Nature Reviews Gastroenterology & Hepatology | Published online 12 Oct 2016; doi:10.1038/nrgastro.2016.167

NAFLD

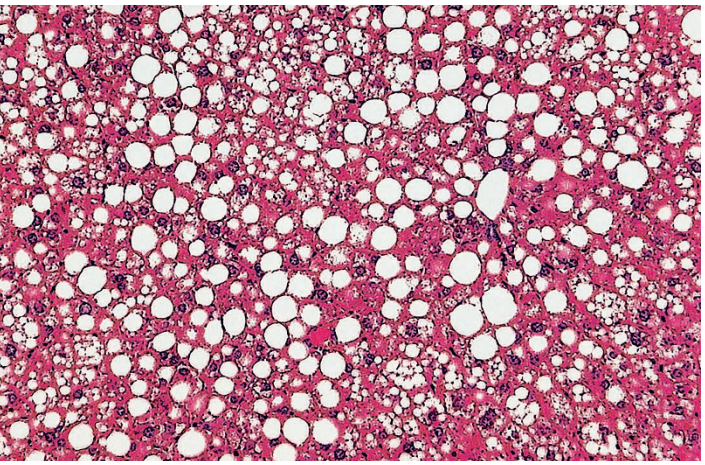
Blocking ileal bile acid uptake safeguards against NAFLD

> ...bile acid signalling has drawn considerable attention for its regulation of hepatic lipid and glucose metabolism...

An orally administered inhibitor of bile acid uptake in the ileum protects against diet-induced NAFLD in mice, according to a new study. The drug, which is not systemically absorbed, also improved glucose tolerance, altered liver bile acid composition and normalized hepatic expression of lipogenic, inflammatory and bile-acid regulatory genes.

Despite NAFLD representing a leading cause of chronic liver disease worldwide, pharmacological treatment options are limited. In the past few years, bile acid signalling has drawn considerable attention for its regulation of hepatic lipid and glucose metabolism, culminating in promising clinical trial results for obeticholic acid — a semi-synthetic bile acid targeting the bile acid receptor (FXR) — in patients with NASH.

Bile acids are synthesized from cholesterol in the liver. About 95% of bile-secreted bile acids are reabsorbed in the ileum via ileal sodium/bile acid cotransporter (ASBT) and return to the liver through the portal vein, maintaining the bile acid pool. Bile acid composition is regulated by numerous factors, including FXR-dependent pathways in the liver and metabolism by the gut microbiota.



Steatotic liver tissue from a mouse fed a NAFLD-inducing diet, stained with haemotoxylin and eosin. Image courtesy of A. Rao and S. Karpen.

In a new study, Saul Karpen and colleagues investigated the effect of SC-435 — an oral, non-systemically absorbed ASBT inhibitor — on diet-induced NAFLD in mice. "Interference with the uptake of bile acids in the distal intestine was predicted to reduce liver cholesterol content, alter whole-body glucose metabolism (perhaps through glucagon-like peptide 1) and change bile acid metabolism by the liver, intestine and microbiota," explains Karpen. To test whether ASBT inhibition could prevent NAFLD, the researchers fed mice a NAFLD-inducing diet (a so-called 'American lifestyle diet' (ALD), comprising a high-fat diet with *ad libitum* access to sucrose water) for 16 weeks, with or without SC-435.

As anticipated, SC-435 inhibited ileal bile acid uptake, resulting in fourfold increased faecal bile acid excretion and upregulation of hepatic bile acid synthesis genes in treated mice. Importantly, inhibition of ASBT also had beneficial effects on the development of fatty liver disease. "We found that mice fed ALD did not accrete fat or cholesterol in their livers (levels of which increased ~fivefold in untreated ALD-fed mice) when placed on the ASBT inhibitor," observes Karpen. Glucose tolerance and systemic insulin sensitivity were also both improved in ALD-fed mice given SC-435, compared with mice not receiving the drug.

Next, the investigators assessed the effects of ASBT inhibition on bile acid pool composition. When compared with chow-fed mice, ALD feeding had no effect on the composition of hepatic bile acids; however, bile acid species were substantially altered in ALD-fed mice given SC-435. "Endogenous bile acids in these mice were much more FXR-agonistic in nature, essentially creating an environment within livers as if they were exposed to their own FXR agonists," Karpen says. "We also found that hundreds of genes whose expressions were altered on ALD returned to normal levels, including the main regulator of fatty acid synthesis, *Srebf1*."

In a separate cohort of mice, Karpen and colleagues assessed whether short-term ASBT inhibition could improve established NAFLD. In ALD-fed mice given SC-435 for 4 weeks, hepatic triglyceride and cholesterol levels were markedly reduced compared with untreated ALD-fed mice, yet glucose tolerance and histological markers of NAFLD severity were not affected.

"With my partner in the lab, Paul Dawson, we plan to address the whole-organism responses to blocking intestinal bile acid uptake, focusing on metabolic and molecular alterations in liver, intestine and the microbiota," concludes Karpen.

Hugh Thomas

ORIGINAL ARTICLE Rao, A. *et al.* Inhibition of ileal bile acid uptake protects against nonalcoholic fatty liver disease in high-fat diet–fed mice. *Sci. Transl. Med.* http://dx.doi.org/10.1126/scitranslmed.aaf4823 (2016)