Fexaramine, a “magic pill” against obesity?

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Introduction

With the worldwide annual death toll of eating too much, too fat and too sweet exceeding the annual death toll of malnutrition (WHO, 2010), the demand for medical interventions is growing. Given the limited success of dietary interventions and the increasing caloric density of food in the industrialized world through added fat and sugar, the wait is for a “magic pill” to treat diet-induced obesity and related metabolic afflictions.

In this recent study, Fang *et al.* (2015) introduce a potentially new type of treatment of obesity and metabolic syndrome. The authors patented a new drug called Fexaramine (Fex), which selectively activates intestinal farnesoid X receptors (FXRs). These FXRs are normally activated by the bile acids, which are released into the small intestine by the gallbladder during digestion. FXR is expressed in diverse tissues, but orally delivered Fex is poorly absorbed into the circulation and only activates intestinal FXR. The results of intestinal-specific FXR activation are promising: Fex treatment of diet-induced obesity (DIO) mice results in considerable metabolic improvements, including reduced diet-induced weight gain, body-wide inflammation and hepatic glucose production. In addition, Fex treatment enhanced thermogenesis and browning of white adipose tissue (WAT).

Changes in bile acid composition and Fgf15

Through the RNA-sequencing of intestinal tissues after Fex treatment, Fang *et al.* identified potential target genes of FXR. Markedly up-regulated was the expression of fibroblast growth factor 15 (Fgf15), which encodes an intestinal endocrine hormone and which is known to activate the thermogenic program in brown adipose tissue (BAT) (Fu *et al.*, 2004). Furthermore Fgf15 suppresses the Cyp7a1 gene in the hepatocytes, which encodes a key enzyme for the production of bile acid. Fgf15 also activates the Cyp7b1 gene, which encodes an enzyme that bypasses the regular bile acid production. These effects result in a different bile acid pool, the composition of which switches to contain less taurocholic and more lithocholic bile acid. The overall size of the bile acid pool is reduced.

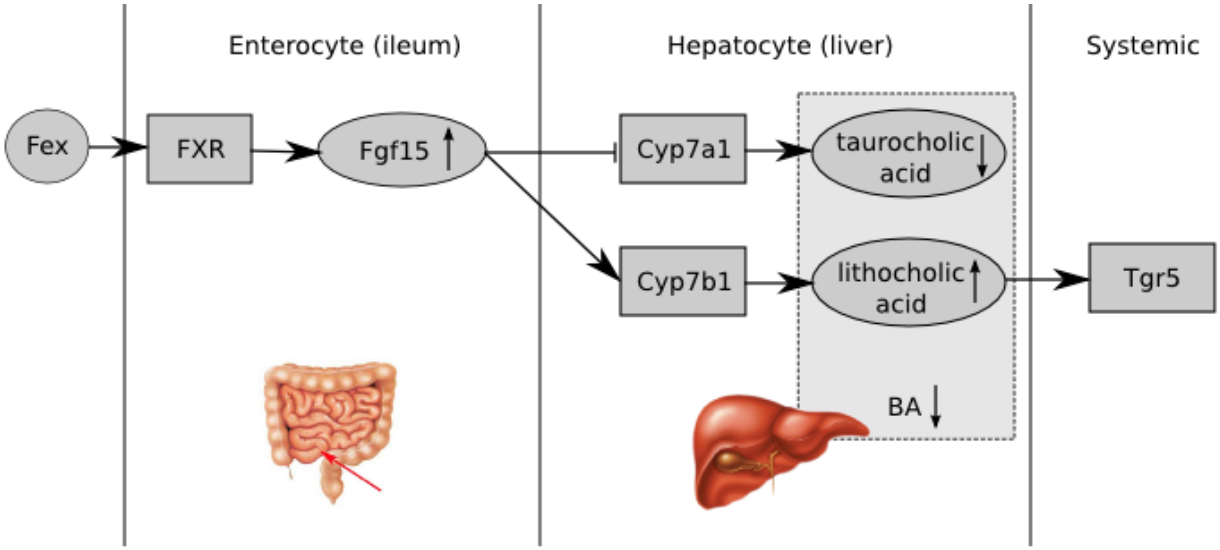

Figure 1. Fang *et al.* (2015) suggest that the positive effects of Fexaramine (Fex) are mediated through the intestine-specific activation of farnesoid X receptors (FXRs), which results in increased expression of fibroblast growth factor 15 (Fgf15). Fgf15 downregulates Cyp7a1 and upregulates Cyp7b1, causing a shift of the bile acid (BA) composition away from taurocholic acid towards lithocholic acid. The greater decrease in taurocholic acid results in an overall decrease of BA, while the increase in lithocholic acids activates Tgr5 type receptors.

Tgr5 activation

The different bile acid composition results in an activation of the Tgr5 receptor in the body. This receptor is most likely activated by the upregulated lithocholic bile acid. The effects as measured by intestinal FXR activation are hypothesized to be due to the activation of the Tgr5 receptor. Direct activation of the Tgr5 receptor leads to an improved glucose homeostasis as measured by a glucose tolerance test and an insulin secretion test. The positive effects of Fex cannot be replicated in $Tgr5^{-/-}$ knockout mice.

Systemic FXR activation

Prior to the study by Fang *et al.*, other researchers have investigated the effects of systemic FXR activation. Treating normal chow-fed mice with a systemic FXR agonist improved metabolic function (Zhang *et al.*, 2006), whereas DIO mice treated with a synthetic FXR agonist did worse than controls on various metabolic measures (Watanabe *et al.,* 2011). Watanabe *et al.* attribute the lowering of energy expenditure in these latter DIO mice to a lowering of the total bile acid pool. It is unclear why the *specific* activation of FXR in the small intestine would make the difference between a distinctly positive and a distinctly negative effect in DIO mice. This is definitely a question that invites further research.

Further research and discussion

The previously mentioned Fex pathway involves the activation of Tgr5 and causes metabolic changes similar to those observed with the systemic administration of a synthetic Tgr5 agonist (Ullmer *et al.*, 2013). Further investigation to pinpoint the precise role that Tgr5 activation

plays in the mediation of the positive effects of Fex is warranted; perhaps some of these effects can be more robustly or safely induced by a Tgr5 agonist. Concerning the possible side-effects of Fex, so far, the authors report none, but whole-body, long-term effects should definitely be investigated before considering pre-clinical trials.

Another important line of future investigation is to use (intestine-only) FXR knockout mice to verify that the effects of Fex don't persist, which would confirm that the positive effects are indeed mediated by the (intestine-specific) activation of Fex.

The authors used wild-type male C57BL/6J mice for most of their study. Similar studies could be done with other, genetically diverse, mouse strains, allowing for the chances that some of the positive phenotypic effects of Fex are genotype-specific. The mixed results of caloric restriction research on mice should serve as a warning to generalize the positive effects of metabolic interventions.

All in all, the results of the study by Fang *et al.* look promising. At the very least, key metabolic pathways in the development of obesity and metabolic syndrome have been illuminated, leaving tantalizing clues for future research into FXR and, hopefully, also Tgr5.

References

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