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LASERS
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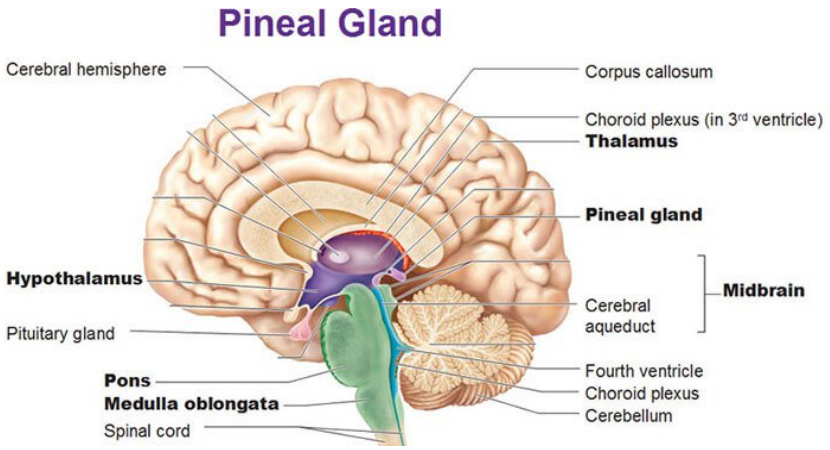
GROUPE LASER
De la SFD
Lasers et technologies apparentées

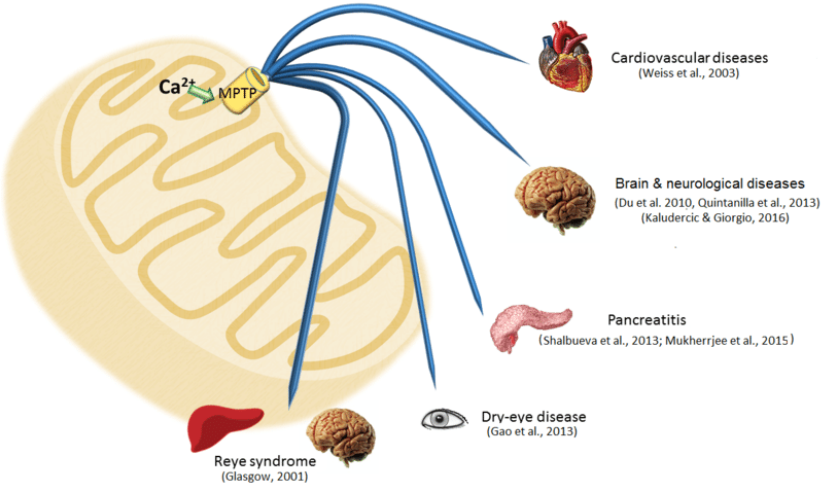
Société Belge de Médecine Esthétique & Lasers
Belgische Vereniging Esthetische Geneeskunde & Lasers
29th CONGRESS / BRUSSELS / APRIL 26-27, 2019
en collaboration avec le / met de medewerking van de
GROUPE LASER DE LA SOCIÉTÉ FRANÇAISE DE DERMATOLOGIE

Anti-Aging Medicine in 2020

Carly Dominique MD



Melatonine

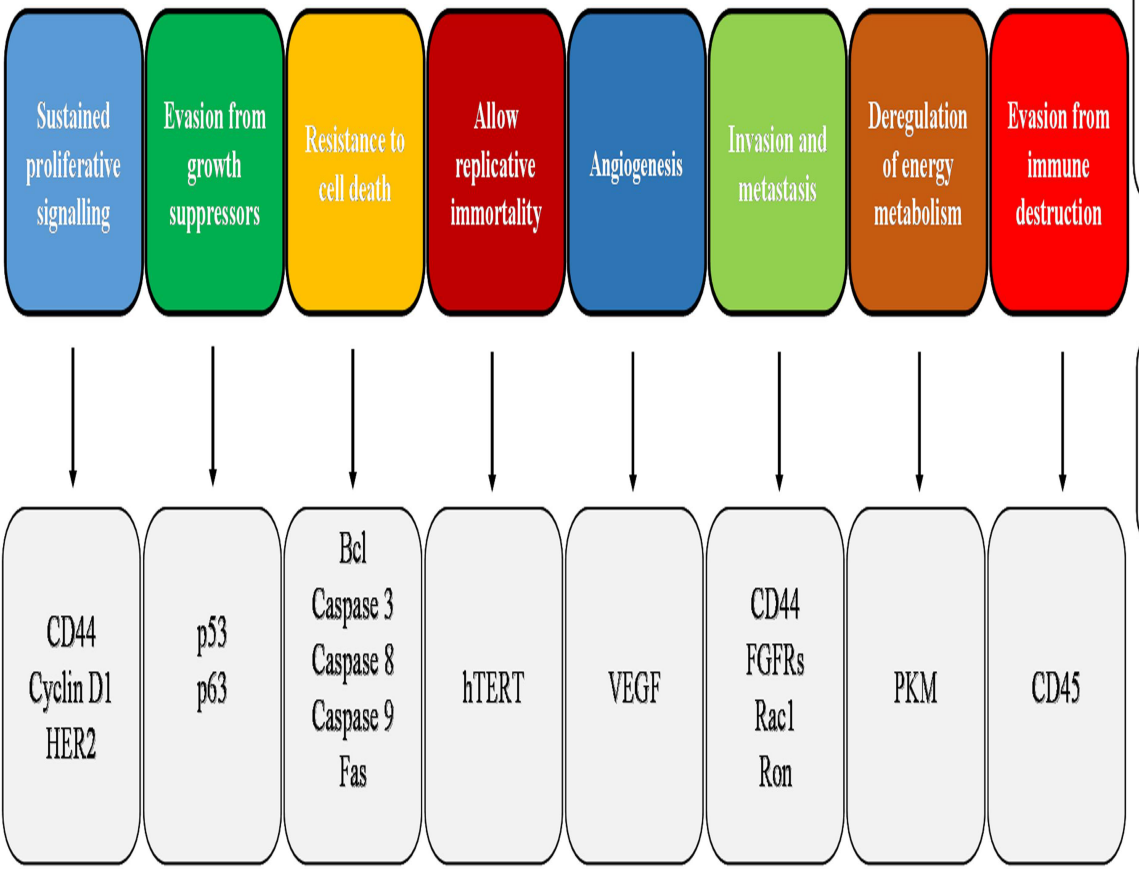


Mitochondrial dysfunction is implicated as the major causative factor in a variety of conditions such as the aging process, I/R, and septic shock. In addition, abnormal mitochondrial function, decreased respiratory enzyme complex activities, increased electron leakage, opening of the mtPT pore, and increased Ca^{2+} entry have all been shown to play a role in the pathophysiology of neurodegenerative disorders such as PD, AD, and HD.

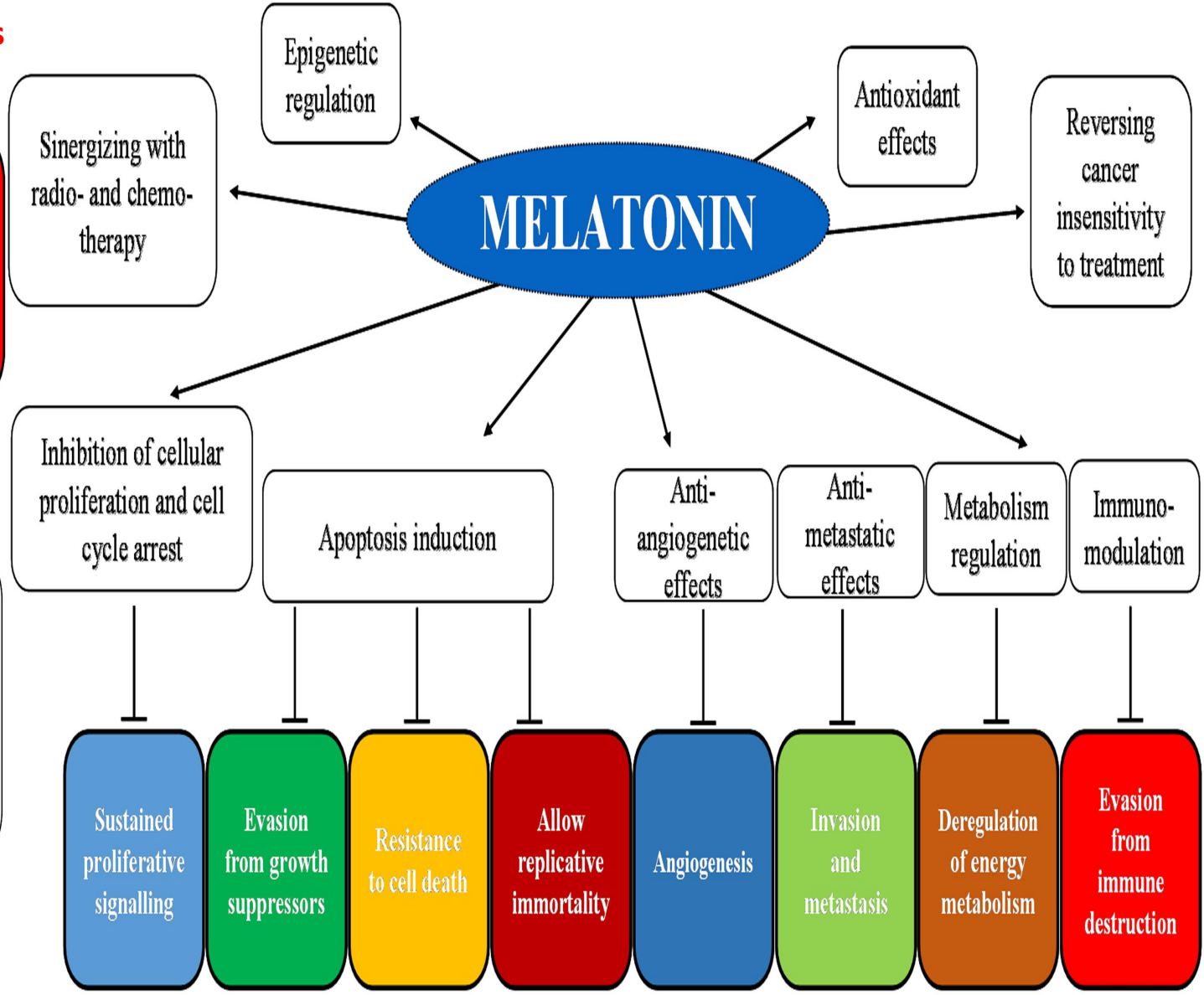
Melatonin in Mitochondrial Dysfunction and Related Disorders
Int J Alzheimers Dis. 2011; 2011: 326320.

http://anti-aging-for-all.com/wp-content/uploads/2014/12/melatonin-benefits.jpeg

Melatonin can regulate epigenetic modifications in cancer cells by both DNA methylation and histone protein remodeling.

