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Intestine FXR agonist ID119031166 modulates ethanol and bile acid metabolism in ethanol-fed hamsters

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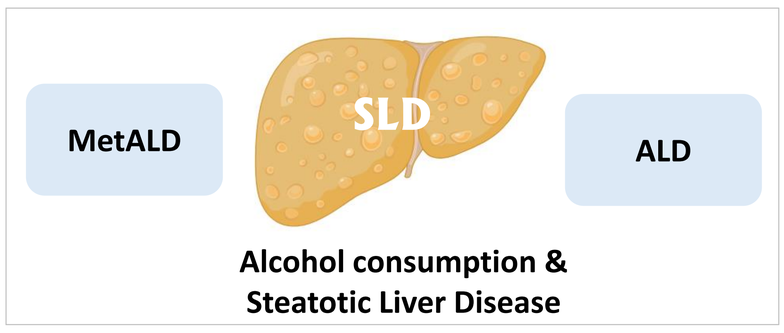
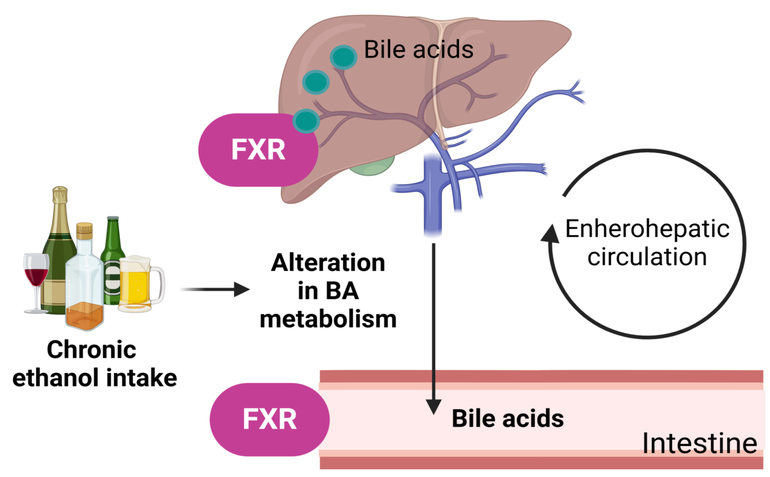
Background

Excessive alcohol use is a global healthcare issue that causes pathological alterations, including alcohol-associated liver disease (ALD). ALD is associated with liver inflammation and damage, as well as increasing fibrosis, and is classified into three major types, each of which is rarely found in its pure form. Furthermore, ALD and metabolic dysfunction-associated steatotic liver disease (MASLD) have been considered as distinctly separate diseases in terms of biology and clinical presentation. Following the newly established nomenclature for steatotic liver disease (SLD), individuals diagnosed with SLD who also have metabolic risk factors and moderately high intake of alcohol will be referred to as having MASLD and increased alcohol intake (MetALD).



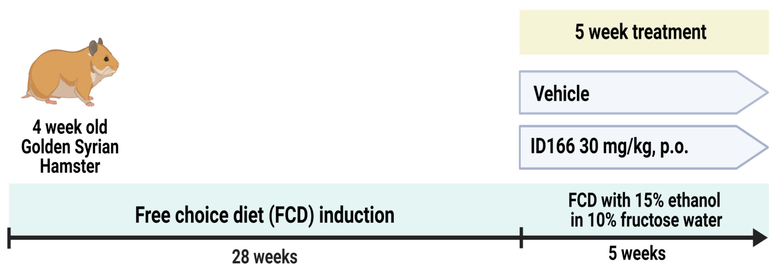
Chronic alcohol intake can cause aberrant changes in the amounts and composition of the BA pool in the human body, aggravating ALD. Farnesoid X receptor (FXR), a master regulator of bile acid metabolism, is mainly expressed in liver and intestine. In particular, intestinal FXR deficiency may play a crucial role in the severity of alcoholic liver disease.



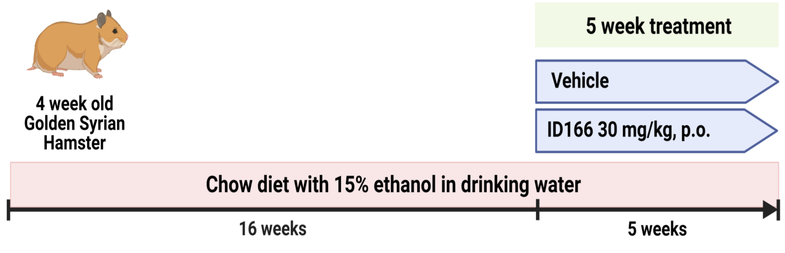
Here, we assessed the potential effects of a novel intestinal FXR agonist ID119031166 (ID166) in hamsters with free access to 15% ethanol and fed either a chow diet or free choice (FC) diet (choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water).

