ESTROGEN DOMINANCE, INFERTILITY AND PATHOGENS

Dr Jessica Peatross

HAS THIS EVER HAPPENED TO YOU?

- Your patient Maria calls to tell you she's on a detox protocol but she's started bleeding and its lasted a week longer than her normal cycles. She's also experiencing quite a bit of inflammation and has already been in two fights with her husband over the last week. Today she woke up with a migraine. She's frustrated and wants to stop the protocol.
- WHAT GIVES?
- Its time to dive into hormones!

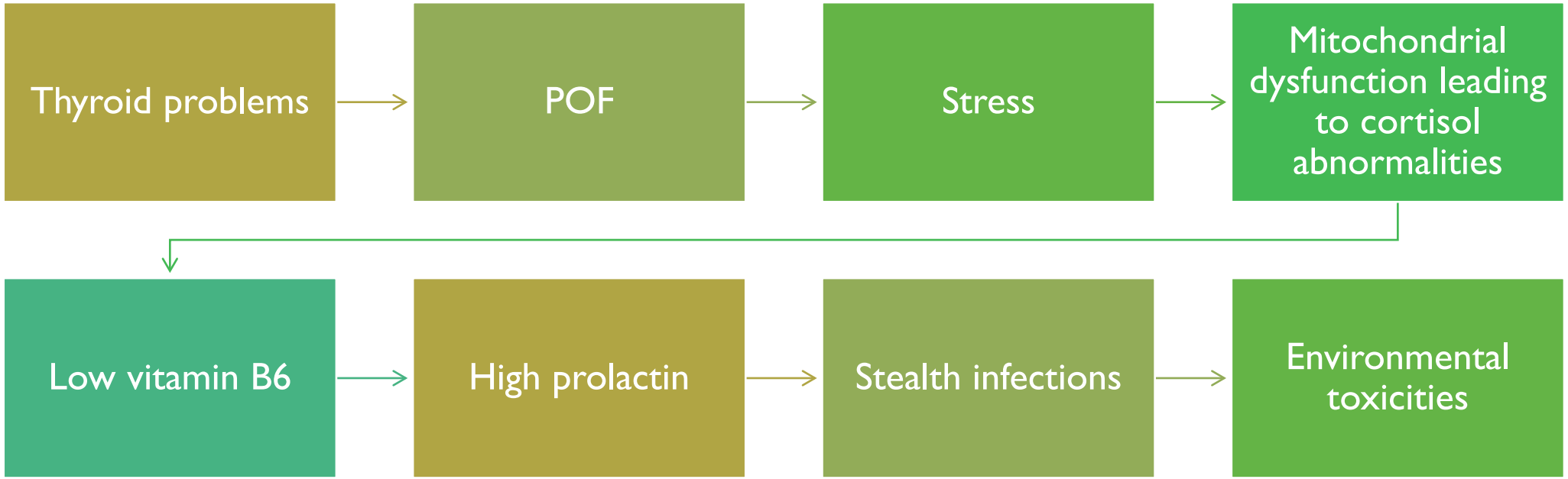
WHAT CAN CAUSE AN ESTROGEN DOMINANCE?

- Poor liver detoxification
- Gut dysbiosis
- Constipation
- Copper toxicity (Paraguard)
- Stress and inflammation
- Stealth infections which drive up inflammation or cytokines
- Mitochondrial dysfunction leading to cortisol abnormalities
- Endocrine disrupters, which include mycotoxins, BPA, phthalates, PFOA
- Alcohol and diet

ESTROGEN DOMINANCE OR PROGESTERONE DEFICIENCY?

- The body views both of the problems as the same
- The body works in ratios, checks and balances
- There are three phases for the metabolism of estrogen--phase one, phase two and the overlooked phase 3 which includes the microbiome.
- Gut health is essential to healthy hormones

WHAT CAN CAUSE A PROGESTERONE DEFICIENCY?



ESTROGEN

Made by the ovaries, adipose, liver, and adrenals. A variety of tissues express estrogen receptors, including, intestine, brain, bone and adipose tissue

Necessary for curves, mood and fertility

If dominant, poses a problem for both men and women

Can be elevated due to too much production or a lack of detoxification in the liver

Premature ovarian failure is often the result of mitochondrial damage and toxin overload =low estrogen

It is critical to consider all phases of metabolism

K.M. Eyster, The estrogen receptors: an overview from different perspectives, Methods Mol. Biol. 1366 (2016) 1–10.

ESTROGEN DOMINANCE SYMPTOMS INCLUDE:

- Premenstrual mood changes
- Painful or lumpy breasts
- Insomnia
- Premenstrual headaches/migraines
- Anxiety
- Infertility
- Recurrent miscarriage
- Unexplained weight gain

PHASE ONE METABOLITES

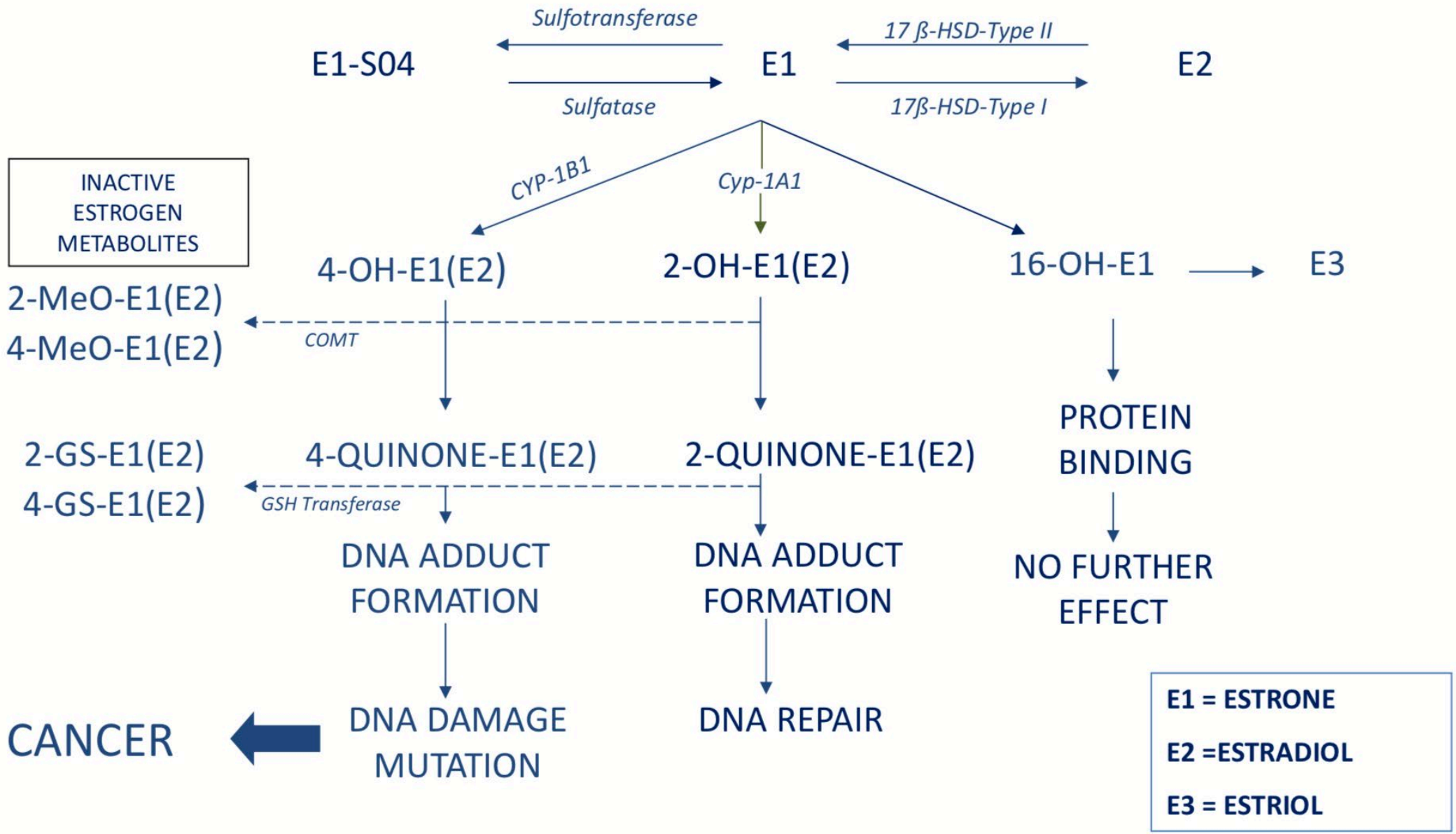
- Estrone (E1) and estradiol (E2) are the primary estrogens in the body. Primarily in the liver, they both undergo hydroxylation by members of the cytochrome P450 (CYP450) enzymes, which attach a hydroxyl (-OH) group to the estrogen.
- 2-hydroxyestrone (2-OH) is formed primarily through CYP1A1
- 4-OH is formed primarily through CYP1B1 (induced by man-made petrochemical toxins (some drugs, oils, plastics, pesticides, household chemicals, etc.)
- 16α-OH is formed primarily through CYP3A4

PHASE ONE METABOLITES

- The 4-OH metabolite has the potential to promote high cancer risk if it is unable to proceed through phase-2 detoxification. In such a case, 4-OH can head down a different pathway to become the free radical, 3,4-quinone, that reacts with DNA and forms depurinating estrogen DNA adducts.
- 2-OH metabolite is generally considered the "safest" and the predominantly preferred metabolite because of its weak binding capacity to the estrogen receptor and its modest proliferative effects.
- 16α-OH metabolite can bind strongly to the estrogen receptor and has quite strong proliferative effects. It is the most estrogenic of all the metabolites.

Moore SC, Matthews CE, Ou Shu X, et al. Endogenous Estrogens, Estrogen Metabolites, and Breast Cancer Risk in Postmenopausal Chinese Women. *J Natl Cancer Inst.* 2016;108(10). Cavalieri E, Chakravarti D, Guttenplan J, et al. Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention. *Biochim Biophys Acta.* 2006;1766(1):63-78. Cavalieri EL, Rogan EG. Depurinating estrogen-DNA adducts, generators of cancer initiation: their minimization leads to cancer prevention. *Clin Transl Med.* 2016;5(12):1-15.

ESTROGEN METABOLISM AND BREAST CANCER RISK



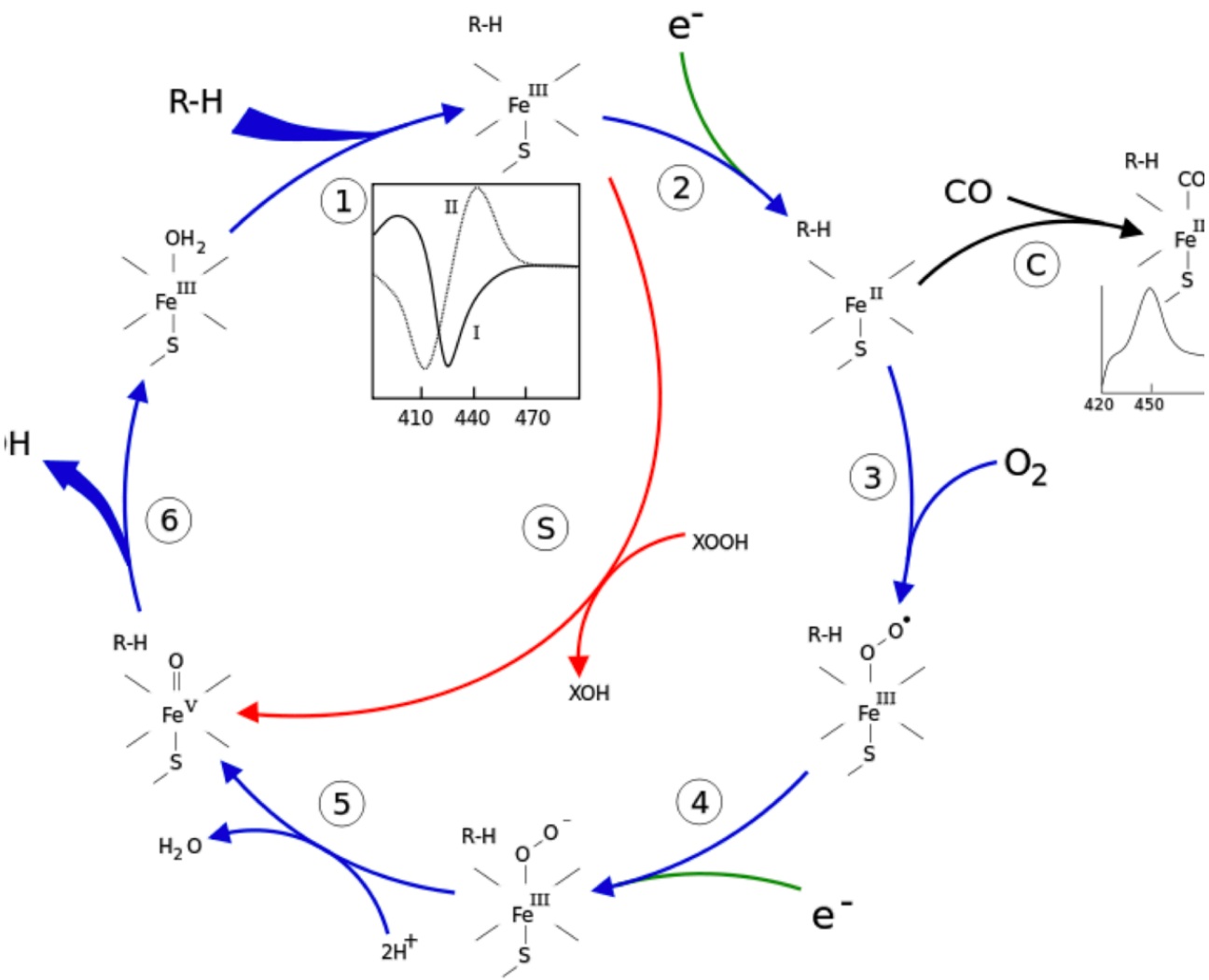
WHAT HELPS CORRECT PHASE ONE?

