The Unappreciated Role of Hormones and the Gut

1

The Expanding Awareness of Hormones

- The gut makes hormones and it is responsive to hormones – all throughout the digestive tract and liver and pancreas.

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There Are More Assaults On Our Hormones

- In-utero
- Breast Milk
- Hormone Altering Chemicals
- Over-the-Counter Medications
- Birth Control Pills
- Plastics
- Microbiome produces hormones and is being paralyzed by EDC's
- Parietal cells produce estrogen and are being attacked by stress and auto-immune diseases

3

Hormone Altering Chemicals From Early On

- Infants and toddlers are constantly exposed to toys at childcare facilities. Toys are made of a variety of plastics that often use endocrine-disrupting chemicals such as bisphenol-A (BPA) and phthalates as their building blocks.
- We have successfully developed wipe tests to evaluate the leachability of BPA and phthalates from toys used at several day care facilities in Philadelphia.
- Our studies have shown an average leaching of 13-280 ng/cm^2 of BPA and phthalates

Environ Monit Assess. 2018 Jan 6;190(2):65. **Plastic toys as a source of exposure to bisphenol-A and phthalates at childcare facilities.**

4

Alter brain-hormone cross-talk

- Results presented here show that the neonatal exposure to BPA alters the hypothalamic pituitary-thyroid axis in adult rats in estrus, possibly with effects on the pituitary and thyroid.
- They also show that BPA alters TSH release from rat PPC through direct actions on the pituitary.
- GUT thryoid AXIS: Thyroid receptor are flush throughout the gut and have a lot to do with contractility, transit time

Toxicol Lett. 2018 Jan 2;285:81-86. **Neonatal exposure to bisphenol A alters the hypothalamic-pituitary-thyroid axis in female rats.**

Thyroid. 2018 Jan 10. **Alterations of the gut microbiota in Hashimoto's thyroiditis patients.**

Endocr Connect. 2017 May;6(4):R52-R58. **Gut-thyroid axis and celiac disease.**

5

Thyroid

- Thyroid disease is common, and its effects on the gastrointestinal system are protean, affecting most hollow organs. Hashimoto disease, the most common cause of hypothyroidism, may be associated with an esophageal motility disorder presenting as dysphagia or heartburn. Dyspepsia, nausea, or vomiting may be due to delayed gastric emptying. Abdominal discomfort, flatulence, and bloating occur in those with bacterial overgrowth and improve with antibiotics. Reduced acid production may be due to autoimmune gastritis or low gastrin levels. Constipation may result from diminished motility,
- The gastrointestinal manifestations of thyroid disease are generally due to reduced motility in hypothyroidism, increased motility in hyperthyroidism, autoimmune gastritis, or esophageal compression by a thyroid process.
- Symptoms usually resolve with treatment of the thyroid disease.
- But not if BPA is compromising thyroid receptor.

- J Clin Gastroenterol. 2010 Jul;44(6):402-6. **The thyroid and the gut.**

6

Blocked Initiation of Reproductive Hormones

- Neonatal exposure to BPA altered reproductive parameters and hypothalamic-pituitary function in female rats.
- To our knowledge, these results demonstrate for the first time that neonatal in vivo BPA permanently affects GnRH pulsatility and pituitary GnRH signaling.
- Gonadotropin-releasing hormone (GnRH) is a neurohormone central to initiation of the reproductive hormone cascade!
- Bisphenol A (BPA) is a component of polycarbonate plastics, epoxy resins, and polystyrene and is found in many products.

Environ Health Perspect. 2009 May;117(5):757-62. **Neonatal exposure to bisphenol a alters reproductive parameters and gonadotropin releasing hormone signaling in female rats.**

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BPA in utero

- Over 6 billion pounds per year of the estrogenic monomer bisphenol A (BPA) are used to manufacture polycarbonate plastic products, in resins lining metal cans, in dental sealants, and in blends with other types of plastic products.
- ubiquitous human exposure to biologically active levels of this chemical.
- BPA exerts estrogenic effects through the classical nuclear estrogen receptors, and BPA acts as a selective estrogen receptor modulator.
- Similar to estradiol, BPA causes changes in some cell functions at concentrations between 1 pM and 1 nM.
- And the range found in human pregnant maternal, fetal, and adult blood and other tissues exceeds these levels. In contrast to these published findings, BPA manufacturers persist.

