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METABOLISM

Adipose and nonadipose effects of FGF21 delineated

> FGF21 signalling to adipose tissue is required for the acute but not the chronic metabolic effects of FGF21

Fibroblast growth factor 21 (FGF21) increases insulin sensitivity and promotes weight loss; however, the exact mechanism and target tissues of FGF21 action are unclear, with both adipose tissues and the central nervous system (CNS) proposed to be involved. In new research published in *Cell Metabolism*, direct FGF21 signalling to adipose tissues is shown to be required for the acute insulin-sensitizing effects of FGF21, but not for its chronic effects on energy expenditure, body weight reduction and secondary improvements in insulin sensitivity.

To investigate the metabolic effects of FGF21 signalling to adipose tissues, the researchers generated mice that lacked the FGF21 co-receptor, β-klotho, specifically in adipose tissues (KLB AdipoKO mice). Although acute treatment with FGF21 increased insulin sensitivity in lean and diet-induced obese (DIO) wild-type mice, this effect was markedly diminished in lean and DIO KLB AdipoKO mice. Conversely, chronic (2 week) treatment with FGF21 still reduced the body weight of DIO KLB AdipoKO mice to a similar extent as that of both vehicle-treated DIO KLB AdipoKO and FGF21-treated DIO wild-type mice.

Moreover, reductions in hepatic and plasma levels of triglycerides, and plasma levels of glucose and insulin, were similar in knockout and wild-type mice. The findings confirm that FGF21 signalling to adipose tissue is required for the acute but not the chronic metabolic effects of FGF21, and are compatible with a previous report that showed that FGF21 signalling to the CNS is required for mediating the energy-expenditure effects of FGF21.

As adipose tissue contains different types of adipocyte, the researchers next generated mice that lacked β-klotho specifically in brown ($UCP1^+$) adipocytes (KLB BatKO mice) to determine which cell type mediates the acute insulin-sensitizing effects of FGF21. Similar to KLB AdipoKO mice, acute administration of FGF21 failed to increase insulin sensitivity in KLB BatKO mice, thereby confirming that FGF21 signalling to brown adipose tissue (BAT) is crucial for the acute insulin-sensitizing effects of FGF21.

The finding that the acute insulin-sensitizing effects of FGF21 are mediated by direct actions on brown and/or beige adipocytes might explain why administration of FGF21 analogues to humans, who have less BAT mass than mice, results in less pronounced glucose-lowering effects than it does in rodents.

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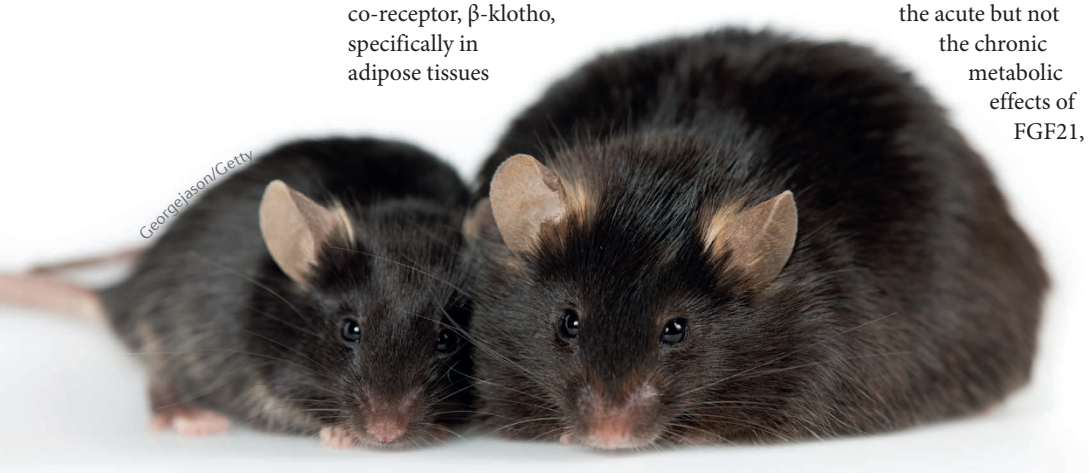

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ORIGINAL ARTICLE BonDurant, L. D. *et al.* FGF21 regulates metabolism through adipose-dependent and -independent mechanisms. *Cell Metab.* **25**, 935–944 (2017)
FURTHER READING Potthoff, M. J. FGF21 and metabolic disease in 2016: A new frontier in FGF21 biology. *Nat. Rev. Endocrinol.* **13**, 74–76 (2017)