Raw carrots and celery, cumin, anise, coriander and broccoli (sulfur), as well as glutathione, N-acetyl cysteine, DIM and active sulforaphane.

B vitamins, magnesium and folate

Hydrogen, oxygen, electrons (electrical conductivity), fulvic acids (Fulvic acid contains more than 77 macro and trace minerals, they are masters at conducting electricity and aiding in absorption)

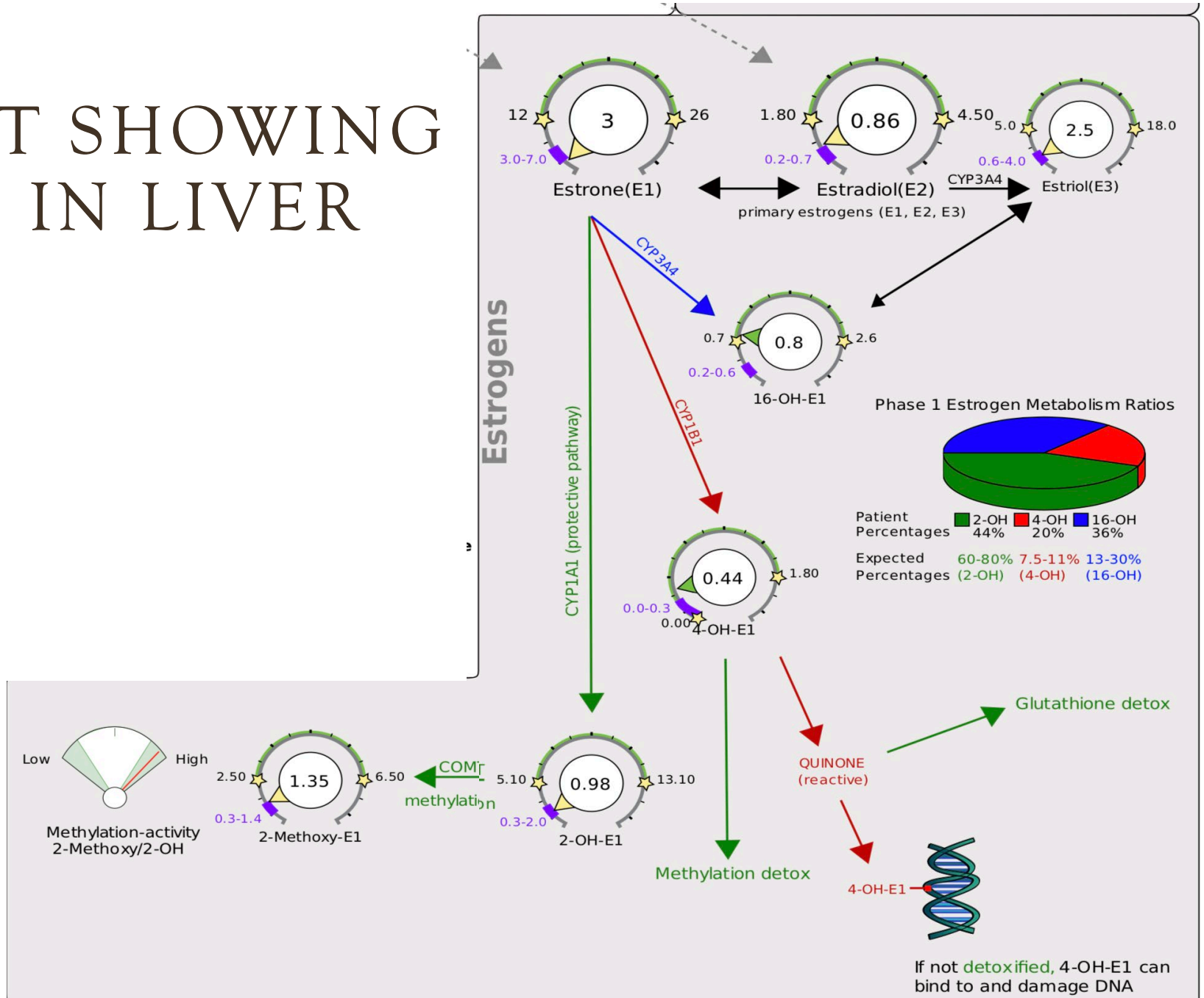
High Hydrogen=low pH and high power for the cell.



- Phase 1 enzymes (CYP450) must be reduced and then oxidized with hydrogen and oxygen in order to be re-used for phase one metabolism
- The availability of hydrogens, oxygens and electrons are crucial for detoxification and energy.
- Which products donate electrons, oxygen and hydrogen?

CELLCORE BIOSCIENCES

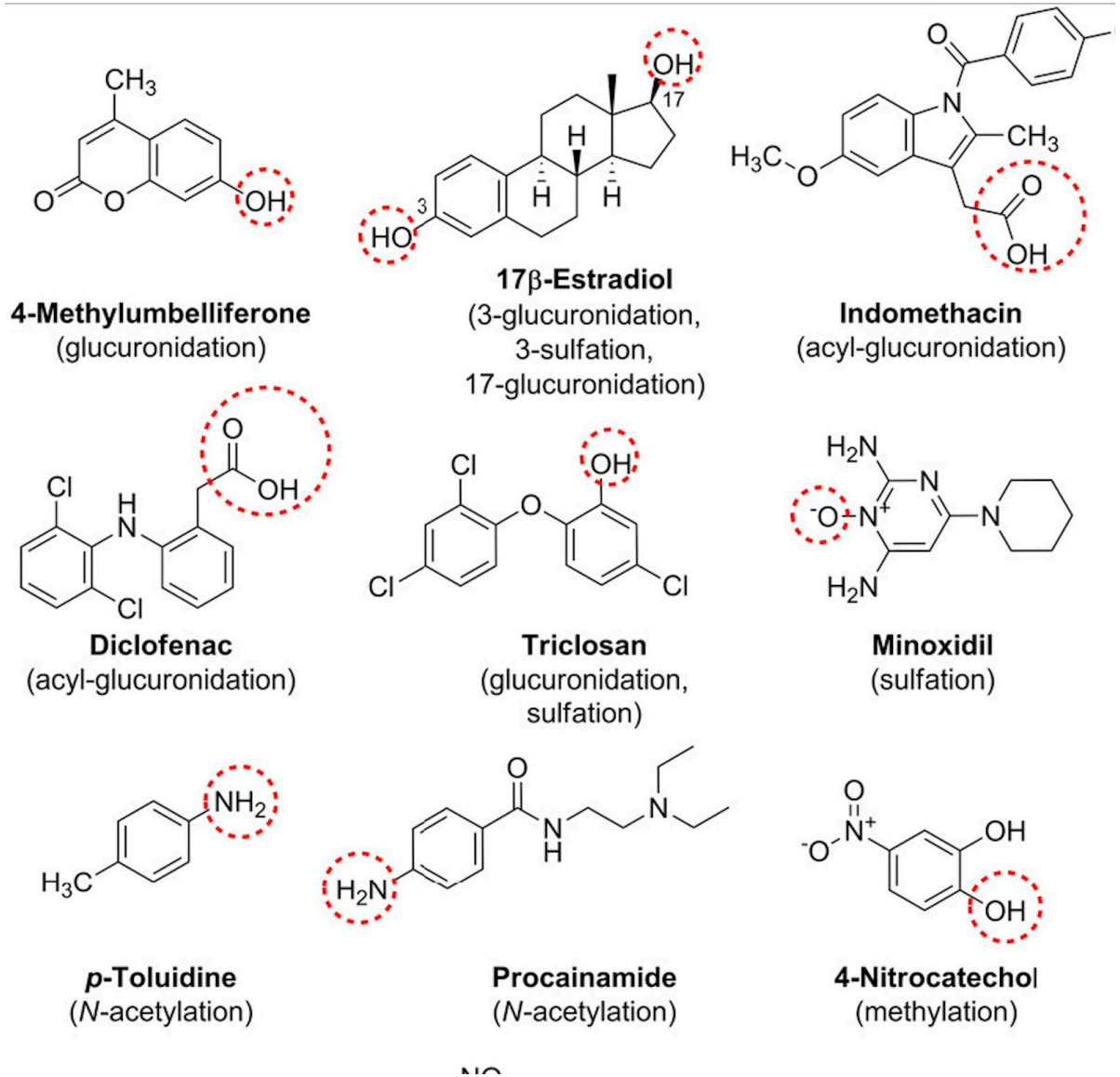
DUTCH TEST SHOWING PHASE TWO IN LIVER



PHASE TWO METABOLITES

- The phase-1 estrogen metabolites, 2-OH and 4-OH, are inactivated in Phase-2 detoxification primarily by methylation via the enzyme catechol-O-methyltransferase (COMT). Other phase-2 pathways include sulfation and glucuronidation
- Phase two is inert and water soluble.

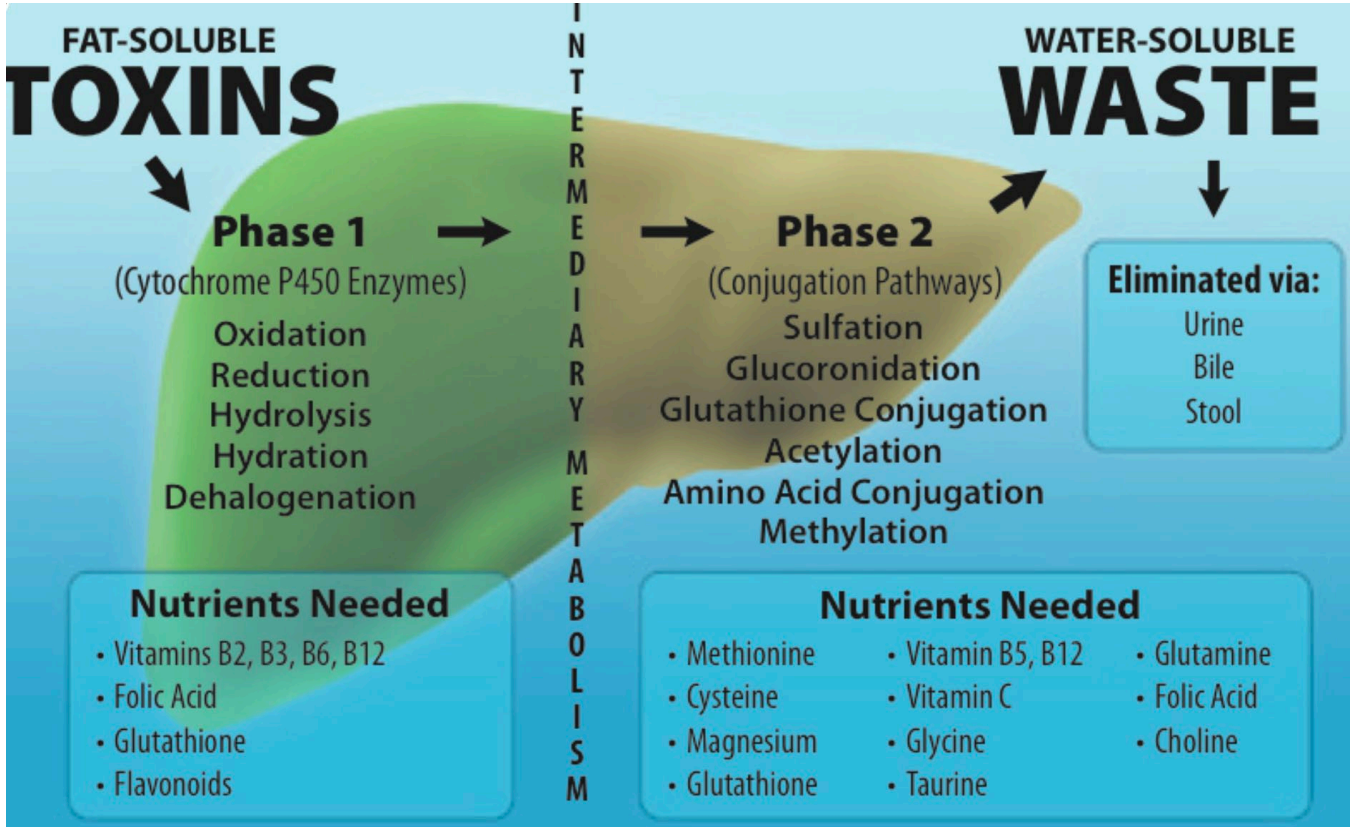
PHASE TWO BIOCHEMISTRY



WHAT HELPS SUPPORT PHASE 2 ESTROGEN DETOX?

