Bull. Environ. Contam. Toxicol. (1998) 61:557-568

Bulletin of Environmental Contamination and Toxicology

The Ah Receptor: A Regulator of the Biochemical and Toxicological Actions of Structurally Diverse Chemicals

M. S. Denison, S. Heath-Pagliuso

Department of Environmental Toxicology, Meyer Hall, University of California, Davis, CA 95616, USA

Received: 27 July 1998/Accepted: 5 October 1998

Halogenated aromatic hydrocarbons (HAHs), such as polychlorinated-dibenzo-p-dioxins (PCDDs), biphenyls (PCBs) and dibenzofurans (PCDFs), and related compounds represent a diverse group of widespread environmental contaminants. PCDD and PCDF formation has been demonstrated to occur during synthesis of various organochlorine products (such as the herbicide 2,4,5-T), as a result of chlorine bleaching of wood pulp, during municipal, hospital and industrial waste incineration, metal production and fossil fuel or wood burning and other sources (Safe 1990; Devito and Birnbaum 1994). PCBs, on the other hand, were produced commercially in extremely large quantities for use in transformers, capacitors, heat transfer and hydraulic fluids and other applications. HAHs represent a class of toxic environmental chemicals which, because of their ubiquitous distribution, fat solubility, resistance to biological and chemical degradation and potential for bioaccumulation and biomagnification, can persist for long periods of time and thus can have a significant impact on the health and well being of humans and animals (Safe 1990; Devito and Birnbaum 1994; Giesy et al. 1994).

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, dioxin), the prototypical and most potent HAH, has gained widespread attention in recent years as one of the most toxic chemicals known. The long biological half-life of TCDD (up to 10 years in humans) and other HAHs, combined with their extremely high toxicity in animals has made them the focus of intensive research for more than 20 years. As presented in Table 1, exposure to TCDD and related HAHs produces a wide variety of species- and tissue-specific toxic and biological effects (Safe 1990; Devito and Birnbaum 1994; Giesy et al. 1994; Hankinson 1995; Safe 1995; Hardell et al. 1994; Brouwer et al. 1994). Although all of these effects have been documented to occur in various animal species, chloracne is the best characterized response to TCDD and related HAHs in humans. More recently, an increase in human cancers and the occurrence of some developmental learning defects in children exposed to HAHs *in utero* has been reported (Hardell et al. 1994; Brouwer et al. 1994). Although the toxicological and biological effects of HAHs in humans are still a matter of intense debate, ongoing epidemiological studies in HAH exposed human populations exposed to HAHs should provide more definitive information as to the human health effects of these chemicals.

Biochemical Action of the Ah Receptor

In order to dissect the molecular mechanism of TCDD/HAH action, investigators have focused their efforts on biochemical responses that are consistently observed

Correspondence to: M. S. Denison

in all species exposed to these chemicals, namely the induction of gene expression. Although these chemicals induce expression of a battery of genes (Table 1), the induction of CYP1A1 and its gene product cytochrome P4501A1 has been used as a model system to define the mechanism of action of HAHs. Biochemical and genetic evidence has indicated that the biochemical mechanism of action of TCDD and related chemicals (HAHs and PAHs (polycyclic aromatic hydrocarbons)) is mediated by the aryl hydrocarbon (Ah) receptor (AhR), an intracellular receptor to which these chemicals bind with high affinity (Figure 1). Mechanistically, the inducing chemical diffuses across the plasma membrane and binds to the AhR complex present in the cytoplasmic compartment. Following ligand binding, the AhR complex undergoes transformation, during which it is released from proteins to which it is associated (including at least two molecules of a heat shock protein of 90 kDa (hsp90) and an additional 37 kDa AhR interacting protein (AIP) (Ma and Whitlock 1997). Liganded AhR complexes subsequently translocate into the nucleus and following their association with the nuclear Arnt (AhR nuclear translocator) protein, and possibly other factors, the AhR complex is converted into its high affinity DNA binding form. The binding of the transformed heteromeric TCDD:AhR complex to its specific DNA recognition sequence, the dioxin responsive element (DRE), upstream of the CYP1A1 gene (as well as other responsive genes), leads to DNA bending, chromatin and nucleosome disruption, increased promoter accessibility and increased CYP1A1 gene transcription (Hankinson 1995; Denison and Whitlock 1995; Whitlock 1996).

