Endocrine Disruption and Epidemic of Receptor Resistance

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Disclosure
Devaki Lindsey Berkson, MA, CNS, DACBN, CAN, ND, is owner of Berkson Health in Austin, TX. She is employed at the Wiseman Family Practice Clinic in Austin, TX and the Integrations Health Center Tulsa, OK. Conflict of interest was resolved through peer review of slide content.

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Learning Objectives

• At the conclusion of this activity, the participant will be able to:
  – Discuss the latest theory of receptor physiology and how this impacts how to assess and treat patients
  – Discuss the difference between endocrinology and intracrinology and how this impacts how you practice
  – Review progesterone and ER-beta resistance and how this impacts testing and treating.

Center for Bioenvironmental Research

Mentor - John McLachlan PhD
Dr. Jan-ake Gustafson – discovered ER beta

Estrogen Receptor + E2

Receptor Physiology

- Zinc – DNA binding domain steroid receptor
- The best characterized domain of steroid Rs is C domain. Contains zinc fingers. Regions of protein which form 3-dimensional structure oriented to bind zinc atom and hormone so creates a shape that can insert into DNA. Blocked by CD; infertility.
- Zinc: essential part of SHBG, natural aromatase inhibitor, zinc blocks T being converted into estrogen; blocked by CD, EDCs

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Physiologic Internet System
Nuclear Receptor Complexity
- The nuclear receptors have long been recognized as critical.
- Ligand-binding pocket of the receptor, the site where agonists, antagonists and drugs interact (SERMs).
- The alternate NR-associated interaction sites that have now been targeted include the co-activators, the zinc fingers of the DNA-binding domain, and the NR response elements.
- The studies thus far have been performed with the estrogen receptors, the androgen receptor (AR), the thyroid hormone receptors, and the pregnane X receptor.

Hormone Family Cross Talk
- The regulation of hormone nuclear receptor gene expression is central to hormone action.
- Any NR can influence the expression of other types of NRs—cross-regulation—thus modifying how a cell responds to a different hormone.
- High Cortisol, block E and T.
- Careful when giving hormone therapy not affecting other hormones, like giving estradiol without T.

EDCs – diverse names
- Hormone disruptor
- Endocrine Disrupting Compounds (EDCs)
- Xenosterogens (XEs)
- Anti-estrogens, anti-androgens, anti-progestins, anti-insulinogens, Obesogens
- Endocrine modulators
- Environmental signaling
- Physiologic Internet e-mailers
Endocrine Disrupting Compounds – What Are They?

- Endocrine-disrupting chemicals (EDCs) are natural or synthetic compounds present in the environment
- Which can interfere with hormone synthesis and normal physiological functions of male and female reproductive organs.
- Through genomic and non-genomic signaling pathways through hormone receptors (and even w/o receptors.)
- New thought – fetal origin of adult disease. Much of EDC issue, not all, is prior to conception and birth. But also seniors (cognition) as the brain is very sensitive to EDCs.


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Critical Windows of Exposure

- Critical Periods: preconception, in-utero, mother’s milk, developing brain, aging brain

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Hormone Deception Beyond

- A comprehensive report on global pollution by endocrine disruptors (EDs), EDs and diabetes and obesity, EDs and the thyroid in highly polluted Slovakia, Ah-receptor: EDs and immune system, EDs and testosterone, EDs and infertility, EDs and autism spectrum, ADHD, impulse control and behavior issues, EDs and human genome.

National Geographic

• Chemical Exposure Linked to Billions in Health Care Costs
• Researchers conclude they are 99% certain that hormone-altering chemicals are linked to attention problems, diabetes, other health problems.
By Elizabeth Grossman, for National Geographic
PUBLISHED March 05, 2015

Question

• If EDCs are global and affecting receptor and response elements
• How accurate are any forms of testing of hormone levels in all patients?

Hijackers Gaining Respect

• Exposure to hormone-disrupting chemicals is likely leading to an increased risk of serious health problems costing at least $275 billion (U.S.) per year in Europe alone.
• The European Union’s debate of national regulation, if approved, would have a profound effect on industries and consumer products worldwide.
• Linda Birnbaum PhD, director of the U.S. National Institute of Environmental Health Sciences, called this a “wake-up call”. (Dr. Birnbaum was main reader for Hormone Deception)
• Also for practitioners: testing, treating, interpreting.
• The researchers detailed the costs related to three types of conditions: neurological effects, such as attention deficit disorders; obesity and diabetes; and male reproductive disorders, including infertility and Berkson adds, sexuality and hippocampal functioning: BRAIN.