Methods

After 28 weeks of FC diet, ID166 30 mg/kg or vehicle were given orally QD to FC diet-fed hamsters with 10% fructose water containing 15% ethanol for 5 weeks.

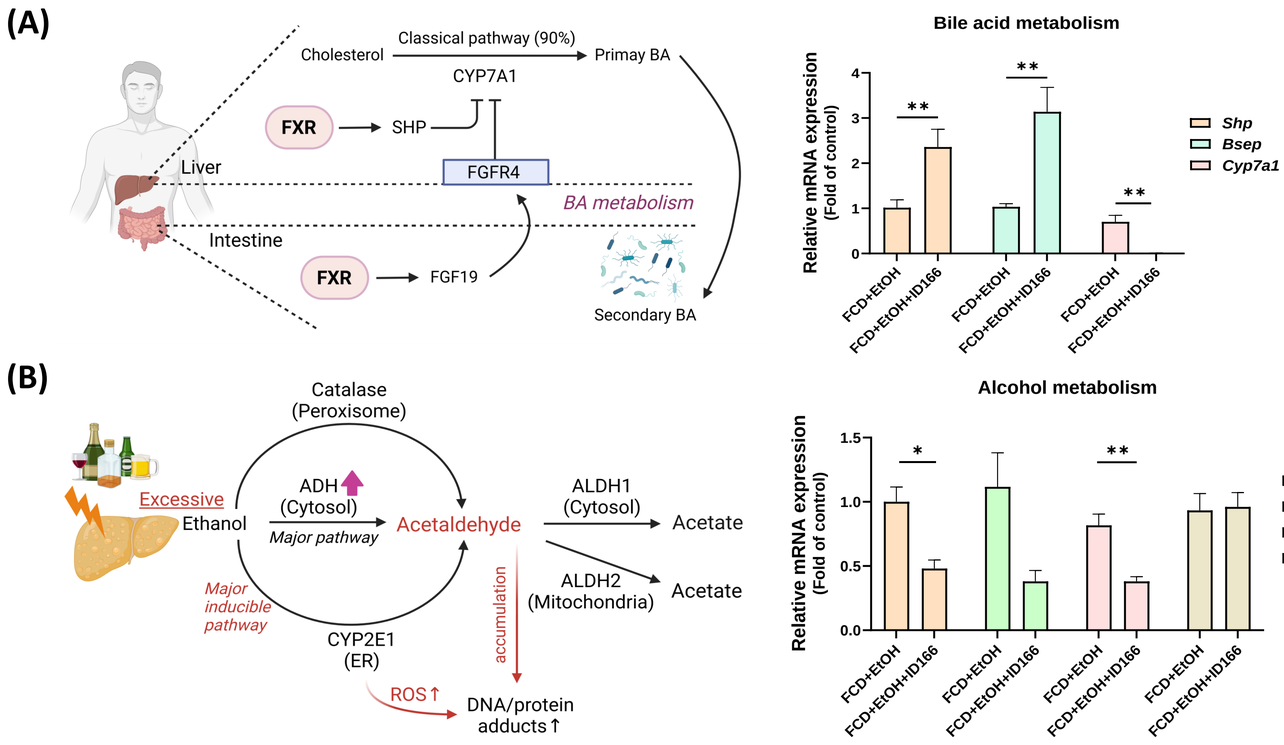


4-week-old hamsters were fed a chow diet with 15% ethanol in drinking water for 16 weeks, then ID166 30 mg/kg or vehicle were given orally QD for 5 weeks.

