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# A STUDY ON THE IMPACT OF ENDOCRINE-DISRUPTING COMPOUNDS ONSEXUALBEHAVIOR

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## ABSTRACT

Aplethoraofhormonesregulatesmanyofthebody'sfunctions,includinggrowthanddevelopment,metabolism,electrolytebalances,andreproduction.Numerousglandsthroughoutthebodyproducehormones. The hypothalamus produces several releasing and inhibiting hormones that act on thepituitary gland, stimulating the release of pituitary hormones. Of the pituitary hormones, severalacts on other glands located in various regions of the body, whereas other pituitary hormonesdirectlyaffecttheirtargetorgans.Otherhormone-producingglandsthroughoutthebodyincludetheadrenal glands, which primarily produce cortisol; the gonads (i.e., ovaries and testes), whichproduce sex hormones; the thyroid, which produces thyroid hormone; the parathyroid, whichproduces parathyroid hormone; and the pancreas, which produces insulin and glucagon. Many ofthese hormones are part of regulatory hormonal cascades involving a hypothalamic hormone, oneormorepituitary hormones, and oneormoretargetgland hormones.

**Keywords:**endocrinefunction;hormones;hypothalamus;pituitarygland;gonadfunction;

## 1. INTRODUCTION

Sexual reproduction in vertebrates requires sexually differentiated behaviors to ensure attractionbetweenpartnersandmating.Thesebehaviorsareakeyfactorinthesuccessofsexualreproduction,on which species survival depends. Males and females adopt different behaviors and posturesduring attraction and mating. Male rodents readily express sexual behavior whenever a receptivefemaleispresent.Duringtheprecopulatoryorappetitivephase,malesengageintheirinvestigation,displayinganolfactorypreferenceforreceptivefemales.Malesgenerateultrasonicvocalizationsinresponse to females or their odors. These vocalizations have characteristics in common with thesongs of songbirds. The emission of courtship vocalizations conveys information about the male'smotivational state and helps to attract the female partner. During the copulatory or consummatoryphase,malesmount,thrust,intromit.Inmalemice,thematingendswithejaculation,wher

easmalerats reach satiety after several ejaculations and do not then copulate again for 1–3 days. In femalerodents, receptivity is constrained by threshold levels of estradiol (E2) following progesteronesecretion, and is, therefore, limited to the estrous phase of the cycle corresponding to the ovulationperiod. The female also participates actively in mating, through three phases of sexual behavior:attractivity, proceptivity, and receptivity. During attractivity, the female stimulates male behaviorbyemittingpheromones.Thefemalethenadoptsseveralproceptivebehaviors(hops,darts,solicitations)in responseto stimulifromthemale.

Sexualbehavioristightlycontrolledbyfinelytunedneuralprocesses,whichbeginduringdevelopment and are tightly regulated by gonadal hormones. These processes may, therefore, behighly sensitive to exposure to endocrine-disrupting compounds (EDC), defined by the WHO andthe Endocrine Society as exogenous chemical substances or a mixture of substances that alter thefunctionsoftheendocrinesystem.ExposuretoEDChasbeenreportedtoalterseveralreproductivefunctions,includingorgandevelopment,germcellproduction,pubertaltiming,andotherphysiologicalprocessesrequiredforfertility,asdocumentedbybothexperimentalandepidemiological studies. Several studies have addressed the effects of exposure to EDC on matingbehavior. Here, we review the experimental studies in rodents performed to address the potentialeffects of exposure to EDC on sexual behavior. We focus on the underlying molecular and neuralprocessesaffectedbysuchexposure,payingparticularinteresttomoleculeswithestrogenicand/orantiandrogenicactivities.ArecentreviewbyGoreetal.providedthegeneralethologicalbackgroundtosexualselectionandreproductivecompetenceinanimalspeciesandtheirsensitivitytoEDC.

## 2. HORMONAL REGULATION OF SEXUAL BEHAVIOR AND UNDERLYING SEXUAL DIMORPHISMSCRITICALPERIODSOFHORMONALREGULATION/PERINATALPERIOD

Since the pioneering work of Phoenix et al., it has become clear that gonadal hormones play a keyroleinthesexualdifferentiationofmatingbehavior.Thisprocessbeginsearly,intheperinatal(lategestationalandearlyneonatal)period.Inmales,testosteronereleasedfromthefetalandneonataltestes permanently potentiates male (masculinization) behavioral and anatomic characteristicswhilst inhibiting female (defeminization) characteristics in the neural circuitry underlying sexualbehavior. Thiscircuitry isstimulated by pheromonal cuesemitted by receptive femalesandtransmitted from the main olfactory epithelium and vomeronasal organ to the main and

accessoryolfactorybulbs,respectively,andthentothechemosensoryresponsivenucleiinthemedialamy

gdala, the bed nucleus of the stria terminalis, and the medial preoptic area, where they areprocessed in behavioral responses. Projections are sent from the hypothalamic paraventricularnucleus to the spinal centers that promote penile erection and ejaculation, including the spinalnucleus of thebulbocavernosus, andthegastrin-releasing peptidesystem.

