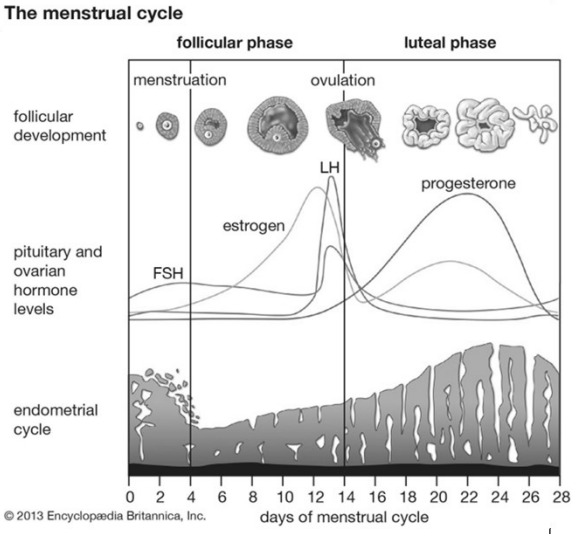
HORMONES
Menstrual Cycle

It is important to understand where we started!

- Menstruation depends on specific signaling
- FSH stimulates estrogen in the Follicular Phase
- Hormone of "youth" & can use this to track HRT
- FSH supports follicle development (egg maturation)
- Estradiol spikes, signaling the spike of LH
- Once LH spikes and drops, progesterone is released
- The luteal phase reveals optimal progesterone with Oxytocin with some estrogen

No conception = menstruation



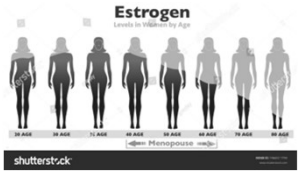
1

HORMONES
Estrogen

ESTROGEN CHANGES

ESTROGEN - ESTRADIOL

- Shift of abundant Estradiol has a major downward trend after 40 years of age
- But happening younger
- And rising in younger males



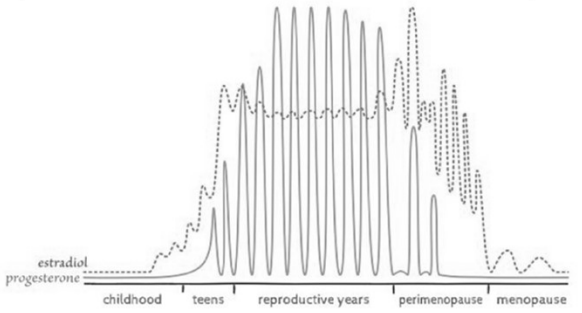


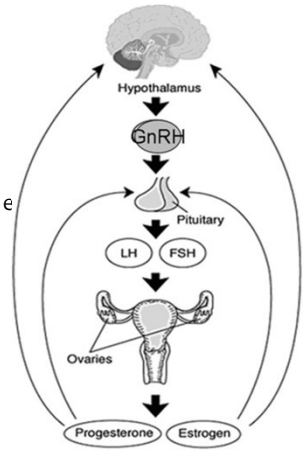
image 1 — hormones through the lifespan, adapted from JC Prior, "Perimenopause lost—reframing the end of menstruation."

Briden, Lara. Hormone Repair Manual.

2

HORMONES
HPO Communication – severe trauma early in life can turn this OFF or EDCs

- The brain signals to the ovaries from the Hypothalamus -> Pituitary -> Ovaries
- The Pituitary releases LH and FSH to signal hormone release and signal to the ovaries



Due to communication and negative feedback, FSH and LH levels are inverse: LH levels get higher when the ovaries need more signal to rele hormone. It is the same with FSH.

FSH is best tested days 3-5 of the menstrual cycle

Anytime in menopause

LH levels are highest as the follicular phase transitions to ovulation

3

HORMONES
Changes in the menstrual cycle

Cycling Female:

- Generally cycles every 28-35 days with a 3-7 day bleed

Peri-Menopause cycle: Oligomenorrhea

Happening younger and younger so always consider it in a "differential diagnosis"

- Irregularities with cycling – sooner than 28 days, later than 35 days, bleeding more frequently, bleeding less than 3 days, or more than 7 days, and volume of blood may be a lot less, or a lot more

Many bleeding issues are insufficient progesterone

Environment is rife with "anti-progestins"

And insufficient iodine

As environment is rife with anti-thyroid EDCs

Menopause:

- No bleeding for 12 or more months

4

Menstruation

- First part of cycle - driven by proliferation GROWTH - driven by ER Alpha Estradiol
- Ovulation – driven by ER beta
- Second part if no pregnancy – driven by deproliferation CONTROLLED GROWTH – driven by ER beta (shedding and period)

5

Perimenopause

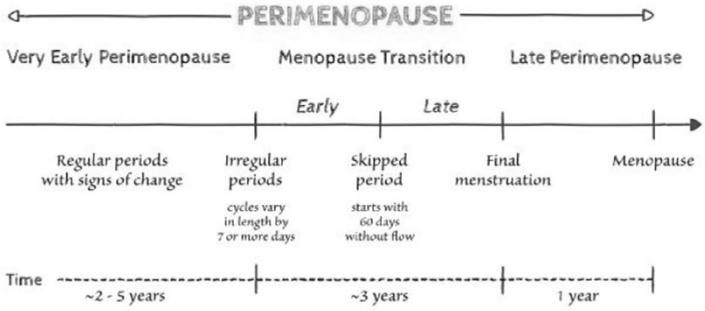
- Heavy bleeding menorrhagia
- Heavy clotting
- Signs of anovulation
- Needing progesterone
- Not progestins

6

HORMONES
Estrogen

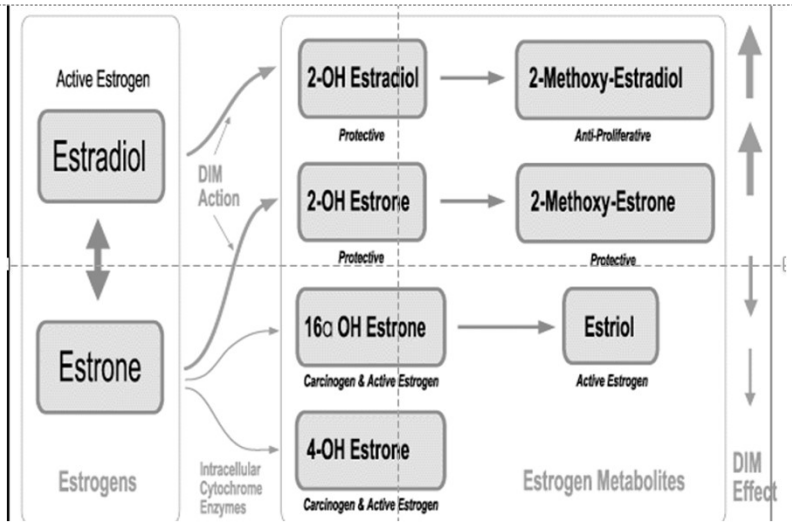
- Phases of Menopause

1. very early perimenopause, when cycles are still regular
2. early menopause transition, from the onset of irregular periods
3. late menopause transition, from the first cycle of more than sixty days
4. late perimenopause, which is the twelve months from the final period
+. menopause, which is the life phase that begins one year after your last period.



Briden, Lara. Hormone Repair Manual.

7



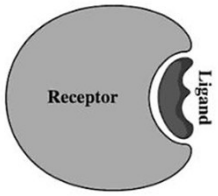
8

Receptor Functionality – can have perfect levels of urine, saliva or blood with inactivated receptors!

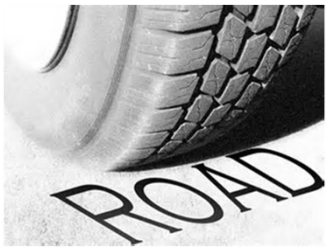
You can have perfect hormone

Levels (blood, urine, saliva) but until

The receptor is activate, none of this matters.



Is where the hormone rubber meets the hormone road.



Inactive Receptor whe
successfully bind it be
to deliver it's message

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9

Nuclear Receptor: 3 Parts

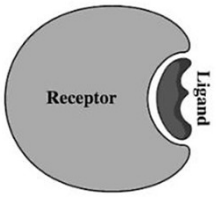
- Receptor
- Ligand (or anti-ligand)
- Co-regulatory proteins
    1. nutrients where what you eat comes to play and (iodine, retinoic acid, magnesium. B6, zinc)
    2. competitive inhibitors

- Recent Prog Horm Res. 2000;55:163-93; discussion 194-5. **Estrogen receptors: selective ligands, partners, and distinctive pharmacology.**

Dr. DL. Berkson©

10

Receptor Functionality
Nutrients



Nutrient Bowl (transcriptional co-factors)

- Zinc (fingers)
- Vitamin B6
- Magnesium
- Iodine
- Vitamin A

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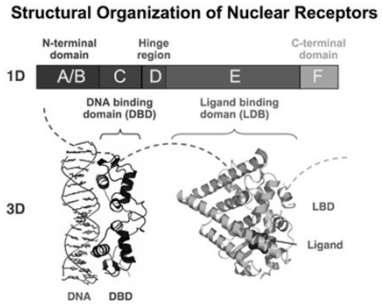
11

Binding Domain
Zinc gives shape for all hormones to dock
Must run RBC zinc to assess all hormone functionality



Zinc finger

- Part of C domain of steroid receptors
- Best characterized domain of steroid receptors is C domain.
- Zinc finger creates a SHAPE that can insert into a specific base pair of DNA
- Essential part of SHBG
- Inhibits aromatase
- Low zinc linked to hormonal issues
- Not responding to endogenous or exogenous hormones
- Leads to low T and high E
- Symptoms of low zinc: easily ill, chronic diarrhea, poor wound healing, ringing in the ears, feet smell, white spots on nails,

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Duration of Signal - Vitamin B6

- Involved in the clearance of estradiol from nuclear receptors
- B6 deficiency > Estrogen dominance (sluggish removal from receptor)
- Estrogen supplementation including birth control pills . Increased need for B6
- Sugar increases need for B6 many chemicals do even flaxseeds.

- Am J Obstet Gynecol. 1976 Aug 15;125(8):1063-9.
- **Effect of oral contraceptives on nutrients. III. Vitamins B6, B12, and folic acid.**
- Biochem Pharmacol. 1976 Nov 1;25(21):2411-3.
- **In vitro trials to counteract the inhibitory effect of beta-oestradiol and ethynyloestradiol on the B6-dependent kynurenine aminotransferase enzyme.**

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13

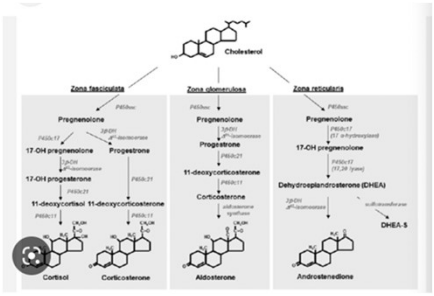
All hormones

Are made from cholesterol and B vitamins

14

Cholesterol + Pantothenic Acid in presence of other B's

- All classes of steroid hormones, glucocorticoids, mineralocorticoids, and sex hormones, are derivatives of cholesterol.
- Synthesis occurs in the placenta and ovaries (estrogens and progestins), testes (testosterone), and adrenal cortex (cortisol, aldosterone, and androgens).



