A Grouped Knowledge Presentation

Disclosure

The following potential conflict of interest relationships are germane to my presentation.

Equipment: N/A
Speakers Bureau: **NA**
Stock Shareholder: N/A
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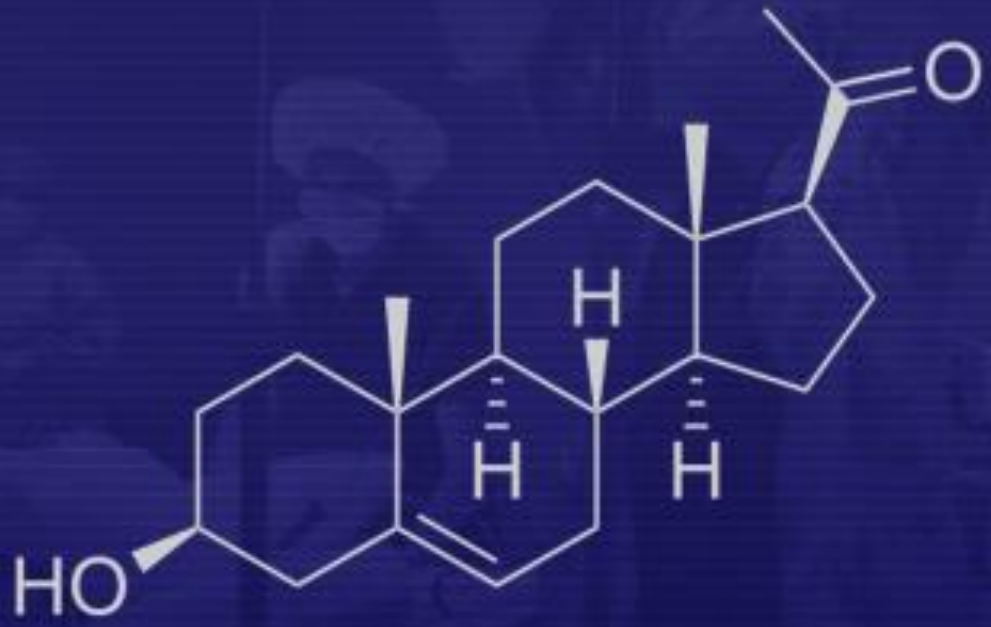
Mark L. Gordon, MD – Millennium Health Centers, Inc.

Then there was: The Mother of All Hormones

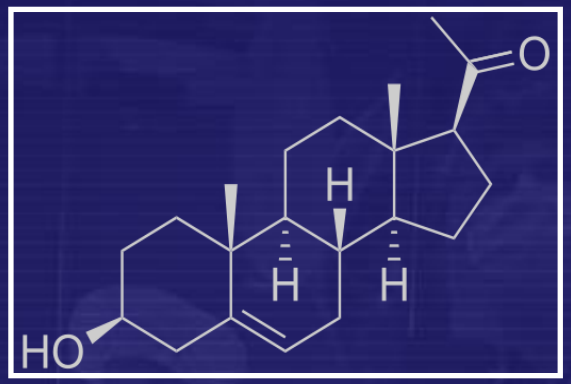
Pregnenolone (P5)



From: The Clinical Application of Interventional Endocrinology, 2007

Giving rise to:

Pregnenolone



1°

Progesterone

Allopregnanolone

Cortisol

Aldosterone

2°

DHEA/DHEA-s

Testosterone

Estradiol

Estriol

From: The Clinical Application of Interventional Endocrinology, 2007

Program Goals

- Enhance your knowledge of DHEA/DHEA-s and Pregnenolone (P5) to optimize neurocognitive and neurobehavioral functionality.
- Improve your knowledge of how to preserve the body's levels of DHEA/DHEA-s and P5 when starting a Hormone Replacement Protocol (HRP).
- Learn the nuances that will make you a leader in the field of HRT since there are too many hacks out there!!

Program Schedule

1. The importance of Pregnenolone as the Mother of All Hormones and the off-springs that it produces.
2. A Holistic approach to Homeostasis while providing Hormone Replacement Protocols.
3. Beneficial effects of DHEA on a number of bodily systems.
4. Case presentations:

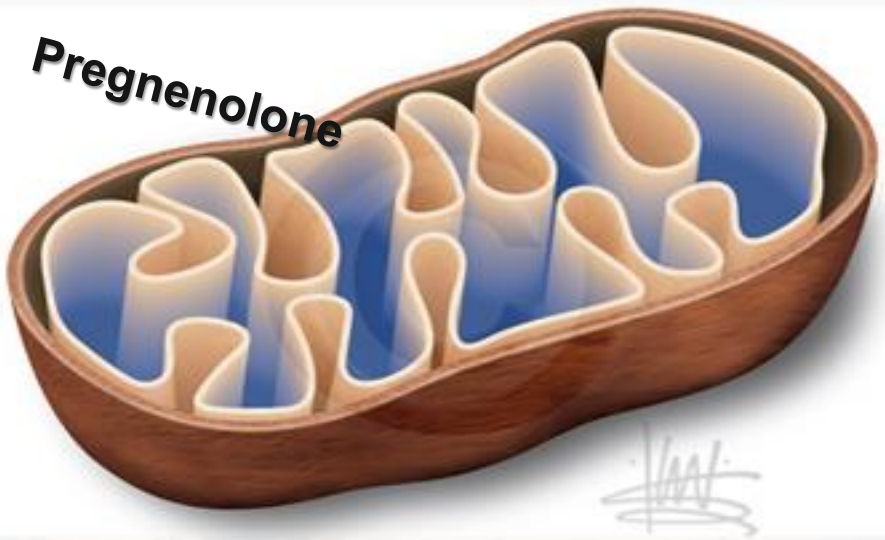
From Cholesterol to Pregnenolone

1. **Cholesterol is transported into the inner lining of the mitochondria by StAR where P450scc or now CYP 11a1 cleaves the side chain of cholesterol creating Pregnenolone.**
   a) Luteinizing Hormone (LH) increases the production of the rate limiting transport molecule StAR.

Cholesterol + StAR C-StAR

+

LH



The Effects of Testosterone, Estrogens, and Opioids on LH

Williams Textbook of Endocrinology

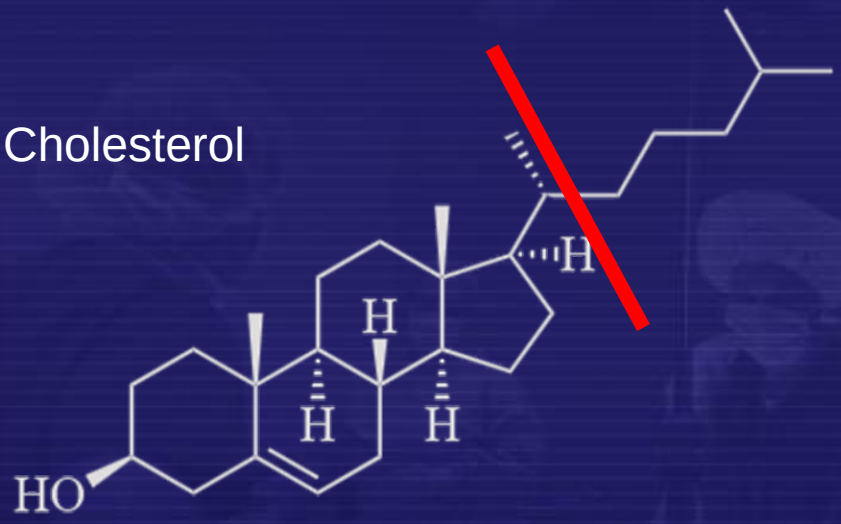
- The negative feed-back loop, relative to Testosterone and Estradiol, will down-regulate the release of FSH/LH from the Anterior Pituitary. Chronic HRT will eventually shut off Luteinizing Hormone production. (**No Pregnenolone**!)

Effect of opioid antagonists on sex hormone secretion. J of Endocrinological Investigation. 2012, 35:2, pp 227–230.

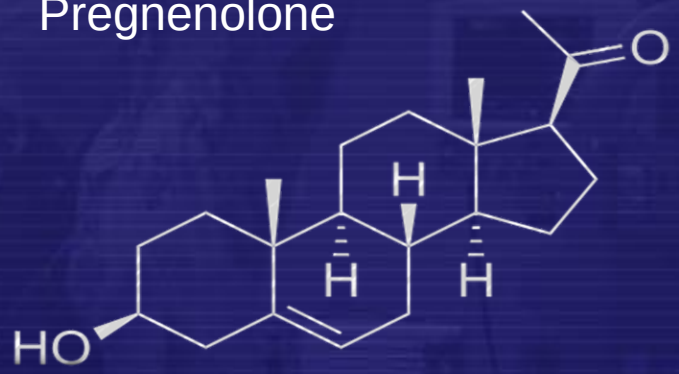
- Opioids decrease the secretion of GnRH from the hypothalamus.

Luteinizing hormone receptor (LHr) mediates neuronal pregnenolone production via up-regulation of steroidogenic acute regulatory protein expression (StAR). J. Neurochem. (2007) 100, 1329–1339. Tianbing Liu, et al; Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, Wisconsin, USA . (2007)

Cholesterol



Pregnenolone



Luteinizing Hormone (LH) stimulates steroidogenesis by up-regulating the rate-limiting transport of cholesterol from the outer to the inner mitochondrial membrane by increasing the expression of the mitochondrial cholesterol transport protein (StAR) **Steroidogenic Acute Regulatory protein**.

STATIN DRUGS MARKEDLY INHIBIT TESTOSTERONE PRODUCTION BY RAT LEYDIG CELLS IN VITRO: IMPLICATIONS FOR MEN

G. R. Klinefelter, J. W. Laskey, and R. P. Amann† *US Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Toxicology Assessment Division, Reproductive Toxicology Facility Durham, NC 27713;

- Statin medications reduced the responsiveness of the Leydig cells' to Luteinizing Hormone by 44%.

Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism. Proceedings of the National Academy of Sciences , USA. 2018. David Møbjerg Kristensen. Danish Headache Center, Department of Neurology, Rigshospitalet, University of Copenhagen

- **Ibuprofen alters the endocrine system via selective transcriptional repression in the human testes, thereby inducing Compensated Hypogonadism.**
  - Ibuprofen down-regulates the LHr sensitivity to its ligan – LH in the Leydig cells.
  - The response of the feed back loop is to increase the production of LH to Compensate for the lack of responsiveness from the Leydig Cells.

The two major pathways; the Primary:

- Pregnenolone's conversion down a pathway leading to Cortisol offers up some sound clinical directions for treatment.

CASE #1:

35 y/o Female, with chronic stress. Irregular menses too.

1) What is her condition called?

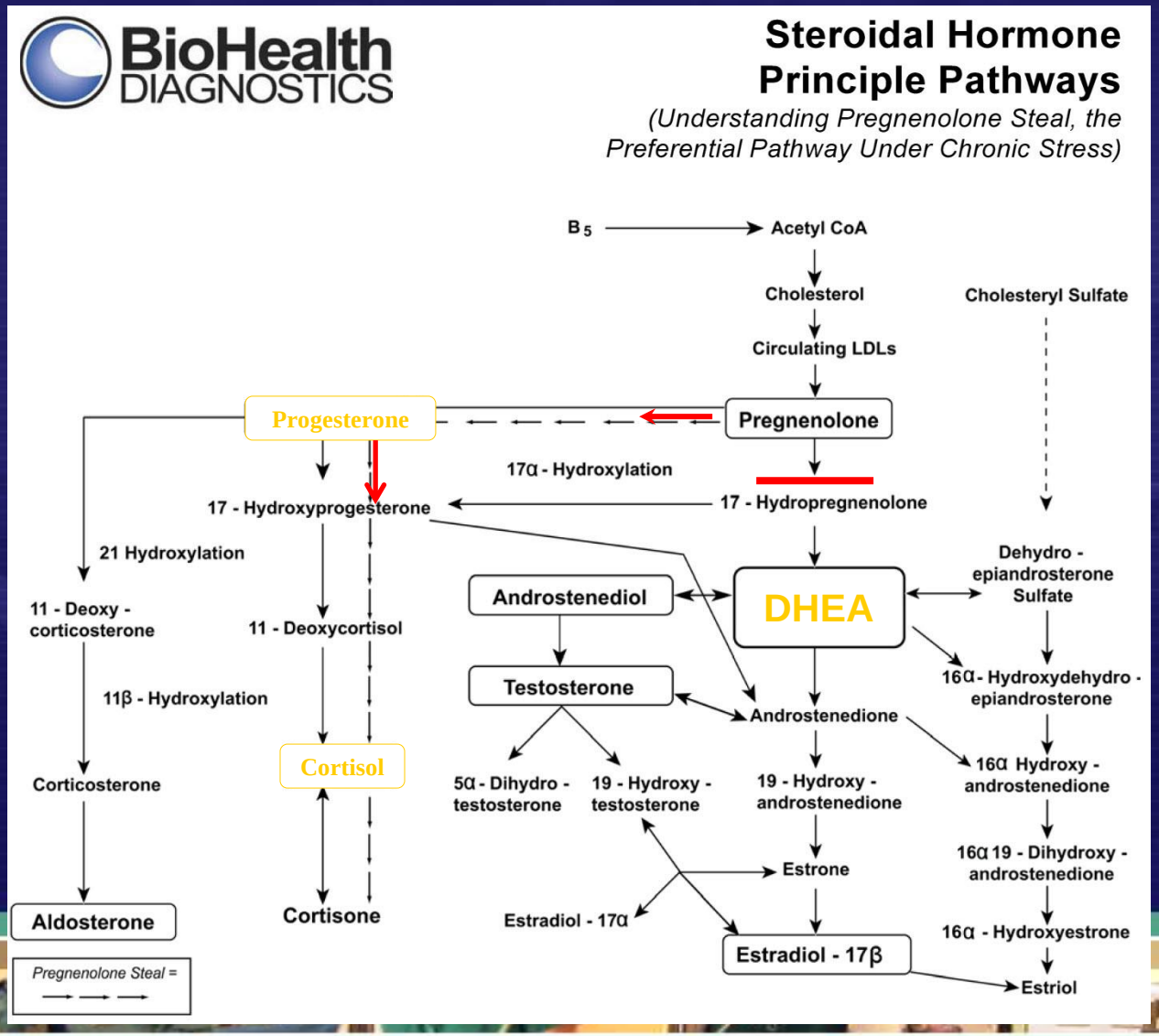
Pregnenolone Steal Syndrome

Lab Test (f)	Result	Median	
Growth Hormone		5ng/ml*	
IGF-1		>200 ng/ml	
IGF-BP3		>4000 ng/ml*	
DHEA-s	117	223 ug/ml*	
Free Testosterone		2-4 pg/ml	
Total Testosterone		44 ng/ml*	
DHT		< 30 ng/dL	
SHBG		75 pg/ml*	
Estrone		<200 pg/ml	
Estradiol (V)		90 pg/ml *	
Pregnenolone	14.3	80-100 ng/dL	
Progesterone (V)	0.21	14 ng/ml*	
ACTH	45	< 35 pg/ml	
Cortisol	17.8	15 ug/dL	

Pregnenolone Steal Syndrome

1. Under extreme stress the body's survival mode is triggered.
2. Pregnenolone's conversion to DHEA is limited so it can convert to Progesterone then 11-Oxycortisone and ultimately to Cortisol.
3. Treatment is to:
   A. Decrease stress
   B. Decrease demand on the Adrenals
   C. Provide for the precursors (DHEA/P5)

Under severe stress, Pregnenolone is shunted towards cortisol and away from DHEA/DHEA-s at the expense of all the androgens and estrogens:



CASE #2:

35 y/o Female, with chronic stress. Irregular menses too.

1) What is her condition called?

Adrenal Fatigue

Lab Test (f)	Result	Median	
Growth Hormone		5ng/ml*	
IGF-1		>200 ng/ml	
IGF-BP3		>4000 ng/ml*	
DHEA-s	183	223 ug/ml*	
Free Testosterone		2-4 pg/ml	
Total Testosterone		44 ng/ml*	
DHT		< 30 ng/dL	
SHBG		75 pg/ml*	
Estrone		<200 pg/ml	
Estradiol (V)		90 pg/ml *	
Pregnenolone	34.3	80-100 ng/dL	
Progesterone (V)	1.14	14 ng/ml*	
ACTH	67.23	<35 pg/ml	
Cortisol	3.65	<15 ug/dL	

NS and NAS

- Neurosteroids (NS) are those that are produced de nova in the brain by the glial cells like astrocytes, oligodendrocytes and microglia.
- Neuroactive Steroids (NAS) are the body's hormones that are produced in the periphery and pass through the BBB into the brain.
- Enzymes responsible for the production of NS have been identified within neurons too.

Multiple Actions of Steroid Hormones—A Focus on Rapid, Non-genomic Effects. The American Society for Pharmacology and Experimental Therapeutics. Vol. 52, No. 4. 2000. Elisabeth Falenstein, et al. Institute of Clinical Pharmacology, Faculty for Clinical Medicine at Mannheim, University of Heidelberg, Mannheim, Germany

- **Slow Action Genomic- NAS**: These receptors act as transcription factors to regulate gene expression by recognizing palindromic hormone response elements (HRE). The classical hormone responses while;
- **Rapid Action Non-Genomic - NS**: These are rapid plasma membrane receptors that modify the Ion-Gated Channels via G-Protein Receptor Modulation.
  - This is how we get such a diversity in hormonal responses in the body and Brain.

Biosynthesis of NeuroSteroids and regulation of their synthesis. International Review of Neurobiology. Vol 46, 2001, Pages 33–60, Synthia H Mellon. Dept of Obstetrics, Gynecology, and Reproductive Sciences, The Metabolic Research Unit University of California-San Francisco. 94143-0556 USA. Hubert Vaudry European Institute for Peptide Research Laboratory of Cellular and Molecular Neuroendocrinology INSERM U-413, UA CNRS, University of Rouen 76821 Mont Saint-Aignan, France.

- The brain, like the gonads, adrenal glands, and placenta, is a steroidogenic organ.
- The steroids synthesized by the brain and by the nervous system have a wide variety of diverse functions.

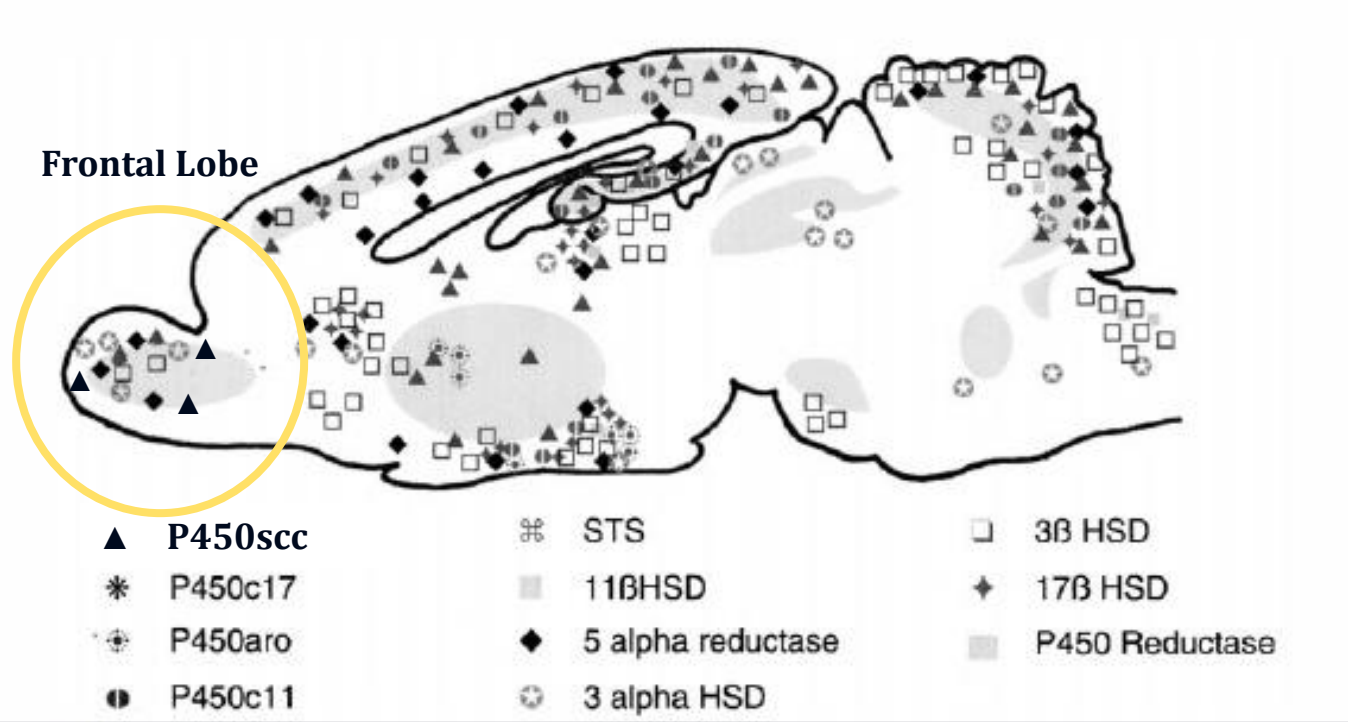
- Neurosteroids mediate their actions not through classic steroid hormone nuclear receptors but through ion-gated neurotransmitter receptors. Therefore, the results are in real-time.