Endocrinology. 2006 Jun;147(6 Suppl):S56-69. **Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure.**

8

BPA blocks normal E Release

- BPA blocks estrogen response on lung development.
- The results suggest that prenatal exposure to BPA at certain concentrations may affect fetal lung development and maturation, and thereby affecting susceptibility to childhood respiratory diseases.
- By altering release of estrogen in target tissues throughout adulthood.

Arch Toxicol. 2017 Dec 23. **Bisphenol A induces DSB-ATM-p53 signaling leading to cell cycle arrest, senescence, autophagy, stress response, and estrogen release in human fetal lung fibroblasts.**

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Low Dose Alters Hormone Ratios

- **BPA Increases E to T ratios in prostate in fetal and in adult but especially in developing male fetus.**
- BPA is known to be a xenoestrogen as it interacts with estrogen receptors and acts as agonist or antagonist.
- BPA plays a role in the pathogenesis of several hormone-dependent tumors such as breast, ovarian, prostate cancer and others.
- BPA effects estrogen epigenetic factors.

Sci Rep. 2018 Jan 11;8(1):490. **Oral exposure of low-dose bisphenol A promotes proliferation of dorsolateral prostate and induces epithelial-mesenchymal transition in aged rats.**

Gene. 2018 Jan 6. pii: S0378-1119(18)30023-4. **The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer.**

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Our Ill Planet is Making our Hormones Ill

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Where's Seinfeld's Protective Bubble When You Need It?

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BPA Gut Dysbiosis

- Gut dysbiosis may result in various diseases, such as metabolic and neurobehavioral disorders. Exposure to endocrine disrupting chemicals (EDCs), including bisphenol A (BPA) and ethinyl estradiol (EE), especially during development, may also increase the risk for such disorders.
- Gut flora and their products may thus be mediating factors for the disease-causing effects of these chemicals.
- To examine the effects of EDCs on the gut microbiome, female and male monogamous and biparental California mice were exposed to BPA (or EE or control diet from peri-conception through weaning.

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BPA Gut Dysbiosis

- 16s rRNA sequencing was performed on bacterial DNA isolated from fecal samples, and analyses performed for P_0 and F_1 males and females.
- Both BPA and EE induced generational and sex-dependent gut microbiome changes.
- Many of the bacteria, e.g. Bacteroides, Mollicutes, Prevotellaceae, Erysipelotrichaceae, Akkermansia, Methanobrevibacter, Sutterella, whose proportions increase with exposure to BPA or EE are associated with different disorders, such as inflammatory bowel disease (IBD), metabolic disorders, and colorectal cancer.
- However, the proportion of the beneficial bacterium, Bifidobacterium, was also elevated in fecal samples.
- Thus, BPA and EE exposure may disrupt the normal gut flora, which may in turn result in systemic effects. **Probiotic supplementation** might be an effective means to mitigate disease-promoting effects of these chemicals.

Gut Microbes. 2016 Nov;7(6):471-485. **Effects of exposure to bisphenol A and ethinyl estradiol on the gut microbiota of parents and their offspring in a rodent model.**

