Farnesoid X receptor is a promising target for modulating lipid accumulation in grass carp, *Ctenopharyngodon idella*

Jing-jing Tian[a], Ya-qi Jin[a,b], Er-meng Yu[a,*], Jin-hui Sun[b], Yun Xia[a], Kai Zhang[a], Zhi-fei Li[a], Wang-bao Gong[a], Guang-jun Wang[a], Jun Xie[a*]

[a] *Pearl River Fisheries Research Institute, Chinese Academy of Fishery Sciences, Guangzhou 510380, China*

[b] *Tianjin Key Lab of Aqua-Ecology and Aquaculture, Tianjin Agricultural University, Tianjin 300384, China*

Corresponding Author: Dr. Er-meng Yu (yem@prfri.ac.cn); Dr. Jun Xie; (xiejunhy01@126.com)

Introduction

Excessive lipid accumulation in cultured grass carp (*Ctenopharyngodon idella)* is one of the greatest challenges in the aquaculture industry, which not only impairs the production benefit but also influences the animal welfare. In the future aquaculture, it is an important strategy to add functional feed additives in diets to effectively control the lipid accumulation, hence it is essential to find key molecular target and explore the pharmaceutical agonists or inhibitors. However, this also risks food safety if these drugs must enter into the body. Farnesoid X receptor (FXR), a member of the nuclear receptor superfamily, is being increasingly recognized as an important node in the regulation of fat content via the intestine of mammals, thus acts as a potential target in fish.

Material and methods

Four isonitrogenous and isoenergetic purified diets (36.0% crude protein and 6.0% crude lipid) were formulated according to the method specified by Lavell (1989). The control diet was administrated with nothing, whereas the second diet was supplemented with the FXR agonist GW4064 (0.1 g/kg), the third diet with FXR inhibitor Gly-β-MCA (2.5 mg/kg). In addition, an antibiotic mixture (ampicillin 200 mg/kg, neomycin 200 mg/kg, gentamicin 200 mg/kg, metronidazole 200 mg/kg, and vancomycin 10 mg/kg) was added to the diet to form the forth diet. The diets were randomly fed juvenile grass carp (9.89±0.2 g) in 12 aquaria (20 individuals/aquarium). Fish were hand-fed to apparent satiation twice daily (at 8:30 and 16:30) for 8 weeks. Afterwards, the fish were sampled and the indexes were tested and analyzed.

Results

1. Dietary GW4064 and glycine-β-muricholic acid (Gly-β-MCA) had no impact on the growth but significantly altered the FXR signaling of juvenile grass carp.

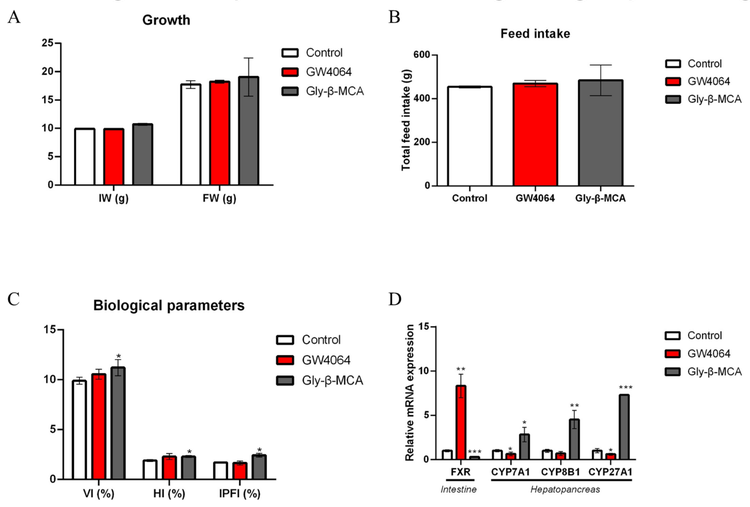

Fig. 1 Effects of dietary supplementation with GW4064 and glycine-β-muricholic acid (Gly-β-MCA) on the growth performance, farnesoid X receptor (FXR) expression of juvenile grass carp.
A, Body weight; B, Feed intake; C, Biological parameters; D, Relative expression of mRNA related to FXR signalling. Statistical significance is denoted with asterisks as follows: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

2. Activation of FXR suppressed lipid accumulation whereas inhibition of FXR promoted lipid accumulation in the liver of juvenile grass carp.