- Phase two pathways: Glutathione conjugation (not the main pain), amino acid conjugation, Methylation, Sulfation*, Acetylation, Glucuronidation*
- Magnesium, B vitamins, glycine, taurine, cysteine, glutamine, inositol, NAC, glutathione

NUTRIENTS NEEDED FOR DETOX



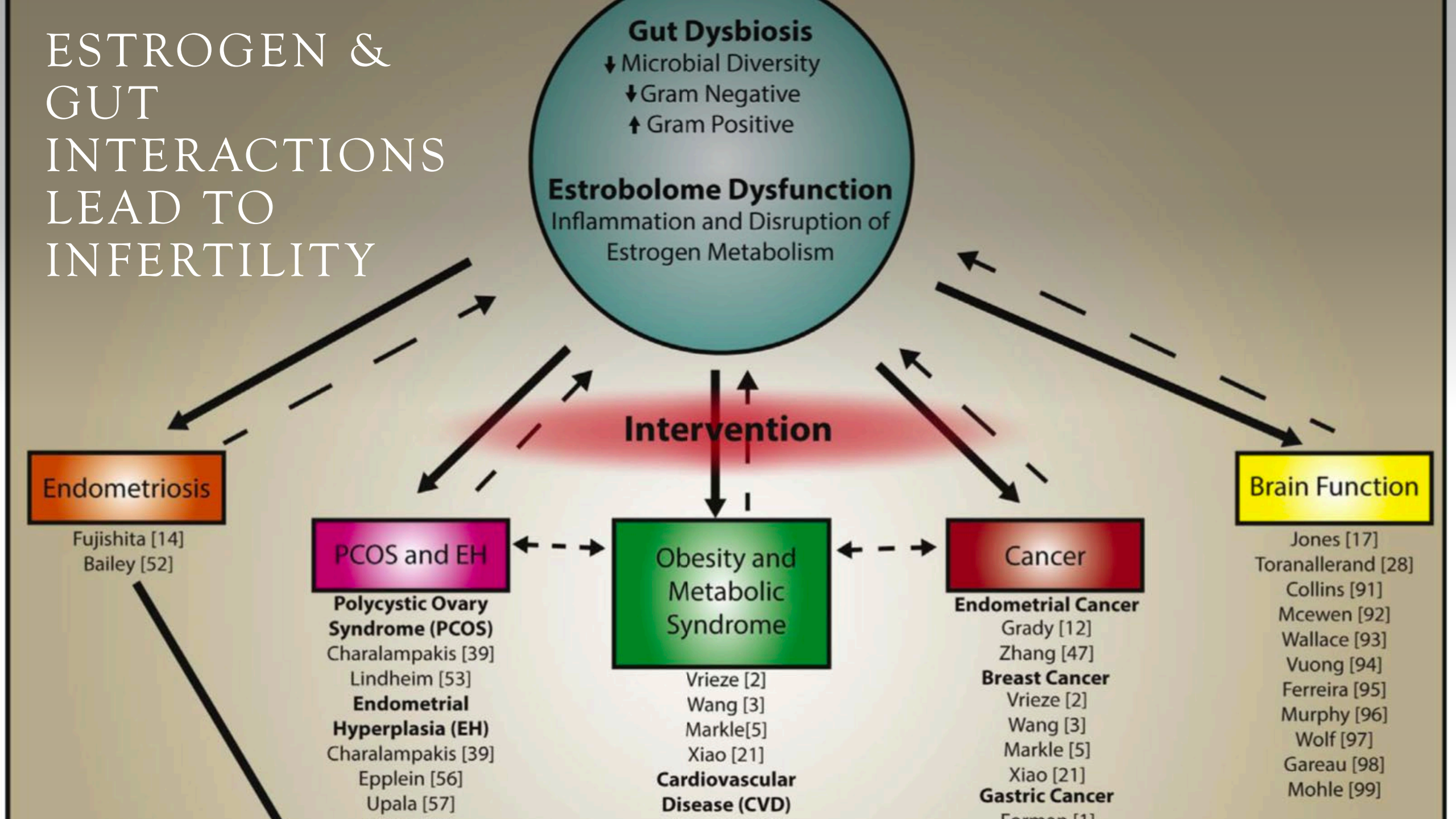
PHASE THREE METABOLITES

The bile and the microbiome make up phase three estrogen metabolism

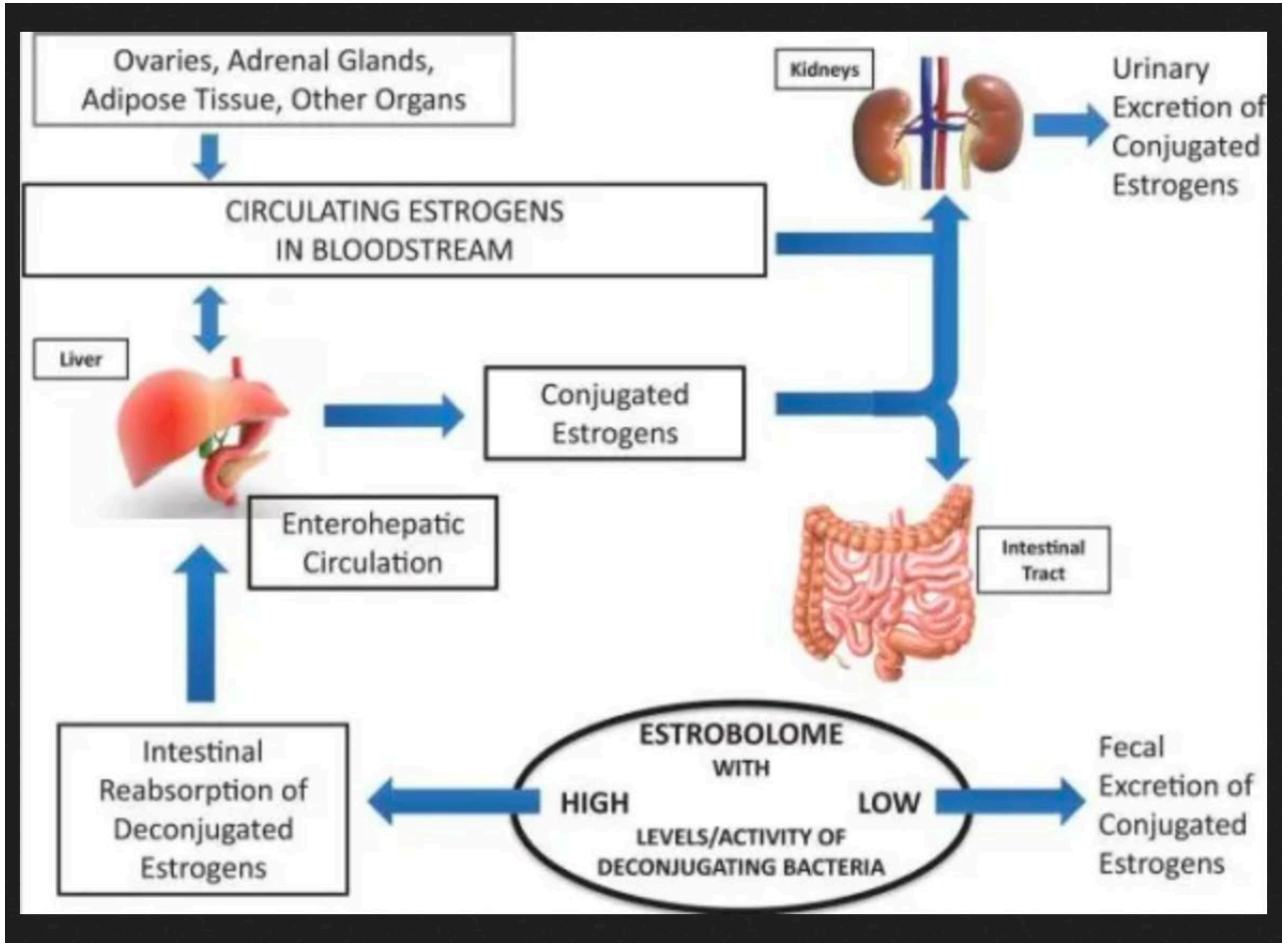
Estrogens are metabolized by microbial secreted β-glucuronidase from their con- jugate forms to their deconjugated forms It is these “active” de-conjugated and unbound estrogens that enter the bloodstream to act on estrogen receptors

Beta glucuronidase is made by an unhealthy estrobolome. You need gluconoridation (blocked by beta glucuronidase).

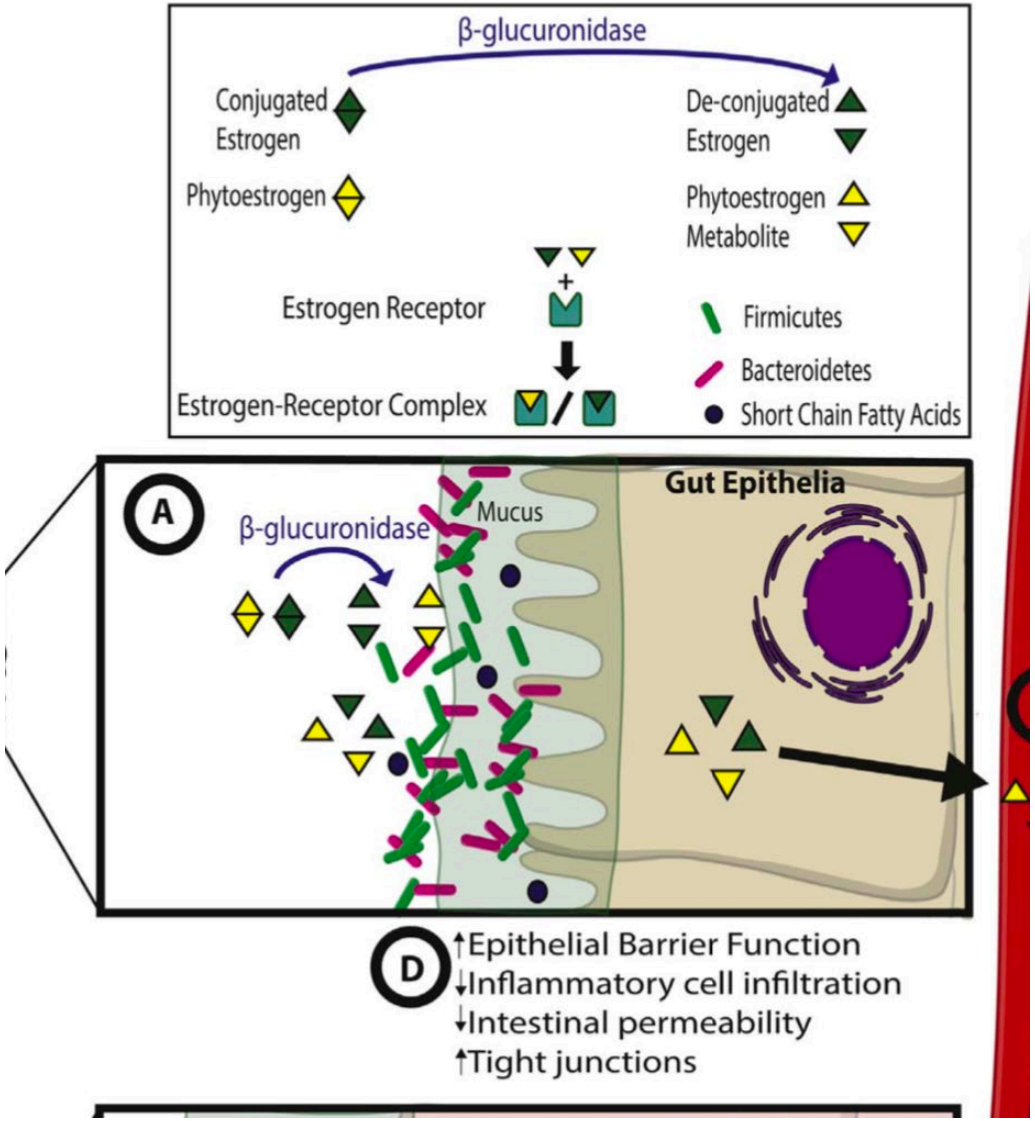
ESTROGEN & GUT INTERACTIONS LEAD TO INFERTILITY



IN A 2016 STUDY, WOMEN WERE INJECTED WITH RADIO-LABELED ESTROGEN. THESE ESTROGENS WERE EXPECTED TO BE FOUND IN THEIR CONJUGATED (DETOXIFIED) FORMS IN THE SUBJECTS' FECES. SURPRISINGLY, RESEARCHERS FOUND THAT 65% OF THE ESTRADIOL HAD REVERSED TO ITS UNCONJUGATED (ACTIVE) FORM, WHICH CAN BE EASILY REABSORBED FROM THE INTESTINE



Cellcore media team-can we make a reproduction of this graph?



