Review article

Mate choice, sexual selection, and endocrine-disrupting chemicals

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ABSTRACT

Humans have disproportionately affected the habitat and survival of species through environmental contamination. Important among these anthropogenic influences is the proliferation of organic chemicals, some of which perturb hormone systems, the latter referred to as endocrine-disrupting chemicals (EDCs). EDCs are widespread in the environment and affect all levels of reproduction, including development of reproductive organs, hormone release and regulation through the life cycle, the development of secondary sexual characteristics, and the maturation and maintenance of adult physiology and behavior. However, what is not well-known is how the confluence of EDC actions on the manifestation of morphological and behavioral sexual traits influences mate choice, a process that requires the reciprocal evaluation of and/or acceptance of a sexual partner. Moreover, the outcomes of EDC-induced perturbations are likely to influence sexual selection; yet this has rarely been directly tested. Here, we provide background on the development and manifestation of sexual traits, reproductive competence, and the neurobiology of sexual behavior, and evidence for their perturbation by EDCs. Selection acts on individuals, with the consequences manifest in populations, and we discuss the implications for EDC contamination of these processes, and the future of species.

1. Introduction

As a species, humans have had a disproportionate influence on the quality of our environment. This accelerated during the Industrial Revolution, when heavy metals and coal contaminated the air, soil, and water. By the mid-1800s the burning of coal in England polluted the air, particularly in the midlands north of Birmingham, the heart of industrialization in that country. This resulted in a shift in the peppered moth morphological phenotype. The normal light color of this species was conspicuous against the accumulated soot on trees and other surfaces, making it easy prey. The less common dark (melanic) phenotype became more prevalent (Kettlewell, 1955). Recent evidence indicates this color shift is attributable to a small suite of genes involving a specific mutation that appeared in 1819 (Van't Hof et al., 2016; van't Hof et al., 2011). As air quality has improved, "the dark-colored peppered moths are vanishing as quickly as they emerged" (Editorial Board, Nature, 2016). This is an early example of an adaptive change in a species in response to anthropogenic contamination, and the potential for humans to influence evolutionary change.

The consequences of the more recent Chemical Revolution, beginning in the mid-twentieth century, have been accumulating over the past 75 years. A subset of these chemicals or their breakdown products

can mimic the action of naturally occurring hormones. These are designated as endocrine-disrupting chemicals (EDCs), defined by an Endocrine Society expert group as "chemicals or mixtures of chemicals that mimic, block, or interfere with hormones in the body's endocrine system" (Zoeller et al., 2012). EDCs have been best studied for their actions on the body's endocrine functions, particularly reproduction, thyroid, metabolism (including diabetes and obesity), and hormone-sensitive cancers such as those of the prostate, breast, and endometrium (Gore et al., 2015).

Of these endocrine systems, the influence of EDCs on reproduction has the deepest history, beginning in the 1960s with Rachel Carson's *Silent Spring* (Carson, 1962). This book called attention to the devastating consequences of widespread pesticide use on wildlife, and brought this issue to the forefront of public awareness for the first time. Since then, hundreds if not thousands of papers have documented adverse reproductive outcomes of a broad spectrum of chemicals, not just pesticides but also industrial chemicals, plastics and plasticizers (Fudvoye et al., 2014; Wang et al., 2016). Of particular importance are studies demonstrating the particular vulnerability of the developing organism. It is not surprising that fetal, infant, and adolescent developmental stages are highly sensitive to EDCs; these are phases of life when endogenous hormones undergo dynamic changes that are

responsible for growth, maturation, and sexual development (Pinson et al., 2016; Walker and Gore, 2017). In the case of reproductive systems, this includes the progressive and sequential development of the reproductive tract, accessory sex structures and secondary sexual characteristics in response to gonadal hormones. The brain's neuroendocrine systems controlling hypothalamic-pituitary-gonadal function also play key roles, as a hypothalamic neural network must develop properly to result in appropriate male- and female-specific reproductive physiology and behavior (Pinson et al., 2016; Walker and Gore, 2017).

Despite the wealth of information on EDCs on reproduction, there is relatively little consideration of how EDCs might alter sexual selection, influence reproductive success, and ultimately, drive evolutionary change (Crews et al., 2007; Jasarevic et al., 2012; Rosenfeld and Trainor, 2014; Skinner, 2015). The vast majority of experimental studies have relied on pairing animals in the laboratory and determining whether offspring were produced. This is a crude measure of reproductive success that does not take into consideration the complexities of mate choice. Thus, the evidence for effects of EDCs on the more subtle yet realistic aspects of mate choice is largely lacking. In this article, we will provide background on sexual selection and discuss areas of research that are needed to connect EDC exposures to this process.

2. Sexual selection: the importance of mutual mate choice

Although the observation of change in form through time, or evolution, had been commented on, Darwin provided the first plausible mechanism through which evolution could be achieved, namely natural selection. Natural selection was believed to work via certain individuals having a functional advantage for breeding and survivorship (Darwin, 1888). As genetics became an established science and was incorporated into evolutionary theory, NeoDarwinians focused on the Biological Species Concept, which asserted that sexual behavior evolved to identify and separate species; change in form and function was due to accumulation of advantageous mutations. This enabled individuals carrying these mutations to be more likely to successfully reproduce and pass on the genetic underpinnings of these functional advantages.

Sexual selection is a mode of natural selection, operating through two processes: *intrasexual* competition, by which members of the same sex compete for access to mates; and *intersexual* selection, with members of one sex choosing mates of the opposite sex. Sexual selection per se comprises two components (Gowaty, 2015). First, the mechanisms involve behavioral, physiological, and opposite-sex mate choice. Second, reproductive success is operationally defined as individuals whose young themselves produce young (i.e., grandchildren). Since evolution depends upon reproductive success, the individual will try to choose the best mate of those available (Carson, 2003). This was a fundamental change in perspective; that is, from viewing behavior as a barrier to hybridization of species to an emphasis on traits that best reflect the overall fitness of the individual. The premise is that certain individuals will be more successful at reproducing due to higher fitness, such as being a more attractive mate or expressing traits that give them an advantage as competitors (Darwin, 1888).

