**Author’s response to reviews**

**Title:** Severe Hypoglycemia Reduces the Shivering Threshold in Rabbits

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**Author’s response to reviews:**

Reviewer 1

We appreciate that the reviewer’s comments. The followings are our point-by-point responses:

1) Why were the animals ventilated with high FiO2’s which result in unphysiologically high paO2’s. These high Levels may have influenced the observed Response.

Response: In our laboratory, we had no air pipeline when we investigated this study, so that we cannot study with lower FiO2. After this study had been finished, our laboratory was repaired to be able to use air pipeline.

2) I don´t think its reasonable to deem rabbits that did not shiver as "shivering". This may in turn influence the results.

Response: We are planning further studies that an electromyography will be used in for us not to deem rabbits that did not shiver as "shivering".
3) I would suggest a more detailed work up of the animals after euthanasia aiming to explore neuromuscular abnormalities responsible for the observed changes

Response: In this study, neuromuscular abnormalities was not explored. We wish to take into consideration these factors in our further studies.

Reviewer 2

We appreciate that the reviewer’s comments. The followings are our point-by-point responses:

1) Glucose concentrations were taken hourly however circulating glucose concentrations can fluctuate markedly over this time scale. Were intermediate readings taken during this period to ensure circulating glucose levels remained within the desired range?

Response: Blood glucose concentrations were actually checked about each 30 minutes in order to fall within the range.

2) To reduce core body temperature and induce hypothermia cold water (10°C) was infused into the colon to reduce core body temperature by 2-3°C per hr. As core body temperature is reduced to a minimum of 34°C this could be up to 2 hrs. When did this cooling occur in relation to the hypoglycaemia i.e. was hypoglycaemia stabilised prior to hypothermia and if so were all animals maintained at their target glucose for the same amount of time prior to the induction of hypoglycaemia? Please clarify.

Response: Blood glucose concentrations were stable about 30 to 60 minutes prior to cooling. We have added a sentence to the manuscript.

3) The colour coding for figure 1 has been mixed up - Control should be red circles and severe hypoglycaemia blue diamonds.

Response: As suggested by the reviewer, we have corrected the pointed color-coding mix-up.
4) A typographical error page 11 line 8 - shiver not shivered.
Response: As suggested by the reviewer, we have corrected the pointed typographical error.

5) Did the authors measure time to reach shivering threshold and if so was there any impact of degree of hypoglycaemia on this parameter? Likewise were any thyroid hormones or glucocorticoids measured in measured in this study? These are known to be altered by both hypothermia and hypoglycaemia - was there any interaction between these parameters?
Response: In this study, time to reach shivering threshold, any thyroid hormones or glucocorticoids were not measured. We wish to take into consideration these factors in our further studies.