Obeticholic Acid Improves Histological, Biochemical and Gene Expression Profiles in Gubra AMLN Mice with Diet-Induced and Biopsy-Confirmed NASH

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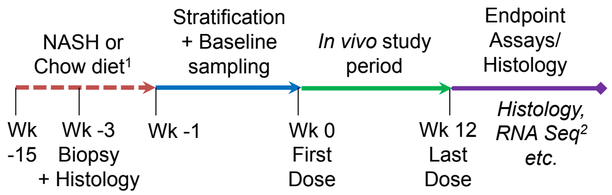
STUDY DESIGN AND METHODS

Tissue Distribution Study

- Chow-fed C57Bl/6 mice (n=8/group) were treated with vehicle (0.5% CMC, PO, QD) or OCA (1, 3, 10 or 30 mg/kg) for 14 days
- Liver and ileum were analyzed for levels of OCA and its tauro- and glyco-conjugates by LC/MS/MS

NASH Study Outline



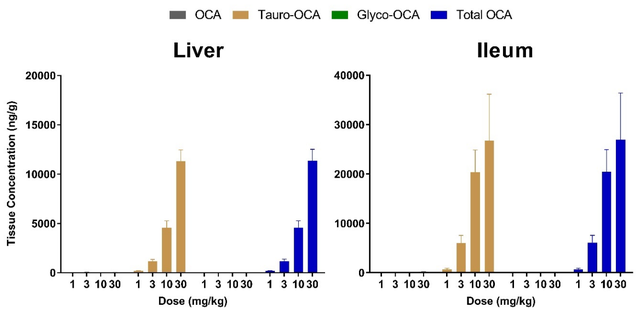
[1]Mice remained on their respective diet for duration of study.
[2]mRNA data from mice treated for 2 weeks (Vehicle or OCA 10 mg/kg).

Liver and Ileum Gene Expression (NASH Study)

- Liver tissue from left lateral lobe, snap frozen, homogenized and RNA was extracted
- RNA Seq libraries were prepared with the KAPA poly-A kit, sequenced on the NextSeq 500 (Illumina)
- Reads were aligned to GRCm38 Ensembl Mus musculus genome using STAR v.2.4.0 and feature counts obtained using Htseq v.0.6.1

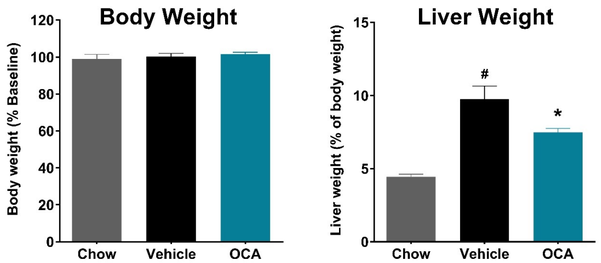
RESULTS

OCA Distribution in the Liver and Ileum



Data are Mean ± SEM.