J Clin Endocrinol Metab. 2015 May;100(5):1792-801. Inflammatory and cardiometabolic risk on obesity: role of environmental xenoestrogens.
Heart Disease

- Some chemicals used in consumer products or manufacturing (e.g., plastics, pesticides) are being linked to obesity and cardiovascular disease.
- In premenopausal women, XEs in plasma seem to be a predictor of 10-year cardiovascular disease risk.

J Clin Endocrinol Metab. 2015 May;100(5):1792-801. Inflammatory and cardiometabolic risk on obesity: role of environmental xenoestrogens

EDCs – Mechanisms/Actions

- Mimic endogenous hormones like estrogen (more ER-alpha more than ER beta)
- ER alpha – growth signals
- ER beta – control signals – anti-oncogene. Some research suggests more vulnerable.
- Alter the way endogenous hormones are produced, metabolized or excreted.
- Modify the number of hormone receptors and thus global signaling.
- Cause methylation defects like in the uterus/endometriosis.
- Stimulate the release of endogenous hormones or endogenous substances that affect the balance of the *hormone family (crossstalk).
- Antagonize endogenous hormones (anti-androgens, anti-progestins, anti-estrogens, excessively pro-estrogenic)
- Metabolites might be more active than parent compound.

Hormone Deception Berkon 2000 McGraw-Hill, Awakened Medicine

Examples of Hormone Disrupters:

Environmental
- Estrogens
- Anti-progestins
- Anti-androgens
- Anti-estrogens
- Anti-thyroid
- Anti-retinoic acid

Feminizing effect?

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Milestones of Reproduction

- This analysis examined 111 EDCs and focused on known reproductive toxicants or chemicals with half-lives >1 year.
- Women with high levels of β-hexachlorocyclohexane (metabolite insecticide lindane), mirex, p,p'-DDE, 1,2,3,4,6,7,8-heptachlorodibenzofuran, mono-(2-ethyl-5-hydroxyhexyl) and mono-(2-ethyl-5-oxohexyl) phthalate, polychlorinated biphenyl congeners -70, -99, -105, -118, -138, -153, -156, -170, and -183
- Had mean ages of menopause 1.9 to 3.8 years earlier than women with lower levels of these chemicals.
- EDC-exposed women were up to 6 times more likely to be menopausal than non-exposed women.

Hormone Disruption Example CD

- High level in placenta make resistant to progesterone
- Zinc finger damage so can’t bind to DNA
- Block normal action of estrogen
- All promote infertility

Early Onset Menarche

- Our findings suggest an association between 2,5-dichlorophenol (herbicides).
- Along with multiple environmental phenols.
- And earlier age of menarche in the general U.S. population


Progesterone Resistance

- Salivary progesterone concentrations, basal body temperatures, and breast blood flow changes (surface temperature method) recorded daily for one cycle.
- 25 controls were compared with 30 women with previous breast cancer. On average the women with previous breast cancer had had surgery 2.4 years previously; the operation was usually mastectomy, leaving the contralateral breast for study.
- Follicular phase (day 1-14) oral temperature averages were statistically indistinguishable between women in the control group and those with previous breast cancer.
- Luteal blood progesterone profiles were considered in the normal range for the controls and patients. However, the women with previous breast cancer exhibited a significantly smaller rise in the luteal phase basal body temperature.
- Progesterone resistance could be a clinical entity and could be important in carcinogenesis and not reflected in blood levels.


PCOS

- Several human studies indicate that PR-mediated signaling pathways in the nucleus are associated with progesterone resistance in women with PCOS.
- Endometrial progesterone resistance in women with PCOS.

HPTE - methoxychlor metabolite

- Decreased progesterone production by corpus luteum
- HPTE directly inhibits P450scc catalytic activity resulting in reduced progesterone formation, and this action was not mediated through estrogen or androgen receptors.

