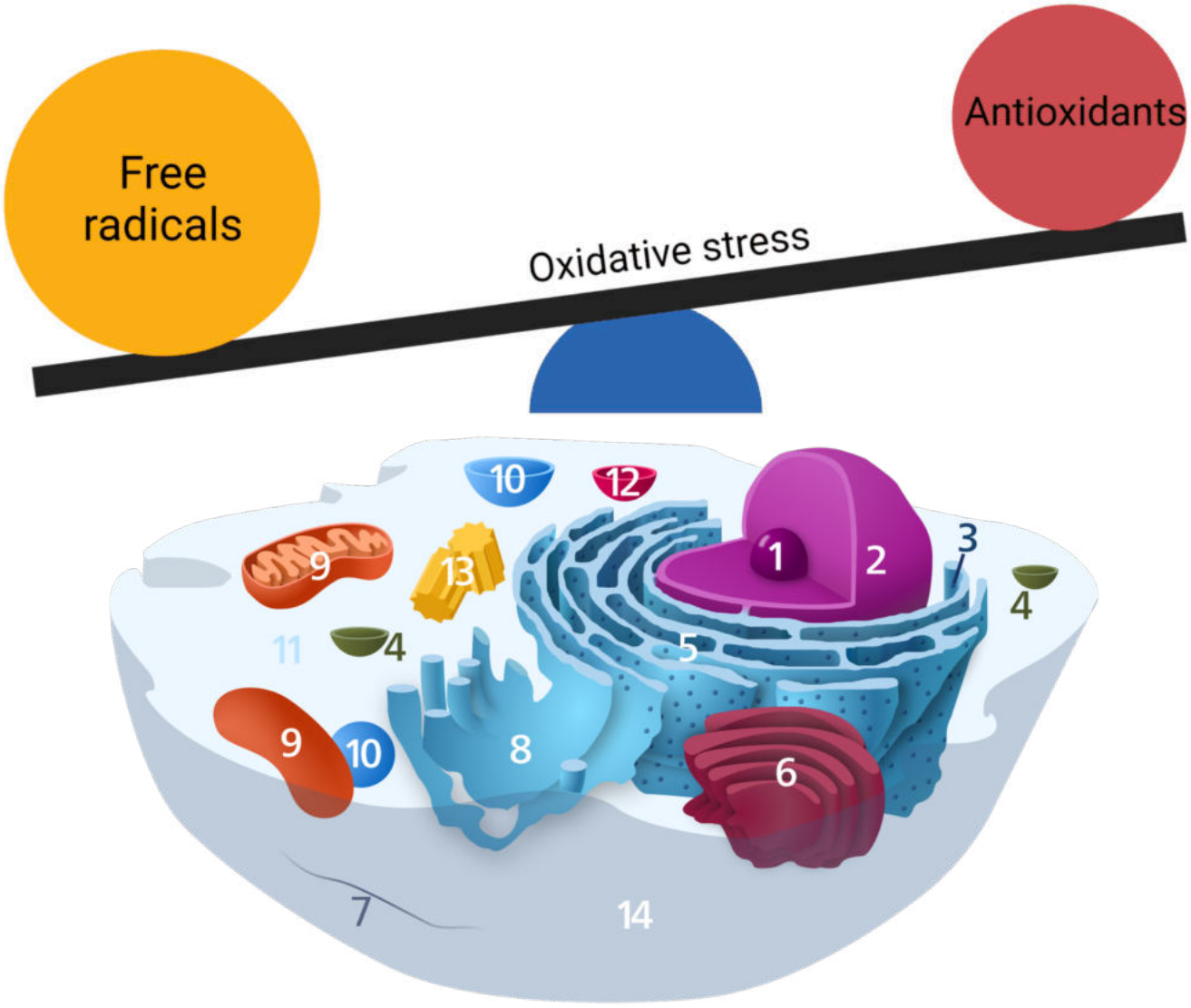
When and how to prescribe testosterone, estrogen and DHEA

Aging Process



Front. Aging Neurosci., 03 June 2022,Sec. Cellular and Molecular Mechanisms of Brain-aging. Volume 14 - 2022

Mitochondria and sex steroid hormones during aging

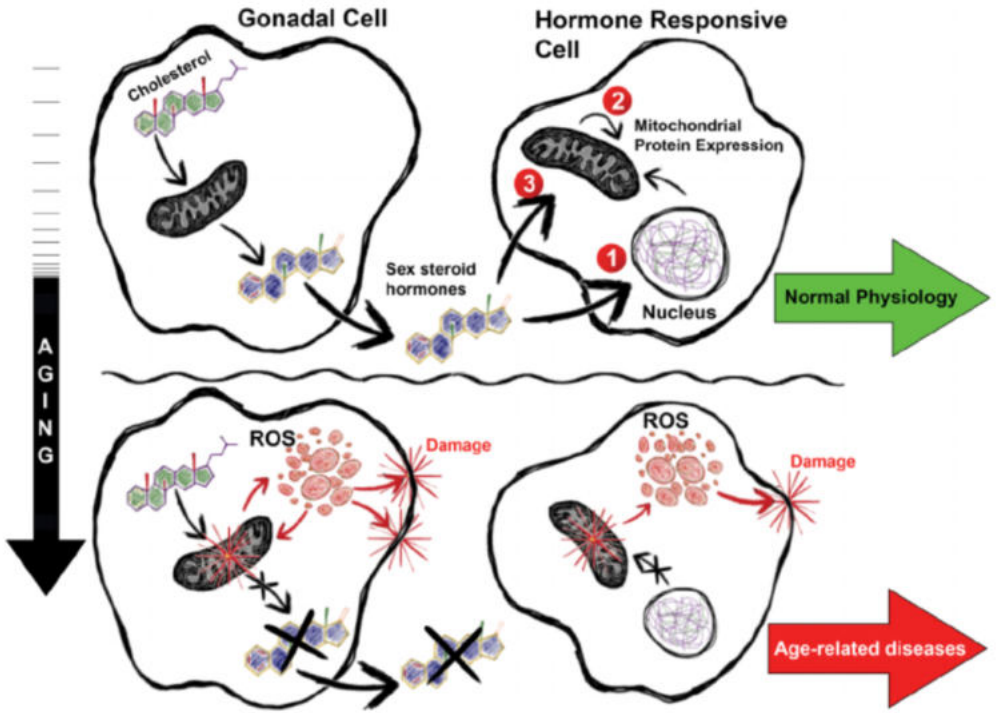
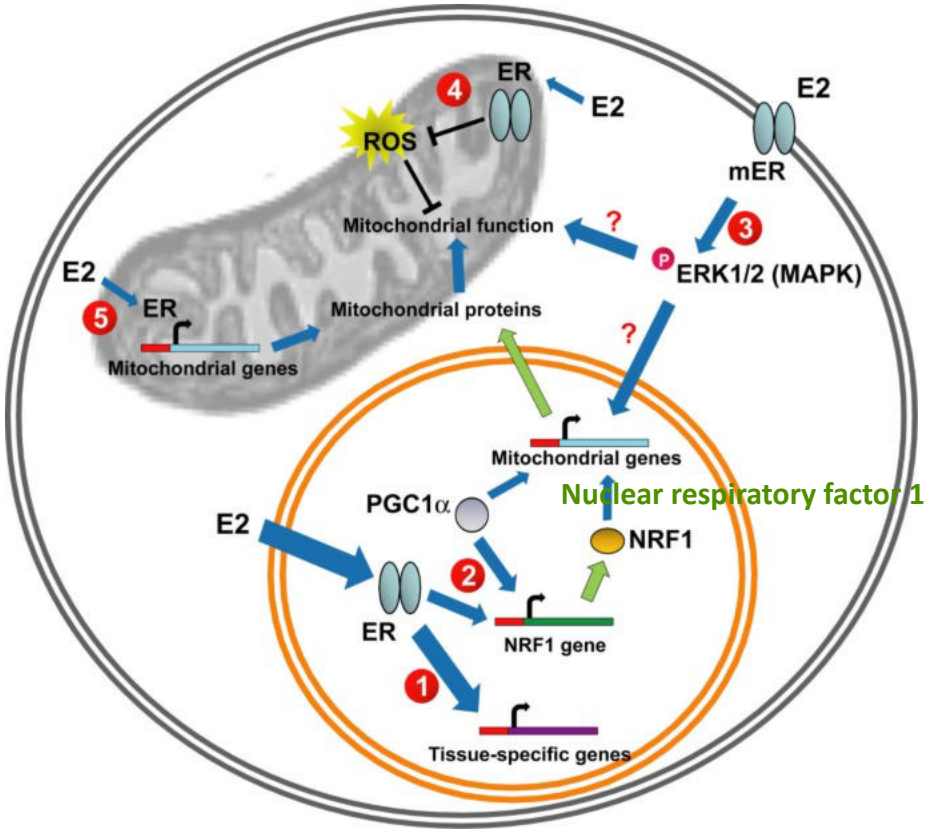


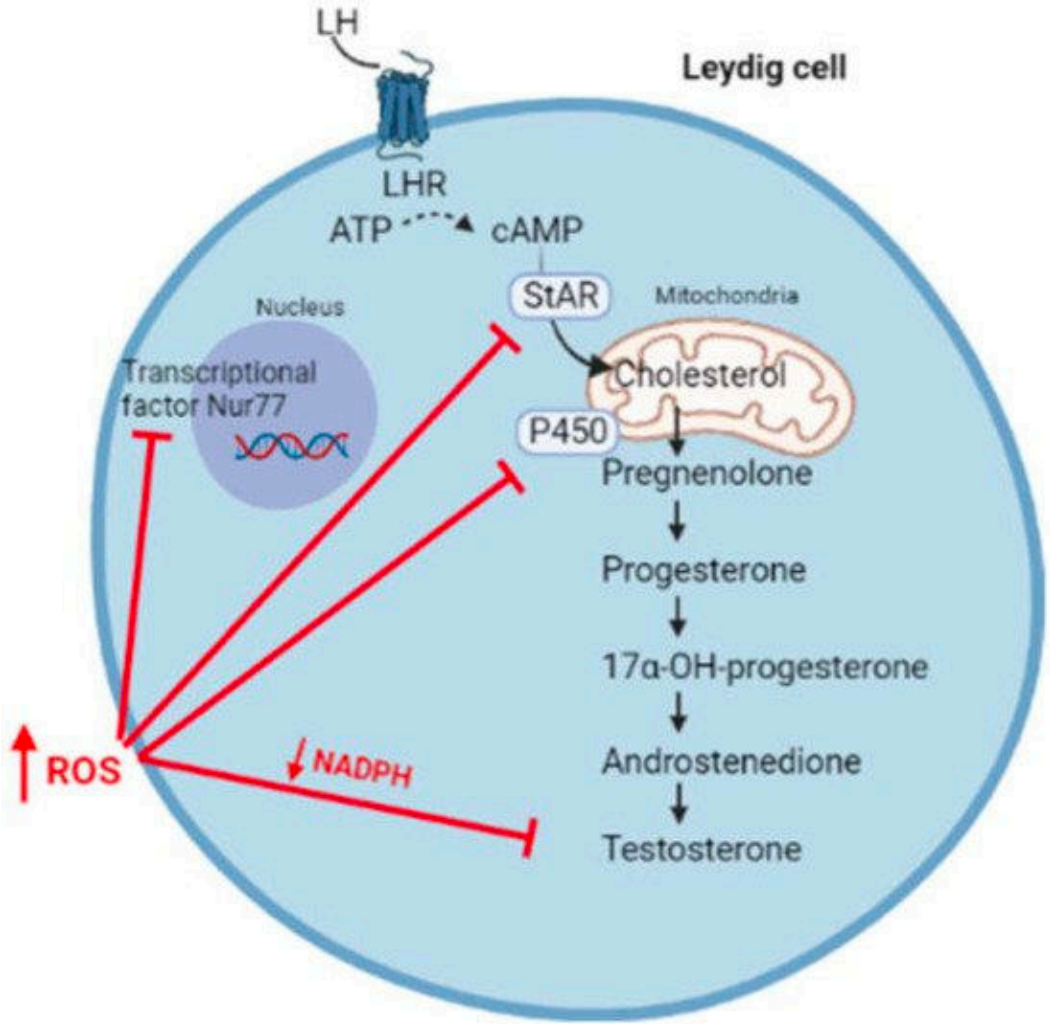
Figure 2 Mitochondria and sex steroid hormones during aging. Mitochondria produce sex steroid hormones in the gonads through initial conversion of cholesterol to pregnenolone. Sex steroid hormones improve and/or maintain mitochondrial function in hormone responsive cells by regulating: 1. gene expression of nuclear-encoded mitochondrial proteins, 2. gene expression of mitochondrial-encoded mitochondrial proteins, and/or 3. activity of mitochondrial proteins. Increased oxidative stress during aging damages gonadal cells and/or impair steroidogenesis. Decline in sex steroid hormone biosynthesis during aging compromises mitochondrial function in hormone responsive tissues and contribute to age-related pathologies.



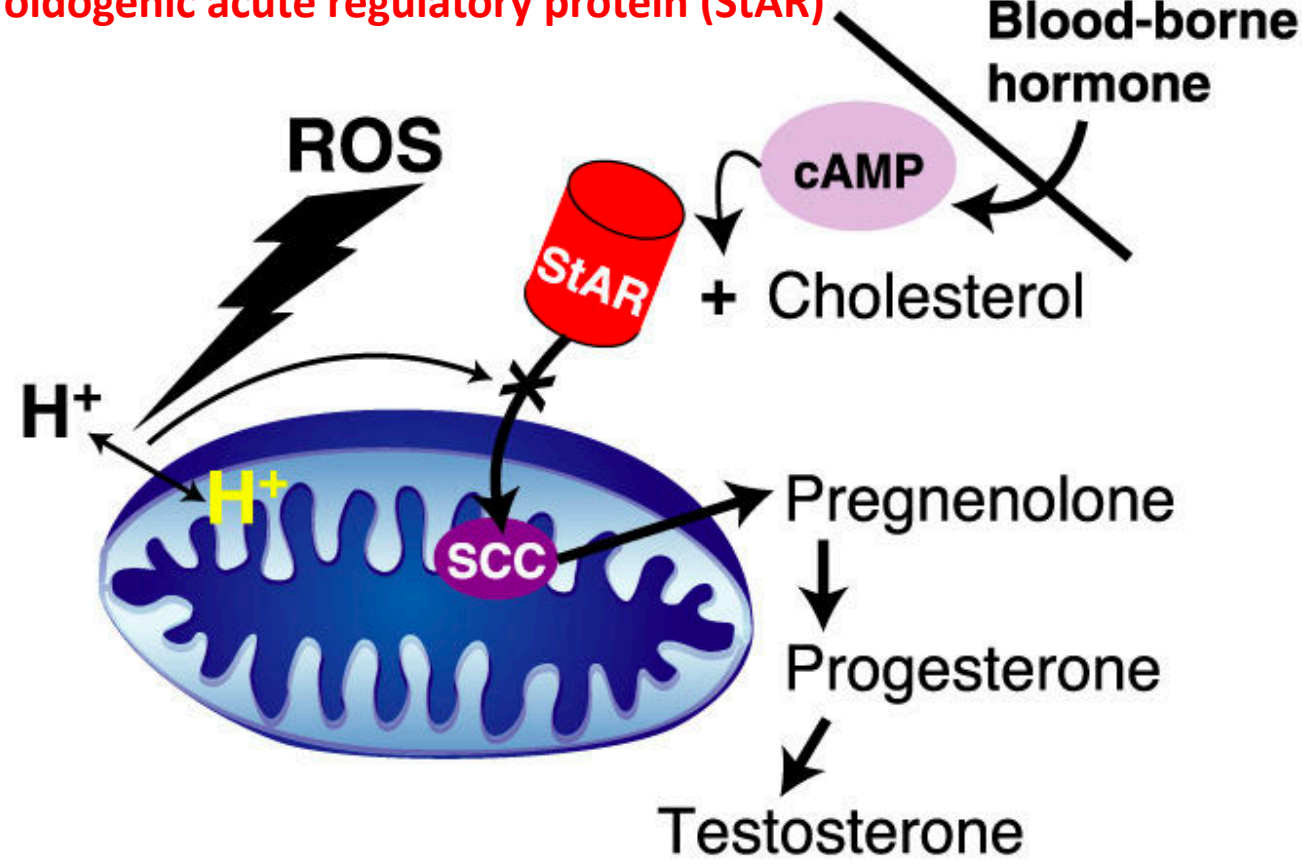
Molecular targets of estrogen in regulating mitochondrial function. 1. Estrogen binds to nuclear estrogen receptors (ERα and ERβ) to directly regulate tissue-specific expression of genes necessary for cellular function. 2. Estrogen binds to nuclear ERs and regulates expression of mitochondrial genes by promoting gene expression of transcription factor NRF1 and enhancing transcriptional activity of PGC1α. 3. Estrogen binds to membrane ERs and activates signaling cascades that protect mitochondria from oxidative damage. 4. Estrogen binds to mitochondrial ERs and limits ROS generation in the mitochondria. 5. Estrogen binds to mitochondrial ERs and regulates transcription of mitochondrial-encoded mitochondrial genes.