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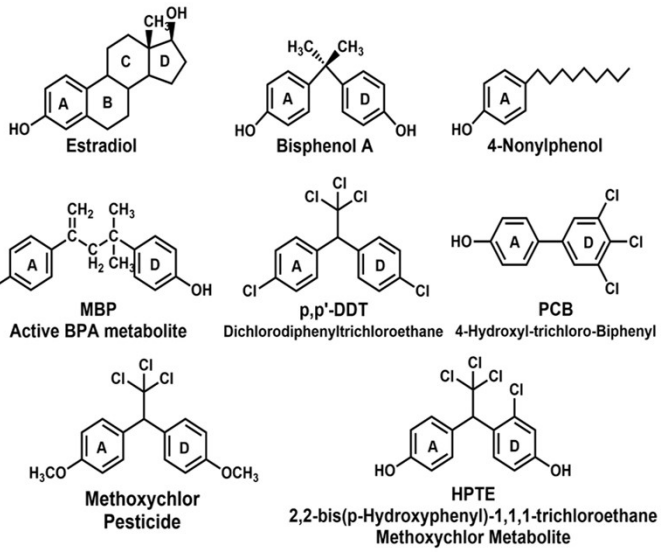
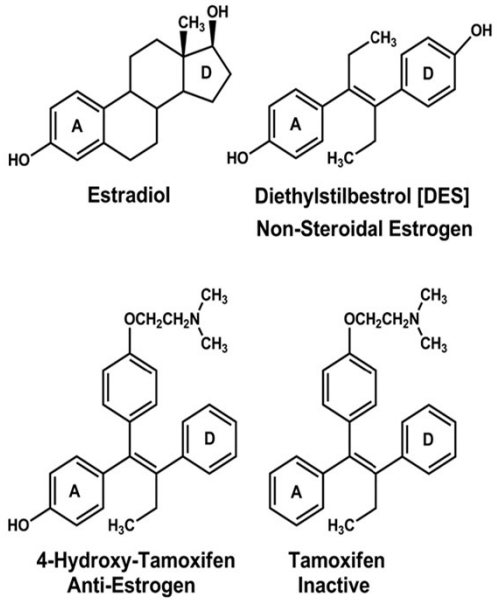
Endocrine Disruptors
Chemicals with Phenolic A Rings



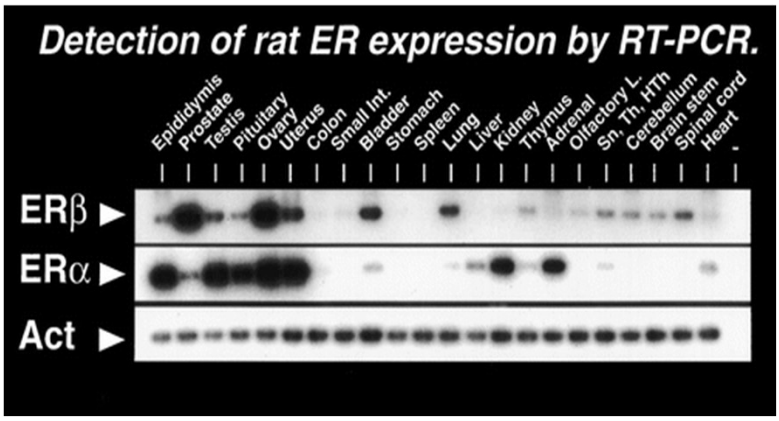
15

Synthetic ER Modulators (SERMS)



16

Differences: Expression of ERα & ERβ



- ERβ: prostate, ovary, uterus, bladder, lung, **gut wall protects against leaky gut, entire GI tract.**
- ERα: epididymis, testis, pituitary, ovary, uterus, kidney, adrenal, placenta, chondrocytes, bones, **entire GI tract, smooth muscle, brain, parietal cell, microbiome**

Kuiper et al. Endocrinology 1997 138:863-870

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Estrogen Receptor

- Estrogen receptors (ERs) are expressed throughout the digestive tract.
- Estrogen receptor Alpha Er1
- Estrogen receptor Beta Er2
- Their expression is lost during colorectal carcinogenesis and ER Beta lack is sign of end-stage colon cancer.
- With ER knock out mice, deficiencies of these receptors cause a significant increase in intestinal abnormalities, and tumor growth, number and size.
- Estrogen receptors play a critical role in restitution of epithelium after injury.

Carcinogenesis vol.30 no.9 pp.1581–1590, 2009. Disruption of estrogen receptor signaling enhances intestinal neoplasia in ApcMin/1 mice

Gastroenterology 2011 Jan. Role of Estrogen Receptor in the Regulation of intestinal Restitution After Mucosal Injury

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Estrogens

- Up-regulate adhesive proteins and pptimize gut wall permeability.
- Heal gut after injuries.
- Protect mitochondria.

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Parietal/Estrogen Relationship

- **The parietal cell** is dependent on the generation of large amounts of ATP. To meet these **high** demands, it is particularly rich in **mitochondria**; in fact it is the **cell** with one of the **highest** densities of **mitochondria** in the human body with fractional volumes reaching up to 40% of the total **cell volume** compared with a mere 5% in chief **cells**.
- There are aromatase enzymes within the parietal cell to protect it's mitochondria.
- And to be part of gut-liver detox system.