Here we focus on reciprocal mate choice, as this is what occurs in nature (Fig. 1). Although not specifically stated by Darwin, it was assumed that the individual chosen must also accept the courting individual as a mate (Carson, 1987). This wisdom has been practiced in animal husbandry since before biblical times. The experimental work on mate choice is relatively recent, dating to F.H.A. Marshall (Marshall, 1936). Lehrman's (1965) pioneering studies on the ring dove, in retrospect, have not been followed. One of the few, and first, studies is that of Huck et al. (Huck et al., 1985) in which female hamsters selected from three potential mates in a large seminatural enclosure. Indeed, in most instances, actual apparati used have been highly artificial, usually limiting choice to one of two individuals under rather spartan conditions. In behavioral ecological research the reproductive state of the

stimulus animals often are not known, while in experimental laboratory work the hormonal states of the stimulus animal are controlled. Finally, it is assumed that the stimulus animals are typical of the species. This last stipulation becomes problematic when we consider the effects of EDCs on individuals.

While we emphasize the importance of mutual mate choice, the choice is typically the female's domain due to her greater investment in producing young. Despite this, the chosen males still have to accept the females as partners. The basis for female choice includes characteristics such as colorful plumage and elaborate song in birds, colorful patterns in scales in reptiles and fish, and courtship dances in many classes; these are some of the traits employed by males to display themselves as attractive mates for female choosers, who evaluate these cues prior to mating (Ryan, 1990). In other mating systems where males are the rare (limiting) sex, e.g., pipefish and phalaropes, the male is courted by females and it is he who chooses the mate.

Individual differences in both the presentation of sexual traits as well as how others perceive these traits matters profoundly. Mate choice experiments in the laboratory, while useful, do not mimic how, in nature, dyadic interactions allow for mutual agreement. Frank Beach early on advocated a 'holistic' approach that included the male and the female as an interacting unit and the importance of individual differences (Beach, 1947; Beach, 1983). This concept was further developed by Daniel S. Lehrman in his studies of the reproductive cycle of the ring dove (Lehrman, 1965). How individual differences are negotiated to form long-lasting bonds was a long-standing research effort with beagles by Beach. For example Beach and LeBoeuf (1967) found that receptive bitches displayed a preference for particular males and would go so far as to attack other males whose advances they did not want. Another remarkable example of how forced, versus free, choice is important is illustrated by the work of Brennan and colleagues (Brennan et al., 2010). In ducks, males will occasionally flock together and forcefully mate with a female. The oviduct of female ducks has evolved in both form and function; there are receptacles that can redirect the penis, and hence impair sperm delivery. This modification is employed during such forced copulations, thereby avoiding insemination. Thus, the performance failure by a partner (unsuccessful fertilization) leads to new mates being sought.

This individual variation is the substance of evolutionary change, and making the correct choice of a mate can dictate a female's reproductive success. This is seen particularly in long-lived species where it has been possible to monitor an individual's lifetime reproductive success. For example, in a now 24-year study in the monogamous blue-footed booby, Drummond and colleagues found that bonded couples that stayed together over several breeding season hatched more eggs, produced more fledglings, and established their clutches earlier than newly coupled birds (Sanchez-Macouzet et al., 2014). In this species, the basis for female choice is the coloration of the males' feet, with bright blue-footed males chosen over darker-footed males. The bright blue pigmentation comes from carotenoid found in fish and, hence, the pigmentation in the feet reflects the foraging ability of the male. The degree of pigmentation is also an indication of the male's immune condition. As males age the quality of the webbing degrades and is indicative of sperm quality (Cronin, 1993; Velando et al., 2006). If females are forced to mate with dark blue-footed males, egg survival is decreased. If the bright-blue feet are masked with dark blue mascara, females will avoid these males (Velando et al., 2006). A similar situation was found in Coulson's 35-year study of kittiwake gulls in Northumberland, England, a species that often pairs for life. Not only do successful kittiwake pairs fledge more young; they also produce eggs faster, indicating that females in these pairs reach breeding condition earlier (Coulson, 2011). Some pairs of kittiwakes, however, were found to have a different mate the next breeding season. About half of these pairs did not re-form, possibly due to death of one partner. In the other half, pairs of kittiwakes "divorced." The cause of divorce could be traced to the failure of the pair to fledge at least one egg the preceding
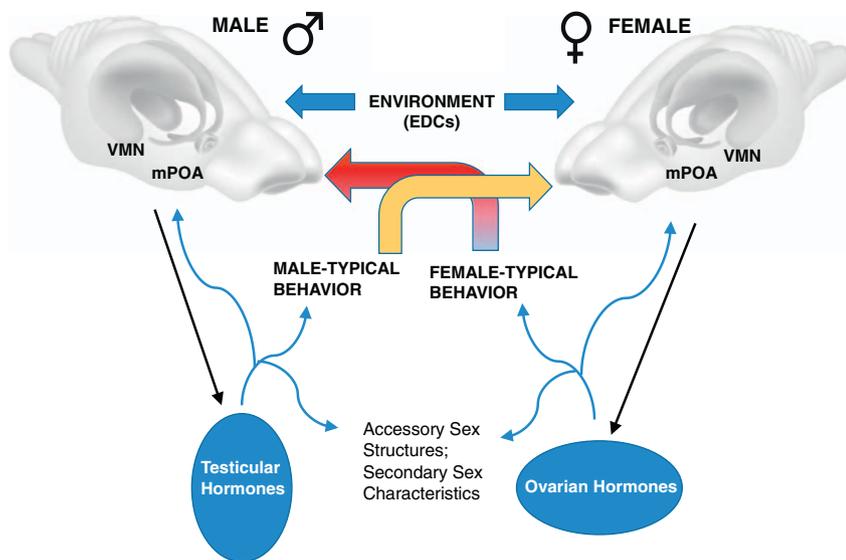
Fig. 1. Model of the complementarity of the sexes during mating. The male and female must interact, assess and choose a mate. In nature this is a mutual choice and is dependent upon a variety of conditions. Changes in the environment, such as EDCs, act upon individuals throughout their life history. If exposure occurs early in life, the entire sexual phenotype can change, rendering such individuals as adults infertile or unable to communicate and perceive signals from other individuals properly. The interaction is reciprocal, which includes both the hormonal feedback loop within each individual (hypothalamic-pituitary-gonadal axis) as well as between the individual and its immediate environment. Within the brain two nuclei, the medial preoptic area (mPOA) and the ventromedial nucleus (VMN) also play complementary roles, where activity in one typically diminishes activity in the latter. The unit of selection in this context is the mating pair, and its reproductive success is paramount for life and evolution.
Modified from Crews (1977).