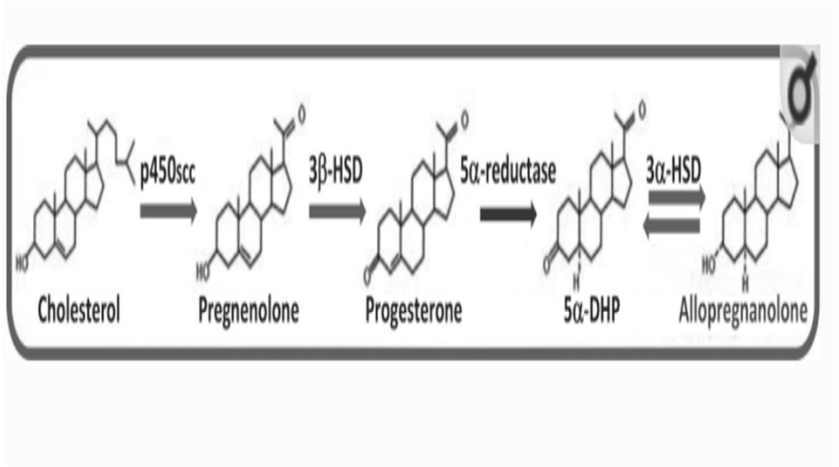
15

Cholesterol – Follow the science

- Cholesterol makes hormones
- New guidelines from AHA is to lower LDL cholesterol from 50 to 70

- Am Geriatr Soc 2020 Feb;68(2):288-296. doi: 10.1111/jgs.16306. Epub 2020 Jan 13.
- **Associations between Serum Levels of Cholesterol and Survival to Age 90 in Postmenopausal Women**

16



Allopregnanolone: From molecular pathophysiology to therapeutics. A historical perspective
Neurobiol Stress. 2020 May; 12: 100215.doi: 10.1016/j.ynstr.2020.100215

- **3 beta hydroxysteroid dehydrogenase** –
- Co-factor is NAD (niacin) (and taurine educe TGFB1)
- **3 alpha hydroxysteroid dehydrogenase** –
- In target tissue regulates how steroid hormones occupy their receptors
- effected by other steroids too such as Er beta, progesterone and T

Structure and function of 3 alpha-hydroxysteroid dehydrogenase. Steroids. 1997 Jan;62(1):101-11. doi: 10.1016/s0039-128x(96)00167-5. PMID: 9029723.

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17

American Heart Association

- In patients with ASCVD (atherosclerotic cardiovascular dx) reduce LDL-C by 50% of present level
- In high risk not over 70 mg/dL statins plus Ezemtibe nonstatin inhibitor of chol absorption
- If LDL-C > 190 use high intensity statins bring LDL under 70
- In diabetics bring to 50
- Case Report of Harvard Professor

18

WHI older women cholesterol study – follow the science

- N = 115,400 tracked in 5 yr survival outcomes from original 161,808
- Lipid subcohort 27,940 those with analytical poss to live to 90 came down to 3.567 that lived to 90
- 1993-90 40 Institutions WHI
- **Conclusion:** Neither higher HDL nor lower LDL levels predicted survival to age 90, **but higher LDL predicted healthy survival.**
- **These findings suggest the need for reevaluation of healthy LDL levels in older women.**
- Am Geriatr Soc 2020 Feb;68(2):288-296. doi: 10.1111/jgs.16306. Epub 2020 Jan 13.
- **Associations between Serum Levels of Cholesterol and Survival to Age 90 in Postmenopausal Women**

19

Elderly LDL

- The Cardiovascular Health Study, men and women with LDL levels above 3.96 mmol/L had.51 times the risk of mortality relative to those with levels lower than 2.48 mmol/L.28
- Over 150 mg/dL lived longer, did better.

- Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA. 1998;279(8):585-592
- Department of Medicine, The Johns Hopkins Medical Institutions, Baltimore, Md, USA.

20

Elderly Higher HDL

- However, in a large study conducted in the Danish Birth Registry cohort (N = 12 937), after adjustment for factors including statin use and education, higher HDL levels were associated with lower mortality in women aged 70 years and older.
- Living long linked to higher LDL and HDL in women. Not sure with males.
- Association of lipoprotein levels with mortality in subjects aged 50 + without previous diabetes or cardiovascular disease: a populationbased register study. Scand J Prim Health Care. 2013;31(3):172-180.

21

Why?

- You make hormones out of cholesterol
- Cells membranes where instant transmembraneous hormones signal, need estrogen
- The human brain is nearly 60 percent fat. We've learned in recent years that fatty acids are among the most crucial molecules that determine your brain's integrity and ability to perform.
- Essential fatty acids and human brain. Acta Neurol Taiwan. 2009 Dec;18(4):231-41. PMID: 20329590.

22

Brain and Myelin

- The brain is the most cholesterol-rich organ in the body and contains almost 25% of the total amount. The majority (70–80%) of this cholesterol is present in myelin, where it fulfils a critical insulating role.
- Myelin is cholesterol rich.
- \The myelin sheath is characterized by a high proportion of lipids (70%–85%) and consequently a low proportion of proteins (15%–30%). In contrast, most biological membranes have approximatively equivalent ratio of proteins to lipids (50% lipid/50% protein)
- Myelin is not a simple homogeneous layer of proteins and lipids. It also contains discrete and dynamic lipid domains in the external leaflet of its plasma membrane called lipid rafts [12,13]. Lipid rafts are characterized by the concentration of selected membrane lipids such as cholesterols, galactosylceramide, and low levels of phosphatidylcholine.
- Myelin Fat Facts: An Overview of Lipids and Fatty Acid Metabolism. Cells. 2020 Mar 27;9(4):812. doi: 10.3390/cells9040812. PMID: 32230947; PMCID: PMC7226731.

23

Overall women of menopausal years

- Higher LDL in older women
- Higher HDL
- Linked to longevity and higher quality of life
- LOW HDL = fatty liver, physical dysfunction, cancer, depression.
- Always gotta track liver as it processes hormones. Fibroscan (liver elastography)
- ALT AST in the higher 20’s and 30’s
- Lower HDL
- Suggest fatty liver – 1 out of 3 Americans has it

24

It's younger populations that elevated cholesterol is more a problem

- Our findings contrast with those from studies of younger populations, in which low HDL and high LDL levels were associated with increased risk of mortality.
- Among the older women in our analytic sample, we did not have measurements of midlife lipid levels to determine if they might provide different associations with survival to age 90.
- Although we excluded baseline users of statins and adjusted for HT use, we could not account for changes over time in use of either that might have influenced our findings.

- Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med. 1990;322(24):1700-1707.

25

Medicare Females

- In conclusion, HDL and LDL measured in women aged 68 to 81 years old were not associated with survival to age 90.
- Higher, but not lower, LDL was associated with healthy survival to age 90.
- WHI

26

What do many countries, like US, do to our elderly?

- We lower their LDL
- We lower their hormones which are brain and mood let along other physiologies protective.
- We add sugar in so many foods it's hard to avoid, to reduce B vitamins that help create our own hormones.
- Then deny them hormones!

27

Low

- Studies suggest low cholesterol makes poor outcomes in sepsis
- REGARDS population N = 30,239
- 70% over 60 years old
- Both genders
- Low LDL was statistically linked to poorer sepsis outcomes

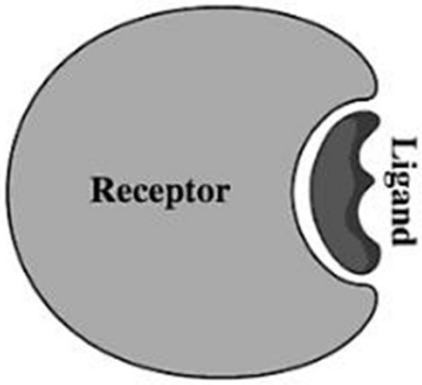
- 2016 Dec 23;20(1):408. doi: 10.1186/s13054-016-1579-8. **Cholesterol levels and long-term rates of community-acquired sepsis**
- **Multi centered ERs in US**

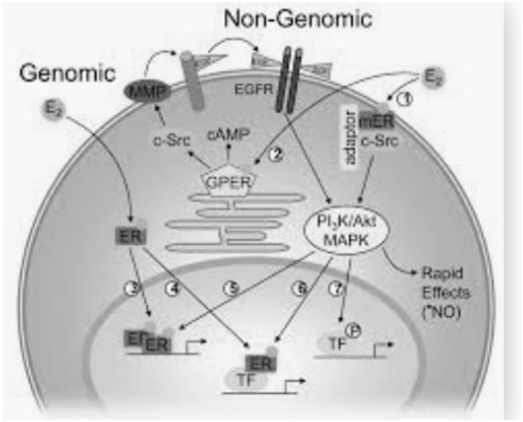
28

Hormone Review

- Genomic – slower – inside cell
- Non-genomic – faster - on cell membrane

29





Ligand Binding

- LIGAND (HORMONE) docks into receptor travels to nucleus delivers message to genes (genomic signaling)

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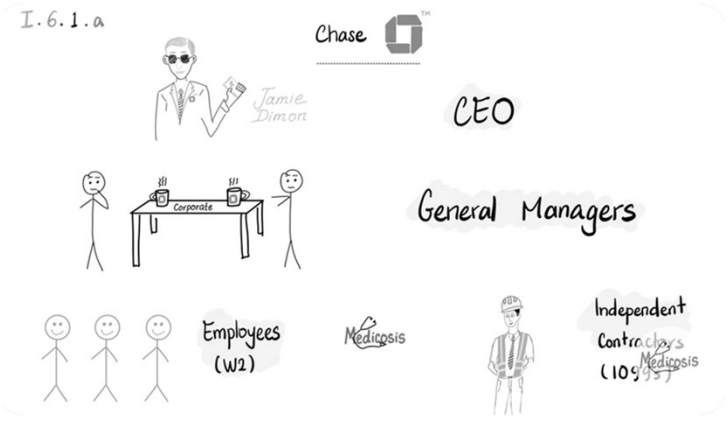
30

Simple Concepts, Huge Implications

- Genomic – activate gene expression in cytoplasm
- Non-genomic – activating kinase cascades in cell membranes
- They can cross-communicate

31

Any company has dominance hierarchy



32

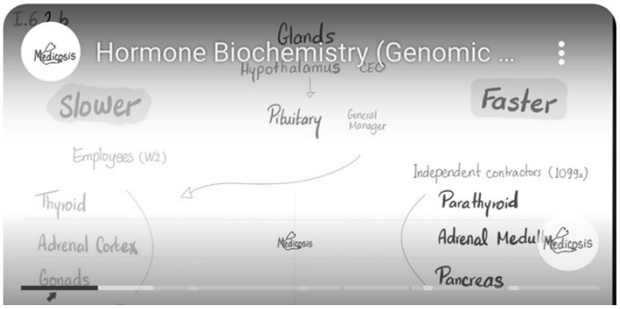
Endocrinologic Analogy

- CEO – hypothalamus
- Pituitary - general manager
- Employees – hired by company must obey - Thyroid, Adrenal Cortex, Gonads obey pituitary esp ant pituitary
- Independent contractors – Parathyroid, Adrenal Medulla, Pancreas

33

For survival

- Most important survival from tiger
- Adrenal medulla secretes epinephrin and norepinephrine (must be independent As important for survival)



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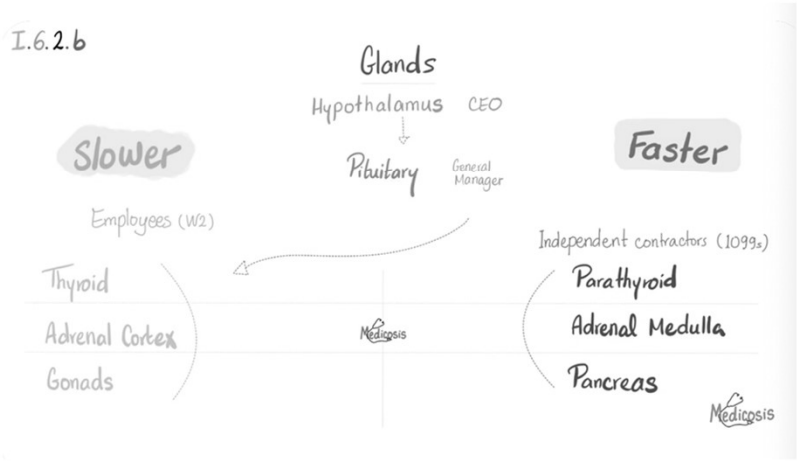
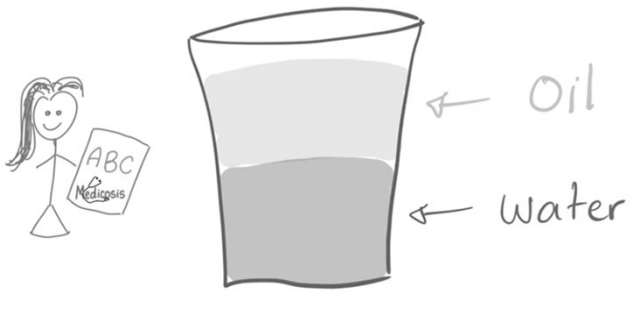


