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REVIEW ARTICLE

Endocrine Disrupters: A Review of Some Sources, Effects, and Mechanisms of Actions on Behaviour and Neuroendocrine Systems

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Some environmental contaminants interact with hormones and may exert adverse consequences as a result of their actions as endocrine disrupting chemicals (EDCs). Exposure in people is typically a result of contamination of the food chain, inhalation of contaminated house dust or occupational exposure. EDCs include pesticides and herbicides (such as dichlorodiphenyl trichloroethane or its metabolites), methoxychlor, biocides, heat stabilisers and chemical catalysts (such as tributyltin), plastic contaminants (e.g. bisphenol A), pharmaceuticals (i.e. diethylstilbestrol; 17α-ethinylestradiol) or dietary components (such as phytoestrogens). The goal of this review is to address the sources, effects and actions of EDCs, with an emphasis on topics discussed at the International Congress on Steroids and the Nervous System. EDCs may alter reproductively-relevant or nonreproductive, sexually-dimorphic behaviours. In addition, EDCs may have significant effects on neurodevelopmental processes, influencing the morphology of sexually-dimorphic cerebral circuits. Exposure to EDCs is more dangerous if it occurs during specific 'critical periods' of life, such as intrauterine, perinatal, juvenile or puberty periods, when organisms are more sensitive to hormonal disruption, compared to other periods. However, exposure to EDCs in adulthood can also alter physiology. Several EDCs are xenoestrogens, which can alter serum lipid concentrations or metabolism enzymes that are necessary for converting cholesterol to steroid hormones. This can ultimately alter the production of oestradiol and/or other steroids. Finally, many EDCs may have actions via (or independent of) classic actions at cognate steroid receptors. EDCs may have effects through numerous other substrates, such as the aryl hydrocarbon receptor, the peroxisome proliferator-activated receptor and the retinoid X receptor, signal transduction pathways, calcium influx and/or neurotransmitter receptors. Thus, EDCs, from varied sources, may have organisational effects during development and/or activational effects in adulthood that influence sexually-dimorphic, reproductively-relevant processes or other functions, by mimicking, antagonising or altering steroidal actions.

Key words: xenoestrogens, dichloro diphenyl trichloroethane, methoxychlor, biocides, tributyltin, bisphenol A, diethylstilbestrol, ethinylestradiol, phytoestrogens, aryl hydrocarbon receptor, the peroxisome proliferator-activated receptor, retinoid X receptor.

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Introduction

Endogenous steroid hormones, during critical periods of development, organise sexual dimorphisms in brain and behaviour and give rise to sex differences in later responses to steroid hormones (1,2). These mechanisms have evolved over time to ensure the survival of species and maximise the fitness of each sex. This delicate balance may be at risk, in part because a growing number of contaminants in the environment can accumulate in exposed individuals and may have adverse consequences as a result of their action as endocrine disrupting chemicals (EDCs). Thousands of chemicals (some banned and some still in use) have been classified as EDCs. They produce their effects by mimicking, antagonising or altering endogenous steroid levels (androgens or oestradiol, E_2) via changing rates of their synthesis or metabolism and/or expression or action at receptor targets.

The goal of this review is to address some of the sources, effects and mechanisms of EDCs. The breadth of this topic precludes a comprehensive coverage of all EDCs. As such, this review focuses on topics that have been part of the ongoing dialogue at The International Congress of Steroids and The Nervous System. First, the sources of common neuroendocrine disrupting compounds are described. Second, the effects of EDCs to alter reproductively-relevant, sexually-dimorphic behaviours are examined, and also whether there are sex differences in the effects of EDCs. Third, the role of EDCs for sexually-dimorphic, nonreproductive behaviours, and in sex-linked developmental disorders (neurodevelopmental, neuropsychiatric, neurodegenerative), is discussed. Fourth, the extent to which these effects of EDCs are differentially programmed (or expressed), based upon critical developmental periods, is addressed. Fifth, species differences in the effects of EDCs, and the ecological systems issues (e.g. food chain), are considered. Sixth, the actions of EDCs via altering steroid metabolism, steroid receptor action and nontraditional receptor targets, as well as altering gonadal steroid dependent neural circuits, are discussed. Thus, this review summarises some of the evidence that EDCs (such as those listed in Table 1) can profoundly alter reproductive responses after adult exposure and that EDC exposure can result in pervasive effects extending throughout the life of their progeny (3,4).

Sources of contaminants

There are varied sources of environmental contaminants. Typical human exposure occurs with environmental contamination of the food chain, especially fresh water fish and meat, contact with contaminated household dust, and occupational exposure (5–10). Some chemicals were banned or otherwise removed from production years ago but persist in the environment. For example, a family of industrial polychlorinated biphenyl (PCB) compounds, often sold as mixtures (Aroclor), generally act as oestrogen mimics and are still found in significant quantities in the environment, although their manufacture in the USA was banned in 1977. In certain uses, PCBs can partially oxidise and themselves become contaminated by extremely toxic compounds, such as polychlorinated dibenzofurans. In some areas, PCB levels in drinking water were in the range 100–450 ng/l; in food products, levels were over 200 mg/kg fresh weight. PCB levels in occupationally-exposed workers were in the range 2.2–290 p.p.m. in adipose tissue and blood concentrations in capacitor manufacturing workers were up to 3.5 μg/ml (11).

Other EDCs are high production volume chemicals found in a myriad of household products. Bisphenol A (BPA), for example, is present in polycarbonate plastics, including beverage and food storage containers, epoxy resins that line the interior of metal cans, and in the ink used for thermal paper receipts. Many textiles contain contaminants, such as flame-retardants, including tetrabromobisphenol A and polybrominated diphenyl ethers. Some individuals have also been exposed to contaminants with adverse effects as a result of medical (diethylstilbestrol; DES), dental (diglycidyl methacrylate) or dietary (phytoestrogens) interventions. Synthetic oestrogens from anticonceptional pills, such as ethinylestradiol, are commonly found in surface water, as a result of their widespread use (12). Thus, exposure to EDCs is ubiquitous and unavoidable and there is growing concern that living in an EDC contaminated world may be contributing to adverse health trends, such as early puberty and infertility, because of growing evidence that a number of EDCs can produce varied effects (13), as described below.