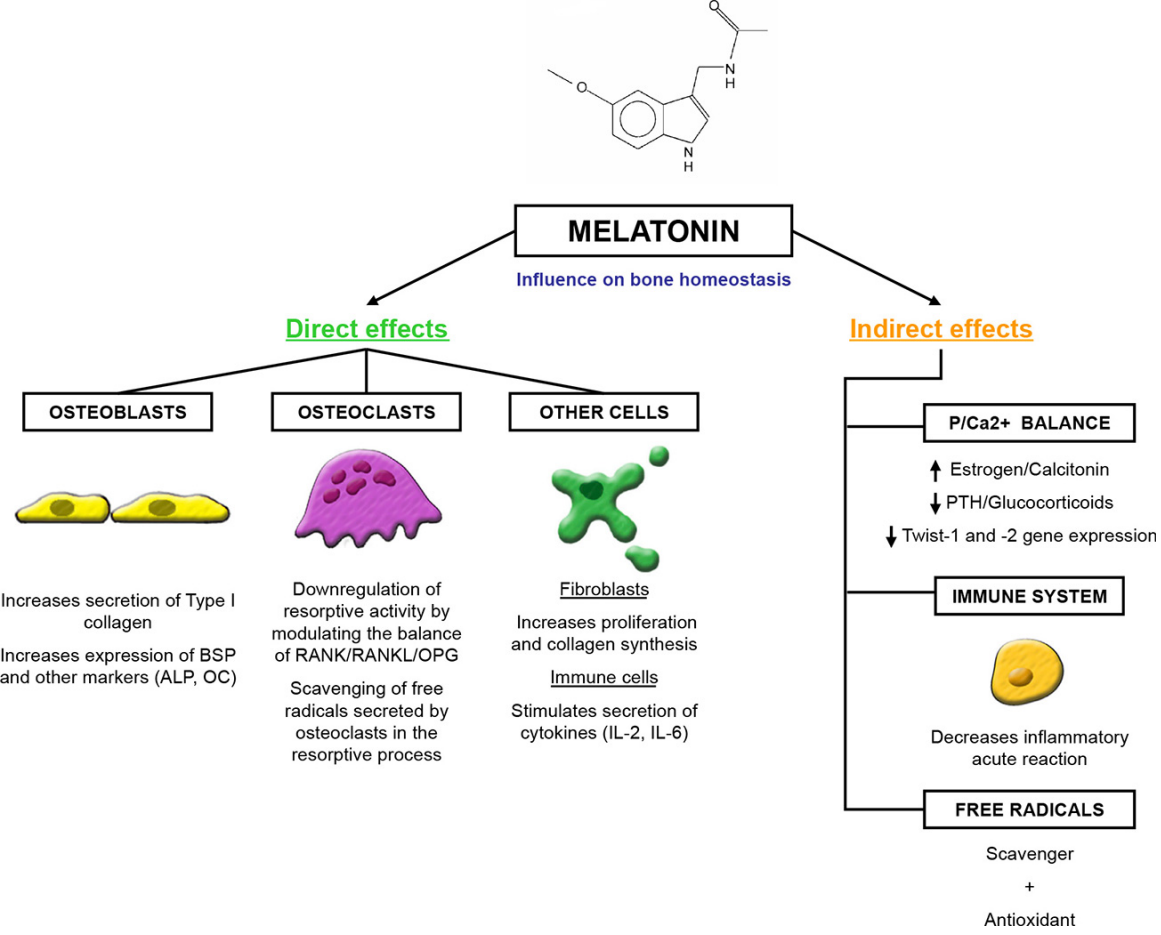


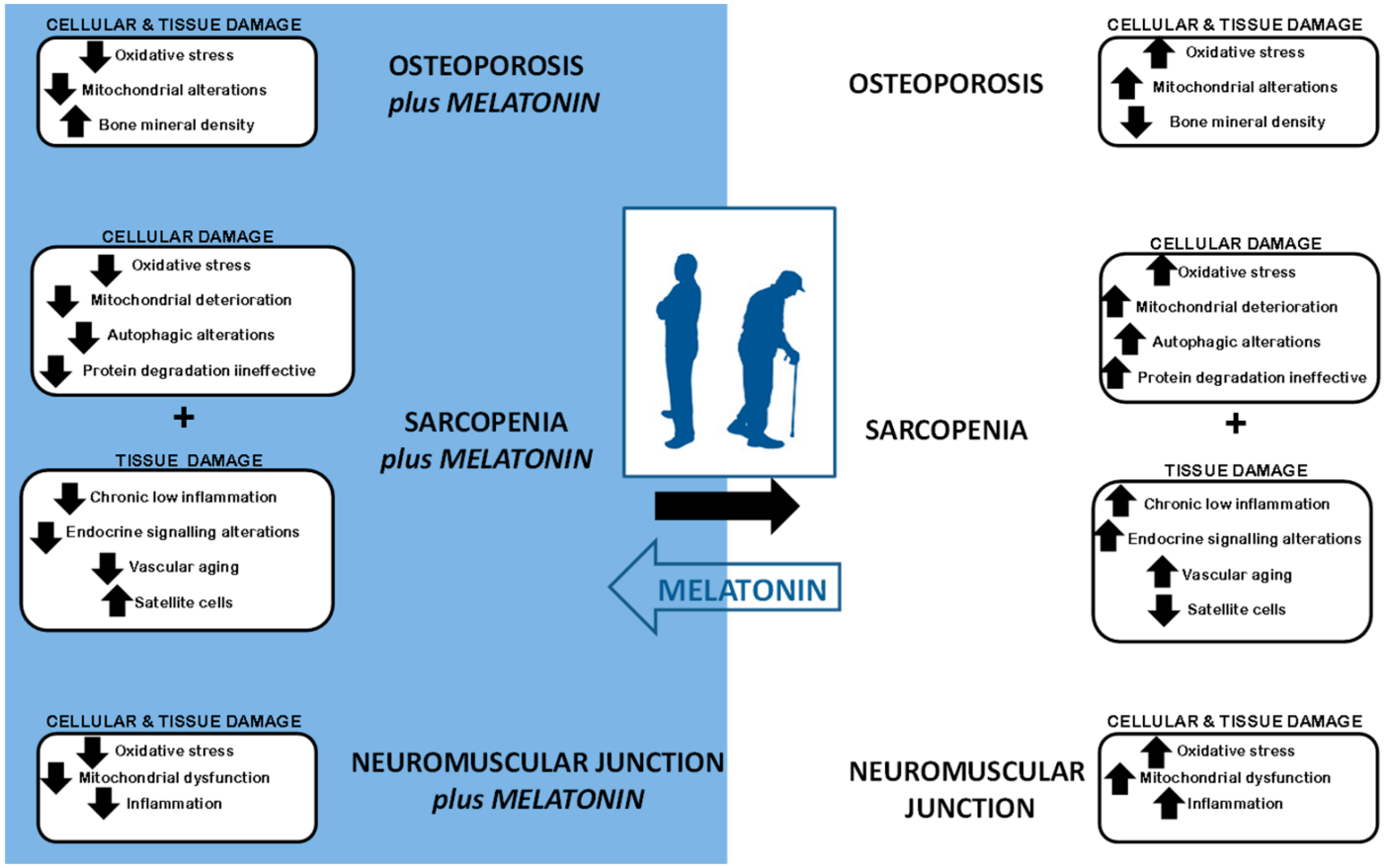
Schematic representation of cancer hallmarks with the indication of the main markers involved in the corresponding hallmark. FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; PKM, pyruvate kinase M; VEGF, vascular endothelial growth factor.



Schematic representation of melatonin's inhibition of cancer hallmarks with an indication of the main target molecules and the corresponding hallmark.

Promising Antineoplastic Actions of Melatonin. Gaia Favero and All. Front. Pharmacol., 16 October 2018 | https://doi.org/10.3389/fphar.2018.01086





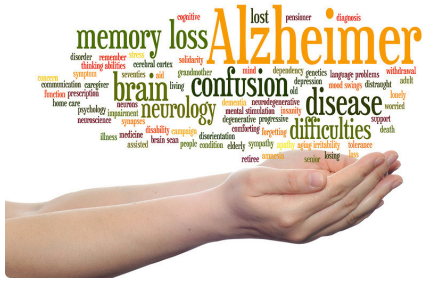
Melatonin positive regulation of bone formation and homeostasis, in combination with the inhibitory effects on bone resorption

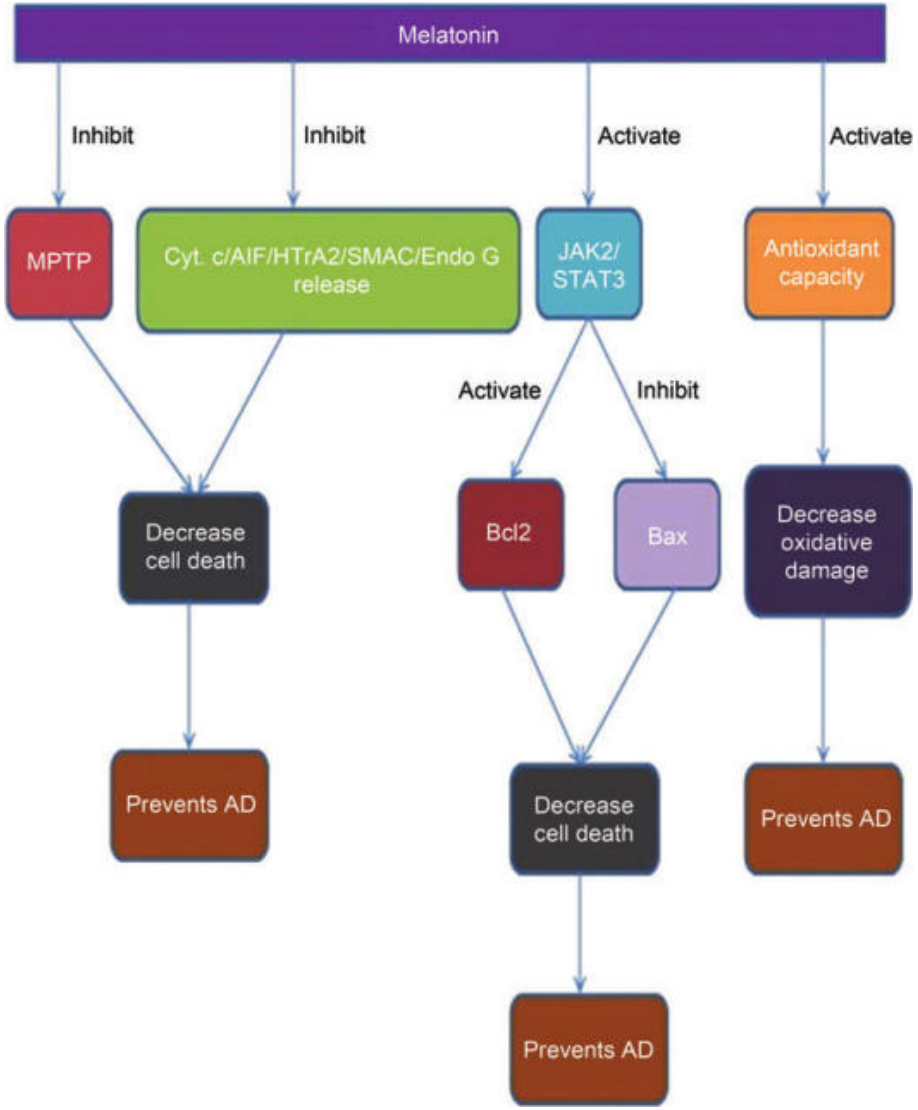
https://www.dtscience.com/the-role-of-melatonin-in-periodontal-and-periimplant-bone-homeostasis-and-regeneration