35

Concept of Polarity and Binding Proteins



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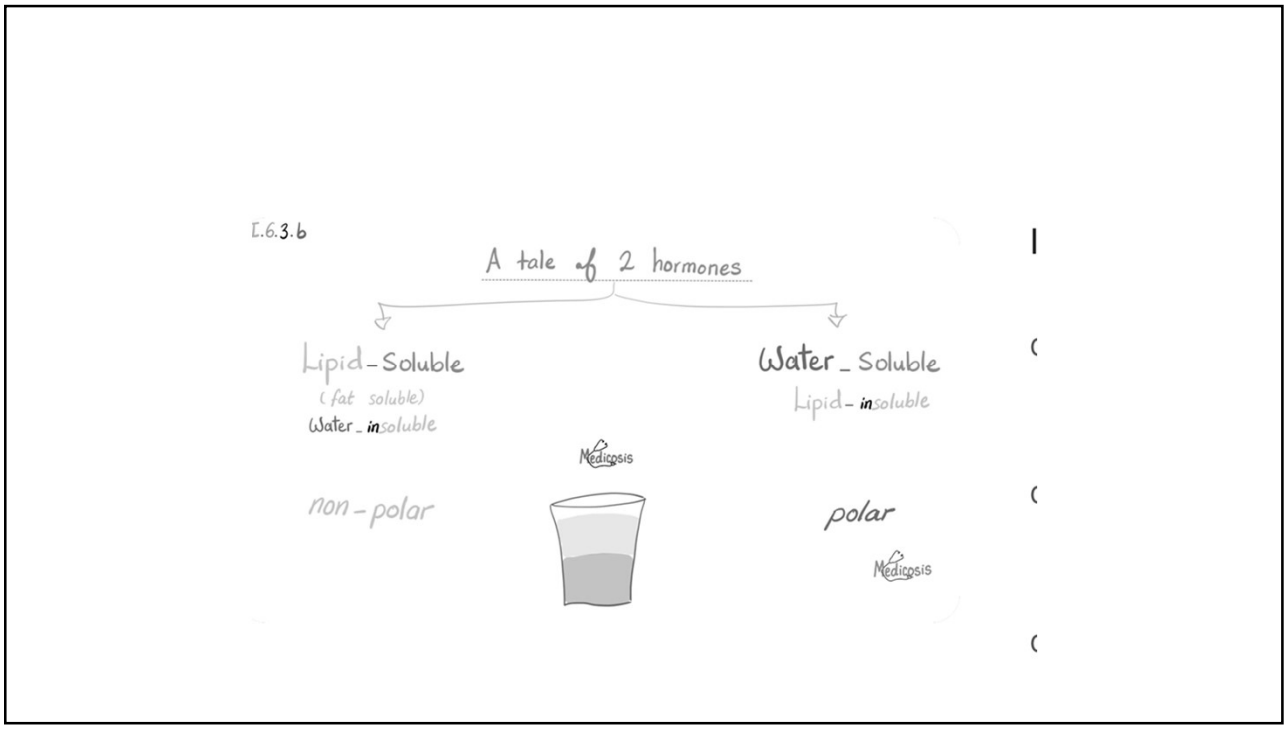
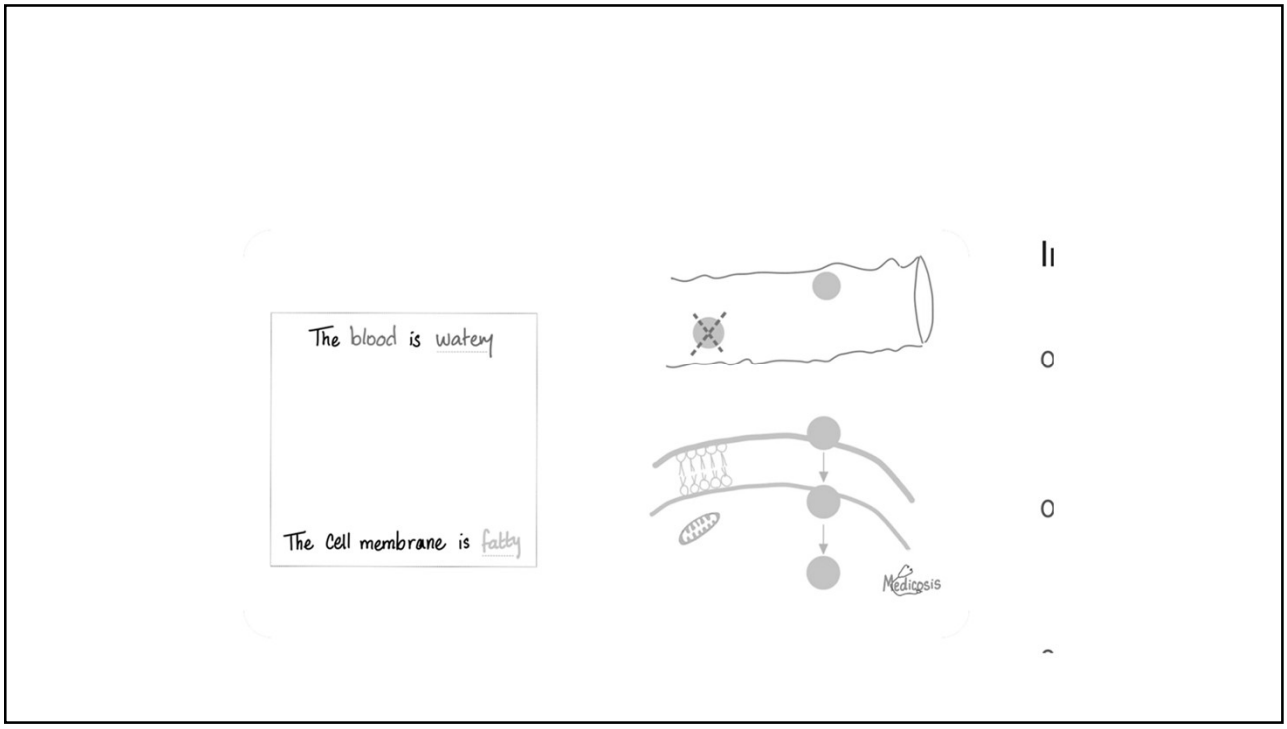
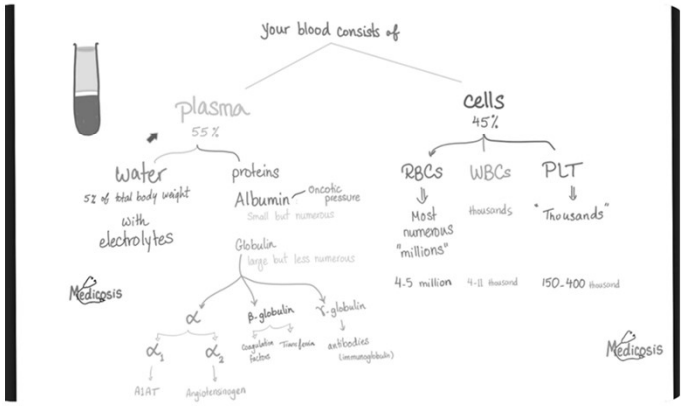

I.6.3.b
A tale of 2 hormones
Lipid-Soluble
(fat soluble)
Water_insoluble
non-polar
Water_Soluble
Lipid-insoluble
polar
Medicosis
Medicosis

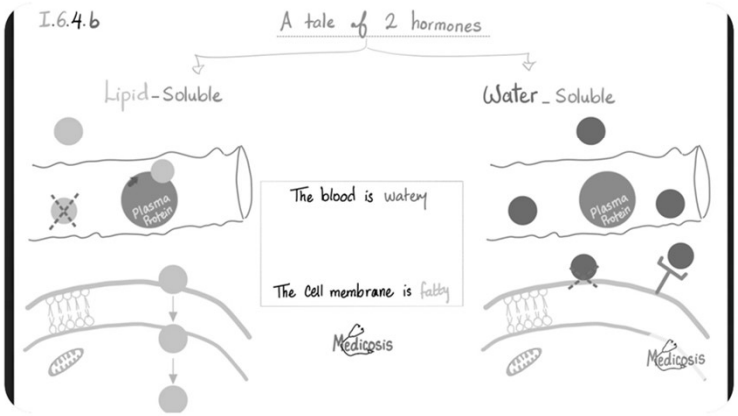
37


The blood is watery
The cell membrane is fatty
Medicosis

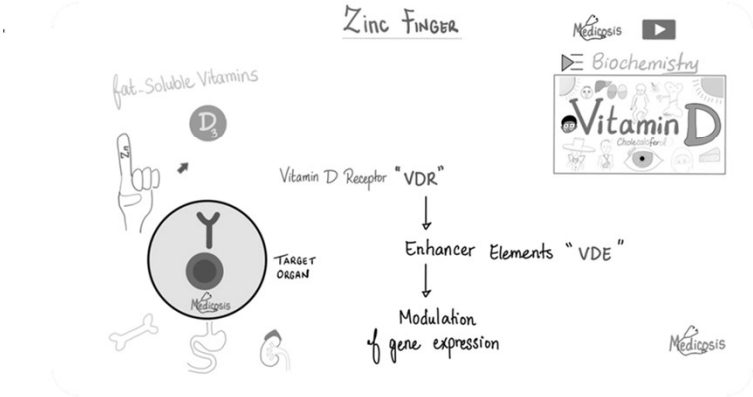
38


Your blood consists of
plasma
55%
cells
45%
water
5% of total body weight
with electrolytes
proteins
Albumin
Oncotic pressure
Small but numerous
Globulin
large but less numerous
RBCs
WBCs
PLT
Most numerous "millions"
thousands
"Thousands"
4.5 million
4-11 thousand
150-400 thousand
α
β-globulin
γ-globulin
α1
α2
coagulation factors
Transferrin
antibodies (immunoglobulin)
AIAT
Angiotensinogen
Medicosis
Medicosis

39


I.6.4.b
A tale of 2 hormones
Lipid-Soluble
Water_Soluble
Plasma Protein
Plasma Protein
The blood is watery
The cell membrane is fatty
Medicosis
Medicosis

40



41

Genomic, Slower, makes proteins to run body (estrogen, testosterone, progesterone, thyroid, adrenal cortex)

- Transcription = to make RNA (genomic)
- Translation = to make proteins

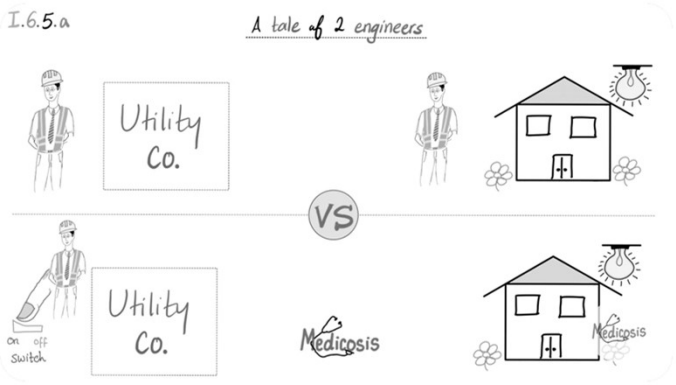
42

Non-genomic

- Rapid acting
- Cell membrane
- G-coupled
- Sends immediate signals for life
- To get hormones just right
- You must know thus, what parathyroids, adrenal medulla and pancreas are doing.

