

Format for ANSWERING REVIEWERS

November 19th 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Molnar_et_al_manuscript_including_figures.doc).

Title: Tyrosine isomers and hormonal signaling. Possible role of hydroxyl free radical in insulin resistance

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Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 13839

First of all, the authors wish to express their thanks to the Reviewer for the thorough check-up of the manuscript. We aimed to address all the listed questions in the hope that answering the questions and correcting the manuscript according to suggestions of the Reviewer would improve quality of the paper.

Please find our responses below:

Question 1: Figures 2, 3, 4, 6, and 7 There are no description about the statistical methods in the figure legends in Figures 2, 3, 4, 6, and 7. The authors should provide what methods are used in the statistical analysis.

Answer 1: Thank You for the kind observation. The original version of the manuscript contained the original subscription to figures, which did not contain the applied statistical methods, as You noted, they were included in the main text of the original, cited papers. We corrected the manuscript, and figure legends now contain the statistical methods, as You suggested, providing an ease for understanding the results.

Question 2: Figure 4 The authors should describe legends more precisely in Figure 4. What is the description of "Insulin (nmol/L)" in the right side of Figure 4? What is the meaning of the marks "?" and ""?*

Answer 2: The original manuscript contained a mistake, namely the figure showing insulin effect was included instead of the figure showing the EPO-effect, as You noticed. The figure was replaced by the proper one, also figure legend was corrected, including explanation of the signs (asterisk and cross) on the figure. Thank you again for pointing out this mistake.

Question 3: Figure 5 I wonder why the authors did not show the effect of insulin on GLUT4 translocation in high glucose medium and the effect of EPO in low glucose medium.

Answer 3: Thank you for the important question. According to the results of our glucose isotope-uptake studies (see Figure 4 of the present paper and the Figure 1a of the original paper by Mikolas et al showing insulin-induced glucose uptake), we expected no detectable change of insulin-induced GLUT4 plasma membrane translocation in high glucose medium. Similarly, in case of EPO-treatment, no GLUT4 trafficking was anticipated in normal glucose containing medium. Our aim was to demonstrate the EPO-induced GLUT4 translocation, as a possible explanation of the increased glucose-uptake in adipocytes at high concentration of glucose in the culture medium. Consequently, no experiments were performed in high glucose medium with insulin-, or in normal glucose with EPO-treatment.

Question 4: Page 15, lines 7-10 The phrase "Panel C shows ... cultured cells; n=10)" should be deleted because panel C was not provided.

Answer 4: The change suggested by the Reviewer was carried out, the sentence is deleted. Thank You for this observation, as well.

Question 5: Spelling errors should be corrected. (Page 6, line 14) "stochiometrically" → "stoichiometrically" (Page 6, line 19) "Homo tirolensis" → "Homo tyrolensis" (Page 17, line 8) "phoshorylation" → "phosphorylation"

Answer 5: Thank You for noticing the spelling errors, as well. All suggested changes were carried out, except for the case of "Homo tirolensis". We would kindly disagree with the suggestion in that case. The name of the Austrian region, where the mummy named „Ötzi" was found is "Tirol", hence the name is "Homo tirolensis" (see Lubec et al. FASEB Journal 8,1166-1169 - 1994), thus the way of spelling used in our original manuscript was correct. All other spelling errors were corrected according to the Reviewer's suggestion.

The authors again wish to thank the Reviewer for the important observations and correction of our mistakes. We hope that we managed to raise the value of the manuscript via the correction, as it was intended by the Reviewer. Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Istvan Wittmann', written over a horizontal line.

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