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Humanin and diabetes mellitus: A review of *in vitro* and *in vivo* studies

Chrysoula Boutari, Panagiotis D Pappas, Theodoros D Theodoridis, Dimitrios Vavilis

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Abstract

Humanin (HN) is a 24-amino acid mitochondrial-derived polypeptide with cytoprotective and anti-apoptotic effects that regulates the mitochondrial functions under stress conditions. Accumulating evidence suggests the role of HN against age-related diseases, such as Alzheimer's disease. The decline in insulin action is a metabolic feature of aging and thus, type 2 diabetes mellitus is considered an age-related disease, as well. It has been suggested that HN increases insulin sensitivity, improves the survival of pancreatic beta cells, and delays the onset of diabetes, actions that could be deployed in the treatment of diabetes. The aim of this review is to present the *in vitro* and *in vivo* studies that examined the role of HN in insulin resistance and diabetes and to discuss its newly emerging role as a therapeutic option against those conditions.

Key Words: Diabetes mellitus; Insulin resistance; Humanin; Aging; Apoptosis; Oxidative stress

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Core Tip: Humanin (HN) exerts cyto-protective and anti-apoptotic effects. Type 2 diabetes mellitus (T2DM) is considered an age-related disease. Beyond the role of HN against age-related diseases, it increases insulin sensitivity, improves the survival of pancreatic beta cells, and delays the onset of diabetes. Altered HN levels could serve as a potential biomarker in prediabetes and T2DM, since they seem to be an effect or a response to the increased reactive oxygen species production, oxidative stress, and reduced mitochondrial DNA copy number-A major and important question is whether HN could be used as a potential therapeutic option for diabetes.

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INTRODUCTION

Twenty years ago, three independent laboratories discovered humanin (HN) (MTRNR2), the first mitochondrial small open reading frame (sORF)-encoded microprotein found to have biological activity. The Hashimoto laboratory discovered HN while searching for survival factors in the unaffected brain section of an Alzheimer's patient[1]. The investigators revealed a cDNA fragment that mapped back to the mitochondrial 16S rRNA. This microprotein was named humanin because it displayed protection against Alzheimer's disease (AD)-related neurotoxicity, an action that the original authors though potentially could retrieve the "humanity" of patients suffering from dementia. Second, Ikonen *et al*[2] found that HN bound insulin like growth factor binding protein 3 (IGFBP3) using a yeast two-hybrid screening system and intensified the protective effects of IGFBP3 against amyloid- β (A β) toxicity. Also, Guo *et al*[3] showed that HN can bind and suppress the apoptotic protein BAX and, subsequently, alleviate cell apoptosis.

Physiologically, HN is produced by tissues in several organs, including kidney, skeletal muscles, brain, heart, and liver[4-6]. Subsequently, it is secreted into the blood circulation and transported to various target cells, protecting in parallel cells against several diseases strongly associated with oxidative stress, mitochondrial dysfunction, and cytotoxicity[7]. Beyond the cytoprotection HN possesses a key role in cell metabolism and mediates the production and secretion of endocrine/paracrine/autocrine protective stress response factors[8]. Additionally, it plays a role in age-related diseases and several metabolic disorders (*e.g.*, cardiovascular diseases [CVD], memory loss, stroke, diabetes type 2 [T2DM]).

Diabetes is a chronic disease that occurs either due to autoimmune destruction of the pancreatic beta cells, leading to absolute insulin deficiency (T1DM) or due to progressive attenuation of insulin secretion on a background of insulin resistance resulting in relative insulin deficiency (T2DM). The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been increasing faster in low- and middle-income countries than in high-income countries. The rising burden of T2DM is a major concern in health care worldwide. In 2017 6.28% of the worldwide population was affected by T2DM. It is disconcerting that the burden of the disease is rising globally, and at a more rapid rate in developed regions such as western Europe[9]. As for the T1DM, its incidence is estimated 15 per 100000 people and the global prevalence 9.5%[10]. Since diabetes and its complications affect individuals' functional capacities and quality of life leading to significant morbidity and premature mortality, effective agents are required for its treatment.