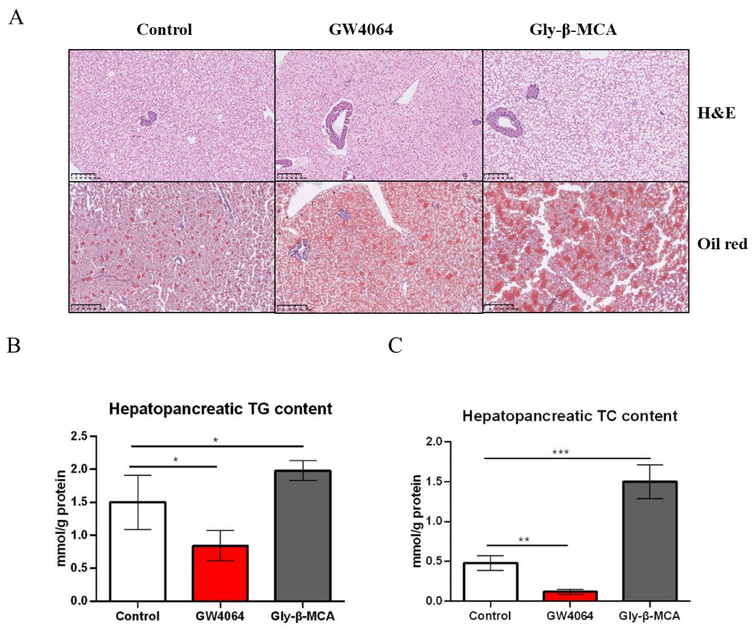

Fig. 2 Effects of dietary supplementation with GW4064 and glycine-β-muricholic acid (Gly-β-MCA) on the lipid accumulation of juvenile grass carp.A, Hepatopancreas histology; B, Hepatopancreatic triglyceride (TG) content; C, Hepatopancreatic total cholesterol (TC) content. Statistical significance is denoted with asterisks as follows: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

3. Administration with antibiotic mixture (ABM) inhibited FXR signalling and promoted hepatic lipid accumulation of juvenile grass carp.

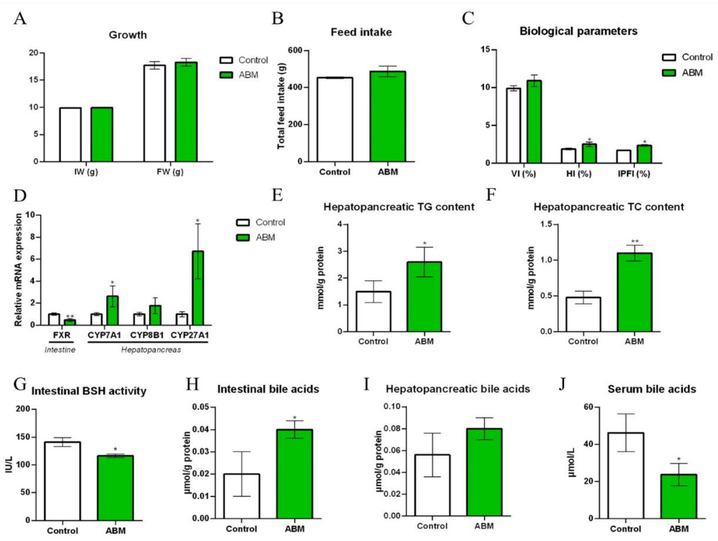

Fig. 3 Effects of dietary supplementation with an antibiotic mixture (ABM) on the growth performance, farnesoid X receptor (FXR) expression, lipid accumulation, bile salt hydrolase (BSH) activity, and bile acid content of juvenile grass carp.
A, Body weight; B, Feed intake; C, Biological parameters; D, Relative expression of mRNA related to FXR signalling; E, Hepatopancreas histology with oil red O staining; F, Hepatopancreatic triglyceride content; G, Hepatopancreatic total cholesterol (TC) content; H, intestinal BSH activity; I, intestinal bile acid level; J, Hepatopancreatic bile acid level; K, Serum bile acid level. Statistical significance is denoted with asterisks as follows: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

