

Insulin Action and Insulin Resistance in the Kidney

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Summary

While there is substantial evidence that the kidney is insulin responsive, it is unclear whether the kidney is susceptible to lipid-induced insulin resistance. In this talk I will discuss recent studies using novel LC-MS/MS methodology combined with stable isotopes of glucose to directly assess renal cortical mitochondrial pyruvate oxidation for the first time. Using this approach I will present data demonstrating that insulin promotes increased renal cortical pyruvate mitochondrial oxidation and that this effect is blunted following chronic high fat feeding. Finally, I will go on to discuss the role of plasma membrane associated *sn*-1,2-diacylglycerols (DAG) in causing activation of Protein Kinase C ϵ (PKC ϵ) leading to increased phosphorylation of the insulin receptor kinase on threonine¹¹⁵⁰ leading to reductions in insulin receptor kinase activity and renal cortical insulin resistance.

References

1. Petersen, M. and Shulman, G.I. Mechanisms of Insulin Action and Insulin Resistance, *Physiological Reviews* 2018 <https://doi.org/10.1152/physrev.00063.2017>
2. Petersen MC, Madiraju AK, Gassaway BM, Marcel M, Nasiri AR, Butrico G, Marcucci MJ, Zhang D, Abudukadier A, Zhang XM, Philbrick W, Hubbard SR, Jurczak MJ, Samuel VT, Rinehart J, **Shulman GI**. Insulin receptor Thr¹¹⁶⁰ phosphorylation mediates lipid-induced hepatic insulin resistance. *J Clin Invest*, 2016;1-11. PMID: 27760050.
3. Lyu K, Zhang D, Song J, Li X, Perry RJ, Samuel VT, Shulman GI. Short-Term Overnutrition Induces White Adipose Tissue Insulin Resistance Through *sn*-1,2-Diacylglycerol – PKC ϵ – Insulin ReceptorT1160 Phosphorylation. *JCI Insight*. 2021; 6(4):e139946. PMCID: PMC7934919, PMID: 33411692.
4. Lyu K, Zhang Y, Zhang D, Kahn M, ter Horst KW, Rodrigues MRS, Gaspar RC, Hirabara SM, Luukkonen PK, Lee S, Bhanot S, Rinehart J, Blume N, Rasch MG, Serlie MJ, Bogan JS, Cline GW, Samuel VT, Shulman GI. A Membrane-Bound Diacylglycerol Species Induces PKC ϵ -Mediated Hepatic Insulin Resistance. *Cell Metabolism*. 2020; 32(4): 654-664. PMCID: PMC7544641, PMID: 32882164