ESTROBOLOME

- Bile acid-secreted conjugated estrogen & phytoestrogens are deconjugated by the gut microbiome through bacterial secretion of β-glucuronidase.
- This enables the metabolized estrogen to be reabsorbed by the gut and translocate into the bloodstream

THE ESTROBOLOME

- What is the estrobolome? It has been described as "the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens, [and which] acts on conjugated estrogens and estrogen metabolites, with downstream physiologic effects."

- Much like the rest of the microbiome, the estrobolome is easily influenced by factors such as Glyphosate, diet, lifestyle, antibiotic use, history of vaginal delivery (or not), age, and alcohol use.

Kwa M, Plottel CS, Blaser MJ, Adams S. The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer. *J Natl Cancer Inst*. 2016;108(8).
Plottel CS, Blaser MJ. Microbiome and malignancy. *Cell Host Microbe*. 2011;10(4):324-335.

THE ESTROBOLOME

- While the Human Microbiome Project found over 50 species of gut bacteria that can encode for beta-glucuronidase, they can be grouped into 4 main phyla: Bacteroidetes, Firmicutes, Verrucomicrobia, and Proteobacteria.
- Beta glucurondiase levels are also linked to obesity, metabolic syndrome, estrogen-related cancers, uterine hyperplasia, endometriosis, infertility, cognitive function, and cardiovascular disease.
- Low F/B ratio is considered beneficial.

Pollet RM, D'Agostino EH, Walton WG, et al. An Atlas of β-Glucuronidases in the Human Intestinal Microbiome. *Structure*. 2017;25(7):967-977.

WHAT HELPS PHASE 3?

- Getting stagnant bile free flowing again! Mold metabolites hide in the bile!
- Yarrow (*Achillea millefolium*) and artichoke may stimulate bile flow as may potentially cumin, garlic and ginger
- Indole-3 carbinol and calcium D glucarate help immensely with high beta glucuronidase.

Benedek B, Geisz N, Jäger W, Thalhammer T, Kopp B. Choleretic effects of yarrow (Achillea millefolium s.l.) in the isolated perfused rat liver. Phytomedicine. 2006 Nov;13(9-10):702-6. doi: 10.1016/j.phymed.2005.10.005. Epub 2005 Nov 21. PMID: 16303291.
Speroni E, Cervellati R, Govoni P, Guizzardi S, Renzulli C, Guerra MC. Efficacy of different Cynara scolymus preparations on liver complaints. J Ethnopharmacol. 2003 Jun;86(2-3):203-11. doi: 10.1016/s0378-8741(03)00076-x. PMID: 12738088.
Yamahara J, Miki K, Chisaka T, Sawada T, Fujimura H, Tomimatsu T, Nakano K, Nohara T. Cholagogic effect of ginger and its active constituents. J Ethnopharmacol. 1985 May;13(2):217-25. doi: 10.1016/0378-8741(85)90009-1. PMID: 4021519.

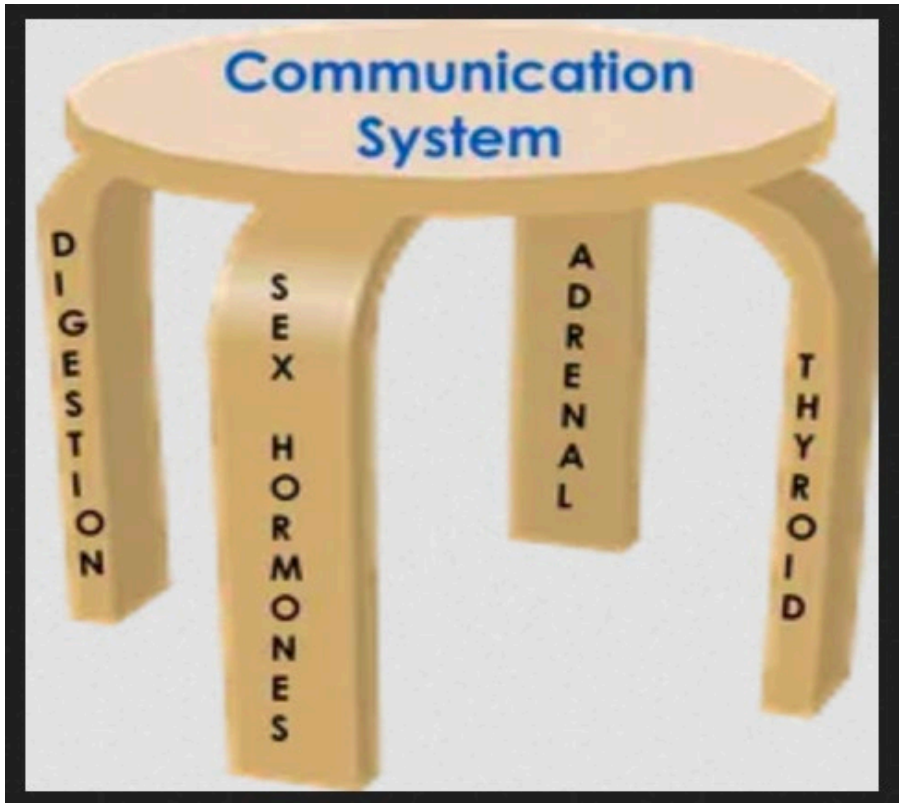
TUDCA'S ROLE IN BILE FLOW

- Don't forget about TUDCA which really helps phase two and three
- TUDCA stimulates bile flow increase by 250%. TUDCA also improves bile quality by increasing the amount of bile salts in bile.
  Am J Physiol Gastrointest Liver Physiol 302: G1035–G1042, 2012.
  https://pubmed.ncbi.nlm.nih.gov/22301109/

  When TUDCA was administered, total fecal bile acid excretion increased markedly.
  Hepatology. 1999 Feb;29(2):320-7.
  https://pubmed.ncbi.nlm.nih.gov/9918905/

  TUDCA enhanced the bile acid transporter- and Nrf2-mediated adaptive response. Free Radic Biol Med. 2017 Nov;112:24-35. https://pubmed.ncbi.nlm.nih.gov/28688954/

HOW DO STEALTH INFECTIONS DRIVE UP ESTROGEN AND TESTOSTERONE?

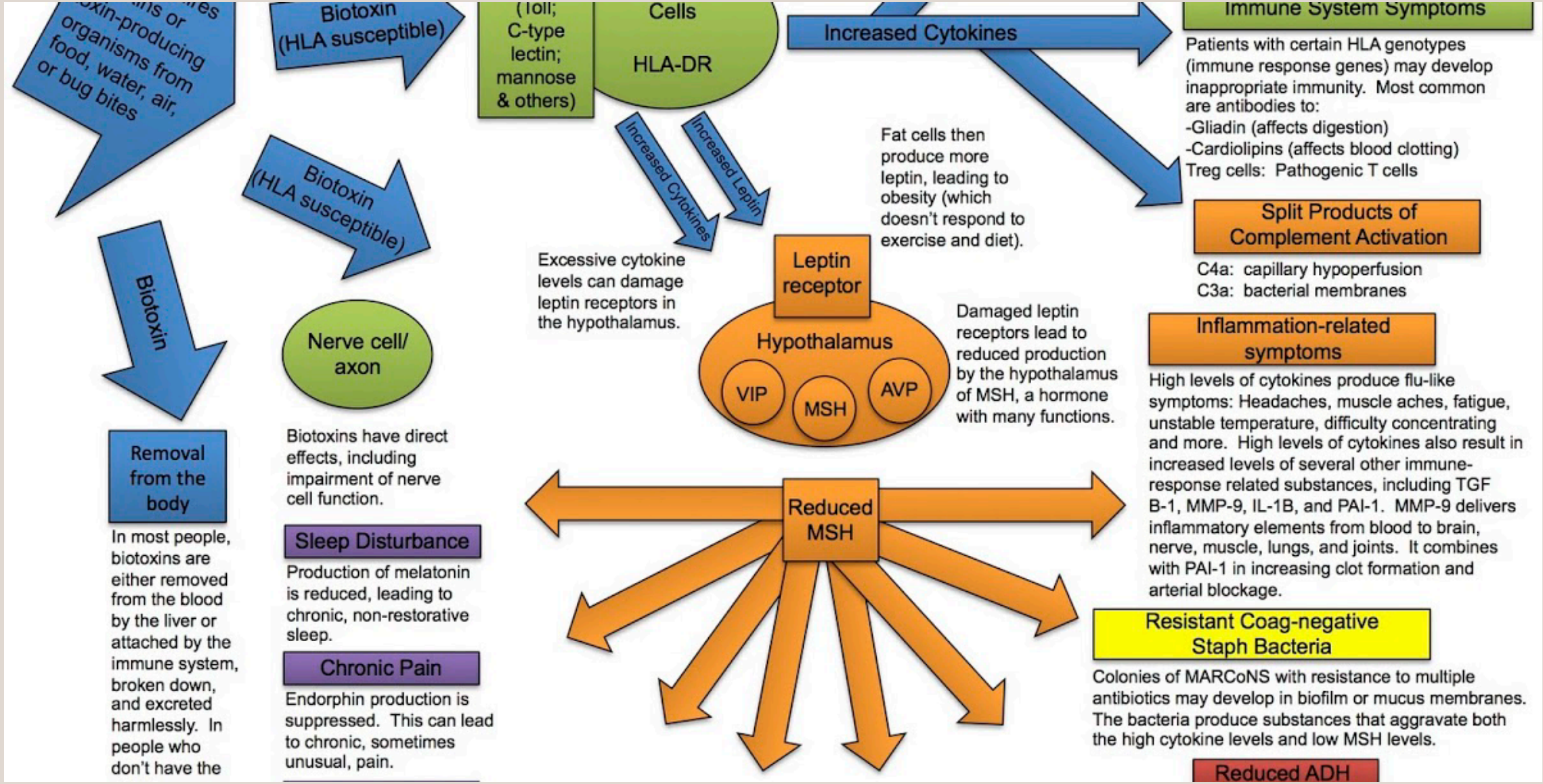


HOW DO STEALTH INFECTIONS DRIVE UP ESTROGEN (AND TESTOSTERONE)?

- Driving up beta-glucuronidase, which blocks glucuronidation in the liver
- Cytokine release including interleukin-6, tumor necrosis factor-alpha, and Interleukin-1 beta which cause inflammation throughout the body
- Constipation
- Mitochondrial dysfunction (biotoxin illness)
- Interfering with cortisol/DHEA by multiple mechanisms
- Appropriate release of histamine due to unwanted microbes
- Endocrine disruption (zearlenone)

LOW GRADE CHRONIC INFLAMMATION

- No Bueno
- Cytokine damage includes autoimmunity, leaky membranes, metabolic issues, and cancer
- Anti inflammatory diets and supplements may help
- Ultimately, the root cause, which is often getting rid of biotoxin illness or manmade toxicities, is imperative.


organisms from food, water, air, or bug bites
Biotoxin (HLA susceptible)
(Toll; C-type lectin; mannose & others)
Cells
HLA-DR
Increased Cytokines
Immune System Symptoms
Patients with certain HLA genotypes (immune response genes) may develop inappropriate immunity. Most common are antibodies to:
-Gliadin (affects digestion)
-Cardiolipins (affects blood clotting)
Treg cells: Pathogenic T cells
Biotoxin (HLA susceptible)
Increased Cytokines
Increased Leptin
Fat cells then produce more leptin, leading to obesity (which doesn't respond to exercise and diet).
Split Products of Complement Activation
C4a: capillary hypoperfusion
C3a: bacterial membranes
Excessive cytokine levels can damage leptin receptors in the hypothalamus.
Leptin receptor
Hypothalamus
VIP
MSH
AVP
Damaged leptin receptors lead to reduced production by the hypothalamus of MSH, a hormone with many functions.
Biotoxin
Nerve cell/ axon
Inflammation-related symptoms
High levels of cytokines produce flu-like symptoms: Headaches, muscle aches, fatigue, unstable temperature, difficulty concentrating and more. High levels of cytokines also result in increased levels of several other immune-response related substances, including TGF B-1, MMP-9, IL-1B, and PAI-1. MMP-9 delivers inflammatory elements from blood to brain, nerve, muscle, lungs, and joints. It combines with PAI-1 in increasing clot formation and arterial blockage.
Reduced MSH
Removal from the body
In most people, biotoxins are either removed from the blood by the liver or attached by the immune system, broken down, and excreted harmlessly. In people who don't have the
Biotoxins have direct effects, including impairment of nerve cell function.
Sleep Disturbance
Production of melatonin is reduced, leading to chronic, non-restorative sleep.
Chronic Pain
Endorphin production is suppressed. This can lead to chronic, sometimes unusual, pain.
Resistant Coag-negative Staph Bacteria
Colonies of MARCoNS with resistance to multiple antibiotics may develop in biofilm or mucus membranes. The bacteria produce substances that aggravate both the high cytokine levels and low MSH levels.
Reduced ADH

HOW DO STEALTH PATHOGENS CAUSE CONSTIPATION LEADING TO HIGH ESTROGEN?

