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ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR BY STRUCTURALLY DIVERSE EXOGENOUS AND ENDOGENOUS CHEMICALS*

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■ **Abstract** The induction of expression of genes for xenobiotic metabolizing enzymes in response to chemical insult is an adaptive response found in most organisms. In vertebrates, the AhR is one of several chemical/ligand-dependent intracellular receptors that can stimulate gene transcription in response to xenobiotics. The ability of the AhR to bind and be activated by a range of structurally divergent chemicals suggests that the AhR contains a rather promiscuous ligand binding site. In addition to synthetic and environmental chemicals, numerous naturally occurring dietary and endogenous AhR ligands have also been identified. In this review, we describe evidence for the structural promiscuity of AhR ligand binding and discuss the current state of knowledge with regards to the activation of the AhR signaling pathway by naturally occurring exogenous and endogenous ligands.

Ah RECEPTOR SIGNAL TRANSDUCTION

The AhR is a ligand-dependent transcription factor that regulates the expression of a battery of genes in a wide range of species and tissues (1–5). Environmental contaminants, such as the HAHs and nonhalogenated PAHs, represent the most extensively characterized classes of AhR ligands (6–9), although naturally occurring ligands do exist. Exposure to TCDD (dioxin), the prototypical and most potent HAH, and related compounds produces a diverse array of species- and tissue-specific toxic and biological effects, the majority of which are AhR dependent

*Abbreviations used in text: AA, arachidonic acid; AhR, aryl hydrocarbon receptor; Arnt, AhR nuclear translocator; BR, bilirubin; BV, biliverdin; CYP1A1, cytochrome P4501A1; DRE, dioxin responsive element; FICZ, 6-formylindolo(3,2b)carbazole; HAH, halogenated aromatic hydrocarbon; I3C, indole 3-carbinol; ICZ, indolo-(3,2,-b)-carbazole; PAH, polycyclic aromatic hydrocarbon; RAR, retinoic acid receptor; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; Trp, tryptophan; UGT*01, UDP-glucuronosyl transferase *01

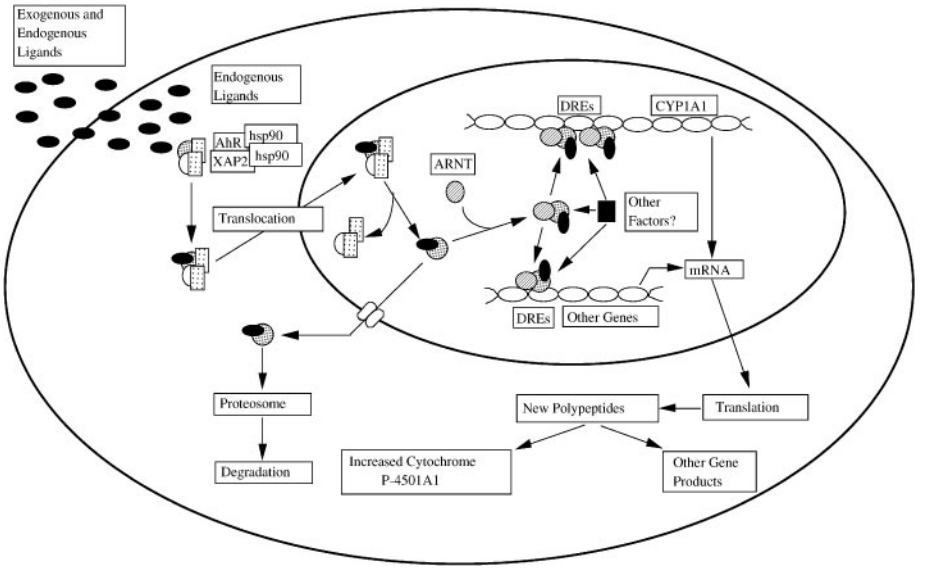

Figure 1 The molecular mechanism of activation of gene expression by the AhR. See text for more details.

(8–11). In fact, knockout of the AhR results in loss of responsiveness to TCDD and related chemicals (12–14). Although numerous genes are regulated by the AhR (6), the best studied are those encoding xenobiotic metabolizing enzymes, such as CYP1A1. The induction of CYP1A1 is one AhR-dependent response that has been consistently observed in most species, and it has been used as the model system to define the mechanism by which the AhR regulates gene expression. The current model of AhR action is presented in Figure 1. The inducing chemical enters the responsive cell and binds with high affinity to the cytosolic AhR, which exists as a multiprotein complex, containing two molecules of the chaperone protein hsp90 (a heat shock protein of 90 kDa), the X-associated protein 2 [XAP2 (15)], and a recently identified 23-kDa co-chaperone protein referred to as p23 (16). Following ligand binding, the AhR is presumed to undergo a conformation change that exposes a nuclear localization sequence(s), resulting in translocation of the complex into the nucleus (17, 18). Release of the ligand:AhR from this complex and its subsequent dimerization with a related nuclear protein called Arnt converts the AhR into its high affinity DNA binding form (1, 19). A nuclear export sequence present in the AhR is responsible for the cytoplasmic shuttling of nuclear AhR complexes that fail to dimerize with Arnt and/or bind to DNA and leads to its ubiquitination and degradation (20). Binding of the heteromeric ligand:AhR:Arnt complex to its specific DNA recognition site, the DRE, upstream of the CYP1A1 and other AhR-responsive genes stimulate transcription of these genes (3, 5, 21). The presence of the AhR and AhR signal transduction pathways in a diverse range

