Progesterone, Pregnenolone

Metabolites and Clinical Relevance

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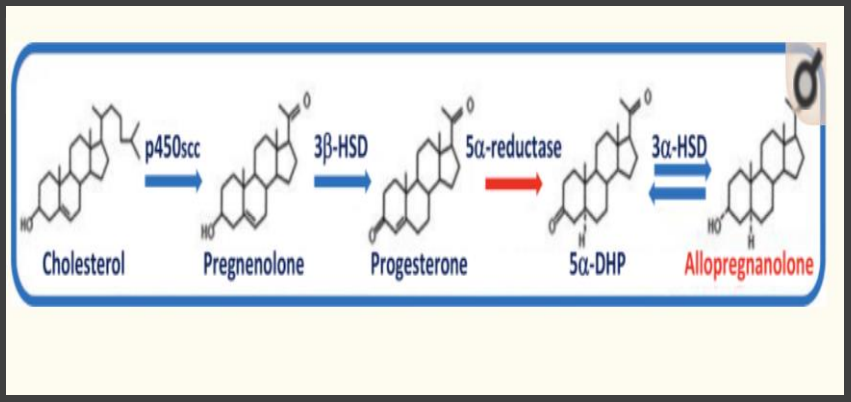

- **3 beta hydroxysteroid dehydrogenase** –
- Co-factor is NAD (niacin)

- **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
- Cofactor – nicotinamide/ niacin/B3

Pantothenic Acid (B5) + cholesterol to form Coenzyme A to then form pregnenolone

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.

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

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Niacin & B6
-Play large role in hormone homeostasis

- Niacin or vitamin B_3 is a water-soluble vitamin used by the body to form the **nicotinamide coenzyme, NAD^+**
- Dietary precursors of nicotinamide adenine dinucleotide (NAD), including nicotinic acid, nicotinamide, and nicotinamide riboside, are collectively referred to as niacin or vitamin B_3.
- The essential amino acid tryptophan can also be converted into NAD via the kynurenine pathway.
- Vitamin B-6 plays a major role in converting tryptophan to niacin.
- Quiet symptoms of B6 deficiency: bending hands in the AM, remembering dreams, fatigue.
- Causes of niacin deficiency include inadequate oral intake, poor bioavailability, oral contraceptives, pesticides, colorings, high fructose corn syrup, processed sugars and processed foods especially high in sugars, processed grains, defective tryptophan absorption, metabolic disorders, and the long-term use of chemo.
- NAD is the sole substrate for PARP enzymes involved in DNA repair activities; thus, **NAD is critical for genome stability**.
- In a recent phase III trial, a daily supraphysiologic dosages of nicotinamide was found to reduce the rate of premalignant skin lesions and nonmelanoma cancers in high-risk subjects.

3-beta hydroxsteroid dehydrogenase co-factors

- In the mitochondria, high levels of progesterone made by mitochondrial HSD
- Requires NAD
- Inhibited by nicotine and its metabolite cotinine - competitive inhibitors of HSD
- As the NAD resides in the mitochondria
- Converts pregnenolone to progesterone
- **Need good mitochondria functionality & NAD (or niacin) to produce adequate progesterone from pregnenolone**
- **That's why niacin is in both formulas to get perfect dose**
- **And to increase skin circulation, especially the face, for attractiveness without welting.**
- Reprod Biol Endocrinol. 2005; 3: 11. doi: 10.1186/1477-7827-3-11
- **Mitochondrial 3 beta-hydroxysteroid dehydrogenase (HSD) is essential for the synthesis of progesterone by corpora lutea: An hypothesis**

Production of Sex Steroid Hormones

- **Pantethine**, the *active form of pantothenic acid* (B5), is a critical nutrient for adrenal function as well as sex steroid synthesis.
- It is converted into an enzyme - co-enzyme A.
- CoA and cholesterol are used to produce pregnenolone which is the up-stream hormone that is converted into progesterone and other sex steroid hormones, or progesterone is converted into either aldosterone or cortisol.

Progesterone production

And it's neurosteroids

Require lots of B vitamins

Especially B6 and Niacin family (B3)

Elevated Acids suggesting B6 insufficiency, NAD insufficiency & steroid hormone imbalance

Chronic Disease Risk Factors

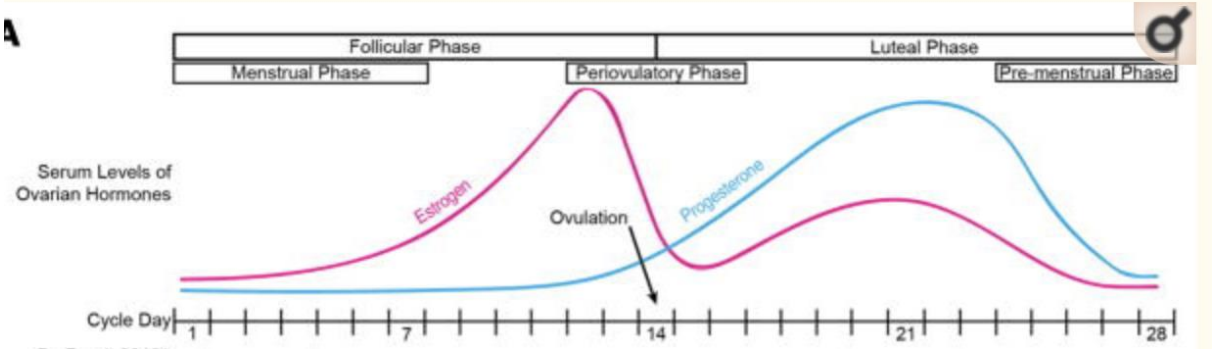
Metabolic Disease

Kynurenic Acid	**3.6**	mg/24hr	0.97 – 4.2
Xanthurenic Acid	**0.86**	mg/24hr	0.31 – 1.34

Kynurenic Acid and **Xanthurenic Acid** are products of tryptophan metabolism that rise in relation to levels of stress and inflammation in the body. High urinary levels may be an early warning sign for vitamin B6 deficiency, metabolic syndrome (insulin resistance) or type II diabetes, which increase the risk of cardiovascular disease, dementia, and other chronic diseases.[1-2] Protein-restricted diets or malabsorption may result in lower levels.

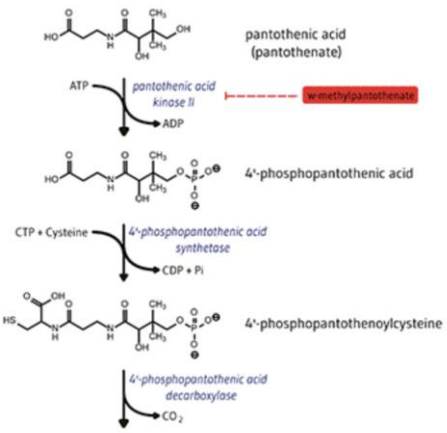
Brain Struct Funct. 2016 Nov; 221(8): 3845–3867. doi: 10.1007/s00429-016-1197-x

Estrogen- and progesterone-mediated structural neuroplasticity in women: evidence from neuroimaging



Pantothenic Acid is Precursor to Coenzyme A

Figure 1. Coenzyme A Synthesis from Pantothenic Acid

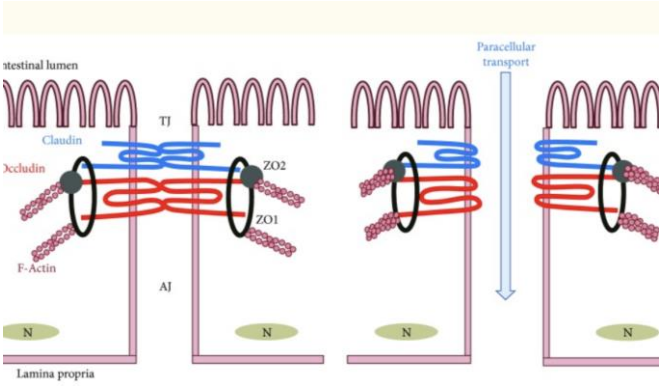


Progesterone's Actions

- Supports Pregnancy "Pro" "Gest"
- One of main pregnancy hormones
- Effects gut wall - this is why often see remission of autoimmune diseases during pregnancy (***occludin)***
- Opposes or helps "police" estrogen so why we see it control endometrial proliferation.
- Known to "oppose" estrogen's growth signals at lining of the uterus
- But also "polices" gut wall integrity
- Proven to protect endometrium with both progestins and bioidentical progesterone.

- Progesterone decreases gut permeability through upregulating occludin expression in primary human gut tissues and Caco-2 cells. Sci Rep. 2019 Jun 10;9(1):8367. doi: 10.1038/s41598-019-44448-0. PMID: 31182728; PMCID: PMC6558054.

Adhesive proteins forming Tight Junctions TJ - hormones



- **Four integral transmembrane proteins are:**
  - **Occludins (progesterone)**
  - **Claudins, (24 Claudin ¾ E2) PTH C14)**
  - **Junctional adhesion molecule (JAM) estriol and**
  - **Tricellulin (androgens)**

- J Immunol Res. 2018; 2018: 2645465. **Tight Junction in the Intestinal Epithelium: Its Association with Diseases and Regulation by Phytochemicals**
- **Mediators of Gut Mucosal Immunity and Inflammation Transcriptional Regulators of Claudins in Epithelial Tight Junctions.** Volume 2015 |Article ID 219843
- Regulation of tight junctions by sex hormones in normal human endometrial epithelial cells and uterus cancer cell line Sawano. Cell Tissue Res. 2013 Nov;354(2):481-94

Progesterone

- Mediates effects through progesterone receptor
- Which is part of the nuclear hormone receptor superfamily of transcription factors.
- PRs are widely distributed widely throughout the body not just on reproductive tissue – such as immune cells, including - granulocytes, NK cells, dendritic cells, T cells and B cells.
- In general, **progesterone switches the immune response from pro-inflammatory to anti-inflammatory**, favoring Treg cell differentiation and promoting down-regulation of IFN-γ production by NK cells, and glucocorticoid-mediated thymocyte apoptosis.

- Immunology. 2019 Jan; 156(1):9-22. doi: 10.1111/imm.13004
- **Impact of sex hormones on immune function and multiple sclerosis development**

Progesterone's many hats

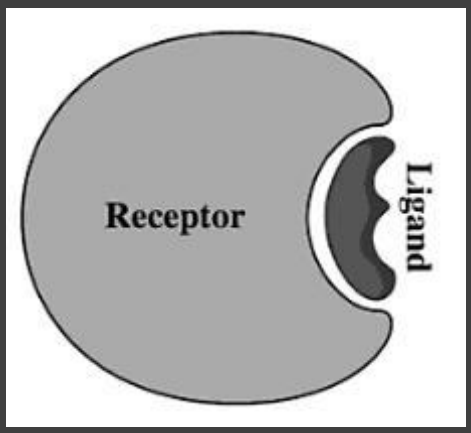
- Balancing hormone with estrogen for endometrial and breast protection
- Immunity
- Inflammation care-taker
- Brain/nervous system care-taker (anti-anxiety hormones)
- Gut wall (enterocytic) integrity
- Anti-anxiety hormone
- Prevents/treats leaky gut as upregulates adhesive protein occludin

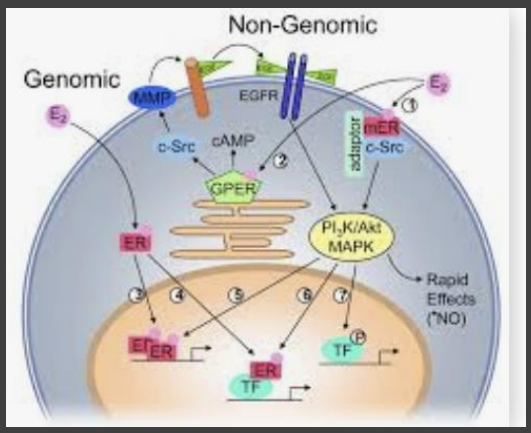
Case for why you don't want to give E without P even if a woman doesn't have a uterus

- Progesterone also mediates reduction of nitric oxide production and expression of toll-like receptors by macrophages and promotes Th2 differentiation *in vitro* as well as expression of co-stimulatory molecules such as CD80, CD86, and CD40, and MHC II.
- In C57BL/6 mice, progesterone therapy causes reduction in the severity of experimental MS model (EAE).
- Whereas estrogens need to be administered before EAE induction, progesterone treatment started as late as 2 weeks after MOG immunization still exerts beneficial effects.
- Immunology. 2019 Jan; 156(1):9-22. doi: 10.1111/imm.13004
- **Impact of sex hormones on immune function and multiple sclerosis development**

Progesterone – part of what keeps a young brain young

- Produced by corpus luteum
- But many tissues
- Can be converted to estradiol and testosterone; numerous P converting enzymes throughout the body.
- Ovary, testis, breast, liver, spleen, gut, brain.
- Numerous studies provided evidence that many of the same P-metabolizing enzymes also exist in tissues that are not directly associated with reproduction.
- These include various regions of the central and peripheral nervous systems (brain, cortex, spinal cord, olfactory bulb, optic lobe, medulla oblongata) **loss of smell as age is partially due to progesterone deficiency so this is one symptom**.
- Cortex corpus callosum, pineal, hypothalamus, pituitary, telencephalon, and neuronal and glial cells).
- **Hugely active in the brain.**
- **Progesterone Metabolites in Breast Cancer.** Endocrinology. 2019 Feb 1;160(2):430-446. doi: 10.1210/en.2018-00990.