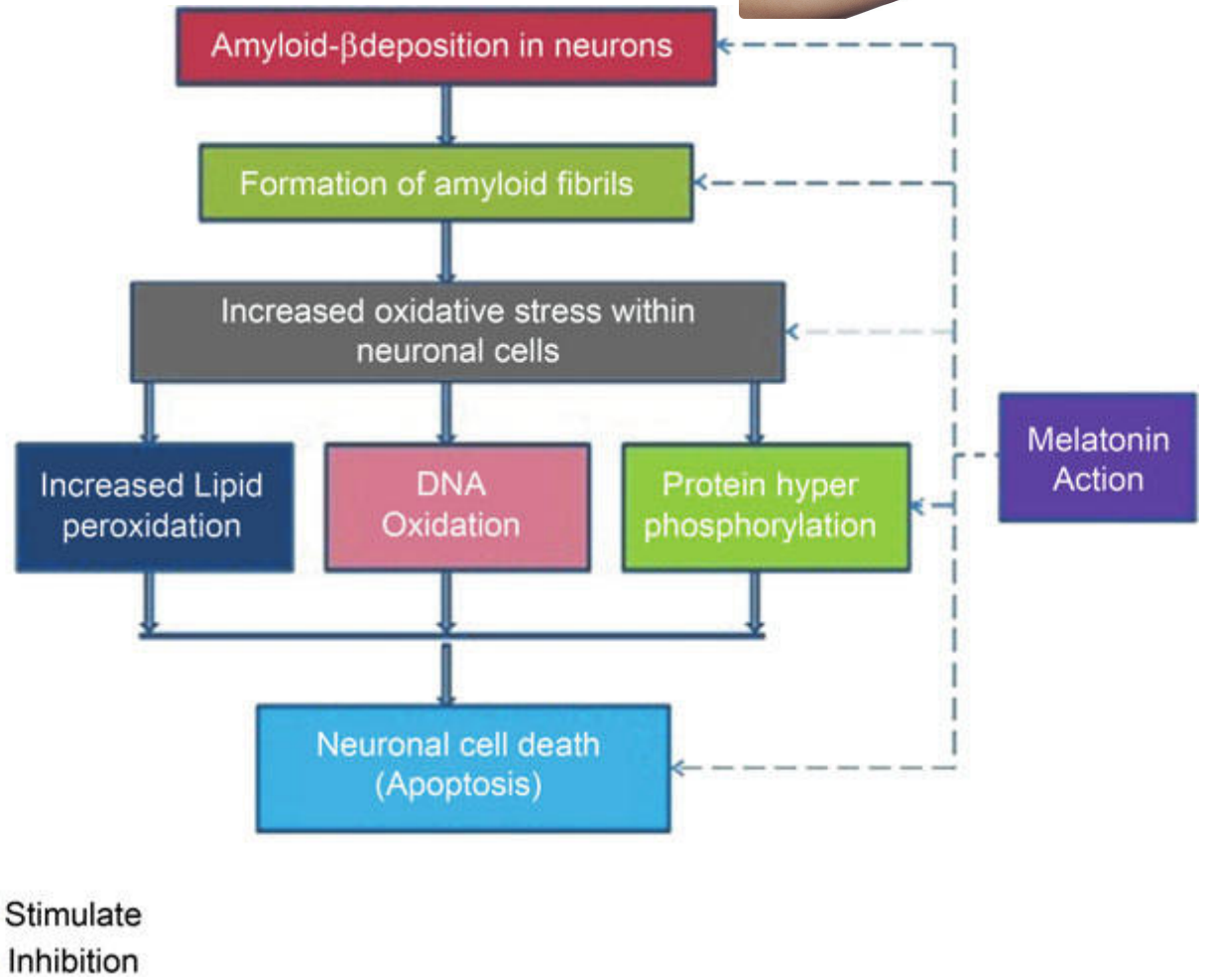
Sarcopenia is a highly burdensome geriatric syndrome. It is commonly associated with osteroporosis and neuromuscular dysfunction. Currently, no effective treatment for this degenerative process has been identified. Melatonin has a high safety profile and no serious toxicity related to melatonin usage has been reported.

Melatonin as a Potential Agent in the Treatment of Sarcopenia. Ana Coto-Montes **and All.** *Int. J. Mol. Sci.* **2016**, *17*(10), 1771

MELATONIN AGAINST NEURODEGENERATIVE DISEASES

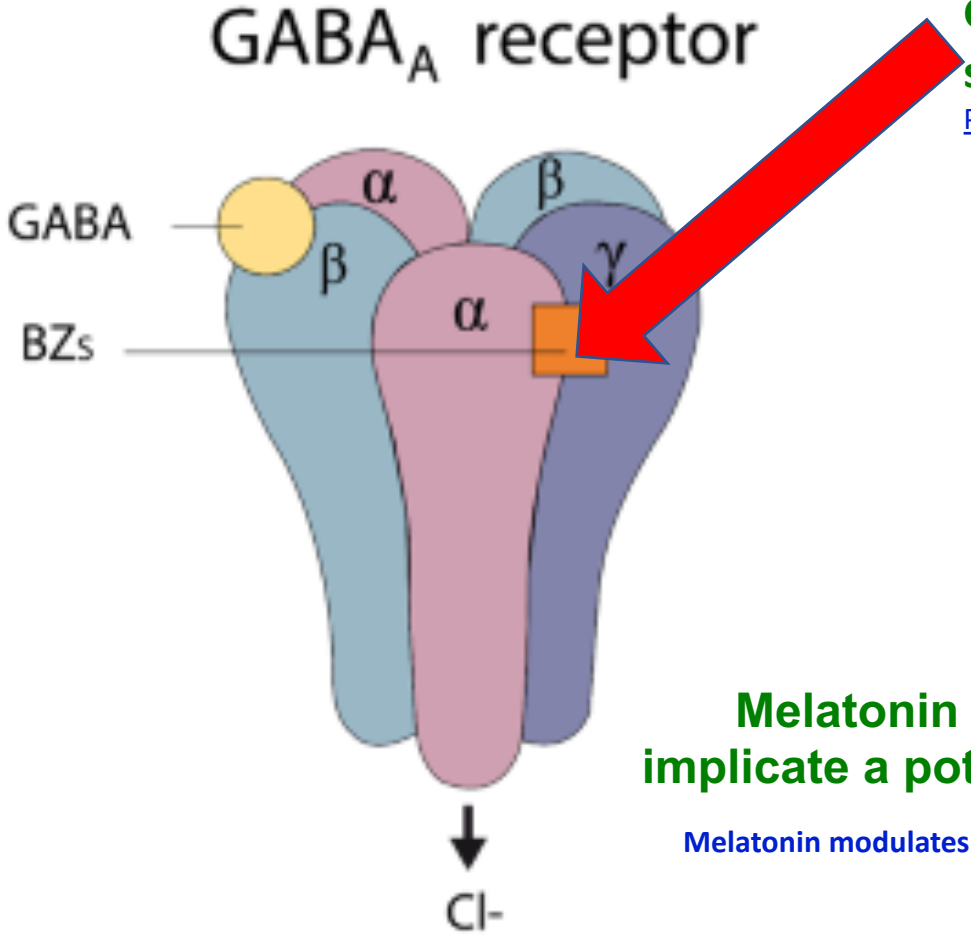






Melatonin: A Potential Anti-Oxidant Therapeutic Agent for Mitochondrial Dysfunctions and Related Disorders. Showkat Ahmad Ganie and All. Rejuvenation Research 19(1) · June 2015

Benzodiazepine receptor agonists (BzRA)



The hypnotic activity of melatonin may be linked to the GABA$_A$ receptor and mediated through the BZP recognition site.

Pharmacology Biochemistry and Behavior. Volume 74, Issue 3, February 2003, Pages 573-578

- Benzodiazepines
- "Z-drugs"
  - Zolpidem
  - Eszopiclone
  - Zaleplon

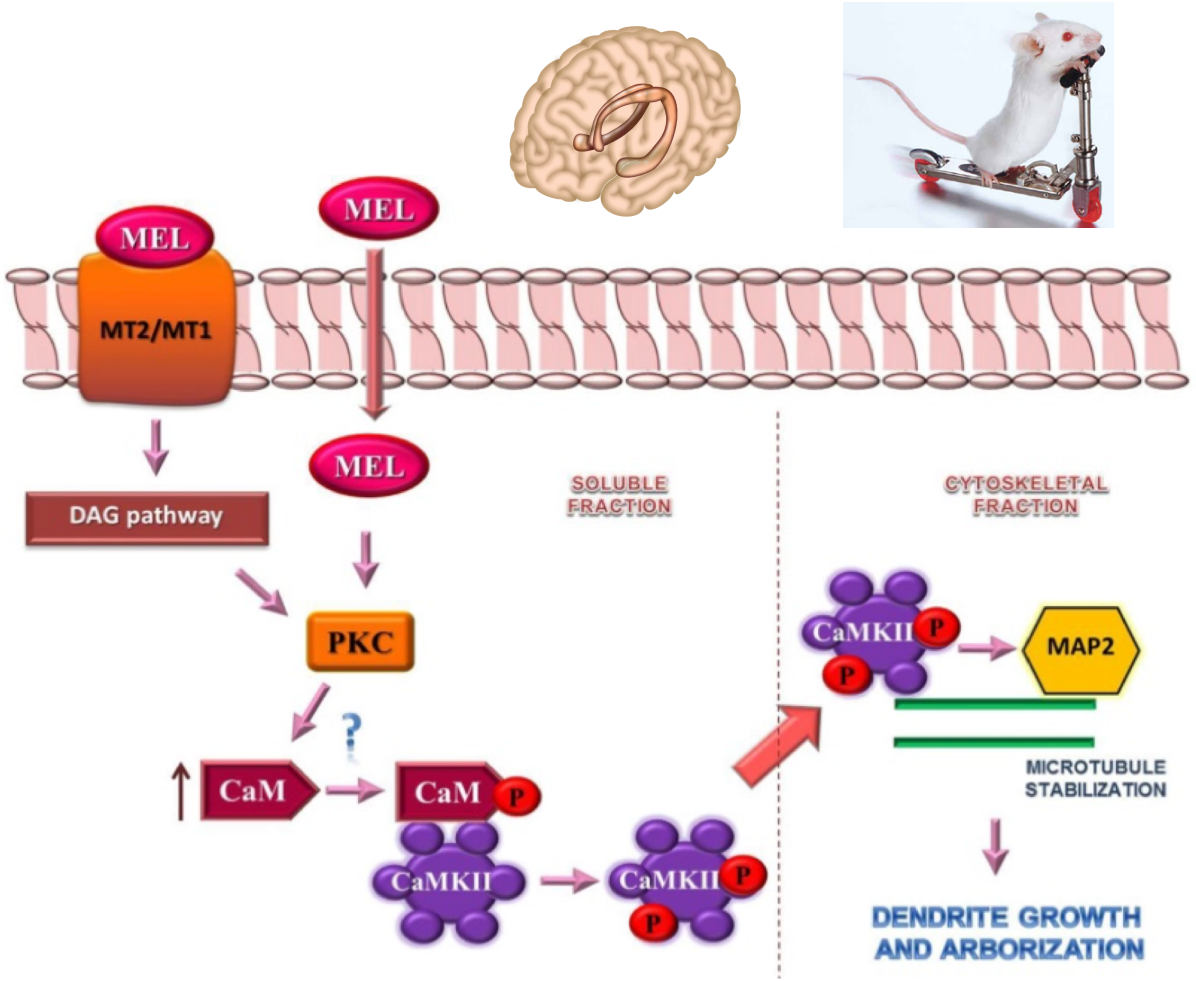
Melatonin has an enhancing effect on the GABAergic system may implicate a potential pathway for the neuroprotective effects of melatonin.