Reproductive Toxicology Volume 32, Issue 1, July 2011, Pages 77–84. The methoxychlor metabolite, HPTE, inhibits rat luteal cell progesterone production

Phthalates - Luteal Progesterone

- To evaluate the influence of phthalates on human luteal cell function.
- Twenty-three normally menstruating patients in the midluteal phase.
- We investigated the effect of di(2-ethylhexyl)phthalate (DEHP), di-n-butyl phthalate, and butyl benzyl phthalate on basal and hCG-induced progesterone.
- DEHP, DBP, and BBP were able to reduce both basal and hCG-stimulated progesterone.
- The results show the ability of phthalates to affect luteal steroidogenesis.


BPA + Paraben Synergy – progesterone receptor changes

Results indicate BPA and IBP may have additionally increased estrogenic potency via an estrogen receptor-mediated pathway and alterations in PR.

Food & Cosmetic Colorings

- Primary biliary cirrhosis (PBC) is a liver disease of unknown cause that occurs most frequently in post-menopausal women. Since the female sex hormone oestrogen can be cholestatic, we hypothesized that PBC may be triggered in part by chronic exposure to xenoestrogens (which may be more active on a background of low endogenous estrogen levels seen in post-menopausal women).
- Chemicals linked to PBC were then screened for xenoestrogen activity in the human ERα-positive MCF-7 breast cancer cell line.
- Using this assay, the coal-derived food and cosmetic colorings--sunset yellow and tartrazine--were identified as novel human ERα activators, activating at typical human exposure dosages.

Toxicology. 2012 Aug 16;298(1-3):40-51. Tartrazine and sunset yellow are xenoestrogens in a new screening assay to identify modulators of human estrogen receptor transcriptional activity.

Receptor Resistance?

- Any hormone
- Insulin
- Thyroid
- Progesterone
- Testosterone
- ER beta
- Vitamin A
- Vitamin D


Signs of Progesterone Resistance

- History of severe dysmenorrhea
- History of spotting
- History of miscarriages
- History of sleep issues
- History of anxiety
- History of endometriosis especially recurrent
- History of brain trauma
- History of elevated hsCRP and/or insulin without large BMI
- Take PR but don’t get benefits (is sleep, calm, improvement of bad estrogen dominance)
- History of nervous system pathologies i.e., MS
- History of adverse estrogen dominance ER alpha

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Possible PRR Female Disorders

- PCOS
- Disruption in timing of puberty (lethally changes sex maturation)
- Early breast development (more sensitive index)
- Early menarche
- Early menopause
- Altered Fertility
- Vaginal adenomysis, endometriosis
- Infertility
- Uterine fibroids
- Breast atypia, cancer
- Reduced duration of lactation
- Menopause issues - insomnia, anxiety, focus

Testosterone Resistance and Low T

- The fetal period is critical for the proper development of the testis and is known as a period of high sensitivity to many EDs.
- Our team has shown in 2009 that a phthalate, mono-(2-ethylhexyl) phthalate (MEHP), has a potential deleterious effect on the development of human male germ cells.
- This result was the first direct experimental proof of the toxic effect of an ED in human testis.
- More recently, we also reported that bisphenol A (BPA) impaired testosterone production in the human fetal testis.

Thyroid Resistance from Antibiotics and Flame Retardants

- Triclosan (TCS) is a broad spectrum antibacterial agent used in personal care, veterinary, industrial and household products. TCS is commonly detected in aquatic ecosystems, as it is only partially removed during the wastewater treatment process.
- It disrupts thyroid hormone homeostasis and possibly the reproductive axis.
- Flame retardants block Thyroid receptor.
EDCs – Insulin Resistance

• There is accumulating evidence suggesting that the increased presence of endocrine-disrupting chemicals (EDCs) in the environment, such as bisphenol A, phthalates and persistent organic pollutants contribute to IR.

• In this review, both in vivo and in vitro experimental data and epidemiological evidence to support an association between EDC exposure and the induction of insulin resistance and/or disruption of pancreatic β-cell function are summarized.

 Diabetes Metab. 2014 Nov 20. Endocrine disruptors: New players in the pathophysiology of type 2 diabetes?