Mitochondrial and sex steroid hormone crosstalk during aging. February 2014. Longevity & Healthspan 3(1):2

High levels of ROS affect steroidogenesis through the inhibition of transcriptional factor Nur77, the synthesis of StAR, enzymatic P450 activity, and by reducing the levels of NADPH cofactor.

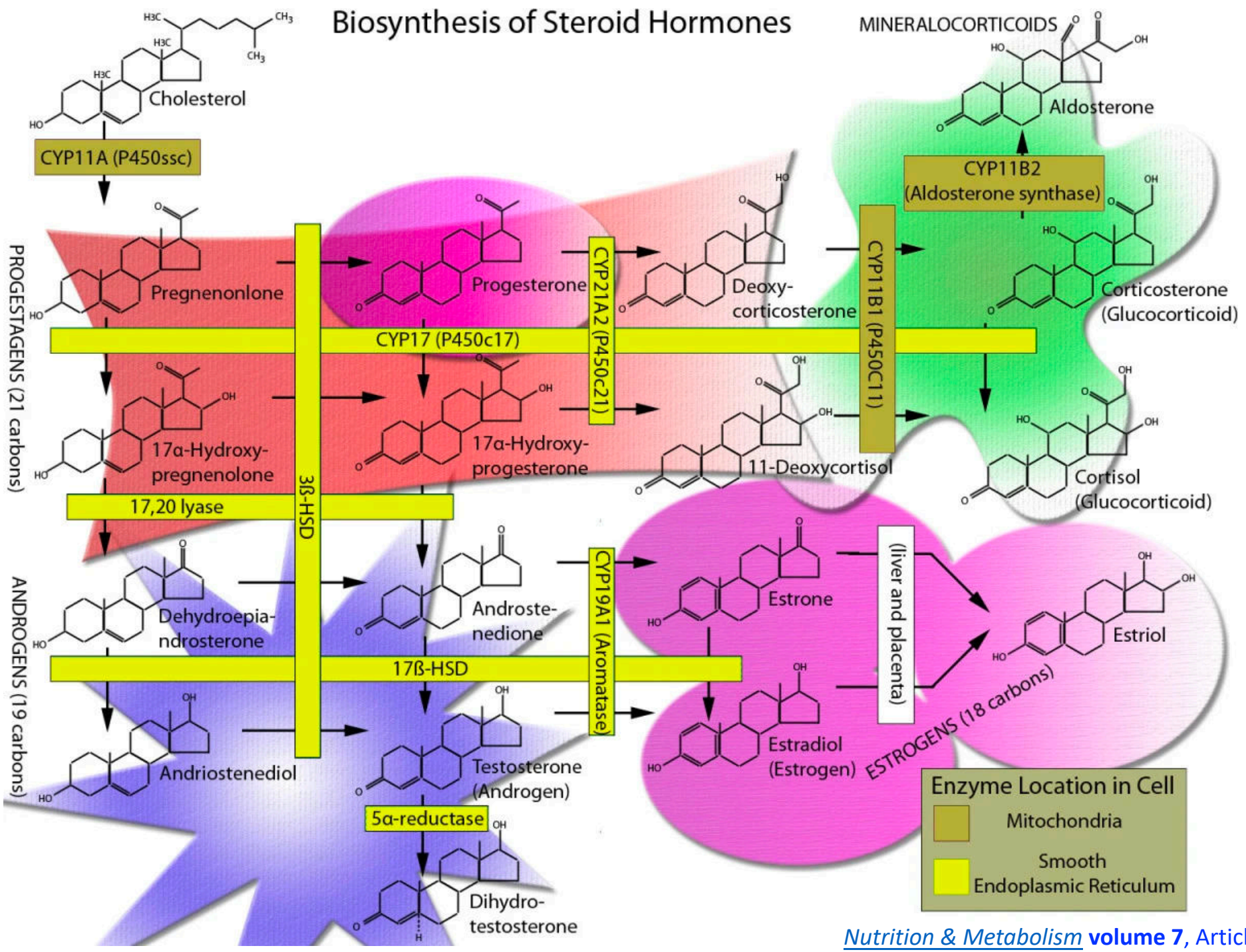


steroidogenic acute regulatory protein (StAR)



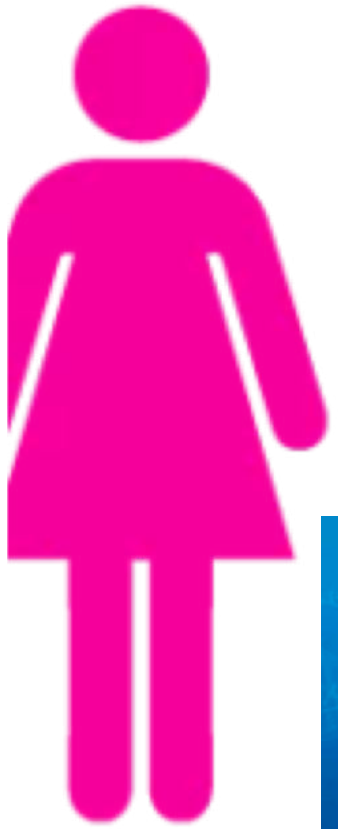
SCIENCE OF AGING KNOWLEDGE ENVIRONMENT. 16 Apr 2003.
Vol 2003, Issue 15 p. nw58

Steroidogenesis, Oxidative Stress and Male Hypogonadism. https://encyclopedia.pub/entry/16609



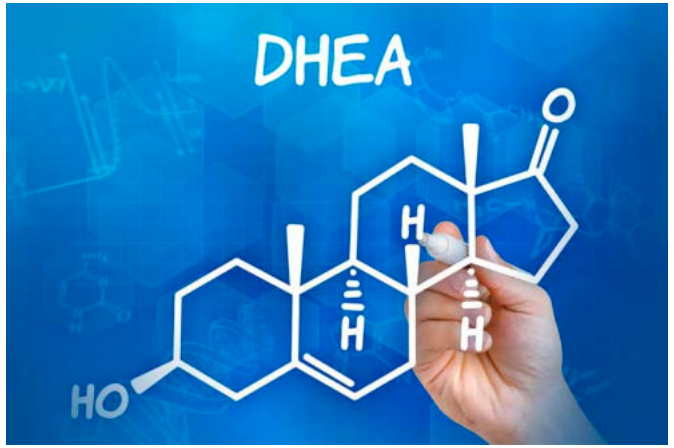
Nutrition & Metabolism **volume 7**, Article number: 47 (2010)

The Hormone Factor



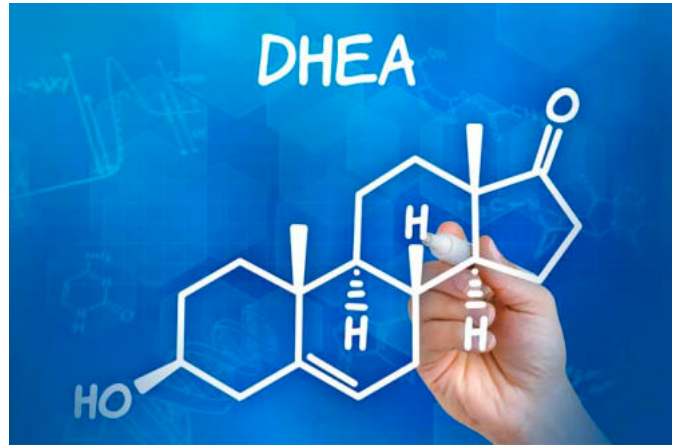
Women

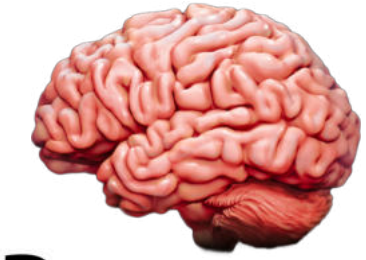
- More Estrogen
- Less Testosterone
- Menopause

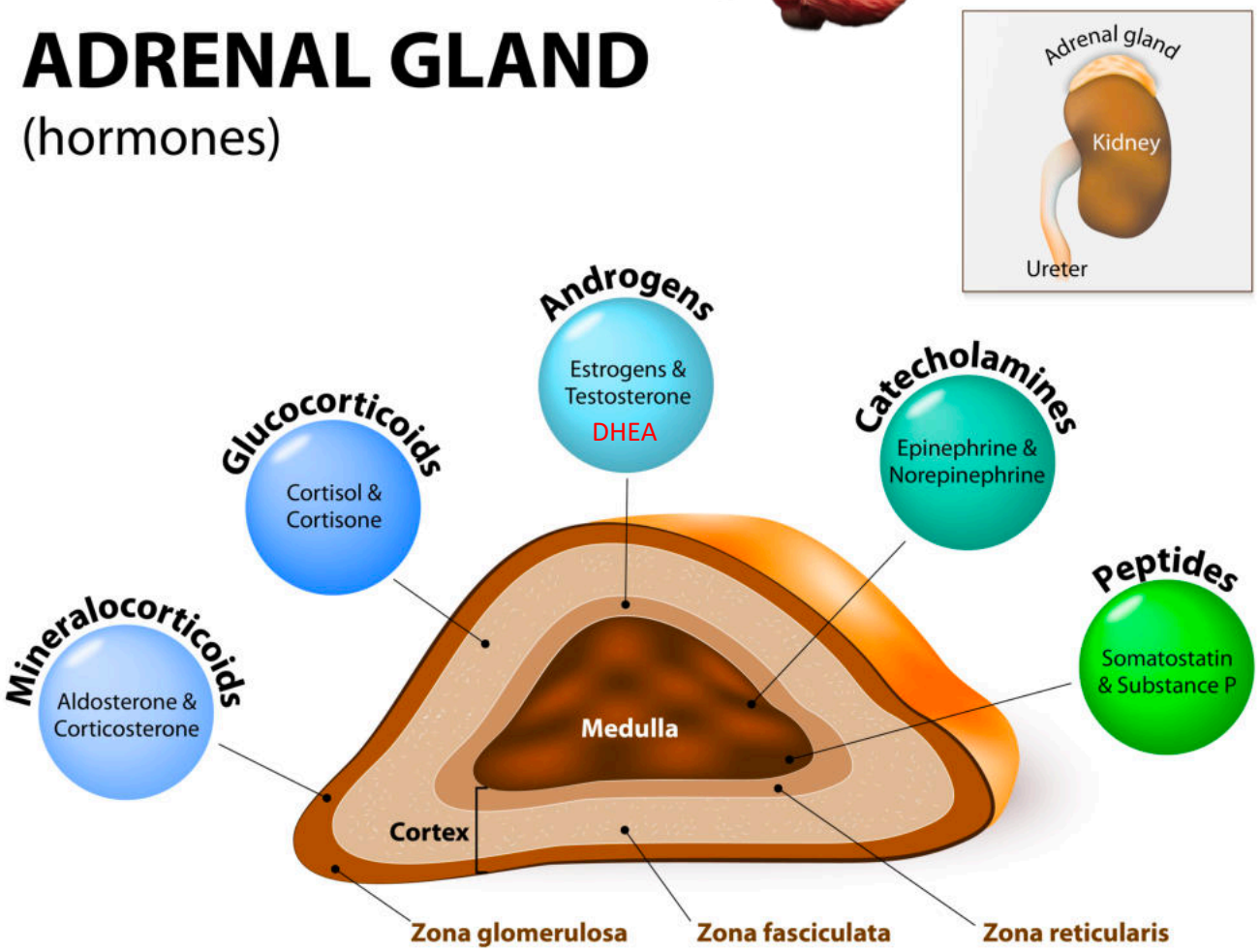


Men

- More Testosteron
- Less Estrogen
- Andropause







DHEAS is the precursor of approximately 50% of androgens in adult men, 75% of active estrogens in premenopausal women, and almost 100% of active estrogens after menopause.

DHEA has a 3- to 10-fold predominance of androgenic over estrogenic activity, and although a small portion of the circulating pool of DHEA is of gonadal origin in men and women, the majority of DHEA, and virtually all DHEAS, is produced by the adrenal cortex.

However, DHEA is also synthesized in the brain, from cholesterol and other hormonal precursors, primarily by astrocytes and oligodendrocytes; indeed, much higher concentrations of DHEAS are found in the brain than in the serum, suggesting that the DHEAS is primarily synthesized *in situ*, rather than being transported across the blood-brain barrier

Dehydroepiandrosterone (DHEA) and DHEA Sulfate: Roles in Brain Function and Disease. Tracey A. Quinn, Stephen R. Robinson and David Walker. 2018. https://www.intechopen.com/chapters/58381

The physiological effects of dehydroepiandrosterone/dehydroepiandrosterone sulphate (DHEA/DHEAS) in humans

Central nervous system

↑ Mood

↓ Anxiety

↓Depression

↑ Cognitive function

↑ Sexual function

Neuro protective

Skin

↑ Sebum production

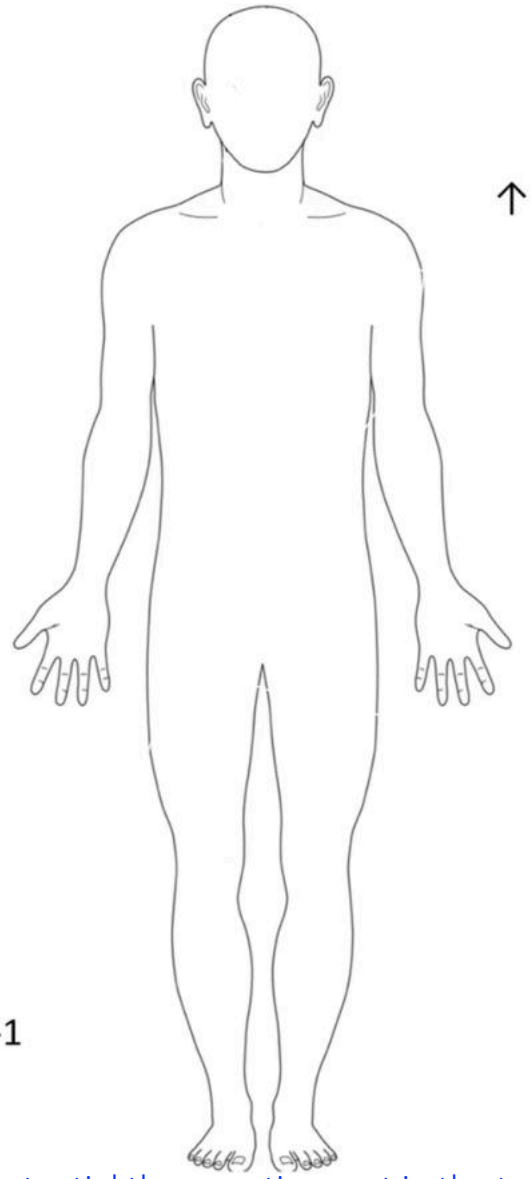
↑ Acne

Metabolism

↑Insulin sensitivity

↓ HDL cholesterol

↑ Insulin-like growth factor-1



Immune system

↓ Plasma cortisol

↑ Neutrophil reactive oxygen species generation

Bone

↑ Bone mineral density

Muscle

↑ Strength

↑ Lean body mass

↓ Fat mass

Other

Anxiolytic

↓ Menopausal thermoregulation disturbances

Restoration to normal DHEA and DHEAS levels are associated with a range of positive biological functions such as, increased (↑) bone mineral density and decreased (↓) fat mass, across a range of body systems that include the bone and central nervous system (CNS), high density lipoprotein (HDL)

Dehydroepiandrosterone: a potential therapeutic agent in the treatment and rehabilitation of the traumatically injured patient. Conor Bentley and All. *Burns & Trauma* volume 7, Article number: 26 (2019)