American Journal of Physiology-**cell** Physiology · 2010. Sascha Kopic · Michael Murek · John P Geibel Yale University

Gastric Parietal Cells: Potent Endocrine Role in Secreting Estrogen as a Possible Regulator of Gastro-Hepatic Axis. Endocrinology (2002) 143 (8): 3162-3170.

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Parietal Cell

- Depend on estrogen for their mitochondrial robustness.
- Aromatase enzymes are robust in human parietal cells and adrenal gland tissue.
- Gastric parietal cells play a potent endocrine role in secreting estrogen that may function as a regulator of the gastro-hepatic axis.
- Hormone replacement helps promote parietal robustness.
- But progesterone can be an anti-acid so careful with P without recognizing insufficient HCL.
- It's important to run anti-gastric parietal cell antibodies. Parietal Cell Antibody, ELISA (QuestCode 15114)

J Nucl Med December 1, 2011 vol. 52 no. 12 PP. 1964-1969 **PET of Aromatase in Gastric Parietal Cells Using ^{11}C-Vorozole**

Endocrinology 143: 3162-3170, 2002**. Gastric Parietal Cells: Potent Endocrine Role in Secreting Estrogen as a Possible Regulator of GastroHepatic Axis**

J Physiol Pharmacol. 2004 Jul;55 Suppl 2:91-104. **The role of female and male sex hormones in the healing process of preexisting lingual and gastric ulcerations.**

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Cadmium/Parietal Cell

- Many heavy metals are endocrine disruptors.
- Male rats exposed to high Cd for 30 d.
- Receiving Cd for 30 d increased the mean blood Cd level, the mean tissue Cd content, and the mean blood pressure.
- The basal acid output fell because Cd decreased the mean parietal cell number per unit from the control value.
- Cd created loss of parietal cell population.
- Displaced normal protective action of estrogen.

Biol Trace Elem Res. 2000 May;74(2):153-70.**Cadmium-induced changes in parietal cell structure and functions of rats.**

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Cadmium/Gut Wall

- Cd reduced basal acid output, mucin content, and mucus thickness.
- It displaced estrogen and thus created gut wall, parietal and gastro-hepatic damage.

Biol Trace Elem Res. 2000 Oct;77(1):65-81.

Cadmium-induced changes in epithelial cells of the rat stomach.

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Estrogen

- Promotes parietal cell function.
- Promotes parietal cell population.
- Is involved in hepatic detox.
- Serum 17β-estradiol levels in obstructive cholestasis induced by bile duct ligation, is derived from 17β-estradiol secreted from the parietal cells in females as well as males.
- When it wans, these systems wan.
- Who is it that helps bridge this?
- Compounding pharmacists.

J Endocrinol Invest. 2016 Apr;39(4):389-400. **17β-Estradiol in the systemic circulation derives mainly from the parietal cells in cholestatic female rats.**

Endocrine. 2016 Aug;53(2):565-73. **Gastric 17β-estradiol in portal vein and liver Esr1 make a circadian rhythm in systemic circulation in male rats.**

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Gastric Estrogen

- Gastric parietal cells synthesize and secrete a large amount of 17β-estradiol into the portal vein.
- In amounts equal to ovarian production.
- This supports P450 detox enzymes.
- If fatty liver or gallbladder disease this estrogen gets shunted systemically and increases risk of cancer.

Endocrine. 2014 Aug;46(3):605-14. **Changes of gastric aromatase and portal venous 17β-estradiol during the postnatal development and estrus cycle in female rats.**

Life Sciences Volume 74, Issue 18, 19 March 2004, Pages 2327-2337 **Estrogen-producing steroidogenic pathways in parietal cells of the rat gastric mucosa**

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Microgenderome

- Microbiome has been labeled the "**microgenderome**" in 2013 by Harvard.
- Healthy microbiome **produces testosterone** that drives immune protection.
- Some EDCs, such as dichlorodiphenyldichloroethylene
- (DDE) and vinclozolin and its metabolites, may interfere with microbiome protection from gender-specific diseases though **inhibition of the AR.**

Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009; 30:293-342.

Endocrine Disruptors 2:1, e964539; December 2014; Published with license by Taylor & Francis Group, LLC. The microbiome as a target for endocrine disruptors: Novel chemicals may disrupt androgen and microbiome-mediated autoimmunity

Science. 2013 Mar 1;339(6123):1044-5. **Immunology. Welcome to the microgenderome.** Flak MB[1], Neves JF, Blumberg RS.

