INVESTIGATING RENAL HANDLING OF HEPCIDIN: IS THERE A ROLE FOR THE MEGALIN RECEPTOR?

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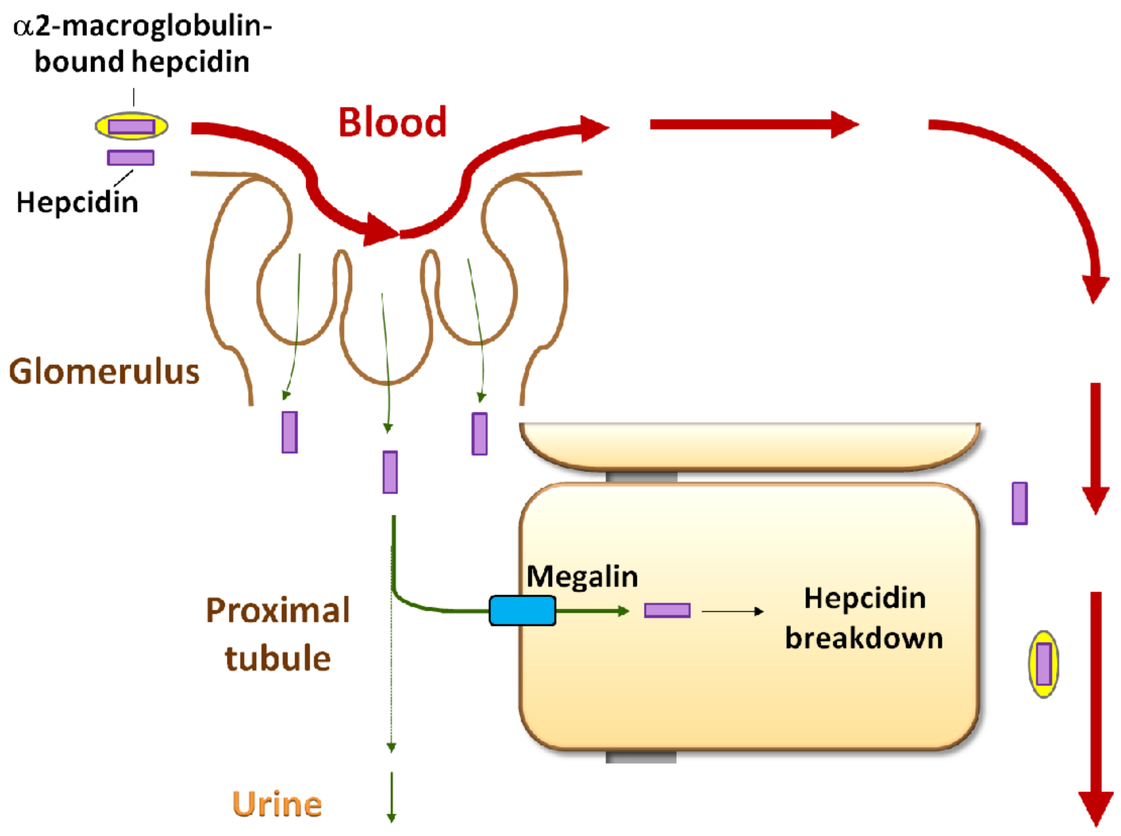
Introduction

Hepcidin is an iron regulating hormone. Recent studies suggest that urinary hepcidin may protect against acute kidney injury after coronary artery bypass surgery by attenuating tubular injury. However, renal handling of hepcidin is unknown.