Effects of EDCs to alter reproductively-relevant, sexually-dimorphic neuroendocrine systems and behaviours

Exposure to EDCs has been associated with a myriad of adverse reproductive outcomes, including reduced female fecundity, longer time to conception, higher miscarriage rates and decreased sperm motility (14,15). Studies examining the effects of EDCs on sexual maturation offer further evidence for a possible connection between EDCs and reproduction (16,17). Emerging evidence supports the long held suspicion that age at menarche is advancing in girls, particularly in developed countries (18,19). This observation has led to the hypothesis that exposure to EDCs could be a contributing factor (20,21). Exposure to EDCs has been associated with earlier age at menarche and sexual development in breast-fed girls (22), although some studies have shown the opposite effect, with girls exposed to EDCs showing delayed sexual maturation (23). This type of nonlinear response, where the effects differ at low and high dosages may be typical for EDCs (24) and is a phenomenon that has raised concern over low-dose exposure (25,26). Mixtures can also influence effects. For example, a report on exposure to EDCs and lead shows that it may advance and delay, respectively, the age of menarche, indicating that EDC exposure in combination with lead and other toxicants needs to be considered when attempting to understand how exposure may influence reproductive health (22).

Adverse effects of EDC exposure on reproductive physiology have also been seen in numerous animal models, particularly when exposure occurs early in development (27,28). In mammal and other vertebrates, EDC exposure during development alters both male and female gonad development, reduction in sperm counts, abnormal sperm, and changes in sexual behaviour, such as demasculinisation and feminisation of male offspring (29–31). Lactational exposure of

Table 1. Summary of common sources and neuroendocrine effects of the most well studied endocrine disrupting compounds.

EDC	Source	Reported behavioural effects	Reported neural effects
Bisphenol A	Polycarbonate plastics, epoxy resins (lining soup and metal cans), thermal paper receipts High volume production chemical Bans or restrictions on use in some countries (not USA)	Altered explorative activity Impaired social interaction/activity Compromised learning and memory Increased anxiety and aggression Decreased male sexual behaviour Increased externalising behaviours in girls	Modified or lost brain sex differences Loss of sex differences in AVPV volume and tyrosine hydroxylase levels Loss of sex difference in locus coeruleus volume Increased oxytocin neurone number in paraventricular nucleus Altered hippocampal spine density Disrupted hypothalamic ER distribution Altered nitric oxide synthase signalling Advanced puberty
Diethylstilbestrol	Potent synthetic oestrogen (pharmaceutical) used from 1938–1971 Recognised to cause reproductive cancers, genital malformations and infertility in humans	Decreased anxiety in females	Demasculinisation of avian AVT system
Ethinyl oestradiol	Synthetic oestrogen used in birth control pills and other pharmaceuticals Present at low levels in municipal water	Decreased response to reward in females	Masculinisation of female hypothalamic development Intersex in fish
Genistein	Legumes, soy and soy based food, soy infant formula, dietary supplements Phytoestrogen produced by plants	Increased exploratory activity in males Altered anxiety-related behaviour	Demasculinisation of avian AVT system Disrupted hypothalamic sexual differentiation Advanced puberty
Organophosphate insecticieds	Pesticides including chloropyrifos, parathion, malathion and diazinon. Also nerve gas including Sarin Bans or restrictions for use in some countries	Associated with attention deficit hyperactivity disorder and behavioural problems in children Altered ultrasonic communication, aggressive behaviour and social interaction in rodents	Acute neurotoxicity (can be lethal) Neurophysiological maturation and differentiation Disruption of serotoninergic and dopaminergic transmission Modified oxytocin and AVP activity
Polychlorinated biphenols	Lubricants, cooling fluids, transformer oil, adhesives, plasticisers Banned from US production in 1979	Decreased explorative activity in females Compromised learning and memory	Modified or lost brain sex differences Disrupted hypothalamic ER distribution
2,3,7,8-tetrachlorodibenzo-p-dioxin	Most toxic of 200+ dioxins Byproduct of combustion, burning of fossil fuels, bleaching during paper production, and polyvinyl chloride plastic production. Preservative for wood, textiles, paint, glue and other products Food contaminant (highest in meat) Potent carcinogen, persistent, bioaccumulates, was a contaminant in Agent Orange	Reduced male sex behaviour	Acute toxicity (can be lethal) Modified or lost brain sex differences Compromised neurodevelopment and myelination Disrupted thyroid hormone action Demasculinisation of the male hypothalamus

rats to Aroclor 1254 (8, 32 or 64 mg/kg to dams) decreased mating behaviour, reproductive success, and ventral prostate and testicular weights of male pups in adulthood (32). Females exposed had delayed puberty, decreased uterine weight, impaired fertility, and irregular oestrous cycles (33). Furthermore, acute exposure to Aroclor 1254 (from neonatal days 1–7) significantly reduced the lordosis quotients of adult female rats in both a paced and nonpaced testing paradigm (34). Exposure to 400 ng/kg per day of 17α-ethinyl oestradiol *in utero* and during lactation induced sterility in exposed rat pairs (35) because it disrupts the oestrous cycle, with females showing permanent oestrus as early as 60 days of age (36). Lower, environmentally-relevant dosages of 4 ng/kg per day produce significant alterations in fecundity (35). Egg exposure to a variety of EDCs permanently alters male copulatory behaviour of the Japanese quail (37–39). These data clearly indicate that developmental exposure to EDCs can adversely affect sexual development in animals, supporting the hypothesis that a similar effect may be occurring in people; however, there are different effects depending upon the chemical nature of the EDC, the type of interaction with hormone receptors, as well as when in development exposure occurs. Because there are many factors that contribute to reproductive functioning, and many ways in which EDCs may alter these factors, it is important to conduct systematic studies in animal models to differentiate between the specific effects of EDCs on reproductive parameters. Timing of exposure is a crucial factor when considering potential behavioural and endocrine consequences in both animals and people.