43

To turn off light bulb in your house which is faster: video #6 (Medicosis)



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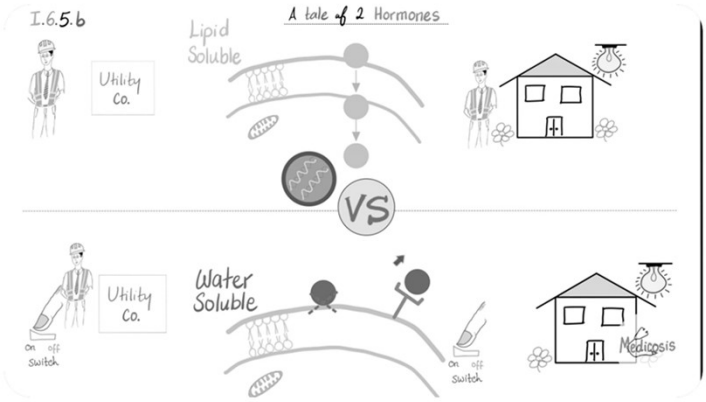
Endocrinology –
Membrane - water soluble flip a switch so it's rapid
Cytoplasm lipid soluble – a lipid soluble has to wait to diffuse across cell membrane, get into & travel through cytoplasm, g find receptor in cytoplasm or nucleus -it's slow acting



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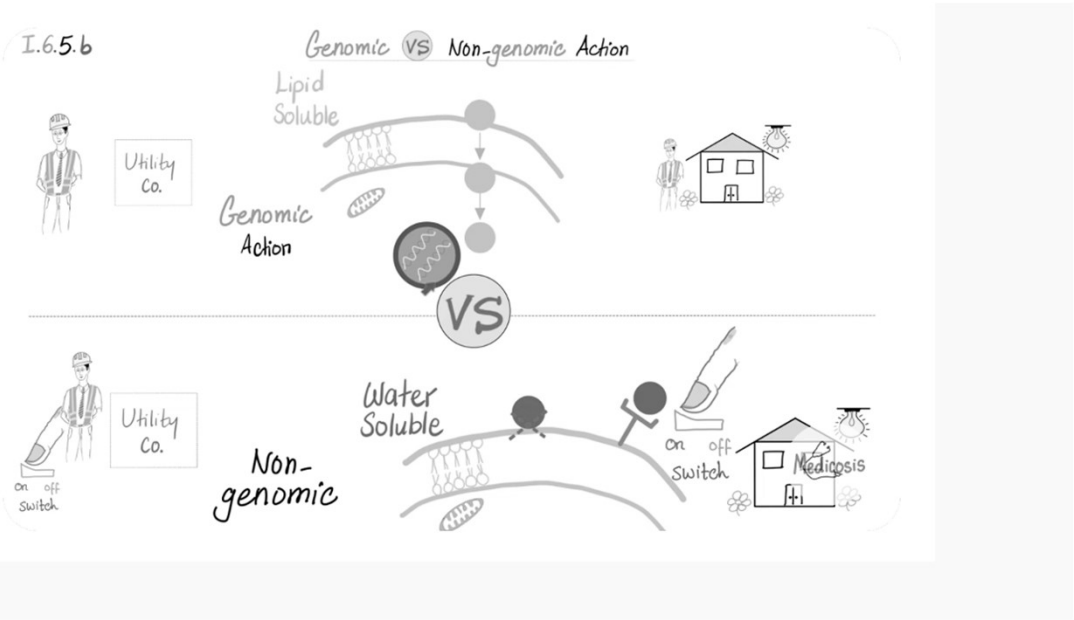

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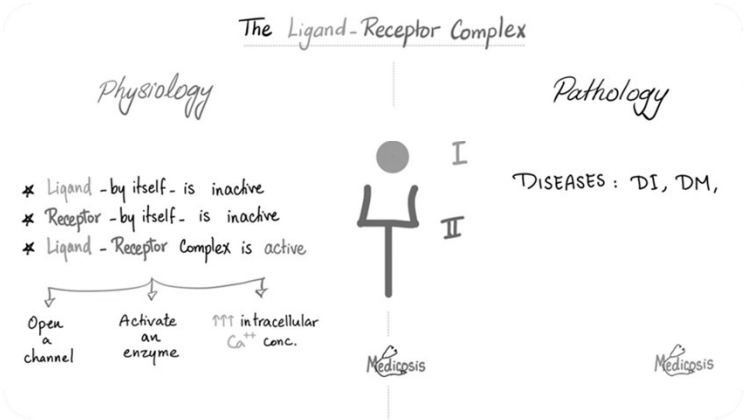
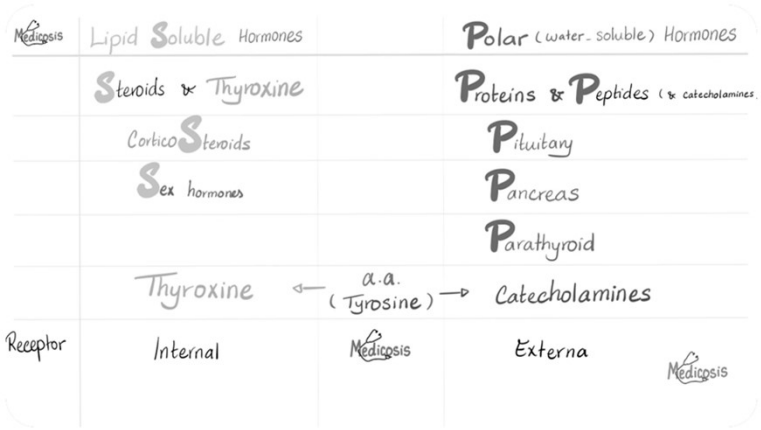


47

Tyrosine plays a critical role in hormone homeostasis (if protein levels in labs are in 5's and 6's not getting sufficient tyrosien)



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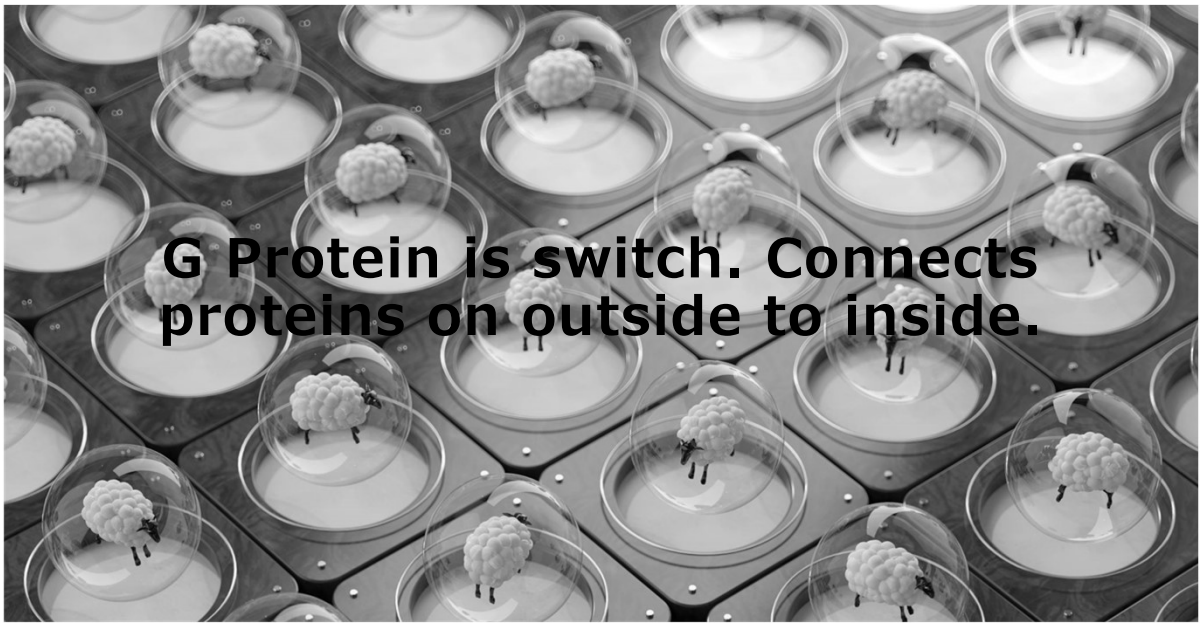
Tyrosine – if do everything right for hormones but not getting right outcome, even after Receptor Detox and Hormone Balance and Protect, try adding in tyrosine.

- Tyrosine helps hormones work.
- And cognition.
- Tyrsosine increases dopamine availability that, in turn, enhances cognitive performance and sense of well-being.
- Foods high in dietary tyrosine include cheese, soybeans, beef, lamb, pork, fish, chicken, nuts, eggs, dairy, beans, and whole grains.
- Look at protein level in blood should be in 7's and albumin should be in 4's.

- Food for thought: association between dietary tyrosine and cognitive performance in younger and older adults. Psychol Res. 2019 Sep;83(6):1097-1106. doi: 10.1007/s00426-017-0957-4. Epub 2017 Dec 18. PMID: 29255945; PMCID: PMC6647184.

49



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Basics

- Estrogen has genomic (Two receptors: ER alpha ER beta) and non-genomic signaling (GPER G-protein coupled estrogen receptor
- Progesterone three receptors PR-A PR-B PR-C G-protein progesterone receptor)
- Testosterone (and DHT) has genomic Two receptors AR-A AR-B and G-protein testosterone receptor
- Signaling different receptors causes different reactions
- To say somethings is estrogenic may not be accurate as ER Alpha and ER Beta may have opposing actions.

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Same hormones signaling different receptors = different actions

- Estrrogen signals ER Alpha – genomic slower - promotes growth
- Estrogen signals ER beta – genomic slower controlled growth
- Estrogen signals GPER – instantaneously gut nervous system
- Same with progesterone
- Same with testosterone
- So there is a lot we do not yet know
- And more receptors being discovered all the time

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So, rapid actors in hormonal signaling system

- Are not just parathyroid, adrenal medulla and pancreas (and insulin)
- But the fasting acting sex steroids

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Hormone Basics

HORMONES

- Estrogens
- Progesterone
- Testosterones
- DHEA
- Cortisol
- Thyroid
- FSH
- Oxytocin
- Insulin

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Estrogen

- The three main estrogens in mammals are estrone, estradiol, and estriol.
- Estrone, or E_1, is a weak estrogen that rises after menopause. But the most proinflammatory estrogen. Measure estrone and estradiol in serum in adults, both genders, you want more estradiol than estrone to reduce inflammation and control growth.
- Estradiol, E_2, was long thought by scientists to be the "workhorse" of the three and most biologically active. This is because it signals "politically correct" to all three receptors.
- Estriol, E_3, the "weakest" of the three, has the highest concentration of any estrogen during pregnancy, and has been used by clinicians as a way to assess fetal well-being, but scientists have long dismissed it as insignificant.
- Now we know it rules epigenetics, especially in the fetus, protects against cancer, reduces inflammation, and is the " Good Estrogen Dominance".
- It upregulates adhesive proteins in the gut.
- It regulates ovulation in the ovary.
- We can use it clinically.

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Estrogen Scale

- It's the balance of receptors in tissues
- That maintains health of tissues
- **ER Alpha – growth**
- **ER Beta - controlled growth**
- Balance between maintains
- Zen health of local tissues from
- Endothelium to hippocampus
- To breast, prostate, fat cells,
- Etc.
- G-PER – instantaneous like gut sense and this
- Keeps expanding

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Estriol drives epigenetic change in mice

- "Humans and some other primates evolved a complex pathway of estriol production that's not seen in most animals," Taylor says. "It was made specifically in pregnancy for a particular function that nobody knew about until now."
- In their new study, a Yale team used estriol to treat pregnant mice, which don't naturally produce the hormone, to better understand its role in reproduction. They then looked at how its administration impacted the offspring's brain and uterus—two organs in mice that have evolved significantly in primates. They found that estriol led to improvements in factors including pregnancy rate, litter size, success of pregnancy, and uterus structure.
- Offspring also showed less anxiety and greater exploratory behavior.
- Next, the team looked for changes in gene expression when the baby mice reached adulthood that may explain these improvements. That generation's offspring revealed many genes that were differentially expressed as a result of the procedure.
- "These mice were exposed as a fetus when their mom was pregnant," says Taylor.
- "We saw permanent changes in gene expression that remained long after the exposure was done."

