The Gut–Liver Axis of Boar Taint

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The gut microbiome is a complex organ that is typically comprised of a couple hundred bacterial species expressing nearly 2 million different genes, which promote the biotransformation of xenobiotics and endogenous compounds and regulate the production of microbial metabolites in response to dietary, genetic, and environmental factors. Microbiota-derived compounds function as signaling molecules between different bacterial species to synchronize bacterial behaviours by altering the microbial population or the gene expression within the gut microbiome, which is known as quorum sensing. Gut-derived compounds also modulate metabolic pathways in the liver and intestines and act as ligands for nuclear receptors and other xenobiotic sensing transcription factors. In response, the liver produces bile to provide feedback to the gut microbiota and regulate further metabolite production. This bidirectional communication between the liver and the gut is referred to as the gut–liver axis and represents an important link between the gut microbiome and nuclear receptor signaling pathways.

boar taint metabolism nuclear receptor

1. Gut-Derived Tryptophan Metabolites

Indole-3-propionic acid (IPA) is an indole derivative synthesized from the reductive metabolism of tryptophan in the gut [1]. In this reductive pathway, tryptophan is converted to indole-3-lactic acid (ILA), indole-3-acrylic acid (IA), and IPA by several species of *Clostridium* and *Peptostreptococcus* expressing the phenyllactate dehydratase gene cluster (*fldAIBC*) [1][2][3]. IPA is an endogenous ligand and activator of PXR, which primarily regulates PXR signaling pathways within the gut to improve gastrointestinal barrier function [4]. IPA is also a ligand for the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that shares 88% of its known activators with PXR [5]. AhR is also expressed in the liver and intestinal tract of pigs, and crosstalk between AhR and PXR was previously found to mediate the cytostatic properties of IPA in breast cancer cells [6][7]. However, PXR signaling is also regulated by negative crosstalk with AhR, which may explain why IPA induces AhR, but not PXR, target genes in the liver of mice [8].

AhR is activated by several other microbial-derived metabolites of tryptophan, including indole and indole-3-acetamide (IAD), which were recently identified as low- and medium- affinity ligands of human PXR, respectively [9]. Indole is produced from the hydrolysis of tryptophan by over 85 different bacterial species expressing tryptophanase [10], and the conversion of tryptophan to IAD is catalyzed by tryptophan-2-monooxygenase [11]. Illés et al. [9] reported that indole and IAD bind directly to the LBD of PXR and induce the PXR target genes, CYP3A4 and multidrug resistance 1 (MDR1), in human intestinal LS180 cells as well as CYP3A4 in primary human

hepatocytes. Moreover, the intestinal anti-inflammatory properties of IPA via PXR are significantly enhanced in the presence of indole [4].

Skatole is also a microbial-derived metabolite of tryptophan that is produced in response to the transient accumulation of indole acetic acid (IAA) in the hindgut of pigs [12]. Numerous bacterial species modulate the conversion of tryptophan to IAA, and several tryptophan metabolites have been identified as precursors of IAA in mice [13]. However, the production of skatole from IAA is limited to four bacterial species in pigs that belong to the *Clostridium* and *Olsenella* genera [14][15]. Skatole is a low affinity ligand and partial agonist of human PXR, but a strong inverse agonist of PXR, CAR, and FXR in pigs [16][17]. Based on this, skatole may indirectly regulate boar taint development by suppressing nuclear receptor signaling pathways that promote the metabolism of boar taint compounds, in addition to accumulating in the fat directly. However, Gray and Squires reported contradictory effects of skatole in primary porcine Leydig cells [18] and hepatocytes [19]. Skatole decreased the expression of *CYP2B22*, the porcine orthologue of *CYP2B6*, and *CYB5R1* in Leydig cells and altered the ratio of 3α/3β-androstenol production by hepatocytes. However, skatole did not affect the total production of 16-androstene or sex steroids, nor the metabolism of androstenone in the testis and liver, respectively. Moreover, skatole did not alter the expression of several genes induced by activators of PXR, CAR, and FXR in both Leydig cells and hepatocytes, suggesting that crosstalk with other transcription factors may influence the suppressive effect of skatole on nuclear receptor signaling pathways.