- Herpes viruses can cause paralytic bowels by affecting nerve function in the rectum
- Eating a diet rich in sugar and processed carbohydrates feeds candida and pathogenic microbes. Excess methane (SIBO) slows motility or movement of waste in the colon which contributes to constipation
- Mycotoxins can create anti-gliadin antibodies which affect GI transit and burrow into mucous membranes
- 1999 study: found "the presence of Lyme disease in the gastrointestinal tract when confirmed by PCR for *B. burgdorferi* DNA in 14 of 20 patients with the diagnosis of Lyme and in two of the control subjects with Crohn's disease."
- GI problems in biotoxin illness may be the result of autonomic dysfunction.
- Roundworms, like Ascarisis, is linked to constipation.

Fried, Martin; Abel, M; Pietruccha, D.; Bal, A. THE SPECTRUM OF GASTROINTESTINAL MANIFESTATIONS IN LYME DISEASE, Journal of Pediatric Gastroenterology & Nutrition: October 1999 - Volume 29 - Issue 4 - p 495

Stolk JM, van Nieuwkoop C, van der Voorn M, van Erp S, van Burgel ND. Ticking off diagnoses of abdominal pain: early neuroborreliosis with radiculopathy. Neth J Med. 2018;76(7):336-338.

VIRUSES CAUSE CONSTIPATION?

[A case of paralytic ileus associated with varicella zoster virus infection]

[Article in Japanese]
Shinsuke Hiramatsu [1], Hiroko Nebiki, Ayako Ueno, Yuhei Wakahara, Hirotsugu Maruyama, Takehisa Suekane, Tomoaki Yamasaki, Eiji Sasaki, Koji Sano, Hiroshi Sato, Takashi Nakai, Yasuko Kawasaki, Kiyohide Kioka

Affiliations + expand

PMID: 23739733

Abstract

A 79-year-old woman with a history of pyothorax was admitted with a 4-day history of abdominal distension. Physical examination revealed marked abdominal distention, absent bowel sounds, and a vesicular rash over the left Th8-10 dermatome. Abdominal radiography showed gaseous distension of the colon and ileum. Colonoscopy excluded any obstructive process of the colon. Laboratory findings yielded positive results for serum IgM and IgG against the varicella zoster virus (VZV) . Paralytic ileus associated with the VZV was therefore diagnosed. The ileus improved after conservative treatment with intravenous acyclovir. Although shingles is frequently encountered, it is a rare cause of paralytic ileus. In the future, the VZV should be considered as one of the causes of paralytic ileus, and complete resolution can be achieved with conservative management.

MOLD AFFECTS THE GUT?

Effects of Mycotoxins on Mucosal Microbial Infection and Related Pathogenesis

Seong-Hwan Park,[1,2,†] Dongwook Kim,[3,†] Juil Kim,[1,2] and Yuseok Moon[1,4,*]

Jiujiang Yu, Academic Editor

Abstract

Go to:

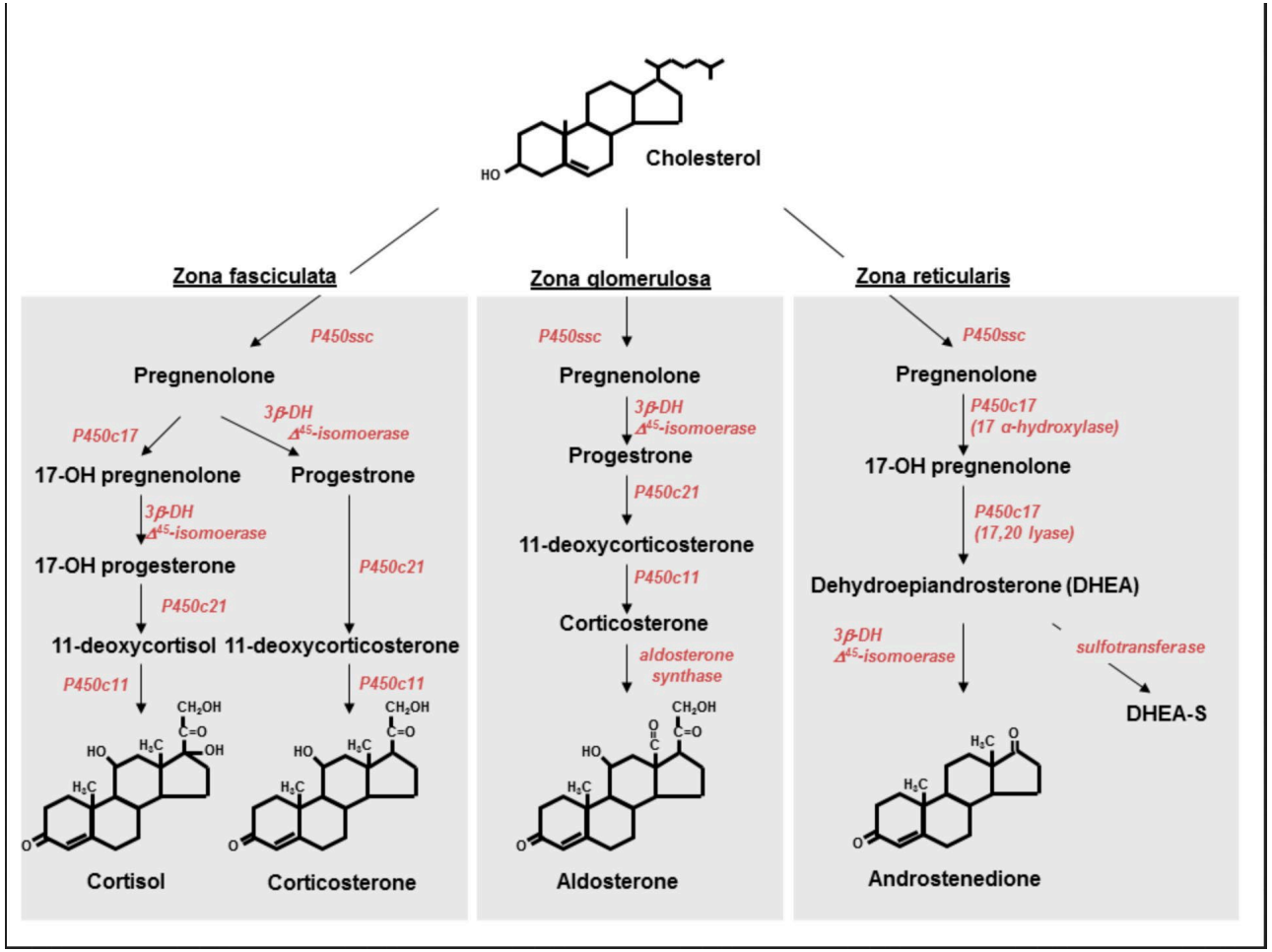
Mycotoxins are fungal secondary metabolites detected in many agricultural commodities and water-damaged indoor environments. Susceptibility to mucosal infectious diseases is closely associated with immune dysfunction caused by mycotoxin exposure in humans and other animals. Many mycotoxins suppress immune function by decreasing the proliferation of activated lymphocytes, impairing phagocytic function of macrophages, and suppressing cytokine production, but some induce hypersensitive responses in different dose regimes. The present review describes various mycotoxin responses to infectious pathogens that trigger mucosa-associated diseases in the gastrointestinal and respiratory tracts of humans and other animals. In particular, it focuses on the effects of mycotoxin exposure on invasion, pathogen clearance, the production of cytokines and immunoglobulins, and the prognostic implications of interactions between infectious pathogens and mycotoxin exposure.

Keywords: Mycotoxins, microbial infection, mucosal pathogenesis

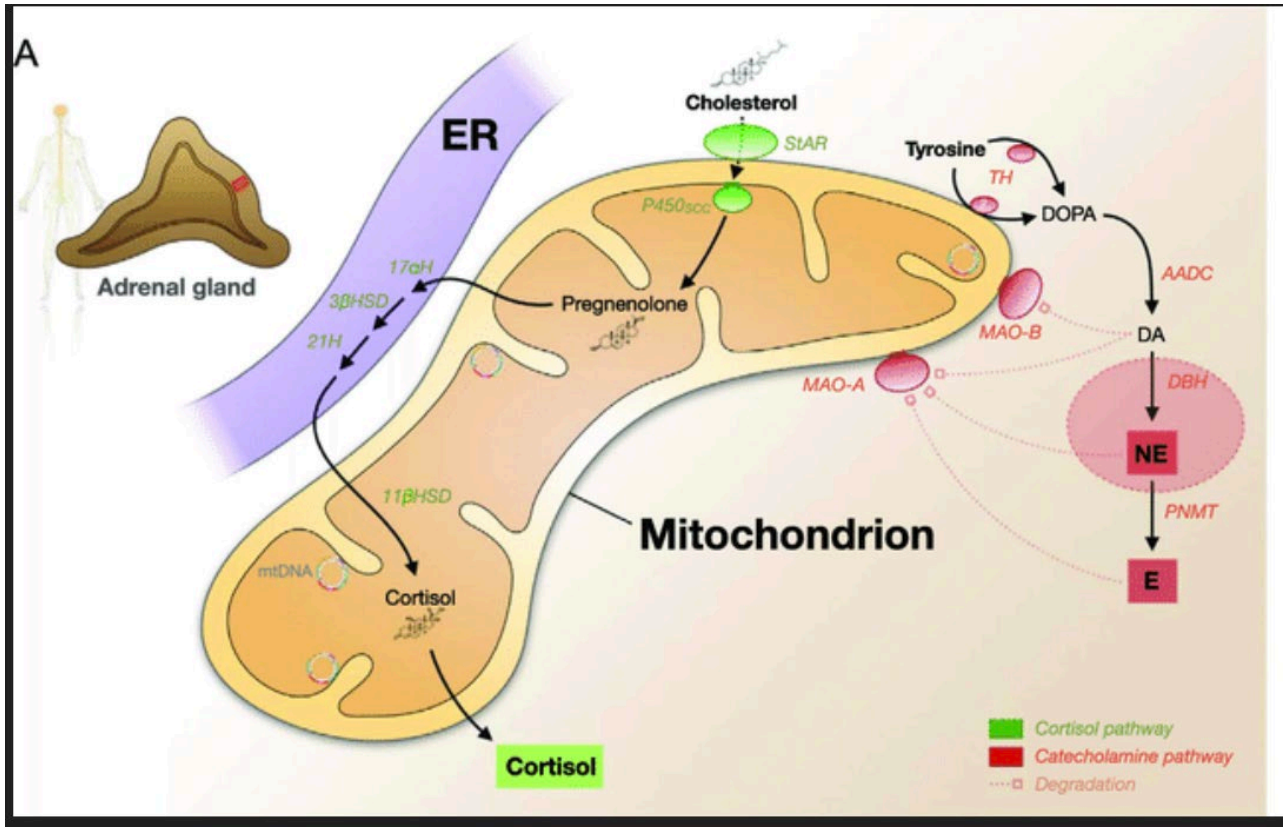
MITOCHONDRIAL DYSFUNCTION TIPS

- Changes in thyroid numbers are a good indicator of reactive oxygen species/mitochondrial function and the thyroid affects sex hormone production
- Mitochondrial dysfunction is implicated in blood sugar regulation. (liver)
- Pregnenolone is made from cholesterol in the mitochondria of adrenal glands
- Sex steroid synthesis involves hydrogenation and oxidation (need hydrogens and oxygens)
- Many of the enzymes involved are cytochrome P450 (located in mitochondria of liver cells)

HOW IS CORTISOL RELATED TO SEX STEROID SYNTHESIS?