Ligand Binding

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

Progesterone Signaling

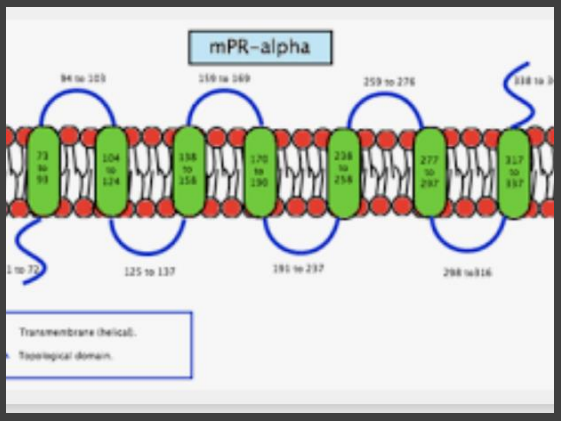
- Ligand binding,
- Slower acting.
- Activation of nuclear progesterone receptors (PRs),
- Two nuclear receptors: PR-A PR-B
- Subsequent activation of genes containing progesterone response elements (PREs) – **genomic** signaling.

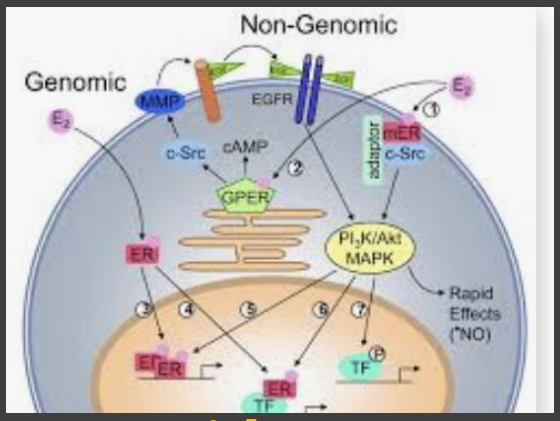
- Progesterone-Mediated Non-Classical Signaling. Trends Endocrinol Metab. 2017 Sep;28(9):656-668. doi: 10.1016/j.tem.2017.05.006. Epub 2017 Jun 23. PMID: 28651856.

Bi- Signals

- Also…
- **Non-Genomic-signaler.**
- Elicits a variety of rapid signaling events independently of transcriptional or genomic regulation.
- This rapid effect mostly takes place in the brain and nervous system to act to rapidly calm.

- Non-genomic progesterone actions in female reproduction. Hum Reprod Update. 2009 Jan-Feb;15(1):119-38. doi: 10.1093/humupd/dmn044. Epub 2008
- Physiology, production and action of progesterone. Acta Obstet Gynecol Scand. 2015 Nov;94 Suppl 161:8-16. doi: 10.1111/aogs.12771. PMID: 26358238.





Progesterone rapid signaling

Transmembrane Rapid Progesterone Actions

Anxiolytic

- Called seven-transmembrane receptors because they pass through the cell membrane seven times.
- Is 7 a holy number?
- Progesterone's calming effect is rapid.
- Like estrogen's treatment of pain/headache/gut is rapid.
- Both transmembraneous.

Progesterone – can affect GABA, oxytocin & Ca++ signaling.

- **It also effects several unrelated receptors,** such as gamma-aminobutyric acid type A (which is why we use it for anxiety) oxytocin (we use it to feel good with our world) and sigma(1) receptors (chaperone protein at the endoplasmic reticulum (ER) that modulates calcium signaling).
- Calcium signaling traffics things in and out of cells, so progesterone has global effects.
- Non-genomic progesterone actions in female reproduction. Hum Reprod Update. 2009 Jan-Feb;15(1):119-38. doi: 10.1093/humupd/dmn044. Epub 2008
- Physiology, production and action of progesterone. Acta Obstet Gynecol Scand. 2015 Nov;94 Suppl 161:8-16. doi: 10.1111/aogs.12771. PMID: 26358238.

Progesterone's Actions

- **Pregnancy**: Progesterone prepares the uterus for implantation of the fertilized ovum and causes the glandular elements of the mammary gland to grow and develop into the secretory epithelium, with the ultimate effect of acting with other hormones like prolactin.
- Helps breast become differentiated into a "milk machine".
- Balance of prolactin and progesterone at other times.
- Prolactin in excess is a dysphoric hormone.
- You can normalize elevated levels, with B6.
- Which is also a co-factor for tryptophan going to niacin and NAD to keep hormones safe.

Progesterone's Actions (growth controller)

- Breast and Endometrium : **Differentiator and anti-proliferator**
- Progesterone might be seen as the differentiating female sex steroid, which inhibits the proliferative effects of estrogen and
- directs the tissue toward its normal differentiated function.
- Regulates ovulation (together with oxytocin)
- Regulates sexual receptivity
- Regulates egg implantation
- Regulates proliferation at breast for differentiation into lactation.
- Regulates endometrial stripe to avoid hyperplastic activity.
- Progestin regulation of cellular proliferation. Endocr Rev. 1990;11(2):266-301.

First Vaginal Pass

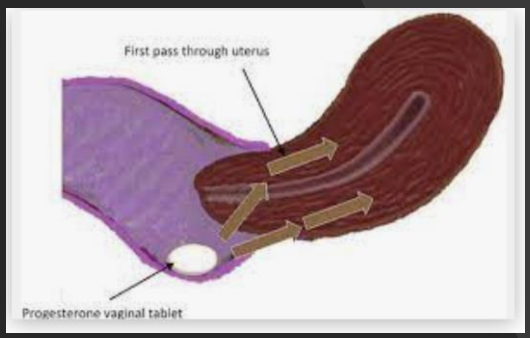
Vaginal progesterone is an effective alternative to systemic administration by oral or intramuscular use.

The first-pass effect is reviewed, as are the most common uses for this route of delivery.

This includes use in hormone replacement therapy, luteal support particularly in assisted reproduction, and avoidance of side-effects of oral progestins and progesterone.

Vaginal progesterone represents a unique therapeutic solution to a number of clinical problems.

Vaginal progesterone and the vaginal first-pass effect. Climacteric. 2018 Aug;21(4):355-357. Department of Endocrinology , Columbia University Medical Center , New York , NY , US



Progesterone

- PR plays a role in breast maintenance.
- Progesterone Receptor (PR), play an essential role in the regulation of **cell proliferation and differentiation** in the mammary gland.
- Regulates breast stem cells.
- The ligand-activated PR actions drive epithelial cell proliferation and the regulation of the stem cell population in the normal breast and breast cancer.
- A critical role in controlling mammary gland tumorigenesis and breast cancer development.

- Progesterone Receptor Signaling Mechanisms. J Mol Biol. 2016 Sep 25;428(19):3831-49. doi: 10.1016/j.jmb.2016.06.020. Epub 2016 Jul 2. PMID: 27380738.
- Molecular mechanisms underlying progesterone receptor action in breast cancer: Insights into cell proliferation and stem cell regulation. Steroids. 2019 Dec;152:108503. doi: 10.1016/j.steroids.2019.108503. Epub 2019 Sep 25. PMID: 31562879.

Progesterone instantaneous signals - mPRs

- Novel novel G protein-coupled receptors
- Rapid cell surface-initiated progesterone actions
- Membrane Progesterone Receptors (mPRs) mPRa mPRb
- mPRs highly expressed in the brain.
- The neurosteroid, allopregnanolone, is an effective ligand for recombinant mPRα with a relative binding affinity of 7.6% that of progesterone. So oral progesterone binds to mPRalpha better than allopregnanolone. But both do.
- So… **mPRs mediate neuroprotective** effects of progesterone and allopregnanolone.

- Membrane progesterone receptors: evidence for neuroprotective, neurosteroid signaling and neuroendocrine functions in neuronal cells. Neuroendocrinology. 2012;96(2):162-71. doi: 10.1159/000339822. Epub 2012 Sep 14. PMID: 22687885; PMCID: PMC3489003

Progesterone actions - ER alpha modulator

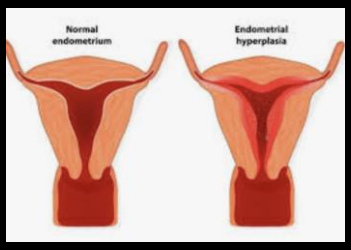
- Modulator of estrogen (some call it “Policer”)
- PR is not merely an ERα-induced gene target but also an ERα-associated protein that modulates its behavior.
- It does this at the endometrium to control excessive proliferation.
- And at the breast.
- Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev. 2016 Jul 26;5(1):121. doi: 10.1186/s13643-016-0294-5. PMID: 27456847; PMCID: PMC4960754.

Anti-proliferative (at the endometrium)

- Progesterone acts physiologically to counteract the proliferative effects of estradiol during the menstrual cycle.
- In postmenopausal women on HRT, progestogens protect the endometrium against the proliferative effects of estrogens in women with a uterus.
- A 1995 meta-analysis of 30 studies reported that use of estrogen alone was associated with a 2.3-fold increased risk of endometrial cancer as compared with no hormone use or without progesterone.

- Progesterone, progestins and the endometrium in perimenopause and in menopausal hormone therapy. Climacteric. 2018 Aug;21(4):321-325. doi: 10.1080/13697137.2018.1446932. Epub 2018 Mar 27. PMID: 29583028.

Endometrial stripe



- In menopause be 5 mm or below
- If not, in most cases, in adequate progesterone replacement, or oral progesterone not leaving sufficient unadulterated progesterone
- To protect uterine lining
- Abnormally thick can be sign of cancer, or insufficient progesterone when replacing estrogen.

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Progesterone's Actions – Breast Protector

Anti-proliferative at the breast

- A meta-analysis of 3 studies involving 86 881 postmenopausal women reported that the use of natural progesterone was associated with a significantly lower risk of breast cancer compared with synthetic progestins.
- Anovulation and low levels of serum progesterone have been associated with a significantly higher risk of breast cancer in premenopausal women.
- *Use of progesterone has been linked to lower rates of uterine and colon cancers and may also be useful in treating other cancers such as ovarian, melanoma, mesothelioma, and prostate.*

- In Defense of Progesterone: A Review of the Literature. Altern Ther Health Med. 2017 Nov;23(6):24-32. PMID: 29055286.
- Progesterone vs. synthetic progestins and the risk of breast cancer: A systematic review and meta-analysis. Syst Rev.
- 2016;5(1):121.
- Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. Breast Cancer Res Treat. 2008;107(1):103-111.

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Anti-proliferative (Global Cancers)

- Use of progesterone has been linked to lower rates of uterine and colon cancers and may also be useful in treating other cancers such as ovarian, melanoma, mesothelioma, and prostate.
- The WHI study reported that use of HRT containing estrogens and progestin significantly reduced the risk of colon cancer, by 28%.