Melatonin modulates the GABAergic response in cultured rat hippocampal neurons. J Pharmacol Sci. 2012;119(2):177-85.

https://psychopharmacologyinstitute.com/sleep-insomnia/psychopharmacology-sleep-wakefulness-understanding-neurotransmitters-pathways-clinical-practice/

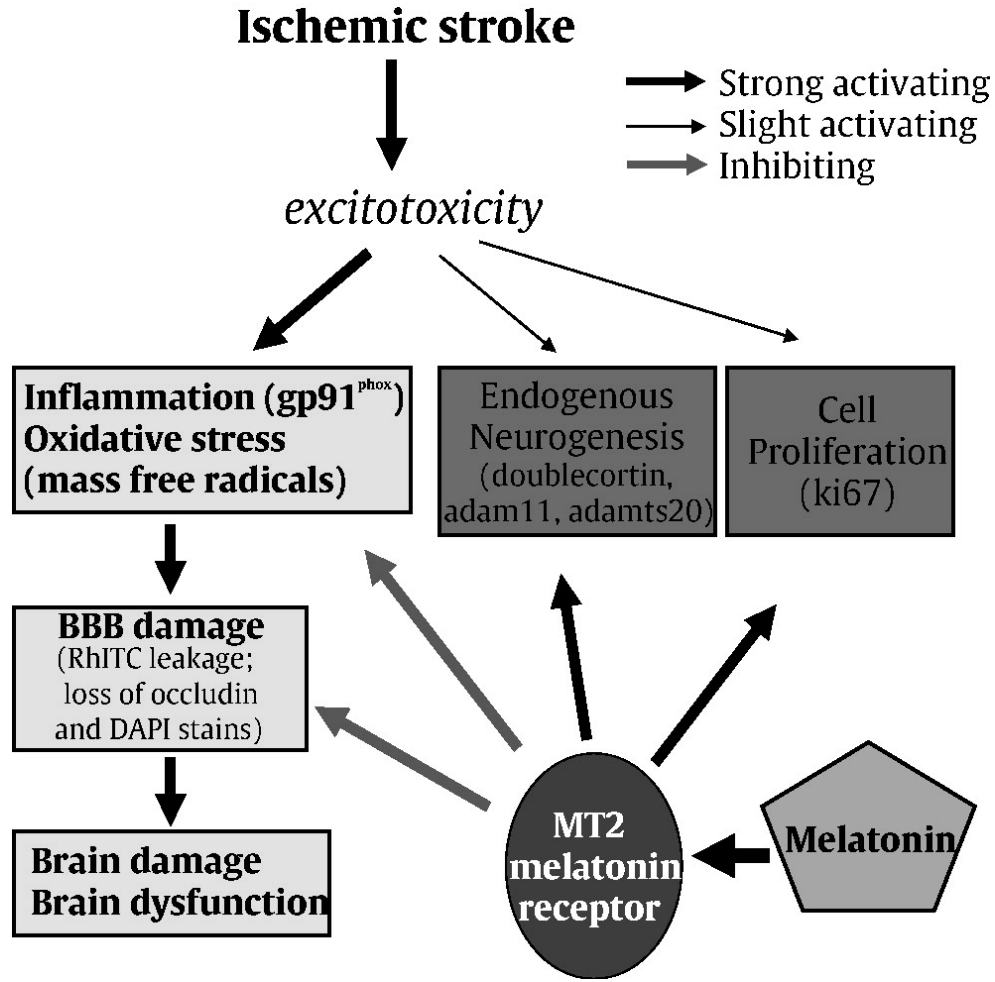
PSYCHOPHARMACOLOGY INSTITUTE

Melatonin stimulates the three stages of dendritogenesis: dendrite formation, enlargement and complexity.

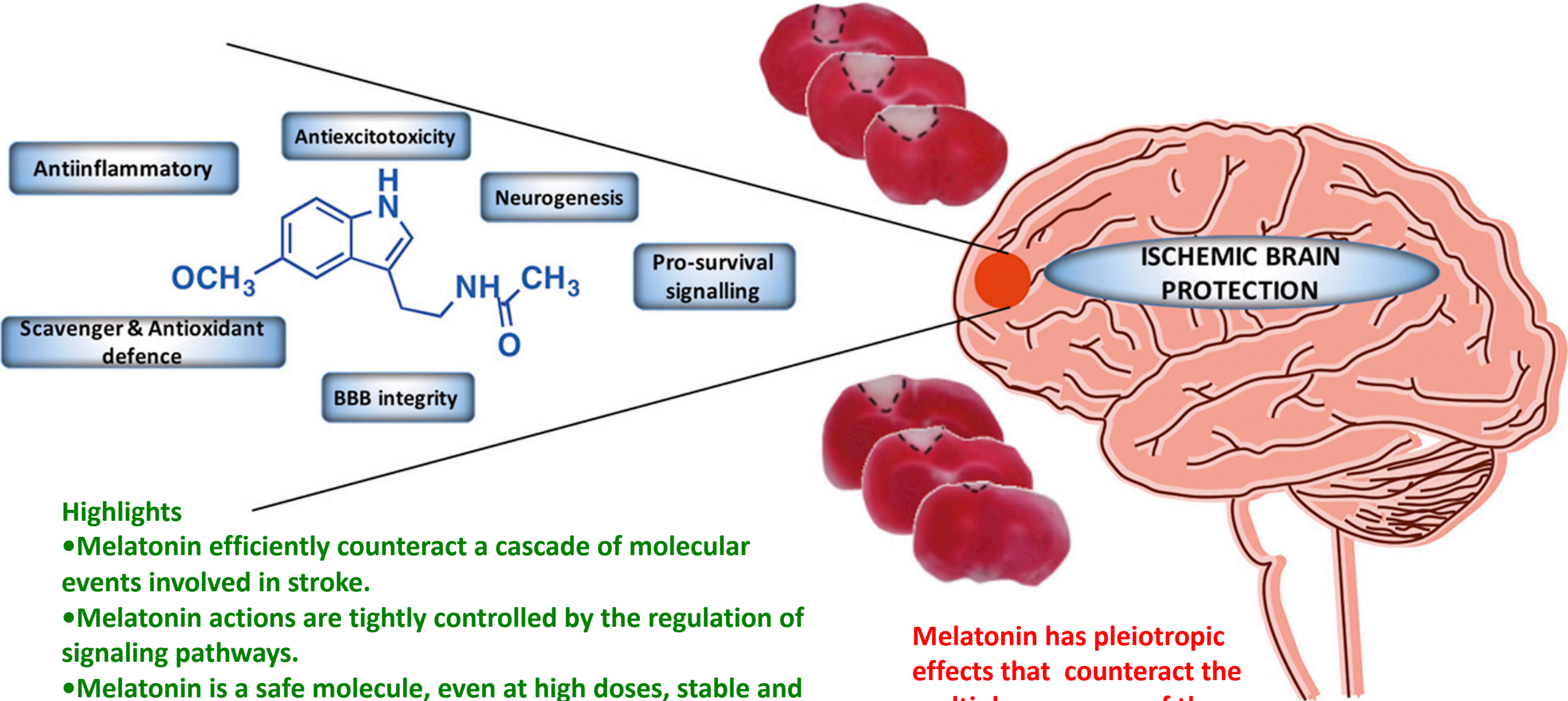


Int. J. Mol. Sci. 2015, 16, 1907-1927;

Melatonin is able to protect mice against stroke by activating MT2 melatonin receptors, which reduces oxidative/inflammatory stress. This results in the preservation of BBB integrity and enhances endogenous neurogenesis by upregulating neurodevelopmental gene/protein expression.



Melatonin ameliorates neural function by promoting endogenous neurogenesis through the MT2 melatonin receptor in ischemic-stroke mice. Chang-MingChern and All. Free Radical Biology and Medicine. Volume 52, Issue 9, 1 May 2012, Pages 1634-1647



Highlights

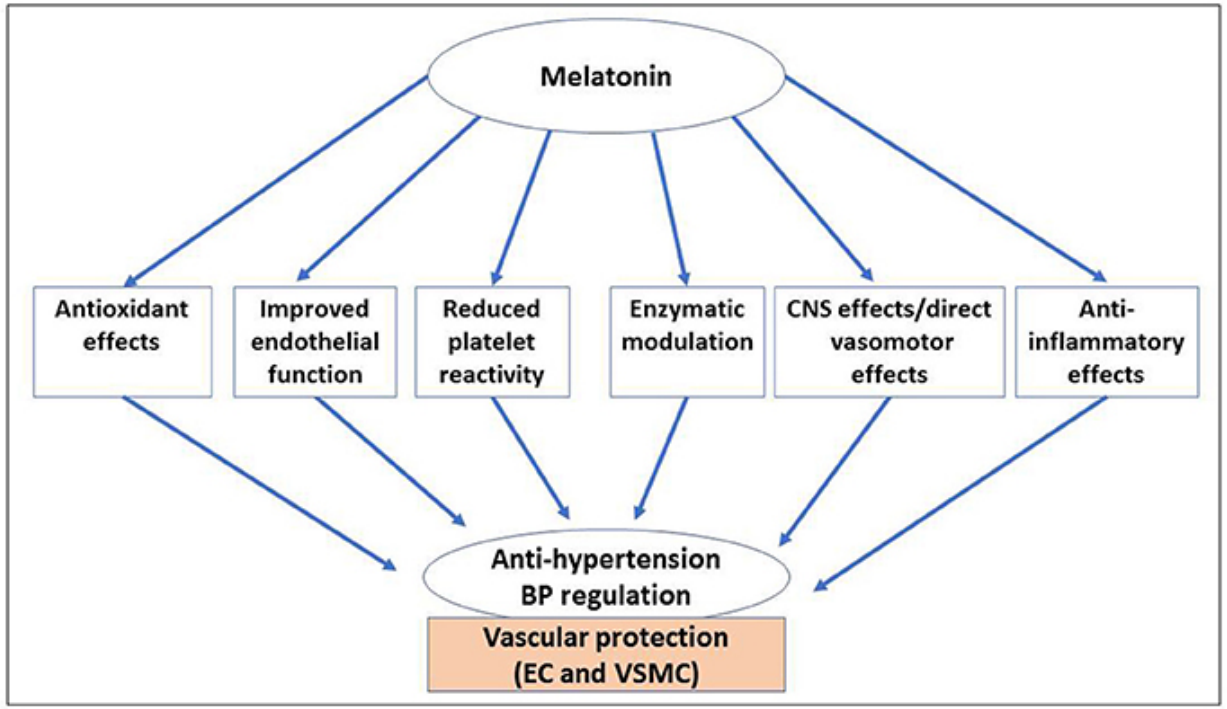
- **Melatonin efficiently counteract a cascade of molecular events involved in stroke.**
- **Melatonin actions are tightly controlled by the regulation of signaling pathways.**
- **Melatonin is a safe molecule, even at high doses, stable and cheap.**
- **Antioxidant therapy with melatonin alone or in combination reduce brain ischemia.**

Melatonin has pleiotropic effects that counteract the multiple processes of the ischemic cascade.

