Postmenopausal estradiol levels and female sex modulate haemodynamic responsiveness in experimental portal hypertension

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Abstract

Background & aims: Sex and 17β-estradiol (E2) influence outcomes of cirrhosis, yet preclinical studies in portal hypertension are conducted predominantly in males. We investigated sex and E2-dependent differences in G protein-coupled estrogen receptor 1 (GPER1) signalling and portal pressure response to PDE5 inhibition (PDE5i) in experimental cirrhosis.

Methods: We assessed sex inclusion in rodent studies by PubMed literature search and analysed human hepatic GPER1 expression by sex and age using bulk RNA-seq. Bile duct ligation was performed in male, ovariectomised (OVX) and sham-operated female rats. E2 was administered 24h before invasive haemodynamic assessment in males and OVX females. Acute PDE5i effects were investigated during haemodynamic measurement.

Results: Of 510 rat and 1,657 mouse studies, 87.3% and 77.3% respectively included males only. Human bulk RNA-seq suggested lower hepatic GPER1 expression in cirrhotic females aged ≥ 50 vs. < 50 years. OVX reduced hepatic - but not aortic - GPER1 expression. E2 reduced portal pressure (mean +/- SEM; 22.6 +/- 1.4 vs. 14.3 +/- 1.1 mmHg, p = 0.009) by lowering hepatic portal vascular resistance (74.4 ± 12.7 vs. 25.4 +/- 3.1 mmHg·min·ml-1·g-1, p = 0.03) only in OVX females. PDE5i decreased portal pressure in males (21.3 +/- 1.2 vs. 16.9 +/- 1.8 mmHg, p = 0.03) irrespective of E2. OVX abolished the PDE5i response, which was restored by E2 (14.3 +/- 1.1 vs. 10.0 +/- 0.9 mmHg, p = 0.04).

Conclusions: In experimental cirrhosis, estradiol depletion in OVX females was associated with reduced hepatic GPER1 expression and a diminished portal pressure response to PDE5i. This highlights sex and menopausal status as key determinants of treatment response in portal hypertension and supports the need for sex-specific validation.

Impact and implications: Sex and hormonal status likely contribute to clinically relevant variability in the pharmacology of portal hypertension. Our work highlights that haemodynamic drug response varies due to sex and estradiol status in pre- and postmenopausal females, yet preclinical studies predominantly rely on male models. Integrating sex and menopausal status into early drug development could improve translational accuracy and anticipate non-responder populations.