The role of EDCs for sexually-dimorphic, nonreproductive behaviours and the incidence of sex-linked developmental disorders

Many behaviours, and the neuroendocrine pathways that regulate them, are sexually dimorphic. These sex dimorphisms reflect adaptive differences for behavioural strategies in coping as a result of sexual selection. Disruptions in these behaviours may lead to reduced social adaptation and impaired responsiveness to environmental demands (40). Exposure to EDCs can alter or eliminate these sex differences and produce striking differences between behavioural responses of males and females that were developmentally exposed to EDCs. This potential for altering sexually-dimorphic behaviours may be relevant for concerns regarding increased developmental, cognitive and/or emotional disabilities reported over the past 30 years (41).

Effects of EDCs on neurodevelopmental processes

EDCs may have particularly significant effects on neurodevelopmental processes because many accumulate in fatty tissues of exposed individuals, are readily transferred across the placenta prenatally, and are expressed in breast milk. In the past, much of the human and wildlife health-related research on pesticides and other EDCs has dealt with more or less immediate toxicity at relatively high dosages, or has been concerned only with the primary mode of action. Field and laboratory studies using different animal models indicate that developmental exposure to low doses of these compounds can affect behaviour in a sex-dimorphic fashion. The mechanisms by which pesticides and other compounds exert EDC-like effects at environmentally-relevant dosages might be different from those involved in their acute neurotoxic effects, and a direct interference with steroid/pituitary/thyroid hormones cannot be excluded.

Notably, there are significant increases in the incidence of attention deficit hyperactivity disorder and autism spectrum disorders (42). Development of psychological disorders with sex-biased prevalence rates may be associated with the disruption of the developmental trajectory and/or maturation of the sexually-dimorphic brain (43). Autism spectrum disorders (44), attention deficit disorder and depression (45) are disorders with sex-biased prevalence rates. Disruption of hormonally-controlled, sexual differentiation of the brain, may increase vulnerability for these (or other) sexually-dimorphic functions. Exposure to endocrine disrupters (e.g. PCBs, BPA) that disrupt hormone function during critical periods of prenatal development may influence susceptibility to sex- and/or hormonally-differentiated aspects of behaviour (46,47). Males are more vulnerable to these disorders, which have salient motor and arousal components. Thus, the increase in the incidence of these disorders may reflect the effects of EDCs on male-typical levels of arousal and/or stress responsiveness.

Environmental factors, such as EDCs, in early life can lead to long-term changes in social and/or sensory function, which are features of some developmental disorders. Multiple types of developmental disorders share many characteristics, including a developmental timeline and dysregulation of both social behaviour and somatosensory function. Sensory impairment is higher in children with neurodevelopmental disorders than in the general population (48). In individuals with autism spectrum disorder, sensory abnormalities are highly prevalent (30–100%) (49). In addition to atypical sensory function, children with developmental disabilities often manifest social problems, such as aggression (50). Thus, it is important to further understand factors that increase susceptibility to psychological disorders (as indicated by differences in the expression of sex-typical behaviour).

Organophosphorous insecticides (OPs) make up approximately 50% of all insecticides used in the world, and are the subject of intensive investigation for their suspected developmental neurotoxicity. These compounds, largely used in agriculture, as well as in the home and garden, for pest control, exert their acute neurotoxic effects through cholinergic hyperstimulation. Subsequent to 2004, several epidemiological studies involving children from both agricultural and urban communities have indicated that developmental OP exposure may affect children's neuropsychological maturation (51). Most of experimental research in this field has focused on the OP chlorpyrifos (CPF), the most widely applied compound in the OP class in the USA and Europe (52). The mechanisms by which CPF interferes with brain and behavioural maturation at environmentally relevant dosages differ from those involved in its acute toxic effects (53). Gestational and neonatal exposure to CPF impairs neuronal differentiation, synaptogenesis and gene expression in rats, and affects neural systems beyond the cholinergic one, such as seroto-

ninergic and dopaminergic transmission, in a sex-dimorphic fashion (54,55).

The neurobehavioural effects of *per se* gestational and/or neonatal exposure to CPF have been extensively characterised in mouse models. Overall, data show that CPF differentially affects behavioural responses in the two sexes (56–59). *In utero* exposure to CPF modified ultrasound emission in neonates and had pro-aggressive effects in adolescent and adult male mice in a social interaction test. In adult females, prenatal CPF altered the pattern of social interaction, either with same-sex partners or with a male-intruder during a test of the defence of the nest. These behavioural changes are accompanied by a permanent alteration in the expression of the hypothalamic neuropeptides, oxytocin and vasopressin, which are key effectors of social and reproductive behaviour in mammals. Furthermore, decreased behavioural responsiveness to antidepressant drugs acting on the serotonin transporter in CPF-exposed males confirms that serotonergic neurotransmission is implicated in the behavioural effects of CPF (60,61).

In a study still in progress (A. Venerosi, S. Tait, L. Ricceri, L. Stecca, A. Mantovani and G. Calamandrei, unpublished data), pregnant females have been fed throughout gestation and lactation with a CPF-supplemented diet to mimic the human exposure scenario. At adulthood, CPF-exposed males display enhanced investigative response towards either familiar or unfamiliar same-sex individuals, whereas CPF females show a delayed onset of social investigation and a lack of reaction to social novelty. In addition, sexually-dimorphic effects have been revealed so far in the hypothalamus: CPF females show a diminished expression of the oxytocin precursor neurophysin I, an increase of oestrogen receptor (ER)α and a decrease of ERβ. ERα and ERβ in the hypothalamus/amygdala circuitry are known to exert a facilitatory role in oxytocinergic control of social recognition in rodents (62). These preliminary data suggest that developmental CPF interferes with the maturation of important sexually-dimorphic neuroendocrine pathways.