STRUCTURE OF HUMANIN PEPTIDE

HN is encoded by a sORF within the gene for the 16S ribosomal subunit in the mitochondrial genome [11]. HN has a positively charged N-terminal (Met-Ala-Pro-Arg), central hydrophobic region (Gly-Phe-Ser-Cys-Leu-Leu-Leu-Leu-Thr-Ser-Glu-Ile-Asp-Leu), and negatively charged C-terminal (Pro-Val-Lys-Arg-Arg-Ala)[1]. Last three amino acid residues in the C-terminal are considered as dispensable because both 21 and 24-amino acid long peptides have indistinguishable intracellular and extracellular effects [12]. Thirteen nuclear-encoded HN isoforms have been identified. HN-like ORF has been named MTRNR2L1 to MTRNR2L13 after the original humanin MTRNR2 gene in the mitochondrial genome. MTRNR2L1 – MTRNR2L10 are expressed in most human tissues, with MTRNR2 being expressed in higher proportion in comparison to the other isoforms. Molecular manipulations of HN at key amino acids lead to changes in chemical characteristics. Additionally, single amino acid substitutions can lead to significant modifications to its biological functions and potency[13].

MECHANISMS OF ACTION

HN exerts its functions after connecting to either intracellular molecules or cell membrane receptors (Figure 1). Immediately after HN's receptor binding, extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation increases[14]. Once ERK1/2 is phosphorylated, it separates from its anchoring proteins, and transfers to other subcellular compartments. ERK1/2, a member of the mitogen-activated protein kinase pathway, participates in several essential cellular processes such as cell proliferation, survival, differentiation, mobility, and apoptosis[15,16]. HN behaves as a link to two different types of receptors: the seven-transmembrane G protein-coupled receptor formyl peptide receptor-like 1 (FPRL1) which plays a role in the cytoprotective properties of HN and a trimeric receptor, consisting of ciliary neurotrophic factor receptor (CNTFR), the cytokine receptor WSX-1 and the transmembrane glycoprotein 130 (GP130) (CNTFR/WSX-1/GP130) which is essential for HN activity and its neuroprotective effects[17]. As regards GP130, it is a transmembrane protein that acts as the signal transduction unit of the IL-6 receptor family[18]. Dimerization of GP130 receptors provokes the stimulation of janus kinases (JAK1 and JAK2), then subsequently provokes signal transducer and activator of transcription 3 (STAT3) and STAT1[19]. The dimerized STATs move to the nucleus and control transcription. The second signaling pathway directed by GP130 recruits SHP-2. SHP-2 is phosphorylated by JAK and interacts with growth-factor receptor bound protein 2 (Grb2), which allows the activation of mitogen-activated protein kinase (MAPK)[19].

HN is regulated by insulin-growth factor 1 (IGF-1) and growth hormone (GH). HN and IGF-1 Levels decrease with age[20]. It has also been suggested that GH inhibits HN levels *via* IGF-1. Treatment with GH or IGF-1 reduces circulating HN levels in both mice and human subjects[21]. To date, HN has been suggested to play a role in various diseases like T2DM[22,23], CVD[4,5], memory loss[24], amyotrophic lateral sclerosis (ALS)[25], stroke[26], and inflammation[12,27]. The main mechanisms that dominate and link these age-related diseases are oxidative stress[28] and mitochondrial dysfunction[29]. Mitochondria are principal sources of reactive oxygen species (ROS) which can cause oxidative stress and injure of the lipids, proteins, and DNA of the cells. This can afflict mitochondrial function, and, subsequently, enhanced ROS production occurs[29]. These circumstances contribute to cellular damage, apoptosis, and cellular ageing, causing ageing and age-related diseases such as Parkinson's disease[30], Alzheimer's disease[31], atherosclerosis[32], heart failure[33], myocardial infarction[34], chronic inflammation[35], kidney disease[36], stroke[37], cancers[38], and many kinds of metabolic disorders[39,40].

Especially concerning diabetes, HN provides protection against apoptosis by binding pro-apoptotic Bax, inhibiting its mitochondrial localization, and lessening Bax-mediated apoptosis activation[3], acting either directly on Bax or through the FPRL-1 receptor[17]. As for its neuroprotective action, which has also a place in the neuroendocrine beta cells protection, it involves HN binding to a complex involving CNTFR/WSX-1/GP130[17] and activation of tyrosine kinases and STAT-3 phosphorylation[41]. Moreover, an important mechanism of cell protection may be *via* interfering with Jun N-terminal kinase (JNK) activity[42]. Important is also the interaction between HN and insulin-like growth factor binding protein-3 (IGFBP-3) which prevents the activation of caspases[2]. Furthermore, an alteration at position [Gly14]-HN (S14G, HNG) seems to induce neurosurvival activity and a substitution of phenylalanine in the 6th position with alanine (F6A, F6AHN) changes the binding of HN to IGFBP-3 and enhances its main effect on glucose metabolism and insulin sensitivity[5].

