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Role of Bile acids in lipid metabolism and their use as feed additives

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Introduction:

Bile acids (BAs) are amphiphilic sterol compounds that contain hydroxyl or carboxyl groups and alkyl groups, which are mainly synthesized from cholesterol by the liver. The bile acids (BAs) and their derivatives exert a variety of metabolic effects through complex and intertwined pathways, thus becoming the attractive target for metabolic syndrome treatment. To modulate the lipid homeostasis, the role of BAs, turn out to be paramount as it is essential for the absorption, transport of dietary lipids, regulation of metabolic enzymes and transporters that are essential for lipid modulation, flux, and excretion. Recently, the application of BAs as a dietary emulsifier on livestock production has raised increasing attention. Dietary supplementation with BAs is known to enhance growth performance, as well as improve lipid metabolism status by regulating the hepatic lipid metabolism-related gene expression and enzyme activities in animals.

Synthesis of bile acids:

Bile acid synthesis is the major pathway for catabolism of cholesterol to bile acids. Bile acids are synthesized in the liver by the classic and alternative pathways (Chiang and Ferrell, 2018). Here, the hepatic enzymes generate free primary BAs such as chenodeoxycholic acid (CDCA) and cholic acid (CA). In gut, the action of bacterial enzymes converts primary BAs into secondary BAs such as deoxycholic acid (DCA) and lithocholic acid (LCA) which are conjugated to taurine or glycine, secreted into the bile and stored in the gallbladder (Kumari *et al.*, 2020).

Mechanism of action of Bile acids in lipid metabolism:

Bile acids are signaling molecules that activate several intracellular signaling pathways (Chiang, 2009). Bile acids are known to activate the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (Li and Chiang, 2014). CA and CDCA are potent endogenous ligands of FXR. FXR plays a critical role in regulation of bile acid synthesis and secretion, and lipid and glucose metabolism in the liver.

Bile acids are the end products of cholesterol catabolism. In the bile acid synthetic pathway CYP7A1 is the first and rate-limiting enzyme. The primary bile acids cholic acid and cheno deoxycholic acid are endogenous ligands of FXR. It is known that FXR stimulates energy metabolism by inducing ApoCII and inhibiting ApoCIII to activate lipoprotein lipase, which hydrolyzes triglycerides carried by very low-density lipoproteins and chylo microns in peripheral tissues. Also, FXR induces peroxisome proliferator–activated receptor a to stimulate fatty acid oxidation and clearance; FXR regulates lipoprotein metabolism by inducing the very low-density lipoprotein receptor and phospholipid transfer protein and inhibiting ApoB1 and microsomal triglyceride transport protein to inhibit very low-density lipoprotein secretion (Chiang, 2015).

The effects of bile acids on energy metabolism may be mainly due to activation of TGR5 by secondary bile acids (T/LCA and T/DCA). TGR5 is a Gαs protein coupled receptor (GPCR) widely expressed in the epithelial cells of the intestine, gallbladder, and liver sinusoid, and in the Kupffer cells but not in hepatocytes. TGR5

activates adenylyl cyclase (AC) to convert ATP to cAMP, which induces protein kinase A to activate cAMP response element binding protein (CREB), which is involved in various cAMP signaling pathways. In muscle and brown adipose tissues, TGR5 induces deiodinase type 2 (DIO2), which converts thyroid hormone thyroxine to 3,5,3=-triiodothyronine and stim ulates energy metabolism in the mitochondria. TGR5 also promotes adipose tissue browning, induces uncoupling proteins, and activates PPAR and PGC-1 to increase mitochondrial oxidative phosphorylation and energy metabolism and to prevent obesity and diabetes (Svensson *et al.*, 2013).

endotoxins out of the body and protect the intestine and liver health,

Bile acids in diet are reported to improve the milk fat content, milk production and health status of lactation cows (Chen *et al.*, 2024). In some cases, bile acid supplementation is considered in poultry diets to enhance fat digestion, especially when high-fat diets are fed or when there are issues with bile production or secretion (Lai *et al.*, 2018). Bile acid supplementation can be a valuable tool in pig nutrition, particularly for improving fat digestion, growth performance, and overall health especially in weaned pigs (Cao *et al.*, 2021). Excessive bile acid supplementation can lead to negative effects such as diarrhea or other gastrointestinal