year. Thus, a pair's experience of reproductive success or failure reinforced or degraded, respectively, the bond between the male and female.

Bluhm (1985) has studied the reproductive consequences of pair incompatibility using canvasback ducks. The reproductive success of females that were allowed to stay with their self-chosen partner was compared with the reproductive success of females that were separated from their self-chosen partner and paired with another male chosen at random. The results were clear-cut. Only females from pairs with self-selected males laid eggs. Females paired with males that were not chosen by her (i.e., force-paired) did not exhibit the changes in pituitary luteinizing hormone secretion essential for ovulation (Bluhm et al., 1983). A similar situation was found in the cockatiel in which reproductive success was enhanced if females were allowed to choose a mate as opposed to forced-pairing (Yamamoto et al., 1989).

Behavioral facilitation of reproductive success has been demonstrated in other species and classes of animals, including fruit flies, lizards, mice, zebra finches and, recently, in pandas. In all of these circumstances, free mate choice promoted reproductive outcomes despite these species practicing very different mating strategies (Crews, 1977; Crews et al., 1986; Crews and Silver, 1985; Crews et al., 1985; Drickamer et al., 2000; Gowaty et al., 2003; Ihle et al., 2015; Martin-Wintle et al., 2015). A well-studied mammalian example is the house mouse, a promiscuous species that exhibits significant increases in reproductive fitness and in offspring fitness with partners they are allowed to choose. When male house mice were allowed to mate with preferred partners, they had fewer fertility problems, increased offspring survivability, and their offspring performed better in tests of aggression when compared to offspring from forced-pairing (Drickamer et al., 2003; Gowaty et al., 2003). When female house mice were allowed to choose their mates, a similar pattern emerged (Drickamer et al., 2000). The profound benefits of free mate choice paradigms have recently been demonstrated for the giant panda. By allowing free mate choice breeding success was increased, resulting in the status of the giant panda being upgraded from endangered to vulnerable (Martin-Wintle et al., 2015). Thus, mate choice is bi-directional, a dynamic reciprocating system focused on reproduction (Crews, 1977; Lehrman, 1965). Both males and females simultaneously evaluate and make decisions about preferred partners vs. non-preferred partners. The correct choice can lead to increased offspring fitness (Ah-King and Gowaty, 2016).

This literature shows that the choice of a sexual partner is based on mate quality cues, which are the result of both its developmental history and experience. Any disruption of sexual cues through shifts in the trajectory of sexual characteristics could change the perception of the quality of a potential mate. This is devastating for an individual, and if it happens within a large number of individuals within a population could have dire consequences, including population declines or even extinction.

3. Reproductive development, hormones, and sexual characteristics

Individuals must attain the morphological and physiological ability to reproduce, a process that depends upon the antecedent events of gonadal sex determination, the subsequent development of the accessory sex structures (reproductive tract and genitalia), and the later maturation of the organism by pubertal hormones, leading to the development of secondary sex characteristics that distinguish males and females and serve as the basis for mate choice (Crews, 1998). In addition, the physiological and behavioral aspects of the sexual phenotype become manifest at the end of the pubertal process, enabling the display of sex-typical behaviors and their coordination with physiological status (e.g. ovulatory function in females, spermatogenic function in males).

Whereas gonadal sex determination is independent of sex hormones, development of the reproductive tract (accessory structures that transport sperm/ova) occurs under the influence of gonadal steroid hormones in a sexually dimorphic manner. While the gonadal steroid hormones – estrogens, androgens, and progestins – show species differences in metabolic pathways, the timing and levels of their synthesis and release differ profoundly between testes and ovaries in developing organisms. The differentiation of the male and female reproductive tracts occurs under the influence of anti-Müllerian hormone and testosterone. The much higher concentrations of androgens in males lead to the masculinization of the genitalia in the fetus; the relative absence of androgens results in female genitalia.

As embryonic development progresses, sexual differentiation of the brain begins to take place due to steroid hormone actions in the nervous system. In brief, gonadal steroids, especially testosterone and estradiol, first organize the brain through actions on their receptors, leading to cellular changes that provide the anatomical framework for appropriate behavioral responses later in life. This process is dependent upon the temporal activation/repression of suites of genes in a cell- and sex-specific manner, and result in sex differences in neuronal and glial birth, survival, connectivity, and phenotype (Davis et al., 1996; Forger

et al., 2004), processes that involve epigenetic molecular programming of relevant genes (Forbes-Lorman et al., 2012; Forger, 2017; McCarthy and Nugent, 2013). In mammalian species, this period of anatomical organization of the brain usually happens in late embryonic/early postnatal development and is followed by a period of quiescence, often protracted, prior to the onset of puberty. Then, the gonads reawaken and begin to synthesize and secrete hormones in a sex-typical manner. Again, the ovaries and testes produce the same hormones, but the absolute concentrations, ratios, and secretion patterns differ radically between the sexes (Walker et al., 2012). The activation of sexually-dimorphic neural circuits enables males and females to engage in sex-typical reproductive behaviors necessary for the initiation and completion of mating.