of species, tissues, and cell types (22–24), combined with its ability to act as a ligand-dependent transcription factor, suggests that many of the toxic and biological effects of AhR ligands result from differential alteration of gene expression in susceptible cells. Because many of the adverse effects of TCDD/HAHs are not observed until days to weeks following chemical exposure (8, 11), the adverse effects of these chemicals likely result from the continuous and inappropriate expression of specific genes in responsive cells. This hypothesis is consistent with the lack of TCDD-like toxic effects produced by PAHs and other relatively weak ligands, which produce only transient activation of the AhR signaling pathway. Although the role of AhR in the toxic and biological effects produced by AhR ligands is well documented, the exact biochemical events and responsible gene products responsible for the adverse effects of these chemicals still remain to be elucidated.

The physiological role of the AhR remains a key question, and to date no high affinity endogenous ligand has been identified. Detailed analysis of AhR ligand binding has predominantly focused on the structurally related HAHs and PAHs; however, recent studies have demonstrated the ability of a structurally diverse range of chemicals to bind to and/or activate AhR-dependent gene expression [reviewed in (6) and (7)]. These results suggest that the AhR has a promiscuous ligand binding site. In addition, the identification and characterization of a variety of naturally occurring AhR ligands has begun to redefine our ideas as to the structural specificity of AhR ligand binding. In this review, we describe recent developments in our understanding of the structural diversity of AhR ligands with an emphasis on those ligands and inducers that are naturally occurring exogenous and endogenous ligands. More details on the AhR and AhR signal transduction can be found in other excellent reviews (1–5, 7, 11).

AhR LIGANDS AND INDUCERS

In this review, AhR ligands have been separated into two major categories, those that are synthetic in nature (i.e., formed as a result of anthropogenic or nonbiological activity) and those that occur naturally (i.e., formed in biological systems as a result of natural processes). The majority of the high affinity AhR ligands that have been identified and characterized to date are members of the first category and include planar, hydrophobic HAHs (such as the polyhalogenated dibenzo-p-dioxins, dibenzofurans, and biphenyls) and PAHs (such as 3-methylcholanthrene, benzo(a)pyrene, benzanthracenes, and benzoflavones), and related compounds (6, 8, 9, 25, 26). The metabolically more stable HAHs represent the most potent class of AhR ligands, with binding affinities in the pM to nM range, whereas the metabolically more labile PAHs bind with relatively lower affinity (nM to μM range). Structure activity relationship analysis using a large number of HAHs and PAHs has suggested that the AhR ligand binding pocket can bind planar ligands with maximal dimensions of 14 Å $\times$ 12 Å $\times$ 5 Å and that high affinity ligand binding appears to be dependent upon key electronic and thermodynamic

characteristics of the ligand (26–31). There are many excellent reviews on the physiochemical characteristics and biological/toxicology potency of these "synthetic" HAH/PAH AhR ligands (26, 31) and they are not discussed here. An interesting recent development is the identification of a relatively large number of AhR ligands whose structure and physiochemical characteristics are dramatically different than that of the "classical" HAH and PAH ligands [reviewed in (6) and (7)]. The structures of some "classical" and "nonclassical" synthetic AhR ligands are shown in Figure 2. Interestingly, high-throughput screening analysis of a combinatorial

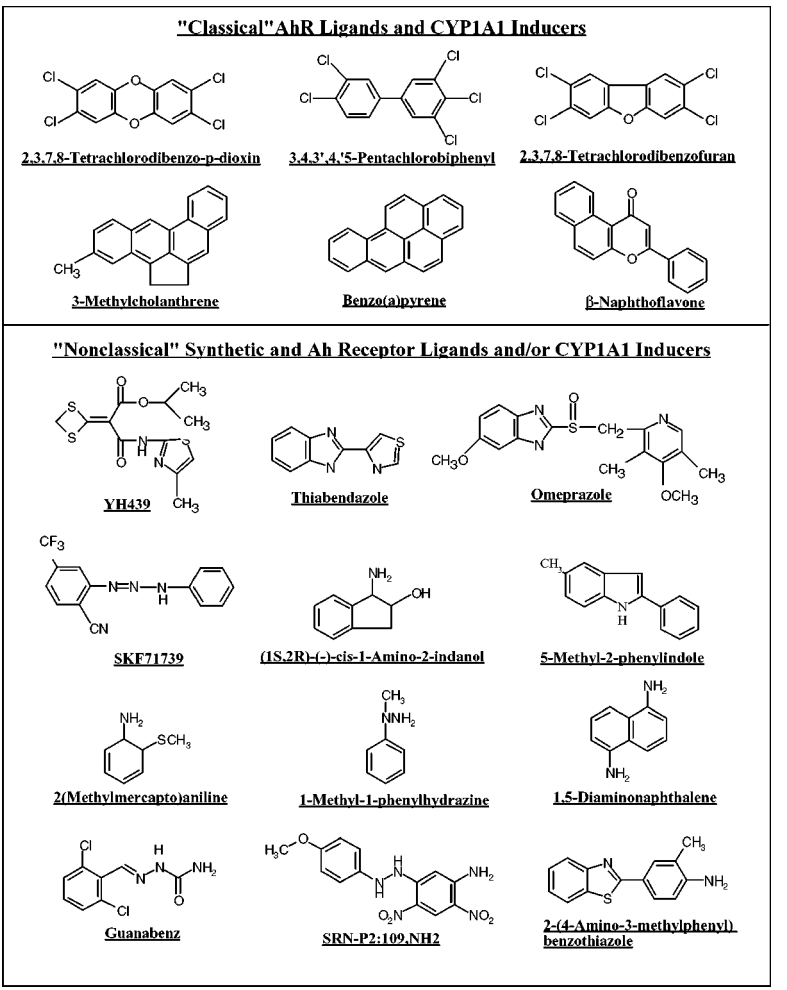

Figure 2 Structures of selected classical and nonclassical AhR ligands and inducers of AhR-dependent gene expression. See text and Reference 6 for more details.