Skatole is a weak activator of AhR in humans and was found to decrease the mRNA expression of PXR in HepaRG cells along with several nuclear receptor target genes, including *CYP3A4*, *CYP2B6*, and *CYP2A6*, and to inhibit the induction of *CYP3A4* by rifampicin. However, the activation of AhR was proposed to de-regulate an unidentified factor mediating crosstalk between AhR, PXR, and basal CYP expression as skatole decreased the expression of CYP2E1, which is not a known target gene of PXR [5]. It is unclear if skatole is a ligand for AhR in pigs; however, the induction of CYP1A by a standard activator of AhR (β-napthoflavone) was demonstrated in primary porcine hepatocyte culture and was presumed to result from the activation of AhR [20][21]. Thus, future research should investigate the skatole-mediated activation of AhR in pigs, and potential crosstalk that is established with other nuclear receptor signaling pathways, to better understand the impact of skatole on the metabolism of boar taint compounds.

2. Short-Chain Fatty Acids

Acetate, propionate, and butyrate are the primary short-chain fatty acids (SCFAs) produced from the microbial fermentation of dietary fibre (e.g., pectin, hemicellulose, lignin, inulin, resistant starch) by anaerobic bacteria in the hindgut [22][23]. As extracellular signaling molecules, SCFAs target G-protein coupled receptors (GPR41, GPR43, GPR109a) to regulate protein kinase-dependent intracellular signaling pathways in the liver and the gut [24][25]. Moreover, propionate and butyrate inhibit histone deacetylases (HDACs) to regulate gene transcription [26]. This suggests that there are several opportunities for crosstalk between SCFAs and nuclear receptor signaling pathways. Interestingly, methoxyacetic acid and valproic acid, which are xenobiotics derived from the SCFAs acetate and valerate, respectively, have been found to enhance the activity of several steroid-activated nuclear

receptors (e.g., estrogen receptor, progesterone receptor) via crosstalk involving mitogen-activated protein kinase signaling and inhibition of histone deacetylase [27]. Acetate, propionate, and butyrate induced histone acetylation and CYP1A1 in both Caco-2 and YAMC cells and enhanced the recruitment of AhR to the promoter [28]. Moreover, the effects of 1,4-dihydroxy-2-naphthoic acid (DHNA), a known activator of AhR, were enhanced in mice cotreated with butyrate and resulted in a 50-fold induction of CYP1A1 in the liver [28]. Butyrate was also reported to regulate CYP1A1 expression directly as a ligand and activator of AhR in human intestinal cells and was shown to induce PXR expression in Caco-2 cells [29][30]. This suggests that SCFAs such as butyrate may regulate nuclear receptor signaling pathways to control the metabolism of boar taint compounds.

3. Bile Acids

The primary bile acids CDCA and CA are cholesterol metabolites produced in the liver. Following synthesis, the primary bile acids are conjugated with glycine or taurine and incorporated into the bile. CDCA and CA are deconjugated by bile salt hydrolase enzymes, which are expressed by many bacterial species, including *Lactobacillus* [31][32][33], *Enterococcus* [34], *Bifidobacterium* [35][36], *Clostridium* [37], and *Bacteroides* [38]. Following deconjugation, approximately 95% of the bile acids released into the gut are re-absorbed and transported back to the liver via the hepatic portal vein bound to albumin or lipoproteins in what is known as the enterohepatic circulation [39][40][41]. Bile acids that escape re-absorption are metabolized in the colon by bacterial flora with 7α-dehydroxylation activity, resulting in the production of the secondary bile acids DCA and LCA from CA and CDCA, respectively [42][43].

As endogenous ligands and activators of FXR, bile acids induce the expression of several enzymes in the liver and gastrointestinal tract to autoregulate subsequent bile acid synthesis, transport, and metabolism and mitigate their potential cytotoxic effects. Upon activation, FXR increases the expression of SHP, which interacts with HNF4α and liver receptor homolog-1 (LRH-1) to inhibit CYP7A1 expression and bile acid synthesis [44]. Bile acids also work through FXR to directly increase the transcription of PXR, which functions as a target receptor for LCA and DCA [45][46]. The bile acid-mediated activation of FXR and PXR upregulates the expression of SULT2A1, UGT2B4, and CYP3A4 to promote bile acid metabolism/detoxification [47][48][49]. Some bile acids, bile acid conjugates, and bile acid metabolites also have inhibitory effects on CAR activity in humans and mice [50]. The metabolism of androstenone and skatole is dependent on many of the same hydroxylation and conjugation reactions that promote bile acid detoxification. Therefore, circulating levels of bile acids may indirectly affect the development of boar taint.