Together, these experimental findings support the hypothesis that *in utero* or neonatal exposure to extremely low dosages of CPF influences neurobehavioural development, affects multiple signalling systems, including those controlling reproduction, with effects on behaviour that are long-term and different in the two sexes. The case of CPF might be prototypic: it is likely that other environmental neurotoxicants, not yet considered as EDCs, might indeed interfere with neuroendocrine functions, possibly increasing vulnerability to sex-biased neurodevelopmental disorders in children.

Cognitive function

There may be sex-specific effects of oestrogenic EDCs on spatial learning, which typically favours males. Yu-Cheng boys that were prenatally exposed to high levels of PCBs and polychlorinated dibenzofurans, when their mothers were accidentally exposed to these contaminants in rice oil, show more disrupted cognitive development, mainly spatial function, than do exposed girls (63). Gestational and lactational exposure to ortho-substituted PCBs produces spatial deficits at adolescence in male mice (64). Prenatal exposure to PCBs 28 or 153 had dose-dependent effects to slow acquisition of the radial arm maze task for female, but not male, rats (65). Notably, gestational exposure to Aroclor 1254 (versus vehicle) produced more working memory errors in the radial arm maze task for male rats, but not female rats (66). Another study showed that, of rats exposed *in utero* and postnatally through weaning to Aroclor 1254, males were more likely to perseverate after a reversal in the radial arm maze task, whereas females were more likely to have association deficits (67). A small body of literature has shown that EDCs may facilitate cognitive function in some cases. For example, exposure of male rats to 17α-ethinyl oestradiol during development (from gestation day 5 to weaning) results in enhanced working memory during a Morris water maze hidden platform acquisition test (68). These observations again highlight the potential for non-linear responses and the complexity of interpreting the ethological-relevance of behavioural outcomes. Collectively, the literature supports the conclusion that exposure to EDCs from early development to adulthood alters spatial memory and also that there may be sex differences in these effects.

Emotional reactivity and stress responses

Gestational or early life exposure to EDCs may influence arousal. It has long been known that exposure to heavy metals, such as lead or mercury, can lead to behavioural disorders in people (69). Epidemiology studies of populations exposed to high levels of PCBs reveal that EDCs may produce similar outcomes (70, 71). Children exposed to PCBs, lead or mercury show inattention, hyperactivity, as well as disordered and/or mildly antisocial behaviour (41,45). There is also evidence for increased aggression (69,72). Prenatal BPA exposure has now been linked with increased externalising behaviours in 2-year old girls (73). Atypical behaviours in infancy and childhood, including compromised social communication, have also been associated with prenatal exposure to phthalates (74) compounds found in soft plastics that act as androgen antagonists.

In animal models, developmental exposure to EDCs produces similar effects. Exposure to polybrominated diphenyl ether 209 on postnatal day 3 disrupts spontaneous motor behaviour in rats (75). Another study that administered BPA to 5-day-old rats observed hyperactivity at 4–5 weeks of age, which was associated with changes in dopamine function in midbrain (76). Mice exposed perinatally (from gestation day 11 to postpartum day 8) to BPA or methoxychlor showed a reversal of sex differences at periadolescence in exploratory activity in a novel open field, elevated plus maze, and social interactions with a conspecific (77,78). Similarly, anxiety, spatial learning and memory, as well as passive avoidance memory, were found to be altered in mice exposed to BPA (40 or 400 g/kg per day) across adolescence and early adulthood, with sex differences eliminated or reversed on many tasks (79). Similar effects of BPA have also been reported in deer mice (*Peromyscus maniculatus*) (80) and rats (81). To our knowledge, there are few published reports of the effects of EDCs on stress reactivity. A recent study revealed that early life stressors, such as cross-fostering, can modulate the effects of BPA on social behaviour and

anxiety (82). This highlights the need for further investigation of the impact of EDCs on hypothalamic-pituitary-adrenal axis function, albeit there is emerging evidence that EDC can alter oxidative stress (83).

EDCs influence brain morphology

Several studies have investigated the effects of EDCs on sexually-dimorphic brain circuits. For example, rats exposed to Aroclor 1221 perinatally had fewer ERβ positive cells in the sexually-dimorphic nucleus of the preoptic area than did vehicle-administered rats (84). Exposure to BPA during the pre- or postnatal period can alter the differentiation of several neural circuits involved in the control of reproductive functions and behaviour. It induces an increase of ERα mRNA and protein expression in the female rat hypothalamus and in the male anterior pituitary (85,86), and also alters the sex specific expression of tyrosine hydroxylase in the rat and mouse anteroventral periventricular nucleus (87,88). Also other systems, such as the rat locus coeruleus (89,90), the mouse nitric oxide producing system (91), and the rat and mouse kisspeptin system (92,93), are affected by precocious exposure to BPA, altering in many cases, their sexually-dimorphic expression.

The family of neurohypophyseal nonapeptides [arginine vasopressin (AVP) in mammals and arginine vasotocin (AVT) in non-mammalian vertebrates] is present in magnocellular system and in the sexually-dimorphic parvocellular systems of the hypothalamus and limbic system. This last system is gonadal hormone-dependent in various vertebrates (94,95). It is involved in the control of male copulatory behaviour in birds (96,97) and in the modulation of aggressive behaviour and other social behaviours in mammals and other vertebrates (98). Administration of exogenous oestrogens demasculinises this system in birds (99), whereas, in mammals, both oestrogens and androgens may contribute to the masculinisation of the system (100–103). In adulthood, gonadal hormones modulate the expression of AVP or AVT, both in the parvocellular (104–106), and in the magnocellular system (107). Thus, the AVP system has been considered as a potential target for the action of EDCs (108,109).

In the Japanese quail, embryonic exposure to different EDCs (DES, genistein or dichloro chlorophenyl ethylene) induced a significant demasculinisation of the sexually-dimorphic parvocellular AVT system (37–39). For other EDCs (ethinylestradiol and methoxychlor), the effects on this neural system were absent or not significant, yet they did affect copulatory behaviour (110). The dissociation between demasculinisation of behaviour and the AVT system suggests that oestrogens induce these effects via at least partly different pathways. As demonstrated through the administration of an ERα selective agonist, propyl pyrazole triol, oestrogen-induced effects on reproductive organ differentiation are mediated by ERα, whereas demasculinisation of male copulatory behaviour and of the AVT-immunoreactive system are probably dependent upon ERβ, which appears earlier during quail embryonic development than does ERα (111).