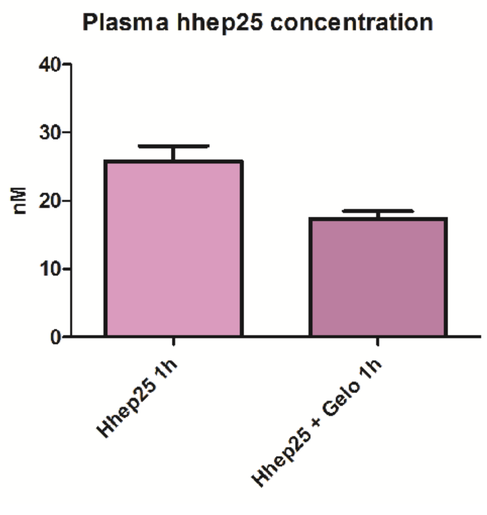
Method

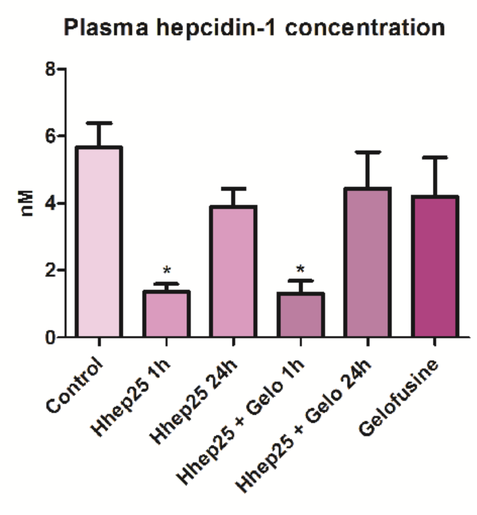
A single dose of 10 µg human hepcidin-25 (hhep25) was injected intraperitoneally in C57Bl/6 mice and urine, plasma and tissue were collected after 1h or 24h. The megalin receptor was blocked by an intravenous injection of Gelofusin® 5 min. prior to hhep25 administration.

Hypothesized renal hepcidin handling

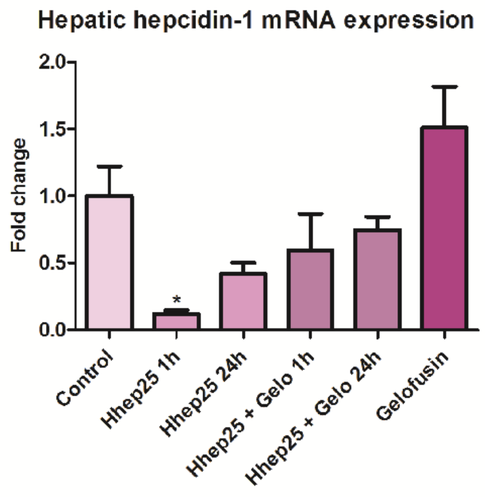


Hhep25 reduces endogenous murine hepcidin-1 production

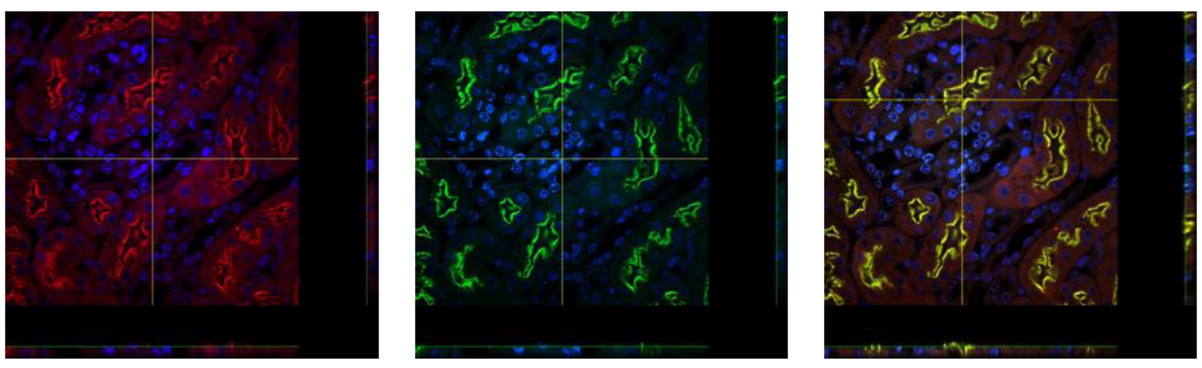




Hhep25 was only detected in plasma 1h after injection. Concurrently, plasma hepcidin-1 concentrations and hepatic hepcidin-1 mRNA expression were reduced. These data demonstrate that hhep25 is biologically active in mouse.
Gelo = Gelofusin® * p<0.05