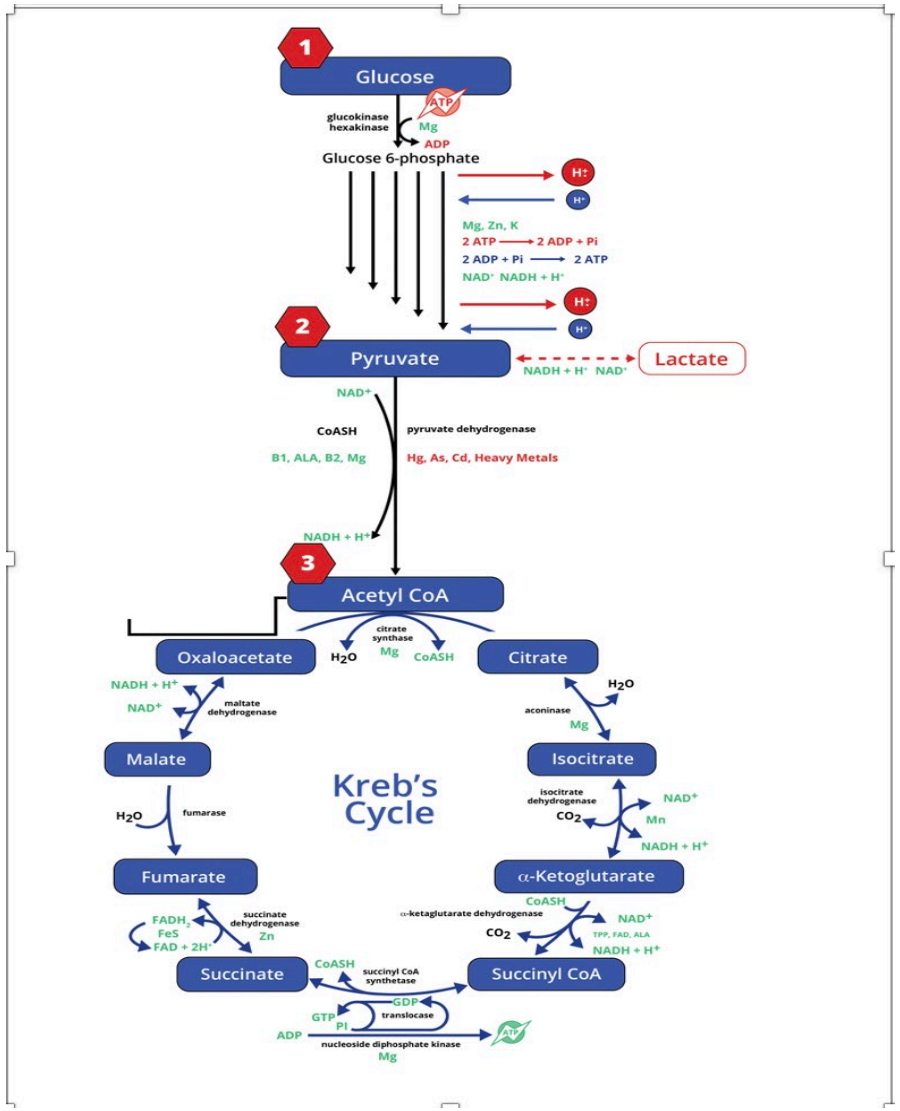
WHERE IS THE MITOCHONDRIA INVOLVED?

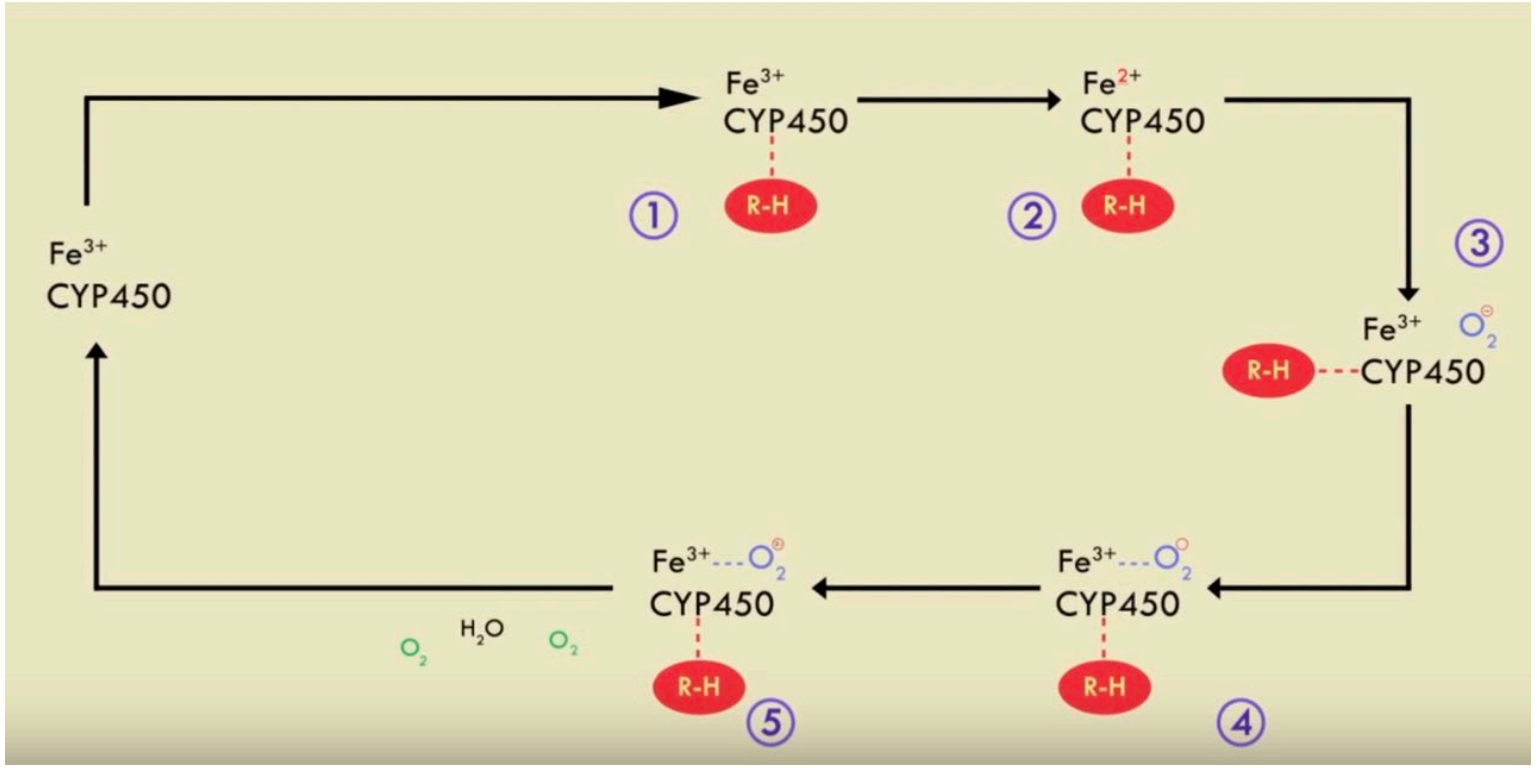


MITOCHONDRIAL DYSFUNCTION

- Environmental toxicities and pathogens likely interrupt steroid synthesis in mitochondria (traffic jam, not a car that's broken down)
- For example, enzyme 3β-Hydroxysteroid dehydrogenase is one of the many enzymes to turn cholesterol into cortisol in the mitochondria. Arsenic, phthalates, PCBs, dioxins they help block this enzyme.

MITOCHONDRIA ARE THE BACKBONE





If you don't have oxygen to enter the Krebs cycle, your CYP enzymes will suffer
Since they don't have enough oxygen to be recycled

CORTISOL AND "ADRENAL FATIGUE"

- Likely through means of early mitochondrial dysfunction
- DUTCH test has recorded high levels of DHEA or cortisol output which has the ability to drive up estrogen levels (due to low metabolized cortisol)
- Your body will divert producing progesterone in lieu of producing cortisol
- High histamine promotes production of more estrogen, and high estrogen promotes high histamine. Cortisol is your body's antidote to histamine.
- Chronic TGF beta, TNF alpha, IL-6 and defensins from WBC are potent suppressors of cortisol. Acutely, drive it up

DRIVING UP CORTISOL LEVELS

- "Adrenal fatigue" is not qualified in the literature, so adrenals do not burn out or stop producing
- Usually there is a backwards diurnal pattern where people have low cortisol in the am and higher cortisol at night-AKA pathogens are nocturnal
- Often cortisol is metabolized slowly and the result is free cortisol rises
- Indeed, unpublished research from Precision Analytical (DUTCH) found that **in 2,000 people with low morning salivary cortisol levels, when total cortisol production is measured via the urine, 85% of those people actually had normal or even high total cortisol production**!

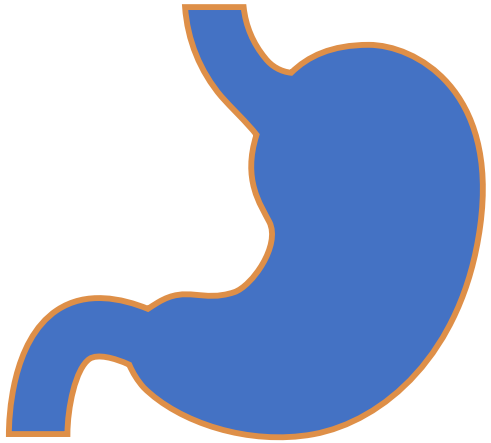
[SERTÖZ ÖÖ., et al. The Neurobiology of Burnout: The HypothalamusPituitary-Adrenal Gland Axis and Other Findings

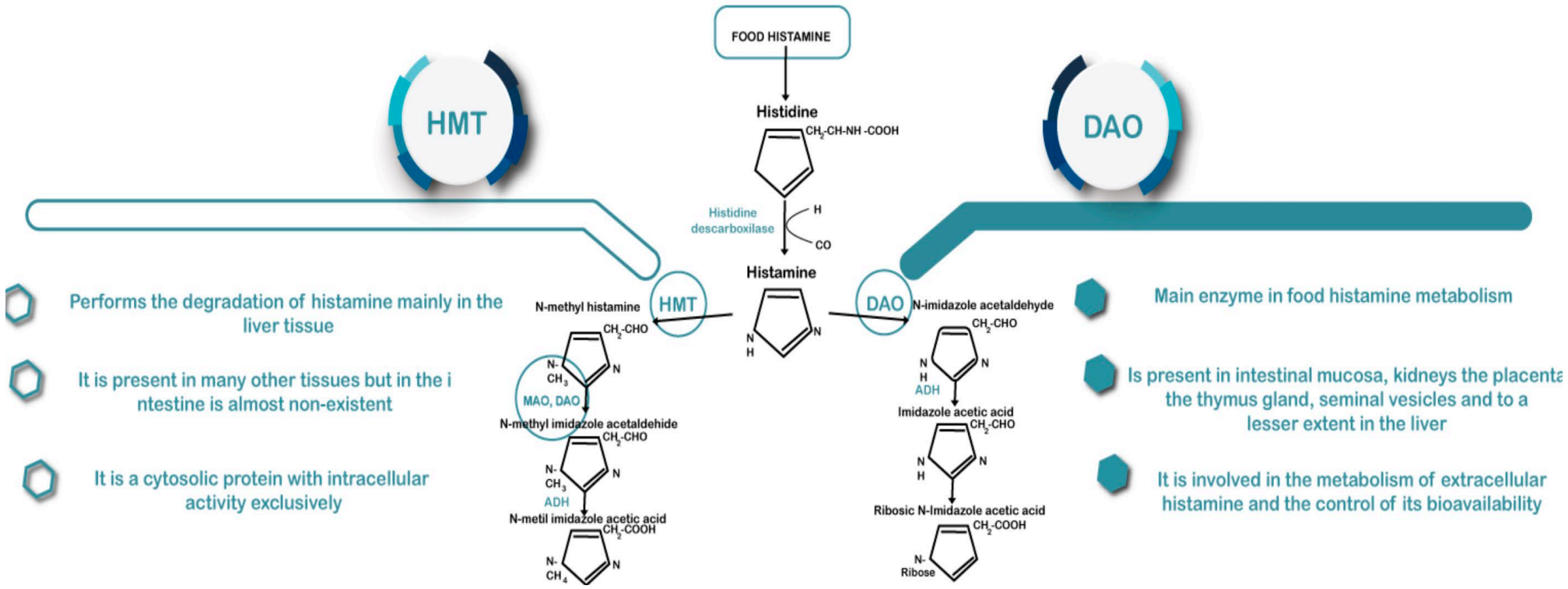
THE ESTROGEN AND HISTAMINE CONNECTION

- Interestingly enough, **histamine** and **estrogen** attach to the same receptors (H1). Because of this, **estrogen** will cause the release of **histamine** from the mast cells present in the reproductive organs of both men and women.
- The more **estrogen** you have, the more **histamine** that will be released into the bloodstream as estrogen lowers DAO enzyme
- More histamine results in more estrogen and ends up in a vicious cycle
- If you have stealth pathogens they can cause an appropriate release of histamine from mast cells, driving up estrogen

CALMING THE HISTAMINE FACTOR

- Root cause infections-go here first
- Focus on liver, gallbladder and gut health which phase one, TUDCA and diet. No sugar or processed carbs and add in healthy fats
- DAO enzyme
- Seed cycling
- Quercetin, NAC, vitamin C





CALMING THE HISTAMINE FACTOR

ENDOCRINE DISRUPTION

- Huge problem with pesticides and environmental toxins known as xenoestrogens
- Mold such as Ochratoxin and zearlenone are known endocrine disrupters that mimic estrogen (dioxins, PCBs, phthalates, herbicide)-raise E2 (mycoestrogens)
- Usually fat soluble toxins so evade many of the processing enzymes
- Alcohol consumption and inflammation negatively affect detoxification, blood sugar regulation, gut microbiome, HPA axis and sleep quality.