- The steroid hormone estriol (E_3) regulates epigenetic programming of fetal mouse brain and reproductive tract. BMC Biol. 2022 May 2;20(1):93. doi: 10.1186/s12915-022-01293-4. PMID: 35491423; PMCID: PMC9059368
- Yale School of Medicine May 03, 2022 Isabella Backman

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Estriol – epigenetic modifier

- The study also uncovered the mechanism through which estriol triggers epigenetic change.
- In contrast to estradiol, the binding of estriol to estrogen receptors on proteins tweaks it into a shape that allows it to bind to epigenetic modifiers, which in turn affects its binding to target genes.
- It is paradoxically a very strong estrogen when one looks at this novel estrogen action.
- "Estriol programs reproductive potential and brain function through epigenetic modification," says Hughes S Taylor MD.
- "It does this by allowing the estrogen receptor to bind with new binding partners that are epigenetic modifiers."
- Hugh Taylor, MDAnita O'Keeffe Young Professor of Obstetrics, Gynecology, and Reproductive Sciences and Professor of Molecular, Cellular, and Developmental Biology; Chair, Obstetrics, Gynecology & Reproductive Sciences; Chief of Obstetrics and Gynecology, Yale-New Haven Hospital

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The effects of “weak estrogens” in plastics

- In 2012, the U.S. Food and Drug Administration (FDA) banned the use of bisphenol A (BPA) in baby bottles and sippy cups. BPA, which is still found in many hard plastics, is a kind of “environmental estrogen”, or endocrine disrupter, a synthetic compound that has weak estrogen-like activity. “People would argue in favor of BPA saying, ‘This is a weak estrogen. It’s nowhere near the potency of estradiol, so it couldn’t possibly have any effect,’” says Taylor. “In reality, bisphenol A works through the same mechanism that estriol does and can interfere with the normal functions of estriol.”
- This research highlights how environmental estrogens like BPA may have the capacity to induce epigenetic programming changes in humans through a mechanism similar to estriol’s.
- So while BPA, like estriol, has often been dismissed as “weak,” it may still capable of having profound biological effects.
- In future studies, the team is seeking to better understand how other estrogens cause epigenetic programming and how to prevent dangerous exposures, especially in pregnant women. They are also interested in learning more about the genes that are regulated by estriol to gain a better understanding of the pathway.
- “Now that we understand this function and mechanism, we’re trying to define what agents in the environment interfere with human development and lead to problems later in life,” says Taylor.
- .Bisphenol A vs. Estriol

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Estriol protects fetal brain and future fertility

- The finding raises the fascinating possibility that if doing so is found to be safe, adding estriol at some point during human pregnancies might become a way to make those pregnancies safer and less prone to complications.
- **Background:** Estriol (E_3) is a steroid hormone formed only during pregnancy in primates including humans. Although E_3 is synthesized at large amounts through a complex pathway involving the fetus and placenta, it is not required for the maintenance of pregnancy and has classically been considered virtually inactive due to associated very weak canonical estrogen signaling. However, estrogen exposure during pregnancy may have an effect on organs both within and outside the reproductive system, and compounds with binding affinity for estrogen receptors weaker than E_3 have been found to impact reproductive organs and the brain. Here, we explore potential effects of E_3 on fetal development using mouse as a model system.
- **Results:** We administered E_3 to pregnant mice, exposing the fetus to E_3. Adult females exposed to E_3 in utero (E_3-mice) had increased fertility and superior pregnancy outcomes. Female and male E_3-mice showed decreased anxiety and increased exploratory behavior. The expression levels and DNA methylation patterns of multiple genes in the uteri and brains of E_3-mice were distinct from controls. E_3 promoted complexing of estrogen receptors with several DNA/histone modifiers and their binding to target genes. E_3 functions by driving epigenetic change, mediated through epigenetic modifier interactions with estrogen receptors rather than through canonical nuclear transcriptional activation.
- **Conclusions:** We identify an unexpected functional role for E_3 in fetal reproductive system and brain. We further identify a novel mechanism of estrogen action, through recruitment of epigenetic modifiers to estrogen receptors and their target genes, which is not correlated with the traditional view of estrogen potency.
- The steroid hormone estriol (E_3) regulates epigenetic programming of fetal mouse brain and reproductive tract. BMC Biol. 2022 May 2;20(1):93. doi: 10.1186/s12915-022-01293-4. PMID: 35491423; PMCID: PMC9059368.
- Measure estriol during pregnancy?

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Estriol (And 2 MEO) Can Be Used To Predict Preeclampsia Risk

- Estriol is produced by the placenta by the conversion of 16-hydroxy-dehydroepiandrosterone sulfate to androgens, which are subsequently aromatized to estriol.
- It has been hypothesized that impaired or reduced activity of placental sulfatase may lower the mid-trimester maternal levels of estriol.[134]
- In 1996, Santolaya-Forgas et al.[135] reported that women with unexplained low second-trimester maternal serum unconjugated estriol had an increased risk of adverse pregnancy outcomes, including preeclampsia, and suggested that measurements of this estrogen could be a useful predictor of complications of pregnancy.
- The accuracy of unconjugated estriol in predicting preeclampsia (using as cut-offs 0.50, 0.85, 0.86, and 0.90 MoM) was reported in five studies (n = 56,513).[118,119,124,136,137]
- In 2009, however, we have witnessed renewed interest in measuring estrogen metabolites for the prediction of preeclampsia. A recent article published in *Nature*[138] described a genetic mouse model of preeclampsia produced by knocking out the catechol-O-methyltransferase (COMT) gene, resulting in reduced 2-methoxyestradiol (2-ME) levels. The authors also reported that circulating levels of both COMT and 2-ME were significantly lower in women with severe preeclampsia, and were embarking on a large study to determine if 2-ME levels decrease before the appearance of human preeclampsia, and their applicability as a predictive test.
- Tests to Predict Preeclampsia Agustin Conde-Agudelo, ... Marshall D. Lindheimer, in Chesley's Hypertensive Disorders in Pregnancy (Third Edition), 2009

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Estriol maintains ovulation

- Estriol signals ER beta
- ER beta signals the corpus luteum to produce progesterone and oxytocin.
- Estriol rules ovulation. Thus you may use it to try to “reboot” ovulatory issues, knowing this physiololgy.

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Estriol Reboot – using estriol to treat premature ovarian failure

- **Abstract**
- **OBJECTIVE:**
- To evaluate the influence of short-term estriol administration (10 d) on the hypothalamus-pituitary function and gonadotropins secretion in patients affected by functional hypothalamic amenorrhea (FHA).
- **STUDY DESIGN:**
- Controlled clinical study on patients with FHA (n = 12) in a clinical research environment.
- **INTERVENTION(S):**
- Hormonal determinations and gonadotropin (luteinizing hormone [LH] and FSH) response to a gonadotropin-releasing hormone (GnRH) bolus (10 µg) at baseline condition and after 10 d of therapy with 2 mg/d of estriol per os.
- **MAIN OUTCOME MEASURE(S):**
- Measurements of plasma LH, FSH, prolactin, estradiol, androstenedione, 17α-hydroxyprogesterone, insulin, cortisol, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine.
- **RESULT(S):**
- After treatment, the FHA patients showed a statistically significant increase of both LH and FSH plasma levels and the significant increase of their responses to the GnRH bolus.
- **CONCLUSION(S):**
- Estriol short-term therapy modulates within 10 d of administration the neuroendocrine control of the hypothalamus-pituitary unit and induces the recovery of both gonadotropins synthesis and secretion in hypogonadotropic patients with FHA.

- Gynecol Endocrinol. 2016;32(3):253-7. doi: 10.3109/09513590.2015.1118452. Epub 2015 Dec 3.
- **Short-term estriol administration modulates hypothalamo-pituitary function in patients with functional hypothalamic amenorrhea (FHA).**

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Young Female

- 30 years old
- Severe anxiety, brain fog, shakes, joint pain
- Oligomenorrhea - Oligomenorrhea is defined as irregular and inconsistent menstrual blood flow in a woman
- FSH 150
- Gave Receptor Detox, Hormone B & Protect, pregnenolone, progesterone,
- Niacinamide
- Within one week no more anxiety

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Case Report – Estriol Reboot

- 29 years old premature ovarian failure
- Gave 10 mg of estriol
- TSH 2.98 Free T3 of 2.2
- She was on levothyroxine 75 mcg
- Added 5 mcg SR T3 or Biotics GTA II (three on rising, has active T3)
- Progesterone mid cycle higher dose halved dose all other days except menstruation should it occur
- Receptor Detox
- Hormone Balance & Protect
- Check thyroid (TSH, Free T3, Free T4, TBG) Many cases of infertility driven by subclinical hypothyroidism.

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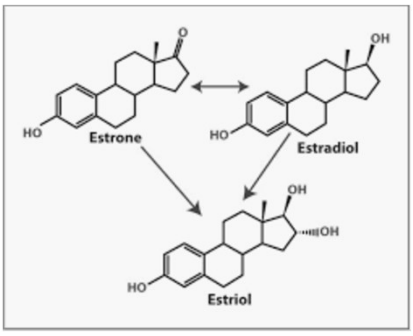
ESTRIOL

- Signals ER beta
- Controls ovulation
- Controls epigenetics
- Controls growth
- Anti-inflammatory
- Anti-carcinogenic
- Anti-sticky (lining of epithelium in blood vessels)
- Can be used in males also since such a weak acting estrogen (1/8th as potent as estradiol)



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Estriol Can be used with MS

- Reboot ovuation (estriol reboot)
- Decrease inflammation esp. in brain
- A PILOT TRIAL OF ESTRIOL TREATMENT IN MULTIPLE SCLEROSIS
- Because estriol is the major estrogen of pregnancy, and because an estriol dose that yielded a pregnancy level in mice was protective in EAE,[88] estriol was administered in a prospective pilot clinical trial to women with MS, in an attempt to recapitulate the protective effect of pregnancy on disease.[111]
- A crossover study was used whereby patients were monitored for 6 months before treatment to establish baseline disease activity; monitoring included cerebral MRI every month and neurologic examination every 3 months.
- The patients were then treated with oral estriol (8 mg/day) for 6 months, then observed for 6 more months in the post-treatment period.
- Six patients with RRMS and four with SPMS finished the 18-month study period. The RRMS subjects were then retreated with oral estriol and progesterone in a 4-month extension phase.
- Estriol treatment resulted in serum estriol levels that approximated levels observed in untreated, healthy control women who were 6 months pregnant.
- When PBMCs were stimulated ex vivo, a favorable shift in cytokine profile (decreased TNF-α, increased IL-10 and IL-5) was observed during treatment, compared with baseline.[112] On serial MRIs, the RRMS patients demonstrated an 80% reduction in gadolinium-enhancing lesions within 3 months of treatment, compared with pretreatment,[111] and this improvement correlated with the favorable shift in cytokine profiles.[112] Importantly, gadolinium-enhancing disease activity gradually returned to baseline in the post-treatment period, and the favorable cytokine shift also returned to baseline. Further, during the 4-month extension phase of the study, both the decrease in brain-enhancing lesions and the favorable immune shift returned on retreatment with estriol in combination with progesterone in the RRMS group. These latter data have important translational implications, because progesterone treatment is needed in combination with estrogen treatment to prevent uterine endometrial hyperplasia when estriol is administered for 1 year or longer. These results indicate that treatment with progesterone in combination with estriol did not neutralize the beneficial effect of estriol treatment on these biomarkers of disease. A multicenter, double-blind, placebo-controlled trial of estriol treatment in RRMS is now ongoing.
- MULTIPLE SCLEROSIS 3 Rhonda Voskuhl, in Blue Books of Neurology, 2010 A PILOT TRIAL OF ESTRIOL TREATMENT IN MULTIPLE SCLEROSIS

