Journal of Steroid Biochemistry & Molecular Biology 127 (2011) 1–3

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Editorial

Endocrine disrupting chemicals☆

The idea that xenobiotic chemicals could inappropriately modulate the endocrine system thereby causing detrimental effects in wildlife and humans was first proposed 20 years ago at the watershed Wingspread Conference [1,2]. These endocrine disrupting chemicals (EDCs) have long been controversial, with a great deal of discussion raging in the scientific literature. Much of this controversy has centered on the doses at which effects of EDCs can be observed and whether these doses are likely to be encountered in vivo. Perhaps not surprisingly, there is a sharp division of opinion among experts from academia (who are able to find significant effects at low, environmentally relevant chemical concentrations) and industry (who appear unable to demonstrate harmful effects of EDCs at most any concentrations likely to be encountered); this debate continues unabated [3]. In 2009, the Endocrine Society published a landmark Scientific Statement (the first in their history) outlining the scientific evidence supporting the existence and detrimental effects of EDCs and underscoring them as a significant concern for public health [4]. This position has been endorsed by the American Medical Association and the consensus of opinion in the scientific community is that more focused research is required to increase our understanding of the effects of EDCs. Many aspects of EDCs have been reviewed in recent years; therefore this special issue is focused on the latest developments concerning pathways, targets and mechanisms for EDC action, new insights into the effects of EDCs on key target tissues or processes and on new insights into the effects of known EDCs.

In industrialized countries obesity and related metabolic diseases have exploded into a global epidemic in the past 20 years. Excessive consumption of unhealthy foods coupled with growing indolence are the generally accepted causes for obesity. The environmental obesogen hypothesis proposes that exposure to certain EDCs during critical stages in development predisposes the exposed individual to weight gain and obesity [5]. Obesogens are chemicals that can influence obesity through a variety of potential mechanisms and pathways. Prime among these is the peroxisome proliferator activated receptor gamma (PPARγ) pathway. The minireview by Janesick and Blumberg highlights obesogens that act through PPARγ either directly, or indirectly [6]. An original research report from the same laboratory demonstrates that the obesogen tributyltin chloride indeed exerts its adipogenic effects through PPARγ, a topic that had previously been controversial [7].

Two other EDCs that have been linked to obesity, among other effects, are perfluorooctanoic acids (PFOA) and bisphenol A (BPA). Perfluoroalkyl acids such as PFOA are ubiquitous in the environment, found in human tissues and are known to be toxic in animals and humans. The review by White et al., focuses on the health effects of PFOA in animal models, identifying new mechanisms of action during sensitive developmental periods [8]. This is complemented with epidemiologic data suggesting that similar outcomes might occur in humans. BPA is among the most highly produced and controversial compounds worldwide. It has broad-ranging health effects and can target multiple endocrine-related pathways, in vivo. The review by Rubin discusses these health effects, together with known and hypothesized mechanisms of action [9]. An original research contribution by Durando et al., reveals that prenatal exposure to BPA promotes angiogenesis and alters the endocrine environment of the mammary gland and could play a role in establishing pre-neoplastic lesions found in these animals [10].

While it is well-established that EDCs that activate the nuclear estrogen receptors alpha and beta (ERα, ERβ) can have deleterious effects on humans and wildlife, an important recent advance in endocrinology has been the realization that estrogens can have non-genomic effects on gene expression via membrane bound receptors and second messenger pathways. Thus, xenoestrogens can act directly on gene expression via the nuclear ERα and ERβ, or indirectly via multiple other cellular signaling pathways, some of which can be activated quickly and at vanishingly low xenoestrogen concentrations. The review by Watson et al., discusses how xenoestrogens act via non-genomic pathways and in particular how they can act in nonmonotonic patterns to elicit effects at concentrations far below those previously thought to be effective [11]. Next, Miyagawa and Iguchi review the mechanisms through which perinatal exposure to xenoestrogens such as diethylstilbestrol lead to persistent reproductive abnormalities by inappropriately stimulating growth factor signaling pathways leading to ligand-independent activation of the nuclear estrogen receptors [12]. This is followed by an original research report from Moore and colleagues showing that exposure to environmental contaminants leads to altered expression of TGFβ superfamily signaling factors in the developing gonads of the American alligator [13]. Their study reveals that exposure to xenoestrogens in complex environmental mixtures can affect non-steroidal signaling pathways. They suggest that such effects may be more prevalent than previously recognized and EDC modulation

☆ Article submitted for the special issue on Endocrine Disruptors.

0960-0760/$ – see front matter
doi:10.1016/j.jsbmb.2011.07.012

of non-steroidal signaling pathways is an important, yet hitherto overlooked research area [13].