Role of Dehydroepiandrosterone and its Sulphate in Skin ageing Process

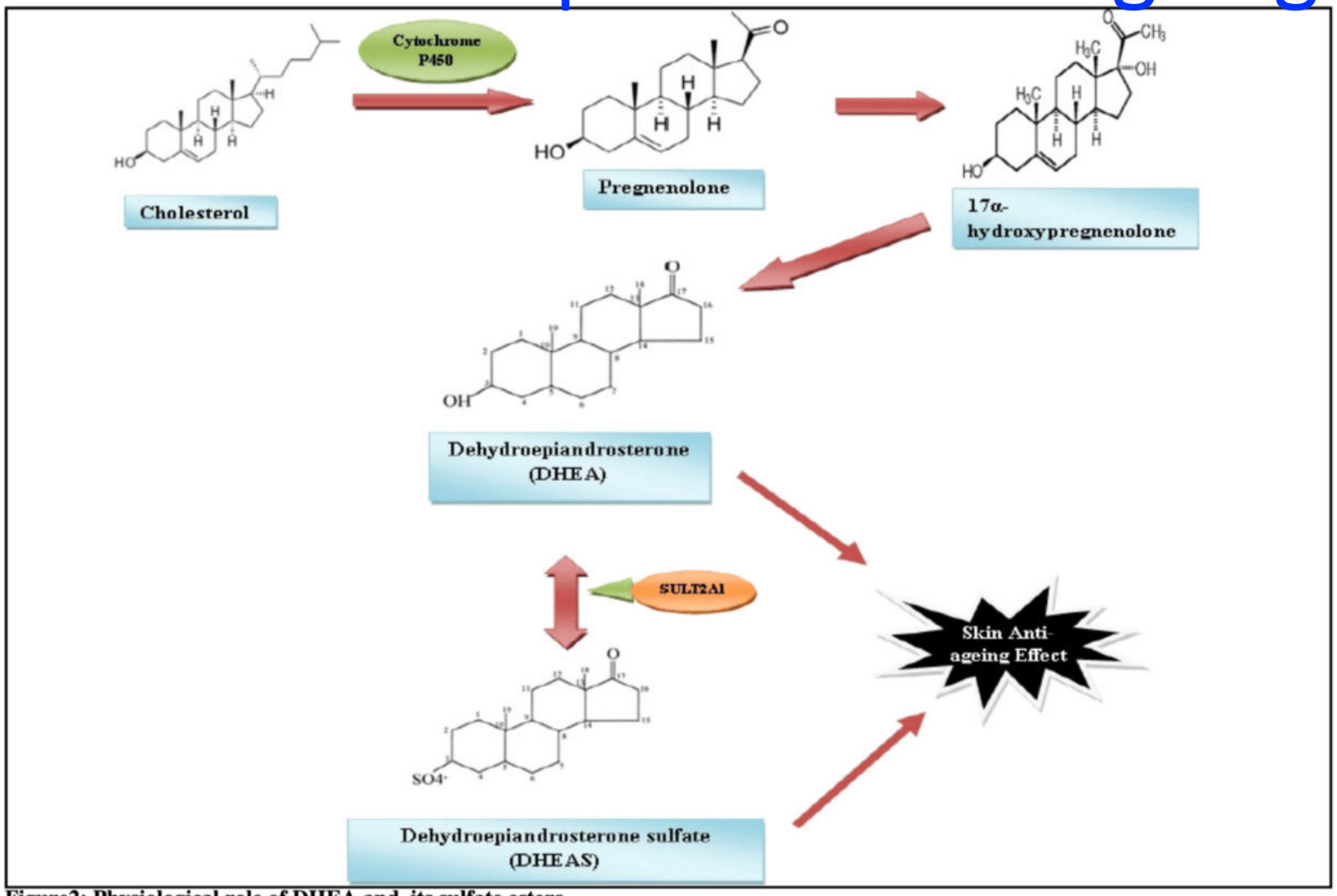


Figure2: Physiological role of DHEA and its sulfate esters.

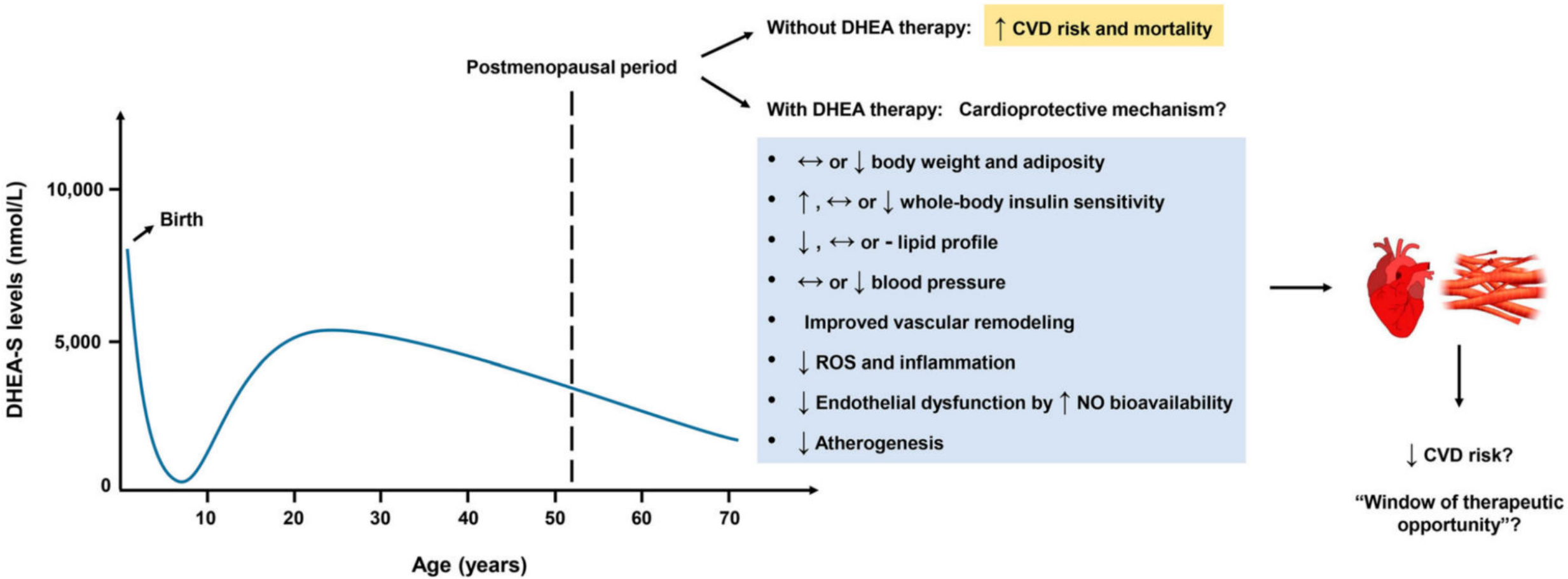
DHEA has the potential to act on different compartments of skin, the extraxellular matrix, the dermis and the epidermal-dermal junction.

DHEA directly interfere with procollagen synthesis and the proliferation and differentiation of keratinocytes. DHEA is a potent wound healing agent and inhibits inflammation etc.

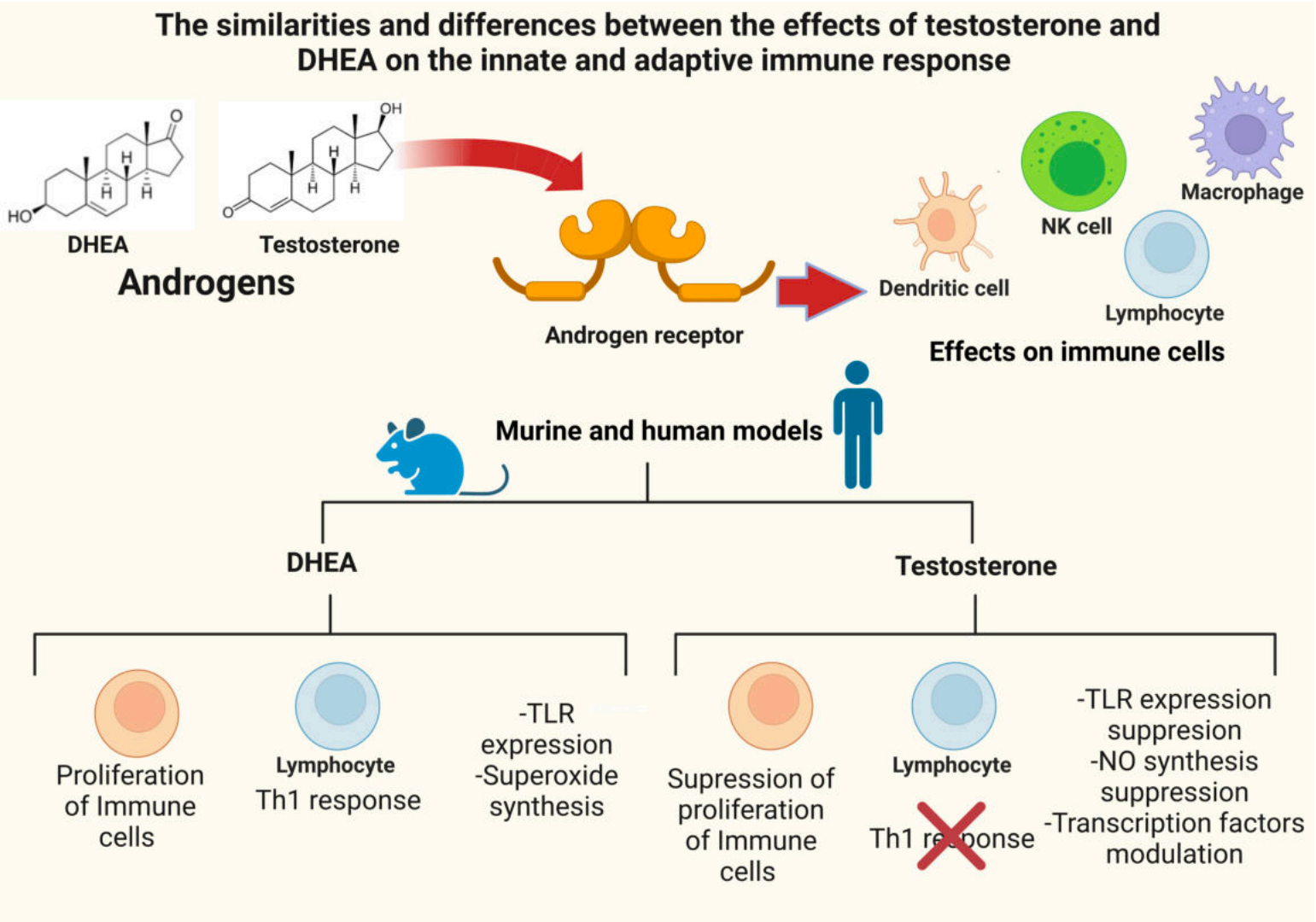
Thus, the DHEA proves itself to be a novel therapeutic target for skin treatment.

The Potentials of Dehydroepiandrosterone (DHEA) in Skin ageing process. Res. J. Topical and Cosmetic Sci. 4(2): July –Dec. 2013 page 43-47

Life-long serum DHEA-S levels in women, based on Rainey et al



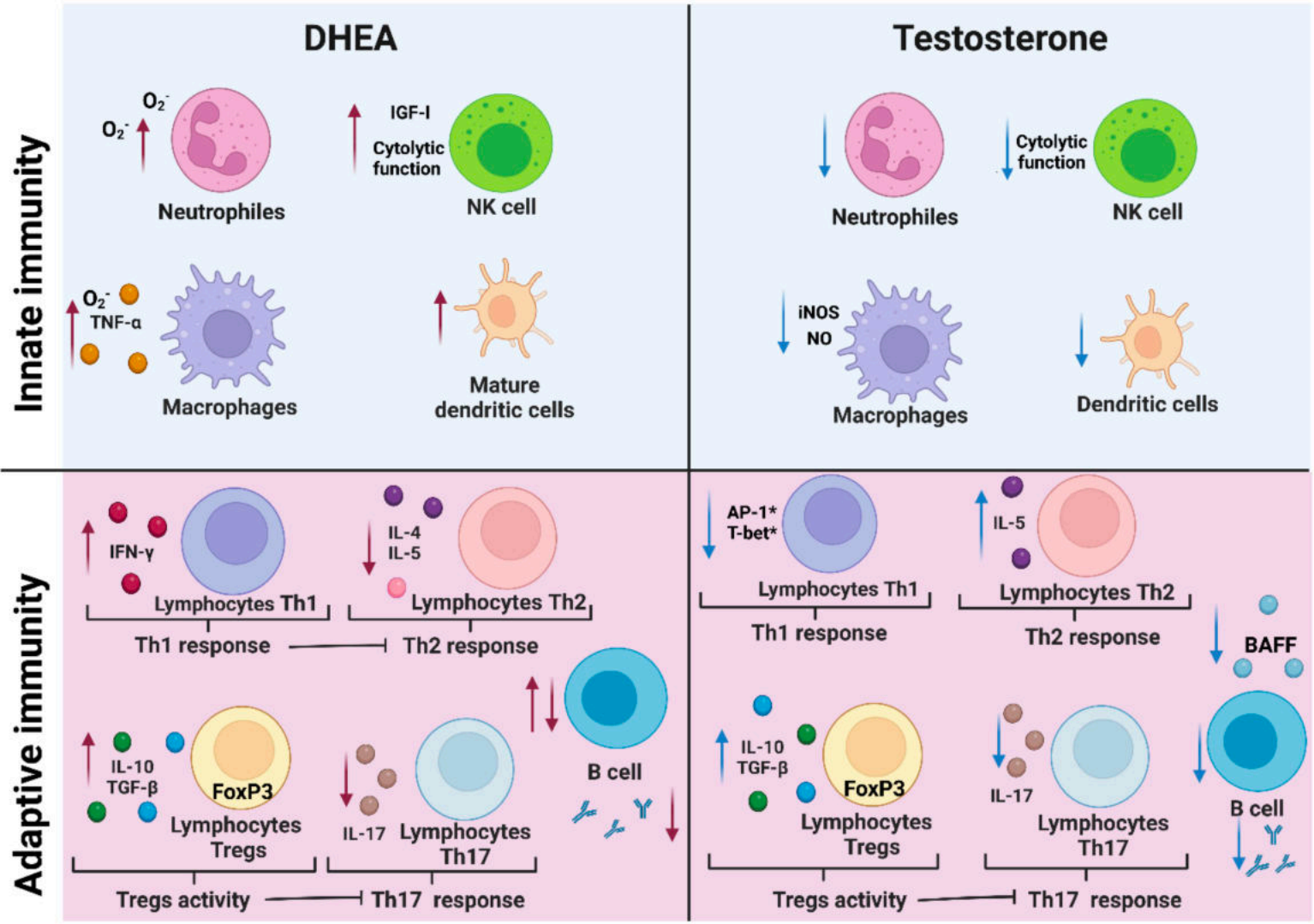
Dehydroepiandrosterone on metabolism and the cardiovascular system in the postmenopausal period. Caio Jordão Teixeira and All. Journal of Molecular Medicine Accepted: 9 October 2019



DHEA and testosterone induce similar but also opposite effects on the immune response. Both steroids promote the activation of regulatory T cells, which suppresses the Th17-type response. However, while testosterone suppresses the inflammatory response, DHEA promotes it, and this modulation is important for understanding the involvement of androgens in infectious (bacterial, viral and parasitic) and autoimmune diseases