Neurosteroids: Expression of Steroidogenic Enzymes and Regulation of Steroid Biosynthesis in the Central Nervous System.

Pharmacological Reviews. Vol. 51, No. 1. (1999). Ayikoe G. Mensah-nyagan, Hubert Vaudry. Et al Institut Fédératif de Recherches Multidisciplinaires sur Les Peptides No. 23, Laboratoire de Neuroendocrinologie Cellulaire et Moléculaire, Institut National de la Sante et de la Recherche Medicale , UA Centre National de la Recherche Scientifique, Université de Rouen, Mont-Saint-Aignan, France; and Centre de Recherches en Endocrinologie Moléculaire, Le Centre Hospitalier de l'Université Laval, Quebec, Canada

- Neurosteroids, which are involved in the regulation of stress responses, anxiety, sleep, neurodegenerative processes, aggressive behavior, and cognitive activities,
- are now considered as key modulating factors of chemical neurotransmission.

NS Regional Production



Schematic representation of an adult brain showing regional expression of enzymes involved in neurosteroidogenesis. P450scc uses the ER-stores of cholesterol to produce pregnenolone in the inner membrane of the mitochondria.

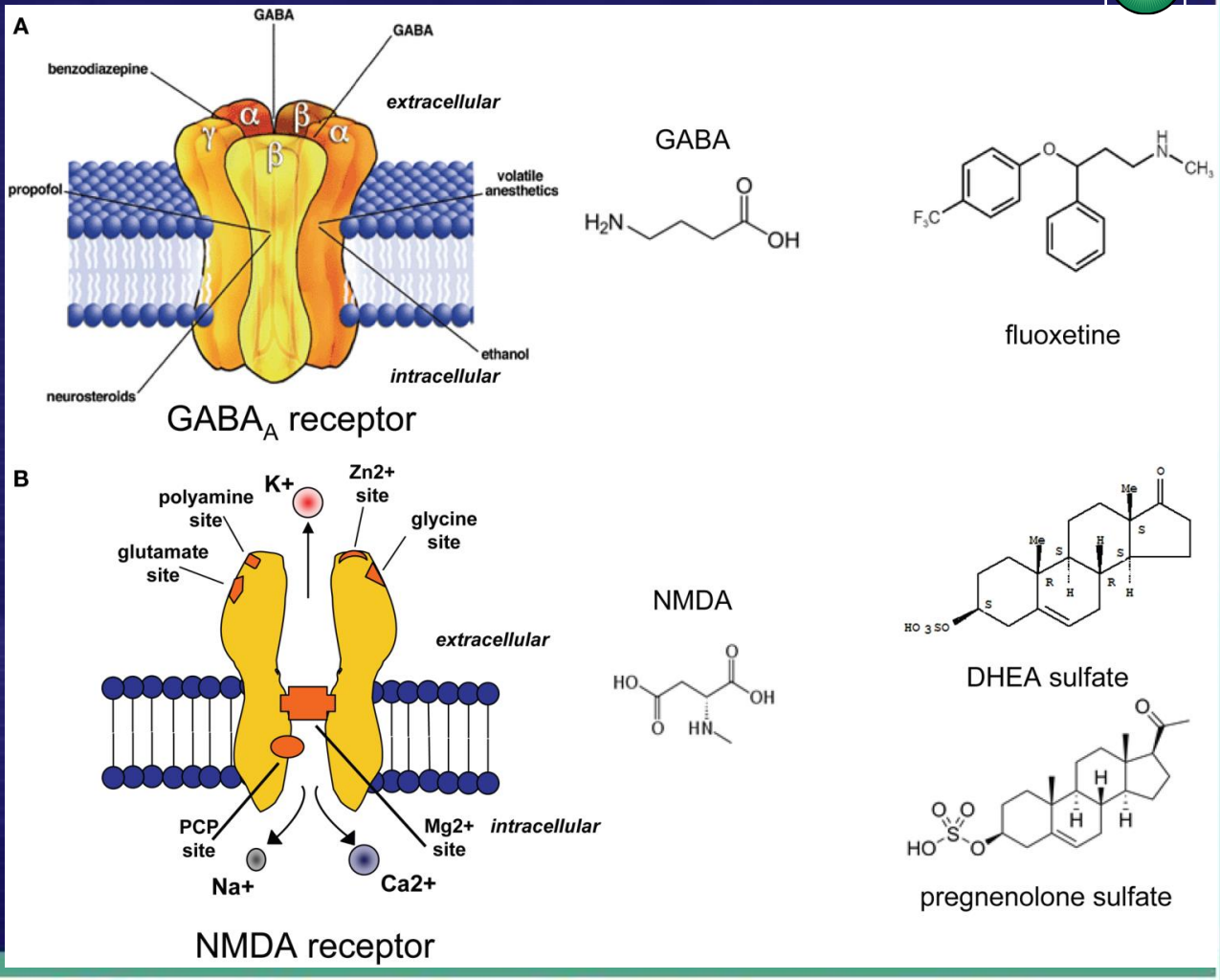
NS Regulation of Production

Enzyme	Substrate	Product	
P450scc	Cholesterol	Pregnenolone	CYP 11A1
3β HSD	Pregnenolone	Progesterone	
P450c11β	11 Deoxycortisol	Cortisol	CYP11B1
P450c11AS	18-OH-Corticosterone	Aldosterone	
3α HSD	Pregnenolone or Progesterone	Allopregnenolone Alloprogesterone	
P450c17	Pregnenolone or Progesterone	DHEA	CYP17A1
3β HSD	DHEA-s	Testosterone	
P450aro	Testosterone	Estradiol	CYP19A

Neurosteroids as neuromodulators in the treatment of anxiety disorders

. Front. Endocrinol., 2011 Patrizia Longone, et al., Rupprecht Molecular Neurobiology Unit, Experimental Neurology, Fondazione Santa Lucia, Rome, Italy. Child Neurology and Psychiatry, Dept of Neuroscience, University of Rome "Tor Vergata,", Rome, Italy. Deptt of Neuroscience, U. of Rome "Tor Vergata,", Rome, Italy. Dept of Psychiatry and Psychotherapy, U. Regensburg, Regensburg, Germany – Slide #3

- The **$GABA_A$ receptor** is an ionotropic receptor and ligand-gated ion channel. Its endogenous ligand is GABA, the major inhibitory neurotransmitter in the central nervous system.
- Upon activation, the $GABA_A$ receptor selectively conducts Cl^- through its pore, resulting in hyperpolarization of the neuron.
- This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring.



A Presynaptic Action of the Neurosteroid Pregnenolone Sulfate on GABAergic Synaptic Transmission. *Mol Pharmacol* 64:857–864, 2003 Zakaria MTCHEDLISHVILI and Jaideep Kapur Department of Neurology, University of Virginia Health Sciences Center, Charlottesville, Virginia

- A comparison of the pre- and postsynaptic effects of PS demonstrated that it was 100-fold more potent in inhibiting presynaptic GABAergic synaptic mechanisms than $GABA_A$ receptors.

- The net effect is a reduction in neurotransmission with potential clinical impact on anxiety, panic attacks, agitation, aggression, and insomnia.

Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. PNAS. Sept 2006. vol. 103 no. 39. Roberto C. Agıs-Balboa, Graziano Pinna, Adrian Zhubi, Ekrem Maloku, Marin Veldic, Erminio Costa, and Alessandro Guidotti. Department of Psychiatry, Psychiatric Institute, University of Illinois, 1601 Taylor Street, Chicago, IL 60612

- The neurosteroids allopregnanolone (ALLO) and tetrahydrodeoxycorticosterone (THDOC) are potent positive allosteric modulators of GABA action at $GABA_A$ receptors.
- A decrease of brain neurosteroid availability has been associated with psychiatric conditions, including anxiety, aggression, pre- menstrual dysphoria, and cognitive and mood disorders.
- Anti-depressants (“SSRIs”) and antipsychotics may exert their beneficial effects, at least in part, by increasing the brain levels of Neurosteroids.