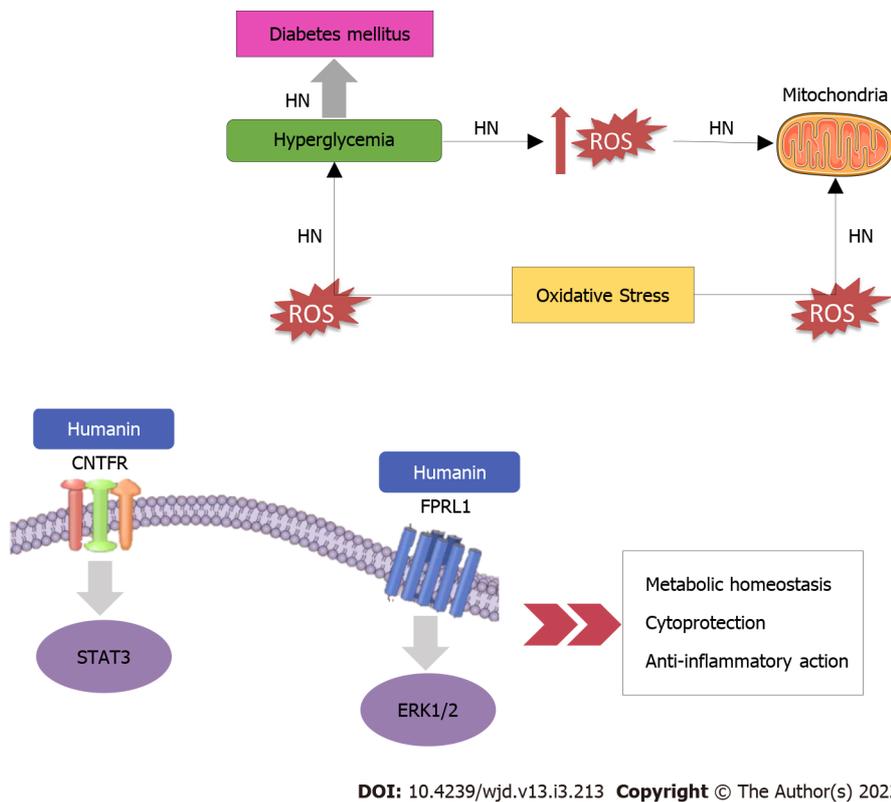
ROLE OF HUMANIN IN THE PATHOGENESIS OF TYPE 1 DIABETES

The role of HN in T1DM has been scarcely investigated. T1DM is characterized by the loss of pancreatic beta cells which results in insulin deficiency. The beta cells destruction, the dominant event in the pathogenesis of T1DM, occurs as a result of the IL-1, TNF- α , and IFN- γ actions which are originated from T cells and macrophages. Since HN is identified as a survival factor[43], it seems to serve also as a survival factor for neuroendocrine beta cells by decreasing cytokine-induced apoptosis and subsequently, improves glucose tolerance and onset of diabetes as it has been demonstrated in NOD mice *in vivo*[44]. Yet, no studies juxtaposing the HN levels in T1DM and T2DM have been published thus far.

ROLE OF HUMANIN IN THE PATHOGENESIS OF TYPE 2 DIABETES

T2DM is one of the most common metabolic diseases. This metabolic disorder and its comorbidities and complications, such as CVD, stroke, chronic kidney disease (CKD), and cancer, are global health problems which, noticeably, diminish quality of life and life expectancy[45-48].

