Crystallographic Analysis and Mimicking of Estradiol Binding: Interpretation and Speculation

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation

Published Version
doi:10.1289/ehp.1307987

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:12185816

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
The correspondence section is a public forum and, as such, is not peer-reviewed. EHP is not responsible for the accuracy, currency, or reliability of personal opinion expressed herein; it is the sole responsibility of the authors. EHP neither endorses nor disputes their published commentary.

Crystallographic Analysis and Mimicking of Estradiol Binding: Interpretation and Speculation
http://dx.doi.org/10.1289/ehp.1307987

In their recent article, Gosavi et al. (2013) presented the results of a crystallographic analysis of the binding of tetrabromobisphenol A (TBBPA) and 3-hydroxy-2,2′,4,4′-tetrabromodiphenyl ether (3-OH-BDE-47) to estrogen sulfotransferase (SULT1E1). The authors demonstrated that the tested molecules fit into the same binding pocket as estradiol. However, although the study’s methodology and interpretation of the crystallographic analysis provide insight into how binding might occur in isolated and in vitro systems, they did not provide evidence that the tested molecules would initiate any biological activity with the relevant estrogen receptors (ERs) or proteins in a human body. For example, the ability of TBBPA to interact with the ER and estrogen-related receptors has been evaluated in recombinant yeast strains, mammalian cell–based assays, and tests developed by the Organisation for Economic Co-operation and Development (Lee et al. 2012; Nakagawa et al. 2007; Ogunbayo et al. 2007, 2008; Reistad et al. 2005, 2007; Strack et al. 2007). Those studies found that TBBPA either did not interact with ERs or that it acted as a weak ER agonist/antagonist with a potency orders of magnitude below that of natural ER ligands. In addition, the data presented by Gosavi et al. (2013) did not include the use of controls to validate the methods. The use of both positive controls (such as diethylstilbestrol and ethinyl estradiol) and a negative control (such as testosterone) would provide validation of the analysis and allow for the quantification and comparison of the two test substances in relation to the binding potentials of the controls.

The authors also speculated about the possible additive effects of the various brominated flame retardants and their metabolites and suggested that low-dose exposure to multiple low-affinity binding compounds may result in endocrine disruption. However, none of the data presented directly addressed this point.

It is highly complex, not well understood, and speculative to extrapolate data on inhibition of enzymes such as SULT1E1 in vitro assay systems to endocrine-system modulation of selective gene expression, receptor binding, and activation and the production of adverse effects that would characterize endocrine disruption in vivo by additivity of different chemicals competing on the same receptors. Only through a more complete understanding of target tissue dosimetry, potency of interaction of the chemical of interest with the macromolecule of interest (e.g., SULT1E1), and subsequent events can one address the likelihood of in vivo additivity.

This work was supported by the North American Flame Retardant Alliance (NAFRA) Panel of the American Chemistry Council, which previously provided funding for travel expenses and honoraria to the authors as members of NAFRA’s Science Advisory Council. The researchers’ scientific conclusions and professional judgments were not subject to the funder’s control.

Thomas G. Osimitz,1 Michael L. Dourson,2 A. Wallace Hayes,3 and Sam Kacew3

1Science Strategies, Charlottesville, Virginia, USA; 2Toxicology Excellence for Risk Assessment (TERA), Cincinnati, Ohio, USA; 3Harvard School of Public Health, Boston, Massachusetts, USA; 4Laughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

E-mail: tom@sciencestrategies.com

REFERENCES


Crystallographic Analysis and Mimicking of Estradiol Binding: Pedersen et al. Respond

http://dx.doi.org/10.1289/ehp.1307987R

Previous studies have addressed the biological effects of brominated flame retardants (Birnbaum and Staskal 2004; Koike et al. 2013; Mariussen and Fonnun 2003; Ogunbayo et al. 2008), including a 2-year bioassay study performed by the National Toxicology Program (NTP), which demonstrated that tetrabromobisphenol A (TBBPA) can induce aggressive uterine tumors in rats (NTP 2013). As pointed out by Osimitz et al., TBBPA has been shown to bind poorly to the estrogen receptor, providing the impetus to study other pathways such as disruption of steroid transport and metabolism. Other groups have demonstrated the ability of TBBPA and flame retardant metabolites to inhibit estrogen sulfotransferase (SULT1E1), with IC50 (median inhibitory concentration) values near the Km for estradiol (Hamers et al. 2008; Kester et al. 2002; Zhang et al. 1998). Our work (Gosavi et al. 2013) was focused solely on understanding the structural mechanism by which these compounds bind to and inhibit SULT1E1’s ability to metabolize estradiol. The results of our work demonstrate that TBBPA and the 3-OH metabolite of BDE-47, although structurally different, bind in a similar manner at the estradiol binding site. This work suggests that these compounds could have an additive effect on the inhibition of this enzyme. We wholeheartedly agree with Osimitz et al. that the results of our work warrant future studies addressing the potential additive effect of these compounds on steroid metabolism in target tissues.

The authors declare that they have no actual or potential competing financial interests.

Lars C. Pedersen,1 Linda S. Birnbaum,2 Rajendra Kumar A. Gosavi,1 and Gabriel A. Knudsen2

1Laboratory of Structural Biology, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; 2Laboratory of Toxicology and Toxicokinetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA

E-mail: pederse2@niehs.nih.gov

REFERENCES


Environmental Health Perspectives • VOLUME 122 | NUMBER 4 | April 2014

A 91

Perspectives Correspondence
Correspondence


NTP (National Toxicology Program). 2013. Toxicology Studies of Tetrabromobisphenol A in F344/NTac Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Tetrabromobisphenol A in Wistar Han (Crl:WI(Han)) Rats and B6CF1/N Mice. TR-587.