In mammals, acute exposure to E_2 stimulates the synthesis of the mRNA AVP (112) and induces a significant increase of AVP immunoreactivity in the magnocellular nuclei of female rat (107). In rats, dietary exposure to phytoestrogen genistein (from prenatal day 7 up to the age of 2.5 months) induced an increase of vasopressin content in hypothalamic extract (113). However, exposure to organoalogen compounds, generally considered to act as antiandrogens, inhibited the release of AVP from SON punches and *in vivo* (114,115). These studies suggest that, also in mammals, the AVP system is a target for the action of EDCs (108).

A few studies have investigated the second neuroypophyseal nonapeptide, oxytocin, produced by the magnocellular nuclei in mammals, and released both centrally into the brain, and peripherally into the circulation. Oxytocin is involved in social recognition and maternal behaviour (116,117). Oral BPA exposure reduces certain maternal behaviours in the female rat, such as licking–grooming and the arched back posture, that are related to oxytocin (35). At the same time, BPA may induce an increase in oxytocin-immunoreactive cell number in the female rat paraventricular nucleus (118), suggesting that it may inhibit oxytocin release. The behavioural effects of EDCs exposure could also be related to alteration of the expression oestrogen-inducible central oxytocin receptors (119), as observed in the cingulate cortex of female pine vole perinatally exposed to methoxychlor (MXC) (120). Together, these data demonstrate that EDCs can negatively affect sexual dimorphisms in the brain (3,4,121).

Other EDCs, such as the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), may have large effects in the brain when prenatally administered. In particular, prenatal exposure to TCDD (700 ng/kg single dose gavage at gestational day 18) affects the offspring with respect to the number of pups born, myelination, weight gain and sex ratio towards females (122–126). The major alterations observed in offspring of TCDD exposed dams were a higher expression of oligodendrocyte precursor cell (OPC) marker mRNA, *Olig-1* and PDGFaR, in the diencephalon and cerebellum and an altered content of myelin basic protein, being lower in the mature cerebellum, diencephalon and medulla oblongata and, conversely, higher in the telencephalon (127). Collectively, these results indicate a long-lasting gliogenesis defect in mature brain after prenatal TCDD exposure (122).

Different molecular mechanisms could be responsible for the described defects. One effect may be related to a direct TCDD effect on OPC via aryl hydrocarbon receptor (AhR), during the critical period of OPC proliferation, migration and maturation (123). Because oligodendrocyte generation, maturation and myelin protein expression are under thyroid hormone control, another possibility could be related to the indirect effects of TCDD on endocrine function (e.g. thyroid dysfunction). Indeed, perinatal TCDD exposure alters maternal, neonatal and infant thyroid function, as well as thyroid hormone nuclear receptor (TR)-mediated gene expression and pathways (128). The cerebellar expression of TRα mRNA was down-regulated during development, whereas TRβ mRNA significantly increased, within the second postnatal week, then returning to basal expression levels at adulthood. The expression of deiodinase enzyme D2 mRNA was very low in the first postnatal days, significantly increased during development and reached a peak after 14 days. By contrast, D3 mRNA was highly expressed at 2 days postnatally, although its expression was drastically down-regulated

during development. These results are in line with what has been already described (129). Interestingly, there are significant differences in the expression of TRα-1 at 14 days postnatally in TCDD-, versus vehicle-exposed, males, but not, female rats. Thus, we can conclude that prenatal exposure to TCDD alters the developmental expression profile of several genes, including myelination and thyroid hormone related genes, thereby affecting the expression profile of one of the main signalling pathways for brain development.

Consideration of critical periods

The point in life when exposure occurs may be critical for the effects of EDC. Critical periods of urogenital tract and nervous system development *in utero* or in early postnatal life are especially sensitive to hormonal disruption. Damage during these 'critical windows of development' may be more likely to be permanent, yet, in mature individuals, ill effects of exposures can be alleviated when the causative agent is removed (130). This is consistent with the idea of greater negative consequences with BPA exposure during infancy/childhood versus adulthood (14). In rats, the effects of EDCs at environmentally-relevant dosages appear to be particularly strong when the exposure is protracted for the entire developmental period (i.e. from gestation to weaning) (35,36). Persistent effects have also been observed when exposure is confined to a specific critical window, such as the neonatal period (131,132). In any case, exposure to EDCs is likely to be continuous in natural populations because they are ubiquitous in the natural and human environment (133).

Exposure to EDCs during other critical periods: perinatal, juvenile and puberty

In rats, exposure to environmentally-relevant concentrations of 17α-ethinyl oestradiol (4 ng/kg per day) from gestation day 5 to weaning (postnatal day 32) has serious effects on sexual behaviour, cognitive function and reproduction (35,36,68). In females, sexually-proceptive behaviour is affected, with a disruption of the timing of appearance of appetitive aspects during the copulatory sequence (36). Reproduction is also affected, with an increase in the number of live pups (35). Similarly, there is an improvement in spatial learning in male rats tested in a Morris water maze (68). Inverted U-shaped dose–response curves are quite common for EDCs ('hormesis') (134), although, even if these effects are positive, they are unlikely to be beneficial (135).