Mitochondrial dysfunction and oxidative stress are involved in the pathogenesis of diabetes. Mitochondria are principal elements for the maintenance of metabolic health and cellular energy homeostasis. Mitochondrial dysfunction causes glycaemic dysregulation and metabolic derangement [49]. It causes inefficiency in the electron transport chain and beta-oxidation, thus triggering insulin



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Figure 1 Mechanisms of action of Humanin in diabetes mellitus. CNTFR: Ciliary Neurotrophic Factor Receptor; ERK1/2: Extracellular signal-regulated protein kinases 1 and 2; FPRL1: Formyl peptide receptor-like 1; HN: Humanin; ROS: Reactive oxygen species; STAT3: Signal transducer and activator of transcription 3.

resistance[50]. Furthermore, hyperglycemia provokes ROS generation which, in turn, causes oxidative stress in several tissues, cellular lipids, proteins, and DNA, and subsequently, provokes chronic inflammation[51]. The accumulation of oxidative damage leads to a decrement of mitochondrial function which can result in increased ROS production[29]. It has been suggested that mitochondrial dysfunction is implicated in diabetes-related complications impairing the kidneys, nervous system, heart and retina, and that mitochondrial dysfunction-related oxidative stress contributes to these complications[52]. Subsequently, an increase in ROS concentrations may provoke HN mobilization from various tissues to the impaired areas, where HN acts against oxidative stress, decreases ROS production, and promotes cell survival[51]. Mitochondrial derived peptides (MDPs), such as HN, have been suggested to play a critical role in reducing oxidative stress[53-55] and improving T2DM[56]. It has also been demonstrated that HN promotes mitochondrial biogenesis in pancreatic β -cells[57].

IN VITRO AND ANIMAL STUDIES

In vitro and animal studies

Considering that diseases related with ageing, named T2DM and neurodegeneration, have been suggested to be associated with mitochondrial dysfunction[58,59], it follows that the mitochondrial-derived peptide HN regulates them (Table 1). Based upon the molecular interaction between HN and IGF1BP-3, that prevents the activation of caspases, and since IGF1BP-3, independent of IGF-1, provokes IR both at the liver and periphery[60,61], Muzumdar *et al*[23] hypothesized that HN, besides its neuroprotective action, may regulate glucose homeostasis. Utilizing state of the art clamp technology, they investigated the role and the mechanism of action of central and peripheral HN in glucose metabolism. They finally demonstrated that infusion of HN improves both hepatic and peripheral insulin sensitivity and that hypothalamic STAT-3 activation is essential for the insulin-sensitizing action of HN. Moreover, treatment with a highly potent HN analog significantly lowered blood glucose in Zucker diabetic fatty rats. As for the levels of HN in tissues like hypothalamus, skeletal muscle, and cortex, they reduced with age in rodents, and its' circulating levels were also diminished with age in humans and mice.

A year later, a group from California[44] investigated whether HN could improve the survival of beta cells and delay or even treat diabetes in NOD mice. HN prevented apoptosis induced by serum starvation in NIT-1 cells and decreased cytokine exposure-related apoptosis (caused by interleukin [IL]-1 β , tumor necrosis factor [TNF] α , and interferon[IFN] γ). STAT3 is considered as a principal survival

