Environ Sci Pollut Res (2013) 20:1219–1224
DOI 10.1007/s11356-012-1203-7

REVIEW ARTICLE

Predicting the sensitivity of fishes to dioxin-like compounds: possible role of the aryl hydrocarbon receptor (AhR) ligand binding domain

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Received: 7 June 2012 / Accepted: 14 September 2012 / Published online: 11 October 2012

Abstract Dioxin-like compounds are chronically toxic to most vertebrates. However, dramatic differences in sensitivity to these chemicals exist both within and among vertebrate classes. A recent study found that in birds, critical amino acid residues in the aryl hydrocarbon receptor (AhR) ligand binding domain are predictive of sensitivity to dioxin-like compounds in a range of species. It is currently unclear whether similar predictive relationships exist for fishes, a group of animals at risk of exposure to dioxin-like compounds. Effects of dioxin-like compounds are mediated through the AhR in fishes and birds. However, AhR dynamics are more complex among fishes. Fishes possess AhRs that can be grouped within at least three distinct clades (AhR1, AhR2, AhR3) with each clade possibly containing multiple isoforms. AhR2 has been shown to be the active form in most teleosts, with AhR1 not binding dioxin-like compounds. The role of AhR3 in dioxin-like toxicity has not been established to date and this clade is only known to be expressed in some cartilaginous fishes. Furthermore, multiple mechanisms of sensitivity to dioxin-like compounds that are not relevant in birds could exist among fishes. Although, at this time, deficiencies exist for the development of such a predictive relationship for application to fishes, successfully establishing such relationships would offer a substantial improvement in assessment of risks of dioxin-like compounds for this class of vertebrates. Elucidation of such relationships would provide a mechanistic foundation for extrapolation among species to allow the identification of the most sensitive fishes, with the ultimate goal of the prediction of risk posed to endangered species that are not easily studied.

Responsible editor: Philippe Garrigues

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Keywords Dioxin · Furan · PCB · Endangered species · Species differences

Introduction

Along with overexploitation and habitat loss, pollution is one cause for the decreases in populations of fishes in aquatic environments. Polychlorinated dibenzodioxins, polychlorinated dibenzofurans, coplanar polychlorinated biphenyls, and a variety of other chemicals that can bind to the aryl hydrocarbon receptor (AhR) are collectively known as dioxin-like compounds. Dioxin-like compounds are of concern because of their ability to bioaccumulate and because they can persist under certain conditions (Birnbaum and DeVito 1995). Dioxin-like compounds share structural similarities and bind with differing affinity to the AhR, which is a ligand-activated transcription factor that mediates expression of a suite of pleiotropic responses, including biotransformation enzymes, and regulates all known effects of exposure to dioxin-like compounds (Okey 2007). The potency of specific dioxin-like compounds is related to the chemical structure of the molecule with planar configurations generally having the greatest affinity for the AhR and therefore the greatest potency (Whyte et al. 2000). Activation of the AhR has been shown to cause a range of adverse effects in vertebrates, including hepatotoxicity, immune suppression, reproductive and endocrine impairment, teratogenicity, carcinogenicity, and loss of weight (Kawajiri and Fujii-Kuriyama 2007). Dioxin-like compounds have been detected in sediments of water bodies worldwide, including China, Korea, Japan, Canada, the USA, and Europe (Gabos et al. 2001; Hilscherova et al. 2003; Marvin et al. 2002; Naile et al. 2011; Wade et al. 2008). Knowledge of the structural features that determine the potency of specific dioxin-like compounds has allowed the development of toxic equivalency factors based on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin equivalents which greatly facilitate the assessment of risk posed by environmental mixtures containing numerous dioxin-like compounds (Van den Berg et al. 1998). However, relatively little is currently known about the specific molecular mechanism that determines differences in sensitivity to dioxin-like compounds among different species. To improve the assessment of risk associated with exposure to dioxin-like compounds, it is therefore warranted to further understand and enable prediction of the sensitivity of aquatic vertebrates, such as fishes, to adverse effects of dioxin-like compounds.