Another EDC that has been controversial in the past is the herbicide atrazine, which has been linked with feminization of male gonads in wildlife [14]. Hayes and colleagues address this controversy by showing that atrazine demasculinizes male gonads in fish, amphibians, reptiles and mammals [15]. They provide a comprehensive review of possible mechanisms and suggest that the most plausible and coherent possibility is that atrazine acts by reducing androgen levels and inducing estrogen synthesis [15]. Continuing on the topic of EDCs interfering with male reproductive health, the review by Luccio-Camelo and Prins discusses the role of EDCs as disruptors of signaling through the androgen receptor [16]. Their review focuses on those EDCs for which there is in vivo evidence linking exposure with perturbations in male reproductive tract development [16]. The subsequent review by Taylor et al. focuses on the mechanisms through which xenoestrogens such as BPA act to perturb male reproductive tract development [17]. They highlight how BPA disrupts prostate development by acting on mesenchymal stem cells to promote epithelial proliferation while inhibiting apoptosis at doses likely to be encountered, in vivo [17].

The aryl hydrocarbon receptor (AhR) is a ligand modulated transcription factor (although not a member of the nuclear hormone receptor superfamily) that is an important mediator of the effects of dioxins and other planar, dioxin-like aryl hydrocarbons. The review by Wataru et al., summarizes what is known about the effects of dioxins on the AhR, focusing on newly revealed mechanisms underlying the observed effects [18]. These pathways include misregulated AhR downstream targets such as cyclooxygenase-2, Wnt/β-catenin signaling, and stimulation of inflammatory cytokine receptors [18]. The next review by Ohtake et al., focuses on the interactions between estrogen and AhR signaling pathways [19]. It has long been known that AhR interferes with signaling through the estrogen and androgen signaling pathways; although, the specific mechanisms were not understood. This review summarizes newly identified molecular mechanisms linking the action of AhR and a ubiquitin ligase with its ability to cross-talk with the ER signaling pathway [19].

Although much has recently been discovered about the effects of EDCs on humans and wildlife, there are still important gaps in our knowledge. For example, the relatively short time over which a decline in reproductive function has occurred argues against a genetic cause. The review by Woodruff highlights what is needed to link epidemiologic studies with those in model organisms so that one can properly understand possible relationships between EDC exposure and health consequences [20]. The review by Muncke provides an important discussion of how EDC migration from food contact materials may be playing a critical, yet unexplored role in human exposure to EDCs [21]. As an example, the following original article by Wagner and Oehlmann reveals that xenoestrogenic activities migrate from commercially available bottled water (and presumably other beverage) containers using an E-screen [22]. Lastly, Schiliro and colleagues provide another original research contribution evaluating estrogenic activity in fruits and vegetables using a similar E-screen, showing that 59% of fruits and vegetables show detectable xenoestrogenic activity [23]. Together, these contributions make the important point that food, beverages and their packaging materials are important sources of human EDC exposure.

Endocrine disruptor research is a broad field that continues to grow. We have tried in this special issue to provide an overview of key topics in this exciting, yet still emerging field. The initial main focus of the field on disturbances in ER function has been extended to other hormones and targets, including membrane receptors, metabolizing enzymes and signaling pathways. Future research will also need to consider disturbances in circadian and ultradian rhythms of hormonal changes as well as epigenetic changes. There is much left to be learned and we hope that this collection of articles spurs future research in the field.

We thank all of the authors who have contributed their time and expertise to this special issue and apologize that space limitations prevented a comprehensive treatment of the entire field. We also appreciate the many reviewers who evaluated the submitted manuscripts and helped to ensure the overall quality of the special issue. Lastly, we thank the editorial staff at Elsevier for their efforts to facilitate production of this issue.