During puberty, the increasing concentrations of gonadal steroid hormones also lead to the development of secondary sexual characteristics of the mature male or female, for the first time. These characteristics play a vital role in sexual selection since they are used as visual indicators of mate quality. Although secondary sexual traits are typically expressed by one sex, the capacity to develop traits typical of the opposite sex is present if inappropriate hormone exposures take place.

Puberty is a transition from adolescent to adult behavior and morphology, occurring under the influence of gonadal steroids. Beginning in puberty and thereafter, sex steroids from both the gonads and adrenals hormones modulate neural networks and context-dependent gene expression such that the individual perceives and responds appropriately to sexual cues from a potential reproductive partner. This occurs in seasonally breeding populations as well as in individuals in populations that do not display discrete breeding periods.

While most of this type of work has been conducted in the laboratory using inbred rodents, a smaller, but comparable body of work has been conducted with songbirds to understand the mechanisms of production and reception of song. However, research with other vertebrate classes is relatively sparse (Kabelik and Crews, 2017). Nevertheless, it is clear that the pubertal process culminates with both the manifestation of characteristics that form the basis for mate choice, as well as the ability to discriminate based on the quality of these traits.

4. EDCs, sexual development, and reproductive capacity

EDCs have been shown to influence every aspect of sexual development studied to date. Early in the field's history, the feminization of male mosquito fish in the effluent waters of a pulp mill was discovered (Howell et al., 1980). Subsequent work on fish in waterways around the world has demonstrated the presence of fish with gonads and accessory sex structures that do not match their genetic or apparent morphological sex (Blazer et al., 2007; Liney et al., 2006). Recapitulation of the chemical exposures in the lab under controlled conditions, especially with estrogenic compounds, affirmed the cause-and-effect relationship between chemical contamination and sexual abnormalities in fish (Rodgers-Gray et al., 2001).

Fetal exposures to EDCs have been linked to a suite of developmental abnormalities in the reproductive system of males that collectively have been referred to as the "testicular dysgenesis syndrome" (Skakkebaek et al., 2016). Animal studies clearly show that exposures to industrial chemicals such as polychlorinated biphenyls (PCBs), plastics/plasticizers (bisphenol A (BPA), phthalates), and pesticides (DDT, methoxychlor) cause anatomical and functional anomalies in male reproductive organs, diminished semen quality, and impaired fertility (Gore et al., 2015). For example, exposure in utero to vinclozolin, an anti-androgenic fungicide, or to the estrogenic pesticide methoxychlor, during late gestation in rodents altered sexual development and reproductive function as the young matured (Chapin et al., 1996; Fisher, 2004; Kelce et al., 1994). These males had increased spermatogenic cell apoptosis, decreased sperm number and motility, and eventual infertility (Cupp et al., 2003; Uzumcu et al., 2004). In

humans, there is epidemiological evidence for associations between higher body burdens (tissue content) of EDCs and poorer reproductive outcomes in the clinic (Buck Louis et al., 2016), consistent with laboratory animal studies. Moreover, the incidence of testicular dysgenesis syndrome in humans has increased over the last half-century, co-incident with the exponential increase in environmental chemicals (Juul et al., 2014; Luccio-Camelo and Prins, 2011). Wildlife are similarly affected, with the best examples provided by PCBs, persistent chemicals that bioaccumulate up the food chain (Borrell et al., 2010; Durante et al., 2016; Sonne, 2010; Sonne et al., 2015).

In females, an "ovarian dysgenesis syndrome" has been proposed, similar to testicular dysgenesis syndrome in males, with the suggestion that EDC exposures are contributing to this phenomenon (Johansson et al., 2017). Ovulatory function (oogenesis and ovulation) in females has been directly linked to EDC exposures in the laboratory. For example, developmental exposures to the pesticide methoxychlor inhibited folliculogenesis and disrupted follicular development as they progressed from primary to antral stages (Uzumcu et al., 2006). In animals, developmental exposures to industrial, agricultural, and food-contact chemicals caused structural changes to the female reproductive tract that diminished ovulatory capacity, perturbed implantation of embryos in the mammalian uterus, and led to subfertility or infertility, among other actions (Wang et al., 2014). In women, endometriosis and other uterine abnormalities are more prevalent in those with higher EDC concentrations in their bodies (Smarr et al., 2016). However, whether this is due to current, prior (including developmental), or cumulative EDC exposures across the lifespan is unknown in humans.

Because secondary sexual characteristics develop under the influence of, and are maintained by, steroid hormones, they are a potential target for EDCs. There are numerous examples of effects of pharmaceuticals and industrial chemicals on hormone-dependent traits of coloration and specialized scales or feathers in fish and birds (reviewed in Lifshitz and St Clair, 2016). These traits may be useful biomarkers of pollution exposure in the wild, but the extent to which they alter mate choice and, ultimately sexual selection, is largely unknown. One example of how a pharmaceutical exposure coloration and influences attractiveness is in the Gulf pipefish, a species in which sexual selection acts on females: they are a polyandrous species, with males receiving eggs from the female and carrying the "pregnancy," and access to males is the limiting resource in reproductive success (Jones and Avise, 1997). Due to this evolutionary pressure, female pipefish have deeply keeled abdomens, a large dorsal fin, and silvery-blue stripes (Partridge et al., 2010). Exposure of adults to 17α-ethinyl estradiol, a component of oral contraceptives that binds with high affinity to estrogen receptors, caused males to develop the silvery-blue stripes typically only displayed by females (Ueda et al., 2005). Treated males were less attractive mates to females and were also infertile.

