

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A summary of the mitochondrial genome

MtDNA is the mitochondrial genome that encodes most mitochondrial proteins. The mitochondrial genome is an 11–28 kilobase circular molecule with minimal intergenomic sections. A substantial non-coding area comprises regulatory elements for both strands' transcription start and termination. mtDNA encodes 37 genes, including 13 polypeptides, two ribosomal RNAs, and 22 transfer RNAs. Paternal mtDNA is degraded during conception. Mitochondrial fusion and fission are required for cell metabolism and mtDNA distribution.[8,9]

Suggested links between mtDNA changes and increased risk of age-related illnesses. Many human illnesses are associated to mitochondrial malfunction and mtDNA change.[10] Non-coding RNAs affect mitochondrial energy state and gene expression in mitochondrial metabolism.[11] Mitochondria produce MDPs, which are protective stress-response peptides.

Among the MDPs there is humanin

Humanin, MOTS-c, and SHLPs are all MDP peptides. Humanin, the first MDP identified in 2001, was named by its promise to restore the "humanity" of Alzheimer's sufferers. Humanin was identified while looking for survival factors in an Alzheimer's patient's undamaged brain. The early research ws in cell culture, then *in vivo* utilizing pharmacological mimics of Alzheimer's disease and an amyloid-beta-precursor protein mutant gene. This innovative idea of retrograde mitochondrial signalling and mitochondrial gene expression was introduced by the discovery of humanin, the first short peptide of its sort. Humanin, originally found as a neuroprotective polypeptide, has recently demonstrated benefits in age-related illnesses.[12]

A humanin open reading frame inside the 16S ribosomal subunit gene encodes humanin.[13] Open reading frames seem to be common in human genomes, and their encoded peptides may have crucial biological activities. Over a thousand nuclear-encoded open reading frames synthesize bioactive peptides.[14]

Human mtDNA contains just 13 critical electron transport chain components and 24 structural RNAs necessary for their translation. The mitochondrial genome has few non-coding nucleotides without introns.[15] The 13 nuclear-encoded humanin isoforms were termed MTRNR2L1 through MTRNR2L13 after the mitochondrial humanin *MTRNR2* gene. These genes are significantly expressed in the heart.[13] These genes may have a role in the genesis and physiopathology of heart diseases. Few researches have looked at how humanin isoform expression is altered.[16]

Because humanin is a short peptide, each amino acid might be mutated individually. Improved chemical characteristics of humanin may be achieved by changing its molecular structure. Humanin's potency and biological functions may be changed by a single amino acid. S14G-humanin (HNG) carries glycine instead of Ser14. Humanin analogue HNGF6A has Ser14 glycine and Phe6 alanine. Amino acids Leu9-Leu11, Pro19-Val20 are essential for human survival. Humanin-C8P, S7A, and L12A are also counterparts (humanin antagonist).[17]

Humanin mechanisms

MDPs are secretory proteins that engage with external processes as well as intracellular activities. Humanin increases ERK1/2 phosphorylation through receptor binding.[18] ERK1/2 is phosphorylated and detached from its anchoring proteins during activation, enabling translocation to different subcellular compartments. Proapoptotic protein translocation to mitochondria is inhibited by humanin (Fig. 1).[19,20]

The first humanin receptor, FPRL1, is associated to neurological illnesses like Alzheimer's. Humanin stimulates calcium mobilization and ERK1/2 signaling in FPRL1. Humanin's cytoprotective effects are G protein-coupled receptor dependent.[19] The trimeric CNTFR/WSX-1/gp130 complex is linked to the gp130/STAT-3 axis, which is required for human activity. Then humanin activates STAT-3, which is essential for neuroprotection.[20]

Humanin is controlled by IGF-1 and growth hormone. Humanin and IGF-1 concentrations decline with aging, while IGF-1 directly reduces humanin concentrations.[21] It has been proposed that growth hormone suppresses MDP levels through IGF-1. The significance of diet and insulin in regulating the growth hormone/IGF axis was recently reviewed.[22] The hypothalamus contains IGFBP-3, which suppresses hepatic insulin activity.[23]