Perinatal testosterone secretion has organizational effects, resulting in structural, neurochemical,andmoleculardifferencesincircuitrybetweenthesexes.Differencesincellnumberand morphology or fiber density between the sexes have frequently been described for the medialamygdala,thebednucleusofthestriaterminalis,andthemedialpreopticarea.Forinstance,therats exuallydimorphicnucleus(SDN)andacorrespondingclusterofcalbindin-immunoreactiveneurons, both located in the medial preoptic area, contain more cells in males than in females.Conversely,neuronsexpressingkisspeptinandtyrosinehydroxylaseintheanteroventralperive ntricular (AVPV) nucleus, a subdivision of the preoptic area involved in the ovulatory surgeof LH, are more numerous in females than in males. The regulation of these neuronal populations,or of other sexually dimorphic features, by perinatal testosterone can be mimicked by E2 becausegonadal testosterone is aromatized into neural E2 by the aromatase cytochrome P450. At themolecularlevel,testosteroneanditsneuralmetaboliteE2alsotriggerdifferencesingeneexpressionbe tweenthesexes, throughlong-lasting changes including epigeneticmodifications.

## 3. PREPUBERTAL/PUBERTALPERIOD

The pubertal period is characterized by the central activation of pulsatile GnRH secretion, whichstimulates the pituitary gonadotropin secretion required for sexual maturation and fertility. Duringthis period, testosterone also exerts long-term effects on behavior to ensure the maturation ofprocesses initiated during the perinatal period. Indeed, the prepubertal castration of male hamstershas been shown to decrease sexual behavior (fewer mountings and intromissions and longer timesto ejaculation) and to shorten the time to lordosis relative to that for males castrated after

puberty.Neuralprocesses,suchascellproliferation,insexuallydimorphicregionsareinfluencedbygona dalhormonesduringtheperipubertalperiod.Infemales,α-fetoproteinlevelsdecreaseafterbirthandthe ovaries begin releasing E2 on a postnatal day (PND) Postnatal/prepubertal E2 secretion playsan active role in the feminization of sexual behavior. Indeed, E2 administration between PND15and PND25 in aromatase knockout mice, which normally have highly impaired lordosis behavior,partially restores this behavior. During this postnatal period, ovarian E2 is also essential for theestablishment of the LH surge, which is synchronized with the receptivity period. In particular,prepubertal E2 activates an increase in kisspeptin expression in the rostral periventricular area ofthethird ventricle.

## 4. ADULTHOOD

In adult males, gonadal testosterone acts on the male neural circuitry to stimulate sexual behavior.This activational effect of testosterone is transient by comparison to the permanent organizationalchangesinducedduringthedevelopmentalandpubertalperiods.Malesexualstimulation isreducedor inhibited by castration but can be restored by hormonal supplementation. Testosterone and itsneural metabolite E2regulate the signalingpathways of neurotransmitters and neuropeptidesplayinganimportantroleindisplaysofsexualbehavior,suchasoxytocin,dopamine,andglutamate.

Cyclic females mate only during the estrous phase and are sexually inactive during the rest of thecycle. The preovulatory surge of E2, which occurs during the proestrus phase, triggers not only anovulatory surge of LH but also the expression of progesterone receptors (PR) in the ventromedialhypothalamus.ProgesteronereleaseunderthecontrolofLHtheninducesfemalereceptivity,whichis perfectly synchronized with ovulation in such species. The increase in E2 levels also relievesconstraints exerted by the inhibitory system through suppression of the inhibition exerted by thelateralseptumandinactivationoftheβ-endorphinsysteminthepreopticarea.Severalneuropeptides and neurotransmitters present in the ventromedial hypothalamus display differencesbetween the sexes. For example, estrogen receptors (ER), PR GABA, and enkephalin are all moreabundantinfemales thaninmalesandareknowntopromotefemalesexualbehavior.