WHAT IS AN ENDOCRINE DISRUPTOR?

C R Biol. Sep-Oct 2017;340(9-10):403-405. doi: 10.1016/j.crvi.2017.07.004.

What is an endocrine disruptor?

Claude Monneret [1]

Affiliations + expand

PMID: 29126512 DOI: 10.1016/j.crvi.2017.07.004

Free article

Abstract

Endocrine disrupting chemicals (EDCs) and potential EDCs are mostly man-made found in various materials. By interfering with the body's endocrine system, endocrine disruptors produce adverse developmental, reproductive, neurological, and immune effects in humans, abnormal growth patterns and neurodevelopmental delays in children. Thus, diethylstilbestrol (DES) a non-steroidal estrogen, which is regarded as a proof of concept, induces clear cell carcinoma among young women. EDCS may be found in plastic bottles and metal food cans (BPA), medical devices (phthalates), detergents, flame retardants (polybrominated diphenyl ethers), food (BPA), toys (phthalates), cosmetics and drugs (parabens), and pesticides (alkyl phenols such as nonylphenol). The deleterious effects of endocrine disruptors constitute a real public health issue. However concerning the mechanisms of action of EDCs, many questions remain unanswered and need further investigations.

MOLD AS AN ENDOCRINE DISRUPTER

Zearalenone as an endocrine disruptor in humans

Karolina Kowalska [1], Dominika Ewa Habrowska-Górczyńska [1], Agnieszka Wanda Piastowska-Ciesielska [2]

Affiliations + expand

PMID: 27771507 DOI: 10.1016/j.etap.2016.10.015

Abstract

Zearalenone (ZEA), a fungal mycotoxin, is present in a wide range of human foods. Many animal studies have found ZEA to possess a disruptive effect on the hormonal balance, mainly due to its similarity to naturally-occurring estrogens. With increasing consciousness of the adverse effects of endocrine disruptors on human health, it is becoming more important to monitor ZEA concentrations in food and identify its potential effects on human health. Based on a review of recent studies on animal models and molecular pathways in which ZEA is reported to have an influence on humans, we postulate that ZEA might act as an endocrine disruptor in humans in a similar way to animals. Moreover, its endocrine-disrupting effect might be also a causative factor i carcinogenesis. This review article summarizes the latest knowledge about the influence of ZEA o the human hormonal balance.

Toxicological effects of regulated mycotoxins and persistent organochloride pesticides: In vitro cytotoxic assessment of single and defined mixtures on MA-10 murine Leydig cell line

Ukpai A Eze [1], John Huntriss [2], Michael N Routledge [3], Yun Yun Gong [4]

Affiliations + expand

PMID: 29307701 DOI: 10.1016/j.tiv.2017.12.019

Free article

Abstract

Epidemiological studies show that there is global decline in male fertility primarily as a result of poor sperm quality and this is attributed to exposure to endocrine disrupting chemicals (EDCs) in the environment, food and pharmaceutical products, including mycotoxins and pesticides. The Leydig cells in the male testes are responsible for producing androgens, hormones that play major roles in male development and reproductive function. Therefore, any toxin that affects the function and morphology of the Leydig cells may result in sub-fertility or infertility. The cytotoxic effects of single and binary mixtures of aflatoxin B_1 (AFB_1), ochratoxin A (OTA), deoxynivalenol (DON), zearalenone (ZEN), alpha-zearalenol (α-ZOL), beta-zearalenol (β-ZOL), 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane (p,p'-DDT) and 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (p,p'-DDE) on a model cell line, the MA-10 Leydig cells, were evaluated using 3-[4,5-dimethylthiazol-2-yl]-2,5-dipenyltetrazolium bromide (MTT) assay after 48h of exposure. With single toxin treatment at doses between 0.1μM and 64μM for 48h, DON was the most cytotoxic to MA-10 cells with a half maximal inhibitory concentration (IC_{50}) value of 12.3μM followed by α-ZOL (IC_{50}: 28μM) and OTA (IC_{50}: 30μM) while the IC_{50} of AFB_1, p,p'-DDT and p,p'-DDE were above the highest concentration

HOW DOES ZEARLENONE WORK?

- Although ZEA is non-steroidal, ZEA and its derivatives act similarly to 17β-estradiol (E_2) by inhibiting the secretion and release of steroid hormones, thus disrupting endogenous estrogenic response during the preovulatory stage and depressing the maturation of ovarian follicles. It increases cell proliferation while also causing cell death.
- ZEA has been shown to cause reproductive disorders in animals and hyperestrogenic disorders in humans, depending on duration of exposure.

Katzenellenbogen, B. S., and Korach, K. S. (1997). A new actor in the estrogen receptor drama–enter ER-beta. *Endocrinology* 138, 861–862. doi: 10.1210/endo.138.3.5080

HOW DOES ZEA WORK?

- The metabolism of ZEA can be divided into two phases including phase-I metabolism and phase-II metabolism.
- At the phase-I, ZEA was catalyzed by 3α-hydroxysteroid dehydrogenase (3α-HSD) or 3β-hydroxysteroid dehydrogenase (3β -HSD) and transformed into α-zearalenol (α-ZEA), β-zearalenol (β-ZEA), zearalanone (ZAN), α-zearalanol (α-ZAL) and β-zearalanol (β-ZAL) and all of which were subsequently conjugated to glucuronic acid –
- At the phase-II these metabolites were glucuronidated and sulfated.

*Filannino A., Stout T.A., Gadella B.M., Sostaric E., Pizzi F., Colenbrander B., Dell'Aquila M.E., Minervini F. Dose-response effects of estrogenic mycotoxins (zearalenone, alpha- and beta-zearalenol) on motility, hyperactivation and the acrosome reaction of stallion sperm. Reprod. Biol. Endocrinol. 2011;9:134. doi: 10.1186/1477-7827-9-134.
*Zheng W., Wang B., Li X., Wang T., Zou H., Gu J., Yuan Y., Liu X., Bai J., Bian J., et al. Zearalenone promotes cell proliferation or causes cell death? Toxins (Basel) 2018;10:184. doi: 10.3390/toxins10050184.

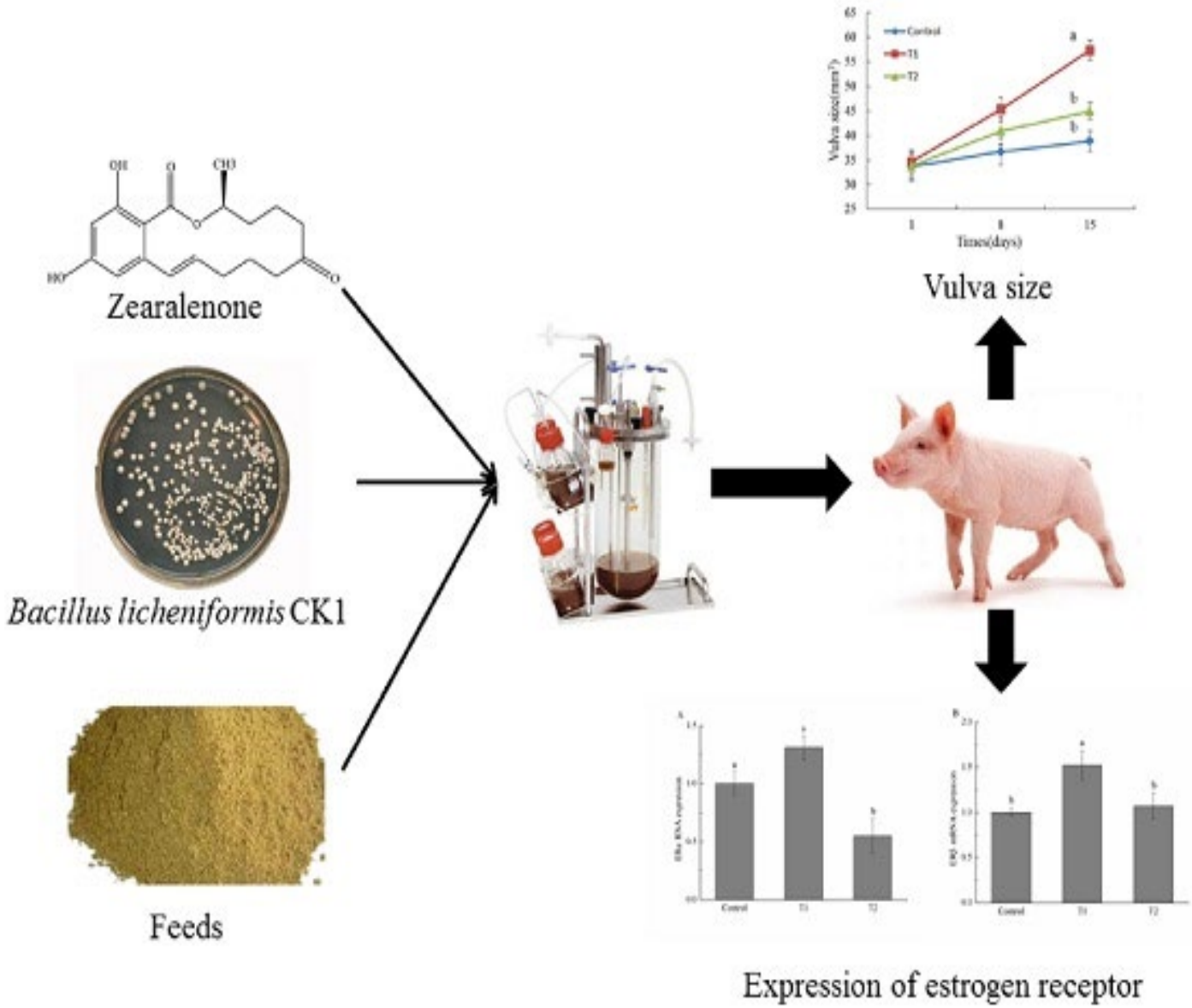
ZEA IN ANIMAL STUDIES

- Zearalenone (ZEA) has been widely used in the United States since 1969 to help cattle grow faster and bigger. Research has now linked zearalenone to early puberty and because of this, the European Union has banned giving zearalenone to cattle.
- ZEA causes sterility in sows by inciting ovarian disorders. Oocytes die in the follicles and ovulation does not occur, despite signs presented during the cycle.
- ZEA and its metabolites were detected in the bile of *E. asinus* (domestic draft animal)

Vanyi, A., Bata, A., Glavits, R., and Kovacs, F. (1994). Perinatal oestrogen syndrome in swine. *Acta Vet. Hung.* 42, 433–446.
Zwierzchowski, W., Przybylowicz, M., Obremski, K., Zielonka, L., Skorska-Wyszynska, E., Gajecka, M., et al. (2005). Level of zearalenone in blood serum and lesions in ovarian follicles of sexually immature gilts in the course of zearalenone micotoxicosis. *Pol. J. Vet. Sci.* 8, 209–218.
Diekman, M. A., and Green, M. L. (1992). Mycotoxins and reproduction in domestic livestock. *J. Anim. Sci.* 70, 1615–1627. doi: 10.2527/1992.7051615x

ESTROGENIC ACTIVITY IN PIGLETS

THE TOXIC EFFECTS OF ZEA ON WEANED PIGLETS (FED MOLDY MAIZE) ARE ASSOCIATED WITH VULVAR HYPERTROPHY AND OVARIAN ATROPHY BUT NOT WITH MAMMARY AND UTERINE ENLARGEMENT



ZEA IN ANIMAL STUDIES

ZEA caused a disorder of the mitochondrial transmembrane and increased the reactive oxygen levels in porcine granulosa cells. Curcumin was able to rescue this process in vitro.

ZEA and its metabolites may induce atresia in porcine follicles.

Zearalenone metabolites can be excreted in milk of exposed sows, resulting in hyperestrogenic effects in their nursing piglets.

