RESPONSE TO COMMENT ON SATIN ET AL.

"Take Me To Your Leader": An Electrophysiological Appraisal of the Role of Hub Cells in Pancreatic Islets. Diabetes 2020;69:830–836

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Diabetes 2020;69:e12–e13 | https://doi.org/10.2337/dbi20-0027

We thank Rutter et al. for commenting in their letter (1) about our recent Perspectives in Diabetes article (2), which was concerned with their hub cell hypothesis.

In the letter, Rutter et al. state that "if a set of assumptions does not readily explain the experimental evidence, one should consider adjustments to the former." While we agree in principle with this statement, we respectfully point out that our reservations about the hub cell model are not based on "assumptions" but on experimental evidence accumulated over many decades and in several independent laboratories.

We acknowledge that we "fail to offer any explanation for [their] optogenetics, photopharmacology, or photoablation studies," but this is the privilege of the skeptic, and we thus suggest that the onus is on them to provide arguments that can convince the field at large. The authors point out in their letter that they have not claimed that "one cell [could] supply enough current to repolarize the entire islet." This is also correct but is certainly not the impression conveyed by Fig. 5*F* of their original article (3). Even so, we can think of no simple electrophysiological mechanism whereby the hyperpolarization of one β-cell would profoundly affect the electrical coupling between the cells of the remainder of the islet, and subsequently their electrical activity. This seems easier to imagine being mediated—as we propose—by diffusible factor(s), such as perhaps somatostatin. They also suggest that "electrical measures of gap junctional conductance are likely underestimated due to series resistance in highly coupled cells," but exactly what this means is not immediately evident to us and this comment certainly needs to be further elaborated.

It is worth reiterating that despite our over 40 years of shared experience patch clamping β-cells in intact islets, we have never seen that hyperpolarization of a β-cell disrupts the electrical activity of the rest of the islet; the β-cells all continue to burst in apparent perfect synchrony. This is clearly problematic for the hub cell hypothesis. Furthermore, we do not find the authors' assumption that this is because the hub cells are impossible to patch convincing. The success of the patch-clamp technique to a large extent reflects its versatility, and over the last several decades a wide variety of cell types (perhaps the majority of cell types in the body) have been successfully studied with this highly useful and widely applicable technique.

When it comes to the possible existence and role of the hub cells, more experimental work using electrophysiology, imaging, and mathematical modeling and combinations of these approaches is required. At the end of the day, regardless of whether we are "hubbites" or "skeptics," it may be useful to remember Sir Arthur Conan Doyle's words: "Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth."

Funding. The research laboratory of L.S.S. is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (R01DK46409). Studies in the laboratories of P.R. are supported by Wellcome Trust, the Swedish Research Council, and The Leona M. and Harry B. Helmsley Charitable Trust.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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References

1. Rutter GA, Ninov N, Salem V, Hobson DJ. Comment on Satin et al. "Take me to your leader": an electrophysiological appraisal of the role of hub cells in pancreatic islets. Diabetes 2020;69:830–836 (Letter). Diabetes 2020;69:e10–e11. DOI: 10.2337/db20-0501

2. Satin LS, Zhang Q, Rorsman P. "Take me to your leader": an electrophysiological appraisal of the role of hub cells in pancreatic islets. Diabetes 2020;69: 830–836

3. Johnston NR, Mitchell RK, Haythorne E, et al. Beta cell hubs dictate pancreatic islet responses to glucose. Cell Metab 2016;24:389–401