Table 1. Species and Tissue-Specific Toxic and Biological Effects Produced by TCDD[a]

· Immunotoxicity	· Induction of Gene Expression
Thymic Involution	Cytochrome P4501A1/2
Immune Suppression	Cytochrome P4501B1
· Dermal Toxicity	Glutathione S-Transferase Ya
Hyperkeratosis	Quinone Reductase
Chloracne	Aldehyde Dehydrogenase 3
· Lethality	UDP-Glucuronosyl Transferase 1*06
· Tumor Promotion	γ-Aminolevulinic Acid Synthase
· Porphyria	Prostaglandin Endoperoxide H Synthase 2
· Wasting Syndrome	Interleukin 1β
· Hepatotoxicity	· Endocrine Disruption
· Teratogenicity	Alterations in Endocrine Homeostasis
Cleft Palate	Reduction in Steroid -Dependent Responses
Hydronephrosis	· Modulation of Cell Growth,
Pericardial Edema	Proliferation and Differentiation
Embryotoxicity	· Modulation of Gap Junction

a. Safe 1990, 1995; Devito and Birnbaum 1994; Hankinson 1995.

Toxicological Actions of the Ah Receptor

In addition to its role in modulating the induction of gene expression, numerous studies also support a role for the AhR in mediating HAH toxicity. Structure-activity relationship studies using a variety of inbred strains of mice which differ in

their AhR functionality and HAH responsiveness have revealed that the ability of PCDDs, PCBs, PCDFs and other HAHs to bind to the AhR not only correlates well with their ability to induce gene expression but also their ability to produce toxicity (Safe 1990; Safe 1995). These data combined with the apparent lack of TCDD-inducible biochemical and toxic effects in AhR-knockout mice (Fernandez-Salguero et al. 1996), strongly support the hypothesis that TCDD-like HAHs exert both their biological and toxic effects via AhR. The presence of an AhR complex in a wide variety of species and tissues (Bank et al. 1992; Hahn et al. 1994, Denison et al. 1991) and its ability to act as a ligand-dependent DNA-binding transactivator of gene expression suggests that many of the toxic and biological effects these chemicals result from differential alteration of gene expression in susceptible cells.

The toxic and biological responses mediated by AhR are not only species- and tissue- specific, but they are also ligand-specific. Although all of the high affinity AhR ligands identified to date (HAHs and PAHs) are planar hydrophobic molecules and are able to induce gene expression in an AhR-dependent manner, PAHs are unable to produce the spectrum of toxic effects observed following exposure to TCDD/HAHs. This difference in toxic potency is likely due to a combination of the higher AhR binding affinity of HAHs (in the pM to nM range for HAHs, compared to nM to mM for PAHs) and the increased resistance of HAHs to metabolic degradation, which results in sustained AhR occupancy by HAHs and persistent activation of gene expression. Given that many of the toxic effects of TCDD/HAHs (wasting and thymic involution) are not observed until several days to weeks following chemical exposure (Devito and Birnbaum 1994), the adverse effects of these chemicals likely result from the continuous and inappropriate expression of specific genes in responsive cells which ultimately results in the delayed toxic responses. Implicit in this hypothesis is the concept that if the concentrations of a PAH AhR ligand are maintained at appropriately high levels within an organism then toxic effects similar to that produced by TCDD should be observed. Consistent

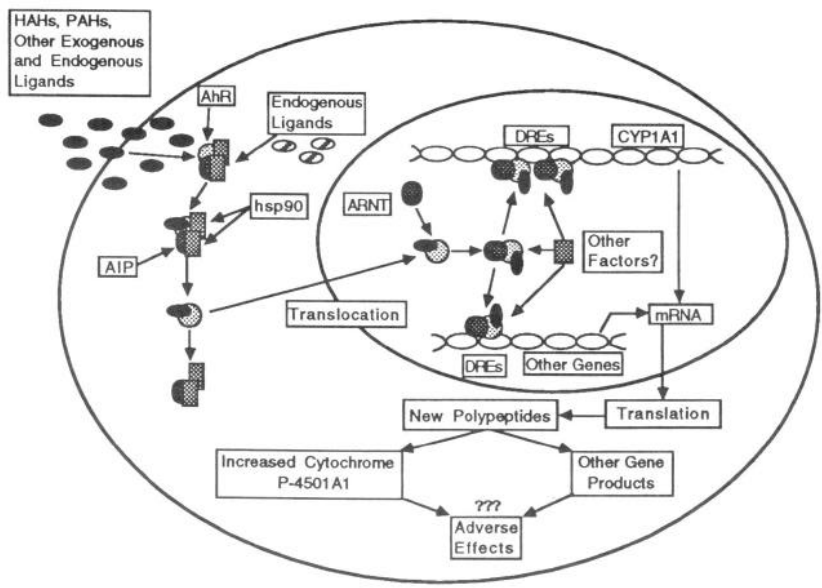

Figure 1. Molecular mechanism of induction of gene expression by Ah receptor ligands. See text for details.

with this hypothesis, a recent study reported that juvenile catfish continually exposed for 90 days to high dietary levels of β-naphthoflavone, a prototypical PAH AhR ligand, exhibited a variety of morphological and toxicological effects similar to those produced by exposure to TCDD (Grady 1992). Although significant advances in the field over the past 10 years have clearly defined the role of AhR in the toxic and biological effects of HAHs and PAHs, the exact biochemical events which lead to the spectrum of species- and tissue-specific toxic responses to these chemicals still remain to be elucidated.

