

Beneficial effects of ornithine phenylacetate to attenuate muscle mass loss and to prevent hepatic encephalopathy in experimental cirrhosis

CR Bosoi¹, M Oliveira¹, MA Clément¹, M Tremblay¹, G Ten Have², NEP Deutz², CF Rose¹

¹Hepato-Neuro Laboratory, CRCHUM, Université de Montréal, Canada, ²Department of Health & Kinesiology, Texas A&M University, USA

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Introduction

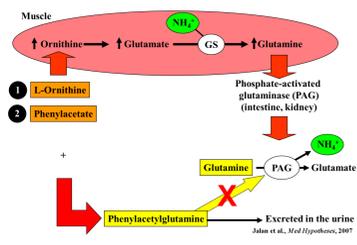
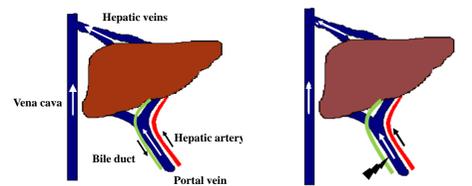
- Chronic liver disease (cirrhosis; CLD) is characterized by numerous metabolic disturbances which lead to complications that impact the clinical outcome
- Sarcopenia, characterized by a deterioration of muscle quantity and quality, leads to a decrease in functional capacity, adversely affecting survival, quality of life and outcome following liver transplantation (Ney et al., *Nutr Clin Pract*, 2015; Montano-Loza et al., *Clin Transl Gastroenterol*, 2015; Hanai et al., *Nutrition*, 2015; Montano-Loza, *World J Gastroenterol*, 2014)
- Hyperammonemia is central in the development of hepatic encephalopathy (HE)
- Cirrhotic patients with sarcopenia have higher ammonia levels and an increased risk of developing HE risk (Montano-Loza et al., *Can J Gastroenterol*, 2016), however the relationship between sarcopenia and hyperammonemia is believed to be bi-directional :
 - Sarcopenia might contribute to the development of HE by further reducing the capacity to reduce ammonia via muscle in cirrhosis (Lucero et Verna, *Clin Liver Dis*, 2015)
 - The toxic effect of ammonia is believed to extend beyond the brain, possibly affecting the muscle (Rose, *Liver Int*, 2014; Qiu et al., *Proc Natl Acad Sci USA*, 2013; Holecek et al., *Amino Acids*, 2011)

Aim

Investigate the effect of lowering blood ammonia using ornithine phenylacetate (OP; OCR-002) on muscle mass in cirrhotic rats following bile-duct ligation.

Animal model: 6-week bile duct ligation (BDL)

Ornithine Phenylacetate (OP); OCR-002



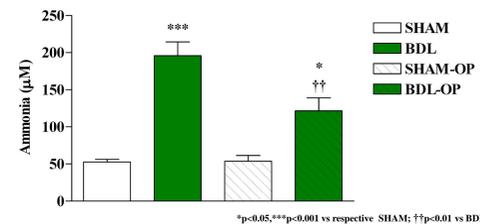
An ammonia-lowering strategy demonstrated to be beneficial in both animal models and patients with CLD (Jover-Cobos et al., *J Hepatol*, 2014; Ventura-Cots et al., *J Clin Gastroenterol*, 2013; Wright et al., *Liver Int*, 2012; Ytrebo et al., *Hepatology*, 2009)

Methods

- Four experimental groups of male Sprague Dawley rats were tested;
 - 1) Sham
 - 2) BDL
 - 3) Sham + OP
 - 4) BDL + OP
- Oral treatment: OP (1g/kg) administered daily by gavage for 5 weeks starting one week following BDL
- Fat and lean mass were evaluated by EchoMRI
- Ammonia: commercial kit based on the reaction of α -ketoglutarate and reduced nicotinamide adenine dinucleotide phosphate in the presence of L-glutamate dehydrogenase
- Brain edema: specific gravimetric technique (Marmarou et al., *J Neurosurg*, 1978)
- Fractional synthesis of protein (FSR) in muscle: based on the rate of incorporation into protein of D₂O administered over a period of 7 days and of three different Phe/Gly tracer cocktails administered as a pulse over a time period of 60 min before sacrifice
- Locomotor activity (day/night) was measured in an infrared beam cage over a period of 24h