chemical library using an AhR-responsive reporter gene system (32) has allowed identification of numerous novel AhR agonists, including several activators whose structures contain only a single unsaturated ring (33). Although the majority of the currently identified nonclassical AhR ligands/agonists are relatively weak inducers of CYP1A1 and/or low affinity AhR ligands (when compared with TCDD), the identification of this striking structural diversity of AhR ligands is important because it indicates that the spectrum of synthetic AhR ligands is likely to be much broader than was originally thought. Thus, attempts to identify endogenous and natural ligands should not be restricted by previous views of the structural requirements for AhR ligands.

NATURALLY OCCURRING DIETARY AhR LIGANDS AND INDUCERS

The greatest source of exposure of animals and humans to AhR ligands (synthetic and natural) comes from the diet. Numerous studies have described and characterized a variety of naturally occurring dietary chemicals that can directly activate and/or inhibit the AhR signaling pathway. The structures of some of these chemicals are shown in Figures 3 and 4. The earliest reports of natural Ah inducers came from observations that extracts of vegetables or vegetable-derived materials could induce CYP1A1 activity (34, 35). Subsequently, the ability of several dietary plant compounds, such as I3C (25, 35), 7,8-dihydrorutacarpine (36), dibenzoylmethanes (37), curcumin (38), and carotinoids [e.g., canthaxanthin, astaxanthin, and the apo-carotinoid, β-apo-8′carotenal (39, 40)], to competitively bind to the AhR and/or induce AhR-dependent gene expression was reported. Conversion of dietary indoles (including I3C and Trp) in the mammalian digestive tract to significantly more potent AhR ligands/agonists (Figure 3) was also demonstrated (35, 41). In fact, ICZ, an acidic condensation product formed from I3C (itself a weak AhR ligand), has perhaps the highest affinity of any "natural" AhR ligand identified to date ($\sim$0.2–3.6 nM), and it is a potent inducer of AhR-dependent gene expression in cells in culture (25, 35). 3,3′-Diindolylmethane, another acidic condensation product of I3C, is also an established AhR agonist (42). The formation of relatively potent AhR ligands from precursors that have little or no AhR agonist activity is significant, especially considering that most dietary ligands are themselves relatively weak AhR ligands/agonists. Flavonoids, including flavones, flavanols, flavanones, and isoflavones, represent the largest group of naturally occurring dietary AhR ligands. Although the majority of these natural plant products are AhR antagonists (43–47), numerous agonists, such as quercetin (48), diosmin (49), tangeritin (50), and tamarixetin (43), have also been identified. In addition to interacting with the AhR, many of these flavonoids are also substrates for CYP1A1 (51). These chemicals are widely distributed in dietary vegetables, fruits, and teas (52–55), and flavonoid levels in human blood have been reported to be in the low μM range (56–58), concentrations sufficient to inhibit/activate the AhR. Thus, it is not surprising that crude extracts of a large number of different