Ischemic brain injury: New insights on the protective role of melatonin. Eva Ramos and All. Free Radical Biology and Medicine. Volume 104, March 2017, Pages 32-53

Cardiovascular Benefits of Dietary Melatonin: A Myth or a Reality ?

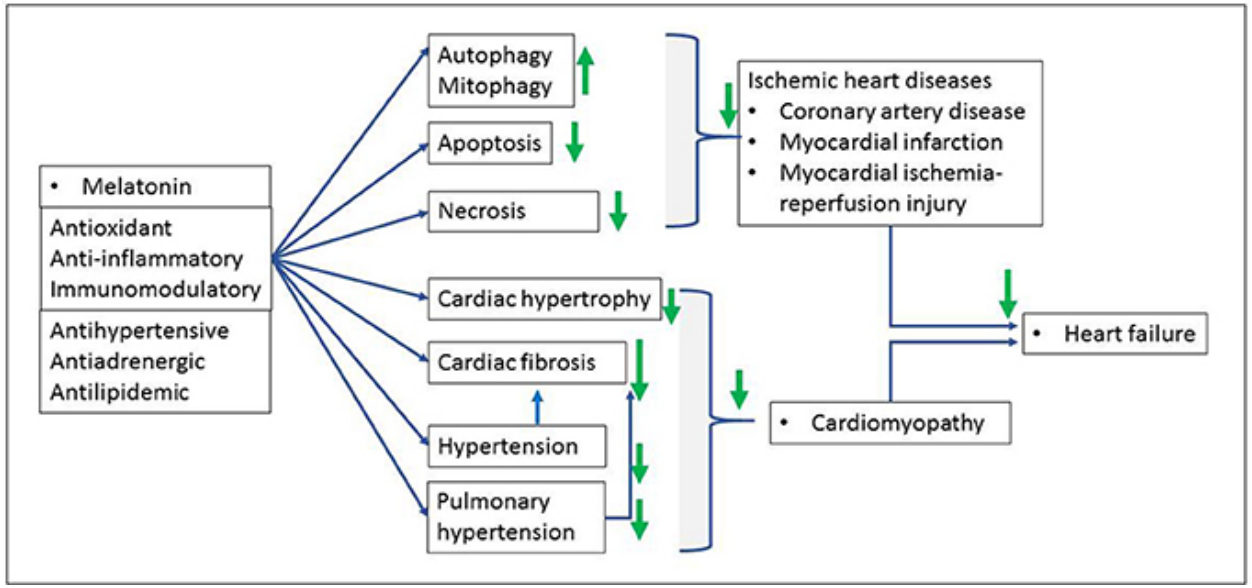
Zukiswa Jiki and All. Front. Physiol., 17 May 2018



Benefits of melatonin in hypertension and vascular pathologies. Melatonin positively affects vascular function (endothelial and smooth vascular muscle cells) via its direct and indirect regulatory effects associated with its strong antioxidant, anti-inflammatory, anti-lipidemic and vasomotor properties (vasodilation), all contributing to BP regulation (anti-hypertensive effects). These effects are also associated with enzymatic modulation, improved endothelial function and a reduced platelet reactivity. BP, blood pressure; CNS, central nervous system; EC, endothelial cells; CSMC, vascular smooth muscle cells.

In summary, preclinical studies clearly suggest the cardiovascular health benefit of both endogenous and supplementary melatonin.

Preclinical studies suggest that melatonin, given at dietary levels, confers cardioprotection



Apelin

cardiac repair and recovery through upregulation of SIRT3.

Sirt3 is a critical factor for Apelin-induced angiogenesis in post-MI

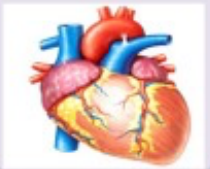
Apelin treatment:

- overexpression of SIRT3
- overexpression of angiopoietins /Tie-2
- Overexpression of VEGF/VEGFR2
- enhancement in the myocardial vascular densities

Stem cell

- Sirt3 is substantial for Bone Marrow Cell therapy
- loss of Sirt3: attenuation of BMC-mediated angiogenesis and cardiac repair in post-MI

SIRT3 mediated cardiac repair



Curcumin → Through SIRT3

- improved cardiac function
- diminished infarct size
- reduced lactate dehydrogenase

Melatonin → Through SIRT3

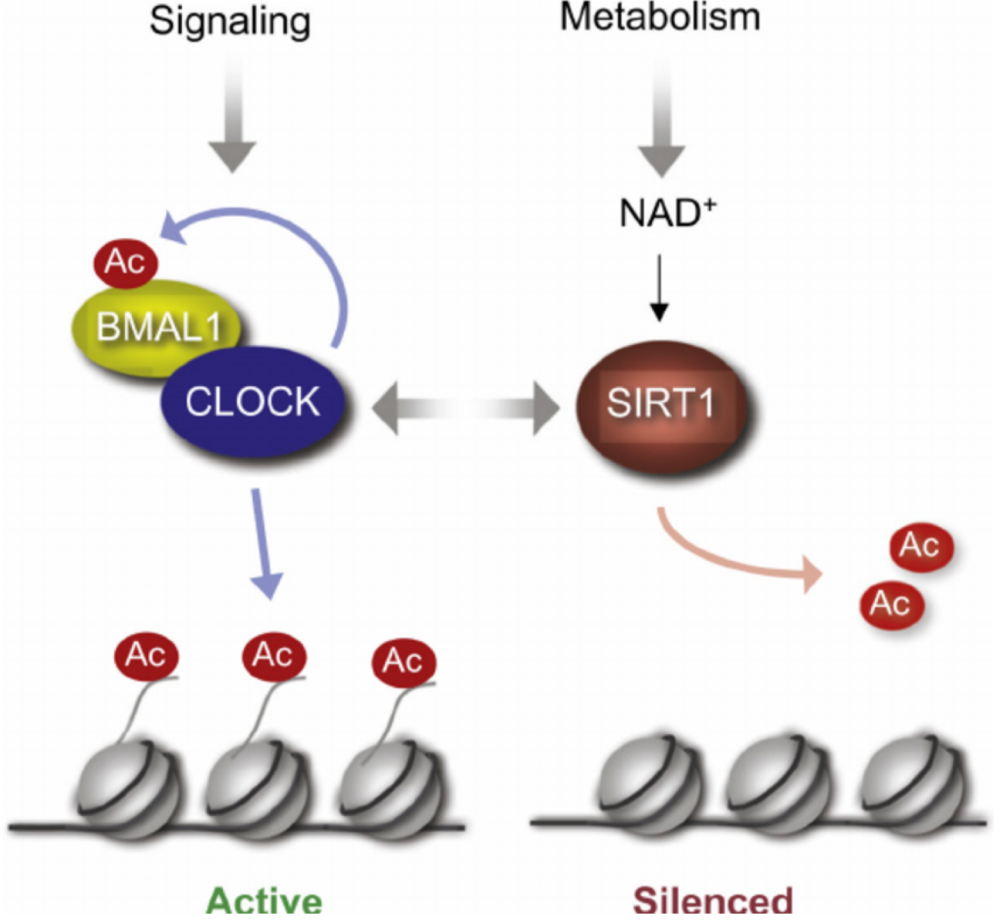
- Reduced infarct size
- decreased LDH release
- diminished the apoptotic index
- attenuated oxidative damage
- AMPK-PGC-1α-SIRT3

Metformin

- overexpression of Sirt3 and the activity of PGC-1a
- improved the cardiac function

Polydatin

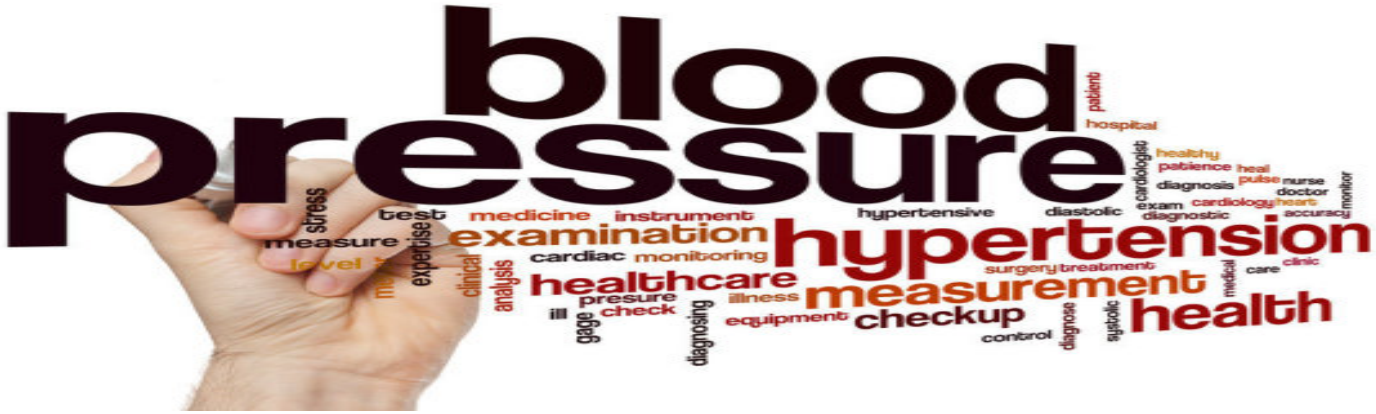
- improved cardiac function through upregultion of SIRT3