References

[1] T. Colborn, C. Clement (Eds.), Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife Human Connection, Princeton Scientific Publishing, Princeton, NJ, 1992.
[2] T. Colborn, D. Dumanoski, J.P. Myers, Our stolen future: are we threatening our fertility, in: Intelligence and Survival?, Penguin Group, New York, 1996.
[3] F.S. vom Saal, B.T. Akingbemi, S.M. Belcher, D.A. Crain, D. Crews, L.C. Guidice, P.A. Hunt, C. Leranth, J.P. Myers, A. Nadal, N. Olea, V. Padmanabhan, C.S. Rosenfeld, A. Schneyer, G. Schoenfelder, C. Sonnenschein, A.M. Soto, R.W. Stahlhut, S.H. Swan, L.N. Vandenberg, H.S. Wang, C.S. Watson, W.V. Welshons, R.T. Zoeller, Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research, Toxicol. Sci. 115 (2) (2010) 612–613, author reply 614–620.
[4] E. Diamanti-Kandarakis, J.P. Bourguignon, L.C. Giudice, R. Hauser, G.S. Prins, A.M. Soto, R.T. Zoeller, A.C. Gore, Endocrine-disrupting chemicals: an Endocrine Society scientific statement, Endocr. Rev. 30 (4) (2009) 293–342.
[5] A. Janesick, B. Blumberg, Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity, Birth Defects Res. C Embryo Today 93 (1) (2011) 34–50.
[6] A. Janesick, B. Blumberg, Minireview: PPARgamma as the target of obesogens, J. Steroid Biochem. Mol. Biol. 127 (2011) 4–8.
[7] X. Li, J. Ycaza, B. Blumberg, The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes, J. Steroid Biochem. Mol. Biol., 127, 9-15.
[8] S.S. White, S. Fenton, E.P. Hines, Endocrine disrupting properties of perfluorooctanoic acid, J. Steroid Biochem. Mol. Biol., 127, 16-26.
[9] B.S. Rubin, Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects, J. Steroid Biochem. Mol. Biol., 127, 27-34.
[10] M. Durando, L. Kass, V. Perdomo, V.L. Bosquiazzo, E.H. Luque, M.M. Munoz-de-Toro, Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling ras, J. Steroid Biochem. Mol. Biol., 127, 35-43.
[11] C.S. Watson, Y.-J. Jeng, J. Guptarak, Endocrine disruption via estrogen receptors that participate in nongenomic signaling pathways, J. Steroid Biochem. Mol. Biol., 127, 44-50.
[12] S. Miyagawa, M. Sato, T. Iguchi, Molecular mechanisms of induction of persistent changes by estrogenic chemicals on female reproductive tracts and external genitalia, J. Steroid Biochem. Mol. Biol., 127, 51-57.
[13] B. Moore, M.R. Milnes, S. Kohno, Y. Katsu, T. Iguchi, T.K. Woodruff, L.J. Guillette, Altered gonadal expression of TGF-β superfamily signaling factors in environmental contaminant-exposed juvenile alligators, J. Steroid Biochem. Mol. Biol., 127, 58-63.
[14] T. Hayes, K. Haston, M. Tsui, A. Hoang, C. Haeffele, A. Vonk, Herbicides: feminization of male frogs in the wild, Nature 419 (6910) (2002) 895–896.
[15] T.B. Hayes, S. de Solla, T. Iguchi, H. Ingraham, P. Kestemont, V. Langlois, E.H. Luque, K. McKoy, M.M. Munoz-de-Toro, T. Oka, C. Oliveira, F. Orton, S. Ruby, M. Suzawa, L.E. Tavera-Mendo, V. Trudeau, A. Victor-Costa, E. Willingham, Demasculinization and feminization of male gonads by atrazine: consistent effects across vertebrate classes, J. Steroid Biochem. Mol. Biol., 127, 64-73.
[16] D.C. Luccio-Camelo, G.S. Prins, Disruption of androgen receptor signaling in males by environmental chemicals, J. Steroid Biochem. Mol. Biol., 127, 74-82.
[17] J.A. Taylor, C.A. Richter, R.L. Ruhlen, F.S. vom Saal, Estrogenic chemicals and drugs: mechanisms for effects on the developing male urogenital system, J. Steroid Biochem. Mol. Biol., 127, 83-95.
[18] Y. Wataru, R.E. Peterson, C. Tohyama, Molecular targets that link dioxin exposure to toxicity phenotypes, J. Steroid Biochem. Mol. Biol., 127, 96-101.
[19] F. Ohtake, Y. Fujii-Kuriyama, K. Kawajiri, S. Kato, Cross-talk of dioxin and estrogen receptor signals through the ubiquitin system, J. Steroid Biochem. Mol. Biol., 127, 102-107.

[20] T.J. Woodruff, Bridging epidemiology and model organisms to increase understanding of endocrine disrupting chemicals and human health effects, J. Steroid Biochem. Mol. Biol., 127, 108-117.
[21] J. Muncke, Endocrine disrupting chemicals and other substances of concern in food contact materials: an updated review of exposure, effect and risk assessment, J. Steroid Biochem. Mol. Biol., 127, 118-127.
[22] M. Wagner, J. Oehlmann, Endocrine disruptors in bottled mineral water: estrogenic activity in the E-Screen, J. Steroid Biochem. Mol. Biol., 127, 128-135.
[23] T. Schiliro, I. Gorrasi, A. Longo, S. Colluccia, G. Gilli, Endocrine disrupting activity in fruits and vegetables evaluated with the E-screen assay in relation to pesticide residues, J. Steroid Biochem. Mol. Biol., 127, 139-146.

Bruce Blumberg*
Taisen Iguchi
Alex Odermatt

* Corresponding author. Tel.: +1 949 824 8573;
fax: +1 949 824 4709.
E-mail address: blumberg@uci.edu (B. Blumberg)

25 July 2011

28 July 2011