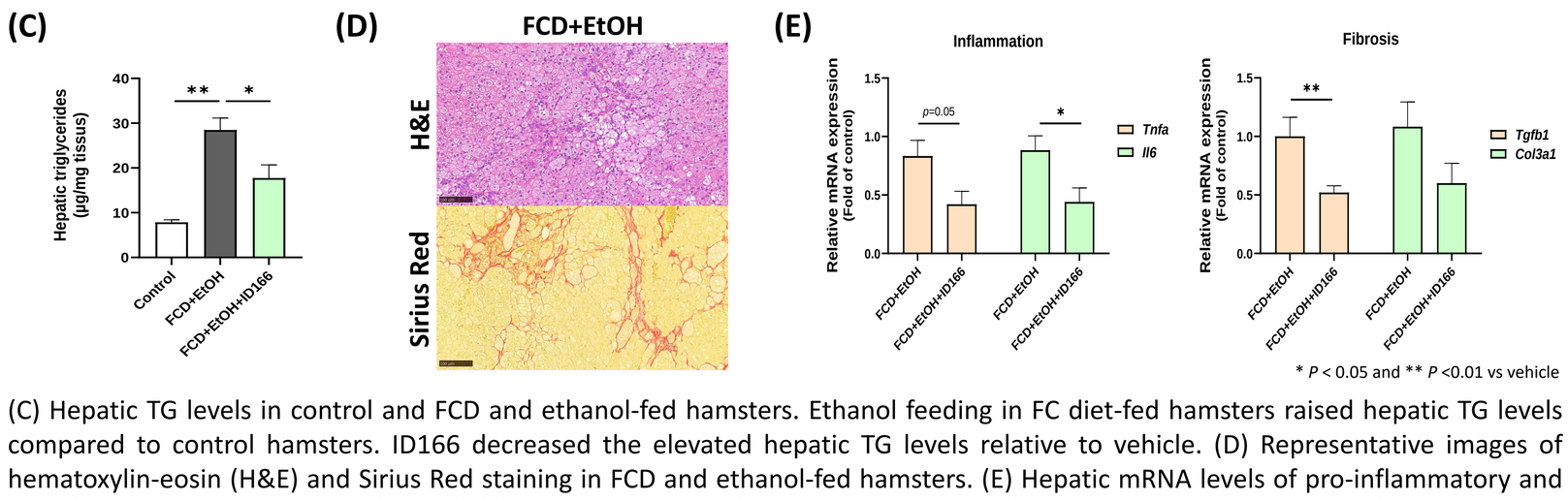


Liver histology and liver parameters were assessed. mRNA expression levels were measured by qPCR.

Results (FC diet)

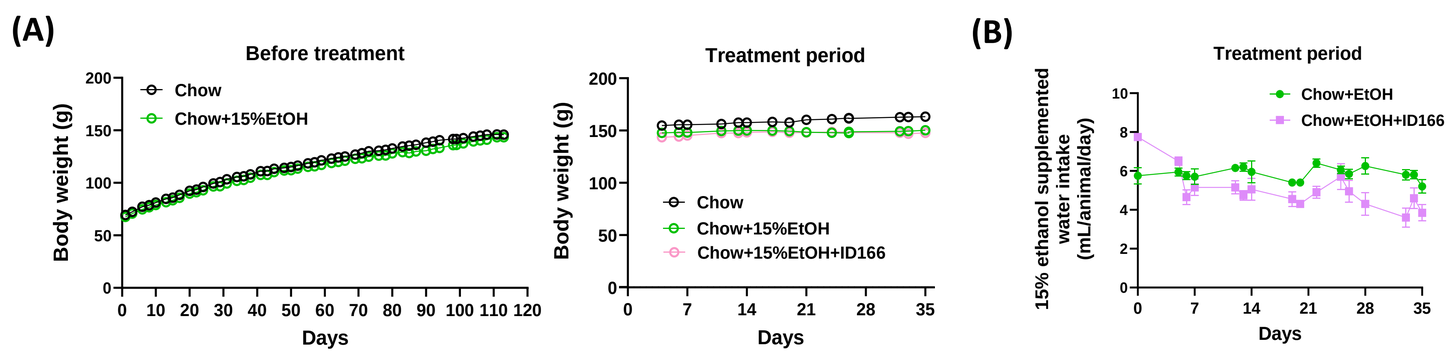


(A) Schematic representation of FXR-mediated bile acid metabolism. In FCD and ethanol-fed hamsters, ID166 markedly up-regulated *Shp* and *Bsep* genes but down-regulated the *Cyp7a1* gene. (B) Ethanol is primarily broken down by the liver's alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes in the oxidative pathway. The detoxifying function of ALDH2 on aldehydes is interfered with by loss or inhibition of its biological activity, which increases oxidative damage to cells and produces reactive oxygen species (ROS), which in turn causes a range of human disorders. Interestingly, a substantial elevation in ADH activity has been reported in the serum of alcoholic fatty liver patients. Compared to vehicle, ID166 significantly reduced the expression levels of *Cyp2e1*, *Adh1* and *Aldh1* genes but did not impact *Aldh2* gene levels.

