**Overall responses to peer-reviewing of the submitted manuscript #30269**

The manuscript has been slightly shortened as requested by one reviewer meanwhile it has concisely received additional data to answer to the other reviewer. We also answered to all the queries of the Editor and the corresponding changes/implementations are highlighted in the revised typescript. We therefore hope that the enclosed revised version is now in agreement with the Word Journal of Diabetes scope/style.

**Specific responses to reviewer #00506397 's comments:**

*This is an excellent study. The authors should be encouraged to carefully revise the manuscript (edit the Discussion) to make it more concise.*

Re: Thank you for your comments and your kind suggestion to shorten the Discussion. In multiple occurrences entire sentences have been deleted and do not appear in the revised version. The word counting was therefore reduced from 2330 to 2040.

*The English writing may benefit from editing by someone who's mother tongue is English.*

Re: Thank you for your reminder. Our revised manuscript has been improved by Anais Briot, one of our colleagues who is not English native, but who spent six years at the Univ. of California - Los Angeles and has acquired a good grasp of knowledge regarding scientific report editing and proofreading. We have acknowledged her editorial support in the revised manuscript while we will not provide any certificate verification from any official proofreading & editing service as recommended.

**Specific responses to reviewer #00495228 's comments:**

*A manuscript by Carpéné et al. describes the effect of a conjugate hexaquis(benzylammonium) decavanadate on lipolysis in adipocytes from multiple species. The studies presented in the manuscript are logical and well designed. The manuscript is well written.*

Re: Thank you very much for reviewing our manuscript. We sincerely acknowledge your careful perusal and your satisfactory perception of our following message: Lowering excessive lipolytic activity in adipocytes by B6V10 has a potential interest for limiting the lipotoxicity that enhances the complications of insulin resistance.

*The only criticism of the manuscript is that little work has been done to characterize the molecular mechanism behind the effects of the compound on lipolysis. Given the specificity of the inhibition on the adrenergic induced lipolysis by the conjugate, it would be logical to examine if the tested compound can antagonize the beta-adrenergic receptor and lower cAMP levels in adipocytes.*

Re: Thank you very much for your comment. We respectfully agree that the molecular signaling involved in the antilipolytic action of the conjugate benzylamine/decavanadate has been poorly investigated in our study, which merely focused interest on whether the compound could be antilipolytic or not. However, it must be mentioned that other insulin-like actions of the conjugate (such as the stimulation of glucose transport into adipocytes) have been extensively investigated in our previous studies, quoted in multiple occurrences in Introduction and Discussion of the manuscript. The references #13-16 of the list correspond to our previous works in which we demonstrated that B6V10 undergoes oxidation in the adipocytes. This produces hydrogen peroxide and generates peroxovanadate, which in turn inhibits phosphatases involved in the 'turn-off' of insulin signaling and thereby activate hexose carrier translocation. Obviously, the mechanisms involved in the insulin- or B6V10-mediated stimulation of glucose transport are not totally identical with those mediating lipolysis inhibition, but one can suppose that the alterations of phosphodiesterases observed in response to the pancreatic hormone also occurred with B6V10. While various phosphorylation states of signaling molecules are altered in the presence of B6V10, the cAMP is expected to be more metabolized into AMP and adenosine, as it is the case with insulin. Currently,

we cannot measure the cAMP levels in adipocytes of the studied species as logically proposed by the reviewer. Nevertheless, we have rearranged the presentation of our data, especially at the end of second section of Results. This paragraph is more clearly devoted to the study of the effect of B6V10 alone (without any presence of beta-adrenergic receptor agonist) and reports the activation of lipogenesis by a mechanism that rules out any involvement of beta-adrenoceptor antagonism. Moreover, the somehow inhibitory influence of B6V10 on the lipolysis activation induced by ANP in human adipocytes (fig. 4B) also argued that the compound acts differently from a beta-adrenoreceptor antagonist, since ANP-induced lipolysis is resistant to beta-blockers (*Moro C, Crampes F, Sengenes C, De Glisezinski I, Galitzky J, Thalamas C, Lafontan M, Berlan M. Atrial natriuretic peptide contributes to physiological control of lipid mobilization in humans. FASEB J. 2004;18(7):908*-).