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Unappreciated Microbiome/Testosterone/Immunity Link

- While others may interfere with enzymes that regulate testosterone concentrations.
- Some chemicals may act as androgen agonists and provide protection.
- But a "healthy" and no dysbiotic microbiome is part of the androgenic signaling that supports the 80% immune function in the gut wall.
- When it gets dysbiotic this androgenic protection may be thwarted.

Endocrine Disruptors 2:1, e964539; December 2014; Published with license by Taylor & Francis Group, LLC. The microbiome as a target for endocrine disruptors: Novel chemicals may disrupt androgen and microbiome-mediated autoimmunity

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Gender differences in autoimmune diseases

- Higher incidence in females vs. males
- Systemic lupus erythematosis, rheumatoid arthritis, Graves disease and multiple sclerosis.
- Though males have more autoimmune nephropathies.
- Differences may be due to sex hormones.

Age and sex associations of 40 autoimmune diseases. Am. J. Med. 1994;96:457–462

28

T anti-inflammatory

- It has been known for decades that females are more susceptible than men to inflammatory autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis, and psoriasis. In addition, female patients with these diseases experience clinical improvements during pregnancy with a temporary "rebound" exacerbation postpartum.
- These clinical observations indicate an effect of sex hormones on disease and suggest the potential use of the male hormone testosterone (and the pregnancy hormone estriol) respectively, for the treatment of MS.
- Both testosterone and estriol have been found to induce **anti-inflammatory as well as neuroprotective effects**. Findings from two recent pilot studies of transdermal testosterone in male MS patients and oral estriol in female MS patients are encouraging.

Prog Brain Res. 2009;175:239-51. **Estrogen and testosterone therapies in multiple sclerosis.**

29

T protects gut wall, gut enteric system, immunity

- Improves bowel regrowth after trauma.
- **Testosterone and gut healing after surgery.** 65 patients who underwent operations for gastric and colorectal diseases (mainly for cancer) had hormones tested before and after surgery and then monitored for their complication rates.
- Patients with lower testosterone levels were prone to higher postoperative complications, and this occurred in *both* men and women.
- **Women need T in their HRT, not just biest and P and often avoided due to misunderstanding and women say they don't want libido, etc**.

J Pediatr Surg. 2005 Mar;40(3):489-95.
Effect of sex and sex hormones on structural intestinal adaptation after massive small bowel resection in rats.
World J Gastroenterol. 2009 Nov 28;15(44):5604-9. **Does testosterone prevent early postoperative complications after gastrointestinal surgery?**

30

Androgens protect microbiota

- Non-obese diabetic mice, females have 1.3-4.4 times higher incidence of type 1 diabetes.
- Gut microbiota differed in males and females, a trend reversed by male castration, confirming that androgens influence gut microbiota.
- Although protection of males did not correlate with blood androgen concentration, hormone-supported expansion of selected microbial lineages may work as a positive-feedback mechanism contributing to the sexual dimorphism of autoimmune diseases.
- Our results favor a bi-directional model of gender bias, **in which hormones and microbes together trigger protective pathways**.

Immunity. 2013 Aug 22;39(2):400-12. **Gender bias in autoimmunity is influenced by microbiota.**

31

Testosterone

- Enhance immunity. Men have less autoimmune disease than women.
- Known for decades that females are more susceptible than men to inflammatory autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis, and psoriasis. In addition, female patients with these diseases experience clinical improvements during pregnancy with a temporary "rebound" exacerbation postpartum.
- These clinical observations indicate an effect of sex hormones on disease and suggest the potential use of the male hormone testosterone and the pregnancy hormone estriol, respectively, for the treatment of MS.
- A growing number of studies using the MS animal model experimental autoimmune encephalomyelitis (EAE) support a therapeutic effect of these hormones.
- Both testosterone and estriol have been found to induce anti-inflammatory as well as neuroprotective effects. Findings from two recent pilot studies of transdermal testosterone in male MS patients and oral estriol in female MS patients are encouraging.

