RESPONSE TO COMMENT ON USSAR ET AL.

Regulation of Glucose Uptake and Enteroendocrine Function by the Intestinal Epithelial Insulin Receptor. Diabetes 2017;66:886–896

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We thank Dr. Brubaker for her letter (1) regarding our recent publication (2). She raised two questions that we agree are very important: choice of proper controls and use of both sexes in animal studies. The use of proper controls for murine, as well as human, studies is essential to account for environmental, genetic, and epigenetic effects, as well as off-target effects of transgenes, drugs, and other manipulations. In fact, we have published on many of the caveats of tissue-specific gene inactivation (3), as well as the impact of genetic background, the microbiome, and the housing and breeding environment on such studies (4,5).

In the current study (2), we were able to take advantage of inherent controls in our experimental design. Specifically, we did not need a "villin-cre only" control because we used the same villin-cre transgenic mice to induce loss of the IGF-I receptor in the intestinal epithelium, and the resultant mice had no phenotype for any of the parameters assessed (2). This indicates not only that the intestinal IGF-I receptor is dispensable for the parameters assessed but also that the villin-cre transgene used in this study itself did not mimic the phenotypes observed in the intestinal epithelial insulin receptor knockout (VILIRKO) mice. Given the commitment of all investigators to minimize stress and pain on experimental animals and to reduce, refine, and replace animal experiments where possible, including an additional "villin-cre only" group is unnecessary and would violate this tenet.

With regard to studying both sexes, although we did not explicitly state this, we routinely assess potential phenotypes in both sexes. As there was no evidence of sexual dimorphism in the phenotype and no hypothesis regarding effects of sex on outcome, we focused on males, both for cost and ethical considerations. We assume that similar considerations drove Dr. Brubaker to do the same in her recent publications involving mice, rats, piglets, and humans, all of which used only males. When we have observed sex differences in other studies, we have followed up on these observations with appropriate experiments, including administration of sex steroids or gonadectomy to understand the mechanism (6). This was not indicated in this study because no sexual dimorphism was observed.

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

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