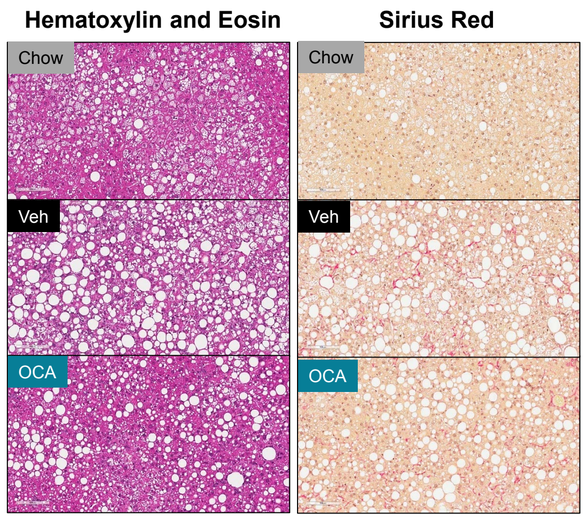
OCA Decreases Liver Weight†



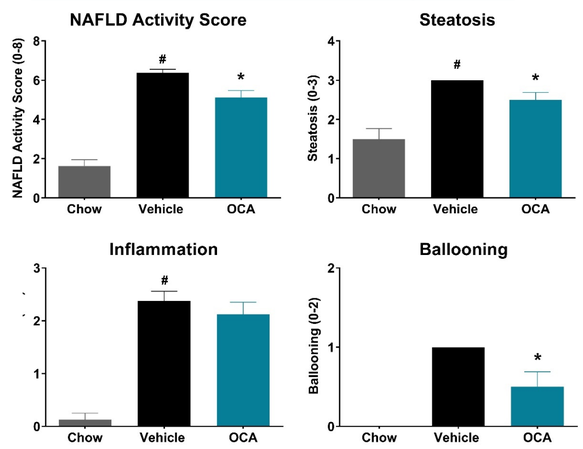
†Data are Mean ± SEM; #p<0.05 Vehicle vs Chow; *p<0.05 OCA vs Vehicle, ANOVA with Dunnett's post-hoc.

RESULTS

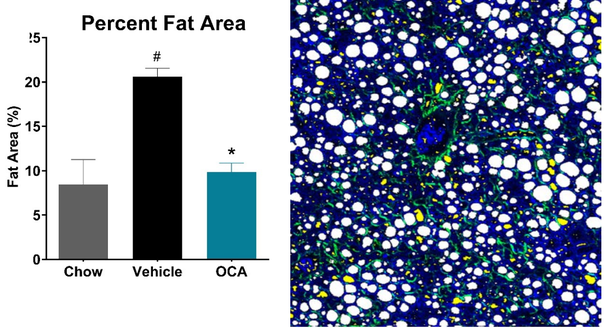
Representative Liver Photomicrographs



OCA Decreases NAFLD Activity Score†



OCA Decreases Steatosis†

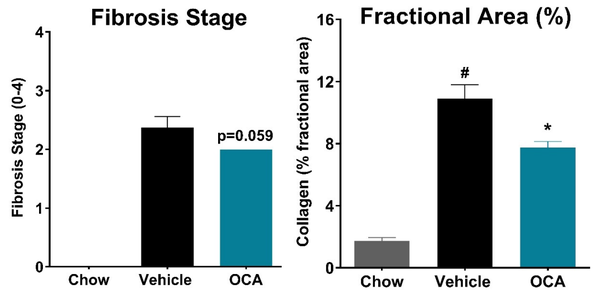


Imaging performed by Genesis Imaging Services (Pharmanest).

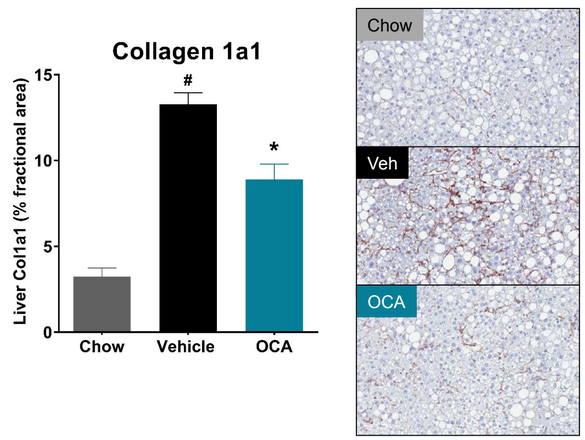
†Data are Mean ± SEM; #p<0.05 Vehicle vs Chow; *p<0.05 OCA vs Vehicle; ANOVA with Dunnett's post-hoc.