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Estriol RRMS

- Relapsing remitting MS is a type of MS where you have relapses (symptoms getting worse) followed by recovery (that's when it's "remitting"). Your disability doesn't get worse between relapses but after each relapse it can end up worse than before.
- More recently, a double-blind, placebo-controlled, multicenter phase 2 trial was conducted to test the safety and efficacy of oral estriol as an add-on treatment in women with RRMS (Voskuhl et al., 2016).
- 164 women aged 18–50 with RRMS were randomly assigned to receive either daily oral estriol (8 mg) or placebo, in combination with daily, injectable glatiramer acetate (20 mg).
- 60 patients receiving estriol and 56 patients in the placebo group finished the study. The primary study endpoint was annualized relapse rate after 24 months of treatment (significance level of sp = 0.10), as confirmed by increase in Expanded Disability Status Scale (EDSS) score.
- The study found an annualized confirmed relapse rate of 0.25 (95% CI 0.17–0.37) relapses per year in the estriol group and 0.37 (95% CI 0.37–1.05) relapses per year in the placebo group.
- The annualized relapse event rate and the time to confirmed relapse were also reduced in the estriol group.
- Estriol was well tolerated with no significant difference in serious adverse events between study groups. Importantly, posthoc MRI studies using volumetry at the 12-month time point showed less cortical gray matter atrophy in the estriol group that in the placebo groups.
- Further, patients in the estriol group without enhancing lesions had less gray matter atrophy than controls, suggesting a direct neuroprotective effect of estriol treatment that is independent of anti-inflammatory effects (Voskuhl et al., 2016). This latter finding suggests that future studies should evaluate estriol treatment in progressive disease. Overall, this recent trial demonstrates that a phase 3 trial of estriol in combination with glatiramer acetate is warranted.
- Clinically Important Hormone Effects on Brain and Behavior R. Voskuhl, Taia T. Wang, in Hormones, Brain and Behavior (Third Edition), 2017

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Estriol MS

- Estrogens have neuroprotective actions depending on estrogen type, dose, and timing in both preclinical models and in women during health and disease.
- Serum neurofilament light chain is a putative biomarker of neurodegeneration in multiple sclerosis, aging, and other neurodegenerative diseases.
- Here, oral treatment with an estrogen unique to pregnancy (estriol) using an 8 mg dose to induce a mid-pregnancy blood estriol level reduced serum neurofilament light chain in nonpregnant MS women at mean age of 37 years.
- This is consistent with estriol-mediated protection from neuro-axonal injury and supports the use of serum neurofilament light chain as a biomarker in MS.
- Decreased neurofilament light chain levels in estriol-treated multiple sclerosis. Ann Clin Transl Neurol. 2022 Aug;9(8):1316-1320. doi: 10.1002/acn3.51622. Epub 2022 Jun 29. PMID: 35770318; PMCID: PMC9380170.
- UCLA Multiple Sclerosis Program, Department of Neurology, David Geffen School of Medicine at the University of California, Los Angeles, California, USA.
- [2]Neurologic Clinic and Policlinic, Departments of Medicine, Biomedicine and Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland.
- [3]Jane and Terry Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California, USA.
- [4]Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, David Geffen School of Medicine at the University of California, Los Angeles, California, USA.

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Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration

- Multiple sclerosis (MS) is a disease characterized by inflammation and demyelination.
- Currently, the cause of MS is unknown. Experimental autoimmune encephalomyelitis (EAE) is the most common mouse model of MS.
- Treatments with the sex hormones, estrogens and androgens, are capable of offering disease protection during EAE and are currently being used in clinical trials of MS.
- Beyond endogenous estrogens and androgens, treatments with selective estrogen receptor modulators (SERMs) for estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) are also capable of providing disease protection.
- This protection includes, but is not limited to, prevention of clinical disease, reduction of CNS inflammation, protection against demyelination, and protection against axonal loss. In EAE, current efforts are focused on using conditional cell specific knockouts of sex hormone receptors to identify the in vivo targets of these estrogens and androgens as well as downstream molecules responsible for disease protection.
- University of California, Los Angeles, Department of Neurology, UCLA Multiple Sclerosis Program, 635 Charles E Young Drive South, Neuroscience Research Building 1, Room 479, Los Angeles, CA 90095, United States. rory.spence@ucla.edu
- Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. Front Neuroendocrinol. 2012 Jan;33(1):105-15. doi: 10.1016/j.yfrne.2011.12.001. Epub 2011 Dec 24. PMID: 22209870; PMCID: PMC3616506.

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Estriol boosts gray matter health (esp good if see white matter dx)

- Gray matter atrophy is an important correlate to clinical disability in multiple sclerosis (MS), and many treatment trials include atrophy as an outcome measure.
- Atrophy has been shown to occur in experimental autoimmune encephalomyelitis (EAE), the most commonly used animal model of MS.
- The clinical severity of EAE is reduced in estrogen-reated mice, but it remains unknown whether estrogen treatment can reduce gray matter atrophy in EAE.
- In this study, mice with EAE were treated with either estrogen receptor (ER)-α ligand or ER-β ligand, and diffusion tensor images (DTI) were collected and neuropathology was performed.
- DTI showed atrophy in the cerebellar gray matter of vehicle-treated EAE mice compared with healthy controls but not in ER-α or ER-β ligand-treated EAE mice.
- Neuropathology demonstrated that Purkinje cell numbers were decreased in vehicle-treated EAE mice, whereas neither ER ligand-treated EAE groups showed a decrease.
- This is the first report of a neuroprotective therapy in EAE that unambiguously prevents gray matter atrophy while sparing a major neuronal cell type. Fractional anisotropy (FA) in the cerebellar white matter was decreased in vehicle- and ER-β ligand-treated but not in ER-α ligand-treated EAE mice. Inflammatory cell infiltration was increased in vehicle- and ER-β ligand-treated but not in ER-α ligand-treated EAE mice. Myelin staining was decreased in vehicle-treated EAE mice and was spared in both ER ligand-treated groups. This is consistent with decreased FA as a potential biomarker for inflammation rather than myelination or axonal damage in the cerebellum in EAE.

- Estrogen treatment prevents gray matter atrophy in experimental autoimmune encephalomyelitis. J Neurosci Res. 2012 Jul;90(7):1310-23. doi: 10.1002/jnr.23019. Epub 2012 Mar 13. PMID: 22411609; PMCID: PMC3350614.

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White Brain Matter – identified on MRI

- White matter is made up of a large network of nerve fibers (axons) in your brain that allows the exchange of information and communication between different areas of your brain. It's called "white matter" because the nerve fibers are covered in a protective sheath called myelin, which gives the tissue its white color.
- The surface and deep areas of your brain contain gray matter, which gets its color from the cell bodies of neurons.
- For your white matter to be healthy, it needs good blood flow and nutrients.
- Decreased blood flow (ischemia) and nutrients to the white matter can cause damage to these nerve fibers (axons) including swelling, breaking and complete loss. Just as your lawn may not look healthy without watering and nutrients (sunlight and fertilizer), your brain can get damaged with poor blood flow and an unhealthy diet.

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Progesterone MS

- Experimental autoimmune encephalomyelitis (EAE), an induced model of Multiple Sclerosis presents spinal cord demyelination, axonal pathology and neuronal dysfunction.
- Previous work has shown that progesterone attenuated the clinical severity, demyelination and neuronal dysfunction of EAE mice (Garay et al., J. Steroid Biochem. Mol. Biol., 2008).
- Here we studied if progesterone also prevented axonal damage, a main cause of neurological disability. To this end, some axonal parameters were compared in EAE mice pretreated with progesterone a week before immunization with MOG(40-54) and in a group of steroid-free EAE mice. On day 16th after EAE induction, we determined in both groups and in control mice: a) axonal density in semithin sections of the spinal cord ventral funiculus; b) appearance of amyloid precursor protein (APP) immunopositive spheroids as an index of damaged axons; c) levels of the growth associated protein GAP43 mRNA and immunopositive cell bodies, as an index of aberrant axonal sprouting. Steroid-naive EAE mice showed decreased axonal density, shrunken axons, abundance of irregular vesicular structures, degenerating APP+ axons, increased expression of GAP43 mRNA and immunoreactive protein in motoneurons. Instead, EAE mice receiving progesterone treatment showed increased axonal counts, high proportion of small diameter axons, reduced APP+ profiles, and decreased GAP43 expression. In conclusion, progesterone enhanced axonal density, decreased axonal damage and prevented GAP43 hyperexpression in the spinal cord of EAE mice.
- Thus, progesterone also exerts protective effects on the axonal pathology developing in EAE mice.

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Protective effects of progesterone administration on axonal pathology in mice with experimental autoimmune encephalomyelitis

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- In conclusion, progesterone enhanced axonal density, decreased axonal damage and prevented GAP43 hyperexpression in the spinal cord of EAE mice. Thus, progesterone also exerts protective effects on the axonal pathology developing in EAE mice.
- Protective effects of progesterone administration on axonal pathology in mice with experimental autoimmune encephalomyelitis. Brain Res. 2009 Aug 4;1283:177-85. doi: 10.1016/j.brainres.2009.04.057. Epub 2009 Jun 2. PMID: 19497309.

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Roles of Progesterone, Testosterone and Their Nuclear Receptors in Central Nervous System Myelination and Remyelination

- Progesterone and testosterone, beyond their roles as sex hormones, are neuroactive steroids, playing crucial regulatory functions within the nervous system. Among these, neuroprotection and myelin regeneration are important ones.
- The present review aims to discuss the stimulatory effects of progesterone and testosterone on the process of myelination and remyelination.
- These effects have been demonstrated in vitro (i.e., organotypic cultures) and in vivo (cuprizone- or lysolecithin-induced demyelination and experimental autoimmune encephalomyelitis (EAE)). Both steroids stimulate myelin formation and regeneration by acting through their respective intracellular receptors: progesterone receptors (PR) and androgen receptors (AR). Activation of these receptors results in multiple events involving direct transcription and translation, regulating general homeostasis, cell proliferation, differentiation, growth and myelination. It also ameliorates immune response as seen in the EAE model, resulting in a significant decrease in inflammation leading to a fast recovery.
- Although natural progesterone and testosterone have a therapeutic potential, their synthetic derivatives-the 19-norprogesterone (nestorone) and 7α-methyl-nortestosterone (MENT), already used as hormonal contraception or in postmenopausal hormone replacement therapies, may offer enhanced benefits for myelin repair.
- We summarize here a recent advancement in the field of myelin biology, to treat demyelinating disorders using the natural as well as synthetic analogs of progesterone and testosterone.
- Protective effects of progesterone administration on axonal pathology in mice with experimental autoimmune encephalomyelitis. Brain Res. 2009 Aug 4;1283:177-85. doi: 10.1016/j.brainres.2009.04.057. Epub 2009 Jun 2. PMID: 19497309.

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Progesterone helps make myelin

- Progesterone is synthesized in the nervous system by neurons and glial cells. Because of their simple structure, plasticity and capacity of regeneration, peripheral nerves are particularly well suited for studying the biosynthesis, mechanisms of action and effects of the hormone.
- Schwann cells, the myelinating glial cells in the peripheral nervous system, synthesize progesterone in response to a diffusible neuronal signal.
- In peripheral nerves, the local synthesis of progesterone plays an important role in the formation of myelin sheaths.
- Progesterone synthesis and myelin formation in peripheral nerves. Brain Res Brain Res Rev. 2001 Nov;37(1-3):343-59. doi: 10.1016/s0165-0173(01)00139-4. PMID: 11744099.

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Neurosteroidogenesis and progesterone anti-inflammatory/neuroprotective effects

- Progesterone shows anti-inflammatory and promyelinating effects in mice with experimental autoimmune encephalomyelitis (EAE), a commonly used model for multiple sclerosis (MS).
- Because neurosteroids have been implicated as protective factors for MS and EAE, we analysed the expression of neurosteroidogenic enzymes in the compromised spinal cord of EAE mice.
- EAE was induced in female C57Bl6 mice, which were then killed on day 16 after induction. Progesterone was given by pellet implantation 1 week before EAE induction. Untreated EAE mice showed decreased mRNAs for the steroidogenic acute regulatory protein (Star), voltage-dependent anion channel (VDAC), cholesterol side-chain cleavage (P450scc), 5α-reductase, 3α-hydroxysteroid dehydrogenase (3α-HSOR) and aromatase, whereas changes of 3β-hydroxysteroid dehydrogenase (3β-HSD) were not significant. mRNA translocator protein (18 kDa) (TSPO) was elevated, concomitantly with a reactive microgliosis. EAE mice also showed abnormal mitochondrial ultrastructure in axons and neuronal bodies, as well as reduced expression of fission and fusion protein mRNAs. Progesterone pretreatment before EAE induction increased Star, VDAC, P450scc, 5α-reductase type I, 3α-HSOR and aromatase mRNAs and did not modify 3β-HSD. TSPO mRNA was decreased, possibly as a result of reversal of microgliosis. Progesterone pretreatment also improved mitochondrial ultrastructure and increased fission/fusion protein mRNAs. These mitochondrial effects may be part of the progesterone recovery of neurosteroidogenesis. The enzymes 3β-HSD, 3α-HSOR and 5α-reductase are also responsible for the formation of androgens. Because MS patients and EAE rodents show changes of central androgen levels, it is likely that, together with progestins and oestrogens, neuroandrogens afford neuroprotection for EAE and MS. The data reviewed suggest that enhanced synthesis of neurosteroids contributes in an auto/paracrine manner to reinforce the neuroprotective and anti-inflammatory effects of exogenous progesterone given to EAE mice.
- Neurosteroidogenesis and progesterone anti-inflammatory/neuroprotective effects. J Neuroendocrinol. 2018 Feb;30(2). doi: 10.1111/jne.12502. PMID: 28675779.

