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PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 71184

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

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05426937
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Greece

Manuscript submission date: 2021-08-30

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-08-30 04:36

Reviewer performed review: 2021-09-01 02:52

Review time: 1 Day and 22 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [ ] Anonymous [Y] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Humanin (HN) is a 24-amino acid mitochondrial-derived polypeptide with cyto-protective 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 β cells, and delays the onset 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. And Summarized as follows: 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 . However, further study is required to determine the contribution of age and other confounding factors that are modifiable, such as fitness level, adiposity, other metabolic comorbidities, such as CVD, stroke, inflammation. This article is well written and of clinical interest. And it also puts forward the current problems and future research directions. There remains scope for future research, particularly 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, additional studies are required to determine the role of HN in the metabolic dysregulation of T2DM.Therefore, I recommend publishing this manuscript.

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Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02623025
Position: Associate Editor
Academic degree: MD, MDS

Professional title: Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Greece

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The article of Chrysoula Boutari et al. entitled "Humanin and Diabetes Mellitus: A review of in vitro and in vivo studie".is an interesting manuscript describing the role and suggesting potential new functions of the Humanin, a Mitochondrial derived peptides (MDPs), on diabetes mellitus. The work is well done but some points need to be revised: 1. It would be appropriate to realize a specific figure of the mechanisms of action of Humanin in diabetes mellitus. 2. It should be explain or hypothesize an explanation for the difference in blood values by comparing type 1 diabetes and type 2 diabetes. 3. Are there any clinical trials on Humanin or analogues such as HNGF6a? 4. It is possible that age can influence Humanin hematic values in the diabetic population, can you discuss on it. 5. It should be nice to deepen the correlations between Humanin and adiponectin

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Manuscript NO: 71184

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

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Reviewer's code: 02455955
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Academic degree: BMed, PhD

Professional title: Dean, Professor

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

General comment The aim of this review is to present the in vitro and in vivo studies that examined the role of humanin in insulin resistance and diabetes and to discuss its newly emerging role as a therapeutic option against those conditions. I believe that the topic is novel especially what role does humanin play in diabetes-related research. The logic of the article description is not clear; the author should highlight the outcome of diabetes research. In addition, the article only introduces the role of humanin in the pathogenesis of type 2 diabetes, and does not discuss other types of diabetes. The title of the article should to be revised. Overall, this review should focus on be the role of humanin in diabetes. Abstract: 1. In the abstract part, the authors presented evidence that humanin increases insulin sensitivity, improves beta cell survival, and delays the onset of diabetes. Is this an vivo study or vitro study? The reason for this review alone does not seem to be convincing. The author should concisely summarize the convincing evidence in the abstract section for review and discussing the current research on humanin and diabetes. Introduction: 2. The author focuses on the discovery process of humanin in the background part. I think the detailed discovery process of humanin is not necessary for this review. The background part should focus on the physiological role of humanin, the current epidemiology and the pathogenesis of diabetes, and the role of humanin in diabetes already found in previous studies. Please focus on the research topic in this part. Structure of HN peptide: 3. The description of humanin structure is not combined to the research outcome. What are the characteristics of the structure of humanin to support its role in diabetes? What are the effects of different isoforms on its mechanism of action? Mechanisms of action: 4. In the second paragraph of this part, the author first explained that humanin is regulated by IGF-1 and GH playing a role in

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various diseases (including diabetes). Then the author discusses that humanin is related to mitochondrial dysfunction, affecting ROS, playing a role in many diseases (excluding diabetes). Are these two mechanisms both related to diabetes? If not, what are the reasons stating the second mechanism? The writing logic is very confusing and cannot be understood well. Role of humanin in type 2 diabetes: 5. The title of the article indicates that the outcome of the study is diabetes, but it seems that the author only describes type 2 diabetes. In addition to type 2 diabetes, diabetes also includes subtypes such as type 1 diabetes and gestational diabetes. 6. Please describe in detail the current epidemiology of diabetes. 7. The purpose of this paragraph is to explain the role of humanin in the pathogenesis of type 2 diabetes. The title of the paragraph should be revise to avoid misunderstand. Clinical trials 8.Since the author looks ahead to the prospects of humanin in the treatment of diabetes in the conclusion part, the existing treatment methods for diabetes should also be in detail be described. 9. The author also describes increased humanin levels in patients with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), and chronic progressive external ophthalmoplegia (CPEO), is this related to the outcome of this review? 10. The existing studies listed by the author do not seem to be clinical trials, but rather observational studies. There are no examples of humanin being used in the treatment of diabetes., which is contrary to the author's prospects for the use of humanin in the treatment of diabetes.

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

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Reviewer's code: 03906428
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Russia

Author's Country/Territory: Greece

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Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The article "Humanin and Diabetes Mellitus: A review of in vitro and in vivo studies" was submitted for review. The abstract contains complete information about the research issues of the humanist, described in the review. Humanin (HN) (MTRNR2), the first mitochondrial microprotein encoded with a small open reading frame (sORF) with biological activity. It has been hypothesized that HN protects cells from oxidative stress and mitochondrial dysfunction and therefore plays a role in age-related diseases and certain metabolic disorders (eg, cardiovascular disease, memory loss, stroke, type 2 diabetes. The review contains main chapters - Introduction, Structure of HN peptide, Mechanisms of action, Role of humanin in type 2 diabetes, In vitro and animal studies, Clinical trials. The Conclusions and Future Prospects section contains information that altered HN levels may serve as a potential biomarker for prediabetes and T2DM. However, further research is needed to determine the effects of age and other factors that can be altered, such as fitness levels, obesity, and other comorbid metabolic diseases such as cardiovascular disease, stroke, and inflammation. An important question is whether HN can be used as a potential therapeutic agent for diabetes. The list of references contains 75 sources, including modern ones, the review is illustrated by 1 Table. Conclusion. The review article can be accepted for publication without changes.

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Author's Country/Territory: Greece

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a review of Humanin's in vivo and in vitro studies in diabetes. The article summarizes its effects and mechanisms, existing in vivo and in vitro studies, and clinical trials. It has a certain degree of innovation, provides new ideas for the treatment of diabetes in the future, and has certain clinical significance. The only drawback is the lack of some insights. The discussion part can be richer in content, even better.