A novel animal model to explore the whole-organism response to 21-hydroxylase deficiency

Andreas Zaucker, Tulay Guran, Nazia Thakur, Angela Taylor, Aliesha Griffin & Nils Krone
University of Birmingham, Birmingham, West Midlands, UK.

Introduction

Challenges in studying CAH (Congenital Adrenal Hyperplasia):
- Comorbidities in CAH patients on long-term treatment not fully understood
- In vitro studies on CAH mutations do not always correlate with patient phenotypes
- 21OH deficiency (21OHD) difficult to study in mice -> mutants are not viable
- Incomplete understanding of systemic consequences of 21OHD

Need for novel in vivo models for 21OHD deficiency
Aim:
To establish a novel in vivo model for 21OHD using zebrafish cyp21a2 mutants

Conclusions:
Zebrafish cyp21a2 mutants are a promising model to study 21OHD
1. 21-hydroxylase is conserved in zebrafish
2. Zebrafish cyp21a2 mutants have impaired GC signalling
3. Zebrafish cyp21a2 mutants have dysregulated HPA axis

Results
5 days zebrafish cyp21a2 mutants have enlarged interrenals (adrenals)
ISH against cyp17a2 (interrenal, blue arrow) in cyp21a2 mutants and siblings

HPA axis
CRH
Hypothalamus
ACTH
Pituitary
CAH
Healthy
Adrenal

Increased expression of ACTH precursor pomca in cyp21a2 mutants
pomca transcript levels in 5 days larva by qPCR (mean ± sd)

Reduced expression of GR targets fkbp5 and pck1 in cyp21a2 mutants
fkbp5 transcript levels in 5 days larva by qPCR (mean ± sd)

Material and Methods
Three cyp21a2 mutant lines were generated by TALEN mediated mutagenesis

Genotyping by BseYI-assay

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