It is obvious that reproductive anomalies associated with developmental EDC exposures are likely to impair successful reproduction. Do these changes play out as making such individuals less likely to be selected as potential mates, and ultimately, affect sexual selection in the species? This is an important question because an apparently healthy individual with underlying physical problems may still be chosen as a mate, a choice that would not be optimal if it is less likely to lead to healthy, surviving offspring. Furthermore, a change in a sexual characteristic may even make an individual appear *more* attractive, and bias selection to a less-fit mate. Finally, the same EDC exposures that cause anatomical/functional changes to the body may have behavioral consequences (e.g. a potential partner may not "act" like a good mate), an outcome that would diminish an individual's likelihood of being chosen.

5. EDCs and reproductive behavior: the complementarity of the sexes

Virtually all aspects of reproduction rely upon the complementarity

of male and female anatomy and behavior (Fig. 1). This theme of reciprocity also exists *within* an individual, namely, the masculine-feminine dichotomy and the capacity to manifest the behavior of the "opposite" sex depending upon the hormonal and social context (Crews, 2010). In the developing brain, the fact that organizational actions of hormones are needed to sculpt the neural circuitry in a manner that enables sex-typical reproductive behavior to be manifest in adulthood underscores the intrinsic nature of this duality, and its plasticity. While this is a deep field and beyond the scope of this article, it is relevant to our review that a complex network of brain nuclei contributes to the neurobiology of reproduction, referred to variously as the social behavior network (Newman, 1999) and more recently, as the social decision-making network (O'Connell and Hofmann, 2012).

EDCs have the potential to perturb any and all levels of inter- and intra-individual complementarity, and thereby diminish reproductive success. The literature on developmental EDC exposure and reproductive behavior is large and has been reviewed (Gore et al., 2015; Zala and Penn, 2004), albeit not in the context of potential implications for sexual selection. Nevertheless, chemicals including atrazine (Belloni et al., 2011), BPA (Jones and Watson, 2012; Negishi et al., 2014; Sullivan et al., 2014; Williams et al., 2013), PCBs, and many others (Mani et al., 2005; Moniz et al., 1999; Moniz et al., 2005) change reproductive behavior in males and females. We will return to this concept of brain, behavior, and sexual selection later, but first we will introduce two key nodes of the social decision making neural network are the medial preoptic area (mPOA) and the ventromedial nucleus (VMN). These nuclei have been a particular focus of work on the neurobiology of masculine and feminine reproductive behaviors, and contribute to individual differences in behavioral plasticity. These regions were first identified based on studies showing that lesions of the mPOA abolish masculine behaviors, and those of the VMN abolish feminine sexual behaviors (Stellar, 1954). This is now recognized as over-simplified with researchers proposing that masculine-feminine behaviors are on a continuum, a process that is dependent upon the mPOA, VMN, and their extended circuitry with each other and with other brain regions. The sex typical differences in behavior are the result of the tone of the activity in the constituent nuclei both individually and as a network. In sexual contexts, the activity in the social decision-making network is a consequence of the individual's developmental history as well as signature events thereafter. Evidence indicates that it pivots according to the reciprocally inhibitory interaction of two root nodes, the mPOA and VMN (Crews, 2010). There is considerable evidence that the mPOA and VMN are functionally related in an opposing fashion. Essential to this oscillation is the bi-directional neural connections between the mPOA and the VMN. Subregions of the mPOA are sexually dimorphic and organized by perinatal gonadal hormone exposures (Jacobson et al., 1980). While the VMN is not as well studied as the mPOA for its structural sexual dimorphisms, it is clear that phenotypic differences in cells of the VMN of males and females differ, including those for progesterone and estrogen receptors that are important for reproductive behavior (Cao and Patisaul, 2011; Yang et al., 2013). To follow is a brief synopsis of studies showing effects of developmental EDC exposures on the mPOA and VMN. Very little of this work utilized animals that were also behaviorally characterized; to our knowledge, no one has conducted studies that truly got at the complementarity of the sexes. This is clearly an important area for future research.

6. The mPOA and VMN: effects of EDCs

The mPOA is a central hub for the control of reproductive physiology and behavior, as well as maternal and other rewarding behaviors (Dominguez and Hull, 2005; Numan et al., 1977). Several EDCs, most notably BPA and polychlorinated biphenyls (PCBs), have been investigated for their actions on the developing mPOA of one or both sexes. We limit discussion to these two EDC classes as examples of their actions in this developing brain region. For the BPA field, it is important

to note that results between labs have differed, probably due to strain, species, timing of exposure, dose and route, and other husbandry or experimental factors, as well as the choice of endpoints. Nevertheless, the majority of papers have shown effects of developmental BPA exposures on sexually-dimorphic characteristics of the mPOA, particularly when cellular phenotypes of target cells (e.g. immunolabeling or gene expression for specific neuropeptides or receptors) were taken into consideration. Negative results (no BPA effect) were found for the volume of the sexually dimorphic nucleus (SDN) of the POA in rats (Takagi et al., 2004), for immunoreactive corticotropin-releasing hormone neurons (Funabashi et al., 2004), and for numbers of calbindin-positive cells in the mPOA of female mice, the latter marker selected to represent the sexually dimorphic nucleus (Naule et al., 2014). Another study in rats found that the SDN of males, but not females, was increased in volume by perinatal BPA treatments (He et al., 2012). Positive results (effects of perinatal BPA exposures) were found for decreased gene expression of estrogen receptor (ER) beta (*Esr2*) in female but not male rats when assessed at adulthood (Rebuli et al., 2014). In another study using only male rats, in utero BPA exposure did not change ER alpha (*Esr1*) mRNA, but increased *Esr2* expression (Ramos et al., 2003). A study on effects of low- or high-dose BPA exposure in female rats showed dose-dependent effects on methylation and expression of *Esr1* as well as ER alpha protein in the mPOA (Monje et al., 2007). In mice, lower-dose BPA exposures abolished the normal sex difference in tyrosine hydroxylase-positive neuronal expression in the POA (Rubin et al., 2006), again indicating that characterizing the phenotype of cells is important in determining whether or not there is an effect of this EDC. Similarly, in male mice, BPA selectively disrupted expression of androgen receptor-positive neurons in the mPOA, but not in other brain regions (Picot et al., 2014). Finally, effects of BPA on numbers of immunoreactive cells expressing neuronal nitric oxide synthase in the mPOA were observed in female but not male mice (Martini et al., 2010).