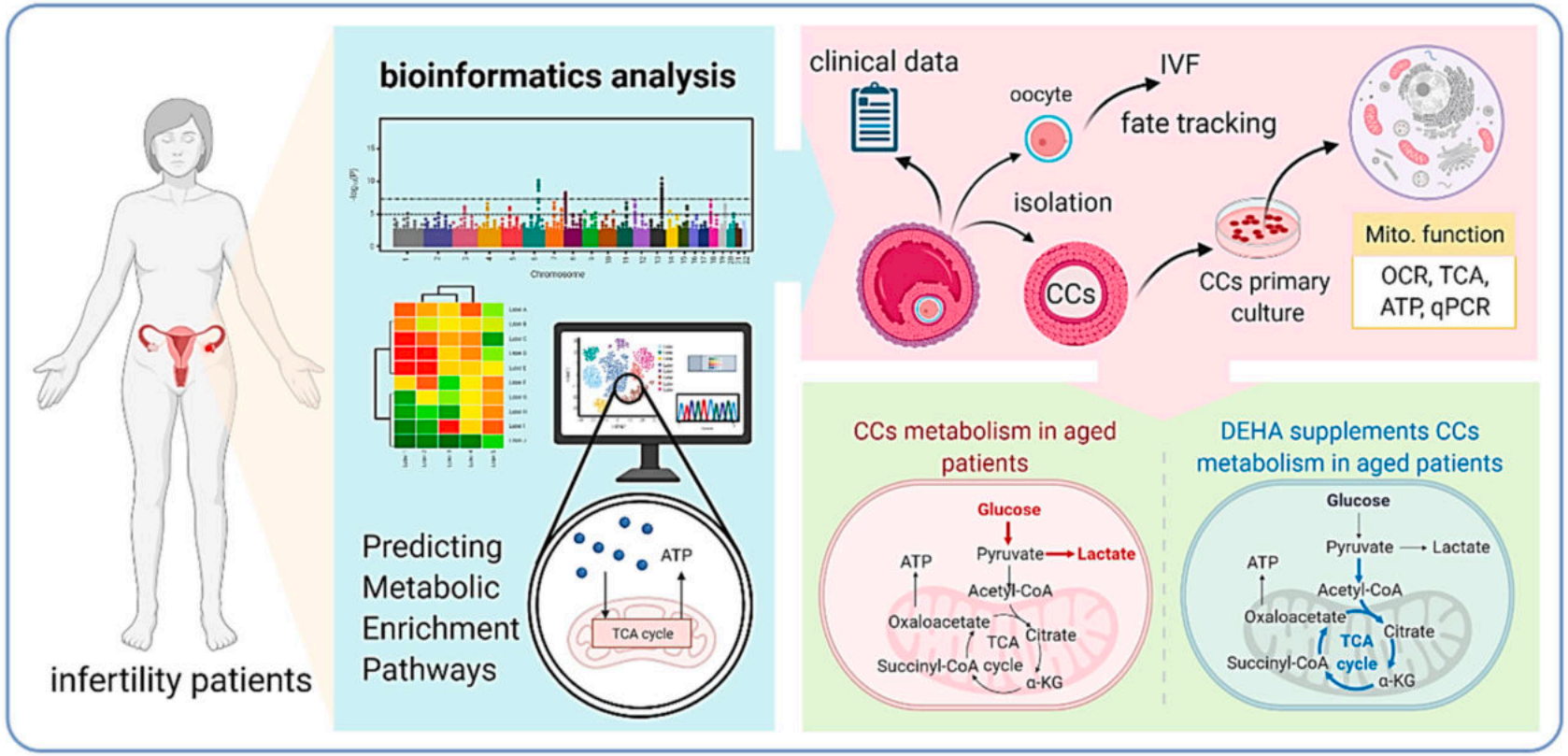
The Similarities and Differences between the Effects of Testosterone and DHEA on the Innate and Adaptive Immune Response. *Biomolecules* 2022, *12*(12), 1768;

Effect of DHEA and testosterone on cells of the innate and adaptive immune response



Nutrients 2021, 13(7), 2449; https://doi.org/10.3390/nu13072449Received: 7 June 2021 / Revised: 14 July 2021 / Accepted: 16 July 2021 / Published: 17 July 2021

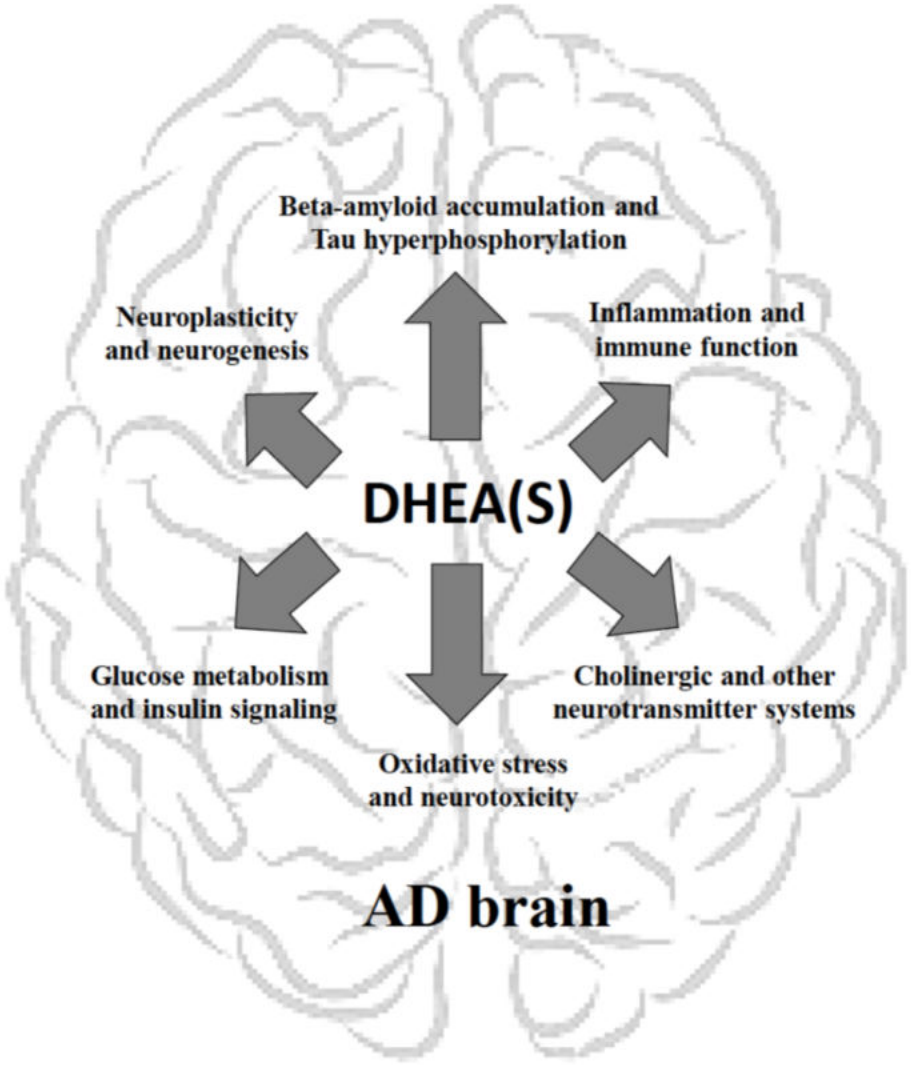
Dehydroepiandrosterone Shifts Energy Metabolism to Increase Mitochondrial Biogenesis in Female Fertility with Advancing Age



This study suggested that DHEA supplementation altered the levels of glycolysis genes and increased mitochondrial oxidative phosphorylation, thereby enhancing the energy metabolism of aging cells and elevating pregnancy rates in infertile patients. Our observations may provide a possible rationale for the clinical use of DHEA supplementation in patients undergoing IVF

Nutrients 2021, 13(7), 2449; https://doi.org/10.3390/nu13072449Received: 7 June 2021 / Revised: 14 July 2021 / Accepted: 16 July 2021 / Published: 17 July 2021

Observed actions in the brain potentially involved in the beneficial effects of DHEA(S) in AD.

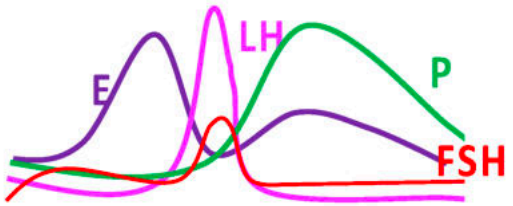


The findings of the most preclinical studies dealing with the effects of DHEA(S) on cognitive functions and other pathophysiological characteristics of AD, including accumulation of β-amyloid protein, tau hy- perphosphorylation, changes in cholinergic and other neuro- transmitter systems, neuroplasticity and neurogenesis, oxida- tive stress, glucose metabolism and insulin signaling, im- mune system function, and many other alternations are quite promising.

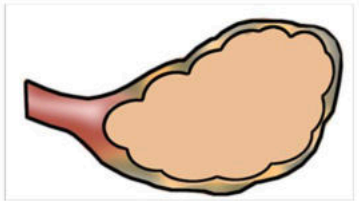
Dehydroepiandrosterone (DHEA) and its Sulphate (DHEAS) in Alzheimer's Disease. Dubravka Svob Stracand All. Current Alzheimer Research, 2020, 17, 1-15

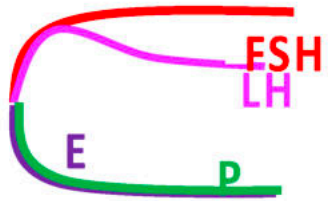

Chaud, Froid,
Chaud, Froid,
Chaud, Froid...
C'est plus une saison
c'est une ménopause !

A. Reproductive age

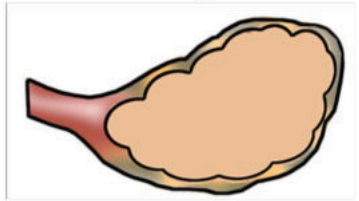


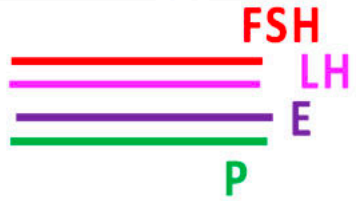
B. Post-menopausal



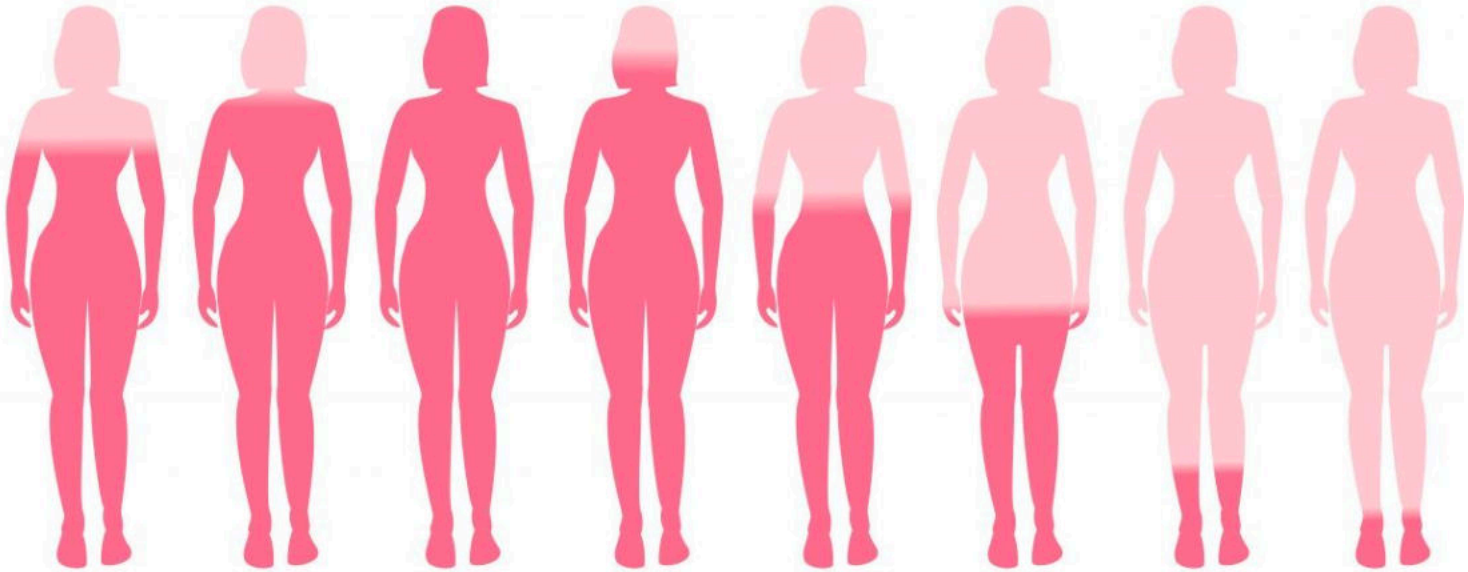


C. Post-menopausal on HRT

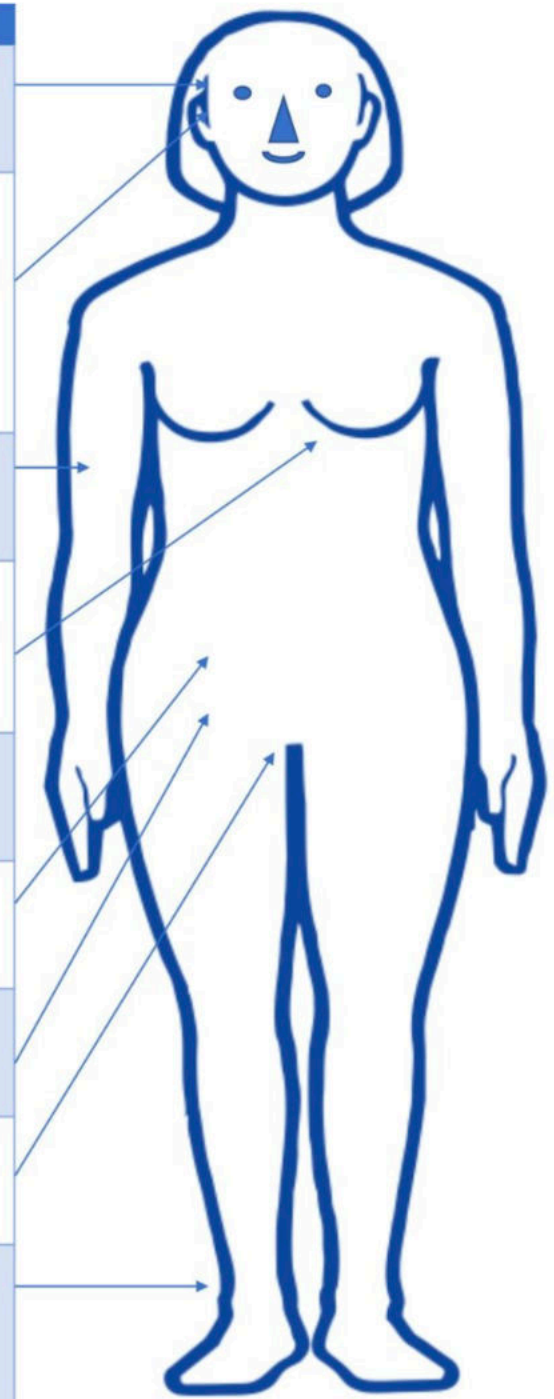




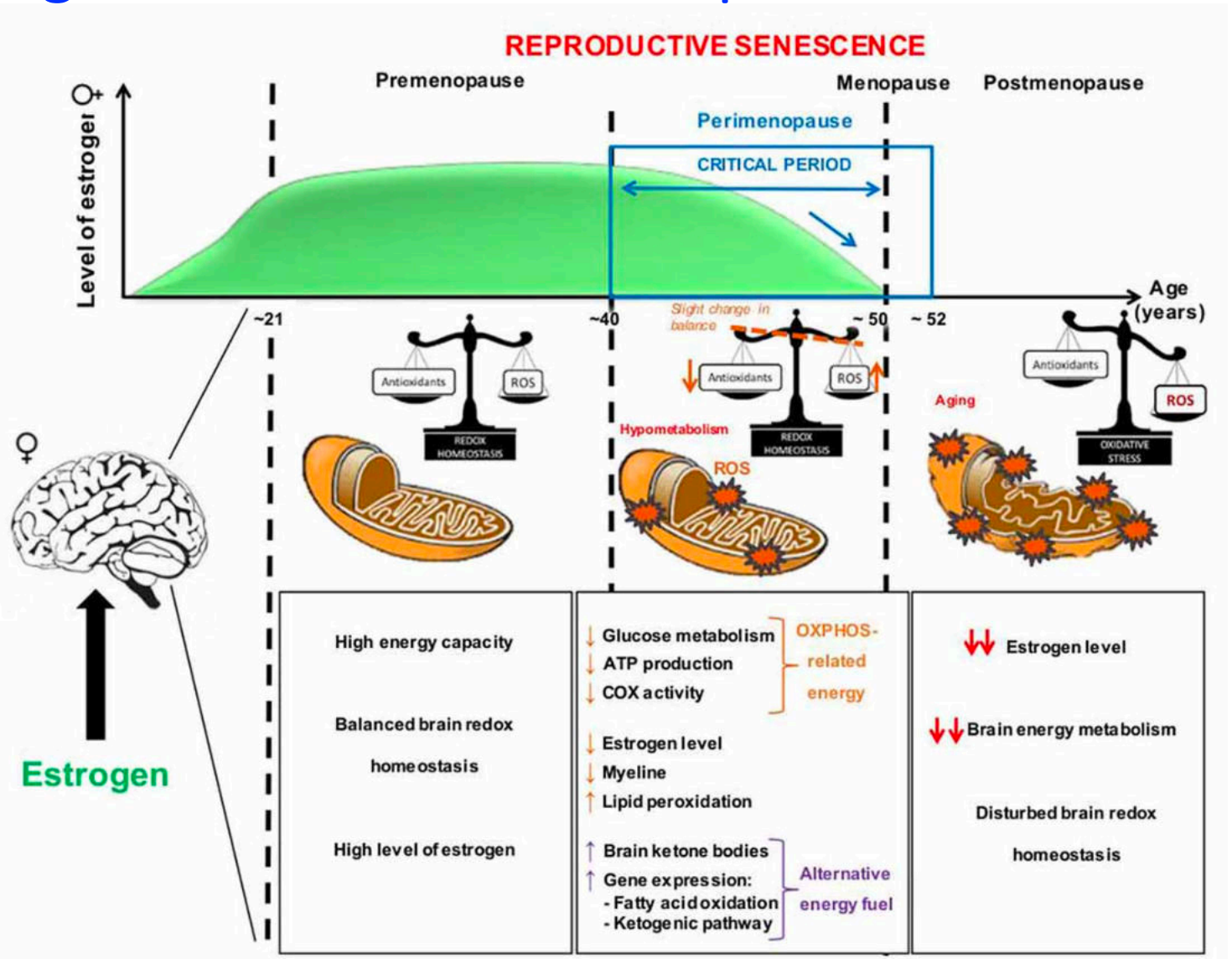
ESTROGEN HORMONE LEVEL



Menopausal Symptoms
Central Nervous System
• Headache
• Stroke
Psychological
• Disturbed Sleep
• Poor Memory
• Impaired cognition
• Depression
• Sexual Dysfunction
Systemic
• Weight gain
• Night Sweats
Cardiovascular
• ↑Cardiovascular Risk
• ↑Risk of venous thromboembolism
Skin
• Hot Flushes
• Thinning of Skin
Renal
• Urinary Incontinence
• Urgency
Transitional Menstruation
• Shorter or Longer Cycle
• Bleeding between Periods
Genital
• Vaginal Dryness
• Painful Intercourse
Musculoskeletal
• Joint Soreness & Stiffness
• Back Pain
• ↓Bone Mass