- In Defense of Progesterone: A Review of the Literature. Altern Ther Health Med. 2017 Nov;23(6):24-32. PMID: 29055286.
- Progesterone vs. synthetic progestins and the risk of breast cancer: A systematic review and meta-analysis. Syst Rev.
- 2016;5(1):121.
- Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. Breast Cancer Res Treat. 2008;107(1):103-111.

Progesterone Malignant Melanoma

- *Progesterone inhibits the growth of progesterone-negative, malignant melanoma cells*.
- Progesterone is effective in downregulating proliferation and increasing apoptosis via mPRs.
- A review of 22 published studies involving 31 407 patients with malignant melanoma reported that 17 studies showed a significant survival advantage for females, suggesting that **progesterone may be useful in controlling malignant melanoma**.
- Survival in mesothelioma was significantly better in 24 females, with 15 younger than 51 years old, than in 28 males, suggesting that progesterone may be protective.
- **Progesterone was found to induce apoptosis in malignant mesothelioma cells**.

Citations Malignant Melanoma

- Effects of progesterone on the growth regulation in classical progesterone receptor-negative malignant melanoma cells. J Huazhong Univ Sci Technolog Med Sci. 2010;30(2):231-234.
- Gender and cutaneous melanoma. Br J Dermatol. 1997;136(5):657-665.
- Effects of sex hormones on survival of peritoneal mesothelioma. World J Surg Oncol. 2015;13:210.
- Progesterone induces apoptosis in malignant mesothelioma cells. Anticancer Res. 2001;21(6a):3871-3874.

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Breast Cancer

- Lower serum progesterone levels linked to poorer survival from breast cancer.
- Especially prior to surgery.
- **A study of 289 premenopausal women with breast cancer reported that overall survival was significantly better among women with progesterone levels exceeding 4 ng/mL.**
- Fifteen-year survival was approximately 80% in women with progesterone levels exceeding 4 ng/mL and approximately 60% in women with progesterone levels lower than 4 ng/mL.

- Serum progesterone and prognosis in operable breast cancer. Br J Cancer. 1996;73(12):1552-1555.
- Safe Hormones, Smart Women Berkson DL Awakened Medicine Press 2000

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Breast Cancer –

- Because progesterone levels are significantly higher during the luteal phase in premenopausal women, some researchers believe that the timing of premenopausal breast cancer surgery may affect breast cancer prognosis.
- **A 2000 meta-analysis reported that premenopausal breast cancer survivorship was improved by an estimated 15% if the surgery was performed during the luteal phase with relatively high serum progesterone**.
- A recent review of 58 studies— 10 in the United States and 48 internationally—reported that premenopausal breast cancer survivorship improved significantly in 20 studies when surgery was performed during the luteal phase and was significantly better in 8 studies when it was performed in the follicular phase, but no significant difference in survivorship existed between the 2 phases in 30 studies.
- Timing of breast cancer surgery in relation to the menstrual cycle: The rise and fall of a hypothesis. Acta Oncol. 2008;47(4):576-579.
- Timing of breast cancer surgery, menstrual phase, and prognosis: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2016;102:1-14.

Progesterone - breast

- Studies with humans and monkeys suggest that natural progesterone may reduce breast tissue proliferation, whereas synthetic progestins, such as MPA, may increase it. Progestins inhibit ER beta.
- One study treated 40 premenopausal women who had breast cancer with a topical gel containing either estrogen, natural progesterone, a combination of estrogen and progesterone, or a placebo, for 10 to 13 days preceding breast cancer surgery.
- Analysis of breast tissue reported that mean mitosis per 1000 cells was significantly higher in women treated with estrogen alone and was significantly lower in women treated with progesterone as compared with women treated with a placebo.
- The mean mitosis per 1000 cells was 0.51 for the placebo-treated patients, 0.17 for the patients receiving progesterone, 0.83 for the patients receiving estrogen, and 0.52 for the patients receiving a combination of estrogen and progesterone.

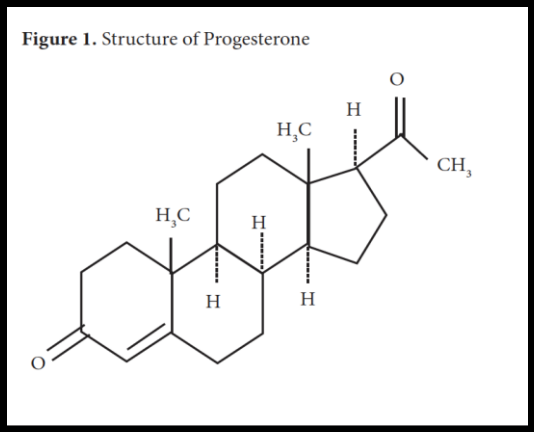
- Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril. 1995;63(4):785-791.

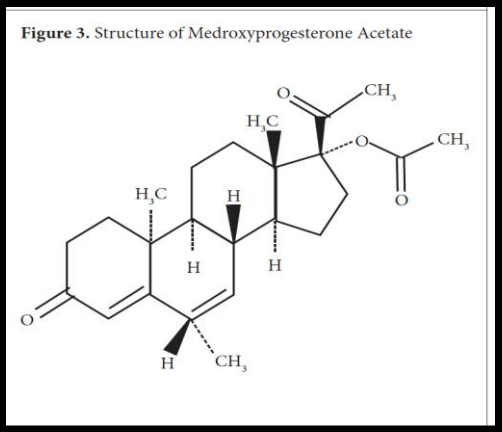
Progesterone - Human Trial Breast Cells

- To study the effect of E2 and P on the epithelial cell cycle of normal human breast in vivo.
- **DESIGN:** Double-blind, randomized study. Topical application to the breast of a gel containing either a placebo, E2, P, or a combination of E2 and P, daily, during the 10 to 13 days preceding breast surgery.
- **PATIENTS:** 40 premenopausal women undergoing breast surgery for the removal of a lump. MAIN OUTCOME MEASURES. Plasma and breast tissue concentrations of E2 and P. Epithelial cell cycle evaluated in normal breast tissue areas by counting mitoses and proliferating cell nuclear antigen immunostaining quantitative analyses.
- **RESULTS:** Increased E2 concentration increases the number of cycling epithelial cells.
- Increased P concentration significantly decreases the number of cycling epithelial cells.
- **CONCLUSION:** Exposure to P for 10 to 13 days **reduces E2-induced proliferation** of normal breast epithelial cells in vivo.
- Fertil Steril. 1995 Apr;63(4):785-91. **Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo.**

Holtorf Bioidentical Hormones

- Published papers were identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT. Papers that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and in vitro results, were selected.
- **RESULTS:**
- Both physiological and clinical data have indicated that **progesterone is associated with a diminished risk for breast cancer, compared with the increased risk associated with synthetic progestins.**
- *Synthetic progestins have a variety of negative cardiovascular effects, which may be avoided with natural progesterone.*
- Postgrad Med. 2009 Jan;121(1):73-85. doi: 10.3810/pgm.2009.01.1949. **The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?**





Progesterone vs. Progestins

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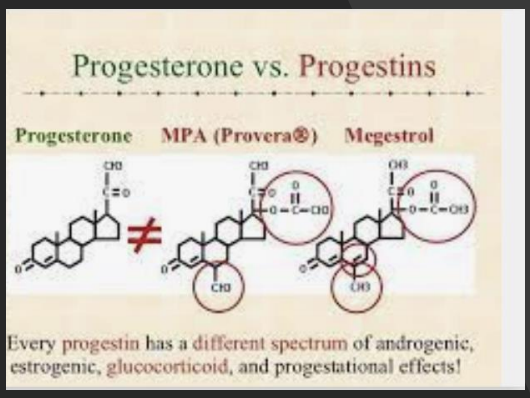
Progesterone vs. progestins

- We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus through 17 May 2016 for studies that enrolled postmenopausal women using progesterone vs. synthetic progestins and reported the outcomes of interest.
- We included two cohort studies and one population-based case-control study out of 3410 citations identified by the search. The included studies enrolled 86,881 postmenopausal women with mean age of 59 years and follow-up range from 3 to 20 years.
- **Progesterone was associated with lower breast cancer risk compared to synthetic progestin**.
- **CONCLUSIONS: Observational studies suggest that in menopausal women, estrogen and progesterone use may be associated with lower breast cancer risk compared to synthetic progestin.**
- **Birth control pills contain synthetic progestins and may be how they are linked to increase risk of bc.**
- Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev. 2016 Jul 26;5(1):121. doi: 10.1186/s13643-016-0294-5. PMID: 27456847; PMCID: PMC4960754.



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Bioidentical Progesterone safer for breasts

- Controlled studies and most observational studies published over the last 5 years suggest that the addition of synthetic progestins to estrogen in hormone replacement therapy (HRT), particularly in continuous-combined regimen, increases the breast cancer (BC) risk compared to estrogen alone.
- By contrast, a recent study suggests that the addition of natural progesterone in cyclic regimen**s does not affect BC risk.**
- More importantly, the progestins used (medroxyprogesterone acetate and 19-Nortestosterone-derivatives) are endowed with some non-progesterone-like effects, which can potentiate the proliferative action of estrogens.
- J Steroid Biochem Mol Biol. 2005 Jul; 96(2): 95–108. doi: 10.1016/j.jsbmb.2005.02.014
  Progestins and progesterone in hormone replacement therapy and the risk of breast cancer

Progesterone - Breast

- In order to investigate the nature of the association of involuntarily delayed 1st birth and breast cancer risk, 1083 white women who had been evaluated and treated for in fertility from 1945-65 were followed prospectively through April 1978 to ascertain their breast cancer incidence.
- These women were categorized as to the cause of infertility into 2 groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH).
- Women in the PD group had 5.4 times the risk of premenopausal breast cancer as compared to women in the NH group
- This excess risk could not be explained by differences between the 2 groups in age at menarche or age at menopause, history of oral contraceptive use, history of benign breast diseases, or age at 1st birth.
- *Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasm compared to the NH* group. The incidence of postmenopausal breast cancer did not differ significantly between the 2 groups. (because all postmenopausal women unless replaced will be P deficient).
- Am J Epidemiol. 1981 Aug;114(2):209-17. **Breast cancer incidence in women with a history of progesterone deficiency.**

Progestins – ER beta

- Some block ER beta activity
- Remember ER beta protects breast tissue from excessive proliferation
- This is how testosterone protects excessive proliferation is by its metabolite 3-beta-diol.
- A metabolite of DHT, 5-alpha-androstane-3-beta-17-beta-diol (3-beta-diol), once considered inactive, is also present in high concentrations in the male and indeed has biological activity. 3-beta-diol does not bind to the androgen receptor, but rather to estrogen receptors ER-alpha and ER-beta, with higher affinity for ER-beta.

- Reprod Biol Endocrinol. 2006; 4: 51. doi: 10.1186/1477-7827-4-51
- **Effects of 3-beta-diol, an androgen metabolite with intrinsic estrogen-like effects, in modulating the aquaporin-9 expression in the rat efferent ductules**
- A-ring reduced metabolites of 19-nor synthetic progestins as subtype selective agonists for ER alpha. Endocrinology. 2001 Sep;142(9):3791-9. doi: 10.1210/endo.142.9.8401. PMID: 11517155.

Progesterone Resistance

- To investigate whether certain physiological responses to luteal progesterone are normal in women previously treated for breast cancer.
- **DESIGN:** Salivary progesterone concentrations, basal body temperatures, and breast blood flow changes (surface temperature method) were all recorded daily for one natural menstrual cycle.
- 25 controls were compared with 30 women with previous breast cancer; all but three participants were parous and the average ages were 39 years (range 28-48) and 40 years (range 29-46), respectively. On average the women with previous breast cancer had had surgery 2.4 years previously; the operation was usually mastectomy, leaving the contralateral breast for study.
- **RESULTS:** Follicular phase (day 1-14) oral temperature averages were statistically indistinguishable between women in the control group and those with previous breast cancer. Luteal progesterone profiles were considered in the normal range for the controls and patients. However, the women with previous breast cancer, on average, exhibited a significantly smaller rise in the luteal phase basal body temperature. Follicular phase breast surface temperature was significantly higher in the breast cancer group (+0.30 degree C). This group showed a highly significant reduction of the luteal heat cycle in their breasts.
- **CONCLUSIONS:** Two progesterone-mediated physiological mechanisms have been found to be significantly less responsive in women with previous breast cancer than controls. The literature has been reviewed. **Progesterone resistance could be a clinical entity and could be important in carcinogenesis.**
- Br J Obstet Gynaecol. 1998 Mar;105(3):345-51. **Progesterone resistance in women who have had breast cancer.**

Symptoms of Progesterone deficiency

- Severe menorrhagia
- Severe dysmenorrhea
- Mid-cycle breakthrough bleeding
- Miscarriages
- Anxiety
- Insomnia
- Mood dysregulation and even possibly aggressive atypical behaviors
- PMS (Katerina Dalton MD)
- History of fibroids, polyps, anxiety prior to menses, atypical early bone loss.
- And since all hormones function and dysfunction together, may be associated with other hormonal issues.

