SXR and the xenobiotic response

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Summary. We previously identified and characterized a nuclear receptor, SXR (steroid and xenobiotic receptor) that is the primary mediator of the xenobiotic response. SXR responds to the presence of endogenous hormones, bioactive dietary compounds, and xenobiotic chemicals by activating transcription of several P450 and drug transporter genes. The pharmacology of SXR differs considerably between rodents and humans in that a number of species-specific activators exist. Activation of SXR is thus a direct molecular assay for the potential of chemicals to exhibit divergent effects in different species. SXR-mediated differences in metabolism provide much of the mechanistic basis underlying the differential susceptibility of humans and laboratory animals to environmental chemicals. Understanding the molecular biology of SXR will enable the derivation of a commonly accepted set of principles that connect laboratory experiments, wildlife exposure data, and human risk. In turn, this will reduce the uncertainty about whether or not the underlying mechanisms of response to chemical exposure are universal, providing important new tools with which to undertake comparative studies of chemical effects between species or individuals in a population.

Keywords. Steroid and xenobiotic receptor, wild life, SXR, xenobiotic response, cytochrome P450

Introduction

When using the results of animal experiments to predict effects on humans a fundamental and often unacknowledged assumption is made. This is that uptake and metabolism of the compound in question as well as the biochemistry and endocrinology of the organism is the same between humans and the animal model. As will be discussed below, this assumption is not always valid. The mammalian xenobiotic response is mediated primarily through the activity of four families of cytochrome P450 (CYP) monooxygenases (CYP1, CYP2, CYP3, and CYP4). Of

these, the CYP3 family is among the most important since it is responsible for the metabolism of more than 60% of clinically used drugs and a corresponding number of xenobiotic chemicals [24]. The CYP2B family is responsible for another 25-30% of drug and xenobiotic metabolism [37]. The ability of organisms to induce CYP enzymes in response to elevated xenobiotic levels is crucial for their survival and normal homeostasis. It has been known for some time that the induction of CYP3 genes by drugs and xenobiotics exhibits significant differences across vertebrate species [2, 9, 14, 15], thus implying that there are differences in metabolism that should be considered. Recent breakthrough studies demonstrated that a single nuclear hormone receptor termed SXR (steroid and xenobiotic receptor)[4], PXR (pregnane X receptor) [13], or PAR (pregnane activated receptor) [3] was responsible for the species-specific regulation of CYP3A genes by drugs and xenobiotic chemicals[1]. SXR is therefore a central regulator of the xenobiotic response. We review what is known about this important xenobiotic sensor and the role that toxicogenomics has to play in understanding the xenobiotic response.

SXR and species-specific xenobiotic metabolism

There is considerable evidence that wildlife and domestic animals have suffered adverse consequences from exposure to environmental chemicals . Some of these effects may result from interactions between environmental chemicals and components of the endocrine system, such as the estrogen and testosterone receptors. Increases in the prevalence of certain cancers (e.g., breast, prostate, testicular, ovarian) may be related to this "endocrine disruption". However, there is significant controversy regarding the nature of the effects (if any) induced by a particular compound and the dose at which the candidate effect is elicited as a direct result of exposure. A greater uncertainty is to what degree the data from wildlife and laboratory animal model systems can be extrapolated to measure the risk of human exposure to the same xenobiotic chemicals. In many cases, the response of animals to chemical exposure is predictive of effects on humans and therefore, appropriate toxic equivalency factors (TEF) can be formulated [31]. In other cases, the connection is more uncertain and the ability to predict human risk does not rest on sound scientific principles.

We showed that SXR is activated by a wide diversity of natural steroids (e.g., pregnanes, estranes and androstanes), dietary compounds (e.g., phytoestrogens), and xenobiotics (e.g., rifampicin, nifedipine, PCN) [4]. SXR exhibits considerable

[1] This receptor will be hereinafter referred to as SXR to accurately reflects its biological activity.

differences in its pharmacology among mammals [4, 12, 17], which may explain species-specific differences in xenobiotic induction of CYP3. The SXR gene is remarkably divergent across mammalian species. As would be expected for orthologous receptors, the rabbit, rodent and human receptors share ~95% amino acid sequence identity in their DNA-binding domains (Fig 1). Surprisingly, the similarity in the ligand binding domain is much less with the receptors sharing only 73-84% amino acid identity (Fig 1) rather than the ~90% typically exhibited by orthologous nuclear receptors. The putative chicken (CXR) and Xenopus (BXR) members of this family are so divergent in sequence (Fig 1) and in their activation profiles [10, 32] that it is likely they are either not orthologs or that their functions have diverged significantly during evolution.