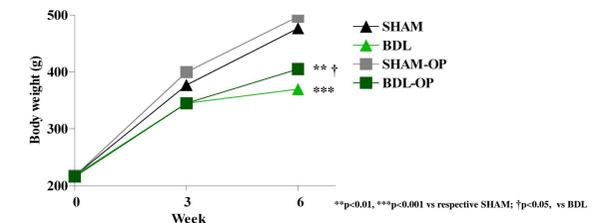
Results

Ammonia



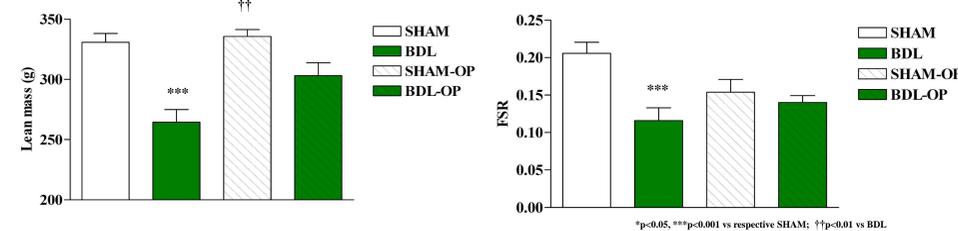
Ammonia increased 4-fold in BDL rats vs sham-operated rats. A significant decrease was observed in OP-treated BDL rats ($p < 0.01$ vs BDL rats).

Body weight



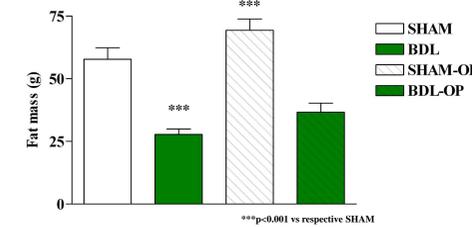
BDL rats gained less body weight compared to sham-operated controls ($p < 0.001$). At 6 weeks, OP-treated BDL rats showed a significant increase in body weight ($p < 0.05$ vs BDL rats).

Muscle mass and protein synthesis



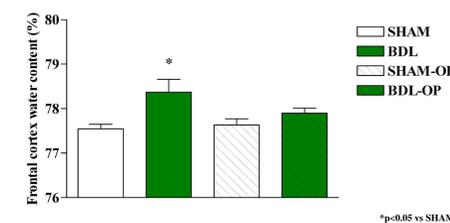
BDL rats demonstrated a lower gain of lean mass and a lower muscle FSR compared to sham-operated controls. OP-treated BDL rats showed a significant higher lean mass ($p < 0.01$ vs BDL rats). OP-treatment reduced muscle FSR in sham-operated animals, but not in BDL rats.

Fat mass



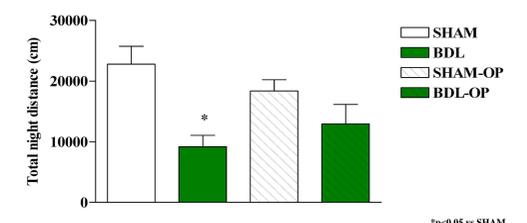
Fat mass decreased in BDL rats compared to sham-operated controls and remained unchanged between the treated and untreated BDL groups.

Brain edema



Frontal cortex water content significantly increased in BDL rats ($p < 0.05$ vs SHAM) and normalized following OP treatment.

Locomotor activity



Locomotor activity in BDL rats was reduced compared with sham-operated controls ($p < 0.05$) but no significant change was found between SHAM and BDL OP-treated rats.

Conclusion

- The new OP oral formulation in rats with CLD efficiently:
 - lowers ammonia
 - preserves muscle mass and function
 - improves locomotor activity
 - protects against the development of brain edema
- Whether the effect of OP on muscle mass loss attenuation is a result of lowering blood ammonia or directly improving muscle metabolism remains to be established



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