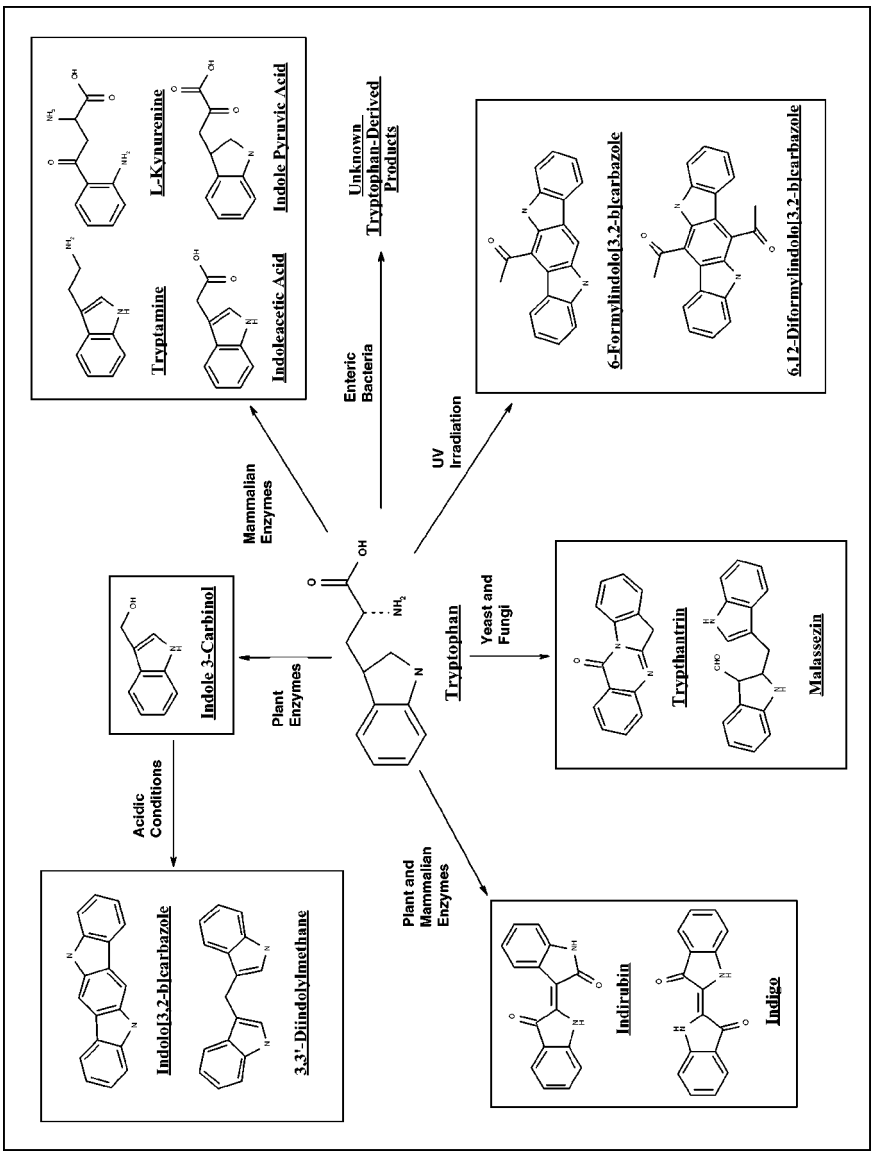

Figure 3 Tryptophan can be converted by a variety of mechanisms into AhR ligands and inducers of AhR-dependent gene expression. See text for details.

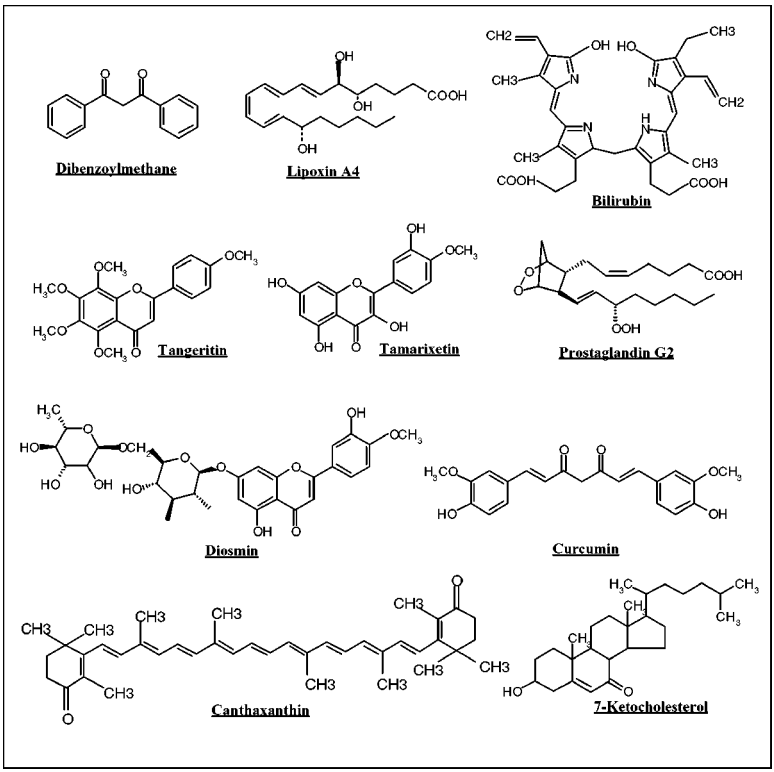

Figure 4 Structures of selected naturally occurring AhR ligands and inducers of AhR-dependent gene expression. See text for details.

vegetables, teas, fruits, and natural herbal products have AhR agonist and/or antagonist activity (59, 60). Thus, plant-derived materials appear to commonly contain AhR ligands or products that can readily be converted into AhR ligands, and as such, they are perhaps the largest class of natural AhR ligands to which humans and animals are exposed.

EVIDENCE FOR ENDOGENOUS LIGANDS FOR THE AhR

The existence of endogenous physiological AhR ligands has been suggested by numerous studies in which the AhR signaling pathway is active in the absence of exogenous ligands. The identification of nuclear AhR complexes in unexposed cells in culture and tissue slices (61–63), combined with the demonstration that disruption of AhR expression using antisense resulted in decreased development of mouse blastocysts (64) and alternations in normal cell cycle progression (65, 66), supports the existence of endogenous AhR ligands. The ability of hydrodynamic shear stress conditions (67) as well as methylcellulose suspension (68, 69) to

induce CYP1A1 in cells in culture and of hyperoxia to induce CYP1A1 in rat lungs and liver in vivo (70, 71) are consistent with the formation of an endogenous AhR ligand in these conditions. The best evidence for a role of the AhR in normal development and physiological/biochemical processes derives from the occurrence of numerous physiological changes and developmental abnormalities in AhR knockout animals (12, 72, 73). These changes are presumed to result from loss of AhR activation by an endogenous ligand, although the identity of the responsible chemical(s) remains to be determined. Recently, however, a variety of endogenous chemicals have been identified that can bind to the AhR and/or active AhR-dependent gene expression. Although the majority of these chemicals are relatively weak when compared to TCDD, these studies confirm that such ligands do exist. Not surprisingly, these endogenous activators represent several structurally distinct classes of chemicals. For this review, we have grouped these "endogenous" ligands into several categories, including indoles, tetrapyroles, AA metabolites, and other ligands. Although the role of these chemicals in AhR signaling in vivo remains to be confirmed, their ability to activate the AhR in vitro and in cells in culture suggests that they may also play a role in regulating AhR function in vivo.

