Reviewer's report

Title: Nutrient-stimulated insulin secretion in mouse islets is critically dependent on intracellular pH: a randomized controlled study

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Reviewer: Noel G Morgan

Reviewer's report:

General
This manuscript describes the outcome of a series of studies designed to investigate the role played by intracellular pH in regulation of insulin secretion from mouse islets. The authors find that pH exerts a significant regulatory control over secretory function and suggest that manipulation of intracellular pH may offer a means to correct secretory defects in diabetic beta cells. The implications are important and the findings novel.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. It is well known that there are marked differences between cytosolic and intragranular pH in beta cells and it is not clear whether the methodology measures an average that includes both (or whether these can be distinguished). An explanation should be provided to indicate how intragranular pH contributes to the measurements recorded and the possible impact of this on the conclusions drawn.

2. A difficulty with the technique employed is that it requires that the islet architecture is disrupted prior to imaging. This presumably alters the cell-cell communication mechanisms that are believed to be critical to correct secretory function. Thus, the authors should discuss the extent to which this may influence the interpretation of studies designed to evaluate the effects of manipulation of intracellular pH. Indeed, is it possible that the loss of secretory response seen upon islet dissociation may reflect impaired intracellular pH regulation? They suggest that the dye (SNARF5) was efficiently loaded into the "beta cell rich" region of the plated islets. How was this determined (how enriched was this region)?

3. Insulin secretion experiments appear to have been conducted with freshly isolated (intact?)islets whereas pH measurements were made in cultured (dissociated?) islets. Are the authors confident that it is valid to extrapolate between these two conditions?

4. The data shown in Fig 3 appear to be repeated in Fig 4a. Thus, Fig 3 is redundant. In addition, the 2.8mM glucose plus DMA control should be included in the figure.

Discretionary Revisions (which the author can choose to ignore)

1. It would be interesting to learn the time-course of the TDP response observed when mouse islets are exposed to glucose and DMA. How long does TDP persist after removal of 16.7mM glucose plus...
2. The postulate that manipulation of pHi might be used to correct the secretory defect seen in type 2 diabetes is interesting and potentially important. Is there any evidence that beta cell pHi is altered in type 2 diabetes?

What next?: Accept after minor essential revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No
Declaration of competing interests:
None