Differences in sensitivity to dioxin-like compounds exist both within and among vertebrate classes. There are at least 24,618 recognized species of fish, making the diversity among fishes greater than that of any other vertebrate class (Nelson 1994). Of these species, the sensitivity to dioxin-like compounds of only a few has been well characterized (Walker et al. 1991; Zabel et al. 1995), and only a handful of the remaining species have been investigated at all (Fig. 1) (Elonen et al. 1998; Whyte et al. 2000; Yamauchi et al. 2006). Embryos of the least sensitive known species of fish, the zebrafish (*Danio rerio*), are 40-fold less sensitive to the effects of 2,3,7,8-TCDD than are embryos of the lake trout (*Salvelinus namaycush*), which is the most sensitive known species of fish (Elonen et al. 1998; Walker et al. 1991). Due to differences in relative sensitivity to dioxin-like compounds among the fishes that have been investigated, there is uncertainty regarding the risk assessment of dioxin-like compounds to this vertebrate group (Elonen et al. 1998; Walker et al. 1991). Considering the relevance of native species of fishes as indicators for aquatic ecosystem health, there is a need for further understanding as to why there is this observed difference in sensitivity between species and ultimately to develop models that will allow prediction of the sensitivity of any species to effects related to exposure to dioxin-like compounds (Elonen et al. 1998; Walker et al. 1991).

Relationships between sensitivity to dioxin-like compounds and structural properties of the ligand binding domain (LBD) of the AhR have been established in birds (Head et al. 2008; Karchner et al. 2006). Structural differences in the LBD of the avian AhR1 are transferable among species of birds and are predictive of sensitivities of embryos to effects of 2,3,7,8-TCDD (Head et al. 2008). This discovery has allowed the use of AhR genotyping as a genetic screen for predicting species sensitivity among any species of birds for application to risk assessment of numerous native species of birds to dioxin-like compounds. No such relationships have yet been reported in fishes.

As the differing potencies of specific dioxin-like compounds have been subject to intensive research over the last years, the objective of this review was to compile the available literature on AhR dynamics among fishes and to identify data gaps preventing the determination of the mechanisms that could result in differences in sensitivity to dioxin-like compounds. Development of such a predictive relationship would

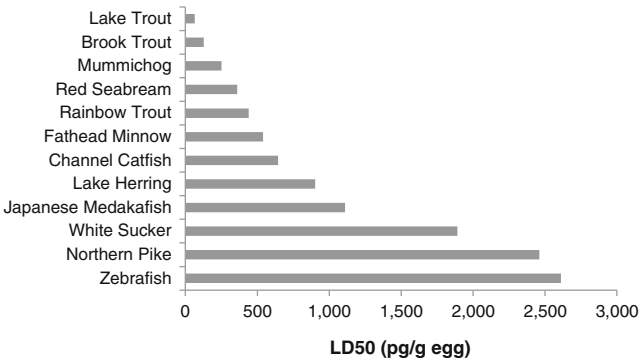

Fig. 1 Relative sensitivity of embryos of fishes to exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Elonen et al. 1998; Johnson et al. 1998; Toomey et al. 2001; Walker et al. 1991, Yamauchi et al. 2005). Sensitivity is expressed as lethal concentration which causes 50% mortality (LD50)

enhance the accuracy of assessing risks posed by dioxin-like compounds in aquatic environments. Furthermore, it would aid in the identification of the most sensitive species that could be at greatest risk, or predict the sensitivity of endangered species whose sensitivity is of great interest. This is important since 149 species of fishes are listed as endangered or threatened in the USA (http://ecos.fws.gov/tess_public/SpeciesReport.do?groups=E&listingType=L&mapstatus=1) with another 62 species protected under the Species at Risk Act in Canada (http://www.dfo-mpo.gc.ca/species-especes/listing-eng.htm). Reducing the use of animals required for research would also be a major benefit of this relationship as only two or more individuals from each species would be required to predict the sensitivity as opposed to hundreds or more required by standard toxicity studies. Since endangered fishes can be difficult to acquire in sufficient numbers for standard toxicity studies, it is difficult to properly ascertain the impact of dioxin-like compounds to these species.

Aryl hydrocarbon receptor dynamics among fishes

As in birds, effects of dioxin-like compounds are mediated through the AhR in fishes. However, numerous differences in AhR dynamics exist between these two groups of vertebrates. Structural properties of the AhR are broadly conserved among classes of vertebrates, but subtle differences in structure can result in distinct differences in function (Hahn 2002). Additionally, multiple mechanisms of dioxin-like sensitivity that are not significant among birds could exist among fishes.

Unlike birds, fishes possess multiple isoforms of the AhR that can be grouped into at least three distinct clades (AhR1, AhR2, AhR3) with each clade possibly containing multiple isoforms. It has been hypothesized that vertebrates underwent ancient genome duplication events with some fishes, such as salmonids and catastomids, undergoing a second such duplication which resulted in multiple AhR clades and multiple AhR isoforms (Le Comber and Smith 2004; Hahn 2001, 2002). In the Atlantic salmon (*Salmo salar*), a total of six distinct AhRs have been discovered, including two AhR1s (α, β) and four AhR2s (α, β, γ, δ) (Hansson and Hahn 2008). Complete redundancy of function after gene duplication is unstable and over time results in inactivation or functional divergence of duplicated genes (Abnet et al. 1999). This raises the question as to the function of the retained AhR isoforms and whether they are significant in determining differential sensitivities among species.