Allopregnanolone

- The biosynthesis of allopregnanolone in the brain starts with the conversion of progesterone into 5α-dihydroprogesterone by **5α-reductase type I**. After that, 3α-hydroxysteroid dehydrogenase converts this intermediate into allopregnanolone.
- Use of Testosterone can deplete the 5-AR1 causing decrease AlloP5 and this is what can cause depression and anxiety in T-Users.
- New medication **Brexanolone is** $34K/yr

Impaired neurosteroid synthesis in Multiple Sclerosis. Brain **2011**: 134; 2703–2721. Farshid Noorbakhsh, Kristofor K. Ellestad,Ferdinand Maingat, Kenneth G. Warren, May H. Han, Lawrence Steinman, Glen B. Baker and Christopher Power. Dept of Medicine (Neurology), University of Alberta, Edmonton, Canada, Dept of Immunology, Tehran University Medical Sciences, Tehran, Iran, Depts of Neurology and Neurological Sciences, Stanford University, Stanford, CA , Dept of Psychiatry, University of Alberta, Edmonton, Canada, Dept of Medical Microbiology and Immunology, University of Alberta, Edmonton, Canada

- These studies are the first report of perturbed neurosteroidogenesis in multiple sclerosis and the related model, which also showed improved outcomes in terms of neurobehavioral deficits, neuropathology and neuromolecular changes with neurosteroid (allopregnanolone) replacement.
- The inflammation associated with demyelination in MS disrupts the glial production of neurosteroids furthering the loss of these neuropermissive hormones.

Progesterone Receptors: Form and Function in Brain. Front Neuroendocrinol. 2008 May ; 29(2): 313–339Roberta Diaz Brinton, Richard F. Thompson, Michael R. Foy, Michel Baudry, Jun Ming Wang, Caleb E Finch, Todd E. Morgan, Frank Z. Stanczyk, Christian J. Pike, and Jon Nilsen. Dept of Pharmacology and Pharmaceutical Sciences, USC, LA, Ca and, Loyola Marymount College, LA, CA, 90045-8405

- Progesterone and its neuroactive metabolites can promote the viability of neurons and function of glial cells within both the central and peripheral nervous system.
- Women have a greater risk of developing multiple sclerosis frequently with the onset of menopause.

https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS

Steroid hormones and neurosteroids in normal and pathological aging of the nervous system. E.E. Baulieu et al, Inserm, 80 rue du Général Leclerc, Kremlin-Bicˆetre, France. Dept of Clinical and Veterinary Medicine, U. of Cambridge, Madingley Road, Cambridge, Instituto Cajal, 37 Avenida Doctor Arce, Madrid, Spain. Dept of Pharmacology, U. of Dundee. Inserm, Domaine de Carreire, Bordeaux, France. Dept of Endocrinology, Center of Excellence on Neurodegenerative Diseases, U. of Milan, Italy. Biological Research Center , Hungary. Institute of Cell Biology, ETH Hönggerberg, Zürich CH-8093, Switzerland.

- In Alzheimer's patients, there was a general trend toward lower levels of neurosteroids in different brain regions, and neurosteroid levels were negatively correlated with two biochemical markers of Alzheimer's disease, the phosphorylated Tau Protein and the β-amyloid peptides.

- The greatest loss of pregnenolone, pregnenolone-s, progesterone, progesterone-s, pregnanolone, pregnanolone-s, and DHEA-s occurs in the **Frontal Lobes**.

The Neurosteroid Allopregnanolone Is Reduced in Prefrontal Cortex in Alzheimer's Disease. Biological Psychiatry. Volume 60, Issue 12. Dec **2006**. Christine E. Marxx Christine E. Marx. Department of Psychiatry and Behavioral Sciences, Durham, North Carolina

- Neurosteroid levels (allopregnanolone-s, pregnenolone-s, dehydroepiandrosterone-s) were determined in postmortem prefrontal cortex (PFC) in subjects with Alzheimer's Disease.
- Subjects with AD demonstrate significant reductions in PFC allopregnanolone levels, a finding that is relevant to neuropathological disease stage severity.

A new strategy in treatment of neurodegenerative diseases: Neurosteroids.

Ankara Üniv Vet Fak Derg, 60, 79-83, 2013. Gül Fatma YARIM
Ondokuz. Ondokuz Mayıs Üniversitesi, Veteriner Fakültesi, Biyokimya Anabilim Dalı, Samsun.

- A large number of studies support the neurosteroids have neuroprotective, myelinating, anti-apoptotic and anti-inflammatory effects.
- Combined administration of 17β-estradiol and progesterone have been demonstrated to protect the brain from demyelination and stimulate remyelination.

17b-Estradiol protects against NMDA-induced excitotoxicity by direct inhibition of NMDA receptors.

Brain Research 761 1997 338–341 Ž. Charles E. Weaver Jr. 1, Mijeong Park-Chung 2, Terrell T. Gibbs 3, David H. Farb. Laboratory of Molecular Neurobiology, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118-2394, USA

- The presence of physiologic levels of 17β Estradiol, during traumatic events, can protect the vulnerability of these Glutamate sub-receptors – the NMDAR, from developing a state of excitotoxicity associated with neuronal death.

ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury. Annals of Emergency Medicine, **2006.**07.932.Wright DW et al.

- Mortality was decreased by 50% in the Progesterone treated group although by 30 days the neurological outcome was the same as in the placebo group.
- On the Glasgow Outcome Score-Extended scale, 55.6% of patients who received progesterone and who had moderate initial brain injury had moderate to good scores at 30 days, compared with none of the placebo patients (no risk ratio estimate possible; *P=0.0202).*

Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury.

Brain Research 1049 (2005) 112 – 119. Edward H. Pettus, David W. Wright, Donald G. Steina, Stuart W. Hoffmana, Dept of Emergency Medicine, Emory University, Evans Building, Room 255, 1648 Pierce Dr NE, Atlanta, GA 30322, USA. Dept of Cell Biology, Emory University, Atlanta, GA 30322, USA

- The initial biomechanical force in TBI causes ionic imbalances, oxidative damage, microglial activation, immune cell invasion, and cytokine release.
- Activation of immune cells, triggers the production of free radicals and pro-inflammatory compounds such as cytokines, prostaglandins, proteases, complement factors, adhesion molecules, and inducible nitric oxide synthase.
- Progesterone treatment given after TBI can reduce edema, necrosis, apoptosis, blood–brain barrier compromise, and the mediators of inflammation.

Astrocytes and Neurosteroids: Metabolism of Pregnenolone and Dehydroepiandrosterone. Regulation by Cell Density

The Journal of Cell Biology, Volume 121, Number 1, April 1993 135-143 Yvette Akwa, Nicole Sanan~s, Monique Gou6zou, Paul Robel, Etienne-Emile Baulieu, and Claude Le Goascogne. INSERM U33, Lab Hormones, 94276 Bicetre Cedlex, France

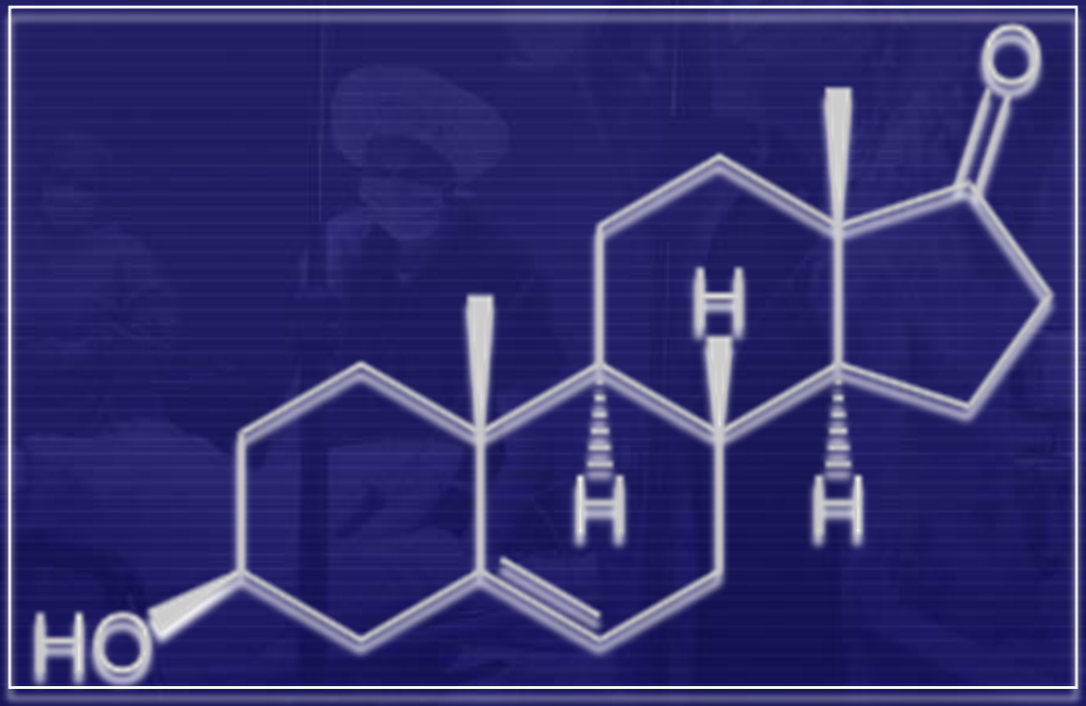
- It was reported that Pregnenolone can be converted to Progesterone in glial cells (mostly, oligodendrocytes).
- Thereafter, progesterone converts to allopregnanolone with neuroprotective and neuroregenerative effects.
- Astrocytes, which participate to the regulation of the CNS function, appear to also be involved in the metabolism of neurosteroids.

❖ The regional loss of Glia is proportionate to the loss of Neurosteroids and presence of neurodegenerative diseases.