Indoles

Numerous laboratories have reported activation of the AhR by indole-containing chemicals whether they are present in the diet or are endogenous substances. The majority of these AhR ligands are formed from Trp as a result of various biological and physiochemical processes (Figure 3). One of the earliest studies reported that UV illumination of tissue culture media induced aryl hydrocarbon hydroxylase, an enzymatic activity generally associated with CYP1A1, and although this effect appeared to result predominantly from histidine oxidation products, Trp was required for this response (74, 75). Subsequent studies demonstrated the ability of UV irradiation to induce CYP1A1 in the skin and liver of rats and mice (76, 77), suggesting that a diffusible AhR ligand was generated in the skin. The results of Paine and coworkers (74, 75), combined with the fact that Trp is a strong near-UV absorbing amino acid, led several groups to examine the ability of Trp photoproducts to induce CYP1A1. These studies led to the identification of several Trp photooxidation products that competitively bind to the AhR with high affinity and can activate the AhR and AhR-dependent gene expression (78–81). Rannug and coworkers (82) determined the structure of two of the photoproducts, the most active being that of FICZ, a chemical with significant structural similarity to the potent exogenous indole ligand ICZ (35). Although formation of FICZ and other photooxidation products in vivo remains to be confirmed, it was hypothesized that Trp photoproducts formed in the skin of UV irradiated animals might be responsible for the CYP1A1 induction response. The relationship between light exposure and Trp and/or Trp-metabolites is well documented. Indole acetic acid, a plant growth regulator, and its precursor, indole-3-acetaldehyde, are formed from Trp in response to light. Serotonin and melatonin, two other Trp-derived biomolecules,

are important neuroendocrine modulators; the latter of which is important in normal circadian rhythms in mammalian species. As a result of this information, it was recently proposed that FICZ and other photooxidation products of Trp may actually be novel chemical messengers of light (80). This hypothesis takes on more potential significance when one considers that other members of the PAS domain superfamily (83–85) include a variety of light-activated photoreceptors and phytochromes (photoactive yellow protein, phototrophins, phytochrome A, and others) and numerous genes involved in circadian rhythm (Clock, Per, White Collar, and others). Further work in this area may provide interesting insights into the role of these Trp photoproducts in normal endogenous signaling pathways.

The ability of other endogenous indoles and indole metabolites to bind to the AhR has also been reported by Miller and coworkers (86) and our laboratory (87). These studies demonstrated that Trp and naturally occurring Trp metabolites (tryptamine and indole acetic acid) can bind to and activate the AhR and AhR-dependent gene expression in both yeast and mammalian cells in culture. Tryptamine was also shown to be a relatively potent competitive inhibitor of CYP1A1-dependent enzymatic activity, suggesting that it may be a substrate for this enzyme (87). More recently, we have also observed that several kyneurinines, additional metabolic breakdown products of Trp, can activate the AhR signaling pathway (88). Because these chemicals are relatively weak ligands and only found at low concentration in cells, they are likely not endogenous activators in normal physiological conditions. However, if cellular concentrations of some Trp metabolites (i.e., tryptamine) are significantly elevated, as can occur during some abnormal conditions (i.e., when monoamine oxidase activity is inhibited), concentrations have been reported to reach levels that are sufficient to activate the AhR [i.e., $\sim$700 nM (89)].

Indigo and indirubin (Figure 3), two Trp metabolites isolated from human urine, were recently reported to activate the AhR in an AhR-Arnt-containing yeast cell bioassay system (90). These chemicals were reported to be extremely potent AhR agonists, with indigo and indirubin being equipotent or 50-fold more potent than TCDD, respectively. However, in mammalian cells these compounds are 50,000- to 100,000-fold less potent than TCDD as activators of the AhR signaling pathway (E. Fairbairn & M.S. Denison, manuscript in preparation). This significant difference in biological potency likely results from a combination of both their predicted metabolic lability in mammalian cells and a technical limitation of the yeast bioassay in accurately measuring the relative activity of TCDD (91). The EC_{50} for induction of AhR-dependent gene expression by TCDD is $\sim$9 nM in the yeast bioassay (90) compared to that of 6–10 pM in mammalian cells (32). In contrast, β-naphthoflavone, a PAH ligand for the AhR is only 3-fold less potent than TCDD in yeast cells (91), whereas it is 5000-fold less potent in mammalian cells (D.H. Han & M.S. Denison, unpublished results). The principal differences in the relative potency of TCDD between yeast and mammalian cells most likely results from the extreme hydrophobic character of TCDD. When TCDD is added to highly aqueous solutions, like that of yeast culture media, there would likely be a significant loss of

TCDD from the media directly onto the wall of the assay microplate. Although the concentration of indirubin and indigo in human serum remains to be established, fetal bovine serum contains ~0.07 nM indirubin, a concentration that is sufficient to activate the AhR in the yeast cell bioassay (90). Finally, it might be questioned as to whether indigo and indirubin should be considered endogenous ligands because they are predominantly derived from plants. However, because these products can also be formed from cytochrome P450- (CYP2A6, 2C19, and 2E1) dependent-metabolism of indole (92, 93) and they have been identified in the urine of patients with pathological conditions such as leukemia and porphyria cutanea tarda (94, 95), it is clear that they can be produced in human in vivo.