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Cycling

- When giving progesterone cycle
- It has been common to give day 15 to 25
- Or if can't sleep without it give it double 2 weeks out of the month and half the other weeks

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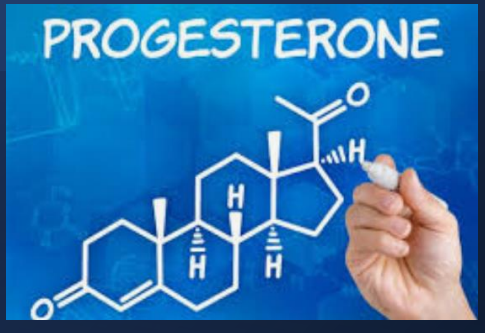
Progesterone Delivery Pathways

- Progesterone acts as a “rheostat” to control ER alpha at the breast.
- Progesterone receptors (PRs) are key modifiers of estrogen receptor (ER) target genes and drivers of luminal breast cancer progression.
- But… what is the best way to get progesterone to the breast.
- And… Progesterone is being found to have opposing pathways.
- It can be metabolized down protective and proliferative pathways.

- Nature. 2015 Jul 16;523(7560):313-7. doi: 10.1038/nature14583. **Progesterone receptor modulates ERα action in breast cancer.**
- Endocrinology. 2019 Feb 1;160(2):430-446. doi: 10.1210/en.2018-00990.
- **Phosphorylated Progesterone Receptor Isoforms Mediate Opposing Stem Cell and Proliferative Breast Cancer Cell Fates.**
- Doctors who concur have women bleed to reduce prolonged chronic progesterone exposure. **Progesterone Metabolites in Breast Cancer.** Endocrinology. 2019 Feb 1;160(2):430-446. doi: 10.1210/en.2018-00990.

Issues with Oral Progesterone? -

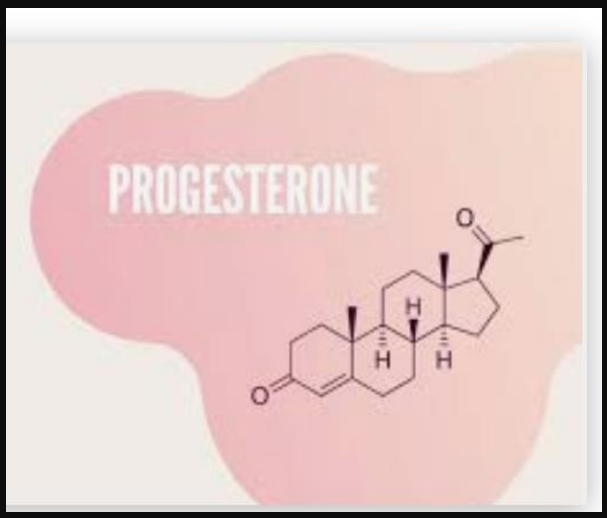


Delivery Modes for HRT

- Oral (sustained release, fast acting)
- Sublinqual
- Topical (added to a base/oil)
- Mucosal (sublinqual, vaginal added to a base)
- Vaginal
- IM
- IV

Which delivery mode

- Delivers the best "**controlled growth**" signals
- At the breast
- At the uterus



Oral vs.

- **Orally** administered progesterone is quickly and thoroughly **metabolized by both the prehepatic gut microflora and then the hepatic (liver)** first pass metabolism,
- Such that very **little unadulterated progesterone** makes it to the breast and uterine tissues.
- In studies by Adlercreutz, Nahoul and Levine, consistently see that oral progesterone is quickly converted to metabolites and that **blood and tissue levels never reach significant levels.**

- Biliary excretion and intestinal metabolism of progesterone and estrogen in man. J Steroid Biochemistry. 1980;13:231-244.
- Comparison of the pharmacokinetics of Crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women. Fertility & Sterility. March 2000;73 (3).
- Profiles of plasma estrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone. Maturitas. 1993;16:185-202.

Oral Progesterone

- Metabolites made within 20 minutes
- Pregnanolone & Allopregnanolone
- Great to calm the nervous system and brain
- Assist with deeper restorative sleep
- Rapid breakdown
- Poorer tissue levels vs. topical/vaginal
- So often just increase the oral dose.
- But in some women this then increases pro-inflammatory pregnane metabolites

- Wiebe J. Progesterone metabolites in breast cancer. Endocrine-Related Cancer. 2006;13: 717–738.
- Wiebe JB, Pawlak KJ, Kwoka A. Mechanism of action of the breast cancer-promoter hormone, 5a-dihydroprogesterone (5aP), involves plasma membrane-associated receptors and MAPK activation. J Steroid Biochemistry & Molecular Biology. 2016;155:166–176.
- Wiebe JP, et al. Progesterone metabolites regulate induction, growth, and suppression of estrogen- and progesterone receptor-negative human breast cell tumors. Breast Cancer Research. 2013, 15:R38.

Much of oral progesterone

- Goes into healthy metabolites.
- But doesn't deliver a lot of controlled growth progesterone.
- To the uterus and especially the breast.

Oral Progesterone

- **Progesterone** is metabolized into pregnanolone & allopregnanolone.
- Progesterone unadulterated from oral lasts about 5 minutes
- Rapidly made into brain hormones (neuro-steroids)
- Potent signalers of GABA (relaxing neurotransmitter)
- Calming neurotransmitter and sleep reboot
- Progesterone un-adulatered **topically** lasts several hours longer than oral.

Oral Progesterone endometrium

- There are dozens of studies exploring the use of oral progesterone to protect the endometrium, showing a wide range of effects depending on dose; but a few consistent findings emerge.
- Oral progesterone can provide endometrial protection; but consistently the studies show that even at lower doses such **as 50 to 100 mg of oral progesterone there is still risk of endometrial proliferation.**
- Even studies of progestins are not perfect and will display a small percentage of proliferative change.
- As doses ascend to 400 mg of oral progesterone, that risk expectantly decreases.
- Dalton used 400 to 900 mg with vaginal suppositories; pregnant women make up to 400 mg/day.

Vaginal vs. Oral

- The study by Levine and Watson is the most compelling evidence.
- They administered either 90 mg of vaginal progesterone or 100 mg of oral and then measured blood values.
- **The vaginal progesterone gel dramatically out-performed the oral**, generating a C-max reading of 10.51 ng/ml compared to the oral progesterone's mere 2.2 ng/ml.
- Not only was the gel greater in peak concentration, it also produced a **long-term effect lasting many more hours than the oral dose.**
- Based upon these findings, **aggressive metabolism of orally administered progesterone could leave the uterus and breast tissue unprotected.**
- Comparison of the pharmacokinetics of Crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women. Fertility & Sterility. March 2000;73 (3).

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Jonet Study 2002

- 336 postmenopausal women were given 1.5 mg of topical estradiol daily for 24 days per month and then either a progestin (10 mg) or oral progesterone (200 mg) for 14 days per month.
- Endometrial biopsy at the end of 18 months of treatment did not show any cases of hyperplasia but **did reveal some proliferative endometrium in a small percentage from both group**s.
- High-dose estradiol for 24 days yet only provide protective progesterone or progestin for a mere 14 days.
- That reflects the very definition of "estrogen dominance," a state in which we expect to see adverse effects from hormone replacement. It's not surprising that there was some breakthrough proliferative change seen; in fact, the surprise is that there wasn't a higher percentage.

- Jondet M, et al. Comparative endometrial histology in postmenopausal women with sequential hormone replacement therapy of estradiol and, either chlormadinone acetate or micronized progesterone. Maturitas. 2002;41:115–21.

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Topical/Vaginal gets to the breast

- Chang showed that when radiolabeled progesterone was given **topically** and then measured in **breast tissue biopsy**
- High levels were identified.

- Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertility & Sterility. April 1995;63 (4).

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Vaginal vs. Intramuscular Injection (IM)

- Miles et al administered topical vaginal progesterone versus IM injections of progesterone, then measured blood and endometrial biopsy.
- **Demonstrated superior tissue delivery using vaginal** progesterone over IM progesterone.

- Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril. 1994 Sep;62(3):485-90.

TOPICAL VS ORAL

- With topical and vaginal delivery methods
- These bypass gut and liver metabolism,
- So true unadulterated progesterone—as measured in the blood stream—is robustly present.

- Comparison of the pharmacokinetics of Crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women. Fertility & Sterility. March 2000;73 (3).

Progesterone Metabolites

- A growing appreciation of progesterone metabolites, and the differences from topical vs oral (pregnenes and pregnanes).
- Still controversial.
- Still not able to be directly applied clinically.
- Progesterone is required for the full proliferative activity of the breasts and may be directly or indirectly involved in either stimulating or inhibiting breast cancer.
- **Oral over 175 mg may promote more pregnanes.**
- Progesterone metabolism, resulting in an increased 5alpha-pregnane:4-pregnene (especially 5alphaP:3alphaHP) ratio, may promote breast cancer by promoting increased cell proliferation and detachment, whereas increases in 4-pregnenes may retard these tumorigenic processes.

- The 4-pregnene and 5alpha-pregnane progesterone metabolites formed in nontumorous and tumorous breast tissue have opposite effects on breast cell proliferation and adhesion. Cancer Res. 2000 Feb 15;60(4):936-43. PMID: 10706108.

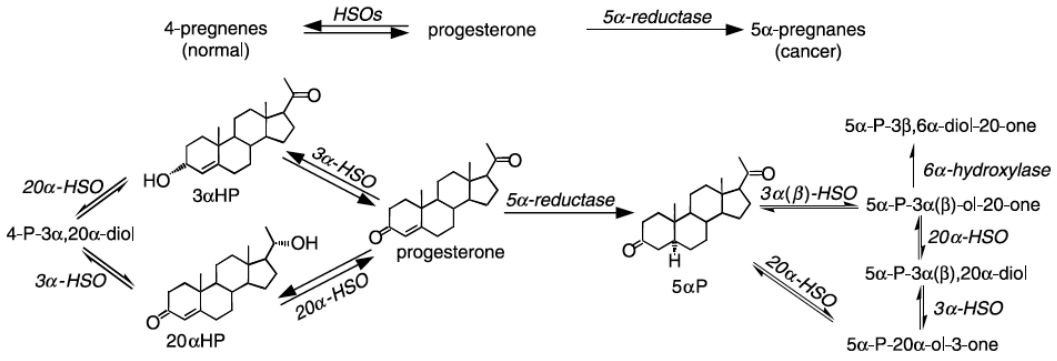
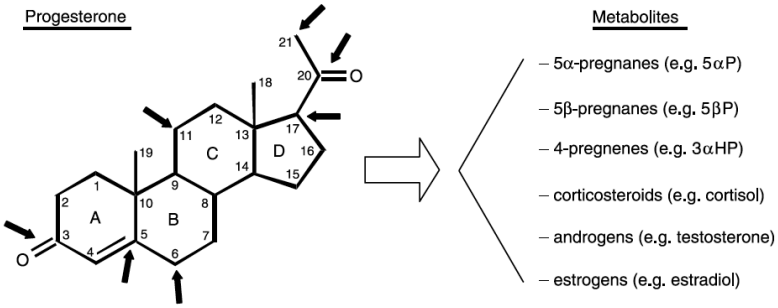


Figure 2 Progesterone conversion to 4-pregnene and 5α-pregnane metabolites by human breast tissues and cell lines. Note that 5α-reductase reaction is not reversible (see text for details; modified from Wiebe *et al.* 2005).

