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ScienceDirect
Reproductive Toxicology 24 (2007) 178–198
Reproductive Toxicology
www.elsevier.com/locate/reprotox

Review

In vitro molecular mechanisms of bisphenol A action☆

Yelena B. Wetherill[a,b], Benson T. Akingbemi[c], Jun Kanno[d], John A. McLachlan[e], Angel Nadal[f], Carlos Sonnenschein[g], Cheryl S. Watson[h], R. Thomas Zoeller[i], Scott M. Belcher[j,*]

[a] *Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115, United States*
[b] *Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, United States*
[c] *Department of Anatomy, Physiology and Pharmacology, Auburn University, AL 36849, United States*
[d] *Division of Cellular and Molecular Toxicology, National Institute of Health Sciences, Tokyo 158-8501, Japan*
[e] *Department of Pharmacology and Environmental Endocrinology Lab, Center for Bioenvironmental Research, Tulane University, New Orleans, LA 70112, United States*
[f] *Instituto de Bioingeniería, Universidad Miguel Hernández de Elche, Elche 03202, Alicante, Spain*
[g] *Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, MA 02111, United States*
[h] *Biochemisty and Molecular Biology Department, University of Texas Medical Branch, Galveston, TX 77555, United States*
[i] *Laboratory of Molecular and Cellular Neurobiology, University of Massachusetts Amherst, MA 01003, United States*
[j] *University of Cincinnati College of Medicine, Department of Pharmacology and Cell Biophysics, Cincinnati, OH 45267, United States*

Received 12 April 2007; accepted 18 May 2007
Available online 29 May 2007

Abstract

Bisphenol A (BPA, 2,2-bis (4-hydroxyphenyl) propane; CAS# 80-05-7) is a chemical used primarily in the manufacture of polycarbonate plastic, epoxy resins and as a non-polymer additive to other plastics. Recent evidence has demonstrated that human and wildlife populations are exposed to levels of BPA which cause adverse reproductive and developmental effects in a number of different wildlife species and laboratory animal models. However, there are major uncertainties surrounding the spectrum of BPA's mechanisms of action, the tissue-specific impacts of exposures, and the critical windows of susceptibility during which target tissues are sensitive to BPA exposures. As a foundation to address some of those uncertainties, this review was prepared by the "*In vitro*" expert sub-panel assembled during the "*Bisphenol A: An Examination of the Relevance of Ecological, In vitro and Laboratory Animal Studies for Assessing Risks to Human Health*" workshop held in Chapel Hill, NC, Nov 28-29, 2006. The specific charge of this expert panel was to review and assess the strength of the published literature pertaining to the mechanisms of BPA action.

Abbreviations: 4-*tert*-OP, 4-tertiary octylphenol; 17α-EE, 17alpha-ethinyl estradiol; AR, androgen receptor; ARE, androgen response element; BADGE, bisphenol A diglycidyl ether; BFDGE, bisphenol F diglycidyl ether; BP-3, *p,p′*-dihydroxybenzphenone; BP-4, 2,2-bis(*m*-methyl-*p*-hydroxyphenyl)propane; BP-5, 2,2-bis(*p*-hydroxyphenyl) perfluoropropane; BPA, 2,2-bis(4-hydroxyphenyl) propane; BPA-OMe, 2,2-bis(4-methoxyphenyl)propane; BPE, 1,1-bis(4-hydroxyphenyl)ethane; BPF, 4,4′-methylenebisphenol; BPM, 4,4′-(1,3-phenylenedisopropylidene)bisphenol; BPP, 4,4′-(1,4-phenylenedisopropylidene)phenol; BPS, 4,4′-sulfonyldiphenol; BPZ, 4,4′-cyclohexylidenebisphenol; DDE, *o,p′*-dichlorodiphenylethylene; *o,p′*-DDT, 1,1,1-trichloro-2-[*o*-chlorophenyl]-2-[*p*-chlorophenyl]ethane; DEHP, bis(2-ethylhexyl)phthalate; DES, diethylstilbesterol; DHT, dihydrotestosterone; DMSO, dimethyl sulfoxide; E2, 17beta-estradiol; EDC, endocrine disrupting chemical; ELISA, enzyme-linked immunosorbent assay; ER, estrogen receptor; ERE, estrogen response element; ETOH, ethanol; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GH, growth hormone; HBSS, Hank's buffered saline solutions; h, hour; HRP, horseradish peroxidase; inos, inducible nitric oxide synthase; KLH, keyhole limpet hemocyanin; LPS, lipopolysaccharide; min, minute; NO, nitric oxide; NP, nonylphenol; OP, octylphenol; PCB, polychlorinated biphenyl; PMA, phorbol 12-myristate 13-acetate; PR, progesterone receptor; PSA, prostrate specific antigen; RIA, radio-immuno assay; RT-PCR, reverse transcription-polymerase chain reaction; RXR, retinoid X receptor; s, second; TCDD, 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin; T3, L-3,3′,5-triiodothyronine; T4, 3,3′,5,5′-tetraiodo-L-thyronine; TR, thyroid hormone receptor.