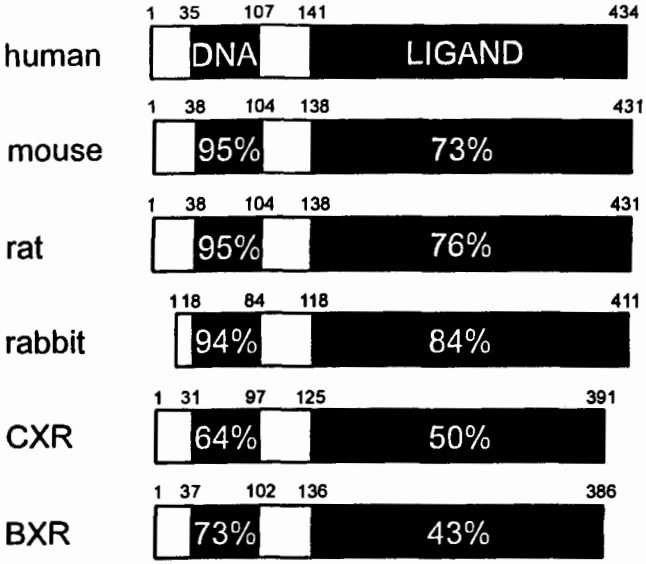

Figure 1. SXR and related genes. Percent amino acid identity is indicated among members of the NR1I12 gene family. CXR is a chicken receptor related to SXR and the bile acid receptor, CAR [10]. BXR is the Xenopus laevis benzoate 'X' receptor that was used to originally identify SXR [4].

Differences in amino acid sequence among the mammalian receptors are responsible for species-specific induction of CYP3 by drugs and xenobiotics [17, 34]. One general observation is that there are significant differences in the xenobiotic response between humans and rodents and that these differences are completely explained by the pharmacology of SXR [4, 12, 13, 17, 18, 36, 37]. For example, the

antibiotic rifampicin, the anti-diabetic drug troglitazone and the cholesterol-reducing drug SR12813 were found to be effective activators of both human and rabbit SXR, but had little activity on mouse or rat SXR [12]. In contrast, pregnenolone 16α-carbonitrile was a more potent activator of rat and mouse SXR than of human or rabbit SXR [12, 19, 27, 28] (Table 1). Corresponding induction of CYP3 SXR target genes in humans, rats, and rabbits was also observed in primary hepatocytes [27].

There is increasing interest in the mechanism by which suspected endocrine disrupting compounds (EDCs) affect humans and other model organisms. This interest, together with the discovery of SXR, has prompted new studies examining the ability of EDCs to stimulate SXR-mediated transcription and CYP3 induction in an effort to determine whether there are species-specific differences in EDC metabolism. The plasticizer diethylhexylphthalate (DEHP) and 4-nonylphenol, an alkylphenol used as a component in pesticides and spermicides, were both found to activate mouse SXR and induce mouse CYP3A1. In contrast, bisphenol A, an estrogenic compound widely used in the manufacture of polycarbonate plastics did not activate mouse SXR [19, 27]. Subsequent studies comparing the activation of SXR between species showed that bisphenol A activated human but not mouse SXR mediated transcription [28]. Our laboratory has confirmed and extended these results to rats and rabbits and a variety of other compounds [27]. These results suggest that the metabolism and, by inference, the biological effects of certain EDCs differs between humans and other mammals. We conclude that activation of SXR across test species can provide an important assay for susceptibility to the effects of EDCs. For example, an EDC that is detoxified or metabolized by an SXR-dependent P450 signaling pathway could accelerate its own breakdown by activating SXR thereby reducing the associated risk. A compound that is "activated" or increased in toxicity by P450 action would be much more toxic if it also activates SXR, increasing the risk. Lastly, a xenobiotic that fails to activate SXR in a given species could then have a greater potential to interact with other nuclear receptors such as the estrogen or androgen receptors, and pose a species-specific risk.