Table 1 *In vivo* and *in vitro* studies on humanin and diabetes mellitus

Ref.	Study model	HN dose	Treatment duration	Results
<i>In vitro</i> studies				
Rochette <i>et al</i> [51], 2014 (HN)	NIT-1 cells	1-10000 nmol/L	24 h	Reduced apoptosis caused by serum starvation in NIT-1 cells and decreased cytokine-induced apoptosis
Hunter and Jones [19], 2015 (HNGF6A)	Isolated islets and cultured murine β cell line	50 ng/ml	15-120 min	Enhanced glucose-stimulated insulin secretion
Qin <i>et al</i> [57], 2018 (HNG)	HUVECs	1 μ M	3 h	Inhibited cell death, nucleus pyknosis and deformation. Diminished the expression of cleaved PARP (which reflects the level of apoptosis as well as ROS) Decreased the level of bax (a pro-apoptotic protein). Increased bcl-2 (an anti-apoptotic agent)
Miller <i>et al</i> [11], 2020 (HNG)	HEK293 and SH-SY5Y cells	100 μ M	30 min	Is a major GP130 agonist which acts through the GP130/IL6ST receptor complex and activates AKT, ERK1/2, and STAT3
Wang <i>et al</i> [50], 2010 (HN)	Pancreatic MIN6 β -cells	25, 50 and 100 μ M	24h or 48 h	Increased the expression of PGC-1 α . Promoted mitochondrial biogenesis. Caused the phosphorylation of AMPK, improved mitochondrial respiration and stimulated ATP generation
Kim <i>et al</i> [60], 2007 (HN)	HUVECs	200 μ M	24 h	Promoted the expression of KLF2. Reduced the expression of VCAM-1 and E-selectin; Impeded the secretion of TNF- α and IL-1 β
<i>In vivo</i> studies				
Animals				
Hunter and Jones [19], 2015 (HNGF6A)	Sprague–Dawley rat	0.07 mg/kg/h	2-30 min	Improved insulin sensitivity and help in decreasing blood glucose level
Gong <i>et al</i> [20], 2014 (HN)	Sprague–Dawley rat	0.375 mg/kg/h	360 min	Decreased blood glucose in Sprague–Dawley rats by STAT-3 phosphorylation
Gong <i>et al</i> [20], 2014 (HNGF6A)	Zucker diabetic fatty rat	0.05 mg/kg/h	90-240 min	Decreased blood glucose in Zucker diabetic fatty rats
Rochette <i>et al</i> [51], 2014 (HN)	NOD mice	0.7 mg/kg/day	6 wk 20 wk	Decreased lymphocyte infiltration in mice pancreata; Delayed or prevented the onset of diabetes in NOD mice (when the treatment was extended up to 20 wk)
Miller <i>et al</i> [11], 2020 (HNG)	Male C57BL/6 mice	5 mg/kg/day	2 wk	Old mice, but not young mice, showed an increase in phosphorylation in AKT and ERK1/2 in the hippocampus
Humans				
Muzumdar <i>et al</i> [61], 2006	Participants attending a diabetes complications screening clinic	-	-	A significant decrease in HN was observed in the IFG group compared to control
Ha[71], 2006	Uncomplicated T1DM patients	-	-	Plasma HN levels were significantly higher in T1DM men by comparison with the healthy control men
do Nascimento <i>et al</i> [72], 2013	Pregnant women with and without GDM	-	-	Serum HN levels were significantly lower in women with GDM compared to controls
Hashimoto <i>et al</i> [42], 2003	Normal, prediabetes and diabetes subjects	-	-	Serum HN concentrations are lower in T2DM and correlate with HbA1c

HUVECs: Human umbilical vein endothelial cells; PARP: Poly ADP-ribose polymerase; ROS: Reactive oxygen species; ERK1/2: Extracellular signal-regulated kinase 1/2; STAT3: Signal transducer and activator of transcription 3; PGC-1 α : PPAR- γ coactivator-1 α ; KLF2: Krüppel-like factor 2; VCAM-1: Vascular cell adhesion molecule 1; TNF- α : Tumor necrosis factor- α ; IL-1 β : Interleukin-1 β ; IFG: Impaired fasting glucose; T1DM: Type 1 diabetes mellitus; GDM: Gestational diabetes mellitus.

signaling protein in beta cells, regulating the pro-survival effects of various growth factors and cytokines. HN activated STAT3 and ERK over a 24-hour time course. Interestingly, HN improved glucose tolerance in NOD mice and after 6 wk of treatment decreased lymphocyte infiltration was observed in their pancreata. When the treatment was extended up to 20 wk the investigators noted that HN delayed or prevented the onset of diabetes in NOD mice.

A few years later, the group we mentioned first[23] hypothesized that HNGF6A, a potent non-IGFBP-3 binding HN analog, may affect acutely and independently insulin secretion, since insulin concen-

trations were not reduced along with hypoglycemia caused by HNGF6A in Sprague Dawley rats[22]. Sprague Dawley rats that received HNGF6A presented higher insulin levels during hyperglycemic clamps compared to controls. Similarly, *in vitro*, HNGF6A enhanced glucose-stimulated insulin secretion in isolated islets and cultured murine β cell line. This effect was dose dependent, combined with ATP production in the β cell, related to the KATP-channel-independent augmentation phase of insulin release[62], and associated with amplified glucose metabolism. These potent effects on insulin secretion in combination with the effects on insulin action suggested a role of HN in the treatment of T2DM.

The protective effects of [Gly14]-Humanin (HNG) against high glucose-induced apoptosis were investigated in human umbilical vein endothelial cells (HUVECs). Pretreatment of HUVECs with HNG inhibited cell death, nucleus pyknosis and deformation[63]. Also, HNG diminished the expression of cleaved poly ADP-ribose polymerase (PARP) which reflects the level of apoptosis as well as reactive oxygen species (ROS). Regarding the level of bax, which is a pro-apoptotic protein, it decreased after pretreatment with HNG, while bcl-2, which exerts anti-apoptotic effects, it increased.

