Evaluation of a hydroxamate-based urease inhibitor in a rodent model of hepatic encephalopathy

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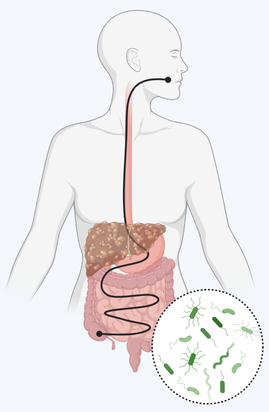
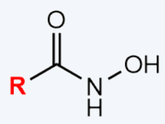
Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric disturbance arising from liver disease.[1] Impaired liver function leads to abated ammonia metabolism and thus to **hyperammonemia**, which can induce cerebral glutamine accumulation causing osmotic stress in astrocytes and alteration of neuronal communication and function.[2]

As ammonia partly originates from urea hydrolysis by **urease-producing bacteria in the colon,**[3] we aimed at identifying a **potent hydroxamate (HA)-based urease inhibitor** and employing colon-targeted delivery systems to maximize the inhibitor's concentration in the colon and minimize systemic exposure.

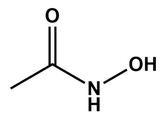


1. Potent HA-based urease inhibitor
2. Colon-targeted delivery for improved efficacy and reduced systemic exposure
3. Urease inhibition in the colon leading to reduced ammonia production

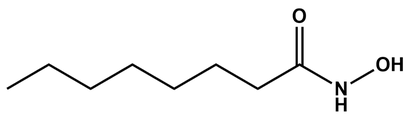


In vitro screening of HA-based urease inhibitors

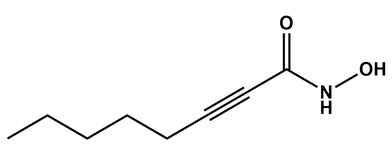
A series of **11 saturated and unsaturated aliphatic HAs** was synthesized and assessed for the urease inhibitory activity in the caecal content of Wistar rats.



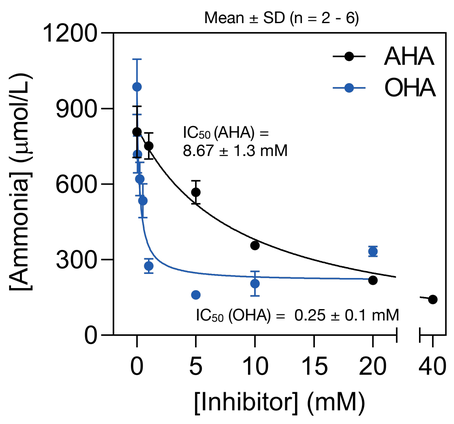
Acetohydroxamic acid (AHA)[4]

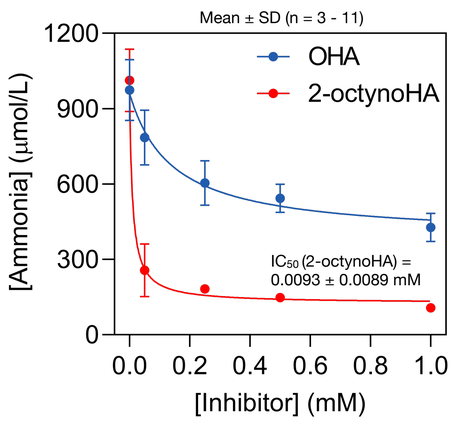


Octanohydroxamic acid (OHA)[5]



2-octynohydroxamic acid (2-octynoHA)

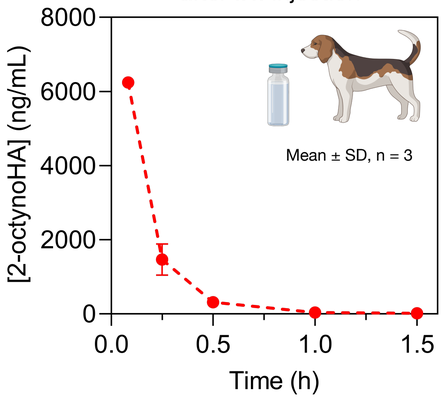


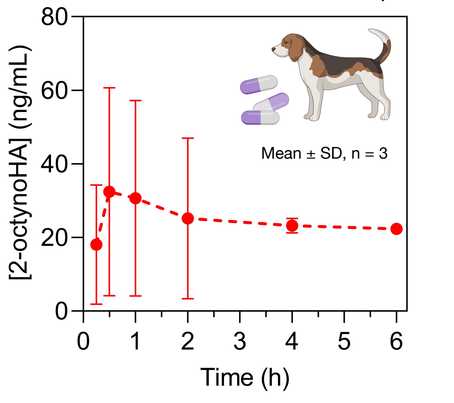


- **8 carbon atoms was the optimal alkyl chain length for urease inhibition[6]**
- **2-octynoHA exhibited the highest potency among tested HAs**

