GLP-1 receptor agonists reduce liver inflammation in a 3-week Non Alcoholic Steato-Hepatitis Mouse Model

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BACKGROUND:

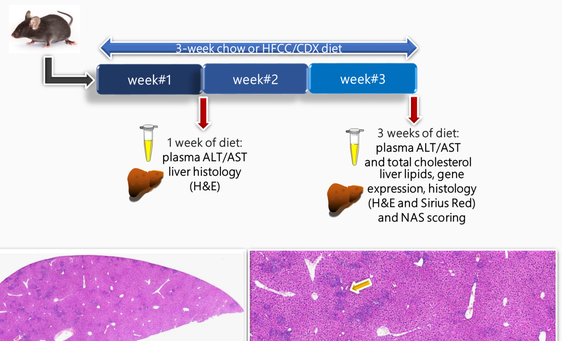
Glucagon-like peptide 1 (GLP-1) receptor agonists are characterized with anti-inflammatory capacity suitable to treat Non Alcoholic Steato-Hepatitis (NASH) as a novel therapeutic alternative. We here evaluated the effect of GLP-1 receptor agonists on liver inflammation in a rapid mouse model of liver inflammation, i.e. the mouse fed a high fat/high cholesterol diet, where cyclodextrin is co-administered to favor hepatic cholesterol loading, liver inflammation and NASH within 3 weeks.

METHODS:

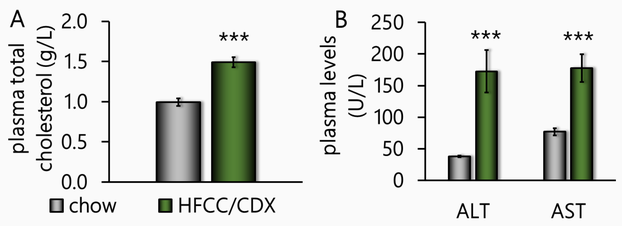
C57BL6/J mice were fed a 60% high fat, 1.25% cholesterol, 0.5% cholic acid diet with 2% cyclodextrin in drinking water (HFCC/CDX diet) for 3 weeks. An ancillary group of chow fed mice were used as negative control. After 1 week of HFCC/CDX diet, mice were treated intraperitoneally for 2 weeks with vehicle or GLP-1 receptor agonists liraglutide at 100µg/kg QD or exendin-4 10µg/kg BID. Data are shown as mean ± SEM.

RESULTS:

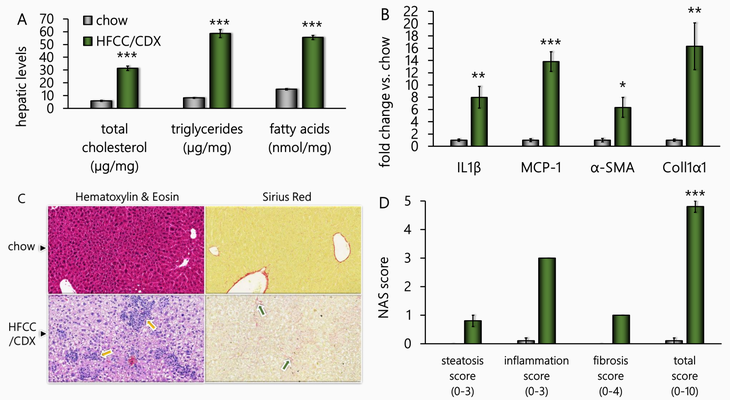
1 HFCC / cyclodextrin combination rapidly induces NASH with strong inflammation



Representative hematoxylin & eosin staining (A) at 1 week of HFCC/CDX diet (yellow arrows indicate inflammatory foci). Plasma transaminases levels (B) and NAS scoring (C) at 1 week of HFCC/CDX diet.

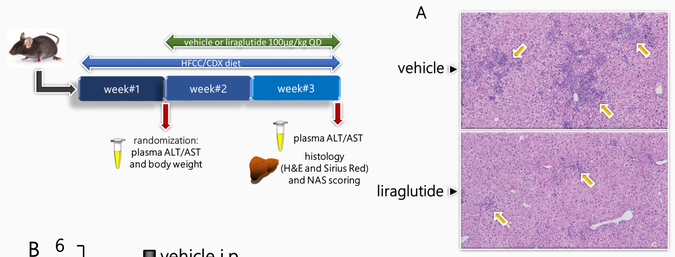


Total cholesterol (A), ALT and AST (B) plasma levels in mice fed a 3-week chow or HFCC/CDX diet.
****p<0.001 vs. chow*



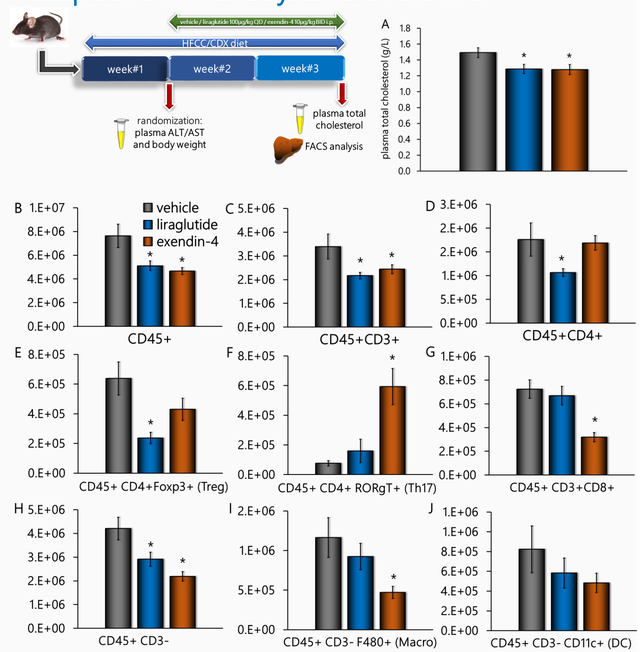
Hepatic lipids levels (A), gene expression (B), representative hematoxylin & eosin (yellow arrows: inflammatory foci) and Sirius Red (green arrows: fibrosis) staining (C), and NAS scoring (D) in mice fed a 3-week chow or HFCC/CDX diet. ****p<0.001 vs. chow*

2 Liraglutide improves NAS score by reducing inflammation



Representative hematoxylin & eosin staining (A) and NAS scoring (B) in mice treated with vehicle or liraglutide. ***p<0.01 vs. vehicle*

3 Both liraglutide and exendin-4 reduce cholesterolemia and impacts innate and adaptative immune systems in the liver



Plasma total cholesterol (A), and hematopoietic CD45+ cells FACS analysis (B-J) in mice treated with vehicle, liraglutide or exendin-4. **p<0.05 vs. vehicle*

CONCLUSION

- Taken together, our data suggest that GLP-1 receptor agonists reduce liver inflammation in our 3-week NASH mouse model.
- This model should be useful to rapidly detect anti-inflammatory effects of novel drugs targeting NASH, including novel GLP-1 analogues.