## 5. MECHANISMSUNDERLYINGTHEHORMONALREGULATIONOFSEXUALBEHAVIOR

Sex steroids regulate sexual behavior principally through nuclear superfamily receptors. As thedetailedmechanismsunderlyingtheexpressionofsexualbehaviorhavebeenlargelyreviewed,thisparagraph summarizes very briefly the genetic studies investigating the relative contribution ofandrogen (AR) and ER. Indeed, the involvement of each of these receptors in this regulation hasbeen studied by ubiquitous gene invalidations. In males, data from the testicular feminizationmutationandglobalARknockoutmodels,bothofwhichresultinafemininephenotype,havesuggestedthatthisreceptorplays somekindofroleintheexpressionofsexualbehaviorinratsandmice. Global ERα knockout mice are infertile and have impaired sexual behavior. Global ERβknockout males have normal sexual behavior, but mutant males derived from an ERβ knockoutmouse line completely devoid of ERβ transcripts are infertile and display a mild impairment ofsexual

behavior. In the global ERα and ERβ knockout models, females are infertile, with muchlowerfrequenciesoflordosisandproceptivebehaviors than wild-typefemales.

The neural role of these receptors was dissected more precisely by conditional gene invalidation,which has the advantage of preserving peripheral receptor expression and not interfering withgonadal and genital tract effects. In males, the estrogenic and androgenic pathways seem to playcomplementary roles in the organization and activation of the neural circuitry underlying sexualbehavior.Theperinatalmasculinizationanddefeminizationofbrainstructuresinvolvetheestrogenic pathway, whereas the neural AR is involved principally in the postnatal organization ofspinal nuclei; however, both pathways seem to be involved in the adult activation of sexualbehavior.

## 6. EFFECTS OFEDC ON SEXUALBEHAVIOR

WeheredescribethedatacollectedforrodentsuptoDecember2017,withaspecialfocusonEDCexhibiting estrogenic/anti-estrogenic or anti-androgenic activities given the nature of signalingpathways involved in the expression of sexual behavior. Table 1 lists the EDC analyzed, with theirestrogenic or anti-androgenic activities, uses, and reference doses established by agencies whenavailable.

**Table1:TheanalyzedEDCpresentedbyhormonalactivity,usesandreferencedosesestablished by agencies whenavailable**

| | Source or use | Reference doses |
|---|---|---|
| *Estrogenic compounds* | | |
| Bisphenol A (BPA) | In polycarbonate plastic used in the manufacture of food containers, dental resins, thermal papers | TDI = 0.004 mg/kg/day (EFSA, 2015)<br>TDI = 0.05 mg/kg/day (US EPA, 2012) |
| Diethylstilbestrol (DES) | Used in cases of preterm labor. Banned in 1971 in the USA and since 1975 in several European countries | |
| Ethinyl estradiol (EE) | Oral contraceptive treatment | |
| Methoxychlor (MXC) | Organochlorine insecticide banned since 2002 in EU and 2003 in the USA. Still present in the environment and used for applications such as mosquito and malaria control in developing countries | ADI: 0.1 mg/kg/day (EU Pesticides Database) |
| Nonylphenol (NP) | Nonionic surfactant used in industrial, agricultural and domestic applications such as soap, cosmetics, paints, herbicides and pesticides, or plastic fabrication | TDI: 0.005 mg/kg/day (Danish EPA, 2000) |
| Phytoestrogens | | |
| Coumestrol | Present in plants (Alfalfa, soybeans…) | |
| Ferutinin | Present in roots of Ferula plants | |
| Isoflavones (daidzein, genistein) | Present in plants (lupin, soybeans, fava beans…) | LOAEL of 35 mg/kg/day for isoflavones with safety factor of 300 (Anses 2015) |
| Resveratrol (RVT) | Present in grapes, blueberries, raspberries… | |
| *Anti-androgenic compounds* | | |
| Phthalates | | |
| Dibutyl phthalate (DBP) | Used in the manufacture of PVC plastics, adhesives, inks | TDI: 0.01 mg/kg/day (EFSA, 2005)<br>DNEL: 0.0067 mg/kg/day (ECHA 2017) |
| Di-(2-ethylhexyl) adipate (DEHA) | Used as a substitute for DEHP (marginal use): PVC, food plastic, cosmetics | |
| Di-(2-ethylexyl)phthalate (DEHP) | Used in PVC, food containers, medical products, automobile… | TDI: 0.050 mg/kg/day (EFSA, 2005)<br>NOAEL: 4.8 mg/kg/day, DNEL: 0.034 mg/kg/day (ECHA 2017) |
| Diisononyl phthalate (DINP) | Used as a replacement for DEHP: PVC, paint, inks, toys, plastic, soles, automobile | Sum DIDP/DINP: 0.15 mg/kg/day (EFSA, 2005) |
| Vinclozolin | Fungicide widely used on fruits and vegetables to avoid rot and mildew | ADI = 0.01 mg/kg/day (WHO, 1998)<br>NOAEL = 1.2 mg/kg/day (US EPA, 2003)<br>ADI = 0.005 mg/kg/day (EU Pesticides Database) |

ADI, acceptable daily intake dose; DNEL, derived no-effect level; LOAEL, lowest observed adverse effect level; NOAEL, no-observed effect level; TDI, tolerable daily intake dose.