720 www.endocrinology-journals.org

Endocrine-Related Cancer (2006) **13** 717–738



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5-alpha reductase (5AR enzyme)

- Converts T to 5a-DHT
- Converts androstenedione to androsterone
- Cortisol to a major metabolite
- DHEA upregulates (so when supplement realize this)
- Progesterone inhibits
- So insufficient progesterone may drive the production of more inflammatory metabolites as much as too much progesterone.
- Elevated 5AR activity is linked to insulin resistance, obesity, PCOS, hirsutism, premature baldness and benign prostatic hypertrophy.
- But also promoting pro-inflammatory progesterone metabolites.
- What helps lower %AR? Evening Prim Rose oil, zinc especially carnosine, losing weight, less processed carbs.

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Wiebe

- He has demonstrated that enzymes for progesterone's breakdown exist in all types of cells and tissues and is not limited to the gut and liver.
- The **enzyme 5-alpha-reductase** will rapidly metabolize progesterone to pregnanolone and pregnanediol, the "pregnane" metabolites.
- These pregnanes are known as neuro-steroids and do offer a calming influence to the brain; but when their production outpaces pregnenes then this ratio drives breast cancer risk.
- Studies using various breast cell lines have shown that 5aP (pregnane) and 3aHP (pregnene) have opposing actions in terms of cell proliferation and adhesion;
- Wiebe wrote: breast cancer cell lines, we consistently measure pregnanes at high levels relative to low pregnene levels.
- **Oral P may have a greater propensity, in some women, to make pregnanes over pregnenes.**

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Clinical Observation

- If breasts are excessively enlarging, pregnanes may be outpacing pregnenes.
- Reduce oral dose or if can't sleep at less, then add another progesterone via a another delivery mode ie topical or vaginal.
- I prefer vaginal but find with mucosal delivery symptom relief to be better BID and this takes a compliant patient.
- Consider adding iodine that helps maintain ideal breast architecture; larger breasts need more iodine than smaller to achieve this.

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Some women's uterus/breast

- Will do fine with oral
- Some might not
- If have a uterus and taking estrogen replacement, should within first 6 to 9 months
- Have a vaginal US
- Need to have an **endometrial stripe of 5 or less.**
- **In postmenopausal women.**
- **Women with a uterus on HRT should have vaginal US's at least the first year after finding the optimal maintenance dose.**

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Topical/Mucosal

- Topical applications either to skin or vaginal mucosa have both proven to be effective delivery tools with satisfactory tissue levels.
- If take oral, sometimes it helps to "add" topical or vaginal to oral

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Patient

- Ex-breast cancer patient
- 150 mg SR Progesterone at night for many years if went lower could not sleep. But…
- Kept having fibrocystic breasts even on iodine.
- Took more and more iodine but didn't go away
- Added 15 mg BID in progesterone vaginally
- Within 48 hours fibrocystic breasts cleared

Breakthrough bleeding

- DiCarlo et al used a 50 mcg estradiol patch with oral (100 & 200 mg) progesterone versus vaginal (100 & 200 mg) progesterone and reported no occurrence of hyperplasia.
- 100 patients randomized 2 groups 100 P or 200 P oral or vaginal. Followed for one year.
- **Fewer bleeding occurrences in those taking progesterone vaginally.**
- **These women had better results so more compliant, in the vaginal delivery group.**
- **Bleeding suggests insufficient progesterone levels.**

- Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. Climacteric. 2010 Oct;13(5):442-6.

Bleeding

- In a follow up study by DiCarlo, they applied the same topical estradiol patch but this time to women taking three different progestins versus oral progesterone (200 mg).
- Followed 100 women through 12 monthly cycles; using estradiol on a daily basis with progesterone or progestin given for 11 days.
- With progestins:
- Bleeding episodes 73.6% of the time.
- Irregular bleeding 8.3%
- Spotting occurrence 10.2% of the time.
- This represents breakthrough bleeding of some type in >92% of the time.
- Oral progestins failed at a higher rate than the oral progesterone at controlling endometrial proliferation.
- Bringing into question taking estrogen all month and progesterone cycled as has been the practice.

Gary Huber DO – Townsend Leter

- The general finding was that higher doses of oral progesterone were more protective than lower doses and more consistently produced an atrophic endometrium, but even **doses of 400 mg orally did not completely halt proliferative changes from occurring**.
- When compared to **topical** progesterone.

- Townsend Letter Home » Articles » February-March 2020 #439-40 » Progesterone Use as Hormone Replacement Therapy: Myths, Facts, and Solutions - **Progesterone Use as Hormone Replacement Therapy: Myths, Facts, and Solutions**

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Progesterone dosage range

- 20mg/d in premenopausal women
- 400 mg/d in pregnant women
- Typical **topical dosages 25 to 60** in divided dosages twice/d
- Oral Sustained Release SR **25 to 150 mg**
- Up to 900 mg/d suppositories Katerina Dalton MD who coined the term “premenstrual syndrome” with her forensic research

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Progesterone dosing

- If have a uterus and irregular bleeding, may not have sufficient P
- If breasts enlarge may be excessive oral
- Oxytocin is best buddies with progesterone and sometimes need oxytocin to “handle” P optimally
- Some women are “reactive to progesterone” and oxytocin or desensitization may be helpful

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Peripheral Neuropathy

- Progesterone is emerging as an important protective agent against various injuries to the nervous system.
- Neuroprotective and remyelinating effects have been documented for this neurosteroid, which is synthesized by, and acts on, the central and peripheral nervous systems.
- DMSO + progesterone topically.

Progesterone - neuropathy

- **Methods:** Rats were unilaterally implanted with a polyethylene cuff around the sciatic nerve, and sensitivity to von Frey filament stimulation was measured over approximately 12 weeks.
- **Results:** Rats given progesterone starting one hour after cuff implantation, and daily until day 4, exhibited tactile hypersensitivity similar to that of vehicle-treated rats for the duration of the study. When progesterone was started one hour after cuff implantation and given daily until day 10, rats exhibited no tactile hypersensitivity in the later part of the study, after treatment had stopped. When progesterone treatment was initiated at 20 days, once the model had been fully established, and given daily for 4 or even 11 days, no differences in withdrawal thresholds were observed compared with controls. Progesterone did not have any effect on withdrawal thresholds when given as a single dose, as measured at 30, 60 and 90 minutes after administration.
- **Conclusion:** These results indicate that progesterone, when administered immediately after nerve injury, and for a sufficient period of time, can prevent the development of neuropathic pain, and may offer new strategies for the treatment of this highly debilitating condition.
- J Pain Res. 2011; 4: 91–101. doi: 10.2147/JPR.S17009
- **Progesterone prevents development of neuropathic pain in a rat model: Timing and duration of treatment are critical**

Progesterone – peripheral neuropathy

- We have assessed whether chronic treatment with progesterone (P), dihydroprogesterone (DHP) or tetrahydroprogesterone (THP) had neuroprotective effects against streptozotocin (STZ)-induced diabetic neuropathy at the neurophysiological, functional, biochemical and neuropathological levels.
- Using gas chromatography coupled to mass-spectrometry, we found that three months of diabetes markedly lowered P plasma levels in male rats, and chronic treatment with P restored them, with protective effects on peripheral nerves.
- In the model of STZ-induced of diabetic neuropathy, chronic treatment for 1 month with P, or with its derivatives, DHP and THP, counteracted the impairment of nerve conduction velocity (NCV) and thermal threshold, restored skin innervation density, and improved Na(+),K(+)-ATPase activity and mRNA levels of myelin proteins, such as glycoprotein zero and peripheral myelin protein 22, suggesting that **these neuroactive steroids, might be useful protective agents in diabetic neuropathy.**
- Neuroscience 2007 Feb 23;144(4):1293-304. doi: 10.1016/j.neuroscience.2006.11.014. Epub 2006 Dec 20. **Progesterone and its derivatives are neuroprotective agents in experimental diabetic neuropathy: a multimodal analysis**
- (2006) Therapeutic approaches to peripheral neuropathy based on neuroactive steroids, Expert Review of Neurotherapeutics, 6:8, 1121-1125, DOI: 10.1586/14737175.6.8.1121

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Pregnancy MS

- Evidence for an effect of pregnancy on MS activity comes from studies reporting 70% decrease in relapse rates during the third trimester compared with pre-pregnancy levels, and increased relapse rates 3–6 months after delivery, to levels almost three times higher than pre-pregnancy ones.
- Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med 1998; **339**:285–91

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MS

- Progesterone been shown to have beneficial effects through protection against excitotoxicity and by enhancing remyelination.
- By contrast, prolactin levels were found to be higher in patients with MS compared with controls, which seems to promote B-cell autoreactivity.
- Furthermore, hyperprolactinemia may be associated with clinical relapses in MS, especially among patients with hypothalamic lesions and/or optic neuritis.
- Progesterone and B6 help reduce.
- Immunology. 2019 Jan; 156(1): 9–22. doi: 10.1111/imm.13004 **Impact of sex hormones on immune function and multiple sclerosis development**

Other Possible Clinical Uses Progesterone

- Progesterone may have a potential benefit in treatment of **traumatic brain injury, various neurological disorders and male related diseases like benign prostatic hypertrophy (BPH), prostate cancer and osteoporosis.**
- Role in osteoporosis.
- Further, it may find utility in nicotine addiction, traumatic brain injury (recently entered Phase III trial) and Alzheimer's disease, diabetic neuropathy and crush injuries. Studies also suggest role of progesterone in stroke, for which further clinical trials are needed. The non genomic actions of progesterone may be in part responsible for these novel actions.

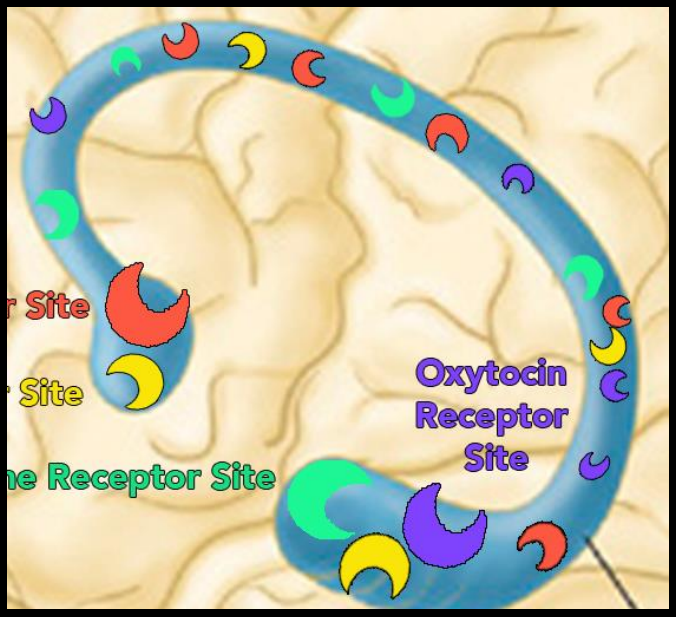
- Novel actions of progesterone: what we know today and what will be the scenario in the future? J Pharm Pharmacol. 2012 Aug;64(8):1040-62. doi: 10.1111/j.2042-7158.2012.01464.x. Epub 2012 Feb 21. PMID: 22775208.

Protects Nervous System

- Progesterone is synthesized and actively metabolized in the central and peripheral nervous system, into neuroactive steroid metabolites, such as dihydroprogesterone, allopregnanolone and isopregnanolone.
- **Progesterone and/or its metabolites exert a variety of effects acting as physiological regulators of neuronal and glial development and plasticity, controlling reproduction, neuroendocrine events, mood and affection**.
- In addition, these neuroactive steroids maintain neural homeostasis and exert neuroprotective actions.
- Progesterone as possible tool.
- Prog Neurobiol. 2014 Feb;113:56-69. doi: 10.1016/j.pneurobio.2013.07.006. **Levels and actions of progesterone and its metabolites in the nervous system during physiological and pathological conditions.**

Progesterone - Alzheimer's

- While some studies indicate that estrogen and progesterone depletion in postmenopausal women might carry a significant risk for developing sporadic Alzheimer's disease, which may be reduced by HT, some studies support and some oppose this.
- This review points to possible reasons for these mixed data by considering the issues of both preclinical and clinical trials, in particular, mode of drug delivery and the representativeness of animal models, timing of HT initiation, type of HT (different types of estrogen compounds, estrogen monotherapy vs. estrogen-progesterone combined therapy.
- Also, subcutaneous, transdermal, oral, or intramuscular), and hormone dosage used, as well as the heterogeneity of the postmenopausal population in clinical trials.
- Drugs Aging. 2016 Nov;33(11):787-808. **Evaluating the Role of Hormone Therapy in Postmenopausal Women with Alzheimer's Disease**



Progesterone's Effects on Cognitive Performance of Male Mice Are Independent of Progestin Receptors but Relate to Increases in $GABA_A$ Activity in the Hippocampus and Cortex. Front Endocrinol (Lausanne). 2021 Jan 11;11:552805. doi: 10.3389/fendo.2020.552805. PMID: 33505354; PMCID: PMC7829189.