In mice, exposure of pregnant dams to low doses of BPA, from prenatal day 10 to postnatal day 8 (5, 10, 20 and 40 μg/kg per -day), induced profound behavioural alterations in adulthood. In our preliminary study (136), males showed an increase in the time spent in the intermediate and central areas of the open field, suggesting that perinatal exposure to BPA may determine anti-anxiety effects. At the same time, we observed a significant increase of the spontaneous activity of mice within the T-maze, suggesting cognitive deficits in animals. BPA-treated mice of both sexes had a strong reduction in the time spent in the arm with opposite-sex bedding; in males, we also observed a reduction in sniffing in the same arm. These findings suggest that BPA may alter the olfactory system and, consequently, sexual behaviour. This is in agreement with the results of our recent study demonstrating alterations in part of nitric oxide synthase system in mice perinatally exposed to BPA (91). By contrast, we have not detected changes in food preference, nor in searching. Finally, we observed alterations of sexual behaviour only in males. In particular, we observed deficits of anogenital and body sniffing, and allo-grooming behaviours. In females, we observed a significant advancement of puberty. In a second experiment, we exposed perinatally-treated mice to a second exposure to BPA from day 31 to day 60. The behavioural alterations were essentially the same. This suggests that some of the effects of BPA on behaviour may be predominantly organisational rather than activational.

Genistein, similar to other phytoestrogens, is largely present in human and laboratory animal diets. Phytoestrogens have recently gained recognition for their beneficial effects on human health, although little is known about their effects on brain circuitries. Experiments carried out on rats fed with a phytoestrogen-rich diet have shown contrasting results on behaviour and related brain areas. To understand whether exposure to genistein during the postnatal critical period of differentiation of brain circuits and behaviours may alter this process, we orally administered male and female mice, from postnatal day 1 to postnatal day 8, genistein (50 mg/kg in sesame oil) or vehicle. Mice were tested at postnatal day 60 for anxiety behaviour, using the elevated plus maze and the open field. The results obtained indicated a strong sexual difference. Indeed, genistein demonstrated an anxiogenic effect in males and an anxiolytic effect in females (137).

Puberty

Maturation and function of the vertebrate reproductive system is coordinated by the hypothalamic-pituitary-gonadal axis. This sexually-dimorphic system encompasses a complex network of hypothalamic neuronal signalling pathways, the most notable of which is the newly-discovered kisspeptin system (138), that enable the sex-appropriate regulation of gonadotrophin secretion by steroid hormones. The neural components of the hypothalamic-pituitary-gonadal axis, including the kisspeptin pathways, are sexually-differentiated by endogenous gonadal hormones (primarily E_2 in rodents but perhaps both oestrogens and androgens in humans) through a series of gestational, pre- and perinatal critical periods (139–142). This sex-specific ontogeny can be manipulated by the exogenous administration of steroid hormones during the neonatal critical period. For example, neonatal administration of oestrogen masculinises the female rodent brain, resulting in the loss of the preovulatory gonadotrophin-releasing hormone (GnRH) surge, whereas castration effectively prevents defeminisation of the male rodent brain (143).

In females, exposure to EDCs during the neonatal period can also perturb the sex-specific organisation of these hypothalamic pathways resulting in an advanced vaginal opening, a hallmark of

rodent puberty, and abnormal oestrous cyclicity (81,144–147). For example, in female rats, exposure to 10 mg/kg genistein, an isoflavone phytoestrogen common to soy-based foods, across only the first few days of life, results in significantly decreased kisspeptin fibre density in the region surrounding GnRH neurones during peripubertal development (146). This male-like pattern of kisspeptin fibre density persists into adulthood (81,93) and is accompanied by an impaired capacity to stimulate GnRH neuronal activity (as measured by the immunoreactivity of both of GnRH and Fos) after ovariectomy and hormone priming (81). These results indicate that disrupted organisation of the kisspeptin signalling pathways may be a novel yet fundamental mechanism by which a suite of reproductive abnormalities are induced, including disrupted timing of pubertal onset, irregular oestrous cycles and premature anovulation.

Exposure to EDCs in adulthood also affects reproductive parameters

To date, there has been much less investigation of the activational effects of EDCs compared to their organisational effects. There is some evidence for EDCs altering the reproductive responses of adults. Men with infertility had significantly higher tetra- and pentachlorinated biphenyls, dichloro chlorophenyl ethylene, dichlorodiphenyl trichloroethane and lindane than controls (148). Lead exposure increases male and female infertility (149,150). Administration of Aroclor 1221 or 1254 during adulthood affected the timing of female sexual behaviour of rats (151) and women consuming a high soy diet experience disrupted menstrual cycles and had difficulty obtaining pregnancy (152). Thus, the extent to which exposure during adulthood may influence previously established sexually-dimorphic behaviours is of continued interest.

Potential mechanisms by which EDCs may produce their effects

The putative mechanism by which EDCs may have their effects needs to be more thoroughly explored. An important question is whether EDCs interact with endogenous E_2. This is relevant not only for women of reproductive age, who have high and fluctuating E_2 levels, but also for children, postmenopausal women and men, whose E_2 levels are low. Although PCBs have long been known to be oestrogenic (153), EDCs vary in their oestrogenic effects. Attempts to establish a relationship between PCBs and their oestrogenic/anti-oestrogenic actions have not reached a consensus (154). A review follows of potential species differences and actions of EDCs.

Effects of endocrine disrupting chemicals mediated by aryl hydrocarbon receptors and CYP1A1

Many effects of EDCs are mediated by the AhR, which is present in various tissues, including the brain (155). This receptor may be responsible for dioxin and dioxin-like PCB intoxications, which create severe clinical problems, such as behavioural and cognitive impairments and an increased number of newborns with improperly formed brains (156). However, it has become evident that AhR may also be involved in neural development, likely through interaction with Wnt signalling (157), in addition to mediating neuronal cell death in response to environmental pollutants.

The molecular mechanism underlying AhR-induced neurotoxicity is largely unknown and is related mainly to necrosis. Prenatal exposure to AhR agonist TCDD resulted in neurodevelopmental deficits, possibly as a result of altered activity of Sp1 factor and increased oxidative stress (158). Exposure to TCDD, 8 weeks before pregnancy, resulted in a 50–75% decrease in serotonergic neurones in the mouse raphe nuclei (159). Furthermore, treating animals or neocortical cell cultures with TCDD altered the expression of NMDA receptor subunits, and could directly influence necrosis of neuronal cells (160,161). Little is known, however, about the apoptotic effects mediated by AhR. This is particularly important because apoptosis occurs at each stage of neural development and may also be attributed to neurodegenerative diseases.