Another group identified a different sORF within the mitochondrial 12S rRNA encoding a 16-amino-acid peptide named MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c) which also regulates insulin sensitivity and metabolic homeostasis[56]. Particularly, MOTS-c treatment in mice protected against age-dependent and high-fat-diet-induced insulin resistance and diet-induced obesity as well. Finally, they suggested that MDPs, like MOTS-c and HN, with such systemic effects may be useful in ameliorating the abnormal metabolism associated with aging in humans and regulating biological processes like weight and metabolic homeostasis.

Kim and his colleagues from California tried to elucidate the signaling pathways underlying HN's cytoprotective roles *in vitro* and *in vivo*[14]. Utilizing multiple models, they showed that HN is a major GP130 agonist which acts through the GP130/IL6ST receptor complex and activates AKT, ERK1/2, and STAT3. PI3K, MEK, and JAK were suggested to be involved in the activation of those three signaling pathways, respectively.

Concerning the effects of HN on mitochondrial biogenesis in pancreatic β -cells, HN treatment in MIN6 β -cells increased the expression of peroxisome proliferator-activated receptor (PPAR) γ coactivator-1 α (PGC-1 α)[57] which promotes mitochondrial biogenesis by activating the expression of nuclear respiratory factor 1 (NRF-1) and mtDNA transcription factor A (TFAM)[64]. Also, HN treatment promoted mitochondrial biogenesis by increasing mitochondrial mass, elevating mitochondrial DNA (mtDNA)/nDNA ratio (reduced mtDNA copy number plays a key role in insulin resistance[65]), and increasing cytochrome B expression. Finally, HN treatment resulted in the phosphorylation of AMPK, which was involved in the induction of PGC-1 α , NRF-1, and TFAM and improved mitochondrial respiration and stimulated ATP generation leading to a possible functional gain of the mitochondria.

In HUVECs also, HN displayed protective action against high-glucose-induced endothelial dysfunction and macrovascular complications[66]. HN treatment promoted the expression of Krüppel-like factor 2 (KLF2), a principal transcriptional regulator of endothelial function, by activating ERK5. In addition, HN significantly reduced the expression of vascular cell adhesion molecule 1 (VCAM-1) and E-selectin, which regulate the adhesion of circulating leukocytes to the endothelium, a principal procedure in the initiation of atherosclerosis. Furthermore, HN impeded the secretion of pro-inflammatory cytokines, such as TNF- α and IL-1 β .

HUMAN SUBJECTS RESEARCH AND CLINICAL TRIALS

Human subjects research and clinical trials

The first attempt to measure HN levels in a clinical population with impaired fasting glucose (IFG) was made in participants attending a diabetes complications screening clinic (DiabHealth)[67,68]. Previous clinical studies reported noticeably increased HN levels in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and chronic progressive external ophthalmoplegia (CPEO), which are associated with excess oxidative stress[69,70]. However, a significant reduction ($P = 0.0001$) in HN was reported in the IFG group ($n = 23$; 204.84 ± 92.87 pg mL⁻¹) compared to control ($n = 58$; 124.3 ± 83.91 pg mL⁻¹) in accord with an adaptive cellular response by HN to a slight raise in fasting blood glucose level (BGL). As we described above, HN protects neuroendocrine β -cells [44] and increases glucose tolerance and insulin sensitivity[20,44]. Moreover, it is considered to interact with hydrogen peroxide and α -actinin-4 which rise during oxidative stress and IFG[71-73] and binds extracellularly with the CNTFR/WSX-1/GP130 receptor[69,74,75]. Interestingly, mild to moderate levels of ROS result in positive adaptive mechanisms of the mitochondria[76]. All these mechanisms, which benefit cell function and survival, lead to a reduction in HN levels, indicating a protective role of HN. However, with disease progression to T2DM and further oxidative stress, mitochondria may upregulate HN levels as observed in studies of Alzheimer's disease and in those of MELAS and CPEO.

These conditions are related to extensive oxidative stress which is also a key feature of DM. Particularly, hyperglycemia causes extended free radical activity and mitochondrial dysfunction which induce oxidative stress and release more ROS[76]. The advanced diseases MELAS and CPEO are

associated with increased plasma HN levels. HN has a protective role and is upregulated with disease progression. On the contrary, the minor elevations of blood glucose levels are combined with a decrease in HN concentrations which supports the protective role of HN when levels are expected to decrease as a result of stimulation of oxidative stress-associated agents that are inhibited by HN. However, with disease progression to T2DM and further oxidative stress, mitochondria increase HN levels, as reported in MELAS and CPEO.

