LIÈGE université
Gembloux
Agro-Bio Tech

Le Corps professoral de

Gembloux Agro-Bio Tech - Université de Liège vous prie

de lui faire l'honneur d'assister à la défense publique de la dissertation originale que

Madame FANG Wei,

Titulaire d'un *master's degree in agriculture*,

présentera en vue de l'obtention du grade et du diplôme de

DOCTEUR EN SCIENCES AGRONOMIQUES ET INGENIERIE BIOLOGIQUE,

le 8 novembre 2019, à 14h00 précises (personne ne sera admis après cette heure),

en l'auditorium Zl (Zoologie, Bât. 9),

Passage des Déportés, 2, à 5030 GEMBLOUX.

Cette dissertation originale a pour titre :

« Effects of dietary fiber and heat stress on cholesterol and bile acids metabolism in pigs ».

Le jury est composé comme suit :

Président : Prof. Y. BECKERS, Professeur ordinaire,
Membres : Prof. N. EVERAERT (Promoteur), Prof. H. ZHANG (Copromoteur - CAAS, Chine), Prof. J. BINDELLE, Prof. J.-L. HORNICK, Prof. T. NIEWOLD (KU Leuven).

UNIVERSITE DE LIEGE – GEMBLOUX AGRO-BIO TECH – SERVICE INSCRIPTIONS ET APPARITORAT
Passage des Déportés, 2 - 5030 Gembloux - Belgique
Téléphone +32(0)81 62 23 45 - Fax +32(0)81 62 21 68 - www.gembloux.ulg.ac.be

Summary

Cholesterol, as a vital role in the human and animal body, is an essential component of all cell membranes and serves as precursors for steroid hormones, bile acids (BAs) and vitamin D. Cholesterol homeostasis is maintained by a subtle balancing act among synthesis, absorption, and excretion. Conversion to BAs from cholesterol is the major route for cholesterol excretion. Furthermore, BAs, as signaling molecules, can coordinate hepatic lipids and energy homeostasis through the nuclear receptor farnesoid X receptor (FXR), and the plasma membrane-bound bile acid receptor (TGR5). In this study, we investigated the effects of dietary fiber and heat exposure on cholesterol and bile acids metabolism in pigs.

Firstly, soluble dietary fibers have been known for their cholesterol-lowering effects for a long time and thereby they are suggested as healthy dietary supplements to reduce the risk of cardiovascular diseases, etc. Pectin, a fruit-extracted DF, can increase fecal excretion of BAs to divert cholesterol to synthesize bile acids. In **Chapter 3**, we demonstrated the lipid-lowering effect of pectin even in pigs fed with a conventional plant-based diet with a normal level of diet. By profiling intestinal BAs and mapping BAs sensors and transporters along the length of intestine, we for the first provided the molecular evidence to support that the ileum and jejunum are the major gut section for BAs re-absorption in pigs. Based upon these data, it shown a great similarity between human and pig regarding intestinal BAs transportation. Pectin in a diet with a normal level of fat did not influence the BAs synthesis and excretion, however, it did upregulate intestine BAs sensors and transporters in the ileum and colon.

Secondly, we investigated the effect heat exposure on cholesterol in pigs. In heat-stressed pigs, lipid metabolism is unique, in contrast to pair-fed counterparts. However, the mechanism of HS acting on cholesterol metabolism remains unclear. In the study, a temperature of 33°C does stress the growing pigs, indicating by 50% reduced feed intake and 300% respiratory rate; however, it did not cause obvious damages. Likewise, we found that, in short-term HS, liver cholesterol synthesis was reduced but serum cholesterol level was increased. long-term HS leaded to cholesterol metabolism alteration in the liver, uptake had reduced and cholesterol distribution to other tissues had increased (**Chapter 4**).

Thirdly, we performed an experiment on BA profiling when pigs were exposed to heat stress (**Chapter 5**). Bile acids are critical for cholesterol homeostasis and new roles in metabolism have been demonstrated recently. In short-term HS (**Chapter 5a**), liver taurocholates, including TLCA, TCDCA, TUDCA, THDCA and THCA were elevated on d3, which at the functional rather than transcriptional level. In contrast, In **Chapter 5b**, taurine-conjugated BAs (TCBA) were reduced in serum and liver after 21d heat exposure. Several TCBAs, such as TUDCA and THDCA, are known as chaperons to inhibit classic endoplasmic reticulum (ER) stress. This could be deleterious to normal function of cells experiencing heat stress. In addition, the long-term HS pigs caused a decreased expression of genes involved in BA synthesis and conjugation as well as efflux and flux transport in liver, which are not caused by feed restriction. It is the first study to comprehensively characterize BA profiles in compartments important to maintain BA homeostasis after heat stress.

In summary, this thesis increased the understanding of cholesterol and bile acids metabolism when pigs supplemented dietary pectin and exposed HS, respectively. Dietary pectin reduced serum cholesterol levels and increased transepithelial transport of BAs in the caecum and apical transport of BAs in the ileum. These results suggested site-specific regulatory effects of pectin on BAs transport in the gut. In addition, heat exposure trigger cholesterol metabolism variation which are not caused by feed restriction. These has helped us to develop a different understanding of HS influences on farm animal, especially in lipid metabolism. Furthermore, heat exposure has profound impacts on liver TCBAs, which independently of nutrient intake, might as elements to protect cells damage during heat stress.