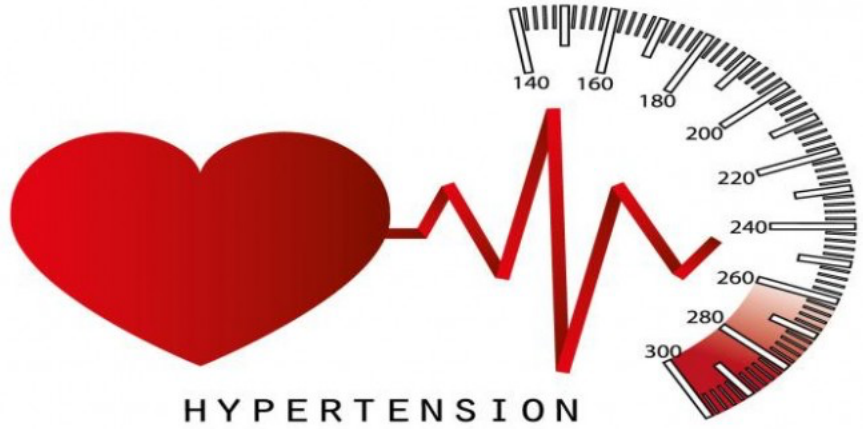


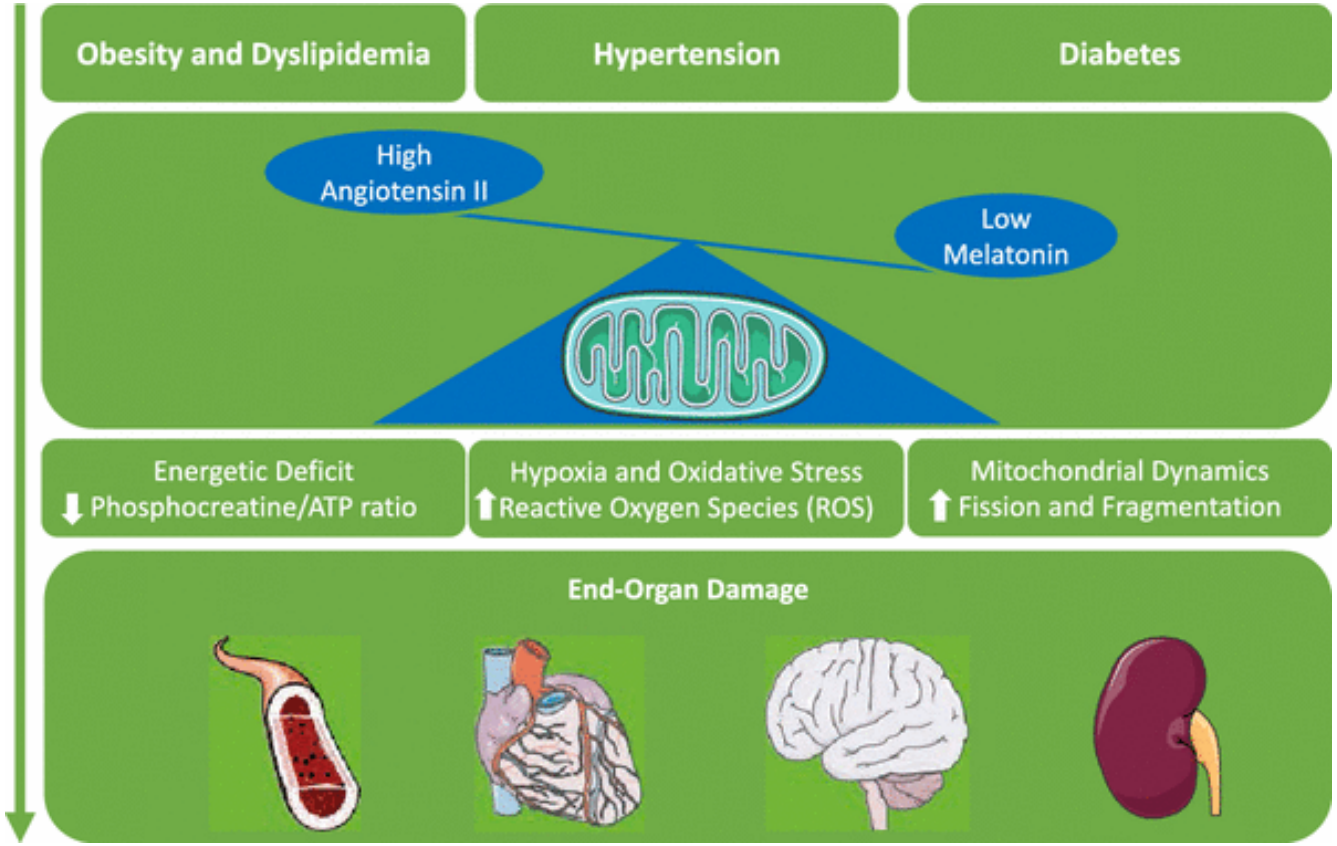
SIRT3, as a potent mitochondrial deacetylase, targets a broad range of substrates that are involved in various biological processes such as, ATP production, oxidative stress and cellular death. An increasing number of recent studies indicated that SIRT3 have critical function in cardiovascular diseases including hypertrophic cardiomyopathy, myocardial infarction, I/R injury and heart failure. Based on beneficial effects on myocardial infarction and IR injury by treatment with metformin, melatonin, Curcumin and Polydatin, which increase the expression and/or activity of SIRT3.

Histone deacetylases (**HDAC**) are a class of enzymes that remove acetyl groups ($O=C-CH_3$) from an ε-N-acetyl lysin. Amino acid on a histone, allowing the histones to wrap the DNA more tightly. This is important because DNA is wrapped around histones, and DNA expression is regulated by acetylation and de-acetylation. Its action is opposite to that of histone acetyltransferases. HDAC proteins are now also called lysine deacetylases (KDAC), to describe their function rather than their target, which also includes non-histone proteins.

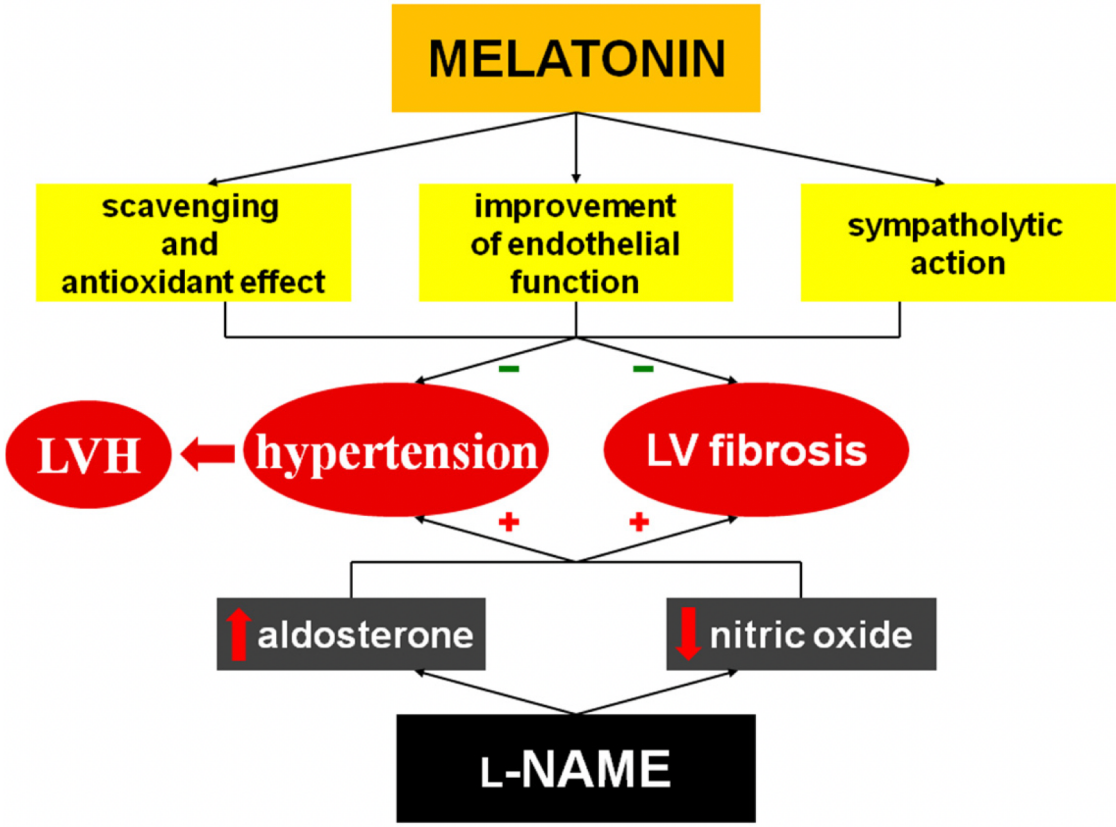
SIRT3-mediated cardiac remodeling/repair following myocardial infarction. Biomedicine & PharmacotherapyVolume 108, December 2018, Pages 367-373







Melatonin, mitochondria and hypertension. Cellular and Molecular Life Sciences November 2017, Volume 74, Issue 21, pp 3955–3964