A few years earlier, another group from Toronto suggested that plasma HN levels were significantly higher in T1D men by comparison with the healthy control men ($P < 0.0001$)[77].

At the end of 2018 Ma *et al*[78] evaluated HN concentrations in pregnant women with and without gestational diabetes mellitus (GDM) aiming to define the role of HN in the development of GDM. 157 women were enrolled in the study. Serum HN levels were significantly lower in women with GDM compared to controls. Like Lee *et al*[21], who found that HN was regulated by IGF-1 in mice and humans, they suggested that the IGF axis influenced the HN levels and affected its normal function in GDM. By performing logistic regression analysis, they also showed that low HN levels were the independent risk factor of GDM and, therefore, might be a predictor for the GDM diagnosis. Additionally, HN levels were significantly negatively correlated with the body weight, body mass index (BMI) and homeostatic model assessment for insulin resistance (HOMA-IR).

The most recent study which attempted to evaluate MDP levels in normal, prediabetes and diabetes subjects enrolled 225 participants[49]. The investigators found that serum HN concentrations are lower in T2DM ($P < 0.0001$) and correlate with HbA1c. Interestingly, HN levels decreased by 62% in the prediabetes group, 66% in diabetes subjects with good control and 77% in uncontrolled diabetes patients compared to participants without diabetes. Also, this study confirmed that there are no significant differences in HN levels between healthy men and women and the levels of HN were not affected by the different anti-diabetic treatment (insulin, metformin, other hypoglycemic regimens) or the duration of therapy. Furthermore, since HN was associated with adiponectin, which has been suggested to be reduced in prediabetes and T2DM[79], it can be concluded that mitochondrial dysfunction contributes to glycemic dysregulation and metabolic effects in T2DM. Adiponectin levels were positively correlated with HN. Adiponectin concentrations decrease in pre-diabetes and DM[79]. It has also been demonstrated that adiponectin knockout mice have reduced mitochondrial content combined with insulin resistance[80]. In addition adiponectin may impair mitochondrial biogenesis[81]. Therefore, the affected mitochondrial function may arise from the low adiponectin levels.

As for the changes in HN levels with ageing, Voigt *et al*[67] showed that HN decreased with age among individuals attending a diabetes complications screening clinic suggesting a protective function of HN and this observation was consistent with a previous study among human and mice[23]. On the contrary, circulating levels of HN increase in age-associated diseases such as T2DM. With disease progression and additional oxidative stress, mitochondria may increase HN levels.

Besides the initial and principal lifestyle interventions for glycemic control in DM, currently, we have various oral and injectable pharmacologic agents at our disposal including metformin, thiazolidinediones, sulfonylureas, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptyl-peptidase 4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and insulin[82]. These medicines can be administered in various dosages and in many combinations in each patient diagnosed with DM. However, there is still room for additional new factors that could efficiently contribute to the management of the disease. Given HN's protective properties, it may represent a novel treatment option to decrease the cellular damage caused by diabetes. Altered HN levels in diabetes could serve as a potential biomarker. Nevertheless, no clinical trials investigating the effects of HN or its analogues (e.g. HNGF6a) administration have thus far been published, albeit it would be an innovative and promising breakthrough in diabetes prevention and treatment.

CONCLUSION

In summary, HN shows cytoprotective effects in many biological processes, including oxidative stress and apoptosis. Altered HN levels could serve as a potential biomarker in prediabetes and T2DM, since they seem to be an effect or a response to the increased ROS production, oxidative stress, and reduced mtDNA copy number which all contribute to IR[83]. However, further study is needed to define the role of age and other modifiable confounding factors, like fitness level, adiposity, other metabolic comorbidities, such as CVD, stroke, inflammation. Undoubtedly, the major and important question is whether HN could be used as a potential therapeutic option for diabetes, that could even replace the current diabetes mellitus treatment strategies soon. Towards this direction, further studies are needed to identify the contribution of HN in the metabolic dysregulation of T2DM.

FOOTNOTES

Author contributions: All authors contributed equally to the writing of the manuscript and have read and approve the final manuscript.

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