

Peer Review

Review of: "High-Resolution Imaging Atlas Reveals Context-Dependent Role of Pancreatic Sympathetic Innervation in Diabetic Mice"

Winfried Neuhuber¹¹ Friedrich-Alexander Universität Erlangen-Nürnberg, Germany

In this interesting study, the authors investigated pancreatic islet alpha and beta cell distribution together with sympathetic innervation in wild type mice and mice made diabetic genetically or by diet (*db/db* and DIO mice, resp.) using immunohistochemistry combined with advanced imaging techniques. To gauge the role of sympathetic innervation on glucose metabolism, selective pancreatic chemical sympathectomy using 6-OHDA was applied. Key results were changes in islet cell patterns and density of sympathetic innervation of alpha and beta cells, resp. Sympathectomy also had some influence on metabolic parameters, e.g., GTT and ITT. I have some critical remarks.

Major:

1. Given the sheet-like structure of the mouse pancreas, I wonder if it was possible to selectively inject (or to drop onto?) 6-OHDA into this organ without significant leakage into the adjacent structures. In particular, contamination of the small intestine may result in sympathectomy of the gut, possibly interfering with glucose resorption. Thus, I suggest adding control experiments to assess how much sympathetic TH positive fibers were reduced in the intestinal wall (it has to be kept in mind that TH not only labels fibers of sympathetic origin but also fibers of enteric nature). In addition, I suggest providing data from the literature and elaborating on this issue in the Discussion.
2. The complex changes in islet cell patterns were elaborately described in the Results section. However, this is somewhat cumbersome to read. Thus, I suggest condensing this data into a table. This table should be much more detailed than the one in the graphical abstract (which is appropriate there).
3. At places, the description in the text does not comply with the figures. E.g., on p 16, it is stated that in *db/db* mice, most alpha cells were found in the core of islets. However, Fig 3H, which was referred to, shows alpha cells almost exclusively in the shell region.

Minor:

1. P3: „prevertebral ganglia“ is the overarching term for celiac, superior, and inferior mesenteric ganglia.
2. If the decrease of a parameter with age is described, it seems counter-intuitive to write the lower value before the higher. I suggest the reverse (e.g., from 51% to 44%).

3. In the Discussion, it was summarized that islets tend to get larger with increasing glucose levels. However, islet size is *decreasing* in DIO mice which show glucosemia.

The objective magnification of the Leica confocal should be given when high-resolution imaging was described.

Declarations

Potential competing interests: No potential competing interests to declare.