PCBs are a family of chemicals and mixtures previously used in industry, but persistent in soil, air, and water around the world. In fact, virtually all humans and wildlife tested have detectable concentrations of PCBs in their body tissues (Jepson et al., 2016). Developmental exposure of rats to a reconstituted mix of PCBs found in human breast milk decreased aromatase activity in a dissection containing the hypothalamic-POA regions of newborn males (Hany et al., 1999). In rat pups exposed prenatally to the PCB mixture, Aroclor 1221, or a reconstituted mix, no effects on mPOA volume or ER alpha-immunoreactive cells was found on the day after birth. However, a gene expression array revealed effects of each PCB mix, in a sex-specific fashion, on specific gene sets (Dickerson et al., 2011a). When siblings of these aforementioned rats were allowed to mature to early adulthood, completely different protein and gene expression results were found, underscoring that the age at phenotyping is important in determining the outcome of prenatal exposure. Specifically, at postnatal day 60, numbers of gonadotropin-releasing hormone neurons in the POA that co-expressed Fos, a marker of neural activation, were significantly suppressed in prenatally-exposed female rats (Dickerson et al., 2011b). In addition, gene expression of androgen receptor, NMDA receptor subunit 2b, insulin-like growth factor-1, and transforming growth factor-beta1, were reduced in the mPOA of female but not male rats exposed to PCBs. In recent unpublished work, we profiled expression of additional genes in the mPOA of animals prenatally exposed to Aroclor 1221, and found that in females, androgen receptor, *Esr1*, *Esr2*, and kisspeptin mRNAs were up-regulated, while in males, only the period 2 gene was affected (up-regulated; Topper et al., unpublished). In a recent study, prenatal or juvenile exposures to Aroclor 1221 decreased expression of androgen receptor, *Esr1*, mu opioid receptor, and oxytocin receptor in the mPOA of male but not female rats (Bell et al., 2016). Another lab exposed rats to the PCB mix Aroclor 1254, or another halogenated organic chemical, polybrominated diphenyl ether (PBDE) 99, and found that while there was no treatment effect on progesterone

receptor mRNA, *Esr1* was increased in both sexes of the PBDE99 higher dose treatment group; *Esr2* was increased by Aroclor 1254 in both sexes; and preproenkephalin mRNA was decreased by all of the EDC treatments (Faass et al., 2013).

The VMN is relatively poorly studied for effects of developmental EDC exposures. In the same study by Faass et al. described above for the mPOA, effects of BPA were also shown in the VMN for mRNAs of progesterone receptor (decreased in females by PBDE99 and Aroclor 1254; increased in males by low-dose PBDE99); *Esr1* (increased by PBDE99 in both sexes); *Esr2* (decreased by PBDE99 in both sexes); and preproenkephalin (increased by low-dose PBDE99, decreased by Aroclor 1254 in both sexes) (Faass et al., 2013). Our lab has also recently quantified expression of 48 genes in the VMN of rats exposed prenatally to Aroclor 1221; results showed that in females 2 genes (vasopressin receptor 1a, neuroligin 3) were up-regulated by the PCB treatment, while in males, no genes were affected by the PCB treatment (Topper et al., unpublished). It is notable that more genes were found in the MPOA of these same rats, with results described above, indicative of a potentially lower sensitivity of the VMN to prenatal PCB exposures compared to the MPOA. Developmental BPA effects in the VMN (ventrolateral subregion) of female rats were studied for serotonin fiber density and ER alpha immunoreactivity; however, results showed no significant differences from control animals (Adewale et al., 2011). By contrast, when exposure to BPA took place during early puberty, a significant up-regulation of ER alpha positive cells was found in the VMN, along with other brain regions (Yu et al., 2015), suggesting that – not surprisingly – timing of exposure influences the outcome.

As a whole, these data on the mPOA and VMN show that prenatal EDC exposures have specific effects on the organization of these brain regions, and that the age of exposure, the dosages, and sex are important factors. Considering the importance of the mPOA and the VMN in the masculine-feminine behavioral spectrum, future work is needed to directly link these neurobiological changes to behavioral outcomes.

7. Connecting EDCs to mate choice and sexual selection: fish

The brain is the organ of behavior, and behavior is the currency of sexual selection. The literature in the field of mate preference effects of EDCs is limited, and most work has been conducted on fish and birds. We begin with fish, as this class has been best studied for exposures to environmental or pharmaceutical compounds, especially estrogens or androgens, consequences for mate choice and, in some instances, the basis for that choice. However, we point out that some of these studies entailed exposures of adult animals, rather than developmental exposures, so results should be interpreted in that context.

