Biochimica et Biophysica Acta 1812 (2011) 964–973

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Sex differences in nuclear receptor-regulated liver metabolic pathways ☆

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ARTICLE INFO

Article history:
Received 23 November 2010
Received in revised form 23 December 2010
Accepted 24 December 2010
Available online 4 January 2011

Keywords:
Nuclear receptors
Liver sex dimorphism
Gender dimorphism
Sexual differences
Nuclear receptor crosstalk

ABSTRACT

Liver metabolism is markedly sex-dimorphic; accordingly, the prevalence of liver diseases is different between sexes. The superfamily of nuclear receptors (NRs) governs the proper expression of key liver metabolism genes by sensing lipid-soluble hormones and dietary lipids. When the expression of those genes is deregulated, disease development is favored. However, we lack a comprehensive picture of the differences between NR actions in males and females. Here, we reviewed explorative studies that assessed NR functions in both sexes, and we propose a first map of sex-dimorphic NR expression in the liver. Our analysis suggested that NRs in the female liver exhibited cross-talk with more liver-protective potential than NRs in male liver. This study provides empirical support to the hypothesis that women are more resilient to some liver diseases than men, based on a more compensative NR network. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

1. Introduction

The hepatic portal vein transports nutrients from the gastrointestinal tract to the liver and ensures that xenobiotics present in food are processed in the liver before they reach the entire circulatory system. Thus, the liver is the major organ for coordinating the circulation of energy-providing metabolic substrates and the disposal of toxic products. In the liver, members of the nuclear receptor (NR) superfamily of transcription factors can sense fluctuating levels of small lipophilic molecules that reflect the body's metabolic status; as a result, NRs promptly adapt the energy homeostasis of the body to environmental changes by modulating the transcription of genes involved in a broad range of metabolic response programs. Female and male livers show considerable sexual dimorphism in gene expression [1], most likely due to differences in the metabolic needs for reproduction. Notably, a recent proteomic study revealed that the expression of liver proteins is affected more by gender than by nutritional status [2]. Despite 25 years of intensive studies on NRs, the research in this field has mainly focused on one sex, primarily males; moreover, in some studies, the sex of the subjects was not even mentioned.

In this review, first, we summarize the current knowledge on hepatic, sex-associated roles of individual NRs. Second, we show that sexual dimorphism affects both the level of individual gene expression and the concerted activities of interconnected genes controlled by NRs. Finally, we discuss the hypothesis that this sex-dimorphic NR "interactome" targets selected pathways in the liver, and deregulation of these pathways may favor the development of sex-biased diseases.

2. Sexual dimorphism in nuclear receptor expression

In the liver, growth hormone (GH) regulates the expression of different genes. GH is synthesized in the CNS pituitary glands. Its secretion from the pituitary is subject to testosterone exposure, which imprints pulsatile GH signaling in males from neonatal life to adulthood [3]; in contrast, pituitary secretion of GH is nearly continuous in females [4]. This is a major factor in establishing and maintaining sexual dimorphism in hepatic gene transcription. This dimorphism has been observed both in the secretion of GH and in the expression of its receptor (GHR). For instance, transcription of a liver-specific GHR (*ghr1*) is higher in females than in male rats [5]. 17β-Estradiol (E2), by increasing or feminizing the GH levels [6], may indirectly affect GHR expression: in fact, E2 treatment induced *ghr1* in male rats; conversely, an ovariectomy or treatment with the antiestrogen, tamoxifen, reduced *ghr1* expression in females [5]. Thus, sexual dimorphism in GH expression is controlled by testosterone, and sexual dimorphism in the GHR appears to be indirectly controlled by estrogen. This sets up a sex-dimorphic hormonal axis, with species-specific characteristics. For instance, the GH secretion pattern is particularly marked in rats [7], wherefore a lot of the information regarding sex differences comes from these animals. Another rodent, the mouse, has a less pronounced sex-dependent GH secretion pattern [8] and the human even less [9], despite sex differences in hepatic gene expression are evident also for mice [10]. The GH axis elicits several intracellular signaling pathways, including

