The beneficial effect of oral Cr supplementation in an early childhood rat model of chronic hepatic encephalopathy: *in vivo* longitudinal ^{1}H and ^{31}P magnetic resonance spectroscopy study.

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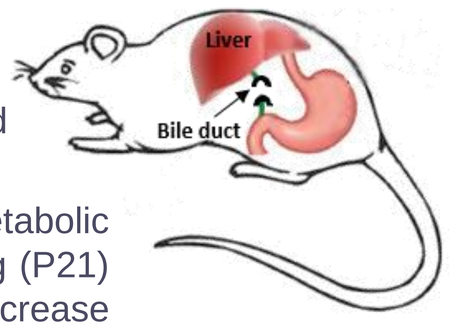
BACKGROUND

- Type C hepatic encephalopathy (C HE) is a complication of chronic liver disease (CLD).
- Children are more affected by CLD than adult patients[1].
- The bile duct ligated rat (BDL) is a model of CLD - induced CHE validated in the adult and developing brain[2,3].
- Rats having acquired CLD as pups display more profound neurometabolic disturbances than adults[3]. Cr-treatment showed a positive effect in young (P21) BDL-rats resulting in less pronounced metabolic changes (smaller Gln increase and PCr decrease)[4].



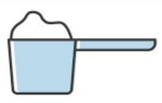
AIMS

→ Test if Cr supplementation dampens the neurometabolic changes observed in CHE in a longitudinal model of CLD acquired in early childhood (**P15**).

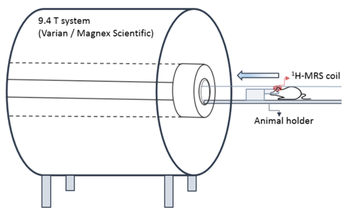
HYPOTHESIS: methods maintaining Cr concentration in type C HE may have potentially far - reaching clinical implications

METHODS

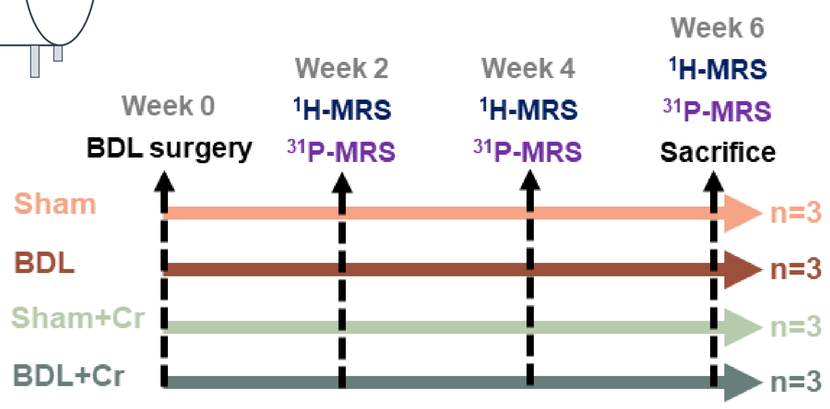
- BDL and sham surgeries were performed on male Wistar rats at **P15**.



Rats from the treated group received **high Cr supplemented diet** with a concentration of **40g/kg**.