The fact that multiple AhR clades are likely present in all fishes is significant. AhR2 has been shown to be the active form in the fishes researched to date, with AhR1 not binding dioxin-like compounds in most species indicating divergent toxicological roles of these two AhR clades (Andreasen et al. 2002; Karchner et al. 2005; Yamauchi et al. 2005). Little information is available regarding the functional significance of the AhR3 clade known only in some cartilaginous fishes, which reduces insight into dynamics of the AhR among these ancient fishes.

AhR1 is primarily expressed in the brain, heart, and gonad (Abnet et al. 1999; Hansson and Hahn 2008; Yamauchi et al. 2005). AhR2 is expressed in all tissues of all species examined to date (Abnet et al. 1999; Hansson and Hahn 2008; Yamauchi et al. 2005). Significant differences in binding affinity have been shown between isoforms of AhR2 in the rainbow trout and Atlantic salmon (Abnet et al. 1999; Hansson and Hahn 2008). In addition to isoform-specific affinity for 2,3,7,8-TCDD, there appears to be tissue-specific expression of these different isoforms, which could mean that there are divergent functional roles for different isoforms of AhR2 (Abnet et al. 1999; Hansson and Hahn 2008). Different isoforms of AhR2 are known to be differentially expressed in tissues of rainbow trout (*Oncorhynchus mykiss*), Atlantic salmon (*S. salar*), and likely in other fishes (Abnet et al. 1999; Hansson and Hahn 2008; Yamauchi et al. 2005). In the rainbow trout, the AhR2β form is more expressed than the AhR2α; with tenfold greater expression in the heart, fourfold greater expression in the liver, and fourfold greater expression in the brain (Abnet et al. 1999). Greater expression of the AhR2β form was also observed in the kidney, blood, spleen, intestine, and ovary (Abnet et al. 1999). Greater expression of AhR2β in the liver and heart is of interest since these are known target organs in which dioxin-like compounds exert their toxic effects on embryos of fishes (Antkiewicz et al. 2005; Yamauchi et al. 2006). Presently, however, the functional significance of individual AhR clades and isoforms is unclear, and without a complete understanding of their function, the underlying role of each AhR in determining sensitivity to dioxin-like compounds remains unknown.

Autoregulation of AhR expression and AhR protein stability have also been implicated in differential sensitivity observed among fishes. However, it is currently unclear whether an upregulation of AhR2 transcript abundance could have an impact on differences in responsiveness to AhR agonists among species or tissues (Andreasen et al. 2002; Doering et al. 2012; Tanguay et al. 1999; Wiseman and Vijayan 2007). It has been hypothesized that differences in AhR protein conformation are a determinant of differences in sensitivities among populations of the Atlantic tomcod (*Microgadus tomcod*) (Wirgin et al. 2011). In this species, differences in amino acid sequences of the LBD were not observed to be related to affinity of binding of ligands. However, amino acid deletions outside of the LBD appeared to affect stability of the protein and therefore result in lesser affinity of binding (Wirgin et al. 2011). Furthermore, the role of expression and function of the aryl hydrocarbon receptor repressor (Evans et al. 2005, 2008; Jenny et al. 2009), aryl hydrocarbon nuclear transporter

(Evans et al. 2008; Fleming et al. 2009; Prasch et al. 2006), and heat shock proteins (Wang et al. 2009; Wiseman and Vijayan 2007) in determining differences in sensitivity among fishes is not completely understood. Other unknown differences in AhR dynamics could also exist between fishes and birds which could complicate the determination of what drives differences in sensitivity between species of fishes.

Application to fishes

There are currently limitations to the discovery of critical amino acid residues in the LBD of the AhR that are predictive of dioxin-like sensitivity among fishes. There is less conservation among AhR sequences of fishes than among birds. Amino acid identity of sequences of the LBD of the AhR2 in fishes can be less than 70 % based on publicly available sequences. This lack of conservation makes it difficult to identify critical amino acids for binding to ligands. Additionally, it has been hypothesized that the responsiveness of salmonids to the effects of AhR agonists could be due, in part, to their expression of multiple, functional AhR genes (Hansson and Hahn 2008). This means that multiple AhR clades and isoforms, and tissue-specific expression could complicate prediction of sensitivities among species that is based on the amino acid sequence of the LBD of the AhR of fishes. Full sequences of AhR2s are only available in GenBank for six species of fishes, with partial sequences from an additional 15 species, and it is likely that all isoforms of AhRs have not yet been identified in most of these species. Finally, the sensitivity to dioxin-like compounds of only a few fishes has been well characterized, and observed differences in embryo lethality could be due in part to development time. Species with longer times of development tend to have greater sensitivity to the effects of 2,3,7,8-TCDD (Elonen et al. 1998). Finally, the implications to the sensitivity of cartilaginous fishes to dioxin-like compounds resulting from expression of AhR3 genes are unknown (Hahn 2002).