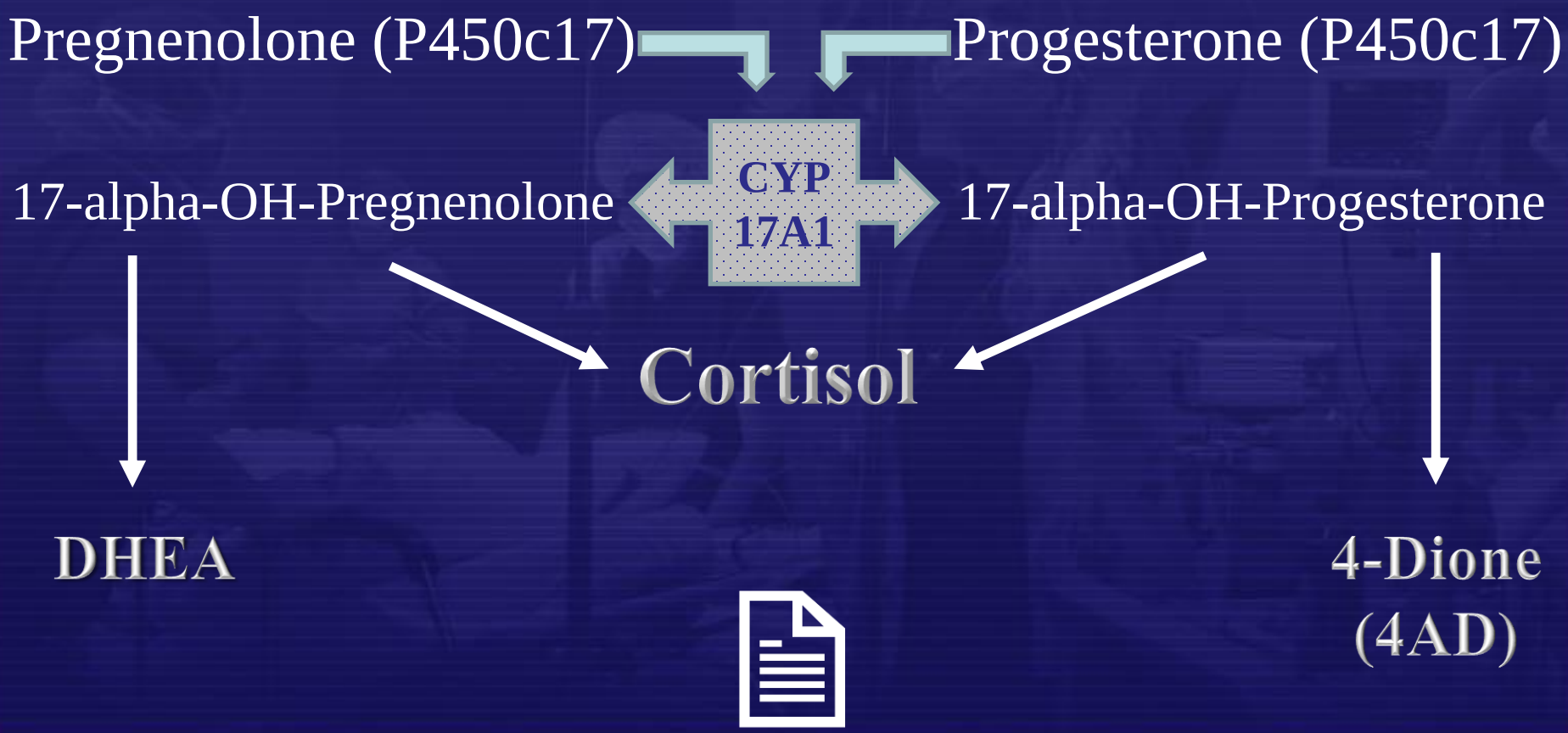
The two major pathways; the Secondary:

- Pregnenolone's conversion to androgens and estrogens.
- Dehydroepiandrosterone and DHEA-s are the most prolific.

DHEA



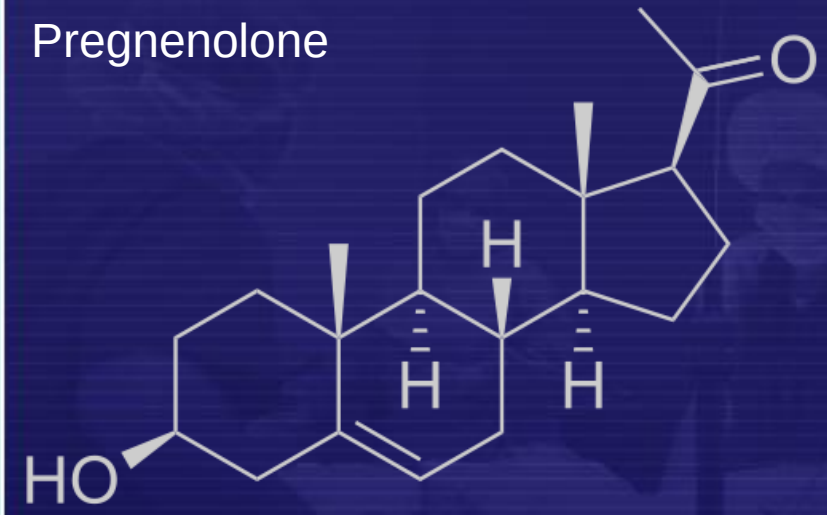
Conversion of pregnenolone to DHEA by human P450c17 Evidence that DHEA is produced from the released intermediate, 17a-OH-pregnenolone. Eur. J. Biochemistry. Penny Soucy and Van Luu-The Medical Research Council Group in Molecular Endocrinology, Oncology and Molecular Endocrinology Research Center, CHUQ Pavillon CHUL and Laval University, Ste-Foy, Quebec, Canada (2000)



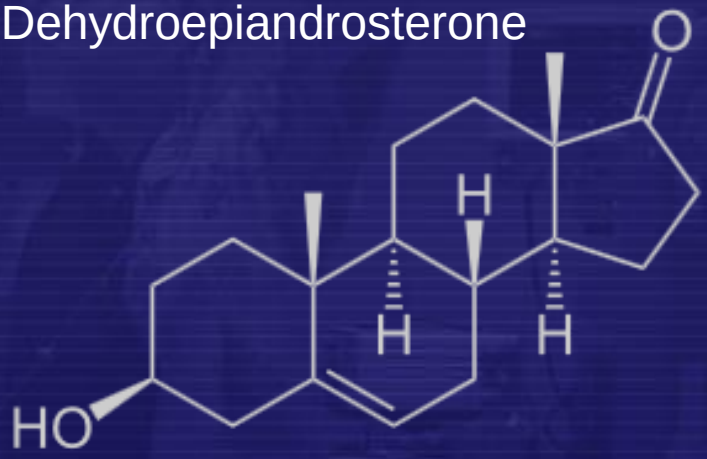
Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids.

Proc. Natl. Acad. Sci. Vol. 95, pp. 4089–4091, April 1998. Etienne-Emile Baulieu* and Paul Robel Institute National de la Sante et de la Recherche Medical, Cedex, France

Pregnenolone



Dehydroepiandrosterone



Dehydroepiandrosterone (DHEA)

- DHEA is a 19-carbon steroid hormone, classified as an adrenal androgen and is rapidly sulfated to DHEA-S, the predominant and active form found circulating in the plasma.
- Plasma levels decline progressively with age beginning around age 40.
- Autoimmune diseases such as SLE, rheumatoid arthritis, and multiple sclerosis might be associated with declining DHEA levels.

Dehydroepiandrosterone (DHEA)

- DHEA is a steroid hormone secreted primarily by the adrenal glands and to a lesser extent by the **brain**, **SKIN**, **testes**, and **ovaries**.
- It is the most abundant circulating steroid in humans and can be converted into other hormones, including estrogen and testosterone.
- It has been characterized as a pleiotropic "buffer hormone," with receptor sites in the liver, kidney, and testes, and has a key role in a wide range of physiological responses.

Dehydroepiandrosterone (DHEA)

- Circulating levels of DHEA decline with age and a relationship has been suggested between lower DHEA levels and heart disease, cancer, diabetes, obesity, chronic fatigue syndrome, AIDS, and Alzheimer's disease.

Dehydroepiandrosterone (DHEA)

- DHEA is metabolized via two pathways- through hepatic circulation or via a cutaneous pathway where it is metabolized by the skin and other tissues sensitive to sex steroids.
- Therefore, **it can cause increased hair and oil production without elevation in DHT**.

Replacement of DHEA in aging men and women. Potential remedial effects.

Annals of NY Academy of Science 1995;774:128-142.
Yen SS, Morales AJ, Khorrram O. (1995)

- Clinical evidence supporting DHEA's use as an anti-aging hormone is inconclusive.
- In one double-blind, cross-over study of 30 subjects, age 40 to 70 years, supplementing 50 mg/day DHEA or placebo for three months, 67 percent of men and 84 percent of women in the DHEA group reported a remarkable increase in physical and psychological well-being; no side effects were noted.

Testosterone and DHEA activate the glucose metabolism-related signaling pathway in skeletal muscle. Am J Physiol Endocrinol Metab 294: E961–E968, 2008.

- DHT is 4 times more anabolic than Testosterone.
- DHT from testosterone and/or DHEA activates glucose transporter-4 (GLUT-4)-regulating pathway in skeletal muscles (Cr).
- Improved production and availability of muscle glycogen helps with muscle growth.

DHEA-s concentrations in asthmatic patients: pilot study. New Zealand Med J 1984; 97:805-808. Dunn PJ, Mahood CB, Speed JF, Jury DR.

- Several clinical studies have demonstrated DHEA, given in doses of 10-74 mg/day, to be of benefit in treating food allergy, multiple chemical sensitivity, asthma, and hereditary angioedema.
- These studies reported a decrease in severity of symptoms regardless of whether patients were receiving corticosteroid therapy or not.

Dehydroepiandrosterone (DHEA)

- Produced in adrenal cortex and brain
- Most abundant steroid hormone
- Precursor to androgens and estrogens
- Low levels associated with;
  - Poor wound healing
  - Decreased myelin production (Oligodendrocytes)
  - Type 2 diabetes
  - Immune dysfunction
  - Cancer
  - Hypertension
  - Cardiovascular disease (IHD)
  - Depression (Depression)
  - Low libido
  - Osteoporosis

Dehydroepiandrosterone (DHEA)

Dosing	Female	Male
Supplemental	10 - 25 mg/day	25 - 50 mg/day
Treatment	25 – 50mg/day	50 – 100mg/day
Experimental	100mg/day	100 – 200mg/day

Side Effects:

- Based upon conversion issues.
- Acne
- Gynecomastia
- Hirsutism

The treatment of SLE requires doses of 50-200 mg/day to show benefits.