Human aging has lately been thoroughly explored molecularly. The studied mechanisms include mitochondrial dysfunction, ROS production, and soluble mitokines.[24] Stress triggers mitokines like humanin. Humanin concentrations decline with aging. A previous study demonstrated a reduction in humanin concentrations in the hypothalamus, skeletal muscle, and brain with age in mice.[25] An analysis of humanin concentrations in plasma from 693 people of varying ages revealed no signs of evolution

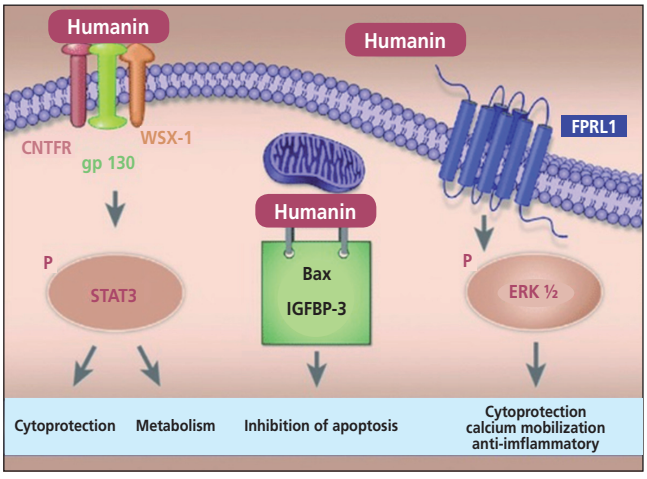

Fig. 1 – Human cellular actions. Humanin works intra- and extracellularly. The apoptotic proteins Bax and IGFBP-3 interact with humanin to suppress apoptosis. Extracellular humanin regulates survival, metabolism, and inflammation through two cell-surface receptors: CNTFR/WSX-1/gp130 (via STAT3) and formyl-peptide receptor-like-1 (FPRL1) (by ERK 1/2 signaling cascade). Phosphorylation.

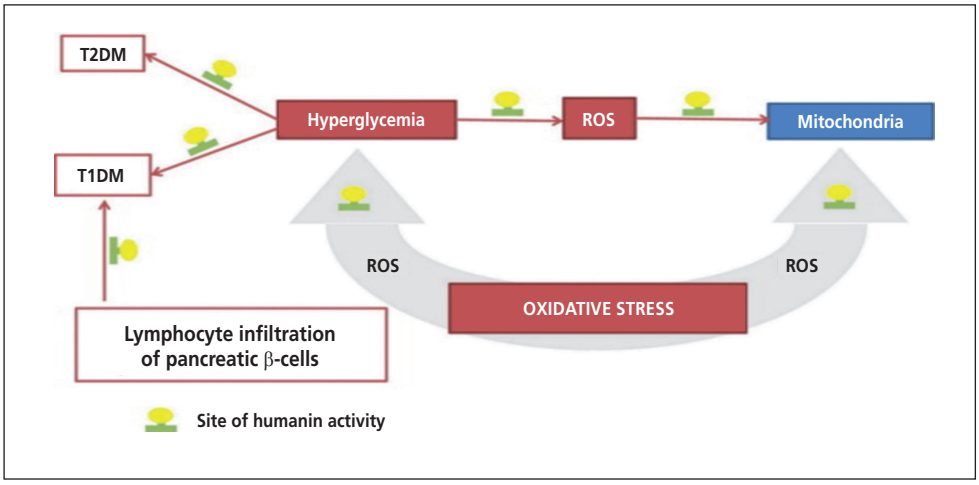

Fig. 2 – Humanin: a peptide involved in mitochondrial signaling as a biomarker for impaired fasting glucose-related oxidative stress.