Abbreviations: NRs, nuclear receptors; ER, estrogen receptor; AR, androgen receptor; GR, glucocorticoid receptor; RXR, retinoic X receptor; LXR, liver X receptor; PPAR, peroxisome proliferator activated receptor; TR, thyroid hormone receptor; PXR, pregnane X receptor; CAR, constitutive androstane receptor

☆ This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

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doi:10.1016/j.bbadis.2010.12.023

the activation of a family of transcription factors called STATs (signal transducer and activators of transcription), which are largely responsible for the sex-dimorphic gene expression in the male liver [11]. Although Stat5b is a major player, it is not by itself responsible for all the observed sex differences in hepatic gene expression. Furthermore, the mechanisms of female predominant hepatic gene expression are so far less clear. Interestingly, some GH-responsive transcription factors enriched in female liver have been recently described [12].

The surgical disruption of the GH axis (e.g., with a hypophysectomy) caused impaired hepatic expression of some nuclear receptors in rats, including the estrogen receptor alpha (ERα, NR3A1) [13] and the glucocorticoid receptor (GR, NR3C1) [14]; this suggested potential GH-dependent sex-dimorphic expression of these receptors. In mice, the influence of pituitary hormones on liver gene expression was recently investigated in both sexes by microarray analysis following hypophysectomy [15]; 10 pituitary-responsive nuclear receptors were found in this dataset (Fig. 1). However, only three receptor genes (namely, *errα (NR3B1)*, *errγ (NR3B3)*, and *rxrγ (NR2B3)*) showed differential response to hypophysectomy in the two sexes, suggesting that, if the pituitary hormones play a regulatory role in NR expression, other factors might determinate their sex-dimorphic expression. Those results gave rise to the question of whether the expression of NRs is really different in male and female livers. We found that this was indeed the case with a simple cross-sectional profiling of NR expression in livers of male and female mice [16]; 17 of the 38 NRs expressed in the liver were sex-dimorphic (Fig. 1). For instance, *rarγ (NR1B3)*, *errβ (NR3B2)*, and *trβ (NR1A2)* were predominantly expressed in male liver, and *errγ*, *rxrγ*, and *pparγ (NR1C3)* were predominantly expressed in female liver. Interestingly, for most hepatic sex-dimorphic NR functions, which are discussed in the following sections, we found no evidence of differential gene expression in our microarray analysis (Fig. 1 and Section 3). This led to two non-mutually exclusive conclusions; first, the data in Fig. 1 may underestimate the global NR sex dimorphism, because it did not take into account the effects that circadian rhythms, fasting-to-feeding transitions, or estrous cycles might have on NR expression; second, sex-dimorphic NR functions might be governed by mechanisms other than mRNA expression levels (i.e., post-translational modifications). For instance, we previously found that a fraction of the hepatic peroxisome proliferator-activated receptor-α (PPARα, NR1C1) protein was sumoylated preferentially in females [16]. Structural modeling of the PPARα ligand-binding domain (LBD) revealed that the agonist-induced change in the LBD conformation caused the sumoylation-targeted Lys358 residue to move to the surface of the molecule, making it available for this modification. In fact, sumoylation of the PPARα LBD triggered the interaction between PPARα and the LXXLL peptide motif of the GA binding protein-alpha (GABPα), which was bound to the steroid oxysterol 7α-hydroxylase cytochrome P450 7b1 (*cyp7b1*) promoter used in the model. Furthermore, despite the "agonist-like" conformation required for sumoylation, the thus-modified PPARα recruits the NR corepressor (NCoR [16,17]). DNA and histone methyltransferases are also recruited, and these methylate a Sp1-binding site near the GABP sites and histones. These events resulted in the loss of Sp1-stimulated expression and, thus, the