Prog Brain Res. 2009;175:239-51. **Estrogen and testosterone therapies in multiple sclerosis.**
Cent Nerv Syst Agents Med Chem. 2009 Jun;9(2):87-94. **Estrogens as potential therapeutic agents in multiple sclerosis**.

32

ER alpha

- ERα is present mainly in mammary gland, uterus, ovary (thecal cells), bone, lungs, male reproductive organs (testes and epididymis), prostate (stroma), liver, adipose tissue,
- And throughout intestinal wall.

Steroids. 2014 Nov 15; 0: 13–29. **Estrogen Receptors Alpha (ERα) and Beta (ERβ): Subtype-Selective Ligands and Clinical Potential**

Cancer Lett. 2016 Mar 1; 372(1): 48–56. **Estrogen Receptor Beta as Target for Colorectal Cancer Prevention.**

J Endocrinol. 2001 Oct;171(1):65-73. **Immunolocalization of estrogen receptor alpha and beta in gastric epithelium and enteric neurons.**

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ER beta

- ERβ is found mainly in the prostate (epithelium), bladder, ovary (granulosa cells), lungs, adipose tissue, immune system, and throughout intestinal wall.
- Both subtypes are markedly expressed in the enteric nervous system and brain.

Steroids. 2014 Nov 15; 0: 13–29. **Estrogen Receptors Alpha (ERα) and Beta (ERβ): Subtype-Selective Ligands and Clinical Potential**

Cancer Lett. 2016 Mar 1; 372(1): 48–56. **Estrogen Receptor Beta as Target for Colorectal Cancer Prevention.**

J Endocrinol. 2001 Oct;171(1):65-73. **Immunolocalization of estrogen receptor alpha and beta in gastric epithelium and enteric neurons.**

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ER alpha vs. ER beta

- ER alpha = growth signals.
- ER beta = controlled growth signals with unappreciated role in the gut.
- Their presence and balance within many tissues oversees health in those tissues or susceptibility to disease.

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Venus vs. Mars

- Colorectal cancer incidence is 35% lower in women than men.

- American Cancer Society (2005) Colorectal Cancer Facts and Figures. Special Edition 2005. American Cancer Society, Atlanta, GA.

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Colon Protection

- In women, high parity, early age at first pregnancy, oral contraceptive use and estrogen replacement therapy are each associated with decreased colorectal cancer risk.
- The Women's Health Initiative study, hormone replacement therapy conferred a 40% reduction in colorectal cancer risk.
- Altogether, these data suggest that estrogens and/or progesterone protect against colorectal cancer.

Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. J. Natl CancerInst., 87, 517–523.

History of childbearing and colorectal cancer risk in women aged less than 60: an analysis of Swedish routine registry data 1960–1984. Int. J. Cancer 1996 66, 170–175.

A prospective study of reproductive factors, oral contraceptive use, and risk of colorectal cancer. 1997 Cancer Epidemiol Biomarkers Prev., 6, 1–5.

Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA, 2002 288, 321–333.

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ERs

- Estrogen ER alpha and estrogen ER beta are expressed throughout the intestinal epithelium

Cloning and characterization of human estrogen receptor beta isoforms. Biochem. Biophys. Res. Commun. 1998 247, 75–78.

Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon. Nat. Genet. 1994 7, 536–540.

Estrogen receptor-beta mRNA variants in human and murine tissues. Mol. Cell. Endocrinol. 1998, 138, 199–203.

Expression of estrogen receptor (ER) subtypes and ERbeta isoforms in colon cancer. Cancer Res 2001, 61, 632–640.

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Nature Never Does Anything Without A Reason

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ERs Protect Against CRC

- Our data indicate that loss of ERa is associated with increased adenoma multiplicity in ApcMin/fl mice,
- Whereas loss of ERb increases the incidence of colon tumors.
- It's desirable to keep signals to ERs going for protection.
- How? HRT

Carcinogenesis vol.30 no.9 pp.1581–1590, 2009
Advance Access publication June 11, 2009
Disruption of estrogen receptor signaling enhances intestinal neoplasia in ApcMin/1 mice

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ER beta vs Polyps

- Colorectal cancer is the leading cause of death in the US.
- A large body of evidence from preclinical studies indicates that expression of the estrogen receptor beta (ERβ/ESR2) demonstrates an inverse relationship with the presence of colorectal polyps and stage of tumors, and can mediate a protective response.
- Natural compounds, including phytoestrogens, or synthetic ERβ selective agonists, can activate or upregulate ERβ in the colon and promote apoptosis in preclinical models and in clinical experience.