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Progesterone reduces neuroinflammation – why? PR receptors on neurons/myelin sheath.

- Previous studies of experimental autoimmune encephalomyelitis (EAE) have shown that progesterone decreases inflammatory cell infiltration and proinflammatory factors, increases myelination and attenuates clinical grade of EAE mice.
- To elucidate potential mediators of these effects, we analyzed the mRNA expression of neurosteroidogenic enzymes in the spinal cord, in view of the protective role of steroids in EAE.
- We also analyzed mitochondrial morphology and dynamics (fusion and fission proteins), considering the role of mitochondria in neurosteroidogenesis. EAE was induced in C57Bl6 mice using MOG_{40-54} and killed on day 16 after induction. Using qPCR, we found in steroid-untreated EAE mice decreased mRNAs for the steroidogenic acute regulatory protein (Star), voltage-dependent anion channel (VDAC), P450scc (cholesterol side-chain cleavage), 5α-reductase, 3α-hydroxysteroid dehydrogenase (3α-HSD) and aromatase, whereas levels of 3β-hydroxysteroid dehydrogenase (3β-HSD) showed a large intra-group variance. We also found increased mRNA expression of 18Kd translocator protein (TSPO), which likely resulted from the reactive microgliosis in this model. EAE mice also showed pathological mitochondrial morphology and reduced expression of fission and fusion protein mRNAs.
- \Most importantly, pretreatment with progesterone a week before EAE induction increased Star,VDAC, P450scc, 5α-reductase type I, 3α-HSD and aromatase mRNAs and did not modify 3β-HSD. TSPO mRNA was decreased, consequent with the inhibition of microgliosis. Mitochondrial morphology was improved and fission/fusion protein mRNAs were enhanced by progesterone treatment. Furthermore, progesterone protective effects on mitochondrial and endoplasmic reticulum may allow the recovery of neurosteroidogenesis. In this way, endogenously synthesized neurosteroids may reinforce the beneficial effects of exogenous progesterone previously shown in MS mice.
- Progesterone treatment modulates mRNA OF neurosteroidogenic enzymes in a murine model of multiple sclerosis. J Steroid Biochem Mol Biol. 2017 Jan;165(Pt B):421-429. doi: 10.1016/j.jsbmb.2016.09.001. Epub 2016 Sep 3. PMID: 27597394.

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Progesterone calms down reactive neuroglia cells (fights brain inflammation)

- Progesterone is a neuroprotective, promyelinating and anti-inflammatory factor for the nervous system. Here, we review the effects of progesterone in models of motoneurone degeneration and neuroinflammation. In neurodegeneration of the Wobbler mouse, a subset of spinal cord motoneurones showed increased activity of nitric oxide synthase (NOS), increased intramitochondrial NOS, decreased activity of respiratory chain complexes, and decreased activity and protein expression of Mn-superoxide dismutase type 2 (MnSOD2). Clinically, Wobblers suffered several degrees of motor impairment. Progesterone treatment restored the expression of neuronal markers, decreased the activity of NOS and enhanced complex I respiratory activity and MnSOD2. Long-term treatment with progesterone increased muscle strength, biceps weight and survival. Collectively, these data suggest that progesterone prevented neurodegeneration. To study the effects of progesterone in neuroinflammation, we employed mice with experimental autoimmune encephalomyelitis (EAE). EAE mice spinal cord showed increased mRNA levels of the inflammatory mediators tumour necrosis factor (TNF)α and its receptor TNFR1, the microglial marker CD11b, inducible NOS and the toll-like receptor 4.
- Progesterone pretreatment of EAE mice blocked the proinflammatory mediators, decreased Iba1+ microglial cells and attenuated clinical signs of EAE. Therefore, reactive glial cells became targets of progesterone anti-inflammatory effects. These results represent a starting point for testing the usefulness of neuroactive steroids in neurological disorders.

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Progesterone

- In mice with experimental autoimmune encephalomyelitis (EAE) pretreatment with progesterone improves clinical signs and decreases the loss of myelin basic protein (MBP) and proteolipid protein (PLP) measured by immunohistochemistry and in situ hybridization.
- Presently, we analyzed if progesterone effects in the spinal cord of EAE mice involved the decreased transcription of local inflammatory mediators and the increased transcription of myelin proteins and myelin transcription factors. C57Bl/6 female mice were divided into controls, EAE and EAE receiving progesterone (100mg implant) 7 days before EAE induction.
- Tissues were collected on day 17 post-immunization. Real time PCR technology demonstrated that progesterone blocked the EAE-induced increase of the proinflammatory mediators tumor necrosis factor alpha (TNFα) and its receptor TNFR1, the microglial marker CD11b and toll-like receptor 4 (TLR4) mRNAs, and increased mRNA expression of PLP and MBP, the myelin transcription factors NKx2.2 and Olig1 and enhanced CC1+oligodendrocyte density respect of untreated EAE mice. Immunocytochemistry demonstrated decreased Iba1+microglial cells. Confocal microscopy demonstrated that TNFα colocalized with glial-fibrillary acidic protein+astrocytes and OX-42+microglial cells.
- Therefore, progesterone treatment improved the clinical signs of EAE, decreased inflammatory glial reactivity and increased myelination. Data suggest that progesterone neuroprotection involves the modulation of transcriptional events in the spinal cord of EAE mice.
- Progesterone down-regulates spinal cord inflammatory mediators and increases myelination in experimental autoimmune encephalomyelitis. Neuroscience. 2012 Dec 13;226:40-50. doi: 10.1016/j.neuroscience.2012.09.032. Epub 2012 Sep 19. PMID: 23000619.

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Progesterone Lungs

- Wherever there are receptors for hormones
- They signal for a reason.
- Can inhibit lung cancer growth but may worsen some cases of fibrosis.
- Conclusions - In summary, the results of our study show that progesterone can inhibit lung adenocarcinoma cell growth via mPRα.
- Progesterone/Org inhibits lung adenocarcinoma cell growth via membrane progesterone receptor alpha. Thorac Cancer. 2020 Aug;11(8):2209-2223. doi: 10.1111/1759-7714.13528. Epub 2020 Jun 11. PMID: 32529777; PMCID: PMC7396388.

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Progesterone in addition to standard of care

- Background Severity of illness in COVID-19 is consistently lower in women. A focus on sex as a biological factor may suggest a potential therapeutic intervention for this disease. We assessed whether adding progesterone to standard of care (SOC) would improve clinical outcomes of hospitalized men with moderate to severe COVID-19.
- Research Question Does short-term subcutaneous administration of progesterone safely improve clinical outcome in hypoxemic men hospitalized with COVID-19?
- Study Design and Methods We conducted a pilot, randomized, open-label, controlled trial of subcutaneous progesterone in men hospitalized with confirmed moderate to severe COVID-19.
- 42 Patients were randomly assigned to receive SOC plus progesterone (100 mg subcutaneously twice daily for up to 5 days) or SOC alone. In addition to assessment of safety, the primary outcome was change in clinical status on day 7. Length of hospital stay and number of days on supplemental oxygen were key secondary outcomes.

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P - Covid Mt

- **Results** Forty-two patients were enrolled from April 2020 to August 2020; 22 were randomized to the control group and 20 to the progesterone group. Two patients from the progesterone group withdrew from the study before receiving progesterone.
- There was a 1.5-point overall improvement in median clinical status score on a seven-point ordinal scale from baseline to day 7 in patients in the progesterone group as compared with control subjects (95% CI, 0.0-2.0; *P* = .024).
- There were no serious adverse events attributable to progesterone.
- Patients treated with progesterone required three fewer days of supplemental oxygen (median, 4.5 vs 7.5 days) and were hospitalized for 2.5 fewer days (median, 7.0 vs 9.5 days) as compared with control subjects.
- **Interretation** Progesterone at a dose of 100 mg, twice daily by subcutaneous injection in addition to SOC, may represent a safe and effective approach for treatment in hypoxemic men with moderate to severe COVID-19.

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These authors made use of knowing P receptors are in lungs and help heal lungs from injury

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- Progesterone in Addition to Standard of Care vs Standard of Care Alone in the Treatment of Men Hospitalized With Moderate to Severe COVID-19: A Randomized, Controlled Pilot Trial. Chest. 2021 Jul;160(1):74-84. doi: 10.1016/j.chest.2021.02.024. Epub 2021 Feb 20. PMID: 33621601; PMCID: PMC7896492.
-

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Case Report chronic pulmonary 65 yo female

- Progesterone
- Her endocrinologist's response
- What he didn't realize

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HORMONES
Estrogen

- Estrogens are the last stop on the steroid pathway
- Estrogens are converted from Testosterone and DHEA (androgens) through aromatization
- Aromatization is a process of conversion through an enzyme from the androgens to estrogen
- Aromatization takes T to E
- It is based on genes and life style

- Modern life is upregulating aromatase activity
- Gynecomastica and feminization in males
- Hormonal imbalance and demand for more progesterone in females all the while the environment is more rife with anti-progestins

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T > E necessary such as in sex differentiation

- Aromatase is expressed in the gonads, placenta, brain, adipose tissue, bone, and highly in the parietal cells.
- Have to track in women and males on testosterone replacement.
- Hormone Balance and protect – grape seed extract
-

-
- Aromatase activity is increased by **age, obesity, insulin, gonadotropins, and alcohol**.
- It also appears to be enhanced in certain estrogen-dependent local tissue next to breast tissue, endometrial cancer, endometriosis, and uterine fibroids.
- And gynecomastica in males.
- Aromatase and gynecomastia. Endocr Relat Cancer. 1999 Jun;6(2):315-24. doi: 10.1677/erc.0.0060315. PMID: 10731125.

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Grape seed extract – nature's perfect AI

- Aromatase is the enzyme that converts androgen to estrogen. It is expressed at higher levels in breast cancer tissues than normal breast tissues. Grape seed extract (GSE) contains high levels of procyanidin dimers that have been shown in our laboratory to be potent inhibitors of aromatase. In this study, GSE was found to inhibit aromatase activity in a dose-dependent manner and reduce androgen-dependent tumor growth in an aromatase-transfected MCF-7 (MCF-7aro) breast cancer xenograft model, agreeing with our previous findings. We have also examined the effect of GSE on aromatase expression. Reverse transcription-PCR experiments showed that treatment with 60 mug/mL of GSE suppressed the levels of exon I.3-, exon PII-, and exon I.6-containing aromatase mRNAs in MCF-7 and SK-BR-3 cells. The levels of exon I.1-containing mRNA, however, did not change with GSE treatment. Transient transfection experiments with luciferase-aromatase promoter I.3/II or I.4 reporter vectors showed the suppression of the promoter activity in a dose-dependent manner. The GSE treatment also led to the down-regulation of two transcription factors, cyclic AMP-responsive element binding protein-1 (CREB-1) and glucocorticoid receptor (GR). CREB-1 and GR are known to up-regulate aromatase gene expression through promoters I.3/II and I.4, respectively. We believe that these results are exciting in that they show GSE to be potentially useful in the prevention/treatment of hormone-dependent breast cancer through the inhibition of aromatase activity as well as its expression.

- Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression. Cancer Res. 2006 Jun 1;66(11):5960-7. doi: 10.1158/0008-5472.CAN-06-0053. PMID: 16740737.