There are few data, including those obtained by ourselves, suggesting that AhR regulates brain apoptosis (162–164). AhR is a ligand-dependent transcription factor that activates the transcription of genes, such as CYP1A1, CYP1A2 and CYP1B1, and oncogenes (165). CYP1A1 is the most commonly and consistently expressed isoform, which is involved in biotransformation, metabolism and detoxification of many environmental contaminants, including polycyclic aromatic hydrocarbons. This cytochrome is also involved in the metabolism of endogenous substrates such as oestradiol (166). EDCs may alter the CYP450 system through binding to the AhR acting as either agonists or antagonists (167). In the absence of ligand, AhR is bound to heat shock protein Hsp90. Upon ligand binding, the AhR translocates into the nucleus whereupon it heterodimerises with the aryl receptor nuclear translocator (ARNT) protein and binds to an AhR DNA recognition site, known as the xenobiotic response element. The location of xenobiotic response element close to the oestrogen response element allows AhR- and ER-mediated transcription processes to be reciprocally affected. At present, both ER subtypes are known to contribute to neuroprotection, although the relative contributions of ERα and ERβ remain unresolved. It is noteworthy that AhR-dependent activation of proteasomes mediates the degradation of ERα (168). We showed, for the first time, co-localisation of AhR with ERβ in neocortical tissue, thus suggesting an interactive action between these receptors (164). One possible interaction is through ARNT, a dimerisation partner of AhR that can act as a potent co-activator of ERβ (169). This supported our biochemical data showing that, among the ERs, ERβ is the most crucial for compromising AhR-mediated neuronal cell death.

Effects of EDCs on E_2 metabolism

EDCs may have effects on E_2 metabolism in a number of ways. Some EDCs can alter serum lipid concentrations, ultimately enhancing the production of E_2 and other steroids. Furthermore, some EDCs can alter the metabolism enzymes that are necessary for converting cholesterol to steroid hormones. Numerous EDCs can activate one of the P450 cytochromes (P450 or CYP), which are

involved in the metabolism of most steroid hormones and EDCs. Environmental contaminants may contain chemicals that induce P450s, are metabolised by P450s, or both. Induction of CYP occurs when EDCs, such as TCDD, bind AhR. There is a firm link between PCBs, enzyme induction and the effects of AhR (170,171). Coplanar PCBs such as TCDD, activate AhR, causing the induction of CYP, which catalyzes the metabolism of many PCB congeners and other endogenous hormones, including E_2 (168,172). The binding of EDCs with AhR can result in anti-oestrogenic activity through increased metabolism and depletion of endogenous E_2 (172). Elevated levels of CYP enzymes, primarily expressed in the liver, but also in brain and other tissues, result in increased E_2 metabolism and excretion. Alternatively, compounds that are metabolised by P450s may produce an oestrogenic effect if they inhibit endogenous oestrogens from being metabolised.

Oestrogens can produce anti-androgenic effects by the inhibition of testicular androgen secretion via blocking secretion of lutenising hormone or by direct suppression of testosterone synthesis by Leydig cells. High levels of PCB-inducible androstenedione formation have also been found (173). PCB exposure reduced testicular microsomal P450s and affected androstenedione formation and 16α-hydroxylation of testosterone. Mitochondrial CYP, the rate-limiting enzyme of steroidogenesis, was inhibited by 50% in testes of animals exposed to EDCs (174). Adult male rats given single doses of TCDD exhibited decreases in plasma testosterone and dihydrotestosterone concentrations by 90% and 75%, respectively, and decreased seminal vesicle and ventral prostate weights (175). PCB 126 can suppress 5α-reduction of testosterone, or progesterone, in liver microsomes (176). A question for further consideration is the importance of the effects of EDC on steroid metabolism to mediate behavioural processes.

Species differences and food-chain effects: metabolism

Among vertebrates, teleost fishes exhibit unique features in terms of neurodevelopment and brain sexualisation. By contrast to a common thinking, teleosts are not primitive vertebrates but vertebrates that belong to a lineage diverging from the tetrapod lineage some 450 million years ago. Among teleosts, there are primitive and highly evolved species. However, all share the property of growing their brains during their entire lifespan, a feature that is supported by the fact that adult fish conserve active radial glia progenitors throughout life. These cells are notably capable of performing asymmetrical divisions that give birth to new neurones not only during embryonic development, but also in adults (177,178). In addition, the radial glial cells of fish are now well documented for expressing steroidogenic enzymes, notably aromatase B, the product of the *cyp19a1b* gene (177–180). This gene is strongly up-regulated by oestrogens and any xenoestrogens capable of activating one of the three zebrafish ERs (177,180–183). In zebrafish embryos and larvae, exposure to oestrogen and oestrogen mimics causes a strong increase of *cyp19a1b* expression that, in contrast, remains low in controls at early developmental stages (184). This means: (i) that radial glia progenitors are direct targets of xenoestrogens and (ii) that this gene is an excellent biomarker of xenoestrogen exposure that can be used both *in vitro* (181) and *in vivo* (177,180) to address current key questions, such as the effects of mixtures and/or the monitoring of environmental samples.