"Classical" AhR Ligands and Ah Inducers

Extensive quantitative structure-activity relationship studies examining the binding of "classical" ligands (primarily HAHs and PAHs) to AhR (Safe 1990; Gillner et al. 1993; Waller and McKinney 1995; Kafafi et al. 1993) and these studies have allowed limited modeling of the AhR ligand binding site. Three dimensional molecular volume mapping and physiochemical characterization studies using a large number of HAH and PAH ligands not only suggest that planar, aromatic and hydrophobic ligands with maximal dimensions of 14 Å x 12 Å x 5 Å can fit into the ligand binding pocket, but that high affinity binding of chemicals to the AhR is also critically dependent upon their electronic and thermodynamic properties (Waller and McKinney 1995; Kafafi et al. 1993). Because of the extensive analysis that has been carried out on the “classical” AhR ligands, it is commonly believed that AhR ligands must share many of the common physiochemical characteristics of these chemicals. Although the results of these AhR modeling studies have provided some information useful for the identification of new AhR ligands, the constraints of the currently defined model are too simplistic, especially given that only HAHs and PAHs were used in these studies, the recent identification and characterization of “nonclassical” AhR ligands and Ah inducers (inducers of AhR regulated genes) and the fact that the majority of the binding data for the modeling studies were derived primarily from a single species. Significant species differences in the ligand binding affinity and rank order potency of binding of a given chemical to the AhR, combined with the recent identification of species-specific differences in the specificity of ligand binding (Denison et al. 1986; Aarts et al. 1996; Kikuchi et al. 1996), raise concerns about the similarities of the AhR ligand binding site across species.

“Non-Classical” AhR Ligands And Inducers

The physiochemical and structural information derived from analysis of HAH/PAH AhR ligands has provided valuable insights on AhR ligand structure, however, these structural preconceptions have also hampered the search for novel classes of exogenous and endogenous ligands which may deviate greatly from the planar, aromatic and hydrophobic nature of “classical” AhR ligands. A significant amount of information has become available in recent years which suggests that the above “dogma” is not entirely correct and that the AhR can be bound and/or activated by “novel” chemicals whose structural and physiochemical properties are inconsistent with currently defined structural requirements for AhR ligands (Table 2 and Figure 2). Although the majority of these chemicals are relatively weak inducers or AhR ligands, when compared with TCDD, their striking structural diversity is clearly evidenced by comparison of the structure of TCDD to that of several inducers in this category (Figure 2). Interestingly some of the synthetic “nonclassical” chemicals, such as the methylenedioxybenzenes, benzimidazole

Table 2. AhR Ligands and/or Inducers of Gene Products Regulated by the AhR.

Chemicals	References
"Classical" AhR ligands and Ah Inducers	
Dibenzo-p-dioxins	Safe, 1990, Waller and McKinney, 1995
Dibenzofuran	Safe, 1990; Waller and McKinney, 1995
Biphenyls	Safe, 1990; Waller and McKinney, 1995
Diphenyl Ethers	Becker et al., 1991
Substituted PAHs	Gillner et al., 1993
Substituted Flavones	Gasiewicz et al., 1996
"Non-Classical" AhR ligands and Ah Inducers	
Synthetic	
Methylenedioxybenzenes	Marcus et al., 1990
Imidazoles and Pyridines	Quattrochi and Tukey, 1993; Kobayashi et al., 1993; Lesca et al. 1995
2-(4'-Chlorophenyl)-benzothiazole	Karenlampi et al., 1989
1,3-Diaryltriazenes	Sweatlock and Gasiewicz, 1986
Thiazolium Compound YH439	Lee et al., 1996
2,3-Diaminotoluene	Cheung et al., 1996
"Natural"	
Indoles	
Indole 3-Carbinol	Gillner et al, 1993; Bjeldanes et al., 1991
Indolo-[3,2]-Carbazole	Gillner et al, 1993; Bjeldanes et al., 1991
Tryptophan-derived Products	Perdew and Babbs, 1991; Helferich and Denison, 1991, 1997; Rannug et al., 1995
Oxidized Carotinoids	Gradelet et al., 1996
Heterocyclic Amines	Kleman et al., 1992
Brevetoxin (PbTX-6)	Washburn et al., 1997