88

Melatonin – another natural AI

- The pineal hormone melatonin may exert a suppressive role on aromatase activity, leading to reduced estrogen biosynthesis. A melatonin-mediated decrease in the expression of aromatase promoters and associated genes would provide suitable evidence of this molecule's efficacy as an aromatase inhibitor. Furthermore, melatonin intensifies radiation-induced anti-aromatase effects and counteracts the unwanted disadvantages of chemotherapeutic agents. In this manner, this review summarizes the inhibitory role of melatonin in aromatase action, suggesting its role as a possible oncostatic molecule in breast cancer.

- Case History BC stage 4 on melatonin 40 mg throughout the day ended up with bone fractures.
- Melatonin as an Oncostatic Molecule Based on Its Anti-Aromatase Role in Breast Cancer. Int J Mol Sci. 2021 Jan 4;22(1):438. doi: 10.3390/ijms22010438. PMID: 33406787; PMCID: PMC7795758.

89

Melatonin AL (works in endothelium so great for plaque formers)

- We conclude that melatonin inhibits aromatase activity and expression in HUVECs by regulating gene expression of specific aromatase promoter regions, thereby reducing the local production of estrogens

- Melatonin modulates aromatase activity and expression in endothelial cells. Oncol Rep. 2013 May;29(5):2058-64. doi: 10.3892/or.2013.2314. Epub 2013 Feb 28. PMID: 23450505.

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Breast Cancer Patient

- Was put on melatonin throughout the day
- Started to fracture
- Too much melatonin in too young of a female – stop menstruation
- Safe Hormones, Smart Women Berkson DL Awakened Medicine Press

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Melatonin many benefits in cancer here's one:

- Most of the current knowledge about the mechanisms by which melatonin inhibits the growth of breast cancer cells point to an interaction of melatonin with estrogen-responsive pathways, thus behaving as an antiestrogenic hormone.
- However, a possible effect of melatonin on the local synthesis of estrogens had not been examined. The objective of this work was to study whether melatonin may modify the aromatase activity in MCF-7 breast cancer cells thus modulating the local estrogen biosynthesis. In MCF-7 cells cultured with testosterone in estradiol-free media, melatonin (1 nM) counteracts the testosterone-induced cell proliferation dependent on the local biosynthesis of estrogens from testosterone by the aromatase activity of the cells. We found that melatonin reduces the aromatase activity (measured by the tritiated water release assay) of MCF-7 cells both at basal conditions and when aromatase activity was stimulated by cAMP or cortisol.
- The greatest inhibition of the aromatase activity was obtained with 1 nm melatonin, the same concentration that gives the highest antiproliferative and anti-invasive effects of MCF-7 cells.
- Finally, by RT-PCR, we found that melatonin downregulates aromatase expression at the transcriptional level in the MCF-7 cells.
- We conclude that melatonin, at physiological concentrations, decreases aromatase activity and expression in MCF-7 cells.
- This aromatase inhibitory effect of melatonin, together with its already known antiestrogenic properties interacting with the estrogen-receptor, makes this indoleamine an interesting tool to be considered in the prevention and treatment of hormone-dependent mammary neoplasias.
- Melatonin modulates aromatase activity in MCF-7 human breast cancer cells. J Pineal Res. 2005 Mar;38(2):136-42. doi: 10.1111/j.1600-079X.2004.00186.x. PMID: 15683469.

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Wherever there are receptors, signals are delivered

- Androgens and estrogens are known to be critical regulators of mammalian physiology and development. While these two classes of steroids share similar structures (in general, estrogens are derived from androgens via the enzyme aromatase), they subserve markedly different functions via their specific receptors.
- For example. ER beta and alpha is all throughout the gut and ER beta is silenced in sync with polyp formation, dx and vulnerability to colorectal cancer.
- Same with esophagus, receptors especially for estrogen and oxytocin and vasopressin.
- In the past, estrogens such as estradiol were thought to be most important in the regulation of female biology, while androgens such as testosterone and dihydrotestosterone were believed to primarily modulate development and physiology in males.
- However, the emergence of patients with deficiencies in androgen or estrogen hormone synthesis or actions, as well as the development of animal models that specifically target androgen- or estrogen-mediated signaling pathways, have revealed that estrogens and androgens regulate critical biological and pathological processes in both males and females.
- In fact, the concept of "male" and "female" hormones is an oversimplification of a complex developmental and biological network of steroid actions that directly impacts many organs. In this Review, we will discuss important roles of estrogens in males and androgens in females.
- Impact of estrogens in males and androgens in females. J Clin Invest. 2019 May 1;129(5):1818-1826. doi: 10.1172/JCI125755. Epub 2019 May 1. PMID: 31042159; PMCID: PMC6486327.

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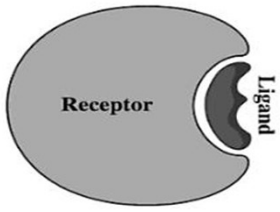
Target Tissue



Contains receptors

- All over the body
- Not just reproductive tissue
- Wherever there are receptors that tissue interacts with hormones
- Treg cells, adhesive proteins between enterocytes, hippocampus where memories live, vocal cords, liver to avoid fatty liver

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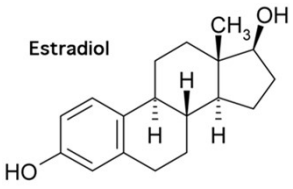
Example Estrogen (estradiol)



- Esophagus
- Kidney
- Brain
- Bone
- Eyes
- Mitochondria energy – yes hormones have a lot to do with mitochondrial functionality and health
- DNA histone epigenetics
- Estrogen is not just a sexy or reproductive hormone

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You can have a decrease in hormonal signaling due to:

- Decrease in hormone
- Blockage of hormone docking due to competitive inhibition
- Or due to hormonal resistance
- You can be resistant to any hormone not use insulin and thyroid, such as progesterone and leptin.

- Br J Obstet Gynaecol. 1998 Mar;105(3):345-51.
- **Progesterone resistance in women who have had breast cancer.**
- Journal of Biomedical Science 2014, 21:2

http://www.jbiomedsci.com/content/21/1/2

- **Endometrial progesterone resistance and PCOS**

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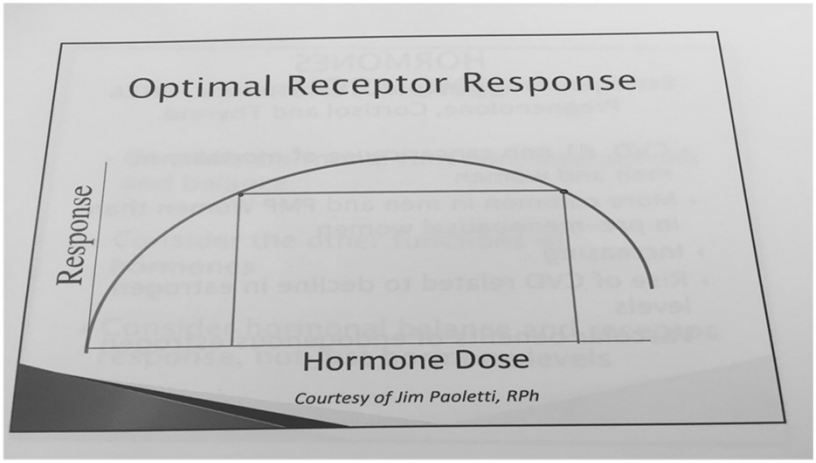
Too much not good, too little not good



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Sex Steroids Bind to Nuclear Receptors

- Nuclear receptors are a family of ligand-regulated transcription factors that are activated by steroid hormones, such as estrogen and progesterone, and various other lipid-soluble signals, including retinoic acid, and thyroid hormone.
- **Nuclear receptors are inactivated** until signaled by lipid-soluble signals (e.g., steroid hormones) that cross the plasma membrane.
- **Once activated**, most function as transcription factors to control gene expression for numerous biological processes.
- Unlike most intercellular messengers, the ligands can cross the plasma membrane and directly interact with nuclear receptors inside the cell, rather than having to act via cell surface receptors.
- But they can also act on cell surface membrane.
- Cold Spring Harb Perspect Biol. 2013 Mar; 5(3): a016709.
- doi: 10.1101/cshperspect.a016709 **Signaling by Nuclear Receptors**

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Jan-Åke Gustafsson PhD
Scientist of Receptor Physiology

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Estrogen Receptors

- ER alpha - growth
- ER beta – controlled growth
- **G protein-coupled estrogen**
- **receptor 1** - instantaneous
- Emotions
- Gut sense

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ER beta overlaps with oxytocin receptors

- In most parts of the body ER beta promotes calm, parasympathetic signaling, maintains gut health and the crypts where new gut cells are made daily
- ER beta protects the brain, central nervous system, enteric (gut nervous) system and the breast and prostate.
- In excess it can cause issues at the lining of blood vessels and in the uterus (linked to endometriosis)
- In corpus luteum ER beta overlaps oxytocin
- So net calming effect.

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Estrogen Metabolism

- In liver.
- In intestines.
- throughout body.
- Why?
- Estrogens are made endocrinologically and processed through liver (inactivated)
- And made locally throughout the body, intracrinology, and need to be metabolized, too.

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Controlled Growth = Less Cancer (And other diseases)

- ✓ **Pregnancy** causes more controlled growth as more estriol exposure. Often autoimmune diseases like MS and eczema to into remission due to estriol tightening gut junctions.
- ✓ **Iodine** helps produce estriol.
- ✓ **Estriol replacement** when on estrogen therapy.
- ✓ **Foods** help promote estriol-like signaling.
- ✓ Soy, Apigenin, Milk Thistle, Dandelion rhubarb, pomegranate, pinto beans, dandelion, resveratrol in grape skins

Steroids. 2015 Jul;99(Pt A):56-60. **Mechanisms of estrogen carcinogenesis: The role of E2/E1-quinone metabolites suggests new approaches to preventive intervention--A review.**

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Estrogen

- Controls mitochondria in brown fat
- Estrogen receptor α controls metabolism in white and brown adipocytes by regulating *Polg1* and mitochondrial remodeling. Sci Transl Med. 2020 Aug 5;12(555):eaax8096. doi: 10.1126/scitranslmed.aax8096. PMID: 32759275; PMCID: PMC8212422.
- The ERRα not only regulates an array of nuclear genes devoted to mitochondrial functions but also numerous mitochondrial DNA genes that ultimately culminates into this organelle's homeostasis. In fact, ERRα expression is correlated with genes whose functional products are part of the mitochondrial physiology.
- Studies have indicated that nearly half of the proteins encoded by the mitochondrial genome are regulated by ERRα.
- Furthermore, new findings also show that ERRα regulate mitochondrial biogenesis and recovery once damaged.
- Studies have indicated that nearly half of the proteins encoded by the mitochondrial genome are regulated by ERRα. Moreover, ERRα controls vital mitochondrial processes such as oxidative metabolism through a network of protein kinases and by regulating the expression of sirtuins like Sirt3. Furthermore, new findings also show that ERRα regulate mitochondrial biogenesis in association with PGC family co-activators such as PGC-1-related co-activator and PGC-1β and also via cross-talk with mitogen-activated protein kinase kinases and PI3K/(AKT) signaling. The current understanding of the pathways and networks shows strong influence of ERRα in coordinating mitochondrial physiology. This review focuses on the new advances made in understanding the complex and important interface between ERRα and mitochondrial physiology.

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Estrogen - Mitochondria

Estrogen protects

- Mitochondria in skeletal muscle.
- In both genders.
- Mitochondria: Target organelles for estrogen action. Postepy Hig Med Dosw (Online). 2017 Jun 8;71(0):454-465. doi: 10.5604/01.3001.0010.3828. PMID: 28665276.

Estrogen

- Estrogen enhances mitochondrial function by enhancing mitochondrial biogenesis and sustaining mitochondrial energy-transducing capacity.
- Mitochondria are an important target of estrogen.
- In both genders.
- Estrogen receptor-β in mitochondria: implications for mitochondrial bioenergetics and tumorigenesis. Ann N Y Acad Sci. 2015 Sep;1350:52-60. doi: 10.1111/nyas.12872. Epub 2015 Aug 24. PMID: 26301952.

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