Progesterone brain protective in-utero

- We hypothesized that low levels of the hormone progesterone is responsible since it is supplied to the fetus maternally and does not only support pregnancy but also promotes brain development in growing baby.
- Following a review of the literature, we report findings from a survey of mothers of autistic children (n=86) compared to mothers of typically-developing children (n=88) regarding obstetrical histories, including five obstetrical risk factors indicative of low progesterone. Using this analysis, the ASD group had significantly more risk factors than controls (1.21 ± 0.09 vs. 0.76 ± 0.08, p<.0001), suggesting low progesterone.
- Thus, results suggest that **low progesterone may be responsible for both obstetrical complications and brain changes associated with autism and that progesterone levels should be routinely monitored in at-risk pregnancies**. Our hypothesis also suggests that ensuring adequate levels of progesterone may decrease the likelihood of autism.
- Med Hypotheses. 2014 Mar;82(3):313-8. doi: 10.1016/j.mehy.2013.12.018. **Low maternal progesterone may contribute to both obstetrical complications and autism.**

Progestins not brain protective

- Progestin exposure linked to higher risk of autism.
- Progestins inhibit ER Beta in the brain.
- Mol Autism. 2017 Aug 17;8:46. doi: 10.1186/s13229-017-0159-3. eCollection 2017. **Prenatal levonorgestrel exposure induces autism-like behavior in offspring through ERβ suppression in the amygdala.**
- Resveratrol ameliorates prenatal progestin exposure-induced autism-like behavior through ERβ activation. Narod S MD.
- Mol Autism. 2018 Aug 2;9:43. doi: 10.1186/s13229-018-0225-5. eCollection 2018. **Resveratrol ameliorates prenatal progestin exposure-induced autism-like behavior through ERβ activation**

5 OBGYN signs of progesterone deficiency

- Low maternal progesterone linked to austism in offspring
- Elevated cortisol
- Vaginal bleeding
- Severe PMS
- Atypical early bone loss

- Low maternal progesterone may contribute to both obstetrical complications and autism. Med Hypotheses. 2014 Mar;82(3):313-8. doi: 10.1016/j.mehy.2013.12.018. Epub 2014 Jan 14. PMID: 24485701.

Progesterone - fibroids (early on)

- There is growing evidence of the crucial role of progesterone pathways in the pathophysiology of uterine fibroids.
- But use when fibroids are small as they develop their own blood supply and become fairly stable as get larger.
- Fibroids in history suggest progesterone insufficiency or resistance.
- Hum Reprod Update. 2016 Nov;22(6):665-686. **Uterine fibroid management: from the present to the future.**

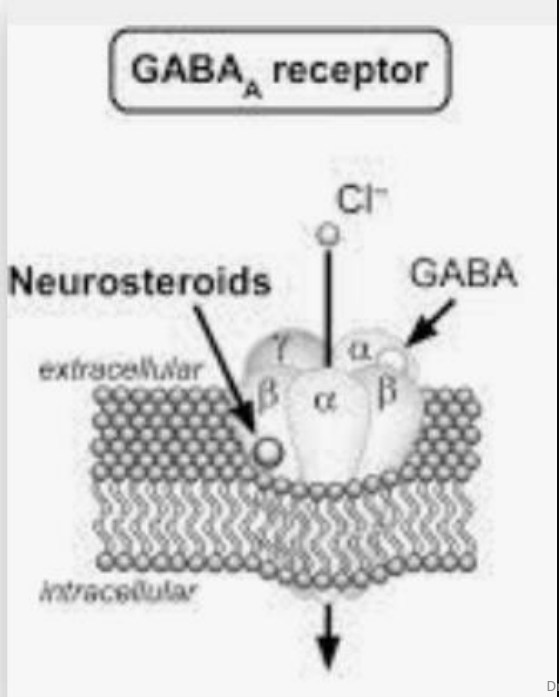
Progesterone - fibroids

- Progesterone antagonizes estrogen-driven growth in the endometrium, and insufficient progesterone action strikingly increases the risk of endometrial cancer.
- In endometriosis, eutopic and ectopic tissues do not respond sufficiently to progesterone and are considered to be **progesterone-resistant**, which contributes to proliferation and survival.
- **Need to give higher dosages of progesterone when progesterone resistance.**
- Or…
- Endocr Rev. 2013 Feb;34(1):130-62. doi: 10.1210/er.2012-1043. **Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer.**

Anti-Inflammatory

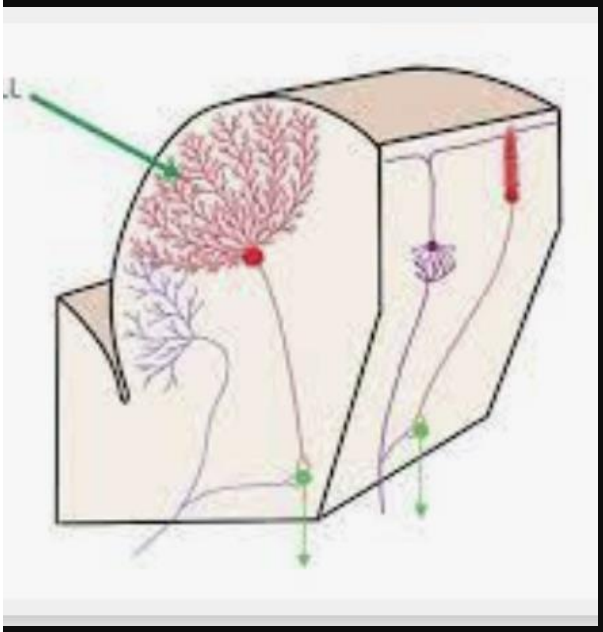
- During pregnancy
- By forward thinking neurologists in neurodegenerative diseases
- In MS

- **The Role of Progesterone and a Novel Progesterone Receptor, Progesterone Receptor Membrane Component 1, in the Inflammatory Response of Fetal Membranes to *Ureaplasma parvum* Infection. Plos One** Published: December 15, 2016
- https://doi.org/10.1371/journal.pone.0168102



Neurosteroids

- These steroids are termed neurosteroids and sometimes referred to as neuroactive steroids.
- As proposed by Baulieu, the term *neurosteroid* "applies to those steroids that are both synthesized in the nervous system, either *de novo* from cholesterol or from steroid hormone precursors like progesterone that accumulate in the nervous system" and in the brain.
- One of the clearest examples of a rapid, non-genomic steroid action on a membrane receptor is the demonstration that the natural metabolites of progesteronei.e., allopregnanolone and allotetrahydroDOC (THDOC), respectively, exert their main actions as powerful endogenous positive allosteric modulators of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at both synaptic and extrasynaptic GABA$_A$ receptors
- Neurosteroids biosynthesis and function. *Trends Endocrinol. Metabol.* 1994 Jan-Feb;5(1):1–8.



Purkinje cells – allopregnanolone protects neurosteroid synthesis

- The brain produces steroids de novo from cholesterol, so-called "neurosteroids."
- The Purkinje cell, a cerebellar neuron, was discovered as a major site of the biosynthesis of neurosteroids including sex steroids, such as progesterone, from cholesterol in the brain.
- Allopregnanolone, a progesterone metabolite, is also synthesized in the cerebellum and acts on the Purkinje cell to prevent cell death of this neuron.
- Recently, the pineal gland was discovered as an important site of the biosynthesis of neurosteroids.
- Allopregnanolone, a major pineal neurosteroid, acts on the Purkinje cell for the survival of this neuron by suppressing the expression of caspase-3, a crucial mediator of apoptosis.
- ASEB Bioadv. 2020 Mar; 2(3): 149–159. doi: 10.1096/fba.2019-00055 **Neuroprotective actions of cerebellar and pineal allopregnanolone on Purkinje cells**

The brain makes hormones so is a neuroendocrine organ.

- *Neuroactive steroids*, a term coined by Paul and Purdy in 1992 refers to "any natural or synthetic steroid that rapidly alters neuronal excitability via non-genomic mechanisms."
- Allopregnanolone present in brain is synthesized, at least in part, independently of the control of the pituitary on peripheral endocrine tissues
- Neuroactive steroids. *Faseb. J.* 1992 Mar;6(6):2311–2322.

Light at night

- We showed that circadian disruption by **light-at-night induced Purkinje cell death** through pineal allopregnanolone (ALLO) activity during early life in chicks.
- Light-at-night exposure affects brain development through pineal allopregnanolone-dependent mechanisms. Elife. 2019 Sep 30;8:e45306. doi: 10.7554/eLife.45306. PMID: 31566568; PMCID: PMC6850767.

Allopregnanolone

- Allopregnanolone is synthesized in the central nervous system either *de novo* from cholesterol or from steroid hormone precursors like progesterone and pregnenolone.
- Over the past 30 years, direct and rapid, non-genomic actions of allopregnanolone and its derivatives via $GABA_A$ receptors have been demonstrated.
- Changes in brain levels of allopregnanolone during pregnancy and in the postpartum period, or during exposure to protracted stress appear to play a crucial role in the pathophysiology of mood disorders.
- The discovery that allopregnanolone at low (nanomolar) concentrations elicits marked anxiolytic, anti-stress and antidepressant effects by facilitating allosterically the action of GABA at extrasynaptic $GABA_A$ receptors has provided new perspectives for the discovery of novel drugs useful for the treatment of mood disorders.
- These findings have led to the seminal clinical studies that recently demonstrated that treatment with allopregnanolone (i.e., brexanolone) can dramatically and rapidly improve the symptoms of postpartum depression in many patients.
- Allopregnanolone: From molecular pathophysiology to therapeutics. A historical perspective. Neurobiol Stress. 2020 Mar 14;12:100215. doi: 10.1016/j.ynstr.2020.100215. PMID: 32435665; PMCID: PMC7231972.

Postpartum

- The increase in brain levels of allopregnanolone during pregnancy and the sudden decrease immediately following parturition have been shown to alter the expression/function of specific $GABA_A$ subunits in the cortico-limbic structures.
- The discovery that allopregnanolone elicits marked anxiolytic and anti-stress effects and selectively facilitate GABA-mediated neurotransmission.
- PPD – progesterone and/or thyroid.
- **Allopregnanolone: From molecular pathophysiology to therapeutics. A historical perspective**
  Neurobiol Stress. 2020 May; 12: 100215. Published online 2020 Mar 14. doi: 10.1016/j.ynstr.2020.100215

Pregnenolone – memory hormone besides major parent hormone

- Pregnenolone and its derivatives promote neuronal activity by enhancing learning and memory, relieving depression, enhancing locomotor activity, and promoting neuronal cell survival.
- They exert these effects by activating various target proteins located in the cytoplasm or cell membrane.
- Pregnenolone and its metabolites bind to receptors such as microtubule-associated proteins and neurotransmitter receptors to elicit a series of reactions including stabilization of microtubules, increase of ion flux into cells, and dopamine release.
- The wide actions of neurosteroids indicate that pregnenolone derivatives have great potential in future treatment of neurological diseases.
- Nongenomic actions of neurosteroid pregnenolone and its metabolites. Steroids. 2016 Jul;111:54-59. doi: 10.1016/j.steroids.2016.01.017. Epub 2016 Feb 1. PMID: 26844377.