Tetrapyroles

The relationship between the AhR and heme biosynthetic and degradation pathways has been previously established. TCDD is known to disrupt heme biosynthesis, resulting in uroporphyria and hepatocellular damage (7, 11, 96, 97). Although the exact mechanism has not yet been defined, this effect has been proposed to result from a combination of AhR-dependent induction of CYP1A2 and the inhibition of uroporphyrin decarboxylase activity (98). In addition, TCDD treatment has also been observed to enhance the degradation of BR, the primary heme degradation product, presumably by its ability to induce AhR- and DRE-dependent expression of CYP1A1, CYP1A2, and UGT*01, enzymes that can metabolize BR. Interestingly, persistent expression of CYP1A1 in congenitally jaundiced Gunn rats that lack functional UDPGT*01 suggested the presence of endogenous AhR ligands in the blood of these animals (99). Subsequent studies demonstrated that BR (Figure 4), present in high levels in the blood of Gunn rats, can induce expression of CYP1A1 and a DRE-dependent reporter gene in a dose- and AhR-dependent manner in cultured cells (100, 101). This induction was observed using physiologically relevant concentrations of BR. In addition, BV, the metabolic precursor of BR, also induced DRE-dependent gene transcription in several species, although it is likely that it does so indirectly by serving as a metabolic precursor of BR. Subsequent experiments have demonstrated not only that BR can directly stimulate AhR transformation and DNA binding in vitro and in cells in culture, but that it is a competitive ligand for the AhR, albeit a relatively weak one (99). Thus, available evidence demonstrates that the heme degradation products BR and possibly BV are ligands and agonists of the AhR signal transduction pathway. The physiological relevance of these results is likely related to BR's ability to simulate its own metabolism. Because congenitally jaundiced Gunn rats or human infants with Crigler-Naijar syndrome type-I lack functional UGT*01, the primary BR detoxification enzyme, the ability of BR to induce expression of CYP1A1/1A2 [both of which can metabolize BR (102, 103)] provides an AhR-dependent feedback mechanism to reduce circulating levels of BR. Support for this hypothesis comes from studies in which oral administration of I3C, a naturally occurring plant product that is converted in acidic conditions in the stomach into the potent AhR

agonist ICZ, to jaundiced Gunn rats or Crigler-Naijar infants resulted in a significant reduction in plasma BR levels in both situations (104). In addition, TCDD pretreatment has been shown to enhance oxidative metabolism of BR as well as biliary excretion of BR-glutathione conjugates in Gunn rats (105). Interestingly, these and other studies (106) demonstrate the utility of AhR agonists as potential therapeutic agents.

Arachidonic Acid Metabolites

A relationship between TCDD, the AhR, and AA metabolites has also been demonstrated. TCDD can increase the release of AA from membranes as a result of its ability to stimulate membrane lipid oxidation and phospholipase A activity (107–111). In addition, it can induce AA-metabolizing cytochrome P450s [such as CYP1A1 (112–114)] as well as prostaglandin synthase H2 [PGSH2 (115, 116)], which converts AA to prostaglandins. TCDD and other AhR ligands are also reported to increase cardiac release of prostaglandins in vitro (117). These results demonstrate an effect of TCDD and the AhR pathway on AA metabolism, but the effect of AA or AA metabolites on the AhR signaling pathway has not been examined. Recently, it was proposed that AA metabolites may play a role in the hydrodynamic shear-stress induction of CYP1A1 in cells in culture (67). Furthermore, suspension of cells in culture in methylcellulose results in CYP1A1 induction (68, 69), an effect proposed to result from the production or release of an endogenous ligand, possibly from the cell membrane in response to changes in membrane conformation/structure. Given the structural diversity and general hydrophobic nature of AhR ligands, it seems reasonable to suggest that some biological lipids and/or steroids may be endogenous AhR ligands. The ability of lipoxin A4 (Figure 4), a lipoxygenase product of AA, and several prostaglandins [most notably prostaglandin G_2 (Figure 4)] to both bind to the AhR and activate AhR-dependent gene expression supports this hypothesis (118, 119). Lipoxin A4 reportedly induces a transient expression of CYP1A1 and that of a DRE-dependent reporter gene at concentrations near physiological in some situations (120) and it is a competitive substrate for CYP1A1 (118). In contrast, the prostaglandins are relatively weak AhR agonists in cells in culture (119), transiently inducing AhR-dependent gene expression only at concentrations >1 μM, much greater than their normal physiological levels (121). However, when one considers that prostaglandins are charged at physiological pH and thus have limited ability to diffuse through biological membranes (122, 123), the actual potency of these chemicals may be significantly greater than that determined in the cell culture experiments (119). It has been reported that prostaglandin concentrations may actually reach 5–10 μM in the proximity of hepatocytes due to nonparenchymal liver cells secreting these "local hormones" into the narrow space of Disse (124). Thus, select prostaglandins, or a combination of prostaglandins, may be able to activate the AhR in vivo. Perhaps the most intriguing aspect of these studies is that although the most active prostaglandins stimulate AhR transformation and DNA binding to a maximum

of 40%–60% of that obtained using TCDD, several prostaglandins induced AhR-dependent reporter gene expression up to a level three- to fivefold greater than that produced by a maximal inducing dose of TCDD (119). It was proposed that this synergistic response resulted from both a direct action on the AhR and activation of a secondary signal transduction system that augments the AhR-dependent gene expression response. Given previous studies demonstrating a synergistic increase in AhR-dependent gene expression following concomitant activation of both the AhR and protein kinase C (125, 126), it is possible that this type of signaling cross-talk mechanism may also occur with the prostaglandins. The specific cellular signaling pathway(s) affected by the prostaglandins responsible for this dramatic increase in AhR-dependent gene expression and whether other AA metabolites or related biological lipids also activate the AhR signaling pathway is currently unknown.