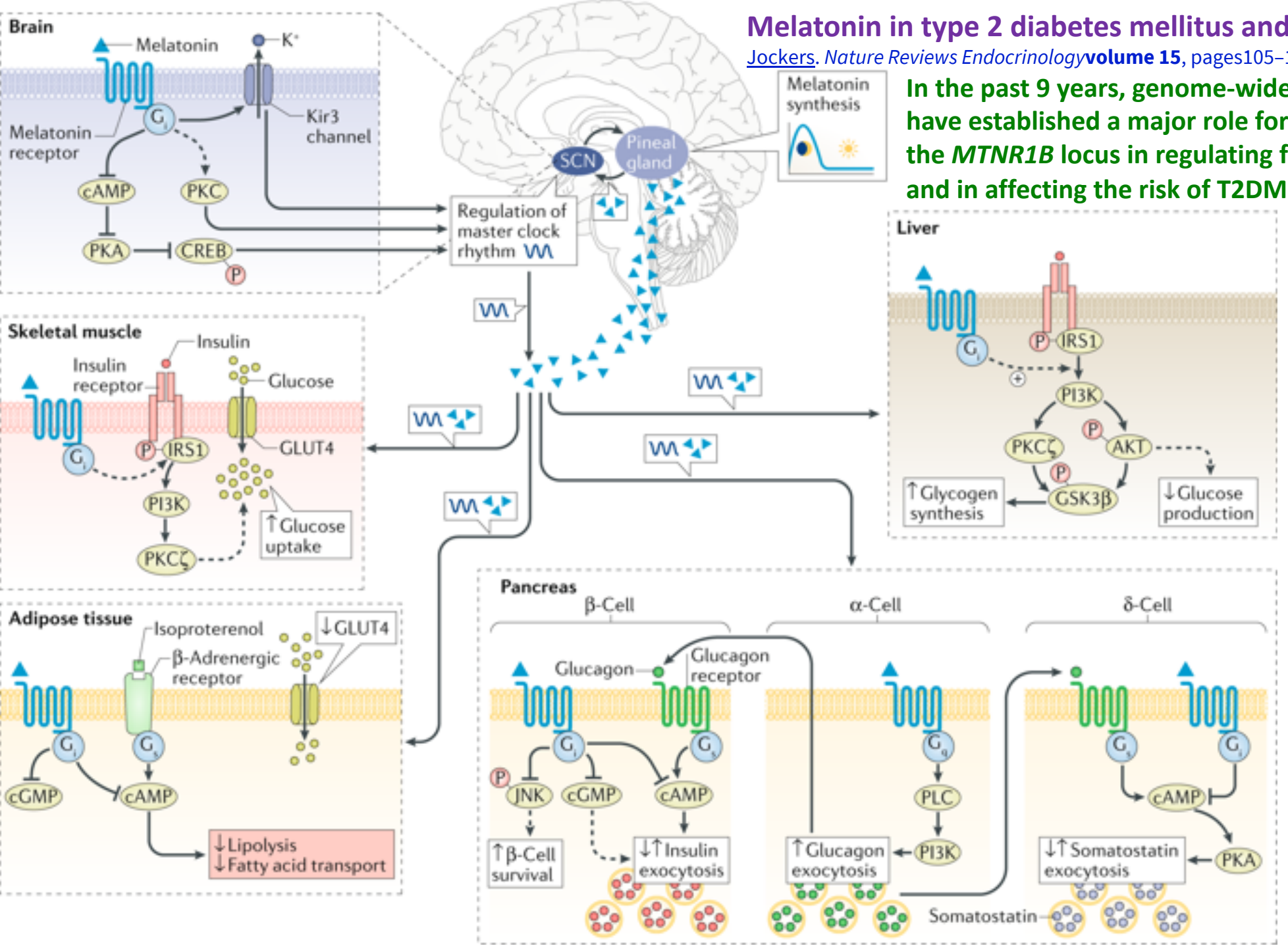


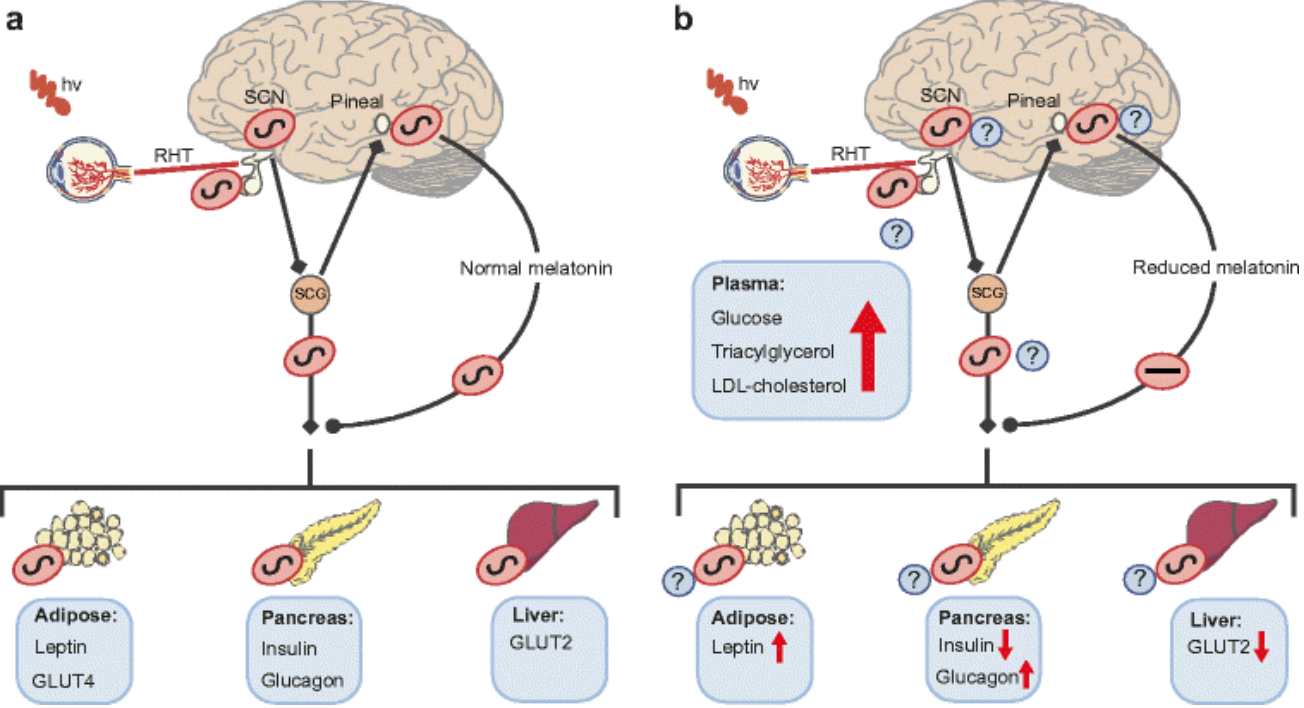
Effect of Melatonin on the Renin-Angiotensin-Aldosterone System in L-NAME-Induced Hypertension. Fedor Simko and All. *Molecules* 2018, *23*, 265;

Melatonin in type 2 diabetes mellitus and obesity. Angeliki Karamitri & Ralf Jockers. *Nature Reviews Endocrinology* **volume 15**, pages105–125 (2019)

In the past 9 years, genome-wide association studies (GWAS) have established a major role for genetic variation within the *MTNR1B* locus in regulating fasting plasma levels of glucose and in affecting the risk of T2DM.

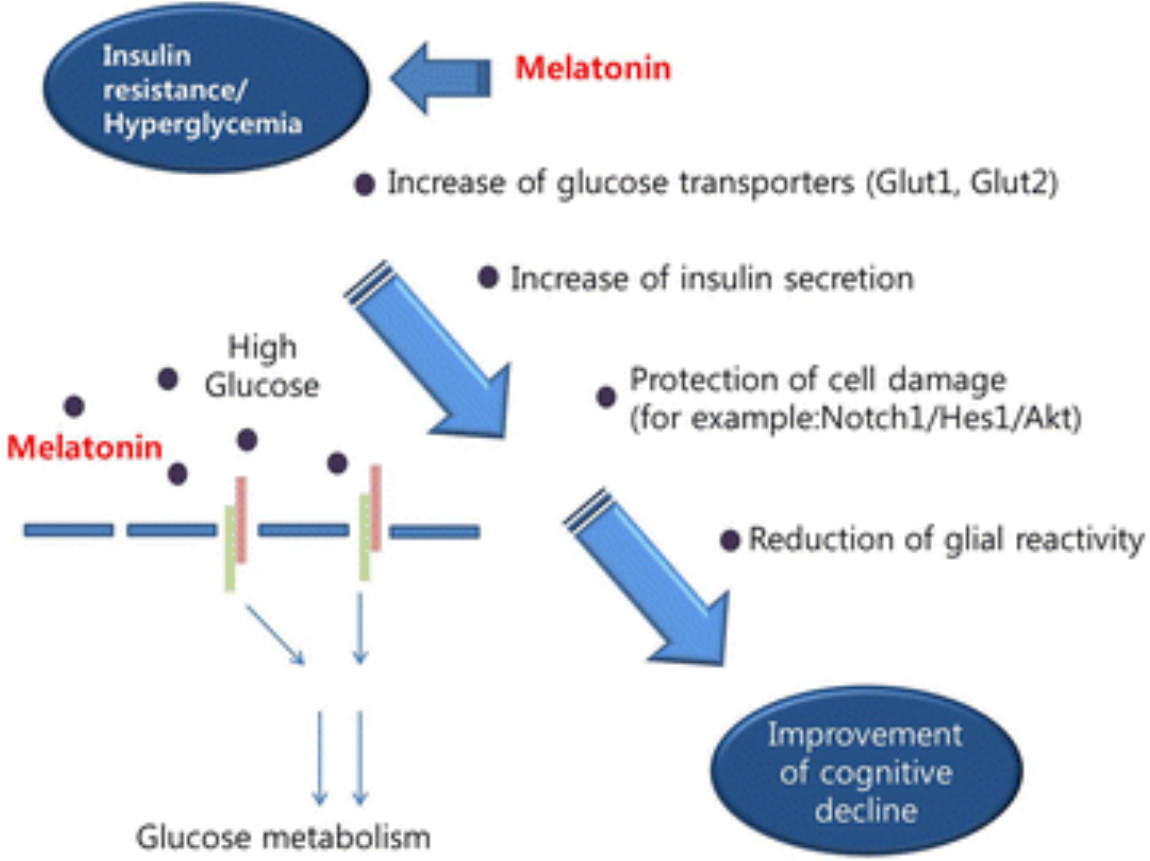
This discovery generated a major interest in the melatonergic system, in particular the melatonin MT_2 receptor (which is encoded by *MTNR1B*).



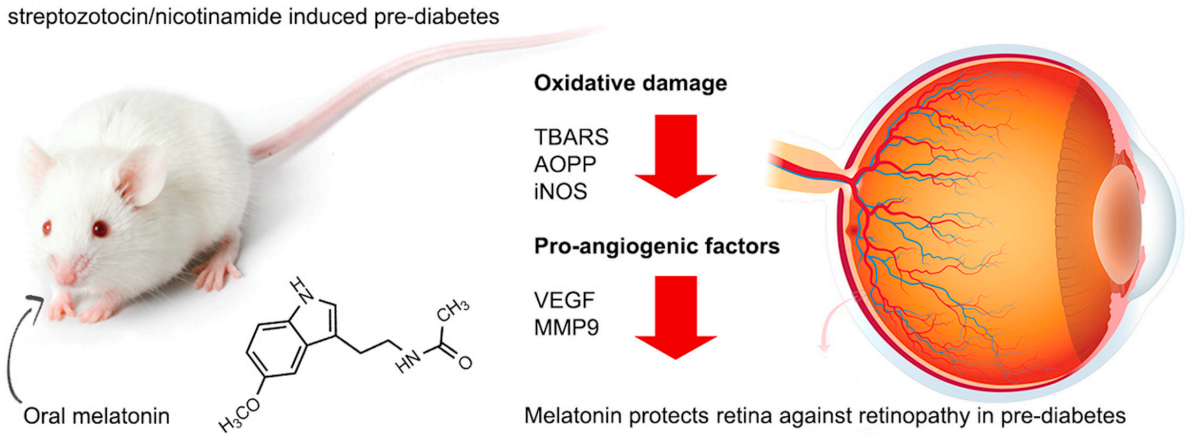


Melatonin affects the insulin secretory activity of the pancreatic beta cell, hepatic glucose metabolism and insulin sensitivity. Individuals with type 2 diabetes mellitus have lower night-time serum melatonin levels and increased risk of comorbid sleep disturbances compared with healthy individuals. Further, reduced melatonin levels, and mutations and/or genetic polymorphisms of the melatonin receptors are associated with an increased risk of developing type 2 diabetes.

Chronomedicine and type 2 diabetes: shining some light on melatonin. Andrew C and All.May 2017, Volume 60, Issue 5, pp 808–822|

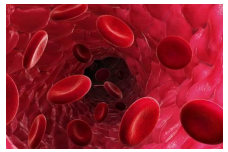


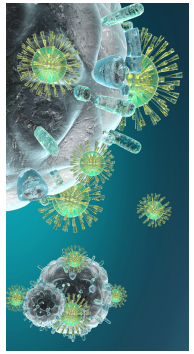
The role of melatonin in the onset and progression of type 3 diabetes. Juhyun Song and All. *Molecular Brain*2017**10**:35

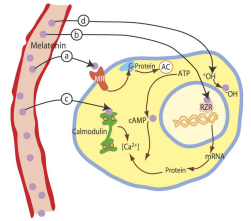


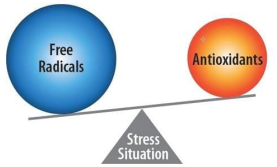
European Journal of Pharmacology. Volume 833, 15 August 2018, Pages 290-297

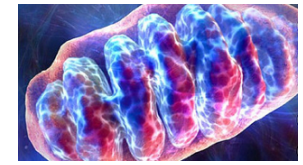
https://www.researchgate.net/figure/The-pleiotropy-of-melatonin-an-overview-of-several-major-actions_fig2_6966803