Cancer Lett. Published online 2015 Dec 18. **Estrogen Receptor Beta as Target for Colorectal Cancer Prevention**

World J Gastroenterol. 2014 Sep 7;20(33):11496-504. **Ulcerative colitis: from inflammation to cancer. Do estrogen receptors have a role?**

41

ER beta

- 48 patients affected by long-lasting pancolitis were retrospectively investigated. Samples were divided into four groups: UC, low-grade dysplasia/high-grade dysplasia (UC-HGD), and CAC (colitis-associated cancer). Normal colon samples were used as controls.
- ER-beta expression revealed an impressive reduction in CAC compared to controls and UC, meanwhile ER-beta level in LGD was comparable to UC.
- **ER-beta fall could be considered as a biomarker of UC-dysplasia progression**. It occurs in HGD and overt neoplasia, while in LGD shows a normal expression.

Scand J Gastroenterol. 2015 Aug;50(8):1002-10. **The sharp decline of beta estrogen receptors expression in long-lasting ulcerative-associated carcinoma.**

42

UC

- Ulcerative colitis (UC) is associated with an increased risk of colorectal cancer (CRC), which has been related to the long-standing chronic inflammation.

Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. Front Immunol. 2012;3:107.

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CRC

- As known, reported risk factors for CRC include extensive disease, young age at diagnosis a family history of CRC, co-existing primary sclerosing cholangitis **and persistent inflammation of the colon**.
- The progression from UC to CRC is a multistep process in which the accumulation of genetic mutations leads to the sequential evolution to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally to cancer.
- And loss of expression of ERBeta.

World J Gastroenterol. 2014 Sep 7; 20(33): 11496–11504. Published online 2014 Sep 7. **Ulcerative colitis: From inflammation to cancer. Do estrogen receptors have a role?**

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ER boosters

- ER alpha is a positive regulator of cellular growth,
- ER beta has an antagonist inhibitory function, mediated by the down-regulation of proto-oncogenes (c-myc and cyclins) and up-regulation of oncosuppressants (p21 and p27), resulting in cell cycle arres.t
- Experiments showing that in various cancers ER alpha is overexpressed and ER beta is down-regulated confirmed *in vitro* studies and demonstrated that cell proliferation is the result of a BALANCE of ER alpha and ER beta.
- Jan-ake is working with Big Pharm to find meds to boost ER beta, but estriol, soy, milk thistle and flaxseeds do.

Dietary, endocrine, and metabolic factors in the development of colorectal cancer. J Gastrointest Cancer. 2012;43:13–19.

Loss of ERbeta expression as a common step in estrogen-dependent tumor progression. Endocr Relat Cancer. 2004

45

ER Beta

- ER beta has been suggested to exert anti-inflammatory and anti-tumorigenic effects in the colon, providing a translational potential to prevent and/or treat inflammatory bowel disease (IBD) and its progression to colitis-associated CRC.
- Estriol boosts ER Beta.

Beneficial effects of estrogen treatment in the HLA-B27 transgenic rat model of inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol. 2004;286:G118–G125.

61. Kennelly R, Kavanagh DO, Hogan AM, Winter DC. Oestrogen and the colon: potential mechanisms for cancer prevention. Lancet Oncol. 2008;9:385–391

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The Good Estrogen Dominance ER Beta

- **Molecular Pathways: Estrogen Pathway in Colorectal Cancer (AS WELL AS T & E CROSS-TALK)**
- Afsaneh Barzi et al.
- *USC Norris Comprehensive Cancer Center, Los Angeles; and Azusa Pacific University, Azusa, California*
- Clin Cancer Res. 2013 Nov 1; 19(21): 10.1158/1078-0432.CCR-13-0325.
- Published online 2013 Aug 21. doi: 10.1158/1078-0432.CCR-13-0325

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ER beta

- Repairs broken DNA fragments.
- Represses oncogenes.
- Tightens gut permeability by up-regulating adhesion proteins
- The data suggest that ERβ may be considered as a dominant-negative regulator of ERα modulating transcriptional responses to estrogens.
- The ratio of ER α vs. β. within a cell may determine the cell sensitivity to estrogens and its biological responses to the hormone.
- *It is not the ligand, it is the multiplicity of receptors* which determines the plethora of estrogen actions.

