

21st April 2014

To

The Editor

World Journal of Diabetes

Dear Sir/ Madam,

Ref: Manuscript no: 9129

Thank you for allowing us to resubmit our manuscript. We have addressed all the comments made by the editor and reviewers and our responses to each of the reviewers are documented below. Our changes in the manuscript are marked in red. We now hope our manuscript will be acceptable for publication.

Reviewer 1 – 02756144

Comments

*One minor concern is that the authors have not precisely introduced how glucose, fatty acids, and amino acids metabolism interplays for energy homeostasis, although they simply mentioned that the interplay is important in Introduction. **Detailed information of the interplay may enhance this review because it provides a motivation why glucose, lipid, and protein simultaneously touch the secretion of insulin--central controller of energy homeostasis.***

Authors reply

We thank the reviewer for his comment. The paragraph in red on page 3 of the manuscript summarises how metabolic coupling factors are generated from glucose, amino acid and fatty acid metabolism to regulate insulin secretion. Details of the interactions between glucose, amino acid and fatty acid metabolism are given throughout the manuscript and the molecular basis of these interactions is described in detail.

Reviewer 2- 00061684

Comments

*This review article an overview how amino acids and fatty acids control insulin secretion and how defects in the enzymes GLUD1 and HADH lead to severe protein induced hyperinsulinaemic hypoglycaemia. Although most of the biochemical pathways described are text book knowledge, their short description is necessary to implement the aspects of the manuscript. **The article is well written but often too full of abbreviations which are easy to mix up between diseases and enzymes; often enzymes are given as abbreviations and never explained, several times as abbreviations with explanations in brackets and several times the other way around. This should be concise. An abbreviation appendix may be useful. Although figures were indicated the ms file provided did not contain any figures.***

Authors reply

We thank the reviewer for his comment. We have now corrected all the abbreviations according to the reviewer's suggestion.

Reviewer 3 – 00503187

Comments

The review by Chandran et al. describes the molecular mechanisms of protein-induced hyperinsulinaemic hypoglycaemia. General comments: 1. The text would be more reader-friendly if the longest paragraphs would have subtitles. 2. It remains open in the Abstract what proteins the two genes mentioned by name encode. 3. The figures are far too small, and their text can't be read on the printout.

Authors reply

We thank the reviewer for his comments.

1. The text has now been made more reader friendly with subtitles throughout the manuscript.
2. Abstract – corrected as suggested by the reviewer
3. Figures – larger Power point decomposable figures are uploaded

Reviewer 4 – 00506294

Comments

This review about: "Molecular Mechanisms of Protein Induced Hyperinsulinaemic Hypoglycemia". is a complete article about this very complicated item; it is an excellent review where the authors analyze the interplay between glucose metabolism and other primary nutrient classes, amino acids and fatty acids and regulation of insulin secretion. Also they treated mitochondrial metabolism of glucose, amino acid and fatty acids that generates metabolic coupling factors. They deeply analyze protein induced hypoglycaemia in patients with mutations in GLUD1 and HADH that provides new mechanistic insights into the regulation of insulin secretion by amino acid and fatty acid metabolism, and also the role of the enzyme glutamate dehydrogenase which integrates both signals from both pathways and controls insulin secretion. Hence GDH seems to play a pivotal role in regulating both amino acid and fatty acid metabolism. They studied protein induced hyperinsulinaemic hypoglycemia observed in patients with mutations in GLUD1, HADH and ABCC8/KCNJ11. GDH and SCHAD that plays important roles in integrating amino acid and fatty acid signals for insulin secretion. The article is well written, without flaws and complete with 100 references about protein induced hyperinsulinaemic hypoglycemia and also 5 explicative figures.

Authors reply

We thank the reviewer for his/her comments

Other changes we have made in the manuscript:

References

We have gone thoroughly through the references and found 4 references repeated in the list and hence deleted. This brings down the references to 96 from 100.

PMID, DOI and PMCID are added as suggested by the editor.

Editor's comments:

Running title, correction of addresses (in affiliation of authors), author contributions, corresponding authors professional title, core tip, DOI/PMCID/PMID added to references and power point decomposable figures added according to editor's suggestion.

Thanking you,

Yours sincerely,

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