drugs and the pesticide Carbaryl, induce CYP1A1 gene expression but do not appear to bind to AhR in competitive assays (Marcus et al. 1990; Lesca et al. 1995; Ledirac et al. 1997). This is difficult to reconcile, especially given what is known about the AhR-dependent nature of the induction of CYP1A1. From a technical standpoint, demonstration of the ability of weak ligands to competitively bind to AhR has been difficult, especially given the extremely high AhR binding affinity of TCDD. In fact, modification of the AhR ligand binding assay to allow direct measurement of competitive binding by lower affinity ligands (i.e. by reducing the concentration of [^{3}H]TCDD and increasing competitor concentrations) has direct competitive AhR binding of various methylenedioxybenzenes, benzimidazole drugs and Carbaryl (Denison et al., unpublished observations). Thus, consistent with what we know about other CYP1A1 inducers, these “non-classical” synthetic chemicals are AhR ligands (albeit weak inducers/ligands) and they activate gene expression in an AhR-dependent manner.

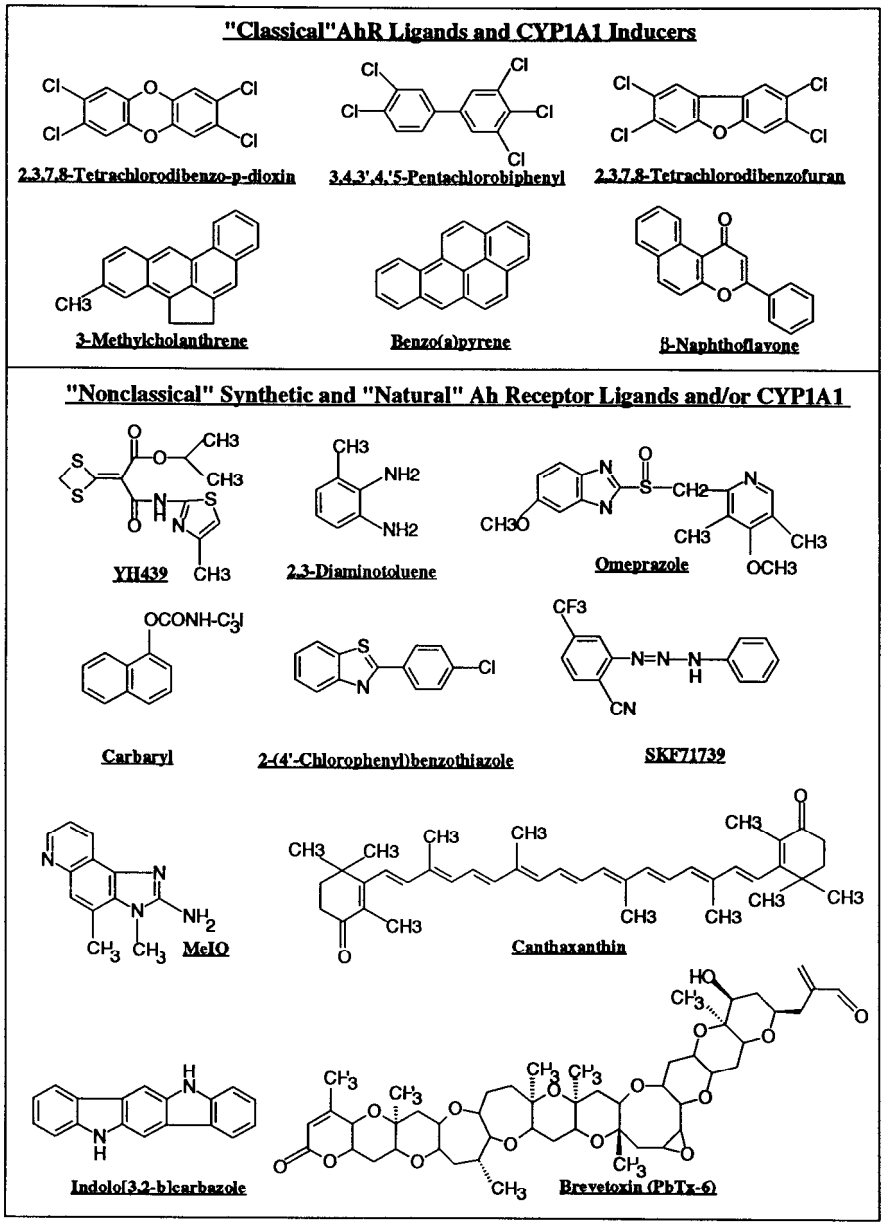

Figure 2. Structures of selected AhR ligands and/or inducers of AhR-dependent gene products.