4. Inhibition of FXR increased lipid synthesis and lipid droplet formation capacity in the liver of juvenile grass carp.

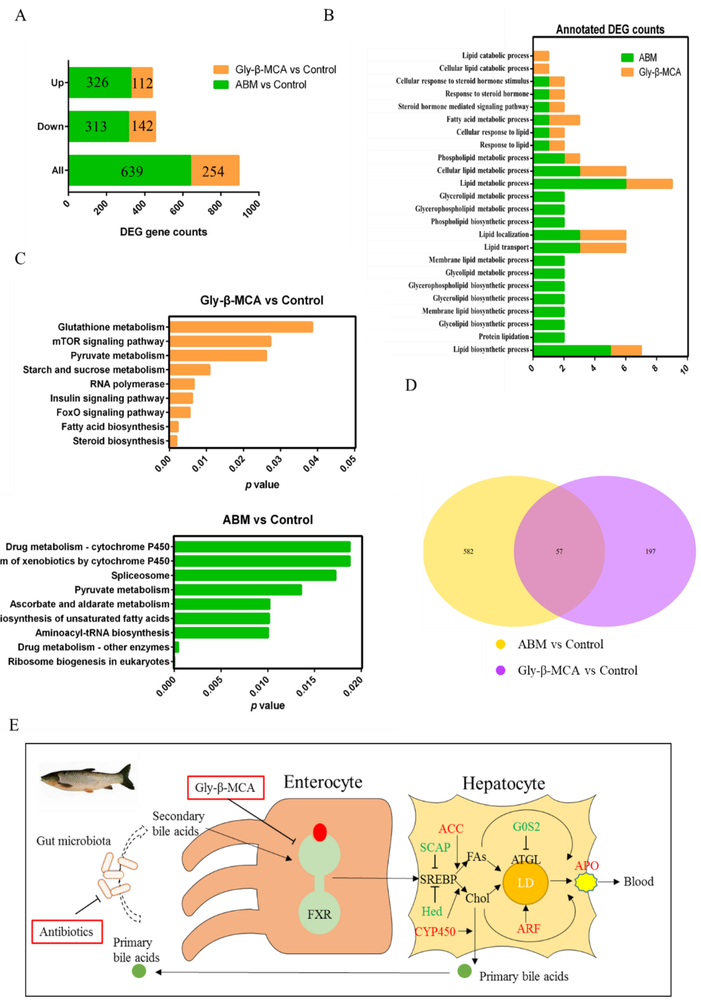

Fig. 4 Comparison of dietary supplementation with glycine-β-muricholic acid (Gly-β-MCA) and an antibiotic mixture (ABM) on the expression characteristics of hepatopancreatic transcripts in juvenile grass carp. A, Number of differentially expressed genes (DEGs); B, Selected significantly enriched lipid metabolism-related biological process Gene Ontology (GO) categories; C, Top 10 significantly enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) objects for the DEGs; D, Venn diagram of DEGs; E, Schematic overview of the proposed regulated genes of farnesoid X receptor (FXR)-related lipid metabolism in grass carp.

Conclusions

Grass carp FXR can be activated by GW4064 and inhibited by Gly-β-MCA and an ABM, which regulate lipid and cholesterol accumulation in the hepatopancreas. Further, the molecular mechanism of de novo FA modulation and cholesterol synthesis can be explained the performance of FXR inhibition. Overall, our study demonstrated that grass carp FXR is a potential target for regulating lipid accumulation and provided references for the study of lipid regulation in teleosts.

Acknowledgements

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