Bisphenol A and other suspected estrogenic endocrine disruptors

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Environmental Endocrine-Disrupting Chemicals (EDCs)

Compounds in the environment that interfere with, block, or mimic effects of natural hormones.

- Plastics (BPA), Plasticizers (phthalates)
- Industry (PCBs, dioxins)
- Pesticides, fungicides (DDT, methoxychlor, vinclozolin)
- Pharmaceuticals (DES, EE)
- Phytoestrogens (soy, alfalfa)
- Heavy metals
Estrogenic EDCs

- BPA
- PCBs
- Pesticides (methoxychlord)
- Phytoestrogens (?)
- Heavy metals

![Bisphenol A](image)
Estrogenic EDCs

Mechanisms of action:

Nuclear hormone receptors – ERα, ERβ
Membrane receptors – GPER (GPR30)
Steroidogenic enzymes (p450 aromatase)
Steroid metabolizing enzymes – steroid sulfatase
Neurotransmitter receptors
EDCs – Brain & Behavior

Estrogenic EDCs

“Fetal/developmental basis of adult disease”

Peripheral hormones, Reproductive function, Behaviors
Bisphenol A (BPA) – background

- Monomer used to manufacture polycarbonate plastics, food liners, dental sealants.
- Used in high volume: >6 billion lbs annually.
- Heat causes hydrolysis and leaching.

Bisphenol A (BPA) – mechanisms of action

- Estrogen receptor agonist/antagonist – up-regulation of Esr1, Esr2
- Androgen receptor antagonist
- Thyroid hormone receptor antagonist
- AhR, RARα, RXRα are up-regulated by BPA
- Enzyme activity
- Epigenetic modifications (DNA methylation)

ER agonist effects are best-studied.
Bisphenol A (BPA) – low doses

- Generally used to refer to “environmentally” or “ecologically” relevant.

- LOAEL EPA reference dose = 50 μg/kg/day

- However: Is there really a LOAEL?
Bisphenol A (BPA) – humans

- Measurable in serum, urine, amniotic fluid, placenta, umbilical cord blood, and human blood.
- Serum levels estimated from 0.2 to 20 ng/ml.
- Amniotic fluid levels measured at 8.3 ng/ml.
- Breast milk: mean 0.61 ng/ml.
- Urine: Numerous studies show detectable BPA.

- Assays include GC-MS, HPLC, ELISA, with sensitivity from 0.01 to 0.5 ng/ml.

Vandenberg et al., Reprod. Toxicol. 24: 139-177 (2007)
Bisphenol A (BPA) – other important considerations

- Gestational/early postnatal exposures and long delay until the manifestation of a dysfunction.

- Multiple mechanisms make prediction of outcomes difficult.

- Likelihood of mixtures of EDC exposures.

- Individual differences in genes and factors regulating gene expression.
Bisphenol A (BPA) – the brain

- Increased aggressive behavior
- Increased motor activity
- Increased pain sensitivity
- Impaired learning & memory
- Decreased maternal behavior
- Impairments in sexual behavior
- Impaired neural plasticity – rodents & non-human primates
- Hypothalamus and brain sexual differentiation are disrupted
Bisphenol A (BPA) – other endocrine targets

- Mammary gland
- Prostate
- Ovary (oocytes)/ Testes (sperm)
- Uterus and vagina/ epididymis & seminal vesicles
- Adipocytes
- Thyroid
- Anti-androgen

Polychlorinated Biphenyls (PCBs)

- Estrogenic EDC
- Persist & bioaccumulate
- Adult exposure - contaminated food
- Developmental exposure - placental and lactational transfer
- Developmental PCB exposure - neurological/reproductive deficits
- Aroclor 1221: PCB used in our lab
PCB effects on P1

Exposure during the critical period of brain sexual differentiation
ERα Expression in the mPOA (P1)

Female

DMSO

A1221

Male

DMSO

A1221

Sarah Dickerson, PhD dissertation (unpub.)
• Apoptosis is lower in females than males.

• PCBs cause increased apoptosis in females – making them more “male-like.”
PCB effects in adulthood

Injections
- Vehicle (DMSO)
- E2 (50 µg)
- A1221 (1 mg/kg)

Birth

Postnatal development, Reproductive cycles, Hypothalamic protein/gene expression, Behavior
Developmental effects

- Eye opening: Advanced in females (PCB).
- Pubertal timing: Advanced in females (EB, PCB), delayed in males (EB, PCB).
- Estrous cyclicity: Prolonged cycles in EB (46%), PCB (33%).
Hypothalamic control of reproduction

EDCs

Kisspeptin

GnRH

ER

FOS
**ERα cells in AVPV (P60)**

- ERα is greater in the AVPV of females than males.
- PCBs cause ERα to decrease in the AVPV of females – making them more “male-like.”

Sarah Dickerson, PhD dissertation (unpub.)
**Kisspeptin in AVPV (P60)**

- Kisspeptin is greater in the AVPV of females than males.

- PCBs cause kisspeptin to decrease in the AVPV of females – making them more “male-like.”

Sarah Dickerson, PhD dissertation (unpub.)
GnRH-Fos co-expression (P60) in females

The co-expression of Fos in GnRH neurons is significantly suppressed in PCB females.

Sarah Dickerson, PhD dissertation (unpub.)
Paced mating behavior in females

- Reproductive success is the ultimate biological outcome.
- Reproductive success is enhanced when the female controls the pace of the mating.
- A paced mating paradigm enables dissection of female-typical behaviors.

Summary

• Exposure to estrogenic EDCs during fetal development has long-term consequences on the molecular and cellular processes controlling reproduction.

• EDCs are associated with the masculinization of the hypothalamus of females.

• Puberty and reproductive physiology are perturbed, and reproductive behaviors are compromised.
Implications

I propose that fetal exposures to EDCs reprogram the hypothalamus, and that this programming permanently compromises reproductive success.

I also believe that these effects may be transmitted to future generations through molecular epigenetic changes.
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