In addition to the above synthetic "non-classical" ligands, several classes of "natural" chemicals which can bind to the AhR, activate AhR transformation and DNA binding and/or induce AhR-dependent gene expression have also been

identified (Table 2 and Figure 2). Like the "nonclassical" synthetic ligands, these chemicals are also relatively weak ligands and inducers, compared to TCDD. The ability of several dietary plant compounds such as indole-3-carbazole (I3C) (Bjeldanes et al. 1991), other indoles and flavones, the oxidized carotinoids, canthaxanthin and astaxanthin (Gradelet et al. 1996) and heterocyclic amines (formed during cooking of meat) to bind to AhR and/or induce AhR-dependent gene expression have been reported. Conversion of dietary indoles (including I3C and tryptophan) in the mammalian digestive tract to significantly more potent AhR ligands (Bjeldanes et al. 1991; Perdew and Babbs 1991), as well as conversion of tryptophan by UV light into several products which bind to AhR with high affinity (Helferich and Denison 1991; Rannug et al. 1995) have also recently been described. Indolo-[3,2-b]-carbazole (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 (~0.2-3.6 nM) and it is a potent inducer of AhR-dependent gene expression in humans and animals (Bjeldanes et al. 1991). More recently, we have determined that endogenous water soluble metabolites of tryptophan, namely tryptamine and indole acetic acid, can not only bind to AhR but also exhibit full AhR agonist activity (Denison et al. 1997). Thus, indoles and indole-derived products represent a major class of “natural” AhR ligands.

Overall, the ability of a wide range of structurally diverse "nonclassical" chemicals to bind to AhR, activate AhR dependent DNA binding and/or induce CYP1A1 gene expression, clearly demonstrates that a greater spectrum of chemicals can interact with and activate this receptor than previously thought. In addition to a variety of synthetic chemicals, there exists at least two classes of "natural" AhR ligands, those of which are endogenous physiological compounds and those of which are dietary in nature. Because most of these “non-classical” chemical structures do not tit the established structural characteristics for known AhR ligands, their identification as ligands supports a reevaluation of the currently accepted views of AhR ligand structure.

Evidence for the Existence of Endogenous Physiologid Ah Receptor Ligands

Several "naturally-occurring" AhR ligands have recently been identified, however, no high affinity physiological endogenous ligand has yet been reported. Activation of AhR-dependent processes in animals and cells in culture in the absence of exogenously added ligand has been observed (Sadek and Allen-Hoffman 1994; Ma and Whitlock 1996; Weiss et al. 1996), and if we assume that AhR activation requires ligand, these observations can be interpreted as indirect evidence for the existence of an endogenous AhR ligand(s). Interestingly, these studies not only suggest the existence of an endogenous AhR activator(s) and support its involvement in the induction of xenobiotic metabolism, but they indicate a role for the AhR in cell proliferation and differentiation and in cell cycle programming. Perhaps the best evidence for an endogenous AhR ligand in animals comes from studies using AhR knockout mice (Fernandez-Salguero et al. 1995; Schmidt et al. 1996). The presence of a spectrum of hepatic defects as well as subtle changes in immune function and effects in other tissues in these AhR(-/-) animals, strongly support a role for the AhR in normal developmental processes. It is presumed that this activation must be mediated by an endogenous physiological ligand present in these specific tissues.

Structural diversity in AhR Ligand Binding: Implications for AhR-Dependent Biomarkers and Bioassays

Numerous aspects of the AhR-dependent mechanism of action (gene expression, keratinization, porphyrin accumulation and AhR ligand/DNA binding) have been developed for use as biomarkers in wildlife (as an indirect indicator of exposure of an organism to HAHs/PAHs) as well as in cells in culture (as a mechanism for rapid detection and characterization of putative AhR ligands). The induction of cytochrome P4501A1-dependent ethoxymsorufm-O-deethylase (EROD) activity in the tissues of laboratory or sentinel animals or in cells in culture is the AhR-specific response that has been used most extensively (Safe 1990; Giesy et al. 1994). Although measurement of the induction of AhR-dependent gene expression in these systems is generally a good indicator of whether a biological system has been exposed to HAHs/PAHs-type chemicals, the promiscuous nature of AhR ligand binding, raises some concerns as to its absolute specificity for use as a biomarker of HAH/PAH exposure/effect. One can envision a situation in which elevated levels of EROD activity observed in an sentinel or test species could be due to chemicals other than HAHs/PAHs (such as exposure to significant levels of dietary AhR ligands). On the other hand, knowledge about the spectrum of chemicals which can interact with AhR could provide some insight into some of the discrepancies commonly found between levels of HAHs/PAHs and EROD activities in test species from environmental exposure studies. The relative contribution of these "non-classical" AhR ligands to the overall level of gene expression and/or other AhR-dependent effects in animals and humans remains to be examined.