☆ SMB is supported by the NIH grants RO1-ES015145 and the University of Cincinnati Center for Environmental Genetics (P30-ES06096). YBW is supported by the NIEHS Kirschstein-National Research Service Award (T32 ES07069-26).

* Corresponding author at: Department of Pharmacology and Cell Biophysics, University of Cincinnati College of Medicine, 231 Albert Sabin Way, P.O. Box 670575, Cincinnati, OH 45267-0575, Untied States. Tel.: +1 513 558 1721; fax: +1 513 558 4329.
E-mail address: scott.belcher@uc.edu (S.M. Belcher).

0890-6238/$ – see front matter
doi:10.1016/j.reprotox.2007.05.010

The resulting document is a detailed review of published studies that have focused on the mechanistic basis of BPA action in diverse experimental models and an assessment of the strength of the evidence regarding the published BPA research.

Keywords: Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl) propane; Endocrine disruption; Endocrine disrupting chemical (EDC); Rapid signaling; Estrogen receptor; Androgen receptor; Thyroid receptor; Thyroid hormone; GPR30; Non-classical membrane estrogen receptor; Immune system; Allergic resonse; *In vitro* mechanisms; Cell specificity; Expert panel review

Contents

1. Introduction

Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl) propane; CAS# 80-05-7) is a chemical used primarily in the manufacture of polycarbonate plastic, epoxy resins and as a non-polymer additive to other plastics. Because of BPA's extensive use in the manufacture of consumer goods and products, including polycarbonate food containers and utensils, dental sealants, protective coatings, some flame retardants, and water supply pipes, there is a widespread and well-documented human exposure to BPA [1,2]. Recent discoveries regarding the environmental distribution and presence of BPA in humans and wildlife have generated persistent scientific, regulatory, and public interest in assessing the potential health risks associated with BPA exposure. The detection of adverse health effects in a number of laboratory animal models upon exposure to environmentally relevant doses of BPA, as well as potential effects on human reproduction and development, have fueled additional concern. While the exposure of wildlife species and humans to BPA has been increasingly reported in the literature, there are research gaps regarding its molecular mechanisms of action, the tissue-specific impacts of exposure, and knowledge of the critical windows of susceptibility, during which target tissues are especially sensitive to BPA.

The lack of an integrated and systemic understanding of BPA's endocrine disruptive actions has considerably complicated risk assessment efforts and safety recommendations by regulatory agencies. Current limitations in understanding the global consequences of BPA exposures include incomplete understanding of the cell/tissue specific actions and effects, a limited understanding of the receptor systems and signaling cascades through which BPA acts, and understanding when these receptors and signaling systems are present and active in target cells at different critical times of sensitivity during the entire life-span.

2. Overview

This white paper was prepared for the *in vitro* expert subpanel assembled during the "Bisphenol A: An Examination of the Relevance of Ecological, *In vitro* and Laboratory Animal Studies for Assessing Risks to Human Health" workshop at the NIEHS. The specific charge of this expert panel was to review and assess the strength of the published literature pertaining to the mechanisms of BPA action. Particular attention was paid to studies employing *in vitro* models and the results, findings and conclusions from those studies were integrated into the broader biological/physiologic context of BPA action. Thus, the goal of