#3661

Bitopertin, a Selective Glycine Transporter 1 Inhibitor, Reduced PPIX Level and Improved Liver Fibrosis in a Mouse Model of Erythropoietic Protoporphyria (EPP)

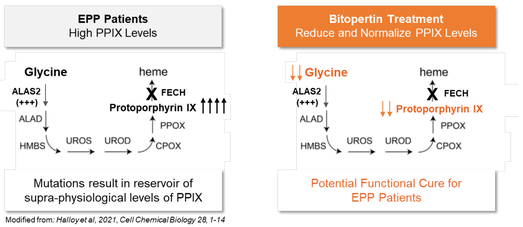
Min Wu[1,3], Sarah Ducamp[2,3], Yi Xiang[1], Juan Putra[2], Mark Fleming[2], Brian MacDonald[1], Paul Schmidt[2]

1. Disc Medicine Inc, Watertown, MA
2. Department of Pathology, Boston Children's Hospital and Harvard Medical School, Boston, MA
3. Both authors contributed equally

INTRODUCTION

Patients with erythropoietic protoporphyria (EPP) have mutations in the *FECH* gene, resulting in the accumulation of the heme synthesis intermediate protoporphyrin IX (PPIX) in red cells. PPIX that is released from RBCs then accumulates in tissues. Cutaneous accumulation of PPIX causes painful photosensitivity that has major negative impacts on the quality of life of affected individuals. Accumulation of PPIX in the liver and biliary tract causes cholestasis that can lead to liver fibrosis and severe hepatopathy.

Bitopertin is a selective and orally available small molecule inhibitor of glycine transporter 1 (GlyT1). Bitopertin was previously evaluated by Roche in a comprehensive clinical program in over 4,000 individuals in other indications which demonstrated the activity of bitopertin as a GlyT1 inhibitor and effects on heme biosynthesis. By limiting glycine uptake into erythroid cells, bitopertin has the potential to reduce the pathological accumulation of the toxic metabolite PPIX in patients with erythropoietic porphyria.