A very high aromatase activity is another feature that makes the brain of adult fish so special and, in a way, similar to that of embryonic mammals (177,185). In mammals, and at least in rodents, it is assumed that aromatase activity is strongly implicated in brain sexualisation (186). It is considered that these effects are mediated in part through a region-specific modulation of apoptosis (187,188). However, aromatase and oestrogens are also important in the regulation of neural development, synaptic plasticity and cell survival outside the classical 'reproductive brain'. Aromatase knocked-out mice have revealed the potential effects in the development of some brain regions, such as the cortex. A wealth of evidence now supports the view that locally-produced oestrogens acting in paracrine or autocrine ways modulate neuronal survival and brain functions. Therefore, it is possible that the high aromatase activity of the permanently developing brain of adult fishes also supports their constant neurogenic activity. In this regard, the fact that aromatase in only expressed in radial glial cells provides an anatomical substrate for such a link between aromatase expression and neurogenesis. These observations may also explain why many species of fish are sequential hermaphrodites and can change sex as adults, a skill that requires great brain plasticity (189). Our current studies now demonstrate that oestrogen-like compounds not only modulate aromatase expression and activity in the radial glial cells, but also their proliferation (N. Diotel, E. Pellegrini, C. Vaillant and O. Kah *et al.* unpublished data). Thus, taken together, these data suggest that xenoestrogens have the potential to disturb adult neurogenesis and sex changes in

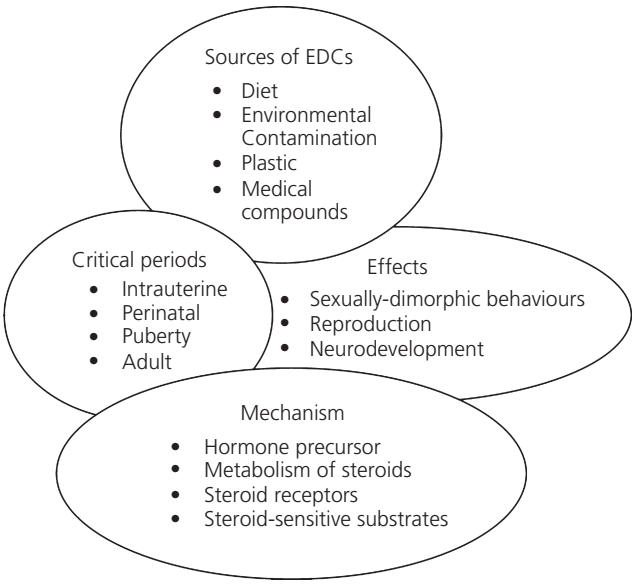

Fig. 1. A schematic representation of varied sources of endocrine disrupting chemicals (EDCs) and how they may influence sexually-dimorphic, reproductive and neurodevelopmental processes, in particular through their actions during critical periods of development. Some of the steroids mechanisms that may mediate the actions of EDCs are included.

adult fish, which would mean that the critical window through which animals are highly susceptible to endocrine disruptors would extend throughout the entire lifespan of fishes.

Obesogenic effects of EDCs

There is growing recognition that some EDCs can act as 'obesogens' and increase the risk of developing metabolic disorders such as diabetes (190–193). One notable obesogen is DES, a synthetic oestrogen initially prescribed to pregnant women to prevent miscarriage, although it was ultimately distributed more widely before its use was discontinued in the late 1970s as a result of prenatal exposure being linked to a higher risk of vaginal clear cell carcinoma (194). Children exposed *in utero* are unfortunately at higher risk for a wide range of neuroendocrine disorders, including reproductive malformations, infertility and testicular cancer (195,196). Emerging evidence now suggests that this population may also be at greater risk for obesity and metabolic disorders (192).

Organotin compounds, such as tributyltin (TBT), are also well recognised obesogens. These compounds are used in agriculture and industry as biocides, heat stabilisers and chemical catalysts (197). They may contaminate water and human foodstuffs, especially shellfish (198–200). As a result of their endocrine-disruptive effects, organotin compounds are toxic to marine species, determining the development of ambiguous genitalia (199) and the increase of androgen levels and the decrease of oestrogens in clam tissues (200). Organotin compounds are peroxisome proliferator-activated receptor (PPAR)γ and retinoid X receptor (RXR) agonists and they stimulate the differentiation of preadipocyte 3T3-L1 cells into adipocytes (200), and modulate, *in vivo*, the expression of PPARγ/RXR target genes in adipose tissue and liver, thus acting as potential obesogens (201). In particular, TBT increases body weight in mammals (202) and disturbs levels of key hormones linked to energy homeostasis (203). These data suggest a peripheral role of TBT on obesity development, although, currently, there are only a few studies investigating the effects of TBT on the central nervous system. In a recent study (204), we demonstrated, for the first time, in an '*in vivo* model', that the oral administration of TBT in adult mice may specifically activate (specific increase of c-fos expression), a key region of the circuits involved in the control of food intake, the ARC nucleus. This nucleus is the source of the neuropeptide Y- and of melanocyte-stimulating hormone-circuits that regulate the stimulation or the depression of the food intake stimulus. Our preliminary results indicate that neuropeptide Y expression is indeed affected by adult exposure to TBT (205), as well as to other EDCs (i.e. BPA and DES) (206).

Other substrates to consider for the actions of EDCs

One challenge to understanding the effects and mechanisms of EDCs is with regard to their many and variable responses and/or actions of E_2-sensitive targets. For example, EDCs can mediate the responses of two orphan receptors of the nuclear receptor family: the constitutive androstane and pregnane X receptors (207). As well, EDCS may have actions at membrane-associated ERs ('nongenomic' actions) (208–210). Similar to E_2, EDCs may have steroid receptor-independent actions through numerous other substrates, such as signal transduction pathways, calcium influx and/or neurotransmitter receptors. Of particular interest is the role that EDCs have via neuropeptide systems (121). Investigations of the extent to which the actions of EDC involve metabolism and/or ER and non-ER mechanisms for behavioural responses are ongoing.

Summary and conclusions

Individuals may be exposed to EDCs from varied sources, including pesticides and herbicides, dust, plastics, medical and/or dietary components (Fig. 1). EDCs can influence reproductively-relevant or nonreproductive, sexually-dimorphic behaviours. Exposure to EDCs during critical phases of development (e.g. perinatal, peripubertal periods) may result in more salient effects on neurodevelopmental and/or reproductive processes. However, exposure to EDCs in adulthood can alter physiological processes, including the production of steroids, and actions via (or independent of) classic cognate steroid receptors. EDCs may have effects through other substrates, such as the AhR and PPAR, as well as retinoid, androstane or pregnane X receptors, neurotransmitters, calcium or signal transduction. EDCs, from varied sources, may organise and/or activate sexually-dimorphic, neurodevelopmental and/or reproductive processes or other functions, by mimicking, antagonising or altering steroidal actions.

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