Author’s response to reviews

Title: OXYTOCIN AND CARDIOPROTECTION IN DIABETES AND OBESITY

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Author’s response to reviews:

Responses to Reviewers Questions:

The Authors would like to thank Reviewers for important comments which in our opinion strongly enriched the quality of our manuscript.

Reviewer #1:

This is a review article on a topic, which is currently intensively investigated. The quality of the review is underlined by the fact that the authors themselves significantly contributed to the field and so they transformed into the review their knowledge and expertise. The general concept of the review is very good. There are only several points which need clarification or correction.

Comments

1. Page 4, 1st line - "Novel applications of OT include" should better be replaced by "Potential novel applications of OT include" – Change has been added.

2. Page 6, 2nd paragraph - By describing cardioprotective effects of oxytocin against MI in animal models of ischemia/reperfusion, the authors somehow overlooked that the first paper on the reduction of infarct size by OT was published in 2009 (ref. 36) before or simultaneously with their own paper in 2010 (ref. 24). This should be corrected. – Revision was introduced and in corrected manuscript the paper of Ondrejcakova et al. (2009) is presented as a first relevant observation (page 6).

3. The authors might consider including another report published by Ondrejcakova et al., Gen Physiol Biophys. 2012 – We have used this valuable comment and commented the paper of Ondrejcakova et al. (2012) on the page 7 of revised version of manuscript.
4. Pages 7-8, chapter on "Obesity and OT treatment". I strongly suggest putting into this chapter the information on possible negative consequences of OT treatment in obese mice on glycemic control published by Altirriba et al. (ref. 47). The reader interested in information on OT treatment of obesity would not find this important information in the chapter on exercise. – This important comment was elaborated in the revised manuscript on the pages 8-9 and following text was presented:

“The ob/ob mouse represents a close counterpart to the human condition of severe obesity, but unlike db/db mice, exhibit leptin deficiency from a mutation in the ob-gene [52]. Ironically, a recent study revealed that OT treatment of ob/ob mice worsened glycemic control, likely from an increased production of corticosterone and stimulation of hepatic gluconeogenesis [50]. The body weight gain-reducing effect was limited to the fat mass only, with decreased lipid uptake, lipogenesis, and inflammation, combined with increased futile cycling in abdominal adipose tissue. Correspondingly, several clinical trials (UKPDS33, ACCORD, ADVANCE, and VADT) demonstrated that intensive glycemic control fails to prevent cardiac complications in diabetics or have even increased cardiovascular mortality [53]. This calls for the development of new strategies capable of preserving heart function in diabetes”. Correspondingly, the appropriate text in the chapter of exercise was reduced.

5. In the chapter starting on page 8, the text should better be divided into paragraphs. – In the new version of manuscript, the chapter was revised and divided in two parts: “The role of exercise in obesity and diabetes” and “The cardiac OT/OTR system and exercise”.

6. Page 9, last 8 lines - This part of the text is not easily understandable, e.g. accumulation of TNF - where?; down-regulation of the OT/OTR - by what?; NPs were restored back to control - but from where? The authors may like to reformulate this part. – The revisions have been introduced in the new version of manuscript (pages 10-11).

7. Has the abbreviation DC been explained? – Abbreviation DC has been presented in the Abstract.

8. Page 10, line 2 - Despite "this" robust effect of exercise - no effect of exercise was described in preceding text. – The sentence was revised.

9. Page 11, 1st paragraph - As the comments to the report by Altirriba et al. were proposed to be moved to another chapter, the last 5 lines of this paragraph can be omitted. – As suggested by Reviewer, the changes were introduced and the text partly transferred (see question No 4).

10. Page 11, 2nd paragraph, line 2 - Please, change the word order to "plasma OT levels".- Change was introduced.

11. The chapter starting on page 11 (e.g. line 5-9) appear to repeat the facts which have been already described in previous chapters. Please, check. Also the message of this chapter is not very clear.
This paragraph was substantially reduced and relevant data to benefit of OT in diabetic cardiomyopathy were preserved.

Reviewer #2: The authors have presented an excellent overview of the role of oxytocin on cardioprotection in diabetes and obesity. I only have minor comments:

1) Abstract, line 1: The authors should be consistent over the abbreviation for OT throughout the manuscript – Consequently abbreviation was revised in the all part of the manuscript.

2) Background, line 17: the authors could also reference that oxytocin is also synthesized in parvocellular paraventricular nucleus neurons – Correction has been added.

3) Background, line 33: The authors could state how much affinity towards OTR relative to the AVP receptors – We have introduced affinity data from the receptor binding studies on transfected cell lines presented by Akerlund et al. (1999).

4) Pg. 6, linle 17: mechanisms – correction introduced

5) Pg. 8, line 12: the authors could add Blevins et al., Am. J. Physiol., 2016 (in press) -

6) Pg. 8, line 9: The references to genetic models of obesity could also be included (Gajdosechova et al., 2014, and Plante et al., 2015) - Following text has been added on page 8 as a response to the questions 5 and 6:

"A recent study of Blevins et al. [47] indicates that chronic that a chronic increase (≈ 21-26 days) of CNS oxytocin signalling not only prevented weight gain induced by HFD but also effectively reduced already established diet-induced obesity. OT also decreased the genetic-induced obesity observed in Zucker rats [48] and db/db mice models [49], which bear a mutation in the leptin receptor gene”.

7) Pg. 8, line 29: the authors could also mention that intranasal OT may also increase OT levels in the circulation if the intranasal delivery device did not sufficiently target the drug to the cribiform plate (reviewed in Meredith, ME et al., AAPS, 2015) – the relevant comment was added in the page 9 of revised version of manuscript.