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Mini Review

Regulation of Porcine Hepatic Cytochrome P450 — Implication for Boar Taint

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ABSTRACT

Cytochrome P450 (CYP450) is the major family of enzymes involved in the metabolism of several xenobiotic and endogenous compounds. Among substrates for CYP450 is the tryptophan metabolite skatole (3-methylindole), one of the major contributors to the off-odour associated with boar-tainted meat. The accumulation of skatole in pigs is highly dependent on the hepatic clearance by CYP450s. In recent years, the porcine CYP450 has attracted attention both in relation to meat quality and as a potential model for human CYP450. The molecular regulation of CYP450 mRNA expression is controlled by several nuclear receptors and transcription factors that are targets for numerous endogenously and exogenously produced agonists and antagonists. Moreover, CYP450 expression and activity are affected by factors such as age, gender and feeding. The regulation of porcine CYP450 has been suggested to have more similarities with human CYP450 than other animal models, including rodents. This article reviews the available data on porcine hepatic CYP450s and its implications for boar taint.

Contents

1. Introduction

Regulation of cytochrome P450 (CYP450) and its importance for xenobiotic clearance in the body has been the focus of numerous studies over the last two decades. Moreover, the involvement of CYP450 enzymes in the metabolism of several endogenously produced compounds

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is well documented. The superfamily of enzymes belonging to the group of CYP450s are hemoproteins with a spectrophotometric peak at 450 nm in their reduced state in complex with CO. CYP450s are often situated in the membranes of the endoplasmic reticulum or mitochondria, oxidising a wide range of substrates in collaboration with NADPH oxidoreductase and/or cytochrome b_5. These reactions are an important part of the general detoxification process usually conducted in two phases, where CYP450 enzymes are responsible for Phase I metabolism [1].

The CYP450 family consists of at least 57 genes in the human body [1]. They are arranged into families based on their amino acid sequence, with isoforms sharing more than 40% being members of the same family (e.g., CYP1, CYP2) and isoforms sharing more than 55% being members of the same subfamily (e.g., CYP1A, CYP1B). Individual isoforms are identified by an additional Arabic number (e.g., CYP1A1, CYP1A2). CYP450s are widely expressed in all living species, with more or less conserved isoforms. Studies have determined high homology between the human and porcine versions of the CYP450, ranging from ~90% for human CYP2A6 and porcine CYP2A19 to ~60% for human CYP2C8 and porcine CYP2C33 [2].

Mammalian CYP450s are expressed in a variety of tissues, including the liver, intestine, kidney, gonads and brain. For most of the CYP450s the highest expression is detected in the liver. The current knowledge on porcine CYP450 identification and tissue-distribution has been summarised by Puccinelli et al. [2].

Similar to general detoxification, the tryptophan metabolite skatole (3-methylindole) is metabolised in two phases, with CYP450 enzymes being involved in Phase I metabolism [3]. Skatole accumulation in pigs has been associated with negative sensory perception of the meat upon heating and consumption, which is a phenomenon known as boar taint [3]. The current practice in several countries to overcome the accumulation of skatole is surgical castration of male piglets before the age of 7 days. However, this practice is highly questioned due to increasing focus on animal welfare and negative production impacts. In this context, alternative methods are needed. In this review, we summarise the current knowledge on the regulation of porcine CYP450 isoforms involved in skatole metabolism (particularly CYP1A, 2A and 2E1), and we suggest how this knowledge might be used to enhance the activity of hepatic CYP450 and thereby potentially minimise the accumulation of skatole in pig meat.

2. Xenobiotic receptors and regulation of mRNA expression

The expression of individual CYP450s is regulated by ligand binding receptors constitutively expressed in hepatocytes and other cell types (e.g., enterocytes), often collectively referred to as xenobiotic receptors (XR) (Fig. 1). Several receptors are known to be involved in the initiation of gene expression, either by direct binding to promoter regions of the gene or by crosstalk with other receptors [4,5]. With respect to the control of skatole metabolising CYP450, the major XRs controlling them are the aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR) and pregnane X receptor (PXR). All of these receptors control a battery of genes, including different CYP450s, Phase II enzymes and drug transporters. Other receptors (e.g., farnesoid X receptor and liver X receptor) and co-factors are also likely involved in tuning the activity of the XRs as co-activator and co-repressors or via crosstalk; however, it is beyond the scope of this review to cover this topic. Readers interested in more detailed information about these regulatory events are directed to other reviews [4,5].