Conclusions

In most biological systems, ligand binding to receptors are generally of high affinity and high chemical specificity. While it has been generally accepted that ligands for AhR are planar, aromatic and hydrophobic molecules which conform to defined structural and electronic characteristics, AhR actually contains a rather "sloppy" or promiscuous ligand binding site. Although at first this might seem to be incompatible with its role as a selective ligand-dependent receptor, a case can be made that this actually confers some adaptive advantage to the organism. If one considers that exposure to AhR ligands induces expression of a variety of distinct detoxification enzymes, each of which exhibits its own broad substrate specificity, the existence of a specific regulatory protein that can recognise and be activated by a spectrum of structurally-diverse chemicals could greatly increase the rate at which these chemicals could be metabolized/detoxified. This would ultimately provide the organism with a greater range of protection from toxic xenobiotics. In fact, many of the AhR ligands identified here are known substrates for P4501A1 and/or other AhR induced genes.

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 to a similar degree and thus induce expression of gene products important for a desired biological activity in a cell-specific manner. We envision that the endogenous physiological AhR ligands have relatively weak affinity, compared to TCDD, and are rapidly degraded by the coordinately induced detoxification enzymes and as such, they would act as transient inducers. In fact, experiments suggesting that inhibition of CYP1A1

activity results in accumulation of an endogenous AhR ligand (Weiss et al. 1996) are compatible with this hypothesis. Application of AhR-based screening techniques for the identification and characterization of new AhR ligands will not only provide us with greater insight into the spectrum of chemicals which can bind to AhR, but structure-activity analysis should provide clues pertaining to the identification of endogenous AhR ligands. Knowledge about the endogenous ligands of AhR and the specific genes which are regulated by this protein in different tissues will not only provide insights into the biochemical and molecular mechanism by which TCDD and related chemicals produce their diverse species and tissue-specific effects, but they will also define the importance of this receptor system in relationship to human health.

Acknowledgments. Our work in this area was supported by the National Institutes of Environmental Health Sciences (ES-07072, ES-07685 and Center Grant ES05707), a NIEHS Superfund Basic Research Grant (ES04699) and the California Agricultural Experiment Station.

REFERENCES

Aarts JMMJG, Denison MS, Cox MA, Schalk MAC, Garrison PM, Tullis K, deHaan LHJ and Brouwer A (1996) Species-specific antagonism of Ah receptor action by 2,2',5,5'-tetrachloro- and 2,2',3,3',4,4'-hexachlorobiphenyl. Eur J Pharm 293: 463-474.

Bank PA, Yao EF, Phelps CL, Harper PA and Denison MS (1992) Species-specific binding of transformed Ah receptor to a dioxin responsive transcriptional enhancer. Eur J Pharm 258: 85-94.

Becker M, Phillips T and Safe S (1991) Polychlorinated diphenyl ethers - a review. Toxicol Environ Chem 33: 189-200.

Bjeldanes LF, Kim J-L, Grose KR, Bartholomew JC and Bradfield CA (1991) Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol in vitro and in vivo: comparisons with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Proc Natl Acad Sci 88: 9543-9547.

Brouwer A, Ahlborg UG, van den Berg M, Birnbaum LS, Boersma RE, Bosveld B, Denison,MS, Hagmar L, Holene E, Huisman M, Jacobson SW, Jacobson JL, Koopman-Esseboom C, Koppe J.G, Kulig BM, Morse DC, Muckle G, Peterson RE, Sauer PJJ, Seegal RF, Smit-van Prooije AE, Touwen BCL, Weisglas-Kuperus N and Winneke G (1994) Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. Eur J Pharm 293: 1-40.

Cheung Y-L, Snelling J, Mohammed NND, Gray TJB and Ioannides C (1996) Interaction with the aromatic hydrocarbon receptor, CYP1A induction, and mutagenicity of a series of diaminotoluenes: implications for their carcinogenicity. Toxicol Appl Pharm 139: 203-211.