Studies do show decreased stallion sperm motility with high doses of ZEA

Qin, X., Cao, M., Lai, F., Yang, F., Ge, W., Zhang, X., et al. (2015). Oxidative stress induced by zearalenone in porcine granulosa cells and its rescue by curcumin in vitro. *PLoS One* 10:e0127551. doi: 10.1371/journal.pone.0127551

Hoffmann B, Landeck A: Testicular endocrine function, seasonality and semen quality of the stallion. Anim Reprod Sci. 1999, 57 (1-2): 89-98. 10.1016/S0378-4320(99)00050-0.

ZEA AND HUMAN STUDIES

- ZEA, at a low concentration, enhanced cell proliferation of a colon carcinoma cell line (HCT116). The highest effect of ZEN was observed at a concentration 10x lower as compared to aflatoxin.
- 2015 study evaluated the involvement of endoplasmic reticulum stress in ZEA-mediated toxicity in human intestine (HCT116) and kidney (HEK293) cells.
- Activation of the endoplasmic reticulum stress response by ZEA is associated with activation of the mitochondrial pathway of apoptosis.
    - = increase in ROS generation/lipid peroxidation, a loss of mitochondrial transmembrane potential and an activation of caspases and DNA damages.

The antioxidant properties of quercetin and crocin help to prevent ER stress and reduce ZEA-induced apoptosis in HCT116 and HEK293 cells.

*Abassi H., Ayed-Boussema I., Shirley S., Abid S., Bacha H., Micheau O. The mycotoxin zearalenone enhances cell proliferation, colony formation and promotes cell migration in the human colon carcinoma cell line hct116. Toxicol. Lett. 2016;254:1–7. doi: 10.1016/j.toxlet.2016.04.012.
*Ben Salem I, Prola A, Boussabbeh M, Guilbert A, Bacha H, Abid-Essefi S, Lemaire C. Crocin and Quercetin protect HCT116 and HEK293 cells from Zearalenone-induced apoptosis by reducing endoplasmic reticulum stress. Cell Stress Chaperones. 2015 Nov;20(6):927-38.

ZEA AND BREAST CANCER

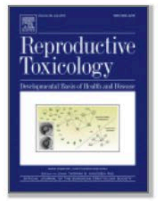
- 2018 study: In order to characterize the estrogenic activity of ZEA, α-ZOL and β-ZOL, the proliferation of ER-positive human breast cancer cells (MCF-7) exposed to these mycotoxins was measured.
- After exposure at levels ranging from 6.25 to 25 μM, cell proliferation was evaluated. Results show the estrogenic activity of ZEA, (α-ZOL and β-ZOL) in MCF-7 cells.
- The relative proliferative effect (RPE) ranged from 10% to 91%

Tatay E, Espín S, García-Fernández AJ, Ruiz MJ. Estrogenic activity of zearalenone, α-zearalenol and β-zearalenol assessed using the E-screen assay in MCF-7 cells. Toxicol Mech Methods. 2018 May;28(4):239-242.

ELSEVIER

Reproductive Toxicology

Volume 38, July 2013, Pages 47-52



Potential endocrine disrupting effect of ochratoxin A on human placental 3β-hydroxysteroid dehydrogenase/isomerase in JEG-3 cells at levels relevant to human exposure ☆

Chit Shing Jackson Woo [a], Murphy Lam Yim Wan [a], Jorma Ahokas [b], Hani El-Nezami [a]

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OCHRATOXIN AND ENDOCRINE DISRUPTION

- It is hypothesized that Ochratoxin may act as an endocrine disruptor by intervening 3β-hydroxysteroid dehydrogenase/isomerase (3β-HSD).

GETTING RID OF XENOBIOTICS AND XENOESTROGENS

- Most important thing you can do is to open your drainage pathways!
- Mitochondria, glmphatic, lymphatic, liver, bile, kidneys, lungs, skin, bowels, breastmilk, and even, cycles.
- Innate way of detoxification, nothing beats the body. You must rattle it awake, gently or more aggressively.
- Remember hormones are chemical communicators and not root cause.

TOP ENDOCRINE DISRUPTERS TO AVOID:

1. dioxins
2. PCBs
3. flame retardants
4. BPA
5. phthalates
6. perchlorate
7. PFCs
8. organophosphate pesticides and atrazine
9. arsenic
10. mercury
11. lead

GETTING RID OF XENOESTROGENS AND XENOBIOTICS

- IR sauna
- Epsom salt baths
- Enemas and colonics
- Binders like HM ET and Viradchem alternated
- Filtering water including shower
- Throw out plastic bottles and go green with household cleaning supplies
- For mold—Carboxy (carbon, polysaccharides, electrolytes, amino acids)
- Estrogen dominance-get to the root cause + cyperus rotundus

INFRARED SAUNA OR EXERCISE

Studies have shown heavy metals like mercury, arsenic, lead and cadmium +fat soluble toxins are removed after exercise (and saunas).

1988 study showed changes to the endocrine system after IR sauna use.

Margaret E. Sears, Kathleen J. Kerr, Riina I. Bray, "Arsenic, Cadmium, Lead, and Mercury in Sweat: A Systematic Review", *Journal of Environmental and Public Health*, vol. 2012, Article ID 184745, 10 pages, 2012. https://doi.org/10.1155/2012/184745

IR SAUNA

How the sauna affects the endocrine system

K Kukkonen-Harjula [1], K Kauppinen

Affiliations + expand

PMID: 3218898

Abstract

The sauna induces changes in the secretion of hormones, some similar to changes induced in any other stress situation and others characteristic of exposure to the sauna. Noradrenaline is usually the only catecholamine raised by the sauna in people accustomed to it. The secretion of the antidiuretic hormone is increased and the renin-angiotensin-aldosterone system is activated. The concentrations of the growth hormone and prolactin, in particular, secreted from the anterior pituitary are increased in the circulation. The concentration of the immunoreactive beta-endorphin in blood may also increase which may reflect the feeling of pleasure or, on the other hand, discomfort induced by the sauna. The views on the effects of the sauna on the secretion of the ACTH and cortisol are partly contradictory, probably due to differing ways of taking the sauna bath. In Finnish sauna takers the concentration of cortisol in blood is not usually increased. The changes induced by the sauna in various hormone concentrations in the circulation are, however, normalized within a couple of hours after the heat stress.

IMPORTANCE OF CYPERUS ROTUNDUS

- Has been shown to act as a selective estrogen receptor modulator
- Has been shown to help uterine fibroids and ovarian cancer
- The sesquiterpenes are the magic sauce
- “has biphasic activities on estrogen receptors which could be useful as an alternative HRT. “

CYPERUS ROTUNDUS IN THE STUDIES

Afr Health Sci. 2016 Dec;16(4):1000-1006. doi: 10.4314/ahs.v16i4.16.

Chemical constituents of Cyperus rotundus L. and their inhibitory effects on uterine fibroids

Ju Ying [1], Xiao Bing [2]

Affiliations + expand

PMID: 28479892 PMCID: PMC5398446 DOI: 10.4314/ahs.v16i4.16

Free PMC article

Abstract

Background: Xiang Fu (Cyperus rotundus L) enters the liver, spleen and triple warmer meridians, and has qi stagnation-removing, qi circulation-promoting, menstruation-regulating and pain-relieving effects. Besides, it can improve ovarian function, and has hypolipidemic, hypoglycemic and neuroprotective actions.

Objectives: To study the biflavone constituents in Cyperus rotundus L and to investigate the effect and mechanism of amentoflavone on inhibition of uterine tumors. Modern chromatographic techniques were applied for isolation and purification of compounds, which were then structurally elucidated based on their physicochemical properties and spectral data.

CYPERUS ROTUNDUS IN THE STUDIES

Research Article

6-Acetoxy Cyperene, a Patchoulane-type Sesquiterpene Isolated from *Cyperus rotundus* Rhizomes Induces Caspase-dependent Apoptosis in Human Ovarian Cancer Cells

Ji-Hye Ahn, Tae-won Lee, Ki-Hee Kim, Hoyong Byun, Byeol Ryu, Kyung-Tae Lee, Dae Sik Jang, Jung-Hye Choi

First published: 10 June 2015 | https://doi.org/10.1002/ptr.5385 | Citations: 13

Abstract

Cyperus rotundus (Cyperaceae) has been widely used in traditional medicine for the treatment of various diseases, including cancer. Although an anti-tumour effect has been suggested for *C. rotundus*, the anti-tumour effects and underlying molecular mechanisms of its bioactive compounds are poorly understood. The *n*-hexane fraction of an ethanol extract of *C. rotundus*

CYPERUS ROTUNDUS IN THE STUDIES

> Biomed Pharmacother. 2019 Jan;109:1313-1318. doi: 10.1016/j.biopha.2018.10.186.
Epub 2018 Nov 9.

Sesquiterpenes from Cyperus rotundus and 4α,5α-oxidoeudesm-11-en-3-one as a potential selective estrogen receptor modulator

Yong Joo Park [1], Hailing Zheng [1], Jong Hwan Kwak [2], Kyu Hyuck Chung [3]

Affiliations + expand

PMID: 30551381 DOI: 10.1016/j.biopha.2018.10.186

Free article

Abstract

Estrogenic activity-oriented fractionation and purification of methanol extract from the rhizome of Cyperus rotundus, a well-known traditional herbal medicine, led to the isolation of six sesquiterpenes. 4α,5α-Oxidoeudesm-11-en-3-one (2) and cyper-11-ene-3,4-dione (3) together with four known sesquiterpenes, cyperotundone (1), caryophyllene α-oxide (4), α-cyperone (5), and isocyperol (6) were obtained from the hexane and dichloromethane fractions. Compounds 2 and 3 were newly isolated from natural resources in particular. To identify the possible use of isolated compounds as an alternative to hormone replacement therapy (HRT), estrogenic activity was evaluated by E-screen assay on MCF-7 BUS cells. Among the all isolated compounds from the rhizome of Cyperus rotundus, newly isolated from natural resource, 2 exhibited the most potent estrogenic activity. In an estrogen sensitive reporter gene assay, 2 significantly increased transcriptional activities. As a phytoestrogen, 2 was assessed by investigating dual action on ER-α and ER-β in competitive binding assay. It was found that 2 exerted higher binding affinity to ER-β than ER-α and it also showed both estrogenic and antiestrogenic effects depending on the E_2

PINE POLLEN

- Pine pollen powder contains aminos, vitamins, minerals, enzymes, fatty acids and androgens.
- Studies from China show it balances testosterone and DHEA
- Increases libido and stamina

MAGNESIUM

- Necessary for phase two liver detoxification and is a pro motility agent
- Aids in cardiac health and is anti anxiety
- Deficiency is common in today's diet
- Used in over 300 reactions in the body
- Most absorbable forms are glycinate and chelated

TUDCA'S ROLE IN HORMONES

All hormonal imbalances come from liver stagnation or improper processing

Hormones

TUDCA inhibits testosterone-induced RAGE expression and AGE accumulation in PCOS.
Endocrinology. 2020 Feb 1;161(2).
https://pubmed.ncbi.nlm.nih.gov/32053721/

TUDCA has been shown to decrease Endoplasmic Reticulum stress induced by high oxidative stress in granulosa cells in ovaries with endometrioma mediating apoptosis of these cells, leading to ovarian dysfunction in patients with endometriosis
Mol Hum Reprod. 2020 Jan 1;26(1):40-52.
https://pubmed.ncbi.nlm.nih.gov/31869409/

TUDCA alleviated Endoplasmic Reticulum stress in Adrenocortical Carcinoma (ACC) and induced autophagy, thereby inhibiting ACC cell apoptosis.
Oncol Lett. 2019 Dec; 18(6): 6475–6482.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6888259/

In PCOS taking TUDCA was found to rebalance proper testosterone levels by decreasing the inflammation in the Granulose cells of antral follicle
Endocrinology. 2019 Jan 1;160(1):119-132.
https://academic.oup.com/endo/article/160/1/119/5171869

TUDCA was shown to prevent aggregating of misfolded proteins, alleviate ER stress, and hinder UPR-mediated cell death in ovarian cortex during aging and senescence therefore represents the important cellular mechanism linked to tissue stability and homeostasis.
Cell Tissue Res. 2018 Dec;374(3):643-652
https://pubmed.ncbi.nlm.nih.gov/30066106/

TUDCA was shown to decreased interstitial fibrosis and collagen deposition in ovaries, accompanied by a reduction in TGF-β1 expression in granulosa cells in female with PCOS.
Sci Rep. 2017 Sep 7;7(1):10824.
https://pubmed.ncbi.nlm.nih.gov/28883502/

WHAT DOES THIS MEAN FOR FUTURE GENERATIONS?

- Infertility is already rising due to rampant toxicities leading to hormonal imbalances.
- Mitochondrial dysfunction is a common denominator for many chronic conditions
- Hormones are not root cause but a chemical communicators showing us there is a bigger problem
- Root causes: stealth infections, corporate toxicities, heavy metals, prolonged stress
- Opening drainage pathways is imperative to success –always give liver support in light of hormonal issues