Other Ligands

The ability of several carotinoids [canthxanthin (Figure 4), astaxanthin, and β-apo-8′-carotinal], but not others (vitamin A, β-carotene, lypene, or lutein), to induce CYP1A1 and other members of the Ah gene battery in rats and mice has been described (39, 40, 127, 128). Although the induction of CYP1A1 in mice by carotinoids was demonstrated to be AhR dependent, neither canthaxanthin nor β-apo-8′-carotinal were observed to competitively bind to the AhR (127). Whether these chemicals are simply weak AhR ligands and unable to compete effectively with the high affinity ligand TCDD or are converted in vivo into more potent ligands/inducers remains to be determined. Dietary carotinoids are cleaved in vivo into retinol and converted into other vitamin A metabolites (retinoids), and previous studies have demonstrated a link between retinoids and the AhR signaling pathway. Not only are various retinoids known to be substrates for CYP1A1 (114, 129–131), but one of the hallmark effects of TCDD is an AhR-dependent alteration in retinoid homeostasis and metabolism, resulting in enhanced retinoid mobilization and decreased hepatic vitamin A levels (7, 11, 132). Also consistent with a role for the AhR in normal retinoid homeostasis is the observation of retinoid accumulation and decreased vitamin A metabolism in the livers of AhR knockout animals (133). This link between retinoids and the AhR, combined with the ability of retinoids to alter gene expression through the retinoid dependent RARs and retinoid X receptor, led several groups to examine the ability of retinoids to directly activate the AhR. Although the initial observation of the ability of retinoic acid to induce CYP1A1 gene expression in human but not rodent cells in culture (112, 134–136) suggested that retinoic acid may be an endogenous ligand, it was subsequently demonstrated that this induction was regulated by RARs and a functional retinoic acid responsive element present in the upstream region of the human, but not rodent, CYP1A1 gene (135). More recently, however, the ability of several synthetic retinoids to directly activate the AhR and AhR-dependent gene expression was observed (136, 137). Although the most AhR-active retinoids in

these studies had the weakest relative affinity for the RARs (136), these studies provide intriguing evidence for the possibility of retinoid or retinoid-like AhR ligands.

The suggested role of the AhR in cardiovascular disease (138–141) led Savouret and coworkers (142) to examine the ability of a series of oxysterols normally present in blood to bind to the AhR. Their analysis revealed that 7-ketocholesterol (Figure 4) could competitively bind to the AhR and function as an AhR antagonist. Ligand binding experiments indicate that the affinity of 7-ketocholesterol for the AhR is $\sim 10^5$ lower than that for TCDD; however, concentrations of 7-ketocholesterol found in blood in vivo are sufficient to inhibit TCDD-induced gene expression in cells in culture (142). Although 7-ketocholesterol is not an AhR agonist, it is possible that it may represent the first identified member of a novel group of AhR ligands in which an endogenous activator does exist.

Ligand-Dependent Versus Ligand-Independent Activation of the AhR

The AhR can be activated by a structurally diverse range of chemicals, and although the ability of many of these chemicals to directly bind to and activate the AhR remains to be confirmed, their ability to induce CYP1A1 and/or activate the AhR and AhR-regulated gene expression in animals or cells in culture indirectly supports their interaction with the AhR. Interestingly, some chemicals have been identified that can induce AhR-dependent gene expression, yet they reportedly fail to competitively bind to the AhR (Table 1). It has been proposed that these chemicals are not AhR ligands themselves, but that they can activate AhR-dependent gene expression indirectly, either via metabolic conversion into a ligand or by their ability to affect some cellular pathway that results in AhR activation. These conclusions are difficult to reconcile, especially given what is known about the AhR-dependent mechanism of gene activation. Although these weak inducers have not been observed to competitively bind to the AhR, they may still be AhR ligands, albeit ligands that bind with relatively low affinity. Demonstration of the ability of weak ligands (Kd in the μM range) to competitively bind to the AhR in standard binding assays is technically challenging, especially given the extremely high AhR binding affinity of TCDD [Kd in the pM range (143)]. Recent modifications of the AhR ligand binding assay that favor competitive binding by weak AhR ligands (i.e., reduction of [^{3}H]TCDD and increased competitor concentration) have been used to demonstrate that carbaryl, previously reported to not bind to the AhR (144, 145), is actually a weak AhR ligand (146). The 300,000-fold lower potency of carbaryl, as compared to TCDD (146), likely explains its inability to competitively displace [^{3}H]TCDD from the AhR ligand binding domain using the ligand binding assay conditions described by those investigators. In addition, the competitive binding of Trp metabolites (namely tryptamine and indole acetic acid) and several benzimidazoles (omeprazole, thiabendazole, albendazole, and