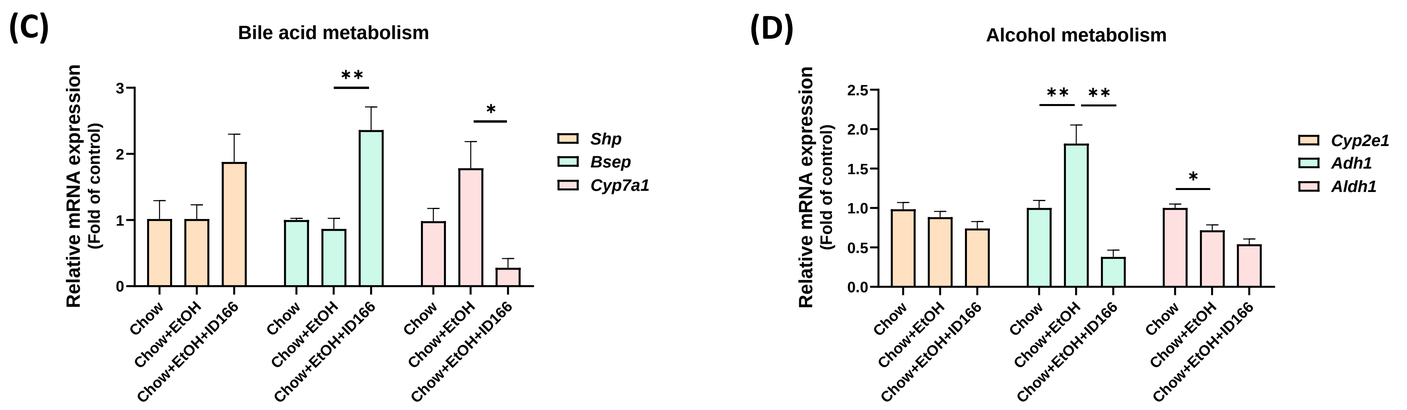


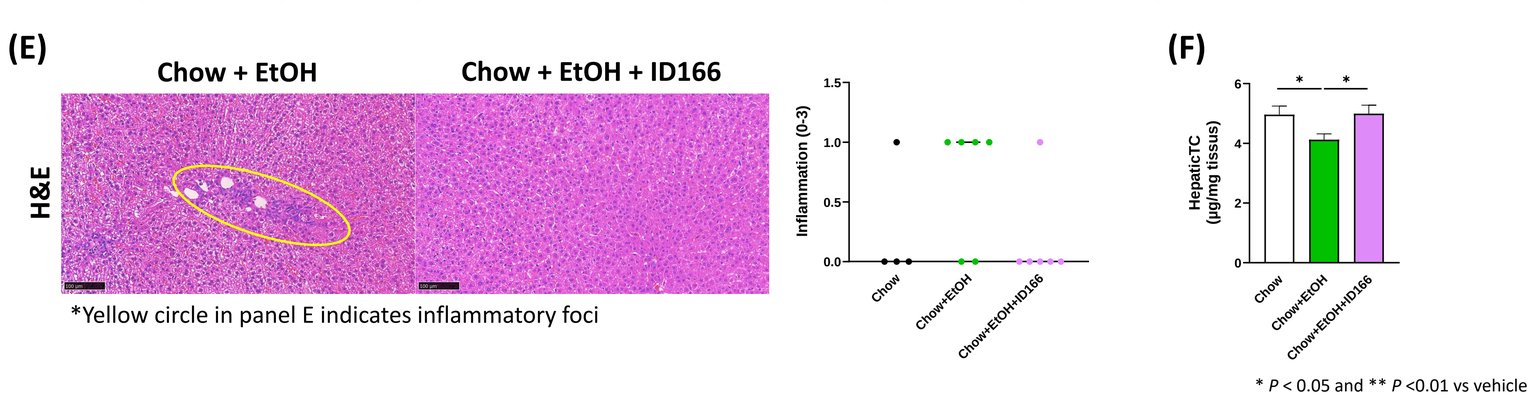
(C) Hepatic TG levels in control and FCD and ethanol-fed hamsters. Ethanol feeding in FC diet-fed hamsters raised hepatic TG levels compared to control hamsters. ID166 decreased the elevated hepatic TG levels relative to vehicle. (D) Representative images of hematoxylin-eosin (H&E) and Sirius Red staining in FCD and ethanol-fed hamsters. (E) Hepatic mRNA levels of pro-inflammatory and pro-fibrotic genes in FCD and ethanol-fed hamsters. ID166 markedly down-regulated *Il6* and *Tgfb1* genes relative to vehicle.

Results (Chow diet)



(A) Body weight in control and ethanol-fed hamsters. (B) Ethanol intake during the treatment period. Compared to vehicle, ID166 reduced ethanol-supplemented water intake.





*Yellow circle in panel E indicates inflammatory foci

* $P < 0.05$ and ** $P < 0.01$ vs vehicle

(C-F) Long-term ethanol intake in chow diet-fed hamsters up-regulated *Cyp7a1* and *Adh1* genes, reduced hepatic TC levels, and induced a higher inflammation score. Compared to vehicle, ID166 significantly down-regulated *Cyp7A1* and *Adh1* genes, reduced inflammation score, and restored liver TC levels.

Conclusion

Our findings suggest that ID119031166 modulates ethanol and bile acid metabolism by regulating key metabolic genes in chronic ethanol exposure.

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Disclosure

An-Na Moon and Dong-Keun Song are employees and stock shareholders of iLeadBMS Co., Ltd. Yoonsuk Lee is a board member and stock shareholder of iLeadBMS Co., Ltd. François Briand is an employee of Physiogenex (a preclinical Contract Research Organization) and has shares in the company. iLeadBMS Co., Ltd. has received research funding from Yunovia Co., Ltd.