Denison, MS, Phelps CL, DeHoog J, Kim HJ. Bank PA, Harper PA and Yao EF (1991) Species variation in Ah receptor transformation and DNA binding. In: Gallo, MA, Scheuplein, RJ and Van Der Heijden, KA (eds) Biological Basis of Risk Assessment of Dioxins and Related Compounds, Banbury Report No. 35. Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York. p 337.

Denison MS, Tullis K, Rogers WJ and Heath-Pagliuso S (1997) Tryptamine and indole acetic acid are endogenous water soluble metabolites of tryptamine that are weak AhR ligands. The Toxicologist, 6, 128.

Denison MS, Vella LM and Okey AB (1986) Structure and function of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: species differences in

molecular properties of the receptor from mouse and rat hepatic cytosol. J Biol Chem 261: 3987-3995.
Denison MS and Whitlock JP, Jr (1995) Xenobiotic-inducible transcription of cytochrome P450 genes. J Biol Chem 270: 18175-18178.
Devito MJ and Birnbaum LS (1994) Toxicology of dioxins and related chemicals. In: A. Schecter, (ed) Dioxins and Health, Plenum Press, New York p 139.
Fernandez-Salguero P, Hilbert D, Rudikoff S, Ward J and Gonzalez F (1996) Aryl-hydrocarbon receptor-deficient mice are resistant to 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced toxicity. Toxicol Appl Pharm 140: 173-179.
Fernandez-Salguero P, Pineau T, Hilbert DM, McPhail T, Lee SST. Kimura S, Nebert DW, Rudikoff S, Ward JM and Gonzalez FJ (1995) Immune system impairment and hepatic fibrosis in mice lacking the dioxin-binding Ah receptor. Science 268: 722-726.
Gasiewicz TA. Kende AS, Rucci G, Whitney B and Willey JJ (1996) Analysis of structural requirements for Ah receptor antagonist activity: ellipticines, flavones, and related compounds. Biochem Pharm 52: 1787-1803.
Giesy JP, Ludwig JP and Tillitt DE (1994) Dioxins, dibenzofurans, PCBs and wildlife. In: A. Schecter (ed) Dioxins and Health, Plenum Press, New York p 249.
Gillner M, Bergman J, Cambillau C, Alexandersson M, Fernstrom B and Gustafsson J-A (1993) Interactions of indolo[3,2-b]carbazoles and related polycyclic aromatic hydrocarbons with specific binding sites for 2,3,7,8-tetrachlorodibenzo-p-dioxin in rat liver. Molec Pharm 44: 336-345.
Gradelet S, Astorg P, Leclerc J, Chevalier J, Vemevaut,M-F and Siess M-H (1996) Effects of canthaxanthin, astaxanthin, lycopene and lutein on liver xenobiotic-metabolizing enzymes in the rat. Xenobiotics 6: 49-63.
Grady AW, Fabacher DL, Frame G and Steadman BL (1992) Morphological deformities in brown bullheads administered dietary β-naphthoflavone. J Aquat Animal Health 4: 7-16
Hahn ME, Poland A, Glover E and Stegeman JJ (1994) Photoaffinity labeling of the Ah receptor: phylogenetic survey of diverse vertebrate and invertebrate species. Arch Biochem Biophys 310: 218-228.
Hankinson O (1995) The aryl hydrocarbon receptor complex. Ann Rev Pharm Toxicol 35: 307-340.
Hardell L, Eriksson M, Axelson O and Hoar Zahm S (1994) Cancer epidemiology. In: A. Schecter (ed) Dioxins and Health, Plenum Press, New York p 525.
Helferich W and Denison MS (1991) Photooxidized products of tryptophan can act as dioxin agonists. Molec Pharm 40: 674-678.
Kafafi SA, Afeefy HY, Said HK and Kafafi AG (1993) Relationship between aryl hydrocarbon receptor binding, induction of aryl hydrocarbon hydroxylase and 7-ethyoxyresorufin o-deethylase enzymes and toxic activities of aromatic xenobiotics in animals. A new model. Chem Res Toxicol 6: 328-334.
Karenlampi SO, Tuome K, Korkalainen M and Raunio H (1989) 2-(4'-Chlorophenyl) benzothiazole is a potent inducer of cytochrome P4501A1 in a human and a mouse cell line. J Biochem 181: 143-148.
Kikuchi H, Kato H, Mizuno M, Hossain A, Ikawa S, Miyazaki J. and Watanabe M (1996) Differences in inducibility of CYP1A1-mRNA by benzimidazole compounds between human and mouse cells: evidences of a human-specific signal transduction pathway for CYP1A1 induction. Arch Biochem Biophys 334: 235-240.

Kleman MI, Overvik E, Mason GGF and Gustafsson J-A (1992) In vitro activation of the dioxin receptor to a DNA-binding form by food-borne heterocyclic amines. Carcin. 13: 1619-1624.