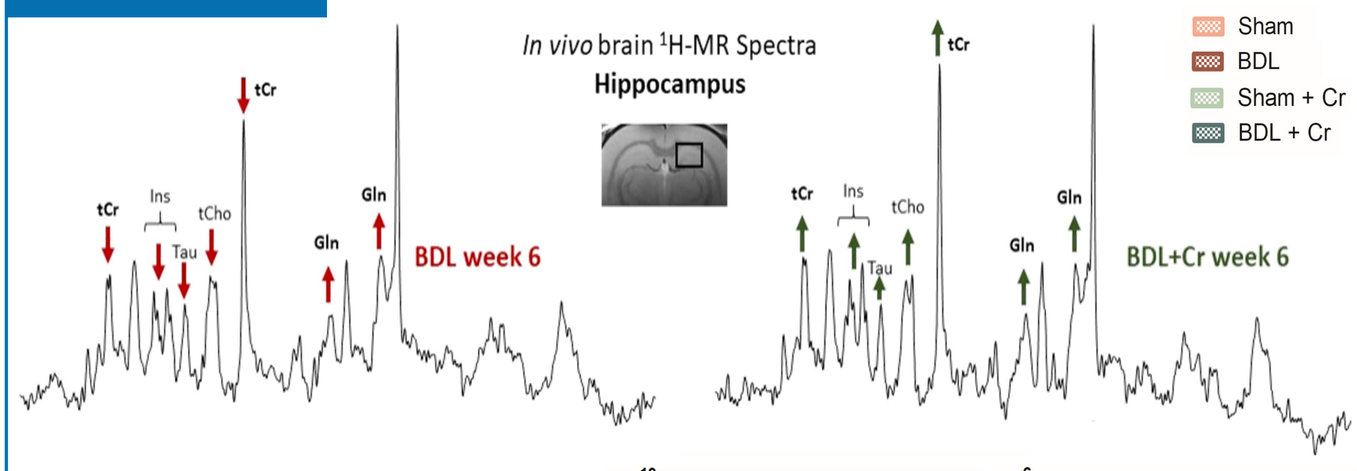


MRS experiments: 9.4T system (Varian / MagnexScientific) + home - built coil (quadrature ^{1}H-loops single ^{31}P-loop).

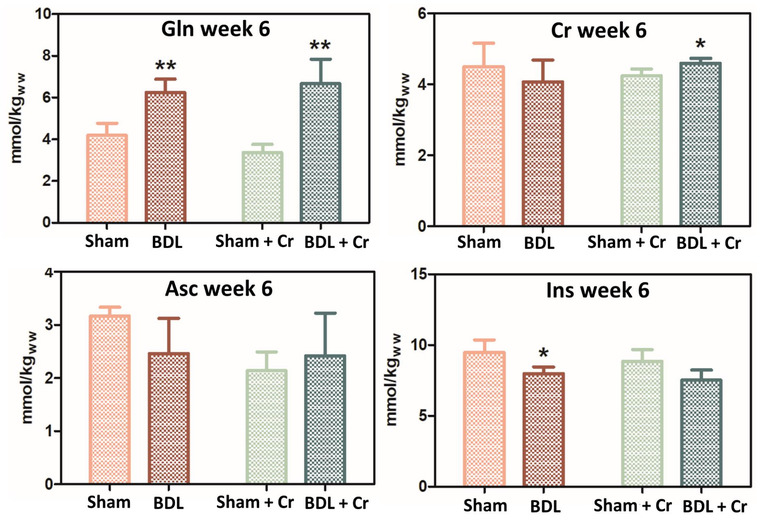


- **^{1}H-MRS** spectra - **hippocampus** (2 x 2.8 x 2 mm^3), SPECIAL[5] sequence (TE=2.8 ms) → quantification LCModel.
- **^{31}P-MRS** spectra → non-selective AHP pulse for excitation, localized by OVS(x,z) + 1D-ISIS(y) in **VOI = 5 x 9 x 9 mm^3**.
- ^{31}P-MR spectra → **quantified using AMARES(jMRUI)[6],** normalized using PCr concentration from ^{1}H-MRS acquired in VOI = 4 x 7.5 x 6.5 mm^3 centered in ^{31}P-VOI.

