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OBESITY

GUT-SPECIFIC FXR AGONISM

Therapy with a farnesoid X receptor (FXR) agonist that acts only on the intestine could be used to treat obesity and the metabolic syndrome, if novel findings in mice are translated to humans.

FXR is important in the synthesis, transport and metabolism of bile acids, and is expressed both in the liver and in the intestine. Previously developed systemic FXR agonists improved metabolism in mice consuming normal chow, but increased weight gain and glucose intolerance in mice with diet-induced obesity (DIO). In mice with a knockout of the gene that encodes FXR, systemic FXR agonists improved glucose homeostasis in animals consuming a high-fat diet, but worsened metabolism in those consuming normal chow.

A research team led by Michael Downes and Ronald Evans reports in *Nature Medicine* that treatment with fexaramine, a synthetic FXR agonist that is administered orally and is poorly absorbed into the circulation, leads to metabolic improvements in mice with DIO. Intestinal FXR agonism led to weight gain and increased sensitivity to insulin in mice with DIO. These effects, which were dose-dependent, were not seen in mice consuming normal chow. Fexaramine also decreased inflammation, improved metabolic profiles and increased browning of white adipose tissue in mice with DIO. The approach was not associated with intestinal toxicity.

According to the researchers, the metabolic improvements they observed are likely to be mediated by *Fgf15*, a gene that was upregulated in mice with DIO taking fexaramine. "However," write the authors, "this explanation alone is not sufficient, as systemic FXR agonists, while robustly inducing Fgf15, do not display many of the benefits of gut-based FXR activation." Differences in bile acid composition in serum when systemic or intestinal FXR agonists are used might be another piece in the puzzle. Specifically, fexaramine increased the relative levels of litocholic acid, a derivative of chenodeoxycholic acid, which could explain the increased energy expenditure observed in mice with DIO.

"These studies uncover a new therapeutic avenue to manipulate energy expenditure without appetite changes," conclude the authors.

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Original article Fang, S. *et al.* Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nat. Med.* doi:10.1038/nm.3760