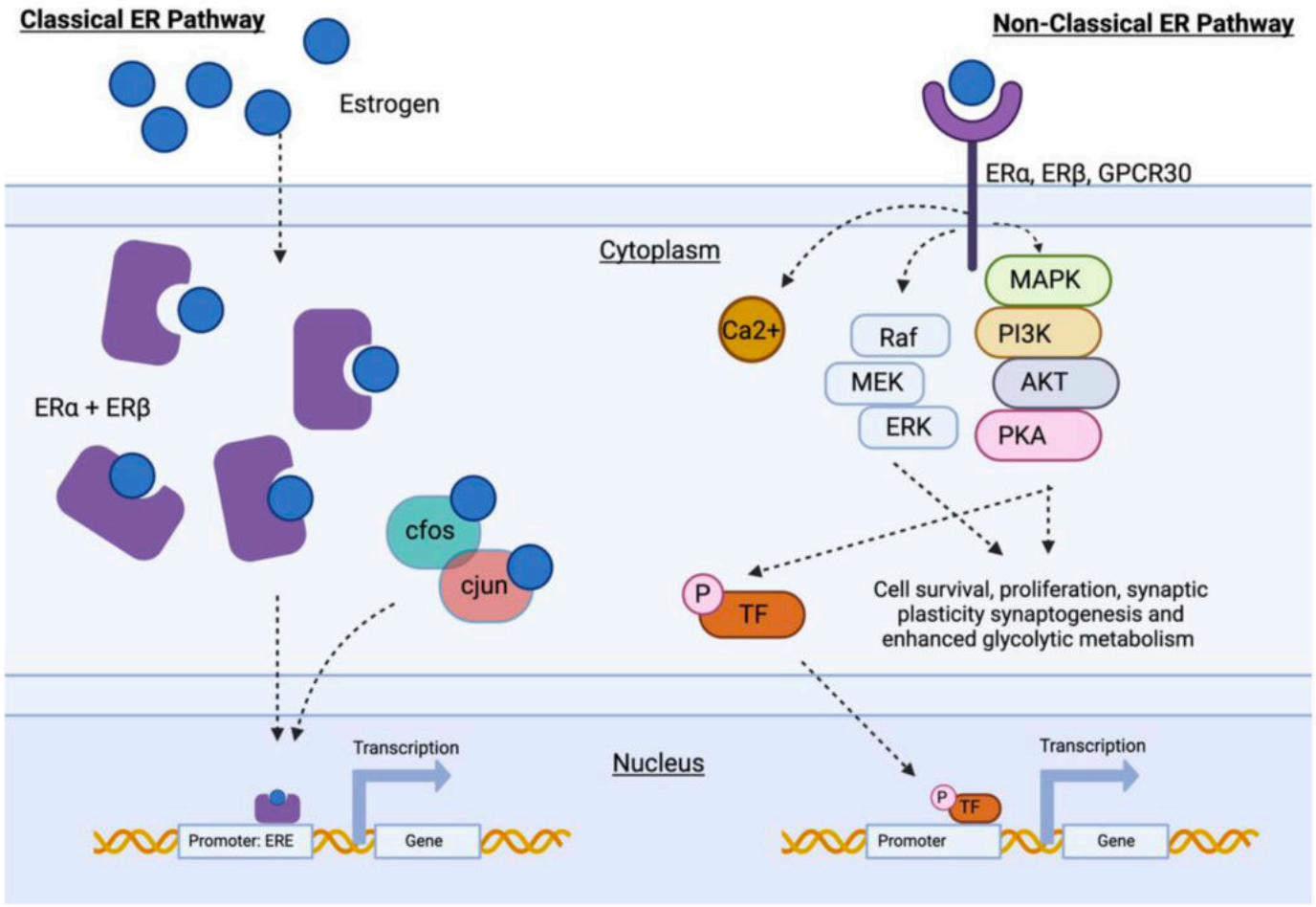


Potential sequence of pathological events occurring at the mitochondrial level during aging and «the critical time period» of decline in estrogen



Front. Aging Neurosci., 27 April 2018. Sec. Cellular and Molecular Mechanisms of Brain-aging. Volume 10 - 2018

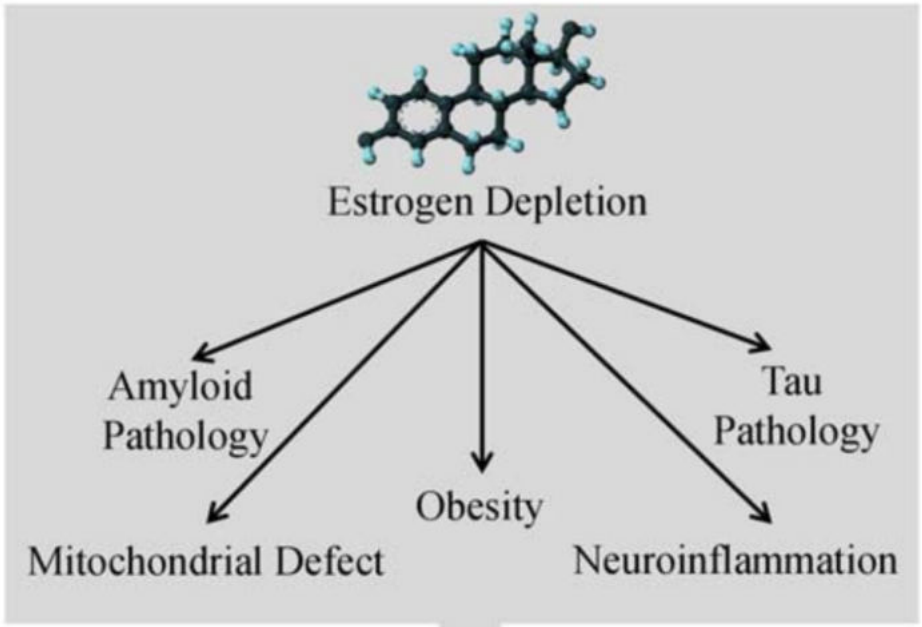
Critical Window Hypothesis



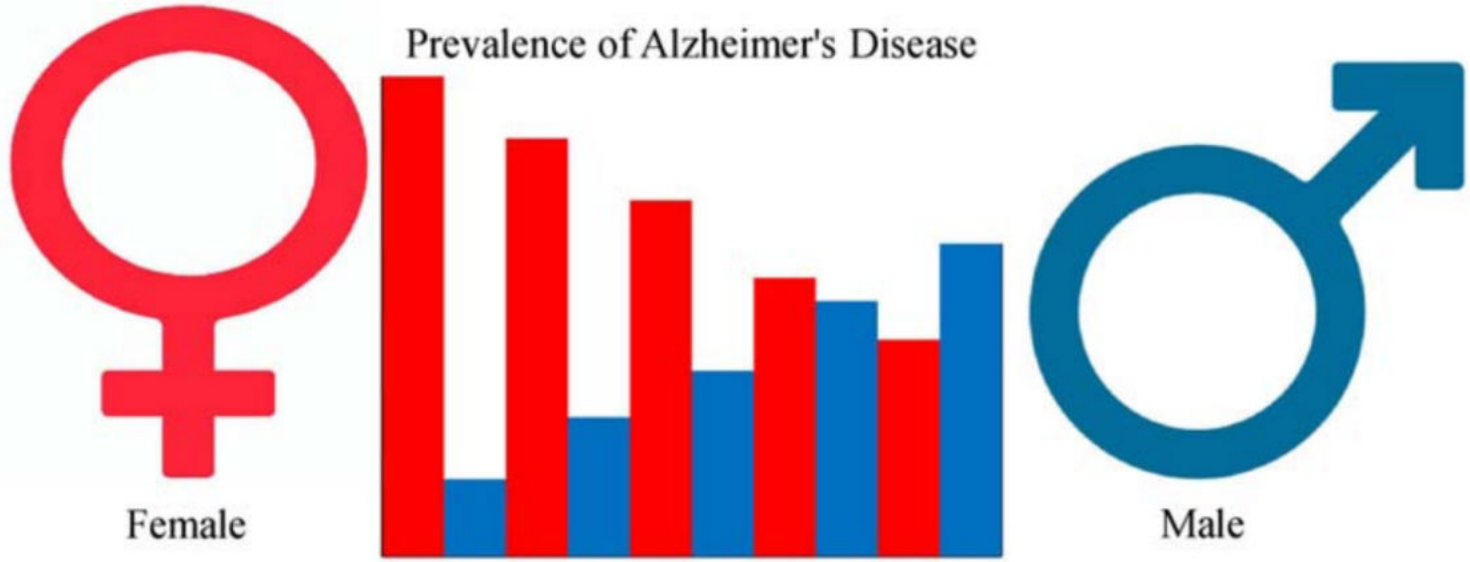
The 'Multi-institute research in Alzheimer's epidemiology' study (MIRAGE); analyzed participants using three age groups: 50–63, 64–71, 72–99. Lower relative risk of AD in HRT users were found in all groups; however, the greatest benefit was experienced by the youngest tertile, an effect that was weakened as age increased.

Aged neural tissue becomes unresponsive to changes in the estrogenic environment. One possibility for this change is that the extended period of depleted estrogen levels cumulatively results in a loss of ER

Replacement Therapy a Risk Factor or a Therapeutic Option for Alzheimer's Disease?. Zoe Brianna Mills, Nadrea Kwakaowsky. Int. J. Mol. Sci. 2023, 24(4), 3205

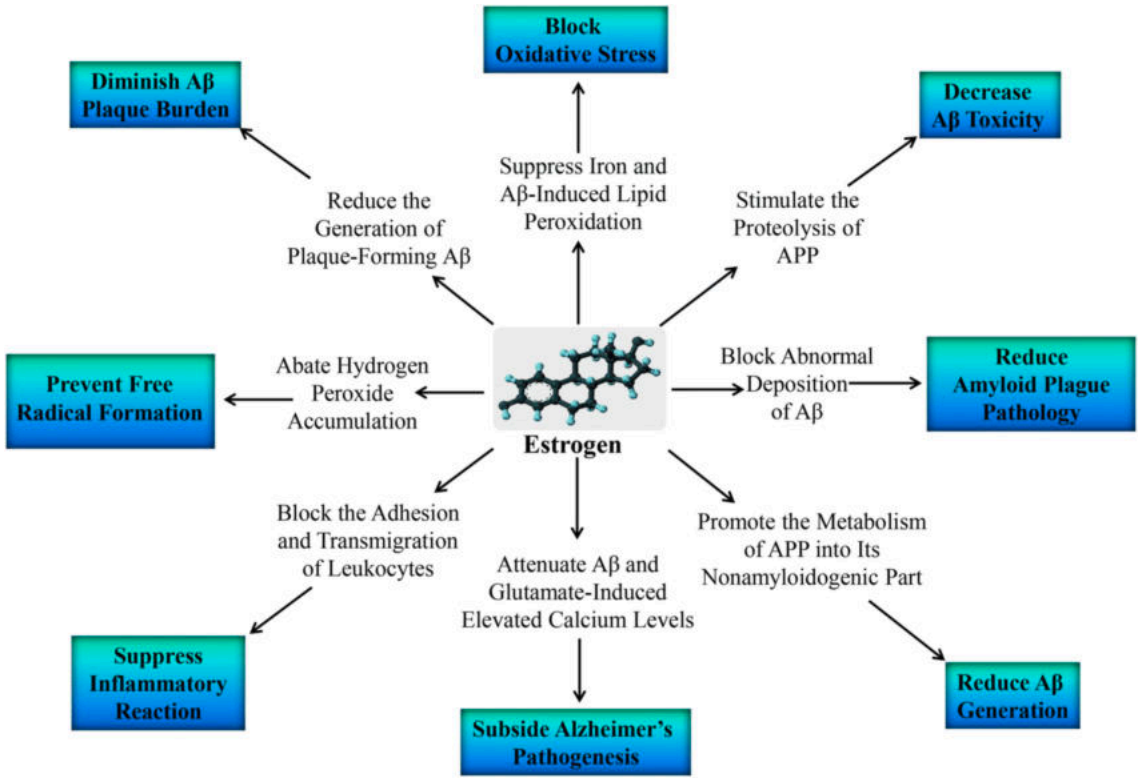


Changes in the brain that happen after menopause owing to depletion of estrogen may make women more vulnerable to Alzheimer's disease than men



Estrogen Signaling in Alzheimer's Disease: Molecular Insights and Therapeutic Targets for Alzheimer's Dementia. Md. Sahab Uddin and all. Springer Nature Published on line 15 April 2020

Replacement Therapy a Risk Factor or a Therapeutic Option for Alzheimer's Disease?



