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Parental effects of endocrine disrupting compounds in aquatic wildlife: Is there evidence of transgenerational inheritance?

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ABSTRACT

The effects of endocrine disrupting compounds (EDCs) on aquatic wildlife are increasingly being recognized for their complexity. Investigators have detected alterations at multiple levels of biological organization in offspring exposed to EDCs through the blood or germ line of the parents, suggesting that generational consequences of EDCs are evident. Exposure to EDCs through the parents is concerning because if the resulting phenotype of the offspring is heritable and affects fitness, then evolutionary consequences may be evident. This review summarizes the evidence for transgenerational effects of EDCs in aquatic wildlife and illustrates cases where alterations appear to be transmitted maternally, paternally, or parentally. The literature indicates that EDC exposure to the parents induces developmental, physiological, endocrinological, and behavioral changes as well as increased mortality of offspring raised in clean environments. What is lacking, however, is a clear demonstration of heritable transgenerational effects in aquatic wildlife. Therefore, it is not known if the parental effects are the result of developmental or phenotypic plasticity or if the altered phenotypes are durably passed to subsequent generations. Epigenetic changes to gene regulation are discussed as a possible mechanism responsible for EDC induced parental effects. Additional research is needed to evaluate if heritable effects of EDCs are evident in aquatic wildlife, as has been demonstrated for terrestrial mammals.

1. Introduction

The role of endocrine disrupting compounds (EDCs) in altering the physiological performance of aquatic wildlife is a topic that continues to garner attention. In particular, the study of EDCs has focused on chemical-induced alterations to the hypothalamus-pituitary-thyroid (Carr and Patiño, 2011) and -gonadal axes (Tyler et al., 1998). As defined by the Endocrine Society, an EDC is "a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment" (Diamanti-Kandarakis et al., 2009). Evidence exists that EDCs induce life-stage dependent physiological responses depending on the developmental state of the organism (Guillette et al., 1995). For example, EDC exposure early in life can induce durable changes that become evident only as an adult (Milston et al., 2003; Schwindt et al., 2014). Of additional concern is the possibility that EDCs induce changes in the parents that can be passed to the offspring and affect their physiological performance (Skinner et al., 2011). This is despite the offspring never having experienced the chemical directly in the environment. Changes observed in subsequent generations following exposure to the parents suggest that those altered phenotypes may be heritable (Skinner et al., 2011). If the changes affect fitness, as has been demonstrated in mammals (Anway et al., 2005), transgenerational inheritance of effects resulting from EDC exposures could influence evolutionary processes (Bossdorf et al., 2008). Despite the extensive use of aquatic organisms in ecotoxicological research, transgenerational effects of EDCs in aquatic wildlife are poorly understood. It has been known for some time that larval stages are more sensitive to EDC exposure than adults (e.g. McKim, 1977), and that female oviparous animals transfer EDCs to their eggs (e.g. Brooks et al., 1997; Miller, 1993). Transgenerational inheritance of EDC effects has been convincingly demonstrated in mammals (Anway et al., 2005; Bruner-Tran and Osteen, 2011; Chamorro-García et al., 2013; Crews et al., 2007; Manikkam et al., 2013, 2012; Wolstenholme et al., 2012). Therefore, the possibility exists that transgenerational consequences of parental EDC exposures exist for aquatic organisms as well. The purpose of this review is to synthesize the current findings and suggest critical research needs related to potential transgenerational effects of EDCs in aquatic organisms.

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Transgenerational effects are alterations in offspring endocrinological, physiological, or developmental performance due to a change in the environment experienced by the parents, or the F0 generation in the case of asexual or parthenogenic organisms. The transgenerational effects may persist over multiple generations even in an unaltered environment (Skinner et al., 2011). This suggests that the effects are passed through the germ line, are thus inherited by the offspring (Skinner et al., 2011), and may have evolutionary consequences (Bossdorf et al., 2008; Jablonka and Raz, 2009). Transgenerational effects can result from a variety of alterations in the parental environment. For example, the nutritional state of zebrafish (*Danio rerio*) parents (Schwerte et al., 2005), environmental temperature in the sheepshead minnow (*Cyprinodon variegatus*) (Salinas and Munch, 2012), and parental disease state of humans (Gluckman et al., 2007) can all induce transgenerational effects. In the field of ecotoxicology, the primary variable of interest with regard to transgenerational effects is exposure to EDCs present in the environment. Transgenerational effects in aquatic ecotoxicology are poorly studied but could play an important role in how aquatic organisms respond to contaminants over multiple generations.

The review begins by addressing the parental, maternal, and paternal effects of EDCs in aquatic vertebrates and invertebrates and is organized by taxa where published literature exists. In all examples discussed herein, the gametes of the parental generation (F0) just prior to fertilization and subsequent effects on all developmental stages are defined as effects on the F1 generation. Likewise, the F1 gametes pre- and post-fertilization and all subsequent effects on the offspring of the F1 generation are defined as effects on the F2 generation. I discuss epigenetics as a mechanism behind transgenerational inheritance of EDC effects and the possibility of such occurrences in aquatic taxa. I conclude the review with a discussion of potentially promising and efficient experimental designs and suggest animal models for detecting transgenerational effects.