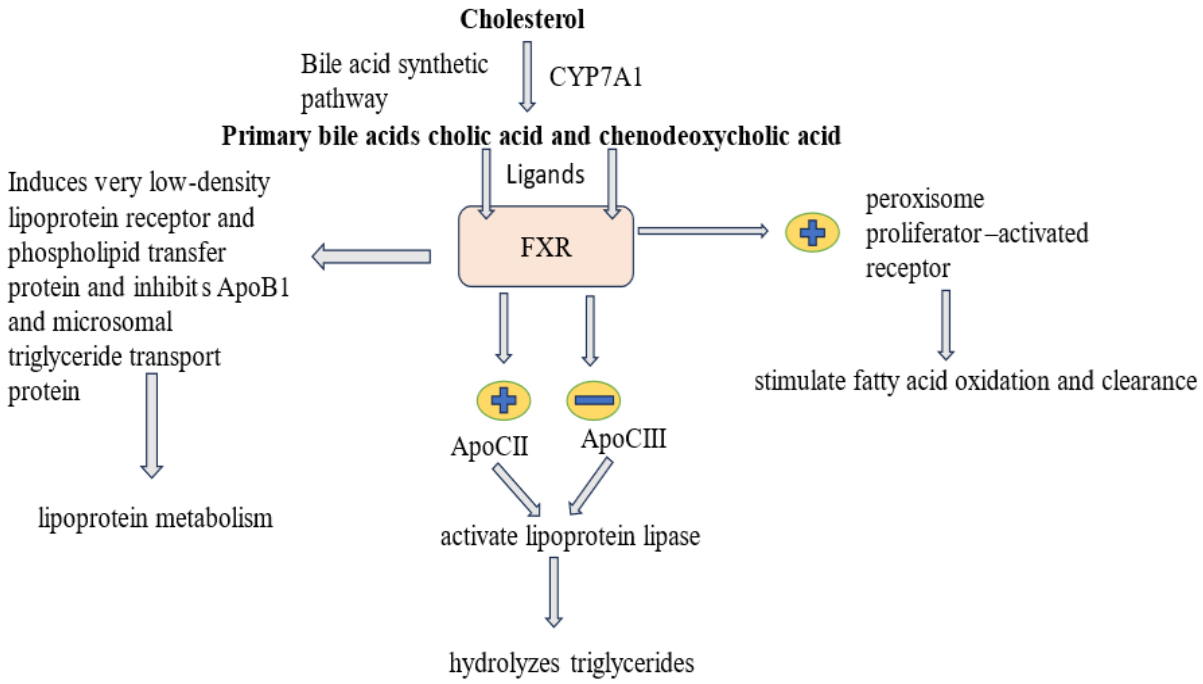

Figure 1. Role of bile acids in lipid metabolism through FXR signalling pathway

Bile acids as feed additives: dietary supplementation of exogenous bile acids (extracted from bile paste by a process of saponification, decolourisation, acidification, purification and desiccation)

as a feed additive in animal diets can effectively improve the utilization and digestibility of fat, provide fat with more energy. Meanwhile, bile acids can also reduce fat deposit in the liver, prevent fatty liver, bind to endotoxins, eliminate

disturbances. Therefore, it should be used judiciously and tailored to the specific needs of the animals and the production system.

Conclusion

Bile acids are specifically known for their role in metabolism. They act through their signalling pathways in the metabolism of biochemical compounds mainly lipids. Because of their metabolizing activity, bile acids can also be considered as exogenous feed supplements to animals, which will not only improve animal performance but also enhance animal health by utilizing the lipids more efficiently. However further studies and trials are also required to

determine the optimal inclusion levels and combinations with other dietary components for specific production goals.

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