Basic Science Paper 4/11/25 ciT1zen science

Exploration of Individual Beta Cell Function Over Time In Vivo

Source: Delgadillo-Silva, L. F., Salazar, S., Lopez Noriega, L., Provencher-Girard, A., Larouche, S., Prat, A., & Rutter, G. A. (2025). Exploration of individual beta cell function over time *in vivo*: effects of hyperglycemia and glucagon-like peptide-1 receptor (GLP1R) agonism. *bioRxiv*, 2025.03.31.646461. doi: https://doi.org/10.1101/2025.03.31.646461
Date: October 26, 2023 (based on the request date)
Key Themes:

- **Developing a Novel In Vivo Monitoring Approach:** The study introduces a new methodology for long-term observation of individual beta cell calcium dynamics within intact islets *in vivo*. This involves engrafting islets into the anterior eye chamber of a host animal, allowing for continuous blood perfusion and near-normal innervation, and subsequently monitoring Ca2+ signaling over time.
- **Stability of Beta Cell Subpopulations Under Normoglycemia:** The research demonstrates that under normal blood glucose levels, the functional characteristics of key beta cell subpopulations, specifically "leader" cells and highly connected "hub" cells, remain stable within the islet network for at least seven days *in vivo*. The overall islet network dynamics also exhibit stability during this period.
- **Impact of Hyperglycemia on Beta Cell Function and Connectivity:** The study reveals that chronic hyperglycemia, induced by a high-fat diet or genetic loss of a *Gck* allele (a model for impaired glucose sensing), significantly disrupts islet function. This disruption is characterized by:
    - "incomplete and abortive Ca2+ waves" within the islets.
    - "overall connectivity was diminished" among beta cells.
    - A "profound" reduction in the number of hub cells.
    - The relative persistence of leader cells despite the hyperglycemic conditions.
- **Restorative Effects of GLP1R Agonism (Exendin-4):** Treatment with the GLP1R agonist Exendin-4 demonstrated a rapid and significant recovery of islet-wide Ca2+ dynamics in hyperglycemic models. Notably, the treatment led to the "re-emergence of hub cells within minutes," suggesting a crucial role for GLP1R signaling in maintaining these highly connected cells. The effects observed *in vivo* were described as "more marked than those observed after analogous treatments in *vitro*," hinting at potential indirect mechanisms at play.
- **Implications for Understanding Beta Cell Dysfunction in Diabetes:** The findings highlight the dynamic nature of beta cell subpopulations in response to metabolic stress and the potential of incretin-based therapies to restore functionality, potentially through both direct and indirect mechanisms within the complex *in vivo* environment.
- **Potential Broad Applicability of the Monitoring Approach:** The authors emphasize the wider potential of their developed *in vivo* imaging technique for studying individual cell function and intercellular communication in various physiological and pathological contexts within a living organism.

Most Important Ideas and Facts:

- **Novel In Vivo Imaging:** The study's primary advancement lies in establishing a reliable method to longitudinally monitor the activity of individual beta cells within their native islet environment *in vivo*. This overcomes limitations of *in vitro* studies and provides a more physiologically relevant context.
- **Stability of Leader and Hub Cells in Normoglycemia:** The observation that "islet network dynamics, and the behavior of individual leaders and hubs, remain stable for at least seven days" under normal conditions suggests a degree of inherent functional organization and resilience within the islet.
- **Hyperglycemia Disrupts Beta Cell Communication and Hub Cell Population:** The finding that hyperglycemia leads to "incomplete and abortive Ca2+ waves and overall connectivity was diminished," coupled with the "lowered profoundly" number of hub cells, underscores the detrimental impact of chronic glucose overload on islet function and the specific vulnerability of hub cells. Leader cells, however, seem more resistant to this initial damage.
- **Rapid Recovery of Hub Cells with GLP1R Agonism:** The swift "re-emergence of hub cells within minutes" of Exendin-4 treatment is a significant finding, suggesting a key role for GLP1R signaling in regulating the population and/or functional state of these critical network nodes.
- **Enhanced In Vivo Effects of GLP1R Agonism:** The observation that Exendin-4's effects were "more marked than those observed after analogous treatments in *vitro*" points towards the importance of the *in vivo* environment, potentially involving paracrine signals, neural inputs, or vascular interactions, in mediating the full therapeutic benefit of GLP1R agonists. This supports the idea that "incretins may act both directly and indirectly on beta cells *in vivo*."

Conclusion:
This study presents a significant methodological advancement for investigating beta cell function *in vivo*. The findings provide valuable insights into the stability of beta cell subpopulations under normal conditions, the detrimental effects of hyperglycemia on islet network dynamics and hub cell populations, and the rapid and potent restorative actions of GLP1R agonists. The observation of enhanced GLP1R agonist effects *in vivo* compared to *in vitro* underscores the importance of the complex physiological environment in understanding and treating beta cell dysfunction in diabetes. The described approach holds considerable promise for future research into the dynamics of individual cells within tissues in living organisms.