## 7. MODEOFACTION

Endocrine disruption of sexual behavior may occur through indirect or direct pathways (Fig. 1).The indirect pathway involves changes in the levels of gonadal hormones, which then affect theorganizationoractivationofneuralstructuresinvolvedintheexpressionofbehavior.Thecirculating levels of gonadal hormones may be modified by dysregulation of the hypothalamicGnRH system and upstream regulators includingkisspeptin neurons and/orthe disruption ofpituitary function or gonadal steroidogenesis. Exposure to EDC can also directly affect the neuralstructures underlying sexual behavior, by interfering with the neural synthesis of hormones, suchas the aromatization of testosterone into E2, binding to and activation of sex steroid receptors, orthe

expression of these receptors. Modes of action involving agonism or antagonism are moredifficult to demonstrate in vivo. They can be suggested or supported by parallel comparisons withthe effects of positive controls, such as estrogens or their analogs, or anti-androgens, such asflutamide, although such comparisons may be limited for the reasons described in the section“Effects ofDevelopmentalversus AdultExposuretoEstrogenicCompounds”.

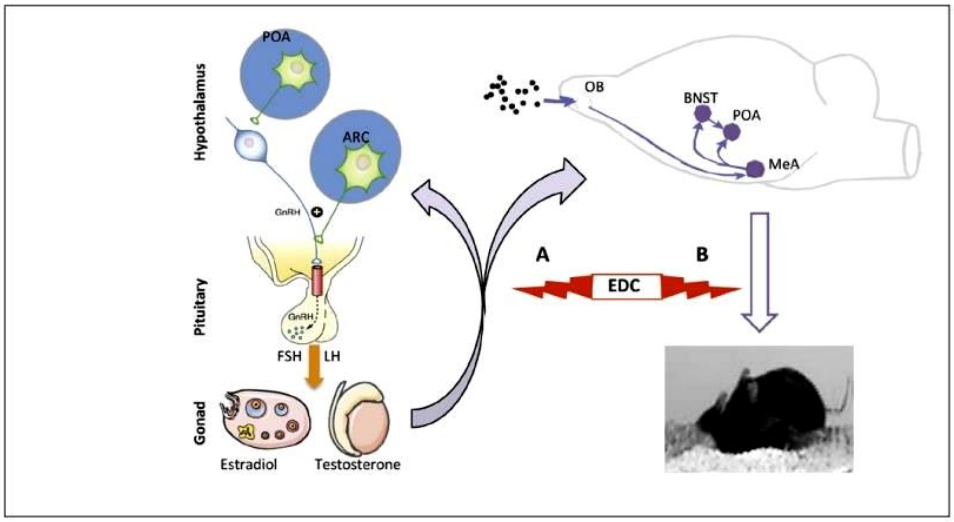


Fig. 1. Exposure to endocrine disrupting compounds (EDC) can alter sexual behavior throughindirect (A) and/or direct pathways (B). A Kisspeptin neurons (green cells) of the preoptic area(POA) and arcuate nucleus (ARC) activate synthesis and liberation of GnRH, which stimulatesgonadotropin hormone (LH, FSH) liberation, and consequently gonadal synthesis and liberation ofsexsteroidhormones.Estradiolandtestosteroneexertinturnafeedbackonthisgonadotropicaxis.Disruptionofthisaxisby EDCmayinterferewiththehormonaldependentregulationoftheneuralstructuresunderlyingsexualbehaviorinmalesandfemales.BSimplifiedschemeofthemaleneuralcircuitry including the olfactory bulb (OB), medial amygdala (MeA), bed nucleus of stria terminalis(BNST),andpreopticarea(POA).EDCcanalsodirectlytargetheseneuralstructures,todisrupthormonalsignaling pathwaysnecessaryto elicitmalesexualbehavior.