Future perspectives and research needs

In order to develop a robust predictive relationship that could be used to determine the sensitivity of any species of fish to any dioxin-like compound, five main steps would be required:

1. The molecular sequencing and characterization of AhR2s in a range of fishes would be necessary. The amino acid sequence of the LBD would be essential, and the tissue-specific patterns of expression of each isoform would facilitate proper assessment. Ideal candidates for sequencing and characterization would include fishes whose sensitivity has been established in embryos (Fig. 1). Examples include: the lake trout (*S. namaycush*), fathead minnow (*Pimephales promelas*), channel catfish (*Ictalurus punctatus*), white sucker (*Catastomus commersoni*), lake herring (*Coregonus artedii*), brook trout (*Salvelinus fontinalis*), and northern pike (*Esox lucius*; Elonen et al. 1998; Johnson et al. 1998).
2. Knowledge of the ligand binding affinity of AhR2s in numerous fishes of known sensitivity would also be necessary to confirm that sensitive fishes have receptors of greater affinity and insensitive species have receptors of lesser affinity. This would ascertain that differences in species sensitivity were primarily driven by differences in ligand binding affinity of the AhR2 and not other factors.
3. Chimeric AhRs substituting hypothesized critical amino acid sequences in the AhR2 of fishes could be used in an attempt to alter the ligand binding affinity of the AhR2 in a sensitive species into that of an insensitive species. Additionally, chimeric AhRs could be used in an attempt to turn responsive AhR2s into unresponsive AhR1s. If successful, this approach would validate which amino acids in the LBD were critical to ligand binding affinity and could be predictive of species differences in sensitivity to dioxin-like compounds.
4. Molecular sequencing and characterization of the completely unknown AhR3 clade in cartilaginous fishes would allow a better interpretation of how these ancient fishes respond to exposure to dioxin-like compounds. It is possible that the AhR3 clade is unresponsive to dioxin-like compounds and these genes have no impact on sensitivity of species. Alternatively, it could have relatively great ligand binding affinity along with the AhR2 clade and be a driver of sensitivity of these fishes. This could complicate the application of a predictive relationship based on amino acid sequences of the LBD in cartilaginous fishes.
5. Differences in ligand binding affinity of the AhR2 might not be the driving factor for observed differences in the sensitivity of species to dioxin-like compounds. Additionally, some fishes, such as salmonids and catostomids, have complex AhR dynamics involving multiple isoforms which could be too complex for robust genetic screening techniques. In this case, a means of integrating potential confounding factors would be required. One option would be development of a regression relationship between embryo lethality LD_{50} values for 2,3,7,8-TCDD and 2,3,7,8-TCDD EC_{50} values for induction of ethoxyresorufin *O*-deethlase or CYP1A

transcript abundance in primary hepatocyte cell culture. This alternate method could predict an ecologically relevant in vivo endpoint (embryo lethality) by use of an in vitro approach. Recently, such a relationship was successfully developed for birds (Head and Kennedy 2010). Since whole cells are employed, this approach would integrate numerous confounding factors, including the effects that expression of multiple, functional AhRs or differences in expression levels would have on differences in the sensitivity of fishes to dioxin-like compounds.

Conclusion

Relatively little information is currently available regarding the sensitivity of fishes to dioxin-like compounds despite these chemical's ubiquitous distribution and great potency to vertebrates. This justifies the development of better methods for the risk assessment of these chemicals in aquatic environments. One novel method is the use of a genetic screen as has recently been developed in birds. However, a genetic screen predictive of sensitivity to dioxin-like compounds among fishes has not yet been demonstrated due to a lack of necessary data. If successfully established, this relationship would allow genotyping of the AhR as a means to aid the risk assessment of any species of fishes to dioxin-like compounds. This would aid recognition of the most sensitive species that could be at greatest risk or predict the sensitivity of endangered species whose sensitivity is of great interest.

Acknowledgments J. Doering was supported through the NSERC CREATE program in Human and Ecological Risk Assessment, the University of Saskatchewan Dean's Scholarship, and the Saskatchewan Innovation and Opportunity Scholarship. M. Hecker was supported through the Canada Research Chair program. J. Giesy was supported through the Canada Research Chair program, an at-large chair professorship at the Department of Biology and Chemistry and State Key Laboratory in Marine Pollution, City University of Hong Kong, and The Einstein Professor Program of the Chinese Academy of Sciences.

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