Estrogen Signaling in Alzheimer's Disease: Molecular Insights and Therapeutic Targets for Alzheimer's Dementia. Md. Sahab Uddin and all. Springer Nature Published on line 15 April 2020

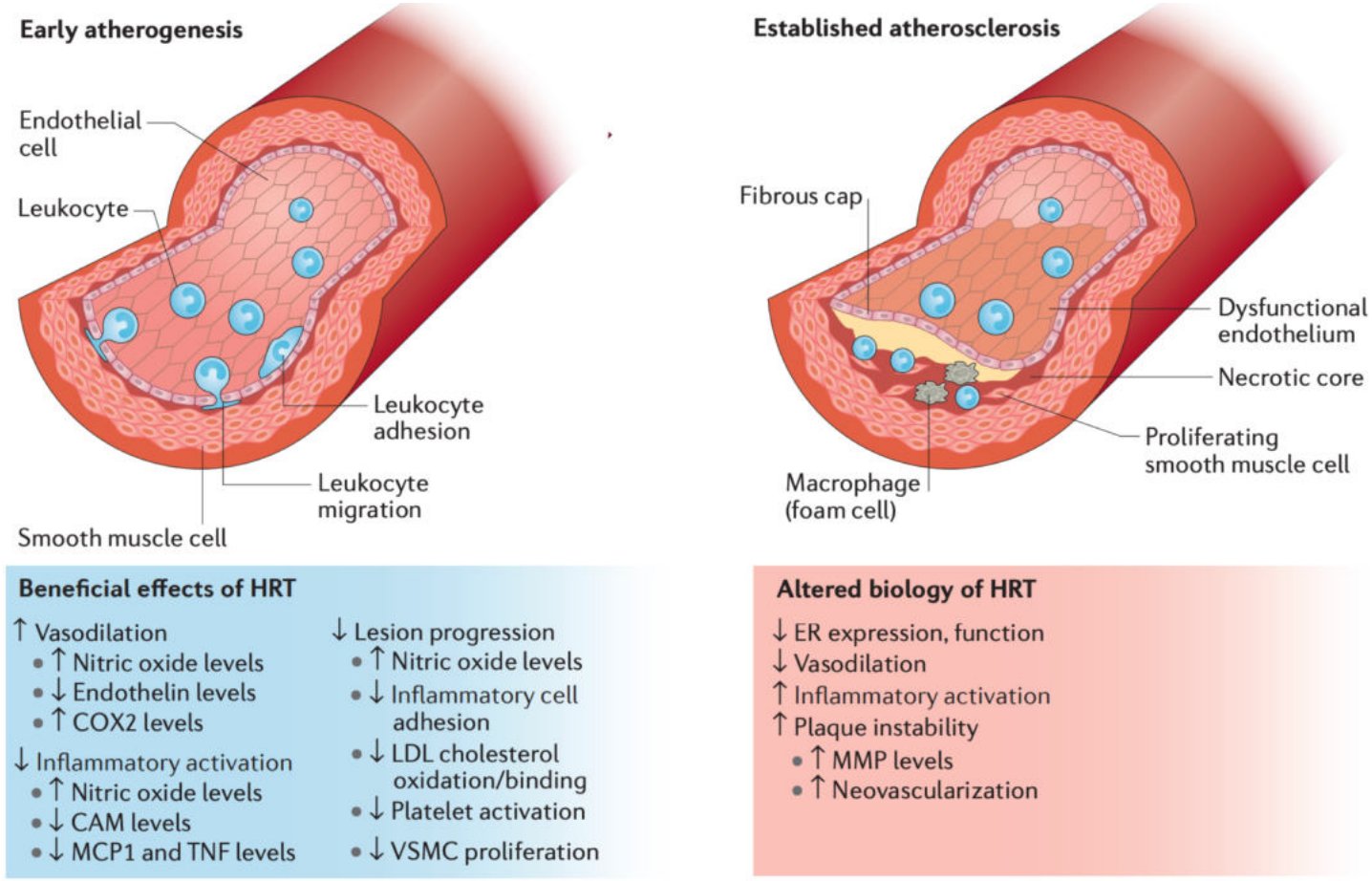
Estrogens have several complex mechanisms of action through which hormones can exert valuable effects on cellular functioning.

Demonstrating the effects of HRT on preserving neuronal health through estrogens ameliorative actions, resulting in beneficial effects on cognitive health and the incidence of dementia, has significant implications for the future of women's health.

The recommendation for HRT use should consider baseline characteristics such as genotype, cardiovascular health, and education, as well as age, dose, and duration of treatment.

Replacement Therapy a Risk Factor or a Therapeutic Option for Alzheimer's Disease?. Zoe Brianna Mills, Nadrea Kwakaowsky. Int. J. Mol. Sci. 2023, 24(4), 3205

Coronary vessels in atherosclerosis



Left panel depicts coronary vessels in a young woman with early atherosclerosis. Right panel depicts coronary vessels in an older (aged >65 years) woman with established atherosclerosis. Various effects of hormone-replacement therapy (HRT) on the vessels in the two stages of atherosclerosis are shown, with benefit in young arteries and altered biology in old arteries. CAMs, cell adhesion molecules; COX2, cyclooxygenase 2; ER, oestrogen receptor; MCP1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; TNF, tumour necrosis factor; VSMC, vascular smooth muscle cell.

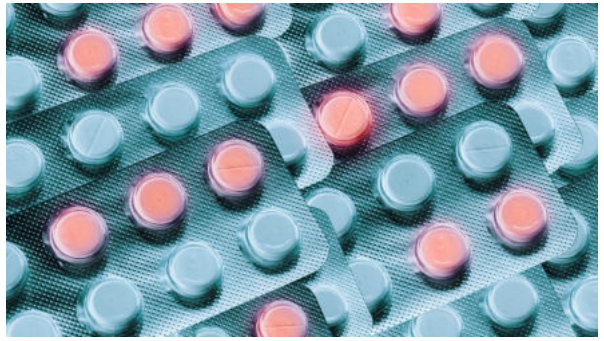
Nature Reviews Endocrinology volume 13, pages220–231 (2017)

Cardiovascular Risk/Benefit Profile of MHT

The aim of this review was to revise the current literature and evaluate the CV risk or benefit following administration of MHT considering several factors such as MHT timing, dose, route of administration, and formulation. *Materials and Methods*: An electronic databases search of MEDLINE (PubMed), Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS, congress abstracts, and Grey literature (Google Scholar; British Library) was performed, with the date range from each database's inception until June 2019. All the studies evaluating MHT and cardiovascular risk, including thromboembolism or stroke, were selected. *Results*: Timing of MHT initiation was shown to be a critical factor in CV risk assessment. In concordance with the "timing hypothesis", healthy symptomatic women who initiated MHT when aged younger than 60 years, or who were within 10 years of menopause onset, have demonstrated a reduction in both coronary heart disease (CHD) risk and all-cause mortality. In particular, MHT therapy was associated with improvement of subclinical signs of atherosclerosis. Venous thromboembolism (VTE) risk is reduced when low doses of oral estrogen are used. Moreover, transdermal hormonal application significantly reduces CV risk compared with oral administration. MHT impact on the CV system is influenced by either factors inherent to the specific regimen, or factors inherent to the specific patient. Hence, individualization of care is necessary. *Conclusion*: CV risk calculation should be considered by clinicians in order to exclude patients with high CV risk, in whom MHT is contraindicated. Assessing risks and benefits in a patient-centered approach according to individual's features, health status, and personal preferences is important in order to realize a safe and effective treatment.

MDPI *Medicina* 2019, *55*(9), 571; https://doi.org/10.3390/medicina55090571

Route of Administration



HRT administration can be administered via oral, transdermal (sprays, patches and gels), or vaginal courses.

The route of administration can have drastic effects on absorption and metabolism. Oral HRT is commonly used in clinical studies due to its ease of administration and compliance checks.

Oral administration has been associated with an increased risk of AD after long-term use.

In ‘Estrogen and Thromboembolism Risk Study’ (ESTHER), the risk of venous thromboembolism was associated with oral but not transdermal estrogen delivery, indicating a clinically relevant difference in the estrogenic effect between these delivery route.

As transdermal and vaginal delivery systems can bypass the ‘first pass’ of the hepatic metabolism, these routes are able to maintain more of the drug’s bioavailability and correlate to higher serum levels at lower doses compared to oral prescriptions.

Differences in safety may also be accounted for by the impact of hepatic protein synthesis and clearance. Deleterious byproducts are produced or are subject to reduced clearance, a process that can also vary further depending on liver health and, as in older age, impairments to liver function can be a significant factor that needs to be accounted for when choosing which route of administration should be used.

Hormone-replacement therapy: current thinking

Earlier observational data showed many benefits of HRT, which include reduced coronary heart disease and overall mortality reduction.

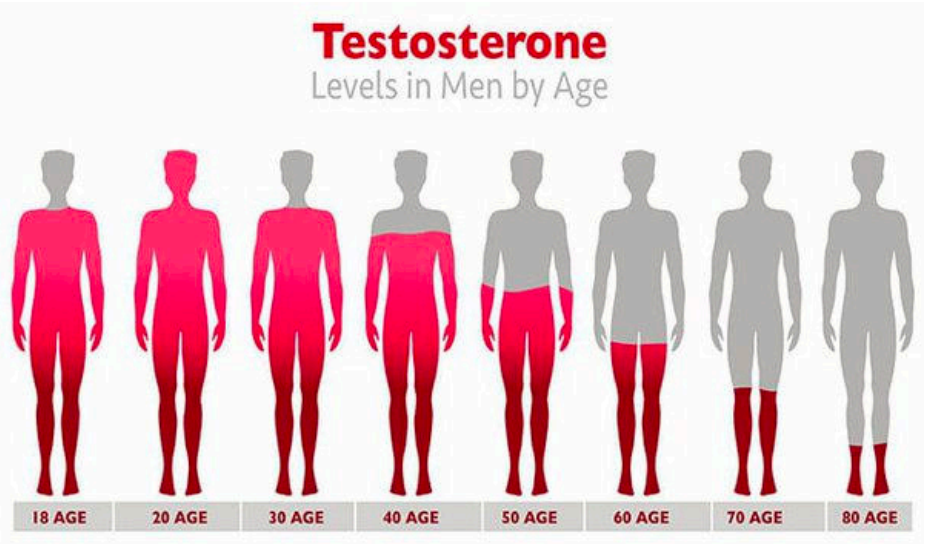
Randomized trials in older women (aged >60 years) have shown no benefit and increased harm.

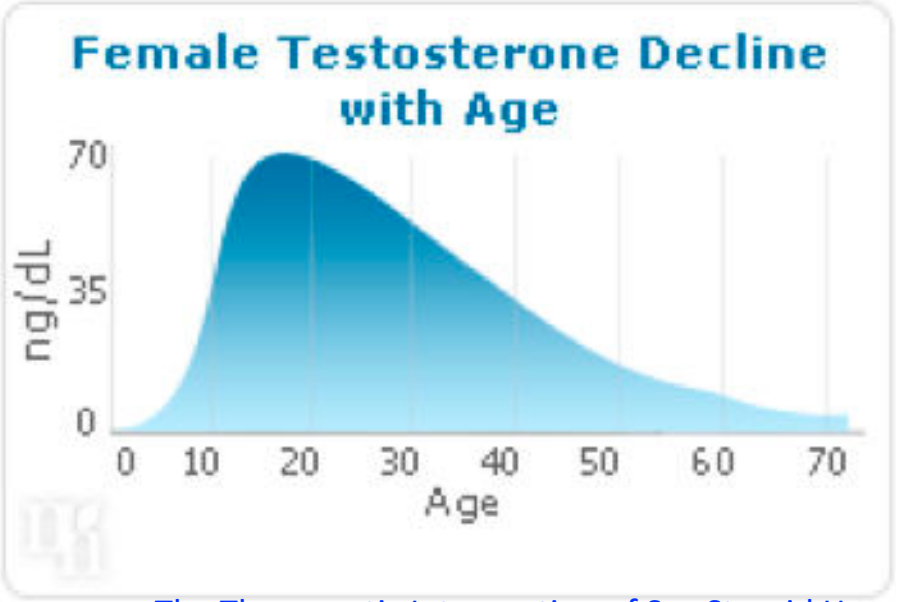
Reassessment of clinical trials in women initiating treatment close to the onset of menopause and newer studies and meta-analyses now show benefit and rare risks

The effects of reduced CHD and mortality in women initiating therapy around menopause suggest a possible role for HRT in primary prevention

Nature Reviews Endocrinology volume 13, pages220–231 (2017)

Testosterone



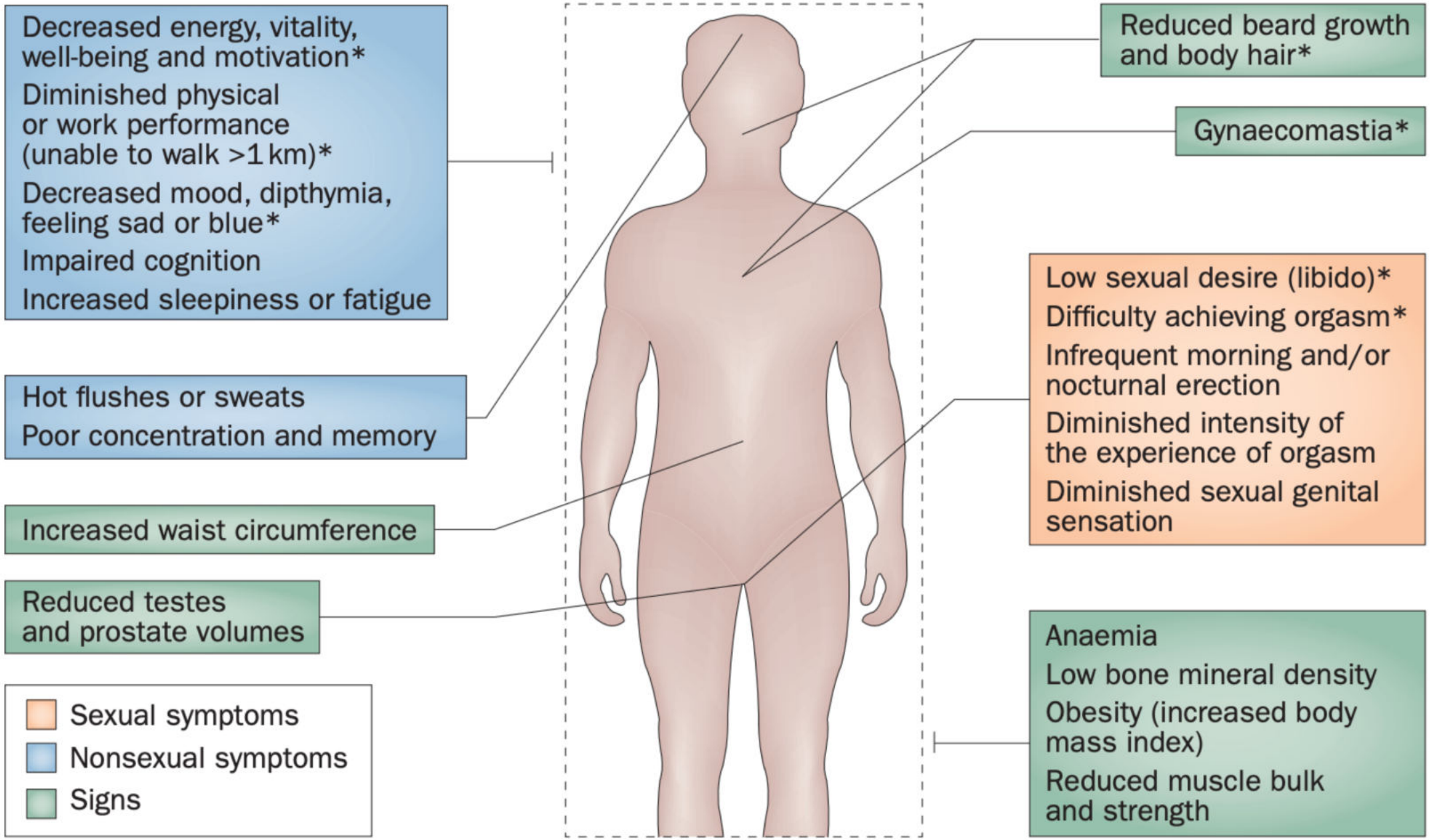


Testosterone, a representative sex steroid hormone, is mainly produced by male Leydig cells and female ovarian thecal cells, and partly by adrenal gland.

As the principal physiological anabolic hormone, testosterone increases protein synthesis in skeletal muscle, promotes muscle regeneration and repair by activation of myo-satellite cells, counteracts muscle proteolysis, and increases intramuscular insulin-like growth factor-1 (IGF-1) levels, etc.

