



Hepatic glucagon action in obesity and type 2 diabetes: insights from mouse models

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Recent studies have proposed that hepatic glucagon resistance is a characteristic and perhaps a driver of metabolic dysfunction in obesity and hepatic steatosis [1]. We thus examined glucagon effects in multiple mouse models of fatty liver disease, obesity and type 2 diabetes (T2D), including BKS-db/db, New Zealand Obese (NZO) and western diet-fed C57Bl/6 mice. We conducted glucagon tolerance tests (10 nmol/kg; IUB288) in these mice and measured blood glucose, liver glycogen, liver protein expression involved in glucagon signalling pathways (e.g. phospho-PKA motif proteins), and liver untargeted metabolomics by liquid chromatography-mass spectrometry. The western diet-fed mice showed impaired blood glucose response to glucagon. However, both NZO and db/db mice responded well to glucagon in terms of blood glucose increase, liver glycogen decrease, and altered phospho-PKA motif protein expression. Liver metabolomics showed glucagon significantly changed 225 metabolites in db/+ mice (control group), while only 81 metabolites were altered in db/db mice. Also, some classic glucagon-regulated metabolites such as cyclic adenosine monophosphate (cAMP) were blunted in db/db mice compared with db/+ mice. Although db/db exhibited a lower amount of altered metabolites compared with db/+ mice, many metabolites were uniquely affected in db/db mice. Of the 81 metabolites changed in db/db mice, 41 shared similarities to db/+ mice, while 40 were not influenced in db/+ mice. Therefore, while some outcome variables confirmed a liver glucagon insensitivity in obese/T2D mice, this was not uniform, and some outcome variables were actually enhanced in obesity/T2D. Our data thus suggest that the concept of glucagon resistance in obesity/T2D is not 'clear-cut' and a more nuanced view of hepatic glucagon action is recommended.

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Reference

[1] Janah, L., Kjeldsen, S., Galsgaard, K. D., Winther-Sørensen, M., Stojanovska, E., Pedersen, J., ... & Wewer Albrechtsen, N. J. (2019). Glucagon receptor signaling and glucagon resistance. *Int J Mol Sci*, **20**(13), 3314.