The similar trans-species SXR activation profiles for compounds such as DEHP and 4-nonylphenol (Table 1) suggests that these compounds will be correspondingly metabolized in rodents and humans. It may be inferred from the differences in the pharmacology of human and rodent SXRs that there are classes of chemicals (e.g., phytoestrogens and bisphenol A) for which metabolism differs between humans and rodents. Therefore, rodents may not be an appropriate model system for studying these compounds. As a general principle, one should be cautious about extrapolating the results of animal testing to human risk assessment for chemicals that differentially activate SXR. Indeed, it may be necessary to separately validate animal models for each compound in question.

An important tool for the study of xenobiotic metabolism was the development of the so-called "humanized" mouse [36]. This animal is deficient in the mouse SXR gene while expressing a human SXR transgene in the liver. This model demonstrates

convincingly that SXR is the key regulator of CYP3A expression. Moreover, the selective activation of target genes in response to species-specific activators was shown to reside in the ligand binding domain of the receptor, rather than in the DNA-binding domain or target DNA-binding elements [36]. This humanized mouse should prove a powerful in vivo system to predict human xenobiotic metabolism in an animal model.

Table 1. Xenobiotic activation of SXR from four mammalian species.

Ligand	*Human*	*Mouse*	*Rat*	*Rabbit*
Rifampicin	+	-	-	+
PCN	-	+	+	+
RU486	+	+	+	+
dexamethasone	-	+	+	+
trans-nonachlor	+	+	+	+
troglitazone	+	-	-	+
SR12813	+	-	-	+
Genistein	+	-	-	+
Coumestrol	+	-	-	+
Bisphenol A	+	-	-	+
4-nonylphenol	+	+	+	-
Phthalic acid	-	-	-	-
DEHP	+	+	+	+

Data is summarized from Blumberg et al. [4] Jones et al. [12] Takeshita et al. [28] and Tabb et al.[27].

Natural allelic variants of SXR

Human SXR displays a broad specificity for a variety of drugs and is a primary regulator of CYP3A4. The levels of CYP3 enzymes show considerable sexual dimorphisms and variation in levels and function among individuals in the population [8]. Variation in CYP3A expression may lead to important differences in drug metabolism, leading to clinically significant differences in drug toxicities and

response. It may also influence the circulating levels of estrogens and the risk of breast cancer [16]. The molecular underpinning of the variations in CYP3A4 expression are unknown at present but it is likely that SXR plays a key role in this process. Approximately 90% of the inter-individual variability in hepatic CYP3A4 activity is genetically determined and several CYP3A4 variants have been reported [21]. However, the reported allelic frequencies and the functional data demonstrate only a limited role of these variants in CYP3A4 expression and activity [6, 33]. Single nucleotide polymorphisms (SNPs) in SXR may be a major contributor to CYP3A4 expression and activity. Since SXR acts as a xenobiotic 'sensor' to mediate the physiological response of multiple drug metabolism genes, identification of functional polymorphisms in SXR might explain the variable induction of CYP3A4 and other drug metabolizing enzymes in response to SXR ligands [5]. It has been reported that different inbred mouse lines differ substantially in their sensitivity to estrogen treatment [25]. The observed differential sensitivity may result from differences in SXR among these strains although this remains to be demonstrated.

The SXR gene consists of nine exons and spans approximately 35 kb in chromosome 13q11-13. Recently, SXR variants were investigated in two ethnic groups: Caucasians and Africans. More than 40 SNPs were identified including seven in the coding region that are non-synonymous, creating new SXR alleles [11, 38]. Three of the seven variants were located N-terminal to the DNA binding domain (E18K, P27S, and G36R) and have no significant effects on DNA-binding or transactivation compared with wild-type SXR. One rare variant (R122Q) is located in the third helix of the SXR DBD. This mutant shows significantly decreased affinity for DNA binding and attenuated transcriptional activity. The other three variants are within the LBD of SXR (D163G and A370T) or close to the LBD (V140M), and show some alterations in the activation properties of SXR [11]. The A370T and V140M variants show 1.5 –2 fold enhancement in the basal expression of a CYP3A4 promoter reporter gene but lack any significant effect on transcriptional activation. In contrast, the D163G variant exhibits lower basal activity and an eight-fold higher induction by rifampicin than wild-type SXR [11].