Bio-availability of oral 50mg of DHEA

The following graph shows the concentration of DHEA in saliva after a single application of 50 mg of DHEA:

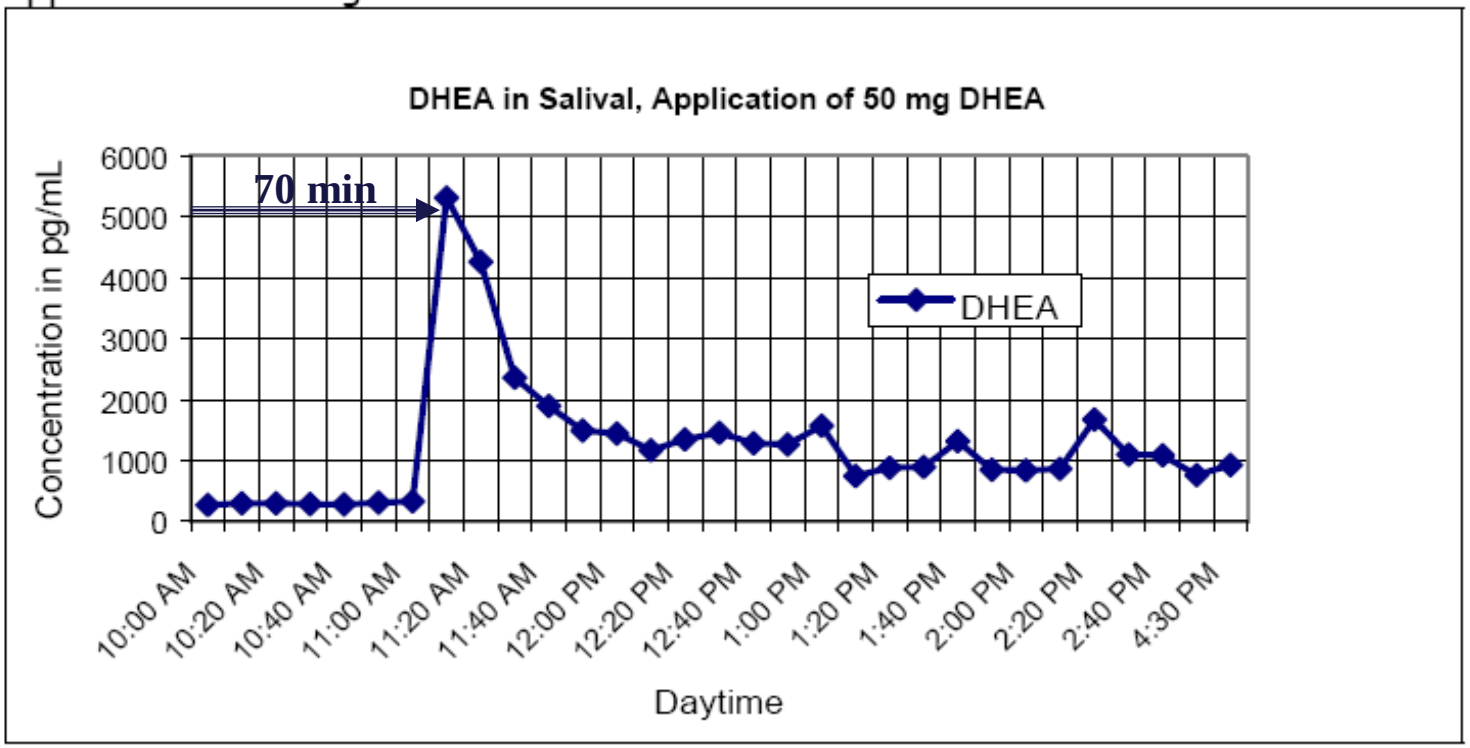


Fig. 48: Concentration of DHEA in the saliva of a young healthy man (27 years) after application of 50 mg DHEA, measured in 10 minute time spans with IBL-LIA.

Bio-conversion of oral 50mg of DHEA

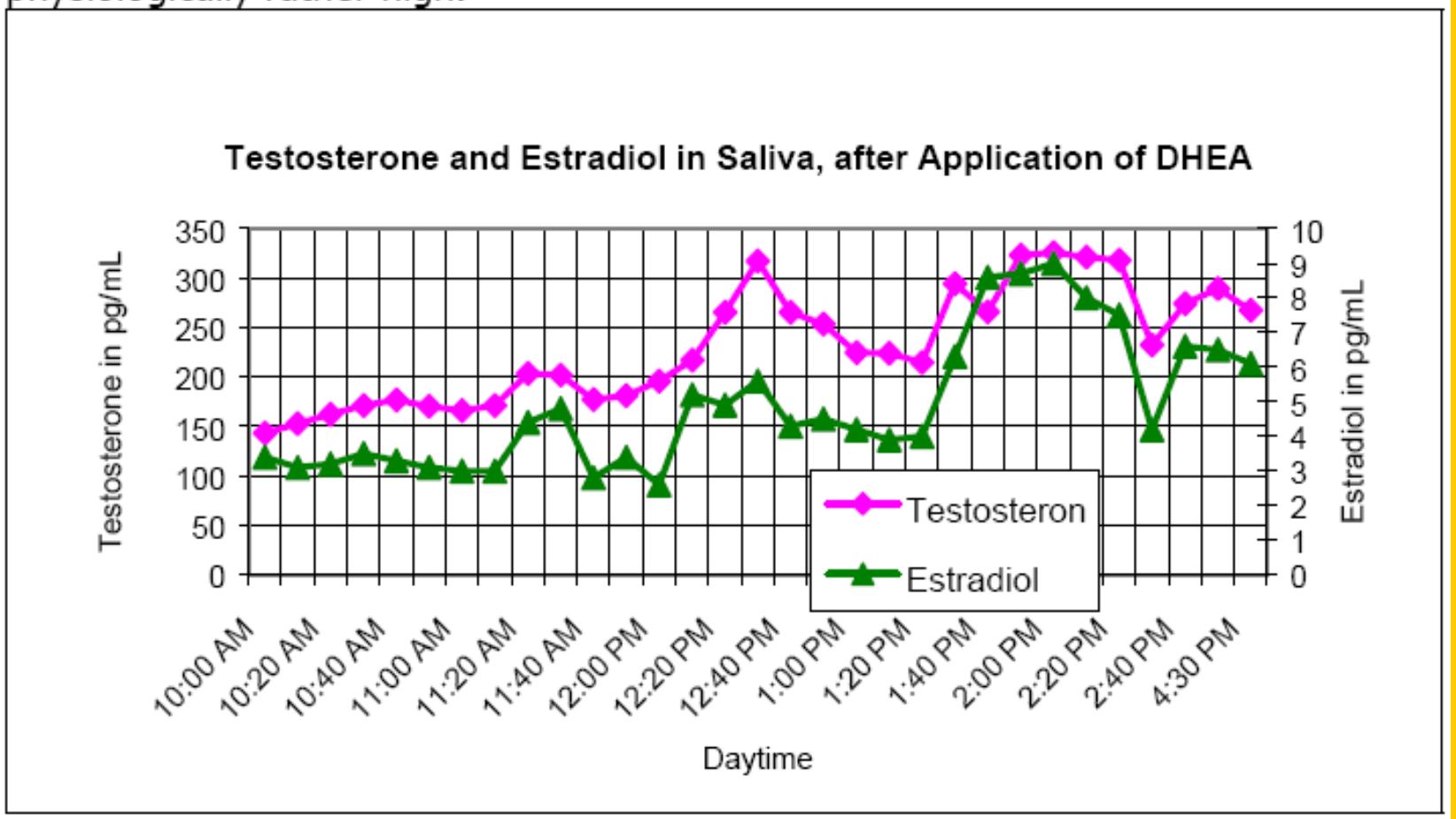


Fig. 49: Concentration of testosterone and estradiol in saliva of a young healthy man (27 years old) after one application of 50 mg DHEA, measured in 10 minutes time span with IBL-LIA

CASE #3:

54 y/o Male on 40mg IM TC Q3 days, 25mg DHEA and 30mg of Pregnenolone.

E1 > E2 due to DHEA-AD-E1

Lab Test (m)	Result	Median	
Growth Hormone		5ng/ml*	
IGF-1		>200 ng/ml	
IGF-BP3		>4000 ng/ml*	
DHEA-s	432	255 ug/ml*	
Free Testosterone	10.43	12-14 pg/ml	
Total Testosterone	632	690 ng/ml*	
DHT		< 55 ng/dL	
SHBG		45 pg/ml*	
Estrone	103	< 60 pg/ml	
Estradiol (V)	37	25 pg/ml *	
Pregnenolone		96 ng/dL	
Progesterone (V)		<0.8 ng/ml*	
Cortisol		<15 ug/dL	

CASE #4:

42 y/o male in SF, close combat training for urban assaults.

Lab Test (m)	Result	Median	
Growth Hormone		5ng/ml*	
IGF-1		>200 ng/ml	
IGF-BP3		>4000 ng/ml*	
DHEA-s	673	255 ug/ml*	
Free Testosterone	4.91	12-14 pg/ml	
Total Testosterone	358	690 ng/ml*	
DHT		< 55 ng/dL	
SHBG		45 pg/ml*	
Estrone		< 60 pg/ml	
Estradiol (V)		25 pg/ml *	
Pregnenolone		96 ng/dL	
Progesterone (V)		<0.8 ng/ml*	
Cortisol		<15 ug/dL	

The Sex Steroid Precursor DHEA Accelerates Cutaneous Wound Healing Via the Estrogen Receptors. J Invest Dermatol 125:1053 – 1062, 2005. Stuart J. Mills, Jason J. Ashworth, Stephen C. Gilliver, Matthew J. Hardman, and Gillian S. Ashcroft Faculty of Life Sciences, Michael Smith Building, Manchester, UK (2005)

- In humans we have observed that DHEA/DHEA-s levels are significantly decreased in subjects with chronic impaired healing states compared to health age-matched controls. We suggest that DHEA treatment is potentially a safe, effective treatment to modulate impaired wound healing states in the elderly.

1. DHEA can accelerate wound healing and dampen local inflammation in an impaired healing model in which mice are estrogen-depleted;

2. DHEA acts in vivo via its conversion to estrogen, and through the ER;

3. macrophage production of pro-inflammatory cytokines is inhibited by DHEA via classical (MIF) and non-classical (IL-6, TNF-a) ER pathways, and MAP kinase/ PI3 kinase pathways (MIF).

