A nutraceutical supplement rich in docosahexaenoic acid improves portal hypertension in a preclinical model of chronic liver disease

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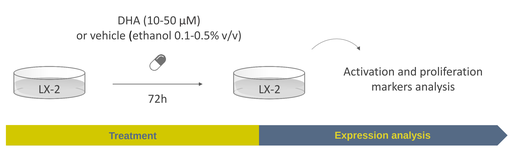
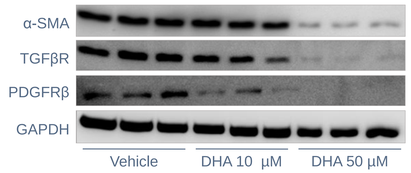
Background and aims

High levels of oxidative stress in the liver play a key role in the pathophysiology of chronic liver disease and portal hypertension (PH). Previous studies demonstrated the effectivity of pharmacological and genetic antioxidant strategies improving PH. However, said strategies have not moved to the bedside. Considering the lack of effective and safe treatments for PH, in this study we evaluated the effects of an antioxidant nutraceutical supplement rich in docosahexaenoic acid triglycerides (DHA) as a possible novel therapy to improve PH.

Methods and results

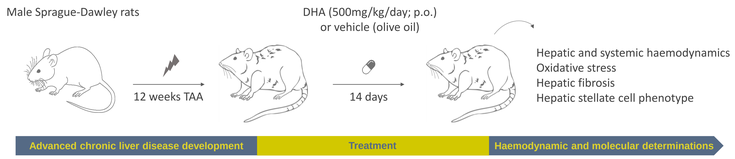
1- Effects of DHA *in vitro*





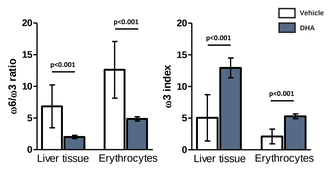
DHA promoted hepatic stellate cells (HSC) deactivation in a concentration-dependent manner (data for 50 µM: -93% in α-SMA, -92% in TGFβ, -98% in PDGFRβ, all p<0.05) without altering their viability.

2- Effects of DHA *in vivo*



Fatty acid bioavailability

Rats with chronic liver disease treated with DHA showed significantly increased ω3 index and decreased the ω6:ω3 fatty acid ratio in erythrocytes and liver, thus confirming the effectiveness of the treatment.



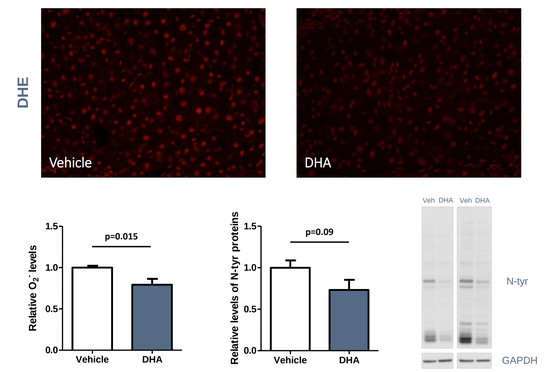
Haemodynamics

Parameter	Vehicle n=11	DHA n=14	Percentage of change	p value
PP (mmHg)	13.91 ± 0.60	12.05 ± 0.57	-13.37	0.03
MAP (mmHg)	116 ± 5	99 ± 6	-14.01	0.06
PBF (ml·min^{-1})	15.66 ± 2.54	18.21 ± 2.31	+16.28	> 0.20
HVR (mmHg·min·ml^{-1})	1.05 ± 0.15	0.79 ± 0.11	-24.57	0.16
SMABF (mL·min^{-1})	8.37 ± 0.91	10.03 ± 1.45	+19.78	> 0.20
HR (beats·min^{-1})	415 ± 13	383 ± 17	-7.90	0.15
Body weight (g)	475 ± 11	506 ± 16	+6.39	0.13
Liver weight (g)	15.19 ± 0.97	15.26 ± 0.90	+0.46	> 0.20
Spleen weight (g)	1.39 ± 0.08	1.32 ± 0.09	-4.62	> 0.20

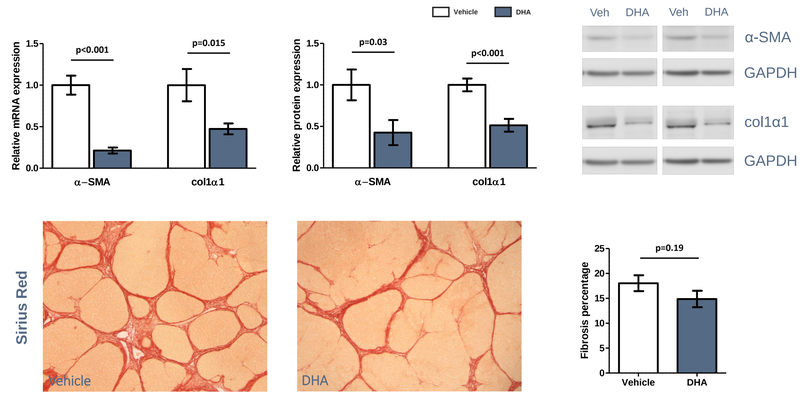
PP: portal pressure; MAP: mean arterial pressure; PBF: portal blood flow; HVR: hepatic vascular resistance; SMABF: superior mesenteric artery blood flow; HR: heart rate

Rats receiving DHA exhibited a significant improvement in PH without changes in portal blood flow, suggesting a reduction in intrahepatic vascular resistance.

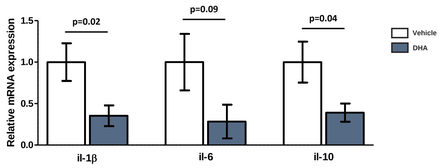
Oxidative stress



HSC phenotype



Inflammation



The mechanisms underlying this hemodynamic improvement included a reduction in intrahepatic oxidative stress (-21% in O_2^- levels) and inflammation (-65% in il-1β, -72% in il-6 and -61% in il-10 mRNA expression), together with HSC deactivation (-57% in α-SMA and -49% col1α1 protein expression) and a tendency to improve hepatic fibrosis (-15%).

Conclusion

The present pre-clinical study demonstrates that an antioxidant nutraceutical supplement rich in DHA improves moderately, but significantly, portal hypertension and chronic liver disease. These results encourage the evaluation of this type of non-pharmacological therapeutic strategy as a new treatment for portal hypertension and cirrhosis.

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