2. Parental effects

Parental effects are those which derive from exposure to both parents in the laboratory or parents collected from the same polluted environment. This does not necessarily indicate that both parents contribute equally to the generational consequences. Rather, one cannot distinguish the difference between the maternal or paternal contributions because both sperm and egg were exposed. In some cases the parents are exposed early in life and allowed to recover for an extended period of time prior to reproduction (e.g. Holdway et al., 2008; Schwindt et al., 2014). In other cases reproductively mature adults are exposed and then transferred to clean water just prior to reproduction (e.g. Foran et al., 2002; Matta et al., 2001). The biological responses observed from parental exposures are diverse and include effects on survival, behavior, growth, reproduction, hormone production, enzymes, and gene expression.

2.1. Fish

17α-ethinylestradiol (EE2), a common constituent in human contraceptive pills, is a frequently used estrogen for studying parental effects in vertebrates and invertebrates (Nash et al., 2004; Schwindt et al., 2014; Segner et al., 2003). To evaluate the parental effects of EE2 on reproductive parameters in the saltwater sheepshead minnow, Zillioux et al. (2001) exposed mixed sex populations to waterborne EE2 (1.7, 18.1, 117, 723 ng/L) from the subadult stage to sexual maturity (Table 1). Mature F0 were removed from EE2 and allowed to reproduce for 14 days in clean water. Hatch success in the F1 was reduced at 18.1 and 117 ng/L compared to water and vehicle controls (triethylene glycol) (Zillioux et al., 2001). Generational effects of EE2 on the zebrafish have also been identified. Compared to water controls, reduced fertilization success of the F1 generation parentally exposed to waterborne EE2 (3, 4.5 ng/L) prior to sexual maturation and then raised in clean water has been observed (Nash et al., 2004; Segner et al., 2003). Likewise, Hill and Janz (2003) observed reduced egg viability and hatchability compared to vehicle (acetone) controls in F1 zebrafish whose parents were exposed to waterborne EE2 (10 ng/L) from 2 to 60 days post hatch and then reared to adulthood in clean water (Table 1). In the fathead minnow (*Pimephales promelas*), reduced F2 embryonic survival and reduced numbers of F2 larvae compared to water controls were observed following EE2 exposure (3.2 ng/L) to the F1 parents early in life (Schwindt et al., 2014) (Table 1). Notably, the effects described above (Hill and Janz, 2003; Nash et al., 2004; Schwindt et al., 2014; Segner et al., 2003) occurred at environmentally relevant EE2 concentrations (Kostich et al., 2013).

Effects on endpoints directly relevant to the endocrine system are also evident following parental EE2 exposure. Adult medaka (*Oryzias latipes*) were exposed to waterborne EE2 (0.2, 5, 500, 2000 ng/L) for 2 weeks and allowed spawn (Foran et al., 2002). Resulting F1 offspring were raised to adulthood (3 months) in clean water and assessed for hepatic estrogen receptor (ER) and vitellogenin (VTG) content (Table 1). VTG is an estrogen responsive protein and used as biomarker of estrogen exposures (Schwindt et al., 2007). Compared to vehicle (ethanol) controls, F1 males parentally exposed to 2000 ng/L showed increased hepatic ER, and hepatic VTG increased in F1 females whose parents were exposed to 0.2 ng/L (Foran et al., 2002). Altogether, the results suggest that EE2 induces a suite of parental effects in fish ranging from decreased survival to improper activation of estrogen signaling pathways.

The detergent additive nonylphenol (NP) binds weakly to ERs (Blair et al., 2000) and induces physiological changes in male fish such as induction of VTG (Pedersen et al., 1999). Parental effects of NP include reduced F1 hatch success (Hill and Janz, 2003; Holdway et al., 2008) but directly relevant endocrine effects can last for years after the original exposure. Schwaiger et al. (2002) exposed F0 rainbow trout (*Oncorhynchus mykiss*) to NP (1.2, 10.4 μg/L) for 4 months and then induced spawning. In the F1 offspring, there was no effect on male VTG or sex ratios, but female VTG was elevated (10.4 μg/L) compared to water controls (Table 1). Interestingly, NP disrupted steroid hormone biosynthesis because 17β-estradiol (E2) was elevated in F1 males and testosterone (T) was 13× higher in treated females (10.4 μg/L) compared to water controls. The effects on the sex steroids were evident even though F1 fish were reared for three years in clean water (Schwaiger et al., 2002).

Compared to the parental effects of EDCs on reproductive endpoints, parental effects on growth and development have received little attention. However, some evidence exists for parental effects of brominated flame retardents on growth and development. Polybrominated diphenyl ethers (PBDE) are currently used as flame retardants, are similar in structure to polychlorinated biphenyls (PCB), and are ubiquitous in the environment (Hooper and McDonald, 2000). Physiological effects following controlled exposures point toward disruption of the thyroid axis (Carr and Patiño, 2011). To assess the parental effects of PBDEs, Yu et al. (2011) exposed F0 zebrafish to a waterborne PBDE mixture (DE-71) (1, 3, 10 μg/L) from the embryo stage to sexual maturation (5 months). PBDE concentrations in the eggs transferred maternally ranged from 1689 to 13,701 (ng/g) (Yu et al., 2011) (Table 1). Decreased F1 hatch success and growth were observed following parental exposures to PBDEs (3 and 10 μg/L) compared to vehicle (dimethyl sulfoxide (DMSO)) controls (Yu et al., 2011).