DHEA-neuroprotection and -neurotoxicity after transient cerebral ischemia in rats

. Journal of Cerebral Blood Flow & Metabolism (2009) 29, 287–296; Zhen Li, et al. Laboratory of Reproductive Medicine, Nanjing Medical University, Jiangsu, China; Dept. of Physiology, Nanjing Medical University, Jiangsu, China; Dept of Physiology, Nagoya University Graduate School of Medicine, Nagoya, Japan; Dept of Molecular Physiology National Institute for Physiological Sciences, Okazaki, Japan. (2009)

- DHEA not only provides ischemic neuroprotection with a long therapeutic opportunity but also exerts;
- neurotoxicity protection when administered during ischemia and early reperfusion,
- which points to the importance of administration timing of DHEA in the clinical treatment of brain damages by the transient brain ischemia including stroke.

1. Relationship between blood and joint tissue DHEA-s levels in rheumatoid arthritis and osteoarthritis. Clinics Exp Rheumatology 1993;11:597-601. de la Torre B, Hedman M, Nilsson E, et al.
2. Low DHEA-s steroid hormone levels in systemic lupus erythematosus (SLE). Clinics Exp Rheumatology 1989;7:583-588. Hedman M, Nilsson E, de la Torre B.
3. DHEA in multiple sclerosis: positive effects on the fatigue syndrome in a non-randomized study. In: Kalimi M, Regelson W, eds. The Biologic Role of DHEA. New York: Walter de Gruyter; 1990:95-100. Calabrese VP, et al.

- Studies have shown DHEA to be of therapeutic value in SLE, rheumatoid arthritis, autoimmune hemolytic anemia, and multiple sclerosis.
- DHEA levels are often low in patients with these diseases, at least in part due to adrenal suppressive drugs such as prednisone.
- A return to normal physiologic levels appears to reduce immune complex formation, inhibit lymphocyte proliferation, and increase stamina and sense of well-being.

Dehydroepiandrosterone sulfate enhances natural killer cell cytotoxicity in humans via locally generated immunoreactive IGF-1.
J Clin Endocrinol Metab 1999 Sep;84(9):3260-7. **Solerte SB.**

- In the presence of DHEA-s, Natural Killer Cells in culture increased in a dose related fashion as did cell production of IGF-1 by the Natural Killer Cells.
- NKC from older patients responded more briskly to DHEA-s.

Nudging Oligodendrocyte Intrinsic Signaling to Remyelinate and Repair: Estrogen Receptor Ligand Effects.

J Steroid Biochem Mol Biol J Steroid Biochem Mol Biol. 6/2016.Anna J. Khalaj, Jonathan Hasselmann, Catherine Augello Spencer Moore, and Seema K. Tiwari-Woodruff, Division of Biomedical Sciences, School of Medicine at the UC, Riverside, Neuroscience Graduate Program, University of California, Riverside

- An enzyme deficiency in the conversion of DHEA to ADIOL is deficient and causes the ER-Beta receptor to fail increasing the expression of the MS susceptible Locus.

$$DHEA = ADIOL = ERBeta = downregulation\ of\ MS\ SL.$$

Dehydroepiandrosterone modulates GHRH, Somatostatin, and angiotensin II action at the pituitary level. Journal of Endocrinology (2005) 185, 165–172C Suárez, J Vela, I García-Tornadú and D Becu-Villalobos Instituto de Biología y Medicina Experimental, CONICET, V, Obligado 2490, Buenos Aires 1428, Argentina.

- DHEA, directly or a metabolite, is able to modulate the hormonal response of the pituitary to hypothalamic regulators.
- **DHEA enhances pituitary Prolactin release and induces GH secretion**.
- These effects could help explain some of the beneficial side effects observed in patients on prolonged DHEA treatments, and therefore, should be taken into account when considering its use.

Double-Blind Treatment of Major Depression With Dehydroepiandrosterone.

American Journal of Psychiatry 1999; 156:646–649. Owen M. Wolkowitz, M.D., Victor I. Reus, M.D., Audrey Keebler, B.A., Nicola Nelson, B.A., Mirit Friedland, B.A., Louann Brizendine, M.D., and Eugene Roberts, Ph.D.

- Open-label or single-blind treatment studies as early as 1952 noted that DHEA treatment improved mood, energy, confidence, interest, and activity levels in patients with "**inadequate personality**" or "**emotional and constitutional immaturity**".
- In a 1994 double-blind trial, Morales et al. demonstrated a significant DHEA-induced increase in sense of well-being in middle-aged and elderly healthy volunteers.

Cytokines and Cognition—The Case for A Head-to-Toe Inflammatory Paradigm

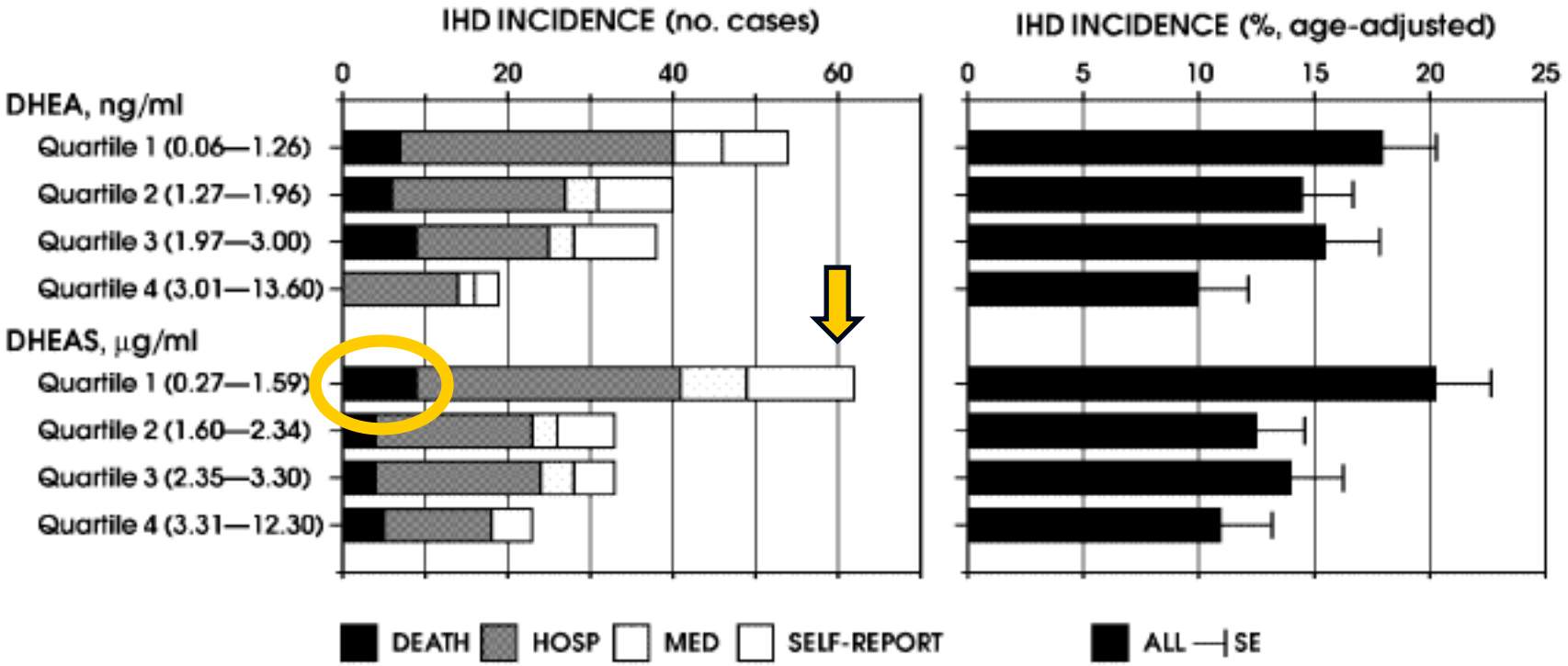
. JAGS 50:2041–2056, 2002. Caleb E. Finch, PhD, et al, St. Vincent Institute on Aging, St. Vincent Hospitals and Health Services, Indianapolis, IN; L Davis School of Gerontology, Dept of Biological Sciences, USC, CA. Div of Geriatrics and Center for the Study of Aging and Human Development, Duke University Med Cent, Durham, NC; and Geriatric Research, Education and Clinical Center, Veterans Affairs Medical Center, Durham, North Carolina.

- Dehydroepiandrosterone (DHEA) inhibits IL-6 secretion from human mononuclear cells in vitro.
- Thus, an age-related increase in IL-6 could be due to a loss of tonic inhibition by DHEA as levels of this adrenal hormone decrease with age.

Low dehydroepiandrosterone and ischemic heart disease in middle-aged men: prospective results from the Massachusetts Male Aging Study. Am J Epidemiology 2001;153:79-89. Feldman HA, Johannes CB, Araujo AB, et al.

- A recent clinical study of 1,167 men was conducted to determine whether serum DHEA and DHEA-S levels could predict ischemic heart disease over a nine-year interval.
- Men with serum DHEA and DHEA-S levels in the lowest quartile at baseline were significantly more likely to develop ischemic heart disease.