White = Fat Droplets
Yellow = Excluded
Green = Collagen
Blue = Auto-flourescence

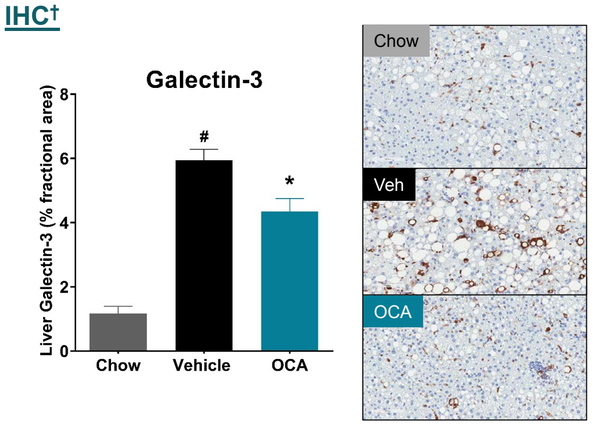
OCA Decreases Fibrosis†



OCA Decreases Collagen 1a1 (Fibrosis) by IHC†

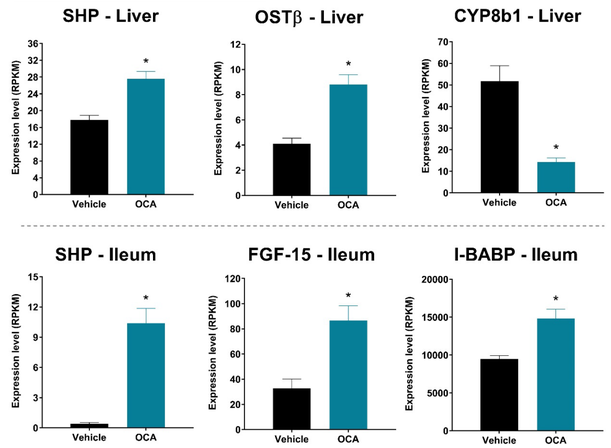


OCA Decreases Galectin-3 (Inflammation) by IHC†

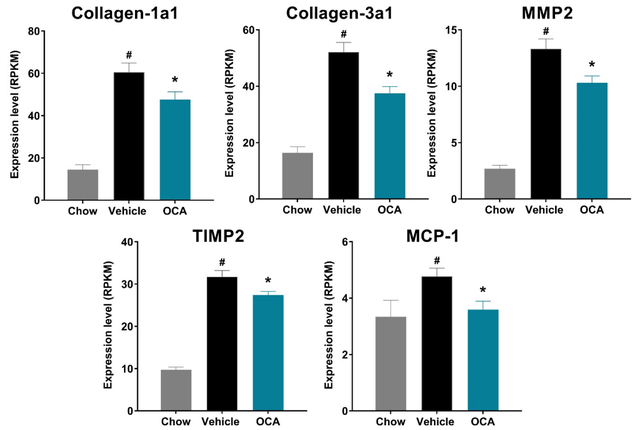


†Data are Mean ± SEM; #p<0.05 Vehicle vs Chow; *p<0.05 OCA vs Vehicle, ANOVA with Dunnett's post-hoc.

OCA Alters Expression of FXR Signaling Genes in the Liver & Ileum†



Effects of OCA on Disease-related Genes in the Liver†



†Data are Mean ± SEM; #p<0.05 Vehicle vs Chow; *p<0.05 OCA vs Vehicle, ANOVA with Dunnett's post-hoc.

CONCLUSIONS

- Obeticholic acid improved histological indices of NASH as assessed by NAS scoring and immunohistochemical methods in Gubra AMLN mice
- Improvements were associated with activation of key FXR signaling genes in the liver and ileum and salutary effects on markers of inflammatory and fibrotic processes
- These findings further confirm the benefits of FXR agonism in a rodent model of diet-induced and biopsy-confirmed NASH

DISCLAIMER

OCA is indicated in the US and EU for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. While OCA has received marketing authorization from the FDA and the European Commission for the treatment of PBC, this drug has not been approved for use by any other regulatory bodies at this time. No conclusions can be drawn concerning the safety or efficacy of OCA in indications other than PBC or in areas outside the US and EU.

ACKNOWLEDGEMENTS

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