Pregnenolone Memory

- We compared the uptake by 11 brain regions and appearance in blood of tritium-labeled pregnenolone and progesterone after intranasal and intravenous (IV) injection.
- But did not vary, whereas the olfactory bulb, hippocampus, and hypothalamus had high uptake rates after intranasal administration.
- Intranasal administration of prenenolone improved memory, whereas progesterone decreased anxiety, thus demonstrating that therapeutic levels of neurosteroids can be delivered to the brain by intranasal administration.

- These results show that either the i.v. or intranasal routes of administration can deliver neurosteroids to blood and brain, but that the two routes have significant differences with intranasal administration favoring some brain regions.
- Eur J Pharmacol. 2010 Sep 1; 641(2-3): 128–134. doi: 10.1016/j.ejphar.2010.05.033 **Brain distribution and behavioral effects of progesterone and pregnenolone after intranasal or intravenous administration**

Pregnenolone – pain reliever

- **Importance:** In response to the national opioid public health crisis, there is an urgent need to develop nonopioid solutions for effective pain management. Neurosteroids are endogenous molecules with pleotropic actions that show promise for safe and effective treatment of chronic low back pain.
- **Objective:** To determine whether adjunctive pregnenolone has therapeutic utility for the treatment of chronic low back pain in Iraq- and Afghanistan-era US military veterans.
- **Design, setting, and participants:** Randomized, double-blind, placebo-controlled clinical trial that enrolled for 42 months, from September 2013 to April 2017. Participants were Iraq- and Afghanistan-era veterans aged 18 to 65 years with chronic low back pain who received treatment in the Durham VA Health Care System in Durham, North Carolina, over 6 weeks. Data analysis began in 2018 and was finalized in March, 2019.
- **Interventions:** Following a 1-week placebo lead-in, participants were randomized to pregnenolone or placebo for 4 weeks. Pregnenolone and placebo were administered at fixed, escalating doses of 100 mg for 1 week, 300 mg for 1 week, and 500 mg for 2 weeks.
-

Pregnenolone – analgesic

- **Conclusions and relevance:** Participants receiving pregnenolone reported a clinically meaningful reduction in low back pain and 2 pain interference domains compared with those receiving placebo.
- Pregnenolone may represent a novel, safe, and potentially efficacious treatment for the alleviation of chronic low back pain in Iraq- and Afghanistan-era veterans.
- Effect of Pregnenolone vs Placebo on Self-reported Chronic Low Back Pain Among US Military Veterans: A Randomized Clinical Trial. JAMA Netw Open. 2020 Mar 2;3(3):e200287. doi: 10.1001/jamanetworkopen.2020.0287. PMID: 32119096; PMCID: PMC7052727.

OA – joint pain

- Sex steroid hormones
- Pregnanolone
- Niacinamide
  - ERT reduced joint pain. 10,739 women.
  - **CONCLUSIONS:** The current findings suggest that estrogen-alone use in postmenopausal women results in a modest but **sustained reduction in the frequency of joint pain.**
  - Menopause. 2018 Nov;25(11):1313-1320. doi: 10.1097/GME.0000000000001235. **Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial.**
  - Niacinamide therapy for joint mobility; therapeutic reversal of a common clinical manifestation of the normal aging process. Conn State Med J. 1953 Jul;17(7):584-9. PMID: 13060032.
  - Niacinamide therapy for osteoarthritis--does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes? Med Hypotheses. 1999 Oct;53(4):350-60. doi: 10.1054/mehy.1998.0792. PMID: 10608273.

Allopregnanolone TMJ pain

- Temporomandibular joint disorder (TMD) is associated with pain in the joint (temporomandibular joint, TMJ) and muscles involved in mastication. TMD pain dissipates following menopause but returns in some women undergoing estrogen replacement therapy.
- Progesterone has both anti-inflammatory and antinociceptive properties, while estrogen's effects on nociception are variable and highly dependent on both natural hormone fluctuations and estrogen dosage during pharmacological treatments, with high doses increasing pain.
- Allopregnanolone, a progesterone metabolite and positive allosteric modulator of the $GABA_A$ receptor, also has antinociceptive properties.
- While progesterone and allopregnanolone are antinociceptive, their effect on estrogen-exacerbated TMD pain has not been determined.
- We hypothesized that removing the source of endogenous ovarian hormones would reduce inflammatory allodynia in the TMJ of rats and both progesterone and allopregnanolone would attenuate the estrogen-provoked return of allodynia. Baseline mechanical sensitivity was measured in female Sprague–Dawley rats.
- Allopregnanolone treatment, whether daily or every other day, also attenuated estrogen-exacerbated allodynia within 1 h of treatment, but only on the first treatment day. These data indicate that when gonadal hormone levels have diminished, treatment with a lower dose of progesterone may be effective at rapidly reducing the estrogen-evoked recurrence of inflammatory mechanical allodynia in the TMJ.
- Front. Integr. Neurosci., 08 May 2020 | https://doi.org/10.3389/fnint.2020.00026 **Progesterone and Allopregnanolone Rapidly Attenuate Estrogen-Associated Mechanical Allodynia in Rats with Persistent Temporomandibular Joint Inflammation**

Pregnenolone – pain 30 to 500 mg

- "Extensive data from preclinical models demonstrate that neurosteroids exhibit pronounced analgesic actions, and data demonstrate that neurosteroids are decreased in the setting of pain symptoms in clinical populations."
- Excerpt From: "Effect of Pregnenolone vs Placebo on Self-reported Chronic Low Back Pain Among US Military Veterans: A Randomized Clinical Trial." Apple Books.

Migraine pain

- **Methods** Thirty women (mean age ± SD: 33.5 ± 7.1) with menstrually-related migraine (MM group) and 30 aged-matched controls (mean age ± SD: 30.9 ± 7.9) participated in the exploratory study. Pregnenolone sulfate and pregnanolone serum levels were analysed by liquid chromatography-tandem mass spectrometry, while estradiol levels by enzyme-linked immunosorbent assay.
- **Results** Serum levels of pregnenolone sulfate and pregnanolone were significantly lower in the MM group than in controls (pregnenolone sulfate: *P* = 0.0328; pregnanolone: *P* = 0.0271, Student's t-test), while estradiol levels were similar. In MM group, pregnenolone sulfate serum levels were negatively correlated with history of migraine.
- **Conclusion** Low levels of both pregnanolone, a positive allosteric modulator of the GABAA receptor, and pregnenolone sulfate, a positive allosteric modulator of the NMDA receptor, involved in memory and learning, could contribute either to **headache pain or the cognitive dysfunctions reported in migraine patients.**
- Overall, our results agree with the hypothesis that migraine is a disorder associated with a loss of neurohormonal integrity, thus supporting the therapeutic potential of restoring low neurosteroid levels in migraine treatment.

- **Comparison of pregnenolone sulfate, pregnanolone and estradiol levels between patients with menstrually-related migraine and controls: an exploratory study** J Headache Pain. 2021; 22(1): 13.

45 yr old female

- 10 years vestibulopathy
- Chronic migraines
- Reduced with low dose estradiol patch to headaches
- Mostly controlled with adding high dose pregnenolone

Pregnenolone Bi-polar Depressions 500 mg

- Depression in bipolar disorder (BPD) is challenging to treat. Therefore, additional medication options are needed.
- In the current report, the effect of the neurosteroid pregnenolone on depressive symptoms in BPD was examined. Adults (n=80) with BPD, depressed mood state, were randomized to pregnenolone (titrated to 500 mg/day) or placebo, as add-on therapy, for 12 weeks.
- Depression remission rates were greater in the pregnenolone group (61%) compared with the placebo group (37%).
- Pregnenolone was well tolerated. The results suggest that pregnenolone may improve depressive symptoms in patients with BPD and can be safely administered.
- Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA.
- [2]1] Department of Psychiatry, Duke University Medical Center, Durham, NC, USA [2] Durham VA Medical Center and VA Mid-Atlantic MIRECC, Durham, NC, USA.
- [3]1] Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA [2] Department of Clinical Sciences, UT Southwestern Medical Center, Dallas, TX, USA.
- A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar depression. Neuropsychopharmacology. 2014 Nov;39(12):2867-73. doi: 10.1038/npp.2014.138. Epub 2014 Jun 11. PMID: 24917198; PMCID: PMC4200497.

Psychiatric Disorders

- Pregnenolone and/or allopregnanolone concentrations are altered in animal models of stress and after consumption of alcohol or cannabis-type drugs, as well as in patients with depression, anxiety, post-traumatic stress disorder or psychosis and/or in those diagnosed with alcohol or cannabis use disorders.
- Preclinical and clinical evidence shows that pregnenolone and allopregnanolone, operating according to a different or common pharmacological profile involving GABAergic and/or endocannabinoid system, may be relevant biomarkers of psychiatric disorders for therapeutic purposes.
- Stress and drug abuse-related disorders: The promising therapeutic value of neurosteroids focus on pregnenolone-progesterone-allopregnanolone pathway. Front Neuroendocrinol. 2019 Oct;55:100789. doi: 10.1016/j.yfrne.2019.100789. Epub 2019 Sep 13. PMID: 31525393.

Manic, Depression 100 mg

- In a proof-of-concept investigation, 70 participants with bipolar disorder or recurrent major depressive disorder and history of substance abuse/dependence (abstinent for > or =14days prior to enrollment) were randomly assigned to receive pregnenolone (titrated to 100mg/day) or placebo for 8weeks.
- A post hoc analysis of completers found a statistically significant reduction in HRSD scores with pregnenolone as compared to placebo.
- Pregnenolone appeared to be safe and well tolerated. Findings suggest that pregnenolone use may be associated with some improvement in manic and depressive symptoms, but not cognition.
- Pregnenolone for cognition and mood in dual diagnosis patients. Psychiatry Res. 2010 Jul 30;178(2):309-12. doi: 10.1016/j.psychres.2009.09.006. Epub 2010 May 21. PMID: 20493557.

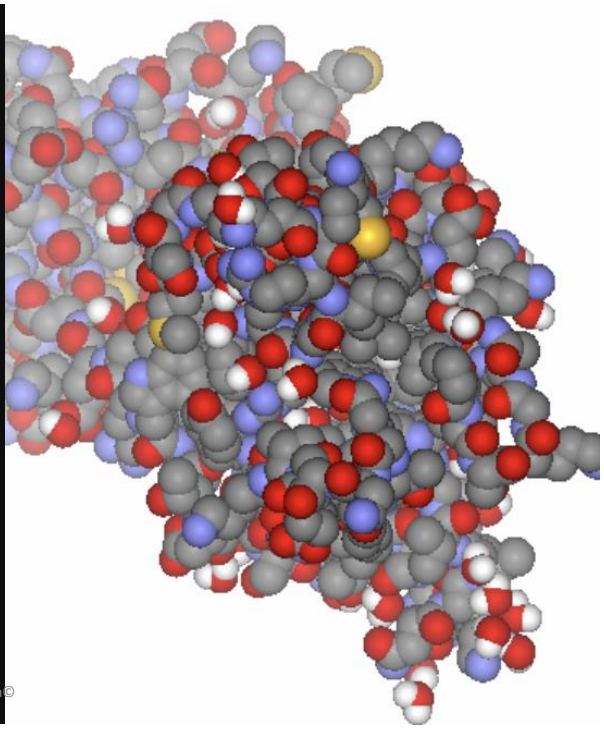
Allopregnanolone – mood

- The neuroactive steroid 3α-5α-tetrahydroprogesterone (allopregnanolone), a metabolite of progesterone, is a positive allosteric modulator of $GABA_A$ receptors, and low levels have been implicated in the etiology of mood disorders.
- Mood issues? Try progesterone. Pregnenolone. And thyroid.
- Remember, progesterone helps move T3 into its receptor.

- Psychoneuroendocrinology. 2020 Feb; 112: 104512.
- Published online 2019 Nov 14. doi: 10.1016/j.psyneuen.2019.104512
- **The Allopregnanolone to Progesterone Ratio Across the Menstrual Cycle and in Menopause**

Progesterone Boosts Brain-derived Neurotrophic Factor (BDNF)

- Progesterone, brain-derived neurotrophic factor and neuroprotection. Neuroscience. 2013 Jun 3;239:84-91. doi: 10.1016/j.neuroscience.2012.09.056. Epub 2012 Oct 2. PMID: 23036620; PMCID: PMC3582842.