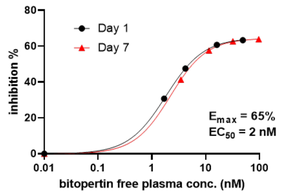


Modified from: *Halloy et al, 2021, Cell Chemical Biology 28, 1-14*

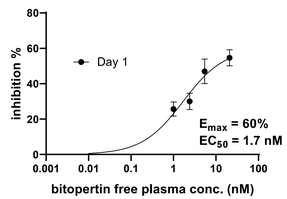
RESULTS

Bitopertin Reduced Glycine Uptake in ex vivo assays

Reduced glycine uptake in rat blood

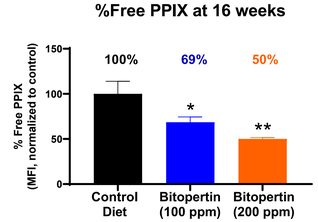


Reduced glycine uptake in mouse blood

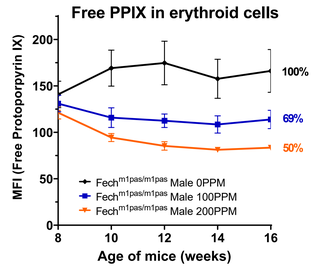


Effect of Bitopertin on PPIX in erythroid cells in EPP Mice

Reduced PPIX in RBCs

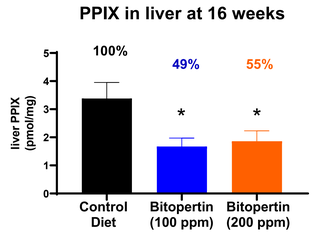


Free PPIX in erythroid cells

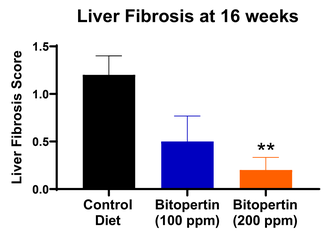


Effect of Bitopertin on Liver Pathophysiology in EPP Mice

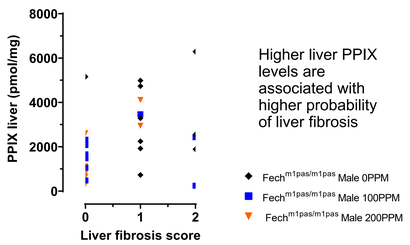
Reduced PPIX in liver



Reduced liver fibrosis



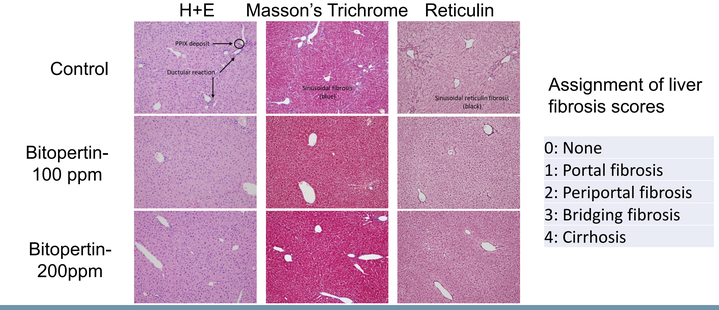
Relationship between liver fibrosis and liver PPIX levels



Reduced ductular reaction (rxn)

Treatment groups	% with ductular rxn (positive/total)
Control diet	60% (6/10)
Bitopertin-100 ppm	30% (3/10)
Bitopertin – 200 ppm	10% (1/10)

Representative images of liver section from treatment groups



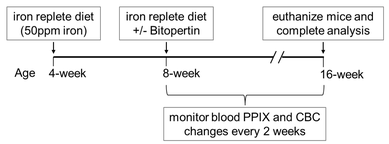
Assignment of liver fibrosis scores

0: None
1: Portal fibrosis
2: Periportal fibrosis
3: Bridging fibrosis
4: Cirrhosis

GOALS AND METHODS

Goal #1: Evaluate the potency of bitopertin in reducing glycine uptake in erythroid cells using an ex vivo glycine uptake assay

Goal #2: Evaluate the effect of bitopertin on plasma PPIX and liver pathophysiology in Fech$^{m1pas/m1pas}$ EPP mice



CONCLUSIONS

- We demonstrate that by inhibiting glycine uptake into erythroid precursors, bitopertin can reduce PPIX accumulation in blood and liver, and reduce histopathological evidence of cholestasis and liver fibrosis in the Fech$^{m1Pas/m1pas}$ EPP mouse model.
- These data suggest that bitopertin may be disease modifying in EPP and may be effective in treating photosensitivity and in modifying the risk of hepatoxicity in patients.
- Clinical trials in EPP patients have been initiated (NCT05308472, ACTRN12622000799752).

REFERENCES

Garcia-Santos D et al. Extracellular glycine is necessary for optimal hemoglobinization of erythroid cells. *Haematologica 2017;102;:1314-1323*

Halloy F et al. Repurposing of glycine transport inhibitors for the treatment of erythropoietic protoporphyria. *Cell Chem Biol 2021; 28;: 1221-1234.e1226*

Lyoumi S et al. Protoporphyrin Retention in Hepatocytes and Kupffer Cells Prevents Sclerosing Cholangitis in Erythropoietic Protoporphyria Mouse Model. *Gastroenterology 2011; 141;: 1509-1519.e1503*

Wang P et al. The essential role of the transporter ABCG2 in the pathophysiology of erythropoietic protoporphyria. *Sci Adv. 2019; 5;: eaaw6127*

ACKNOWLEDGEMENTS

Thank you to the DISC Nonclinical and CMC Teams

CONTACT INFORMATION

Min Wu, PhD, Vice President of Biology, Disc Medicine

mwu@discmedicine.com