Like bile acids, androstenone is also thought to be recycled in the gut through the enterohepatic circulation. The inclusion of non-nutritive sorbent materials, most notably activated charcoal, in finishing diets was previously reported to significantly decrease fat androstenone concentrations [51]. While the mechanism behind this is unclear, it was proposed that dietary sorbent materials may disrupt the enterohepatic circulation of androstenone to promote excretion. This suggests that dietary sorbent materials may also indirectly alter nuclear receptor signaling pathways by reducing circulating levels of bile acids and bile acid derivatives. Therefore, future research aimed at characterizing the disruption of the enterohepatic circulation by dietary sorbent materials should also consider the

potential effect of these binding agents on the activation or inhibition of PXR, CAR, and FXR, and the downstream consequences on the metabolism of androstenone and skatole.

4. Diet

The production of microbiota-derived compounds in the gut is highly dependent on the composition of the diet, and several dietary compounds have been investigated as a treatment strategy for boar taint. Most notably, raw potato starch, sugar beet pulp, chicory inulin, and other fermentable fibre sources can significantly reduce the synthesis of skatole in the hindgut; however, the exact mechanism behind this is not well understood.

Claus et al. [52] attributed the effects of fermentable carbohydrates to the production of butyrate, which was shown to act in the gastrointestinal tract to inhibit apoptosis of colon crypt cells and reduce the production of cell debris that would otherwise provide a source of tryptophan for skatole synthesis. However, opposite effects on skatole synthesis and apoptosis have been reported following butyrate treatment via intracecal infusion [53]. Interestingly, butyrate can promote either growth stimulatory or apoptotic effects in human colorectal tumour cell lines in the absence and presence of glucose, respectively [54]. Therefore, this may explain the controversial effects of butyrate on skatole synthesis.

Diets containing high levels of sugar beet pulp or chicory root effectively decrease fecal skatole concentrations and simultaneously increase the synthesis of IPA [53][55]. Although it has been suggested that fermentable carbohydrates may alter the microbial metabolism of tryptophan to favour the synthesis of IPA over skatole, IPA may alternatively act through nuclear receptor signaling pathways to promote skatole metabolism and clearance. Although the exact mechanism is unclear, the hepatic expression of CYP2E1 was increased in pigs fed sugar beet pulp [56]. Moreover, dietary supplementation with dried chicory root was reported to significantly increase the hepatic expression of CYP1A2 and CYP2A19 at the mRNA and protein level and CYP2E1 at the mRNA level relative to boars fed a standard control diet [57]. This suggests a possible link between IPA synthesis from the fermentation of dietary fibre, nuclear receptor activation, and boar taint metabolism. However, chicory root contains several sesquiterpene lactones, and some of these compounds (e.g., artemisinin) are established nuclear receptor agonists [58], which may alternatively explain these results.

In addition to chicory root, several plant species and herbal medicines contain active compounds capable of selectively regulating nuclear receptor signaling pathways [59][60]. For example, oleanolic acid is a selective modulator of FXR found in many plant species and is used in Chinese herbal medicine for its hepatoprotective and anti-inflammatory effects [61]. Diallyl sulfide is an active ingredient found in garlic and an agonist of CAR, which has been reported to inhibit the activity of CYP2E1 in vivo and induce the expression of several CYP450s, including CYP1A, CYP2B, and CYP3A [62]141142[63]. Moreover, hyperforin, from *Hypericum perforatum* or St. John's Wort, is a high-affinity agonist of PXR [64], and the phytoestrogen coumestrol is a PXR antagonist [65]. Several compounds are also targets for multiple nuclear receptors, including ginkgolide A, a terpenoid found in *Ginkgo biloba*, which is an agonist of both PXR and CAR [66][67][68] and (Z)-guggulsterone, a plant sterol found in guggul plant (*Commiphora mukul*) resin, which is an agonist of PXR, antagonist of FXR, and inverse agonist of CAR [69][70].

Many natural products also contain fermentable carbohydrates that can increase the production of SCFAs, and several have been reported to modulate the composition of the gut microbiome (reviewed in [71]). Therefore, natural products may be a promising dietary treatment strategy for preventing the development of boar taint.

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