Progesterone/Thyroid Cross-talk

- Blood samples collected from 29 women (aged between 19 and 35 years) during the luteal phase of the menstrual cycle (between days 18 and 23 of the cycle) showed that deficiency in thyroid hormone level is related to a decrease in progesterone (P4) secretion.
- Insufficient T3 leads to less progesterone.
- Progesterone convert T4 to T3
- Helps move free T3 onto its receptor.

- An evidence for the transcriptional regulation of iodothyronine deiodinase 2 by progesterone in ovarectomized rats. J Physiol Biochem. 2014 Jun;70(2):331-9. doi: 10.1007/s13105-013-0307-y. Epub 2013 Dec 23. PMID: 24362948.
- Triiodothyronine (T3) modulates hCG-regulated progesterone secretion, cAMP accumulation and DNA content in cultured human luteinized granulosa cells. Mol Cell Endocrinol. 1993 Oct;96(1-2):125-31. doi: 10.1016/0303-7207(93)90102-p. PMID: 8276127.
- Thyroid hormone stimulates progesterone release from human luteal cells by generating a proteinaceous factor. J Endocrinol. 1998 Sep;158(3):319-25. doi: 10.1677/joe.0.1580319. PMID: 9846161.

Thyroid works in consort with allopregnanelone to effect GABA

- Mounting evidence of T3's nongenomic effect on adult brain tissue.
- T3 structure resembles the structure of neurosteroids.
- While it lacks a steroid's fundamental four-ring molecular group, T3 has a nearly identical volume and shape to neurosteroids.
- Thyroid hormone can access the brain via the blood-brain barrier; nerve terminal fractions show T3 concentrations.
- Progesterone helps T3 nestle into its receptor site.
- PLoS One. 2019; 14(10): e0223272. doi: 10.1371/journal.pone.0223272
- **L-3,3',5-triiodothyronine and pregnenolone sulfate inhibit *Torpedo* nicotinic acetylcholine receptors**

Alzheimer's - allopregnanolone

- **Background:** Few data are currently available investigating neurosteroids (NS) in Alzheimer's disease (AD).
- **Methods:** Neurosteroid levels (allopregnanolone, pregnenolone, dehydroepiandrosterone [DHEA]) were determined in postmortem PFC in 14 male subjects with AD and 15 cognitively intact male control subjects.
- **Results:** Subjects with AD exhibit significant reductions in allopregnanolone compared with cognitively intact control subjects (median levels = 2.50 ng/g vs. 5.59 ng/g, respectively; p = .02).
- Allopregnanolone levels are inversely correlated with neuropathological disease stages.
- **Conclusions:** Subjects with AD demonstrate significant reductions in PFC allopregnanolone levels, a finding that may be relevant to neuropathological disease stage severity.
- The neurosteroid allopregnanolone is reduced in prefrontal cortex in Alzheimer's disease. Biol Psychiatry. 2006 Dec 15;60(12):1287-94. doi: 10.1016/j.biopsych.2006.06.017. Epub 2006 Sep 25. PMID: 16997284.

Progesterone – bone
(why just use uterus as marker to replace?)

- Estradiol (E2) is women's dominant 'bone hormone' since it is essential for development of adolescent peak bone mineral density (BMD) and physiological levels prevent the rapid (3-week) bone resorption that causes most adult BMD loss.
- However, deceasing E2 levels trigger bone resorption/loss.
- Progesterone (P4) is E2's physiological partner, collaborating with E2 in every cell/tissue; its bone 'job' is to increase P4-receptor-mediated, slow (3-4 months) osteoblastic new bone formation.
- When menstrual cycles are normal length and normally ovulatory, E2 and P4 are balanced and BMD is stable.
- However, clinically normal cycles commonly have ovulatory disturbances (anovulation, short luteal phases) and low P4 levels; these are more frequent in teen and perimenopausal women and increased by everyday stressors: energy insufficiency, emotional/social/economic threats and illness. Meta-analysis shows that almost 1%/year spinal BMD loss occurs in those with greater than median (~31%) of ovulatory disturbed cycles. Prevention of osteoporosis and fragility fractures requires the reversal of stressors, detection and treatment of teen-to-perimenopausal recurrent cycle/ovulatory disturbances with cyclic oral micronized progesterone.
- Low 'Peak Perimenopausal BMD' is likely the primary risk for fragility fractures in later life.
- Progesterone plus estradiol or other antiresorptive therapies adds 0.68%/year and may be a highly effective osteoporosis treatment.
- Progesterone for the prevention and treatment of osteoporosis in women. Climacteric. 2018 Aug;21(4):366-374. doi: 10.1080/13697137.2018.1467400. Epub 2018 Jul 2. PMID: 29962257.

Progesterone - lungs

- Administration of exogenous progesterone (at concentrations that mimic the luteal phase) to progesterone-depleted adult female mice conferred protection from both lethal and sublethal influenza A virus (IAV) infection.
- Progesterone treatment altered the inflammatory environment of the lungs but had no effects on viral load.
- Progesterone treatment promoted faster recovery by increasing TGF-β, IL-6, IL-22, numbers of regulatory Th17 cells expressing CD39, and cellular proliferation, reducing protein leakage into the airway, improving pulmonary function, and upregulating the epidermal growth factor amphiregulin in the lungs
- Our results illustrate that progesterone is a critical host factor mediating production of AREG by epithelial cells and pulmonary tissue repair following infection, which has important implications for women's health.
- Progesterone-Based Therapy Protects Against Influenza by Promoting Lung Repair and Recovery in Females. PLoS Pathog. 2016 Sep 15;12(9):e1005840. doi: 10.1371/journal.ppat.1005840. PMID: 27631986; PMCID: PMC5025002.

Progesterone - seizures

- The anti-seizure effects of progesterone family compounds have long been known. Over the years, however, most studies have focused on progesterone and on its secondary metabolite allopregnanolone (ALLO), with less attention being paid to its primary metabolite 5a-dihydroprogesterone (DHP).
- Progesterone and ALLO have also shown anti-seizure effects in clinical trials.
- A large Phase III trial has revealed that female patients with premenstrual exacerbations of seizures benefit most from progesterone therapy.
- A liquid suspension of ALLO has also been tested in patients with supra-refractory status epilepticus with some success in a small phase II trial.
- Progesterone's anti-seizure effects are mostly independent of its genomic receptors and are, in large part, due to its active metabolites..
- Progesterone, 5a-dihydropogesterone and allopregnanolone's effects on seizures: A review of animal and clinical studies. Seizure. 2018 Dec;63:26-36. doi: 10.1016/j.seizure.2018.10.012. Epub 2018 Oct 28. PMID: 30391663.

Progesterone - myelin repair

- Progesterone plays an important role in developmental myelination and in myelin repair, and the aging nervous system appears to remain sensitive to some of progesterone's beneficial effects.
- Progesterone promotes the formation of new myelin sheaths.
- Recognition of the important pleiotropic effects of progesterone opens novel perspectives for the treatment of brain lesions and diseases of the nervous system.
- Over the last decade, there have been a growing number of studies showing that exogenous administration of progesterone or some of its metabolites can be successfully used to treat traumatic brain and spinal cord injury, as well as ischemic stroke.
- Progesterone can also be synthesized by neurons and by glial cells within the nervous system. Progesterone: therapeutic opportunities for neuroprotection and myelin repair. Pharmacol Ther. 2007 Oct;116(1):77-106. doi: 10.1016/j.pharmthera.2007.06.001. Epub 2007 Jun 18. PMID: 17659348.

Progesterone - stroke

- We also highlight the key role of PR signaling as well as potential additional mechanisms by which progesterone may provide cerebroprotection.
- Steroids in Stroke with Special Reference to Progesterone. Cell Mol Neurobiol. 2019 May;39(4):551-568. doi: 10.1007/s10571-018-0627-0. Epub 2018 Oct 9. PMID: 30302630.

Progesterone Stroke (timing, dose)

- **There is strong evidence that progesterone reduces the infarct volume and improves functional recovery in experimental models of stroke (see systematic reviews.**
- Dose–response studies showed that the optimal neuroprotective dose is 8 mg/kg.
- Of note, progesterone provides neuroprotection even when administered as late as 6 h after ischemia.
- The observed transient increase of endogenous cerebral levels of progesterone after stroke may provide an early endogenous neuroprotection that may contribute to this large therapeutic window.

- Is progesterone a candidate neuroprotective factor for treatment following ischemic stroke? Neuroscientist 2009, 15, 324–332.
- Progesterone treatment for experimental stroke: An individual animal meta-analysis. J. Cereb. Blood Flow Metab. 2013, 33, 1362–1372.

Key role of progesterone in stroke

- Thus, we have shown that at 6 h and 24 h post-MCAO, PR-dependent signaling of endogenous **brain progesterone limited the extent of infarct size and the impairment of motor functions.**
- Decreased motor deficient in mice models.

- Progesterone in the Brain: Hormone, Neurosteroid and Neuroprotectant. Int J Mol Sci. 2020 Jul 24;21(15):5271. doi: 10.3390/ijms21155271. PMID: 32722286; PMCID: PMC7432434.

Three Anti-Aging Musketeers

- **Progesterone Pregnenolone & DHEA**
- Pregnenolone is largely converted into two other "youth-associated"or "anti-aging" protective hormones, progesterone and DHEA.

Pregnanolone Dosages

- 10 to 100 mg/day
- At the age of 30, both men and women produce roughly 30 to 50 mg. of pregnenolone daily.
- Well absorbed orally.
- Some take daily
- Some once or twice a week
- Dr. Peat: One dose of approximately 300 mg keeps acting for about a week, as absorption continues along the intestine, and as it is "recycled" in the body.

Oral Pregnenolone

- 50 or 100 mg oral pregnenolone robustly increases urinary levels of progesterone metabolites pregnanediol and pregnanolone (and/or their breakdown products).
- Oral pregnenolone is preferentially metabolized into the neurosteroid allopregnanolone.
- **Transdermal pregnenolone does not increase urinary levels, is not as effective as oral**.
- **Oral pregnenolone is preferentially metabolized into the neurosteroid allopregnanolone rather than other steroids i.e. cortisol**.
- Helps boost restorative deeper REM sleep.

Investigations on changes in $^{13}C/^{12}C$ ratios of endogenous urinary steroids after pregnenolone administration. *Drug Test Anal.* ***3*** *(5): 283–90. 2011*

Allopregnanolone elevations following pregnenolone administration are associated with enhanced activation of emotion regulation neurocircuits. *Biol. Psychiatry.* ***73*** *(11): 1045–53. 2013*

Uses

- Memory
- Boost Orgasm
- Improve sleep
- Boost production of downstream hormones
- Be careful in history of hormonally driven cancers, recommend 10mg/d a few years out of diagnosis/treatment
- Anti-aging

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Other Uses of Pregnenolone Replacement

- Clinically, pregnenolone has been shown to have a "face-lifting" effect.
- Improved circulation to the skin,
- Along with both products with ideal amount of niacin/niacinamide.
- Plus, actual contraction of some muscle-like cells in the skin.
- A similar effect can improve joint mobility in arthritis, tissue elasticity in the lungs, and even eyesight.

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Anti-fibrotic

- Studies have shown it to be protective of "fibrous tissues" in general,
- Tamps down TGFB1 (in excess, “drives” all fibrosis) (best when added to taurine

- Promotes estrogen balance: Is a protector of ER alpha signals out of control and the potential issue of tumors causes by excess ER alpha estrogen.

Raymond Peat, MA, PhD (Univ. of Oregon)

Endocrine Physiologist

Sex “Steroids” & OA

- Often very helpful for joint pain
- Much aches and pains of aging are due to hormonal wanning
- Hormone boosting
- Along with niacinamide 500- 1000 mg TID
- Is a great program for OA and non-specific pain
- You can add oxytocin to this nasal spray several times a day if the above is not putting most of the pain into remission.
- . Patient with shoulder pain
- Menopause. 2013 Jun; 20(6): 10.1097/GME.0b013e31828392c4.
- doi: 10.1097/GME.0b013e31828392c4
- **Estrogen Alone and Joint Symptoms in the Women’s Health Initiative Randomized Trial**