Bertram and colleagues investigated how adult exposure to 17β-trenbolone, an androgen receptor agonist used in agriculture, affected guppy mate choice (Bertram et al., 2015). Adult animals were exposed to environmentally relevant concentrations, or unexposed, for 21 days, and combinations of unexposed or exposed male and female guppies were paired. Males were monitored for courtship behavior and sneaking attempts (surreptitious approaches of the female by the male). Females were scored for active affiliation with the male. Male guppies, irrespective of their own treatment, showed significantly more courting events towards unexposed versus exposed females. Sneaking behavior was lowest in unexposed males towards unexposed females, and highest in unexposed males towards exposed females; the other two combinations (exposed males-unexposed females; exposed males-exposed females) were intermediate (Bertram et al., 2015). Another mate choice study by this same group, using the same 17β-trenbolone exposure, tested female choice in guppies in a 3-chambered apparatus (Tomkins et al., 2016). The female was placed in the center chamber and given a choice between an unexposed and an exposed male. The treatment of the female significantly affected the outcome: trenbolone-treated females spent significantly less time associating with males. Moreover, only unexposed females showed discrimination between the male

stimulus fish, with less time spent associating with exposed over unexposed males. This result suggests that the choosiness of a female is perturbed by exposure to this environmental androgen. The basis for these outcomes, however, is not known, as the males in this study did not differ significantly in orange pigmentation, a secondary sex characteristic in this species. A similar finding was made for mosquitofish exposed to trenbolone, in which treatment decreased time that females spent in association with males, but did not affect the males' behavior (Saaristo et al., 2013). Another mosquitofish study utilized animals collected from two sites, one proximate to a wastewater treatment (WWTP) plant or a second "pristine" site in Victoria, Australia (Saaristo et al., 2014). Following acclimation to the lab, animals were allowed to interact across a divider and scored for behaviors towards WWTP or control opposite-sex partners. The major finding was that WWTP-males spent more time (compared to control males) orienting towards females, regardless of female treatment history, chasing them, and making more gonopodial thrusts (in this species the anal fin is sexually dimorphic, being used as an intromittent organ by the male).

BPA treatment of adult male zebra fish for 7 weeks (low dose: 50 ng/L; high dose: 500 ng/L) increased aggressive behaviors to males, and decreased courtship behavior of females, in a dose-dependent manner (Li et al., 2017). When given a choice between BPA- and control-treated males, females preferred control to low-dose BPA males.

In contrast to the prior studies conducted in adult fish, a few studies have tested effects of early life exposures to EDCs. Male guppies were treated with a low or high dose of the pesticide atrazine (1 or 13.5 μg/L), vehicle, or untreated (control) during breeding and through gestation, and the following behavioral outcomes were assessed in the male offspring: courtship displays, gonopodium swings, forced copulatory attempts, and combative/aggressive behaviors towards untreated rivals (Shenoy, 2014). In addition, the attractiveness of males to females was tested in a 3-chambered apparatus, in which a female placed in the center was given a choice between a treated and untreated male. A lower percentage of atrazine-treated males, relative to control (untreated or vehicle-treated) engaged in courtship displays, gonopodium swings, or forced copulation, and atrazine-treated males also showed fewer numbers of these behaviors. Female preference tests showed that the lower-dose atrazine exposed males were significantly less preferred compared to an untreated male.

Another developmental study was conducted in the amarillo fish exposed developmentally to the organophosphorus insecticide methyl parathion from birth through 90 days of age (Arellano-Aguilar and Macias Garcia, 2008). Male courtship, female preference, and morphology and color, were assessed. Exposed male fish were smaller, and ornamental fin size, coloration, and display rates were compromised compared to unexposed males. Females made shorter-duration visits to exposed males. Interestingly, unexposed females refused to mate with these suboptimal mates, and in those matings that occurred between exposed individual, offspring survival was reduced, potentially reducing the size of amarillo fish populations.

As mentioned previously, NeoDarwinian theory is based on the Biological Species Concept. A primary focus of the Concept is pre- and post-mating mechanisms that ensure that species did not hybridize, particularly when congener species expand geographic ranges to overlap with native species. Working with two species of common stream fish, Ward and Blum (Ward and Blum, 2012) documented the breakdown of these reproductive isolating mechanisms after exposure to BPA. These closely related stream species (red shiner and blacktail shiner) depend normally upon male secondary sexual characteristics (visual signals) to identify appropriate mating partners. Typically these species are allopatric (non-overlapping geographic ranges) but have points of contact where hybridization has been documented. Behavioral responses of female and male red shiners and blacktail shiners were examined using dual-choice mate choice assays. BPA exposure of adult fish led to both a degradation of the coloration of breeding males, but also altered the perception by females of the stimulus males. Both males

and females exposed to BPA treatment failed to discriminate between conspecific and heterospecific males. Although the reproductive success of such couplings was not examined, this study extends individual-level selection to evolutionary consequences for populations, and hence species.

This demonstration that exposure to BPA can break down reproductive isolating mechanisms between species by acting at the level of the individual has been supplemented by quantitative modeling to evaluate the rapid disruption in mating signals after EDC exposure. Senior et al. (2014) found that within a relatively short time frame, disruption of mating signals led to a lasting loss of female preference. However, these studies focused on the introduction of EDCs, and did not consider the body burden already present in animals.

An important and unique study was conducted in natural populations of fathead minnows in the Experimental Lake Area in northwestern Ontario. Over a 7-year period, populations that were exposed to the pharmaceutical estrogen, ethinyl estradiol, displayed abnormal gonads (intersex), and defects in spermatogenesis and testicular development in males, and folliculogenesis in females (Kidd et al., 2007). Both males and females had elevated vitellogenin production in the liver; in the males this is indicative of feminization. These outcomes led to impaired reproduction and the complete collapse of the population (Kidd et al., 2007). However, as a population study, mate choice and effects on individuals were not studied in that report, something that would be extremely interesting for future research.