RESULTS ^{1}H-MRS

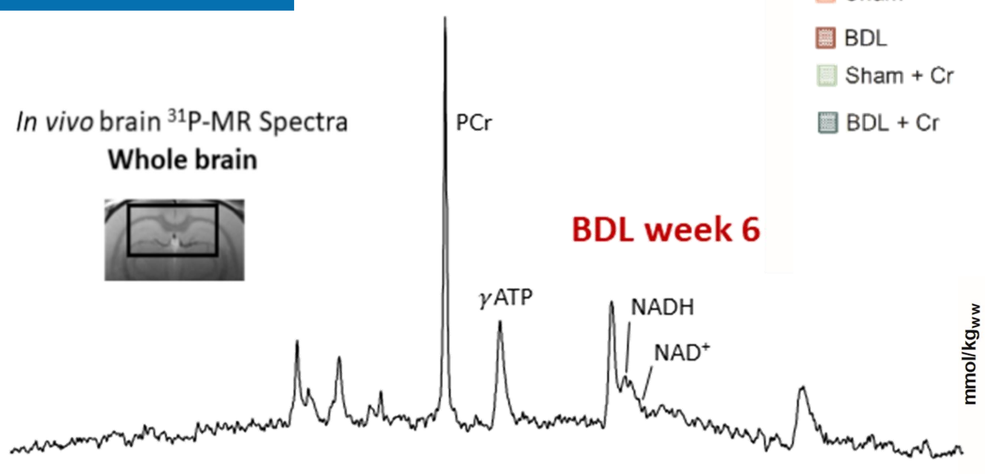


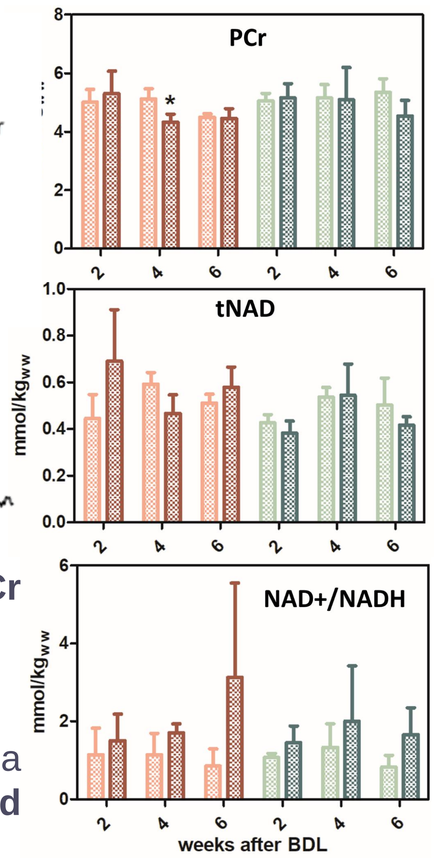
- **Cr-treatment seemed to restore the decrease in Cr and tCr → higher Cr in BDL+Cr (+13% at week 6).**
- Treatment seems to have a **positive effect on other osmolytes** (Ins, Tau and tCho) → less significant decrease in BDL+Cr



- Decrease of ascorbate is a hallmark of HE → Cr-treatment restored Asc in BDL rats emphasizing the **antioxidant role of Cr.**

RESULTS ^{31}P-MRS





- **PCr** concentration at **week4** was **stable** for **BDL+Cr** compared to **BDL** which had a **significant decrease**.
- **BDL+Cr** rats have a more stable tNAD pool.
- For **non-treated BDL** higher variations in tNAD → a **more unstable redox state** indicating **an increased oxidative stress.**

CONCLUSION

- Our preliminary results showed an **improved neurometabolic profile due to Cr supplementation** accentuating the **antioxidant role of Cr. BDL+Cr** rats have a more stable tNAD pool.
- The **positive effect on Asc and other osmolytes** marks the need for combinatorial treatments in C HE.
- Additional studies are required to investigate if these differences due to Cr supplementation translate also into different neurological outcome.

REFERENCES

(1) Cagnon et al. *Brain Res Rev (2007)*; Nicholas et al. *J Pediatr. (2014)*; (2) Braissant et al. *J Hepatol. (2019)*; (3) Rackayova et al. *Sci Rep. (2020)*; (4) Rackayova et al. ISMRM (2017); (5) Mlynarik et al. *Mag Reason Med* (2000); (6) Vanhamme et al. 1997

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