Kobayashi Y, Matsuura Y, Kotani E, Fukuda T, Aoyagi T, Tobinaga S, Yoshida T and Kuroiwa Y (1993) Stuctural requirements of the induction of hepatic microsomal cytochrome P450 by imidazole- and pyridine-containing compounds in rats. J Biochem 114: 697-701.

Ledirac N, Delescluse C, de Sousa G, Pralavorio M, Lesca P, Amichot M, Berge JB and Rahmani R (1997) Carbaryl induces CYP1A1 gene expression in HepG2 cells and HaCaT cells but is not a ligand of the human hepatic Ah receptor. Toxicol Appl Pharm 144: 177-182.

Lee IJ, Jeong KS, Roberts BJ, Kallarakal AT, Fernandez-Salguero P, Gonzalez FJ and Song BJ (1996) Transcriptional induction of the cytochrome P4501A1 gene by a thiazolium compound, YH439, Molec Pharm, 49: 980-988.

Lesca P, Peryt B, Larrieu G, Alvinerie M, Galtier P, Daujat M, Maurel P and Hoogenboom L (1995) Evidence for the ligand-independent activation of the Ah receptor. Biochem Biophys Res Comm 209,474-482.

Ma Q and Whitlock JP Jr. (1996) The aromatic hydrocarbon receptor modulates the Hepa 1c1c7 cell cycle and differentiated state independently of dioxin. Molec Cell Biol 16: 2144-2150.

Ma Q and Whitlock JP Jr. (1997) A Novel Cytoplasmic Protein That Interacts with the Ah Receptor, Contains Tetratricopeptide Repeat Motifs, and Augments the Transcriptional Response to 2,3,7,8-Tetrachlorodibenzo-p-dioxin. J Biol Chem 14: 8878-8884.

Marcus CB, Wilson, NM, Jefcoate CR, Wilkinson CF and Gmiecinski CJ (1990) Selective induction of cytochrome P450 isozymes in rat liver by 4-n-alkyl-methylenedioxybenzenes. Arch Biochem Biophys 277: 8-16.

Perdew GH and Babbs CF (1991) Production of Ah receptor ligands in rat fecal suspensions containing tryptophan or indole-3-carbinol. Nutr Cancer 16: 209-218.

Quattrochi LC and Tukey RH (1993) Nuclear uptake of the Ah (dioxin) receptor in response to omeprazole: transcriptional activation of the human CYP1A1 gene. Molec Pharm 43: 504-508.

Rannug U, Rannug A, Sjoberg U, Li H, Westerhold R and Bergman A (1995) Structure elucidation of two tryptophan-derived, high affinity Ah receptor ligands. Curr Biol 2: 841-845.

Sadek CM and Allen-Hoffman BL (1994) Suspension-mediated induction of hepalclc7 CYP1a-1 expression is dependent on the Ah receptor signal transduction pathway. J Biol Chem 269: 31505-31509.

Safe S (1990) Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). Crit Rev Toxicol 21: 51-88.

Safe S (1995) Modulation of gene expression and endocrine response pathways by 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds. Pharm Therap 67: 247-281.

Schmidt J, Su G, Reddy J, Simon, M. and Bradfield, C. (1996) Characterization of a murine Ahr null allele: Involvement of the Ah receptor in hepatic growth and development. Proc Natl Acad Sci 93: 6731-6736.

Sweatlock JA and Gasiewicz TA (1986) The interaction of 1,3-diaryltriazenes with the Ah receptor. Chemosphere 15: 1687-1690.

Waller CL and McKinney JD (1995) Three-dimensional quantitative structure-activity relationships of dioxins and dioxin-like compounds: model validation and Ah receptor characterization. Chem Res Toxicol 8: 847-858.

Washburn BS. Rein KS, Baden DG. Walsh PJ, Hinton DE, Tullis K and Denison MS (1997) Brevetoxin (PbTx-6), a nonaromatic marine neurotoxin is a ligand of the aryl hydrocarbon receptor. Arch Biochem Biophys 343: 149-156.

Weiss C, Kolluri SK, Kiefer F and Gottlicher M (1996) Complementation of Ah receptor deficiency in hepatoma cells: negative feedback regulation and cell cycle control by the Ah receptor. Exper Cell Res 226: 154-163.

Whitlock JP Jr., Okino S, Dong L, Ko H, Clarke-Katzenberg R, Ma Q and Li H (1996) Induction of cytochrome P4501A1: a model for analyzing mammalian gene transcription. Faseb J 10: 809-818.