Pharmacokinetics (PK) of 2-octynoHA in dogs

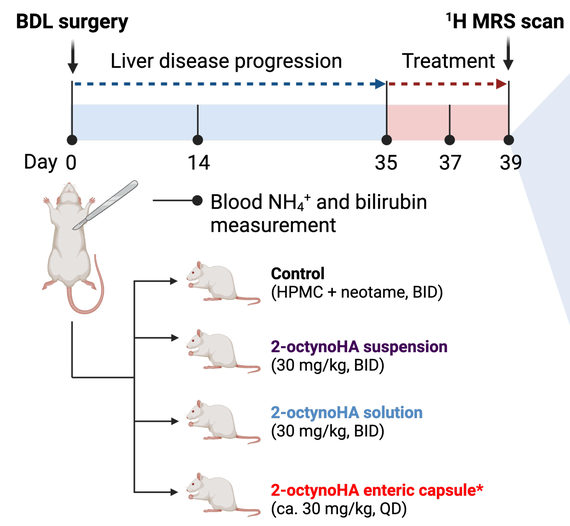
PK of 2-octynoHA was assessed in beagle dogs following I.V. injection, P.O. administration of uncoated capsules and coated capsules for colonic delivery.



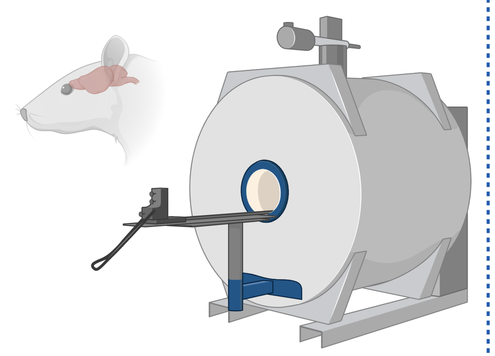


- **Administration of coated capsules resulted in decreased plasma concentrations of 2-octynoHA (below LLOQ) confirming low systemic exposure**

Efficacy of 2-octynoHA in bile duct ligated (BDL) rats

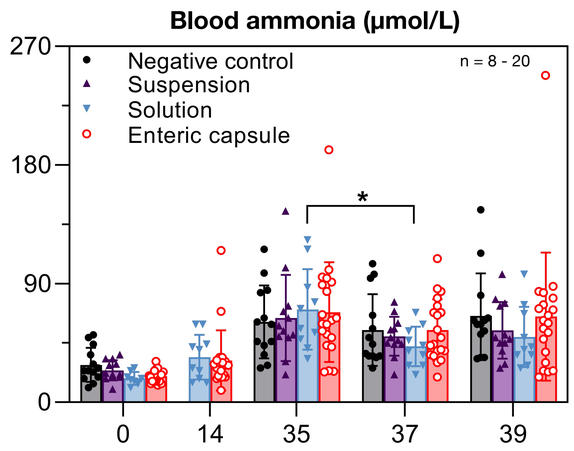


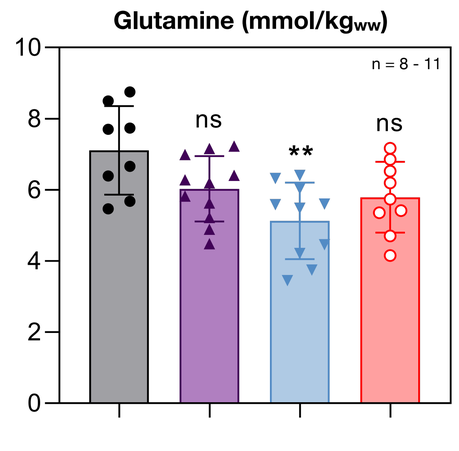
* Capsules (size 9h) were coated with 15% (w/w) Eudragit L100 solution for colonic delivery