EDCs – Obesity – fatty pancreas (and perhaps even NAFLD syndrome)

• The worldwide obesity epidemic is paralleled by a rise in the incidence of pancreatic disorders ranging from “fatty” pancreas to pancreatitis and cancer. Body fat accumulation and pancreatic dysfunctions have common pathways, mainly acting through insulin resistance and low-grade inflammation.

• An early origin is common, starting in pediatric age or during the fetal life in response to endocrine disruptor chemicals (EDCs) or parental exposure to toxins.

• A "fatty pancreas" - The fat is a target of EDCs and of the cytotoxic/mutagenic effects of heavy metals, and is the site of bioaccumulation of lipophilic and persistent pollutants.


EDCs- Hippocampus – Anti Androgens

• The hippocampus synthesizes estrogen and androgen in addition to the circulating sex steroids.

• Synaptic modulation by hippocampus-derived estrogen or androgen is essential to maintain healthy memory processes.

• It has been doubted that the level of hippocampus-derived estrogen and androgen may not be high enough to modulate synaptic plasticity.

• The E2 level in the hippocampus is approximately 8nM for the male and 0.5-2nM for the female, which is much higher than that in circulation.

• The level of T and DHT is also higher than that in circulation. Taken together, hippocampus-derived E2, T, and DHT play a major role in modulation of synaptic plasticity.

Brain

- This study investigates prenatal exposure to two ubiquitous endocrine disruptors, the phthalate esters and bisphenol A (BPA), and social behavior in a sample of adolescent inner-city children.
- Third trimester urines of women enrolled in the Mount Sinai Children's Environmental Health Study between 1998 and 2002 (n=404) were analyzed for phthalate metabolites and BPA.
- Mother-child pairs were asked to return for a follow-up assessment when the child was between the ages of 7 and 9 years.

Endocrine disruptors and childhood social impairment

Autism Spectrum - Phthalates

- At this visit, mothers completed the Social Responsiveness Scale, a quantitative scale for measuring the severity of social impairment related to Autistic Spectrum Disorders in the general population.
- No significant association with BPA was found.
- Prenatal phthalate exposure was positive link.
- Even mild degrees of impaired social functioning in otherwise healthy individuals can have very important adverse effects over a child's lifetime.

Endocrine disruptors and childhood social impairment

Medical Conditions Among Adult Offspring Prenatally Exposed to DES

- Associations between prenatal DES exposure and the occurrence of cardiovascular disease, diabetes, osteoporosis, and related conditions among 5590 female and 2657 male offspring followed from 1994 through 2006.
- The associations did not differ by dose and timing of DES exposure, nor, in the women, by the presence or absence of vaginal epithelial changes (a marker of DES host susceptibility).
- These data link prenatal exposure to DES to diverse diseases of contemporary life.

Epidemiology. 2013 May;24(3):430-8 NIH
DES - Medical Problems
- Insulin Resistance
- Diabetes – 50% increased risk
- Heart disease
- Hypertension
- High cholesterol
- Osteoporosis
- Discogenic Disease
- Cancers especially breast and prostate

EDCs- OBESOGENS
- With the increasing obesity prevalence in children it is imperative to explore the role of EDC as Obesogens.
- Current evidence suggests a link between early life exposure to some industrial by-products, synthetic hormones and cigarette smoke with weight gain.
- Weight loss should include DETOX.

EDCs – Obesity
- PA in urine and MEP, DBP and PA in serum showed statistically significant differences between the control and obese groups.
- Nail polish, make-up, lip stick, microwaving in plastic, food shrink wrapped, plastic bottles especially with acidic liquids like fruit juice.
DES – Breast Cancer

- A cohort of 4821 exposed women and 2095 unexposed women, most of whom were first identified in the mid-1970s, were followed by mailed questionnaires for an average of 19 years.
- DES exposure was not associated with an increased risk of breast cancer in women under 40 years, but among women aged 40 and older the rate ratio was 2.5 (95% CI = 1.0-6.3). The rate ratio for the association of DES exposure with estrogen receptor-positive tumors was 1.9 (95% CI = 0.8-4.5).
- 85% increase in risk of breast cancer after the age of 40.
- 85% increased risk of endometriosis and adenomyosis incidence.


Thanks

- Dr. John McLachlan
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- Judith McCarthy – ex-editor at McGraw-Hill

Thank you

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