TABLE 1 Chemicals that are reported to activate the AhR and induce AhR-dependent gene expression, yet do not competitively bind to the AhR

Chemical	Reference
Omeprazole	(148, 150)
Thiabendazole	(162)
Oxfendazole	(163)
Myristicin	(164)
Methylenedioxyphenyls (isosafrole, PBO)	(157, 165)
Carbaryl	(144, 145)
Mevinolin	(166)
Canathaxanthin	(128)
β-Apo-8′-carotinal	(128)
11-Ethoxy-cyclopenta(a)phenanthrene-17-one	(167)
Primaquine	(168)
Caffeine	(169)
Cypermethrin	(170)
Diflubenzuron	(170)
Tetrachlorvinphos	(170)
Lanosperole	(171)
Nicotine	(172)
Pyridines	(173)

fenbendazole) has also been observed (87, 147), even though these chemicals were previously reported to induce AhR-dependent gene expression in a ligand independent manner (148–151). Not only are these binding results consistent with what is known about other CYP1A1 inducers and AhR activators, but it is likely that many (if not all) of the other chemicals that reportedly induce in an AhR-independent manner (Table 1) are actually weak AhR ligands. The absolute requirement for the AhR in the chemical-inducible response, combined with the demonstration that some "ligand independent" inducers actually bind to the AhR, raises questions as to the existence of these proposed alternative induction pathways. Unlike other ligand-dependent receptors (i.e., steroid hormone receptors) that can be activated in a ligand-independent manner by processes such as phosphorylation (152, 153), ligand-independent activation for the AhR remains to be confirmed. Accordingly, in our view, the available data are still consistent with the established mechanism in which the ability of a chemical(s) to activate AhR-dependent gene expression is dependent upon its interaction with the AhR ligand binding site.

CONCLUDING COMMENTS

In most biological systems, ligand binding to receptors is generally of high affinity and high chemical specificity. However, the structural diversity of AhR ligands is somewhat similar to that reported for the peroxisome proliferator activated receptor and pregnane X receptor, orphan receptors of the steroid hormone receptor superfamily that also respond to xenobiotics (154–157). Although the rather "sloppy" or promiscuous ligand binding specificity of these xenobiotic receptors may at first seem to be incompatible with their role as selective ligand-dependent receptors, a case can be made that this characteristic may actually confer some adaptive advantage to the organism. These receptors are known to induce expression of cytochrome P450s as well as that of other xenobiotic metabolizing enzymes (at least in the case of the AhR). Because activation of these receptor systems enhances expression of numerous detoxification enzymes, each of which exhibits broad substrate specificity, the promiscuous ligand binding activity of these receptors would provide the organism with a greater dynamic range of "chemical detection" and metabolism. In addition to xenobiotic-mediated induction, the promiscuous nature of AhR ligand binding could also increase the spectrum of endogenous chemicals that could activate AhR. One can imagine that distinct endogenous ligands present in different cell types could activate AhR and thus induce expression of gene products important for a desired biological activity in a cell-specific manner. Although it is possible that there is a high affinity endogenous AhR ligand, one has yet to be identified. We envision the existence of numerous endogenous physiological AhR ligands that have relatively weak affinity compared to TCDD and are rapidly degraded by the coordinately induced detoxification enzymes. Accordingly, these endogenous ligands would act as transient inducers of AhR-dependent gene expression, a situation similar to that produced by the prostaglandins (119). In fact, many AhR ligands are known substrates for CYP1A1 and/or other members of the Ah gene battery. The observation of elevated levels of AhR-dependent gene expression, as well as reduced cytosolic AhR concentrations in cells lacking CYP1A1 activity, and loss of this constitutive AhR-dependent response when CYP1A1 activity was restored are also consistent with these enzymes metabolizing an endogenous AhR ligand(s) (63, 66). Purification and characterization of the endogenous AhR inducer from CYP1A1 deficient cells and other tissues containing constitutively active AhR complexes is an interesting direction for future research.

The structural diversity of CYP1A1 inducers was first reported by Owens & Nebert (158), who demonstrated the ability of numerous hydrophobic compounds to induce CYP1A1-associated enzyme activity. Although the list of inducers has expanded greatly since that time, the actual spectrum of chemicals that can bind to and activate the AhR is still an area of ongoing research. Elucidation of the spectrum of physiochemical and structural characteristics of AhR ligands may provide insights into the identity of other exogenous and endogenous ligands for the AhR. The recent development of several very sensitive, rapid, and high throughput AhR-based screening bioassay systems (32, 159, 160) now provides avenues in

which to identify, isolate, and characterize AhR ligands from a variety of matrices and biological samples. Although tissue fractionation approaches had failed to identify endogenous ligands in the past, the increased sensitivity of these new screening bioassays should improve chances of identifying these ligands. Similar cell bioassay approaches have been successfully utilized to identify endogenous ligands for orphan nuclear receptors (161). In addition, the recently published homology model of the murine AhR ligand binding site (162) will now allow detailed modeling studies of the binding and specificity of these diverse ligands to the AhR. These are exciting areas for future studies. Overall, identification and characterization of the spectrum of endogenous and exogenous ligands of the AhR will provide insights into the biochemical and molecular mechanisms by which ligands can activate the AhR signaling pathway, but they will also facilitate studies into the endogenous role of this novel receptor system.

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