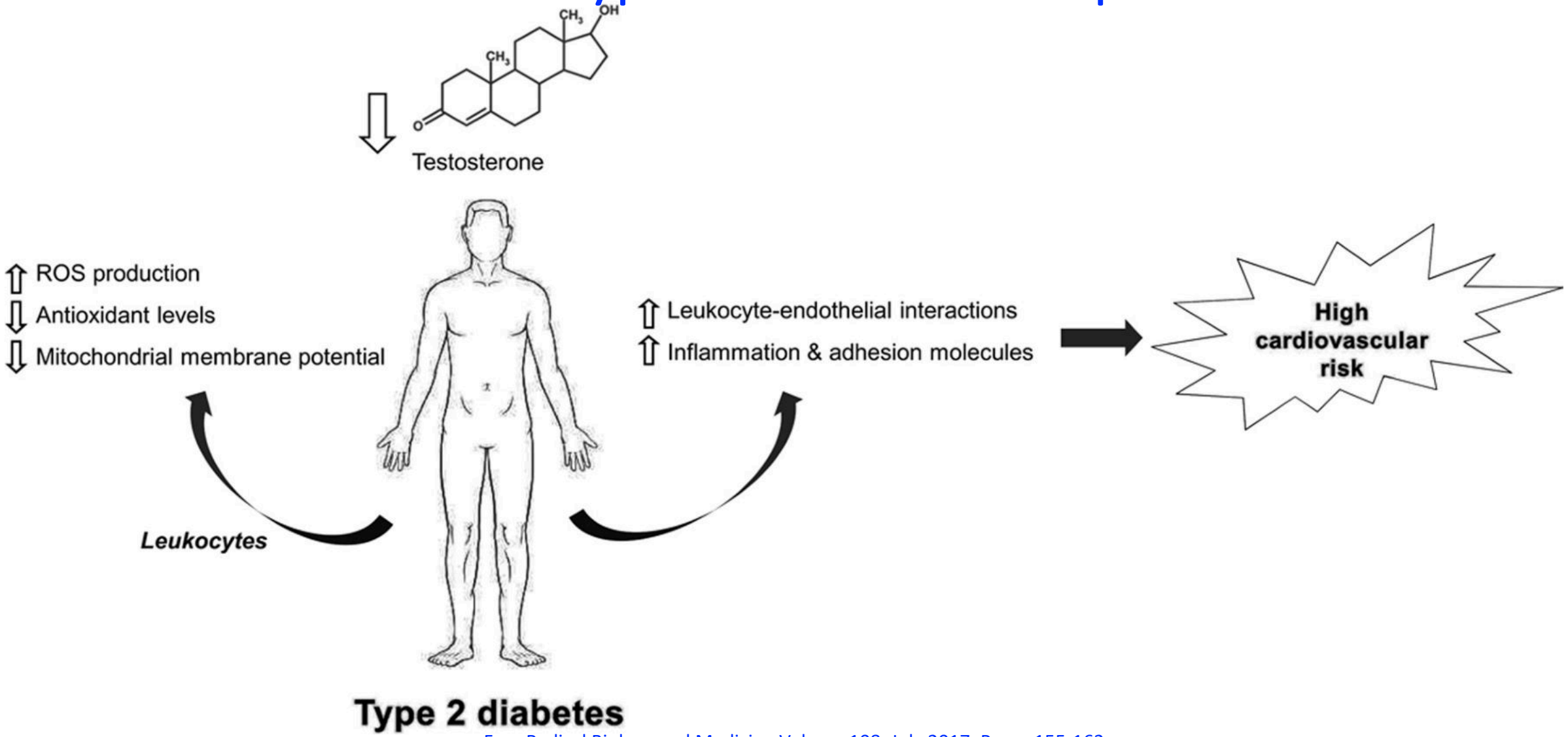
During aging, testosterone levels in healthy men fall by 1% annually from the age of 30. For women, the testosterone levels at 40 years of age are about 50% of those at 20 years of age.

The Therapeutic Intervention of Sex Steroid Hormones for Sarcopenia. Front. Med., 25 October 2021. Sec. Geriatric Medicine. Volume 8 - 2021

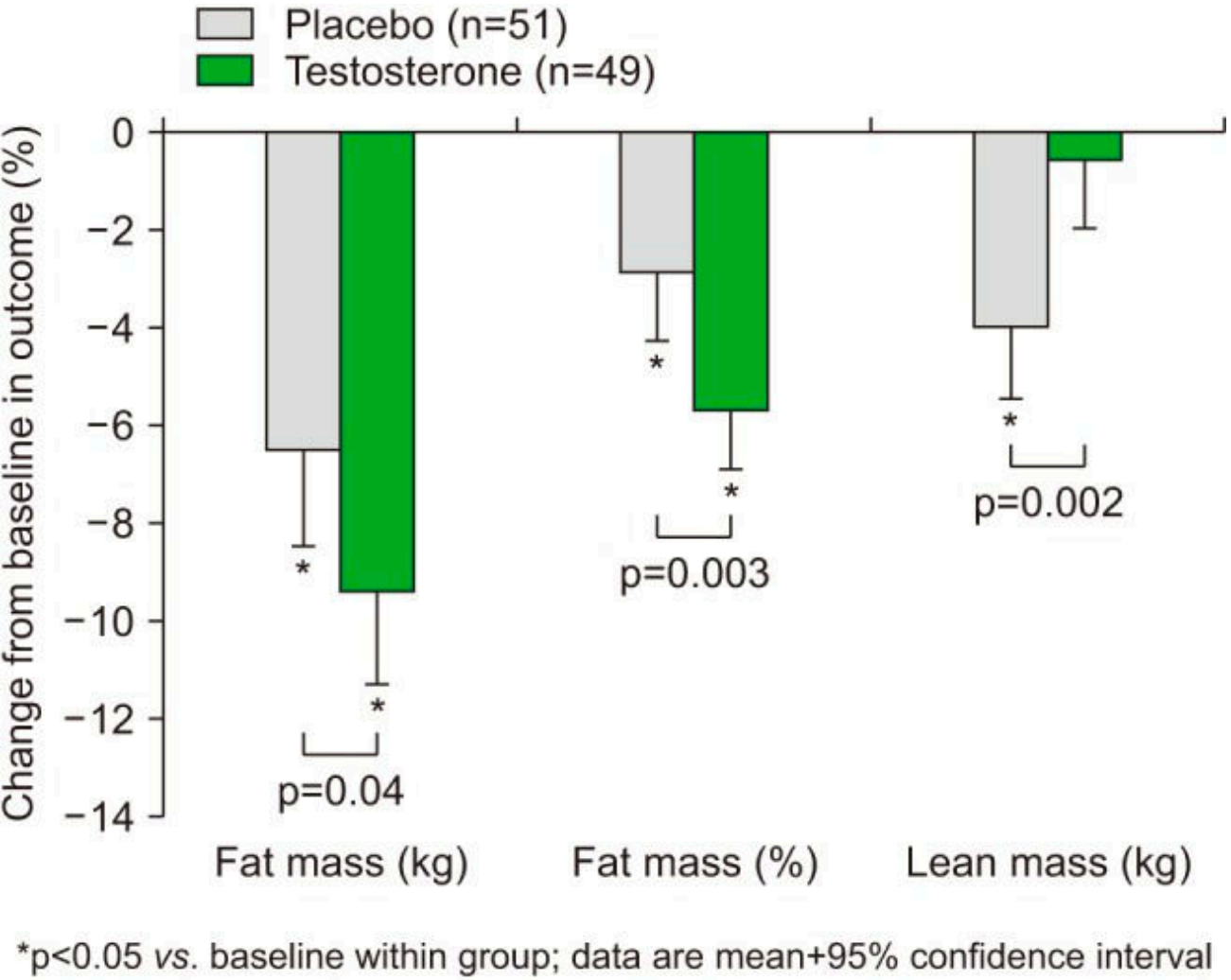


The practical management of testosterone deficiency in men. Antonio Aversa, Abraham Morgentaler. Nature Reviews Urology volume 12, pages641–650 (2015)

Low testosterone levels are related to oxidative stress, mitochondrial dysfunction and altered subclinical atherosclerotic markers in type 2 diabetic male patients



Free Radical Biology and Medicine Volume 108, July 2017, Pages 155-162



*p<0.05 *vs.* baseline within group; data are mean+95% confidence interval

The low levels of testosterone frequently seen in men with T2DM are associated with increased comorbidity and mortality. Studies with testosterone therapy suggest significant benefits in sexual function, quality of life, glycaemic control, anaemia, bone density, fat, and lean muscle mass. Longitudinal studies on CV and all-cause mortality have several logistic problems, related to potential increased mortality associated with inadequately treated patients and possible selection bias.

Type 2 Diabetes and Testosterone Therapy. Hackett G. World J Mens Health. 2019 Jan; 37(1): 31–44

Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial

Testosterone treatment for 2 years reduced the proportion of participants with type 2 diabetes beyond the effects of a lifestyle programme. Increases in haematocrit might be treatment limiting. Longer-term durability, safety, and cardiovascular effects of the intervention remain to be further investigated.

Gary Wittert, Karen Bracken, Kristy P Robledo, and All. Lancet Diabetes Endocrinol 2021; 9: 32–45

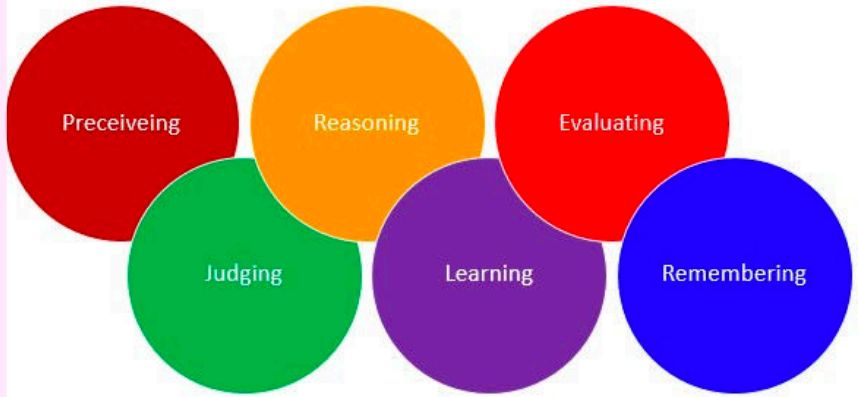
RUPA HEALTH

Low Female Testosterone Signs & Symptoms

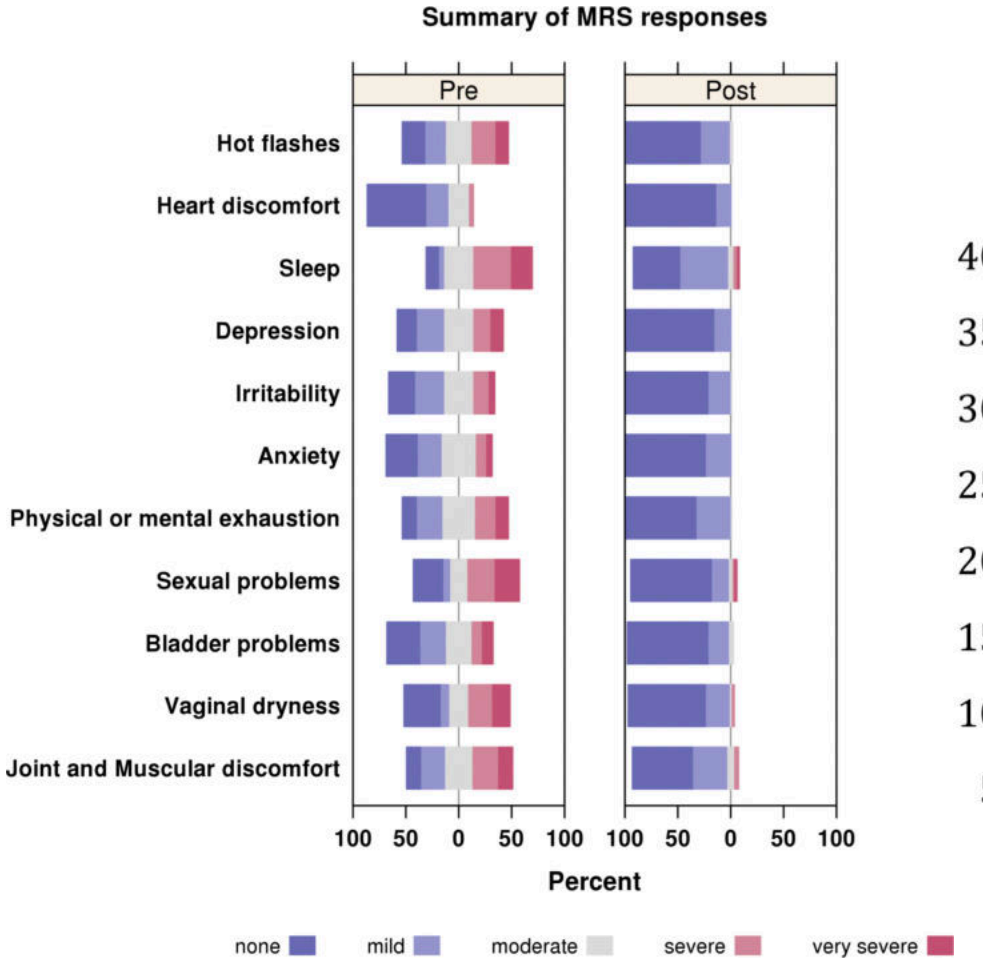
1. Low Libido
2. Muscle Weakness
3. Unexplained Fatigue
4. Depressed Mood
5. Decreased Sense of Personal Wellbeing
6. Weight Gain

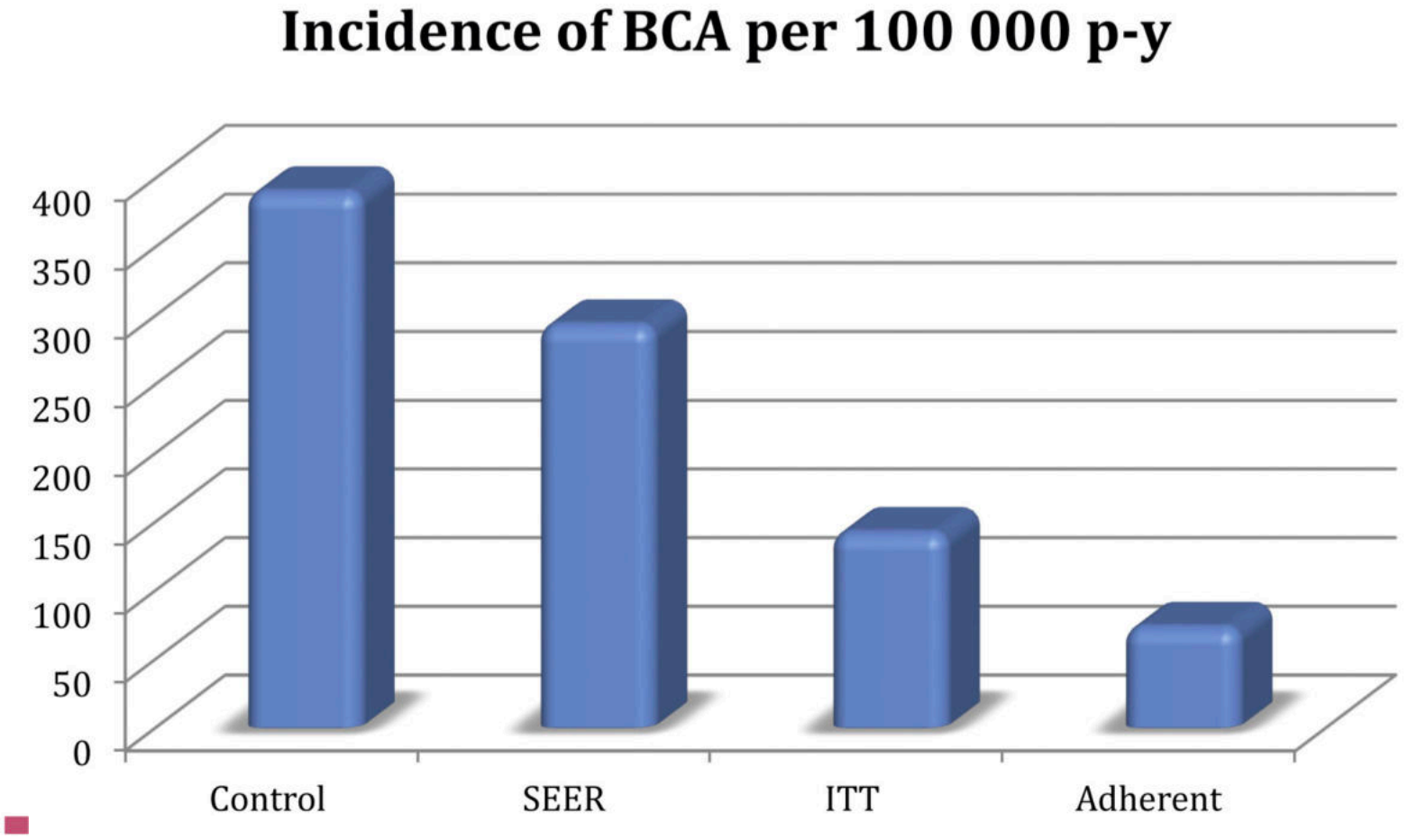
Cognitive impairment

Cognition



Incidence of BCA per 100,000 person-years, 5-year interim analysis results: Age-matched controls (390/100,000), Age-specific SEER expected incidence rates (293/100,000), T therapy, intent to treat group (142/100,000), T therapy, patients adherent to therapy (73/100,000)





Testosterone and breast cancer prevention. R. Glaser, C. Dimitrakakis. Maturitas Volume 82, Issue 3, November 2015, Pages 291-295

Androgen receptor agonists as breast cancer therapeutics

One mechanistic possibility for this is that activated AR may sequester necessary transcription co-factors, including p300 and SRC-3, away from ER, preventing ER from using them to transcribe its own

