Reviewer's report

Title: Amiloride derivatives as potential therapeutic agents for type 2 diabetes: A randomized controlled study

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Reviewer: Hans-Juergen Mest

Reviewer's report:

The reviewer realized a discrepancy between the title of the manuscript and the studies done. The title promises in vivo studies leading to conclusions for treatment of type 2 diabetes. In reality all studies done were based on islets isolated from two diabetic mouse strains. The information relating to these animals is very poor. The reviewer misses information regarding the age of the animals, body weight, glucose levels, and insulin levels. The "problem" described by the authors on page 10 is based on the facts mentioned above. The animals develop diabetes over time and these changes have a strong influence on insulin secretion. The different phases of insulin secretion are strongly influenced by the age/diabetic status. In an early stage the first phase of insulin secretion is intact. Within a short time frame the first phase is impaired. The relevance of the data shown is dependent on these facts. It is well known that a type 2 diabetic patient has an impaired first phase of insulin secretion.

The protocol of the in vivo study is not given. What was the parameter for randomization (title)? What procedure was done to control the real dose given in the drinking water? It is not possible to keep only one animal in a cage. Was the compound plasma level determined? If not, a precise dosing is not possible. An oral gavage is the only alternative.

It is difficult for the reviewer to assess the data under these circumstances. Based on these data the conclusion seems to be very optimistic that amiloride derivatives have potential therapeutic value. The islet studies are well done. Why don't the authors show ph-measurements in NON islets?

It has been shown that normalization of blood glucose in db/db mice resulted in a normalization of insulin secretion from islets subsequently isolated. What are the blood glucose levels of your mice after the one-week treatment? Can the improved insulin secretion be due to lowered blood glucose levels?

Do the depicted differences in ph-changes between WT islets and islets from diabetic animals (Fig 1) go along with a change in the kinetics of insulin secretion? (Perifusion of isolated islets)

Fig 2: depiction of fractional insulin release is an accepted method. A comparison of diabetic and non-diabetic animals, however, requires the display of absolute amounts of released insulin, especially if a compound is thought to normalize secretion.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
'I declare that I have no competing interests'