Low Dehydroepiandrosterone and Ischemic Heart Disease in Middle-aged Men: Prospective Results from the Massachusetts Male Aging Study. Am J Epidemiol Vol. 153, No. 1, 2001



Summary

1. **When providing HRT you need to add DHEA and P5 (DHEA-P5).**
2. **Any cause of neuroinflammation will require DHEA-P5.**
3. **Neuroprotection inferred by both these products is worth the investment.**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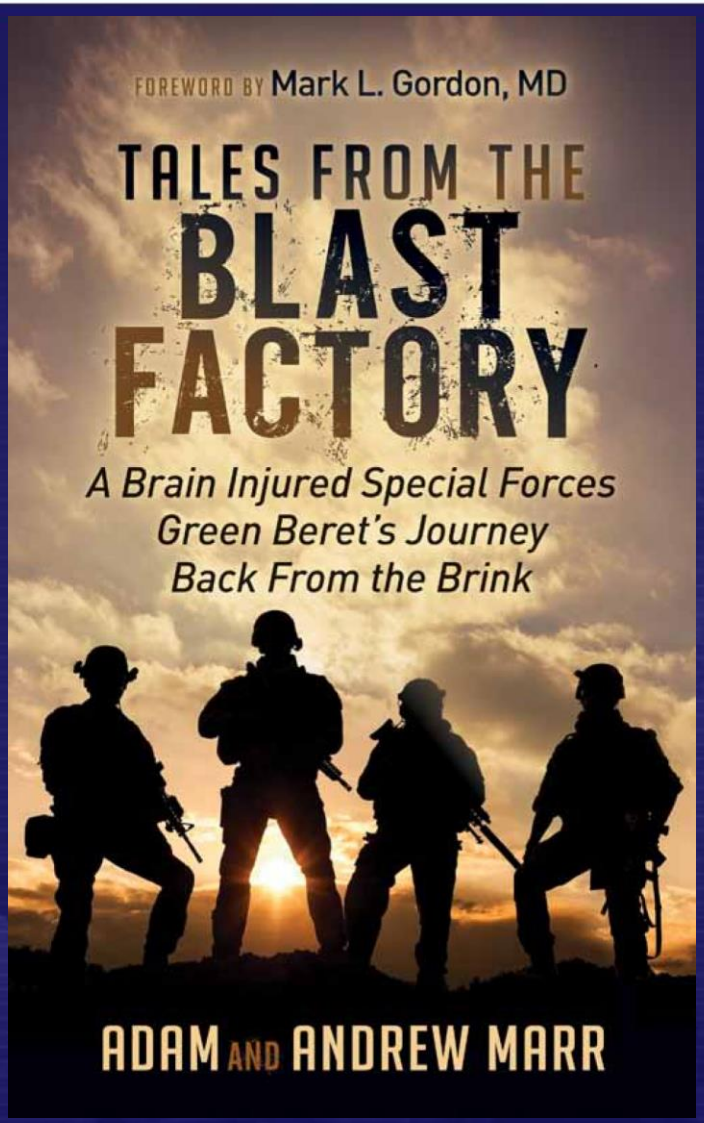

www.WAFTBI.org

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Dr. Mark L. Gordon, a residency trained, board certified, Family Physician, branched out into Endocrinology over 20 years ago just to develop a fascination in the field of Neuroendocrinology; the science of brain hormones.

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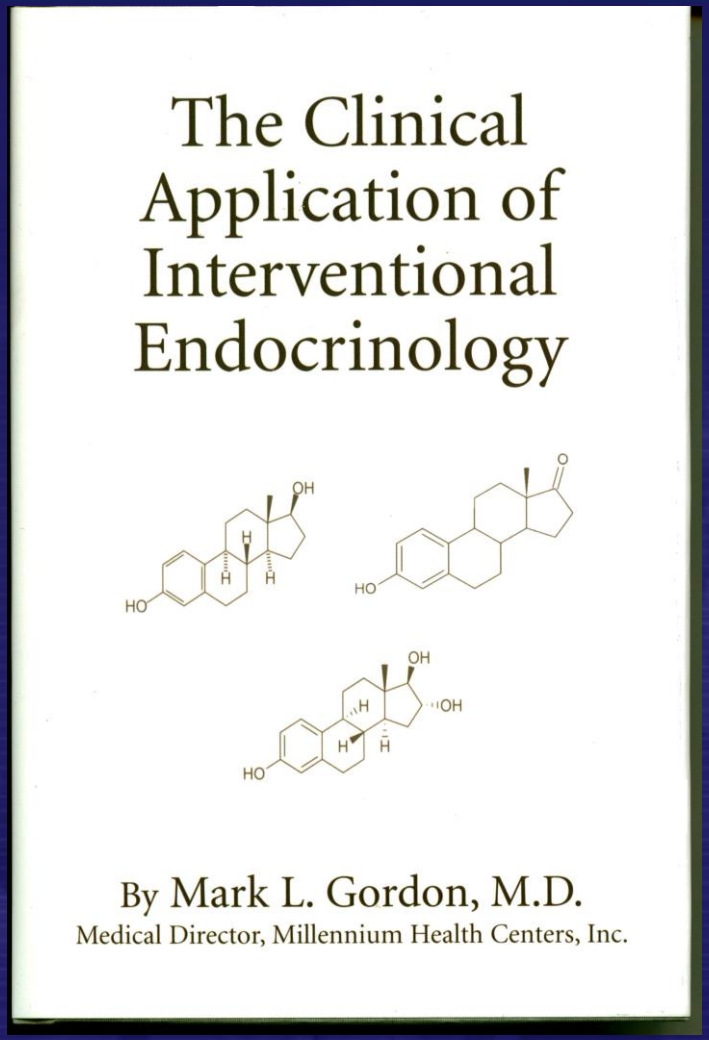

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INTRODUCING

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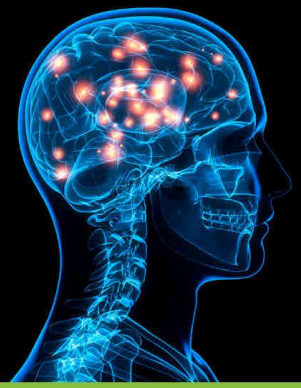

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- Guarana
- Rhodiola rosea
- Quercetin
- Vitamin B12
- EGCG

B is for Brain:
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Composition:
- PQQ
- Vitamin CoQ10
- Vitamin B1
- Vitamin B2
- Vitamin B5
- Vitamin B12

Most common combinations:
1. Pre-breakfast: 1 teaspoon of CME and one teaspoon BC2.
2. Pre-breakfast: 1 teaspoon of BC2 and one teaspoon B4B.
3. Pre-breakfast: 1 teaspoon of CME, 1 teaspoon BC2, and ½ to 1 teaspoon of B4B.

Note: Any ONE of these combinations can be mixed in 4oz(120cc) of water or carbonated water and then consumed. We have found that the on-set of effects is faster.

*US FDA Data on file.

To learn about our Brain Health Programs please visit **www.TBIHelpNow.org**

Directions: Take 2.5 to 5 milliliters (1/2 to 1 teaspoon) in the morning, or as directed by your healthcare provider. **Shake before using, refrigerate after opening and use within 45 days. This product is intended for oral use only.**

Warning: Do not use if you are pregnant, nursing, or under the age of 18. Consult a healthcare professional before using this, or any other dietary supplement, especially if you have a medical condition or if you are taking any medications. Immediately discontinue use and consult a healthcare professional if you experience any adverse reactions. KEEP OUT OF REACH OF CHILDREN. Do not use if safety seal is damaged or missing.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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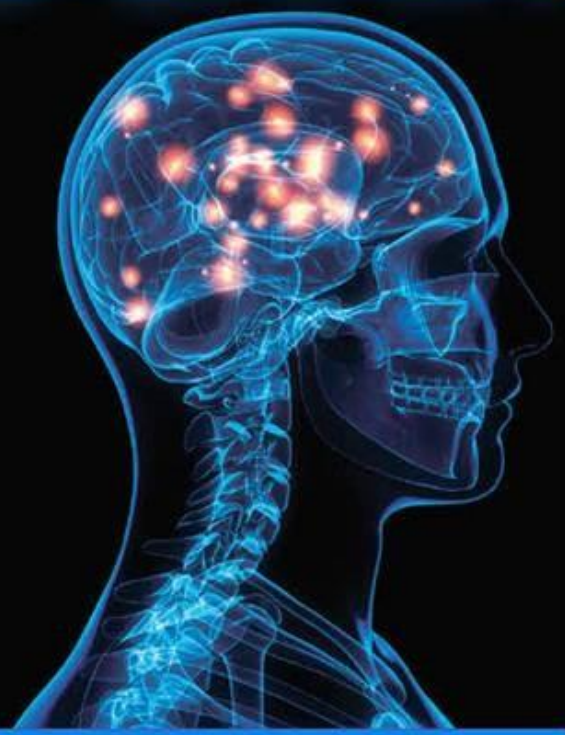
B is for BRAIN



CoQ10, PQQ, B1, B2, B6, B12

Supports Memory and Cognitive Health*

Dietary Supplement

5.07 FL. OZ. (150mL)

Supplement Facts

Serving Size: 1 tsp (5 ml)
Servings Per Bottle: 60

Amount Per Serving		%DV
Thiamin	1 mg	67
Riboflavin	25mg	1471
Vitamin B12 (as Methylcobalamin)	250mcg	4167
Pantothenic Acid	125mg	1250
Proprietary Blend: CoQ10, Medium Chain Triglycerides (from palm kernel), PQQ	60 mg	†

† Daily Value (DV) not established.

Other Ingredients: Purified Water, Non-GMO Sunflower Lecithin***, Glycerin (from palm kernel), Natural Flavors, Stevia Leaf Extract (as glucosylsteviosides), Potassium Sorbate

***Essential Lipid Blend

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Directions: 1 tsp (5mL) 30 minutes before breakfast and 30 minutes before dinner.

Warning:
Not intended for use by anyone less than 10 years of age without a physician's directions. Do not consume the product if you are pregnant or nursing. If you experience any adverse reaction immediately discontinue use and consult your physician. Keep out of reach of children. Do not use if seal is broken or missing.

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Brain Care II

Developed in Conjunction with the Millennium-Warrior Angels Foundation TBI Project

5.07 FL. OZ. (150mL)

Supplement Facts

Serving Size 1 tsp (5mL)
Servings Per Container 30

Amount Per Serving	%DV*
Proprietary Blend: Water, DHA, Gamma-Tocopherol, NAC, Quercetin, Vitamin C Palmitate, and EGCG	400mg*

*Daily Value (DV) not established

Other Ingredients:
Water, Phospholipids, Maltodextrin, Natural Flavors, Potassium Sorbate and Sodium Benzoate (to preserve freshness), Sodium Citrate, Citric Acid.

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