8. Connecting EDCs to mate choice and sexual selection: birds

Bird species have some of the most elaborate and costly secondary sexual characteristics, from coloration to songs to displays. The neural pathways involved in the production of bird song are well characterized (Schlinger, 1997). Estrogens and the aromatization of testosterone to estradiol play a crucial role in the masculinization of discrete nuclei that control bird song and control the degree of neural plasticity within these regions (Arnold and Schlinger, 1993; Soma et al., 2004).

Early work in zebra finches showed that treatment of hatchlings with estradiol benzoate between 5 and 11 days of age created severe sex-specific impairments in reproduction (Millam et al., 2001). Egg production was reduced, egg cracking increased, missing eggs increased, and the number of hatched chicks was severely reduced. These data were a springboard for future work delving into this question.

The song centers in the songbird brain are sensitive to hormones and susceptible to EDCs (Millam et al., 2001; Quaglino et al., 2002). Treatment of female zebra finches with PCBs (Aroclor 1248) prior to egg laying led to decreased volume of the male and female offspring's nuclei robustus arcopallialis (RA), but no change in another brain region (Hoogesteijn et al., 2008). Another study related body burdens of PCBs in song sparrows and black-capped chickadees to song qualities in New York state, where there has been widespread PCB contamination (DeLeon et al., 2013). Although relationships were complex, certain aspects of the song were associated with higher PCB concentrations.

The behavioral outcomes of EDC treatment were illustrated in a study of adult wild-caught male starlings exposed to an EDC mixture (BPA, dioctylphthalate, and dibutylphthalate). These animals spent more time singing, with longer bouts and a wider repertoire (Markman et al., 2008). Specifically, EDC exposed males had a more complex song repertoire, and spent more time singing with longer song bouts, than did non-EDC exposed males. Wild-caught female starlings preferred songs from EDC as opposed to control males. In the males, the brain region responsible for song production, the hyperstriatum ventrale, pars caudalis (HVc), had a larger volume in EDC males (Markman et al., 2008). The chemical-exposed males also had depressed indices of immune function. The interpretation of this important study is that EDCs make the male starlings more attractive, yet they are less fit as males. Unfortunately, subsequent reproductive outcomes were not determined to enable one to truly conclude whether sexual selection had been altered.

9. Conclusions and future directions

Endocrine disrupting chemicals pose a threat to reproductive success at many levels. Developmental exposure to EDCs can influence the formation of sexual organs, hormone profiles, and brain nuclei that can lead to disruptions in sexual organ development, the expression of secondary sexual traits, and behavior. Alterations to these systems can result in impaired infertility, difficulty in conceiving, and decreased offspring viability. EDCs during sensitive periods can alter the timing of underlying patterns of gene expression leading to characteristics that are inconsistent with the genetic or gonadal sex. Such 'transgender' individuals present confusing cues to potential mates.

How has environmental contamination altered wild populations, and is it acting through the abnormal modifications to brain organization, and hence behavior? There are many reports of EDC-altered individuals in wildlife, only two examples come to mind. Gibbs and Bryan (Gibbs and Bryan, 1996) have documented the extinction of a population of the American oyster drill, due to EDC contamination (Gibbs and Bryan, 1996). The second example is that of Kidd et al. (2007) mentioned above. As pointed out earlier (Crews et al., 2000), animals continue to live and reproduce in contaminated environments. How is this possible? In very large and mobile populations such as killifish (Reid et al., 2016) populations have adapted to local conditions of pollution. Field studies indicate that the outcome depends upon many factors, such as short generation time, population size, whether the biomass is contiguous or isolated, and whether it has a genomic structure that allows for adaptive blunting or re-tuning of systems that are directly sensitive to the contaminants. The consequences of such changes are marked, particularly when considering that the genetic regulation of other signaling systems may also be affected.

Thus, to answer how environmental contamination has altered wild populations requires access to the ancestors, yet even relatively recent generations usually are absent. It is possible to obtain body burden information from museum specimens, but to our knowledge this has not been done. With such information it would be possible to establish possible parameters of the changes wrought by chemical exposures.

The question that can be addressed is whether altered individuals are capable of finding mates and reproducing. Disregarding those individuals incapable of reproducing (e.g., absence of oviducts or vasa differentia), how do individuals identify potential sexual partners? The limited work in this area in rodents showed that males descending from endocrine-disrupted progenitors were not preferred (Crews et al., 2007); we note that this work was conducted in a transgenerational context as opposed to direct exposure. EDC-fed male starlings were preferred over control males due to their more complex song, despite their being immunocompromised (Markman et al., 2008). Breeding of these animals beyond the first generation was not done, so the generational consequences of this choice are unknown.

Another question that can be addressed is: do EDCs act in a complementary manner on a putative 'male' brain and the putative 'female' brain? Almost all laboratory studies of EDC action focused on a single sex. In those few instances where both sexes were studied in the same laboratory, the work was not extended to the ultimate question of whether exposed animals can in fact successfully mate and, if so, who do they want to mate with? If they cannot mate, then the mode and manner of reproductive patterns become important when we consider the course of evolution. Crews et al. (2007) argue that in most mammals, males disperse at sexual maturity. Thus, on migration to an uncontaminated site will females avoid mating with these males? In birds, young females are more likely to disperse. Thus, EDC-altered females, if they were receptive to courtship of uncontaminated males, would have a significant impact on the population — unless males were able to detect and preferentially breed with unaffected females.

Although a wide spectrum of mating strategies is observed in

nature, one common thread ties them all together. Individual animals display choices for particular partners and that choice of a mate is a cornerstone of its reproductive success. Recognized for centuries as a common breeding method, it is only recently that the scientific basis for the importance of mate choice has been established. This challenges investigators to study mature animals of both sexes simultaneously to determine what the mate preferences of affected animals are, how this information is communicated, and whether pairs can indeed reproduce. Selection acts on individuals, but the consequences for evolution are at the population level. The future of EDC research needs to makes these connections.

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