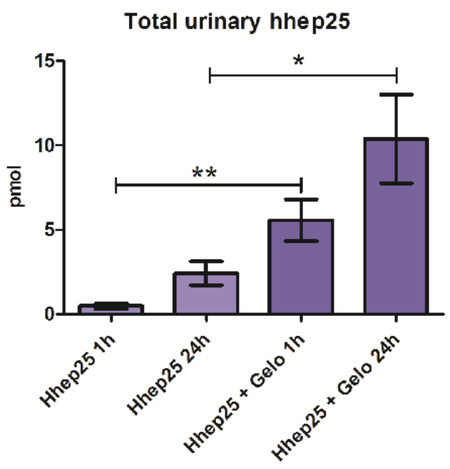


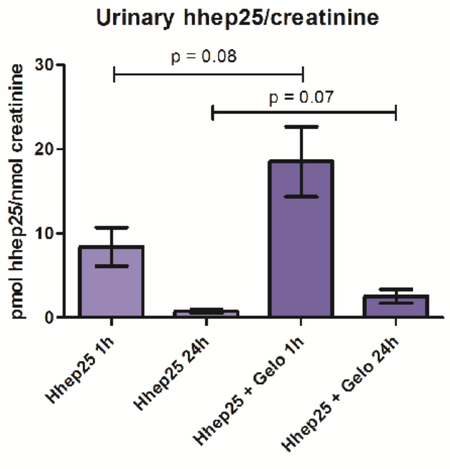
Hhep25 colocalizes with the megalin receptor on the apical membrane of the proximal tubule

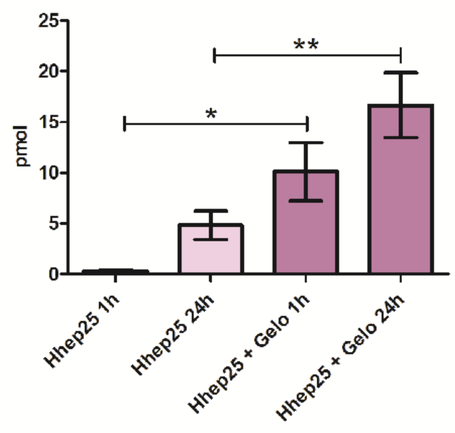


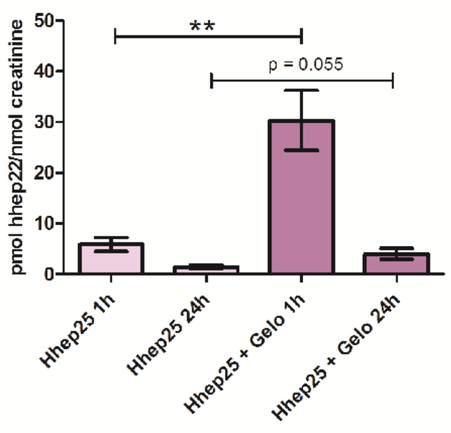
Hhep25 | Megalin | Merged

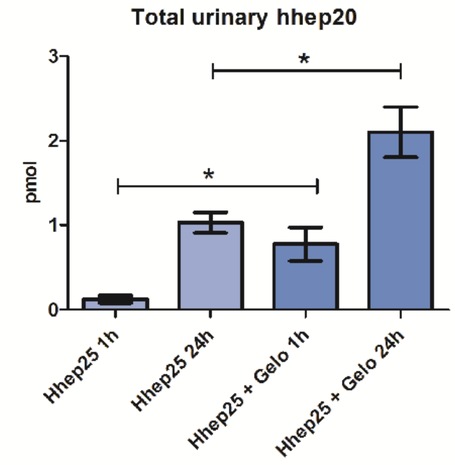
Urinary hhep25 cleavage and excretion is enhanced by Gelofusin®

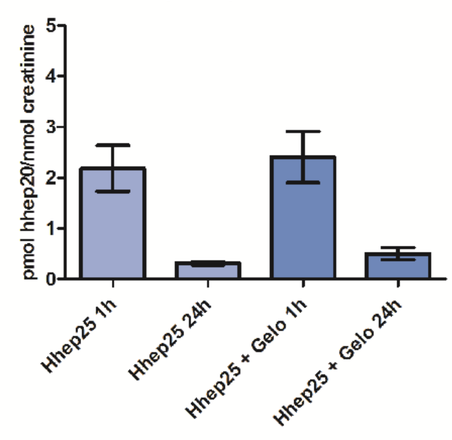












After injection in mice, hhep-25 and its smaller isoforms are excreted in urine in the first 24 hours. Excretion is enhanced by Gelofusin® pretreatment and highest after 1 hr. * p<0.05 ** p<0.01

Conclusion

Our data suggest that circulating hhep25 is filtrated by the glomerulus and subsequently degraded and/or reabsorbed via the megalin receptor.

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