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Hormones Robust in the Gut

- The widespread expression of the sex steroid, thyroid and adrenal receptors (Satellite dishes) in gastric and intestinal mucosal lineages, particularly the epithelium, suggest regulatory roles of these hormones on digestion, immune funtion, metabolism, growth, differentiation, prevention of disease and useful in healing.

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Translation into practice

- T - important as part of HT in women, not just males
- T- boosts gut immunity (autoimmune diseases, history of DHEA) and protection
- T Metabolites boost ER beta and hormonal cancer prevention
- T – anxiolytic
- Anti-androgens EDCs
- Family of hormones

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ER beta vs. ER alpha

- Growth vs. Controlled Growth
- Biest. T metab.
- 3B-diol)
- Apigenin
- Milk thistle
- Dandelion
- Flax

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ER beta & JAM-A – gut permeability caretaker

- **Oestradiol decreases colonic permeability through oestrogen receptor beta-mediated up-regulation of gut protective proteins (occludin and junctional adhesion molecule-A) in epithelial cells.**
- Braniste V, et al
- Institut National de la Recherche Agronomique, Toulouse, France.
- J Physiol. 2009 Jul 1;587(Pt 13):3317-28. doi: 10.1113/jphysiol.2009.169300. Epub 2009 May 11.

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Oxytocin – TJs - Leaky Gut

- Enteric neurons express oxytocin; moreover, enteric neurons and enterocytes express OT receptors. We tested hypotheses that OT/OTR signaling contributes to enteric nervous system-related gastrointestinal physiology protecting transit time, permeability and proliferation and renewal of cell wall cells.
- GI functions and OT effects were compared in OTR-knockout (OTRKO) and wild-type (WT) mice.
- Villi and crypts were shorter in OTRKO than in WT mice, and transit-amplifying cell proliferation in OTRKO crypts was deficient. Macromolecular intestinal permeability in OTRKO was greater than WT mice, and experimental colitis was more severe in OTRKO mice; moreover, OT protected WT animals from colitis.
- Observations suggest that OT/OTR signaling acts as a brake on intestinal motility, decreases mucosal activation of enteric neurons, and promotes enteric neuronal development and/or survival. It also regulates proliferation of crypt cells and mucosal permeability; moreover OT/OTR signaling is protective against inflammation.

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Healthy Gut Has Vagal Tone

- Oxytocin/ ERB help contribute to this (estriol/T)
- Meditation boosts vagal tone and oxytocin blood levels.

- Physiol Behav. 2016 Oct 15;165:223-30. **Exogenous oxytocin reduces signs of sickness behavior and modifies heart rate fluctuations of endotoxemic rats.**

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Oxytocin – TJs - Colitis

- **The intestinal mucosa is abnormal in OTRKO mice.**
- **The intestinal barrier is significantly more permeable in OTRKO mice than in WT littermates.**
- **The severity of experimental colitis in OTRKO mice is significantly greater than that in WT littermates.**
- **Exogenous OT protects mice from TNBS-induced colitis.**

Welch MG, **Margolis KG**, **Li Z**, **Gershon MD**. Oxytocin regulates gastrointestinal motility, inflammation, macromolecular permeability, and mucosal maintenance in mice. Am ***J Physiol Gastrointest Liver Physiol*.** 2014 Oct 15;307(8):G848-62.

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Tightners vs. Openers Gut Wall

- Tighteners – mucus, vitamin A, B1, ERB, T metab, oxytocin, P. niurii
- Openers – super glue sticky molecules, lectins. Glutenins, gliadins, Digestive Enzyme insufficiencies, Maldigestion from other routes, Food allergies/intolerances - Large polypeptides mechanical damage, Magnesium deficiency – natural anti-histamine, medications like PPIs for more than one month

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Estriol clinical

- Leaky gut
- Inflammatory bowel disease
- Chronic diarrhea
- HPA axis issues - functional hypothalamic amenorrhea, long term use of BCP
- Inflammatory issues (IC)
- Autoimmune dx
- Breast cancer (estriol, 2MEO, Oxytocin)

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