RESPONSE TO COMMENT ON BU ET AL.

Insulin Regulates Lipolysis and Fat Mass by Upregulating Growth/Differentiation Factor 3 in Adipose Tissue Macrophages. Diabetes 2018;67:1761–1772

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My coauthors and I thank Dr. Ibáñez (1) for his comments on our article (2). We agree that the effect of gene deficiency cannot be properly judged by the comparison between mice with different genetic backgrounds. We, however, did not actually compare the effect of activin receptor–like kinase 7 (ALK7) deficiency between C57BL/6 and BALB/c mice but examined the effect of insulin within each single strain (2). We showed that in vivo insulin administration affects fat metabolism and mass in ALK7-intact C57BL/6 mice, whereas the same treatment does not in ALK7-deficient BALB/c mice (see Fig. 5*B* in ref. 2). These two findings are separate and independent. You can instead compare the ALK7-dependent insulin effect between Tsumura, Suzuki, obese diabetes (TSOD) and T.B-*Nidd5/3* mice (see Fig. 5*A* in ref. 2), the latter of which is a congenic strain that shares the genome of TSOD mouse except the 1.0-Mb interval containing the mutation of the *Acvr1c* gene encoding ALK7 (3). Thus, our conclusion is not based on the comparison of ALK7 function between C57BL/6 and BALB/c mice. As pointed out, loss of any particular gene may cause different phenotypes among mouse strains. In fact, although Dr. Ibáñez's group reported that aged, global ALK7 knockout mice in an C57BL/6 background exhibit increased triglyceride content in liver and increased glucose-stimulated insulin secretion in isolated pancreatic islets compared with the control strain (4), we could not find either of them in ALK7-deficient T.B-*Nidd5/3* mice compared with the parental TSOD mice (3). Furthermore, direct comparison between mRNA and protein levels of ALK7 revealed that ALK7 expression in islets is much lower, and almost negligible, compared with that in white adipose tissue of TSOD mice (3). Therefore, it is risky to generalize any phenotypic effect observed in a single strain. We thus used both TSOD and C57BL/6 strains to examine the function of the newly identified, insulin-GDF3 (growth/differentiation factor 3)-ALK7 pathway. It is natural for us to have compared the phenotypes between wild-type and global ALK7-deficient mice because we originally found the ALK7 natural mutation by looking for loss of phenotype using the F2 progeny and congenic strains between the TSOD and BALB/c strains (3,5). Furthermore, we would have liked to estimate the relative importance of this pathway compared with other signaling pathways in the simultaneous presence of ALK7 and/or insulin receptor expressed in other tissues. As a result, we found that either macrophage depletion or GDF3-deficient bone marrow transplantation negates the ALK7-dependent insulin effect on fat metabolism and mass (2). Given that we established GDF3 as an ALK7 ligand acting on adipocytes under nutrient-excess conditions among all the transforming growth factor-β members and adipose tissue macrophages as GDF3-producing cells from many kinds of experiments, it is very unlikely that the observed insulin effect on adipose tissue is mediated via ALK7 expressed in other tissues. Although we are not reluctant to use the so-called, fat-specific ALK7-deficient mice that Ibáñez and colleagues generated (6), it is our concern that the AP2-CRE gene used to deplete ALK7 is not specifically expressed in adipocytes but is also known to be highly expressed in macrophages where GDF3 is expressed.

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

References

1. Ibáñez CF. Comment on Bu et al. Insulin regulates lipolysis and fat mass by upregulating growth/differentiation factor 3 in adipose macrophages.

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2. Bu Y, Okunishi K, Yogosawa S, et al. Insulin regulates lipolysis and fat mass by upregulating growth/differentiation factor 3 in adipose macrophages. Diabetes 2018;67:1761–1772

3. Yogosawa S, Mizutani S, Ogawa Y, Izumi T. Activin receptor-like kinase 7 suppresses lipolysis to accumulate fat in obesity through downregulation of peroxisome proliferator-activated receptor γ and C/EBPα. Diabetes 2013;62:115–123

4. Bertolino P, Holmberg R, Reissmann E, Andersson O, Berggren PO, Ibáñez CF. Activin B receptor ALK7 is a negative regulator of pancreatic beta-cell function. Proc Natl Acad Sci U S A 2008;105:7246–7251

5. Hirayama I, Yi Z, Izumi S, et al. Genetic analysis of obese diabetes in the TSOD mouse. Diabetes 1999;48:1183–1191

6. Guo T, Marmol P, Moliner A, et al. Adipocyte ALK7 links nutrient overload to catecholamine resistance in obesity. eLife 2014;3:e03245