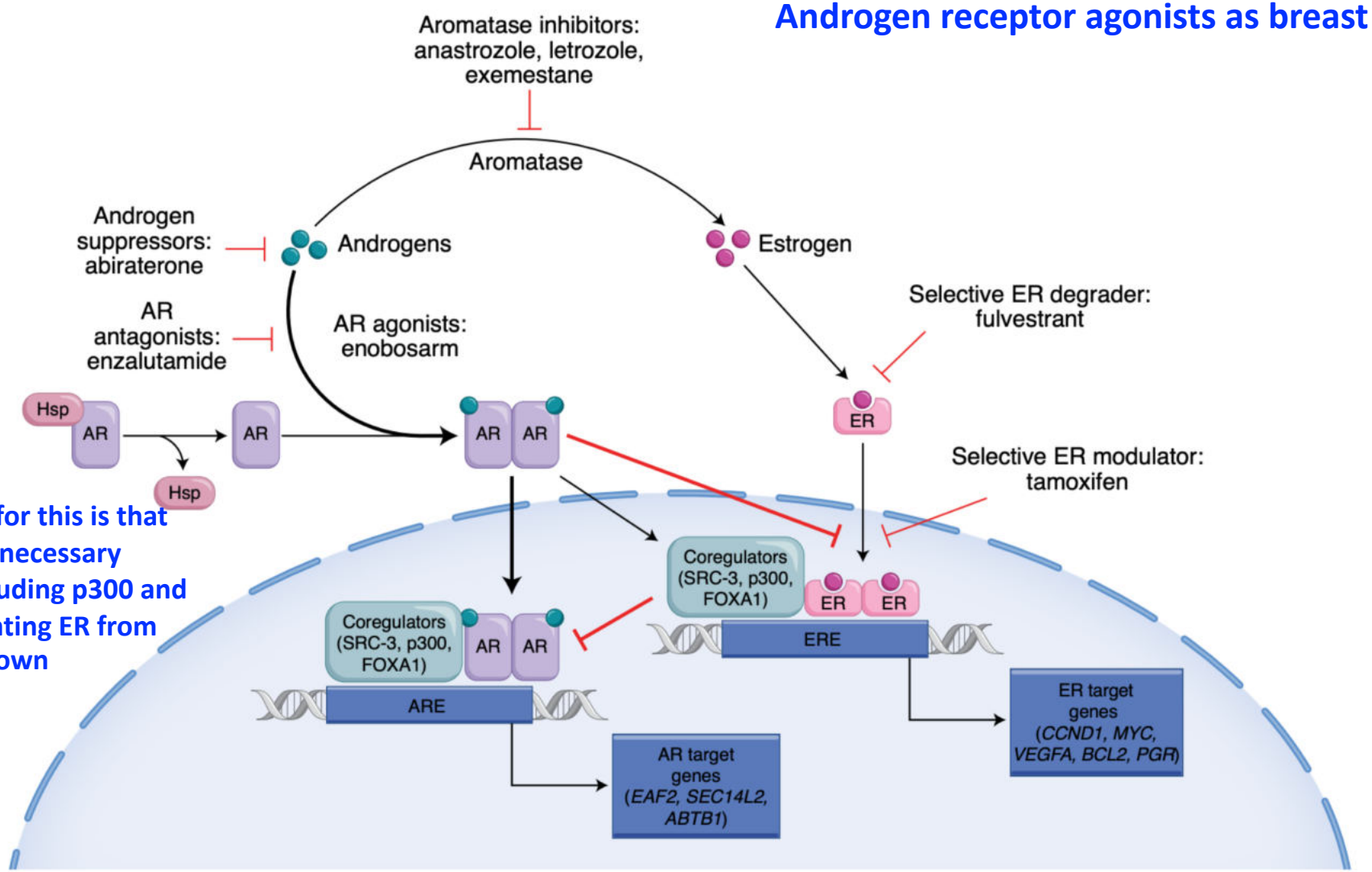
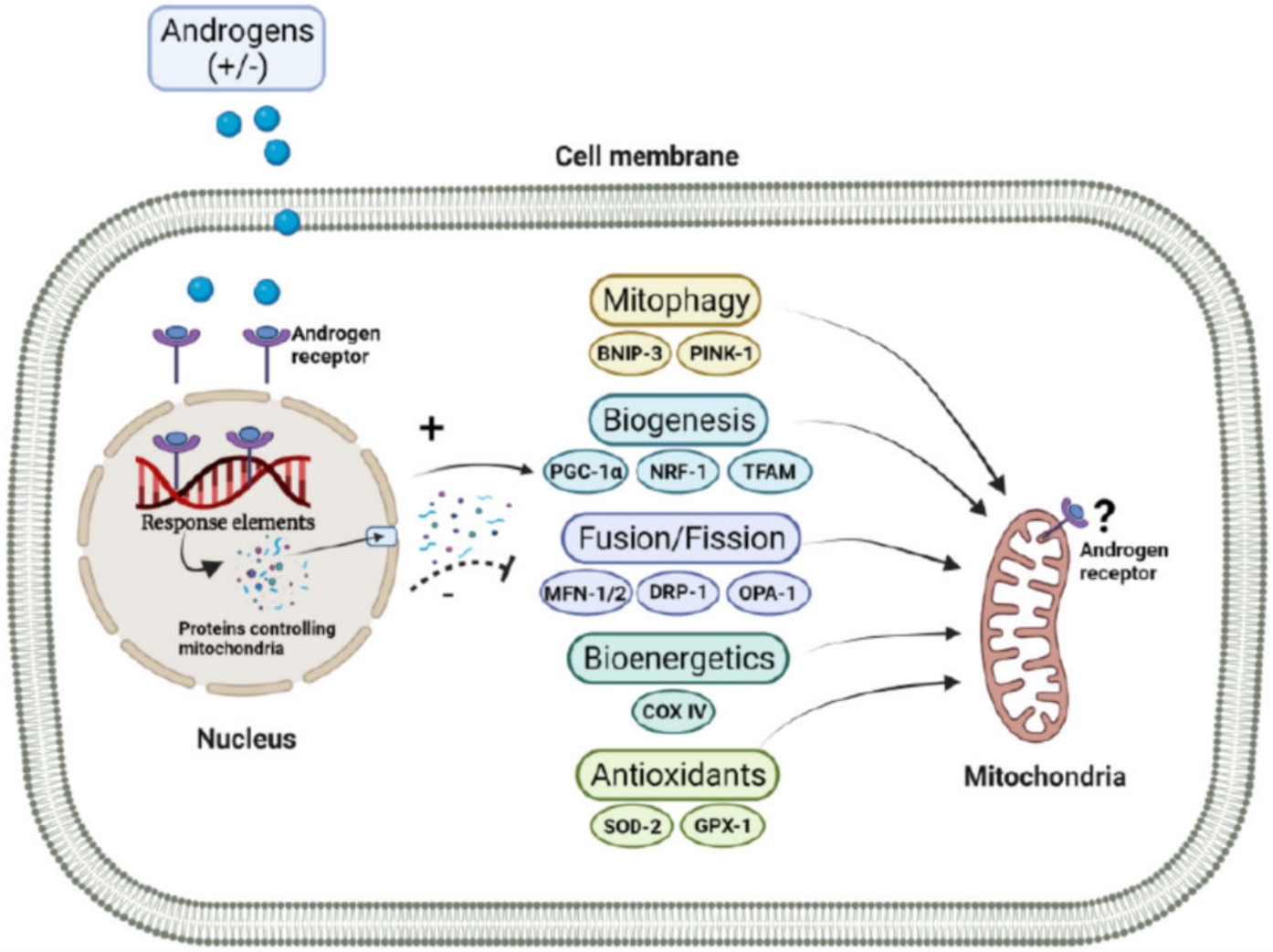


Fig. 1 | AR and ER signaling and crosstalk in breast cancer. Hickley et al. demonstrate the anti-tumor impact of AR agonists (such as enobosarm) in models of ER-positive breast cancer, both through the upregulation of AR target genes and through the displacement of ER and sequestration of its coregulators, which prevents the expression of ER target genes[1]. The sites of action of other therapeutics that target steroid-hormone-receptor pathways are also shown. Hsp, heat-shock protein; ARE, androgen-response element; ERE, estrogen-response element.

Role of androgens and androgen receptor in control of mitochondrial function



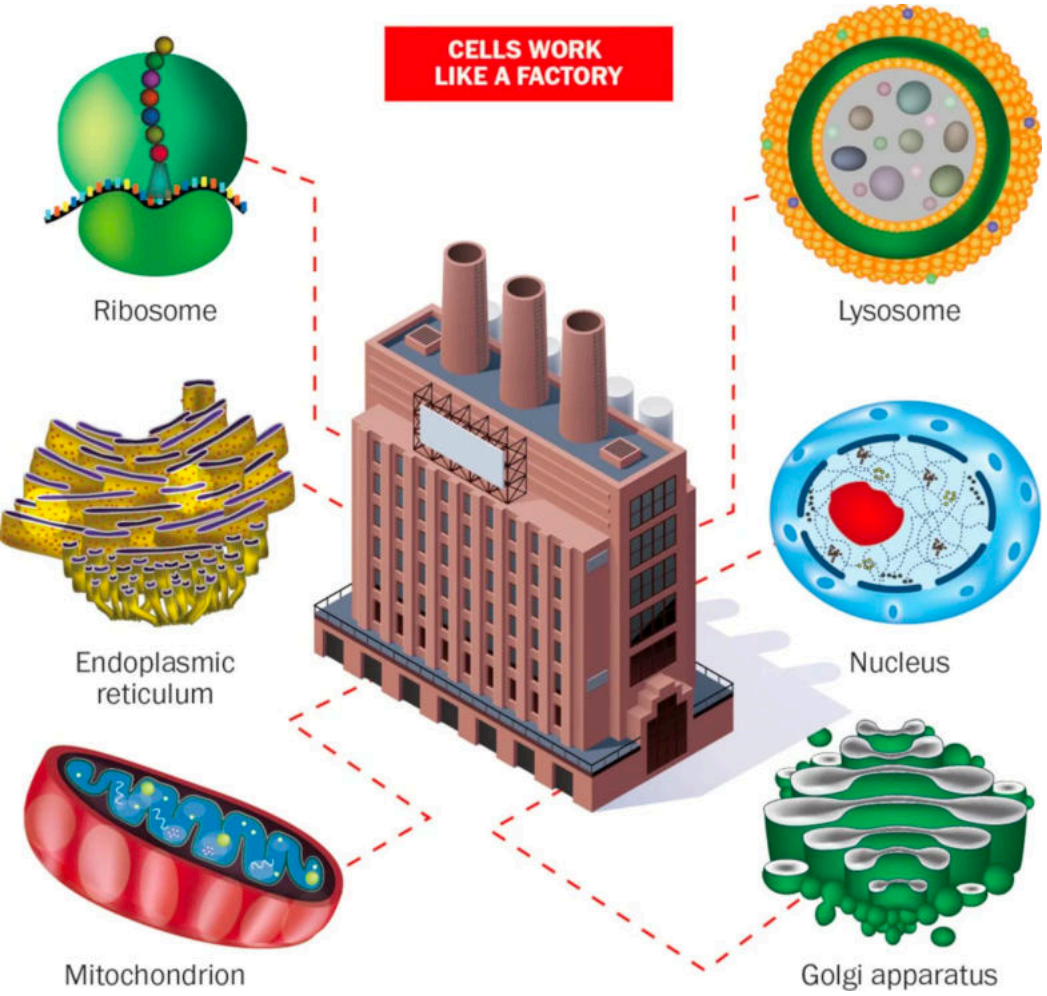
The classical mechanism of androgen action is via ligand-dependent binding with the nuclear transcription factor, androgen receptor (AR), cytosolic AR can also activate second messenger signaling pathways.
The effects that androgens have on mitochondrial structure and function with emphasis on biogenesis, fusion/fission, mitophagy, bioenergetics (oxidative phosphorylation), and reactive oxygen species production.
The nucleus and mitochondria work in tandem to control mitochondrial

American Journal Off Physiology. Cell Physiology. Irshad Ahmad and Annie E. Newell-ugatePublished Online 02 SEP 2022.

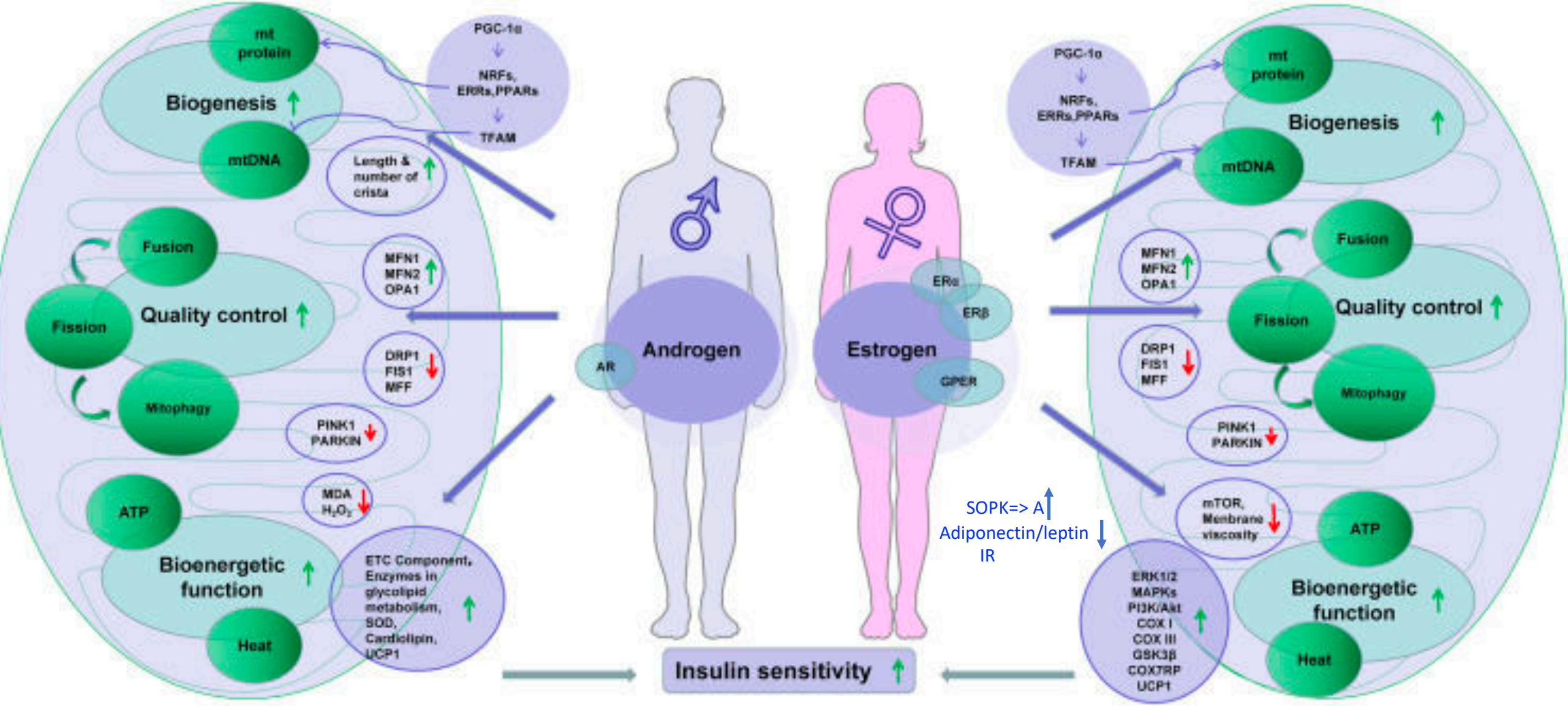
How to prescribe DHEA, Oestrogen, Testosterone

	Men	Women
DHEA	350 ug/dL	250 ug/dL
Oestradiol	< 35ng/L	80 ng/L (PM)
Total testosterone	5 à 10.000 pg/ml	500 ng/L
Free testosterone	180 à 280 pg/mL	10-15 ng/L
Androstanediol-glucuronide	10 à 22 ng/ml	6-8 ng/ml
SHBG	20 à 55 pmol/ml	8-12 mg/24 H
Total 17 Keto-Steroids	8-12 mg/24 H	8-12 mg/24 H

*Take home message



- Nutritionnal and Functional Medicine check up
- Correct deficiencies
- Ensure to preserve functional mitochondria
- Avoid excessive oxydative stress
- Hormones are messengers that optimize cell function and are essential to increase cell lifespan and that way contribuing to increase our healthy lifespan
- Critical Window



Mitochondria in Sex Hormone-Induced Disorder of Energy Metabolism in Males and Females. Lijun Yin and All. Front Endocrinol (Lausanne). 2021; 12: 749451