2.1. Aryl hydrocarbon receptor

The AhR is known to control the expression of genes such as CYP1A1, 1A2 and 1B1. AhR is located in the cytosol where it is kept in complex

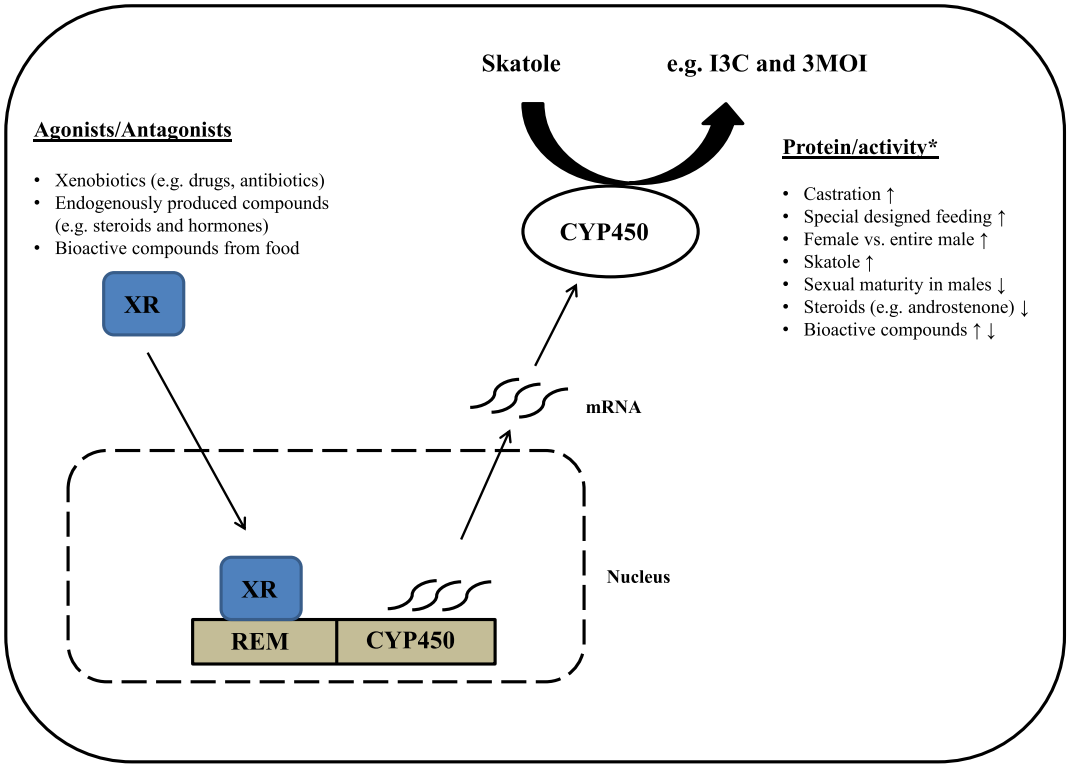

Fig. 1. Simplistic model of the events from xenobiotic receptor activation to skatole metabolism. Upon activation, the xenobiotic receptor translocates into the nucleus, where it interacts with response elements of the DNA, initiating gene transcription. Ultimately, this increases the expression of skatole-metabolising cytochrome P450 enzymes and thereby improving skatole clearance from the liver. Several events have been shown to regulate the CYP450 dependent activity and thereby potentially interact with the skatole metabolism. * Arrows indicate increased (↑) or decreased (↓) expression/activity of CYP450 in comparison to control groups. XR: xenobiotic receptor; REM: response element; CYP450: cytochrome P450; I3C: indole-3-carbinol; 3MOI: 3-methyloxindole.