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Effects of the environmental estrogenic contaminants bisphenol A and 17α-ethinyl estradiol on sexual development and adult behaviors in aquatic wildlife species

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ABSTRACT

Endocrine disrupting chemicals (EDCs), including the mass-produced component of plastics, bisphenol A (BPA) are widely prevalent in aquatic and terrestrial habitats. Many aquatic species, such as fish, amphibians, aquatic reptiles and mammals, are exposed daily to high concentrations of BPA and ethinyl estradiol (EE2), estrogen in birth control pills. In this review, we will predominantly focus on BPA and EE2, well-described estrogenic EDCs. First, the evidence that BPA and EE2 are detectable in almost all bodies of water will be discussed. We will consider how BPA affects sexual and neural development in these species, as these effects have been the best characterized across taxa. For instance, such chemicals have been in many cases reported to cause sex-reversal of males to females. Even if these chemicals do not overtly alter the gonadal sex, there are indications that several EDCs might demasculinize male-specific behaviors that are essential for attracting a mate. In so doing, these chemicals may reduce the likelihood that these males reproduce. If exposed males do reproduce, the concern is that they will then be passing on compromised genetic fitness to their offspring and transmitting potential transgenerational effects through their sperm epigenome. We will thus consider how diverse epigenetic changes might be a unifying mechanism of how BPA and EE2 disrupt several processes across species. Such changes might also serve as universal species diagnostic biomarkers of BPA and other EDCs exposure. Lastly, the evidence that estrogenic EDCs-induced effects in aquatic species might translate to humans will be considered.

Abbreviations: AGD, anogenital distance; AR, androgen receptor; AOPs, adverse outcome pathways; BMPO, benzo(a)pyrene monooxygenase; BPA, bisphenol A; CYP1A1, cytochrome P450 family 1 subfamily A polypeptide 1; *Cyp19a1a*, aromatase; DES, diethylstilbestrol; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; *Dnmts*, DNA methyltransferases; EDC(s), endocrine disrupting compound(s); EPA, Environmental Protection Agency; EE2, ethinyl estradiol; ER(s), estrogen receptors; ESR1, estrogen receptor 1 (alpha); ESR2, estrogen receptor 2 (beta); *Fshb*, follicle stimulating hormone beta; FW, feed weight; GnRH, gonadotropin-releasing hormone; GPER, G protein-coupled estrogen receptor 1; GSD, genetic sex determination; GSI, gonadosomatic index; IAP, intracisternal A particle; *Kiss1*, kisspeptin 1; LOD, limits of detection; *Lhb*, luteinizing hormone beta; MeCP2, methyl-CpG binding protein 2; NOAEL, no observable adverse effect level; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PGC, primordial germ cells; ppm, part per million; T_3, 3,5,3′-triiodo-L-thyroxine; TSP, temperature sensitive period; TSD, temperature sex determination; VTG, vitellogenin (protein product); *Vtg*, vitellogenin (transcript).

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1. Introduction

"*Between animal and human medicine there is no dividing line – nor should there be*" (Quote from Physician Dr. Rudolf Virchow 1856, cited by Klauder (1958)). While the idea of "*one health, one medicine*" was recognized two centuries ago, it has recently regained currency as it is increasingly appreciated that the genomes, gene expression, and physiologies of humans and other animals share many commonalities. Therefore, environmental-induced disruptions discovered in animals are relevant to human populations.

1.1. Endocrine disrupting chemicals

To date, one of most common classes of environmental contaminants are endocrine disrupting chemicals (EDCs). The Endocrine Society defines an EDC as any chemical that can interfere with any aspect of hormone action. EDCs typically bind to hormone receptors and can activate, or repress and/or interfere with hormone synthesis and metabolism. EDCs act via nuclear receptors, nonnuclear steroid hormone receptors (e.g., membrane, non-steroid receptors (e.g., neurotransmitter receptors such as the serotonin receptor, dopamine receptor, norepinephrine receptor), orphan receptors (e.g., aryl hydrocarbon receptor), enzymatic pathways involved in steroid biosynthesis and/or metabolism, and numerous other mechanisms that converge upon endocrine-controlled and reproductive systems (Diamanti-Kandarakis et al., 2009). In addition to binding directly to receptors, EDCs can alter expression of genes required for reproductive and immune functions through epigenetic mechanisms.

Most EDCs are manufactured chemicals (Diamanti-Kandarakis et al., 2009), and, of these, bisphenol A (BPA) is one of the most widely produced (Environment Canada, 2008; Galloway et al., 2010), with production reported to be 15 billion pounds in 2013 (GrandViewResearch, 2014; Vandenberg et al., 2013). The global BPA market is expected to reach USD 20.03 billion by 2020 (GrandViewResearch, 2014; Vandenberg et al., 2013). BPA is used in numerous products and applications, including polycarbonate plastic, the lining of metal food cans, some dental sealants and thermal receipt paper, food and water preparation and storage vessels, household products and many other uses. The pervasiveness of this chemical (Environment Canada, 2008) predicts widespread and continued exposure of animals and humans (Vandenberg et al., 2013). BPA is almost ubiquitously found in people; detectable in the urine of 93% of the US population (Calafat et al., 2008), as well as in fetal plasma, placenta (vom Saal et al., 2007), and in breast milk (Vandenberg et al., 2007).