It may be concluded that variation in SXR plays a role in the inter-individual variability of CYP3A4 expression and drug response. In addition, SXR polymorphisms could also influence individual predisposition to tumors caused by environmental carcinogens, including liver and lung cancer [7, 22]. Recently, SXR was also shown to be a lithocholic acid sensor that controls the biosynthesis and metabolism of bile acids [35]. Thus, SXR variants may be associated with physiological and pathophysiological changes in steroid, cholesterol or bile acid levels as well as the xenobiotic response.

SXR mediates xenobiotic metabolism and efflux

Many pharmacological agents are transported out of cells by intestinal P-glycoprotein (MDR1) and inactivated by liver cytochrome P450 enzymes. Both P-glycoprotein and P450 enzymes possess broad substrate specificity and the genes encoding these proteins share the ability to be upregulated by the nuclear receptor SXR [26]. Its expression in hepatocytes, cells lining the intestine and in proximal renal tubules [29, 30] suggests that P-glycoprotein plays a physiological role as a defense mechanism against potential toxic substances encountered in the diet and through environmental exposure. Both SXR and MDR1 are co-expressed in a variety of tissues including liver, kidney and placenta allowing a coordinate regulation of metabolism and excretion via xenobiotic activation of SXR.

Expression of MDR1 can be problematic in designing effective strategies for cancer treatment and other forms of chemotherapy. Identification of SXR as a key regulator of MDR1 suggests that chemotherapies which do not activate SXR and thereby induce drug clearance might be more effective. This is illustrated by the efficacy of taxol versus taxotere as anti-neoplastic agents. The superior pharmacokinetic properties of taxotere are due to its inability to activate SXR and induce SXR target genes involved in drug clearance [26]. Just as genetic variability plays a role in the pharmacology of SXR, germline polymorphisms have been found in MDR1, and these could modulate response to xenobiotics and predict the success of chemotherapies in different individuals [23]. Likewise, this same genetic variability could determine how well an individual is able to clear cells of an assault by harmful xenobiotics or EDCs.

Placental expression of SXR and its target genes may indicate a regulation of fetal exposure to endogenous steroids and xenobiotics *in utero*. Cytochrome P450s and P-glycoprotein expression have been detected in placenta [1, 20]. The unique transient high levels of steroid hormone that a fetus is exposed to during pregnancy induce SXR and CYP3A target gene expression in perinatal mice implying a role for SXR in regulation of fetal steroid hormone levels during pregnancy. Likewise, fetal exposure to, or protection from the effects of harmful xenobiotics or EDCs may be determined by regulation via SXR in the placenta. Whether or not an EDC is able to activate or block the action of human SXR could determine downstream effects on fetal development including malformations and endocrine disruption.

Conclusion and Prospects

Understanding how the xenobiotic response differs between individual humans, different animal species or even among different laboratory strains of the same species

is essential to developing high quality models and characterizations of risk from chemical exposure. The recent identification of the nuclear receptor SXR provides a key that can be used to greatly expand our understanding of the pathways that control and modulate the response to toxic environmental chemicals in the body. It is now clear that there are many commonalities but also specific differences in the way organisms respond to chemical exposure. A significant difficulty in deriving a commonly accepted set of principles that connect laboratory experiments, wildlife exposure data and human risk is the uncertainty about whether the underlying mechanisms of response to chemical exposure are universal or different. SXR shows strong similarities as well as important differences in its response to natural and xenobiotic chemicals across mammalian species. SXR may be used as an assay to identify chemicals that are metabolized differently between humans and rodents and even between humans. This provides an important new tool with which to undertake comparative studies of chemical effects between individuals in a population, whether it is inbred laboratory animal strains or different human ethnic groups.

Toxicogenomics will be increasingly important in furthering our understanding of the xenobiotic response. It will be necessary to identify the full spectrum of SXR-responsive genes and to determine which of these are responsible for individual variations in xenobiotic and drug metabolism. High throughput screening and profiling techniques will generate fingerprints of exposure to particular xenobiotics and enable the rapid detection of individual differences in gene expression. This will facilitate a molecular dissection of the xenobiotic response and lead to the development of improved tools for risk assessment.

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