(from 21 to 113 years). Humanin plasma concentrations are highest in centenarians. These data support the hypothesis that humanin is a biological age marker. Humanin and its homologues may have anti-aging benefits. Both humanin and MOTS-c boost interleukin-6, interleukin-1, interleukin-8, and interleukin-10 production in senescent cells.[26]

Oxidative stress and humanin

Humanin's antioxidant, anti-inflammatory, and antiapoptotic activities have been researched thoroughly, as well as its relationship to oxidative stress has been researched. Oxidative stress is connected to intracellular damage, including DNA damage. It may cause organ failure and cell death. Most cellular ROS are assumed to be produced by mitochondria. Atmospheres utilize oxygen, generating superoxide. In mitochondria, oxidative phosphorylation (OXPHOS) creates ATP. Mitochondria produce ATP through proton transfer. Managing ATP production and breakdown is vital to all life. An inner mitochondrial membrane protein complex transfers electrons from NADH to oxygen. The principal electron leakage sites are I and III. RNS and ROS are metabolic by-products that may be toxic or beneficial.[12]

Inflammation is thought to be caused by ROS/RNS. Lack of enzymatic (superoxide dismutases) or non-enzymatic antioxidant defenses causes it (glutathione). Oxidative stress causes DNA damage in the nucleus, leading to organ failure and cell death. Excess glucose and oxidative phosphorylation harm mitochondria. Inducing ER stress generates ROS. Mitochondrial ROS worsen ER stress because they are connected. Antioxidant humanin treatment decreases caspase activity and improves glutathione levels.[27,28]

HNG inhibits mitochondrial complex 1 activity, preventing mitochondrial dysfunction and oxidative stress. Apoptotic rate and oxidative stress are reduced by humanin in cellular and animal studies. HNG maintains mitochondrial membrane potential and ATP concentrations via its intracellular antioxidant capabilities. Recent study has revealed humanin's anti-apoptotic molecular activity. Cell death is controlled by the B-cell lymphoma 2 protein family. BAX, an apoptosis regulator, is required for mitochondrial apoptosis. As a result, humanin inhibits cytosolic BAX recruitment and oligomerization.[29]

Humanin and inflammation

MDPs reduce inflammation and oxidative stress in both *vivo* and *in vitro*. An excess of ROS in the cell damages components and triggers cell death pathways. Free radical production and/or antioxidant defense are linked to redox imbalance. An iron redox pair keeps the cell's redox status within physiological limits. Cell death by oxidative stress has a function in atherosclerosis inflammation. Pretreatment with humanin reduced ROS and apoptosis by 50%. Humanin and MOTS-c proteins were recently examined in advanced chronic renal disease patients and healthy controls. Humanin levels are associated with TNF-α levels in renal disease.[30,31] Humanin's anti-inflammatory properties suggest it may help cure hyperglycemia-induced endothelial impairment. TNF-α and interleukin-1 secretion were reduced by humanin therapy in high hyperglycemia. These proinflammatory cytokines were downregulated together with VCAM-1 and E-selectin.[32]

Humanin and type 2 diabetes

Diabetes is linked to mitochondrial dysfunction and oxidative stress. Diabetes mellitus type 2 is associated with mitochondrial impairment. The disease's specific processes are unclear, although evidence is mounting that hyperglycemia-induced oxidative stress induces oxidative stress in several organs. Oxidative stress is linked to chronic inflammation in type 2 diabetics. MDPs may help improve type 2 diabetes. Hypoglycated hemoglobin and humanin concentrations decrease in type 2 diabetes (HbA_{1c}). A significant rise in ROS concentrations may work to attract humanin from various tissues to damaged sites. Humanin acts as an antioxidant in these settings, perhaps preserving cell life. Humanin prevents apoptosis in human aortic endothelial cells by reducing ROS generation (Fig. 2).[33,34]

Humanin has been shown to affect pancreatic lipid metabolism and amino acid plasma concentrations. Humanin involvement in several clinical diseases is growing. For diabetic caused cellular damage, Humanin's defensive properties may be unique. Humanin levels may be a type 2 diabetes indicator.[35]

Cardiovascular diseases (CVDs)

Humanin is found in cardiomyocytes. During times of stress, the left ventricle produces more. Aspects of humanin's cardioprotective activities are presumed extracellular. Humanin inhibits apoptosis in the vasculature and the heart. Endocrine glands produce humanin, which is present in the endothelium of human blood vessels. Plasma humanin levels drop with age, perhaps indicating atherosclerosis. Humanin levels in patients with CVD are lower than in healthy controls. It inhibits endothelial function. Symptomatic persons have more endogenous humanin in plaque samples than asymptomatic ones. Somewhere between cardiovascular and metabolic diseases. Humanin levels in CVD may be a stress response.[36,37]