The National Toxicology Program (2008) determined there is "*some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A*", although this report prepared in 2007 does not include the most current findings about BPA (Vandenberg et al., 2013). A second NIH-sponsored report published in 2007, the Chapel Hill Consensus Statement, indicated that extensive data in rodents identified the potential for adverse outcomes in humans due to exposure during critical periods of development, and that the changes would likely be irreversible (vom Saal et al., 2007). Ethical considerations, however, make any study of potential vulnerabilities in children to BPA limited to epidemiological approaches that reveal correlations but not causation (Collaer and Hines, 1995; Rochester, 2013; Trasande et al., 2012).

Another environmental estrogen that is prevalent globally is 17α-ethinyl estradiol (EE2), the active estrogen in birth control pills (Caldwell et al., 2012; Hinteman et al., 2006; Kostich et al., 2013; Lu et al., 2011; Pojana et al., 2004; Zhou et al., 2012). As discussed below, this chemical is also present in a range of aquatic sources and has been reported to have widespread effects in various aquatic species. Moreover, EE2 is considered the FDA-approved positive control for BPA studies that are to be used to guide policy decisions. In this review, we will consider the effects of BPA and EE2 in various taxa. This review will primarily focus on the known effects of these two chemicals in the aquatic taxa that are at the greatest risk for exposure. Effects observed in these populations will very likely translate to humans.

Past research has provided a comprehensive analysis of BPA and EE2 concentrations in a variety of water sources (Caldwell et al., 2012; Environment Canada, 2008; Flint et al., 2012; Hinteman et al., 2006; Kang et al., 2007; Kostich et al., 2013; Lu et al., 2011; Pojana et al., 2004; Zhou et al., 2012). Recent advancements in measuring estrogenic activity and assaying for select EDCs have permitted even finer-tuned assessments of aquatic contamination. BPA has been identified in both ground and surface waters, while EE2 is primarily found in surface water sources (Crain et al., 2007; Environment Canada, 2008; Flint et al., 2012; Kang et al., 2007). It is now recognized that sites deemed by the Environmental Protection Agency (EPA) as Superfund sites are contaminated with a variety of EDCs, including BPA (Agency, 1974). Fish, amphibian, aquatic reptile and mammalian species in these areas may be considered the "*canaries in the mine*", as they may be at the greatest risk (Vandenberg et al., 2013). We will thus first consider the concentrations of these chemicals in the different water sources and potential bio-indicators.

Normal development of the reproductive system and programming of later adult behavioral and cognitive traits are dependent upon the correct concentration and timing of exposure of the organs to steroid hormones, in particular estrogen and testosterone (Arnold and Breedlove, 1985; Forest, 1983; Gilmore, 2002; Morris et al., 2004; Nakamura, 2010; Nugent et al., 2012; Phoenix et al., 1959; Robinson, 2006; Schulz et al., 2009). Sex steroid hormones also play a key role in the timing of the transitions between prematurational stages of development, in the scheduling of reproduction, and in determining onset of senescence. Androgens and estrogens might also affect these processes through initiation of epigenetic changes (Gabory et al., 2009, 2011; Matsuda et al., 2012; Menger et al., 2010). Moreover, these hormones influence sex determination in fish, amphibians, and reptiles (Baroiller and D'Cotta, 2001; Crews et al., 1995; Dumond et al., 2008; Elf, 2003; Jeyasuria and Place, 1998; Nakamura, 2009, 2010; Pieau et al., 1999, 2001; Ramsey and Crews, 2009; Wibbels et al., 1998; Yao and Capel, 2005). For these reasons, sexual development and later adult behaviors in various species are hypothesized to be vulnerable to developmental exposure to EDCs, including BPA and EE2. Skewed sex ratios in the above species may also serve as a barometer for the presence of these chemicals in the local environment (Guillette, 2000).

We will next consider the effects of these EDCs on sexual and brain development in fish, amphibians, and aquatic reptiles and mammals, even though specific effects in aquatic reptile species with temperature sex determination (TSD) may not fully translate to mammals and humans with genetic sex determination (GSD). In male fish, amphibians, and reptiles, BPA and other estrogenic chemicals are known to bind to ERs and induce the production of vitellogenin (VTG) (Crane et al., 2007; Goksoyr, 2006; Marin and Matozzo, 2004; Palmer and Palmer, 1995; Porte et al., 2006; Sumpter and Jobling, 1995). Therefore, this protein, along with several other genes and their protein products listed below are considered circulating biomarkers of exposure in these species, but similar diagnostic biomarkers have not been identified in mammalian species, including humans. Potential candidates for