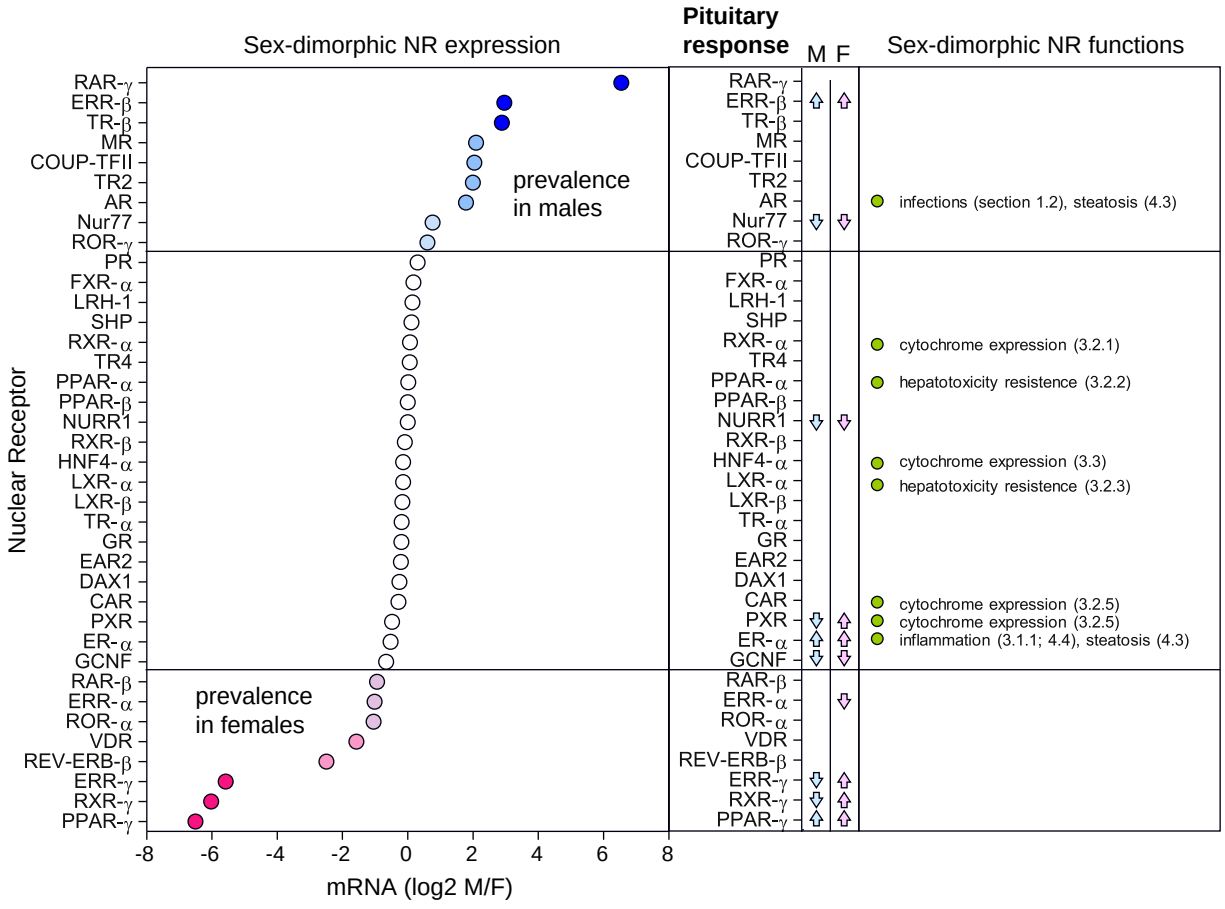

Fig. 1. Sexual dimorphism in nuclear receptor expression and function. This microarray-derived data show nuclear receptor mRNA expression levels in the liver from a previous study [16]. Sex differences are expressed as the log2 of the ratio between the absolute signals obtained in male vs. female livers harvested 2 h after dark (ZT14). The intensity of the color is proportional to the prevalence of expression in females (pink) or males (blue). The impact of pituitary hormones on NR expression in liver (positive response: arrow up, negative response: arrow down) was observed in a gene expression study on the effect of hypophysectomy in both sexes [15]. Known sex-dimorphic nuclear receptor functions are indicated (green dots). The text in the right column indicates the appropriate section in which they are discussed.