Humanin preserves endothelial function and reduces oxidative stress and apoptosis. The aortic endothelium contains humanin. HNGF6A treatment reduced aortic plaque apoptosis and nitrotyrosine immunoreactivity. Changes in heart structure and function accompany underlying illnesses. The aged heart has fibrotic remodelling. Interstitial remodelling seems to deteriorate with aging. Heart physiology alters cellular, extracellular, and whole-heart with age. Aging myocyte loss might be apoptotic or necrotic. Diastolic dysfunction occurs in the aged heart, and myocardial fibrosis is certainly a factor.[38]

Exogenous humanin therapy may benefit aged hearts due to its cytoprotective actions under oxidative stress. Humanin protects against myocardial ischemia/reperfusion damage by reducing cardiac mitochondrial dysfunction and ischemic area. Exogenous HNG reduces cardiac fibrosis and apoptosis in aged rats. The HNG-pretreated group had smaller infarcts than the vehicle-treated group at first, but not afterwards. The endogenous humanin concentration decreased after ischemia/reperfusion, whereas the total humanin concentration rose (in HNG-treated groups) after ischemia and at the commencement of reperfusion.[39] It's been reported that humanin isoform genes may be linked to cardiac problems. Researchers are looking at hereditary heart disease risk. Most humanin research has compared the expression of humanin-like isoform genes between persons. There is evidence relating humanin-like nuclear isoform DNA nucleotide variations to coronary heart disease. The *MTRNR2L2* and *MTRNR2L8* gene regions have the most alterations. Isoform gene copy number is changed in CHD arteries.[40] No influence of obesity or other metabolic diseases on genetic scores.

Recent studies

Humanin is neuroprotective and cytoprotective in animals. Humanin overexpression in C. elegans increases longevity depending on daf-16/Foxo. Like exogenous humanin therapy, humanin transgenic mice exhibit improved resistance against harmful insults. Humanin analogue HNG enhances metabolic healthspan metrics and lowers inflammatory markers in middle-aged rats when given twice weekly. Humanin levels normally fall with age in many species, but not in the naked mole-rat, a model of minimal senescence. Also, offspring of centenarians had higher circulating humanin levels than age-matched control participants. Humanin levels are reduced in disorders including Alzheimer's and MELAS, which further links humanin to healthspan. These studies are the first to correlate humanin to greater health and longevity.[41]

Humanin, MOTS-c, and small humanin-like peptide1-6 (SHLP1-6) are currently known MDPs. They are novel metabolic regulators that help sustain mitochondrial function and cell survival under stress. *In vivo* and *in vitro*, MDPs have been shown to affect cell survival, metabolism, stress response, and inflammation. Recent study has indicated that MDPs have considerable influence on cardiovascular disease development (CVD). A new class of biomarkers or treatment targets for CVD, MDPs.[42] Eltermaa et al. discovered no statistically significant associations between genetic variants in human nuclear isoform gene regions and coronary artery disease.[16]

Bioactive microproteins, MDPs, influence cellular metabolism. Two humanin and MOTS-c polymorphisms are linked to cognitive decline and diabetes, indicating a precise role for MDPs in disease modification. There may be hundreds more MDPs. MDPs are a novel type of microproteins encoded by short open reading frames. An overview of MDPs with a biological and therapeutic emphasis.[44] Dabravolski et al. focused on current developments in understanding MDP-cardiovascular risk factor interactions. MDPs were also studied as new biomarkers and therapeutic targets.[45] According to Chai et al.[46] reduced humanin is an independent risk factor for CVD.

Conclusion

Inherent in mitochondria, MDPs are linked to human metabolism and age-related ailments. *In vivo*, they are essential for metabolic balance and cell protection. MDPs may be a potential target for treating cardiovascular illness, protecting myocardial and endothelial cells, and maintaining cell homeostasis. Because endogenous humanin is elevated in cardiovascular disease, a serum marker role for humanin is expected. Atherosclerosis in patients with endothelial dysfunction may be treated with humanin. It may be used to treat or prevent age-related illnesses.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

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