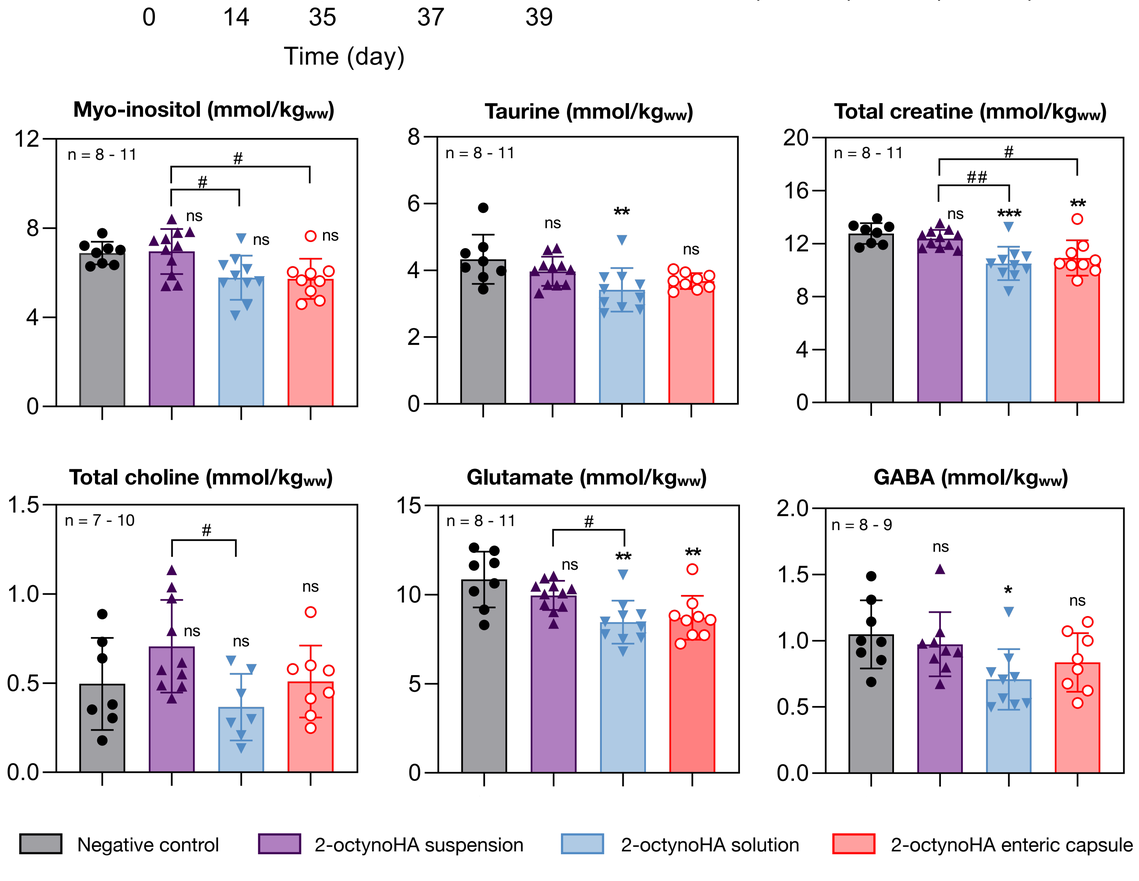


Measurement of 14 metabolites in the cerebellum by *in vivo* 1H MRS on 9.4T MRI system

- All data are expressed as mean ± SD from n animals
- For blood ammonia levels: *p < 0.05
- For brain metabolites: *p < 0.05, **p < 0.01, ***p < 0.001, ns – not significant *vs.* control; for other comparisons: #p < 0.05, ##p < 0.01







- **Animals receiving 2-octynoHA solution exhibited lower blood ammonia and brain glutamine levels *vs.* control group**
- **The lack of efficacy of colonic formulation might be attributed to low solubility of 2-octynoHA in the absence of solubilizing agents**

Conclusions

1. *In vitro* anti-ureolytic activity of 2-octynoHA exceeds that of HAs previously investigated in clinical trials.
2. Colon-targeted formulation of 2-octynoHA might reduce systemic exposure to the compound.
3. Oral administration of 2-octynoHA led to reduced ammonemia and brain glutamine in BDL rats.

Acknowledgements

The authors gratefully acknowledge financial support from Carigest SA.
All illustrations were created with BioRender.com.

References

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