## 8. DEVELOPMENTALEXPOSURE

Three of 12 studies on male rats reporting developmental effects of EDC on behaviors described adecrease in adult hormone levels following exposure to BPA, genistein, and resveratrol. The other9studiesfoundnoeffectsonadultlevelsoftestosterone,E2,andgonadotropins.Inmice,nochangein hormone levels was observed following exposure to BPA or EE. Exposure to methoxychlor

didnot change basal hormone levelsbut preventedthe increase intestosterone levelsfollowingexposure to females. The observed impairment of male sexual behavior does not, therefore, seemto be systematically linked to changes in hormone levels. However, these findings do not rule outthe possibility of transient changes in hormone levels during the exposure period, particularly ifexposure occurs during development, thereby inducing long-term changes to the neural processesor hormonal signaling pathways underlying male behavior. Interestingly, long-term changes in thelevelsofthesexsteroidreceptors,ERandPR,havebeenreportedtobeinducedbyprenatalandpostnatal exposure to BPA, DES or methoxychlor in the whole hypothalamus or more specificallyhypothalamic areas (preoptic area, ventromedial hypothalamus), bed nucleus of stria terminalis ormedial amygdala of rats, and mice. However, no effects of such exposure were reported in 2 othermouse studies in the same brain areas. Changes in total hypothalamic gene expression wereobserved for BPA and EE, or for neuropeptides involved in social behavior, such as AVP in themedialamygdalaandlateralseptumand oxytocininthehypothalamus.

## 9. ADULTEXPOSURE

Inmalerats,changesinmalesexualbehaviorfollowingexposuretophytoestrogenswereassociatedwith lower levels of testosterone. In mice, the impairment of sexual behavior following chronicadultexposuretoBPA,NPorDEHPwasassociatedwithunchangedhormonallevelsandintegrity ofthehypothalamic-pituitary-gonadalaxis,togetherwithchangesinthelevelofsexsteroidreceptorexpression. In particular, DEHP down-regulated AR protein and mRNA levels in the neuralcircuitryinvolvedinsexualbehavior,whileboththeNumbersofARandERα-immunoreactivecellswere affected by NP exposure. The exposure of adult females to resveratrol or BPA increased E2levelsinbothratsandmice.Interestingly,regardlessofitsbehavioraleffects,exposuretophytoestrogensorBPAincreasedthelevelsofERα,ERβorPRexpressioninthepreopticarea,theventromedialhypothalamusor theparaventricularnucleus.

## 10. CONCLUSION

Several observations can be made based on the data concerning the impact of EDC on sexualbehaviorreviewedhere.Ingeneral,sexualbehaviorappearstobehighlysensitivetoEDC,andcanbe added to the endpoints generally used in assessments of the risks of exposure to EDC and theirpotentialimpactonreproduction.Likeotherreproductiveendpoints,thebehavioraleffectsinduced

by exposure to EDC depend on the period of exposure. The developmental and pubertal stages areparticularly vulnerable due to the organizational effects of hormones during these periods, butexposureinadultsmayalsohaveeffects,thedosesusedinseveralstudieshavingelicitedeffectsatdose s below thereferencedose. Effects mayalso dependon thesexof theanimals

The amounts of data published differ considerably between EDC compounds. The most frequentlyinvestigated compounds are estrogen-like molecules, such as BPA and phytoestrogens. However,publishedstudieshavenotaddressedallpossibleperiodsofexposureinbothsexes.Developme ntalexposure to BPA or phytoestrogens has been extensively studied in both males and females, butadultexposuretophytoestrogenshasbeenstudiedonlyinfemales.Muchmorestudiesarerequiredfor other estrogenic or anti-androgenic compounds, for which fewer data are available, regardlessoftheexposureperiodconsidered.

Another interesting observation is that changes in the level of expression of sex steroid receptors(ER, AR, PR) have been widely documented in both males and females. This finding stronglysuggests that EDC may act, at least partly, through changes in the neural signaling pathwaysunderlying sexual behavior, either directly through epigenetic modifications to the ERα promoter,asreportedfordevelopmentalexposuretoBPA,orthroughasyetunidentifiedpathways,asfort hedown-regulation of AR induced by the exposure of adults to DEHP. Finally, although caution isrequired when extrapolating findings from rodents to other species, these altered processes may beofconsiderablerelevanceinbothhumansandwildlife.Theregulationoflibidoanderectilefunctionor reproductive behaviors by sex steroid hormones at the neural level is highly conserved acrossspecies. In this context, human studies have reported an association between a decrease in sexualactivity and exposure to environmental doses of DEHP and BPA, but the mechanisms underlyingtheseeffectsremain unclear.

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