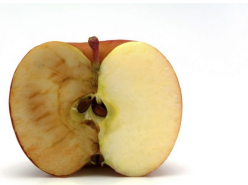








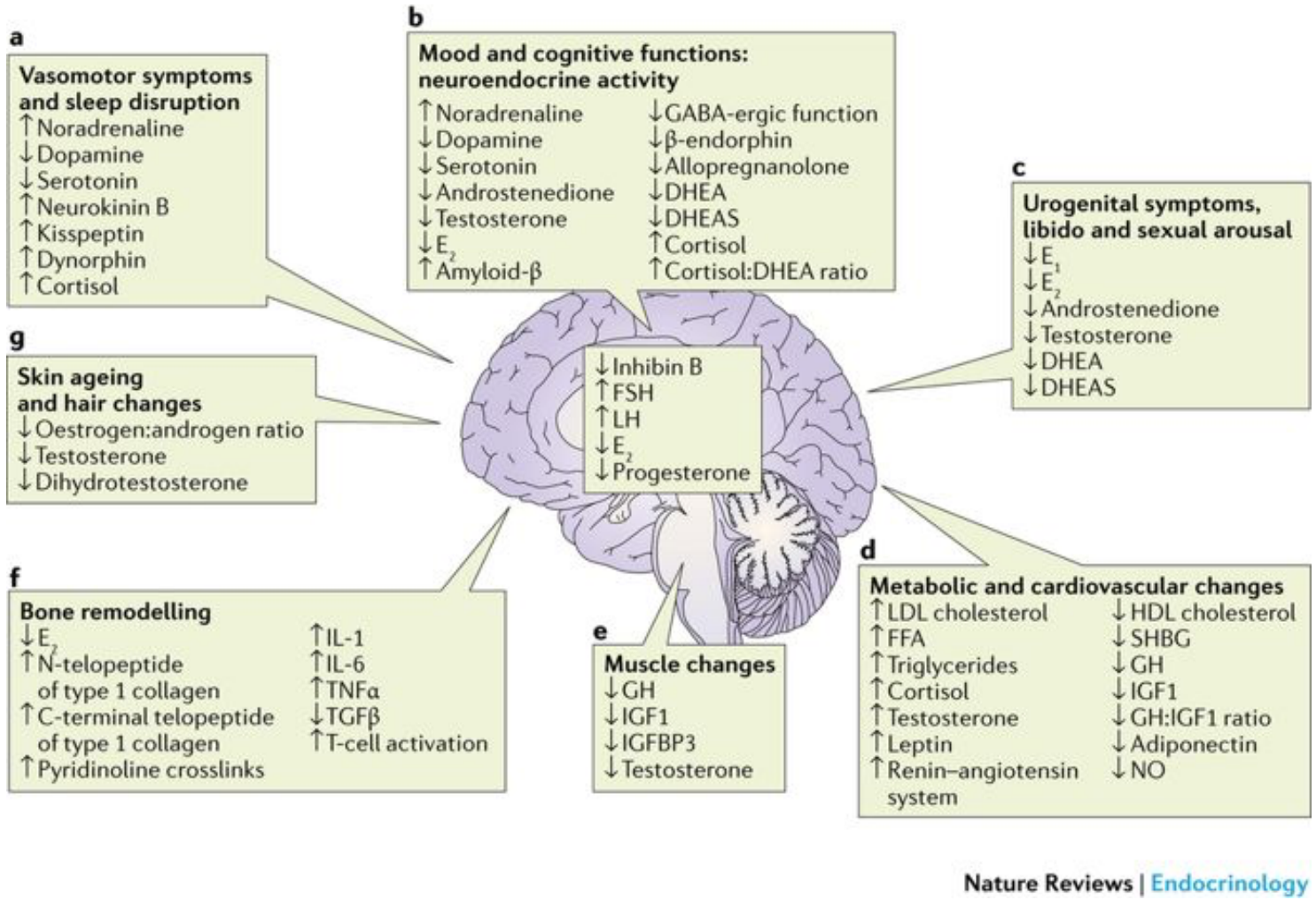


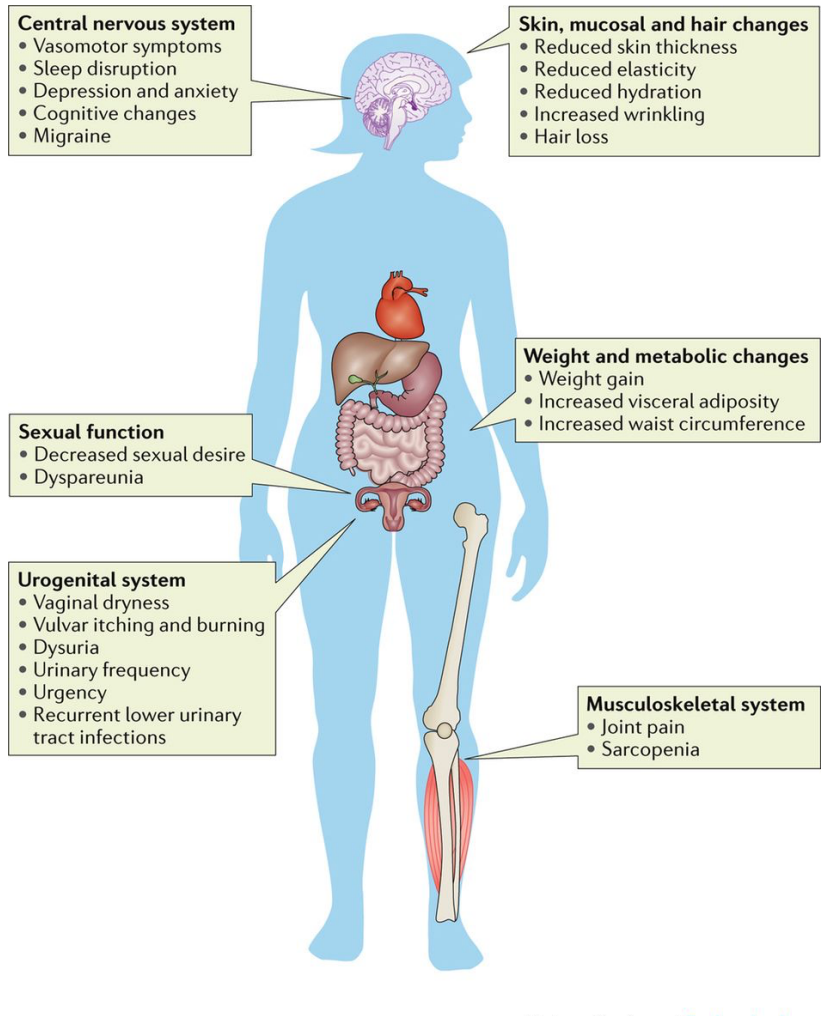


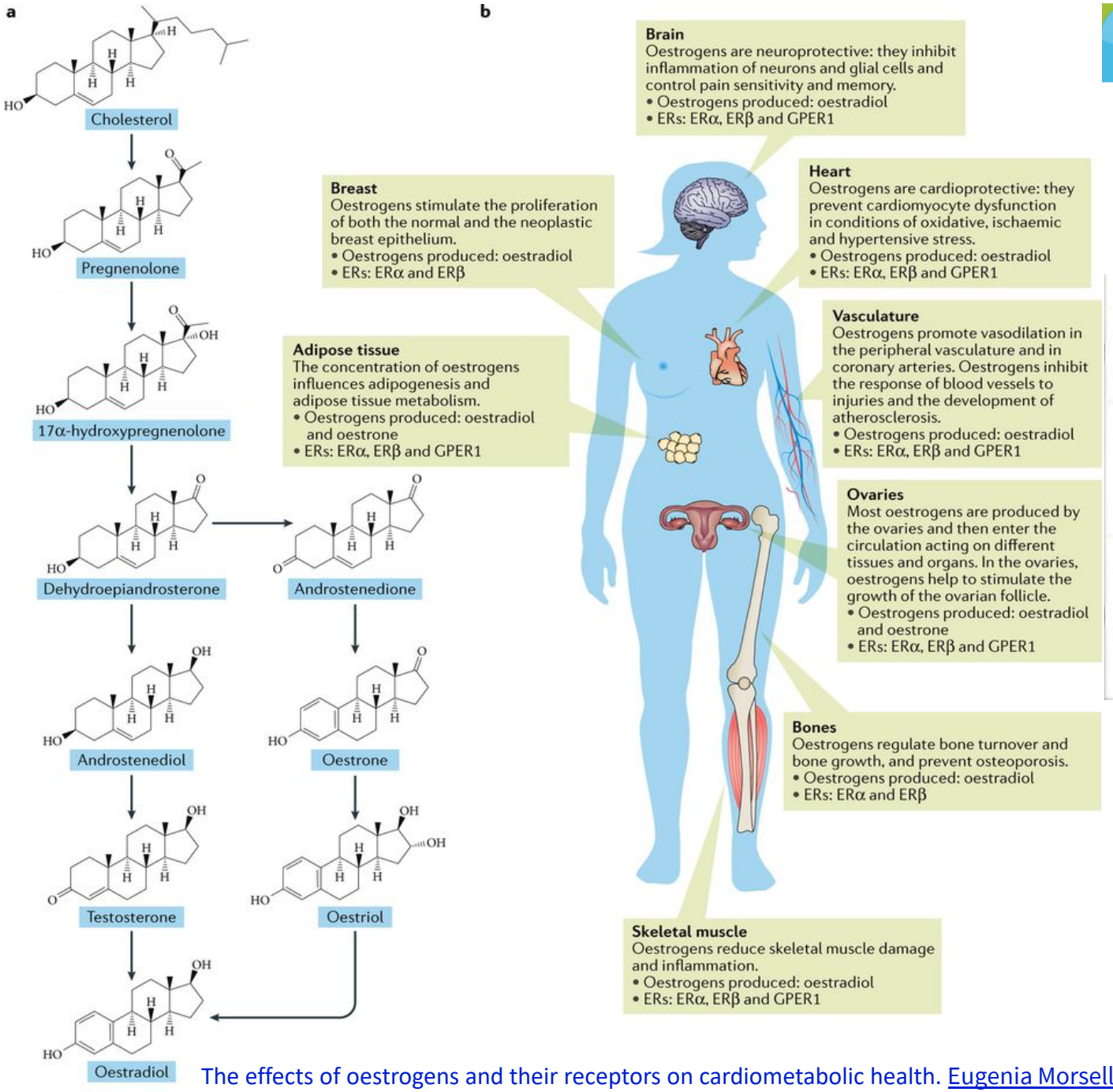
Melatonin: Buffering the Immune System. Int J Mol Sci. 2013 Apr; 14(4): 8638–8683.

Symptoms of menopause global prevalence, physiology and implications.Patrizia Monteleone and all.

Nature Reviews Endocrinology **volume 14**, pages 199–215 (2018)

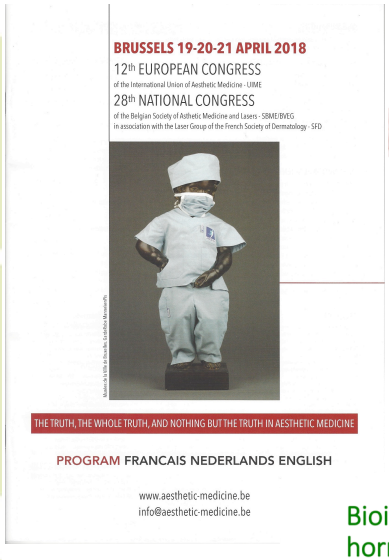






Santévitalité

Optimisez votre Santé



All you sould know about menopause hormone replacement therapy in 2018

Bioidentical menopausal hormone therapy: registered hormones (non-oral estradiol ± progesterone) are optimal

Benefits:

- Improved live quality
- Cardioprotection
- Fractures preventions

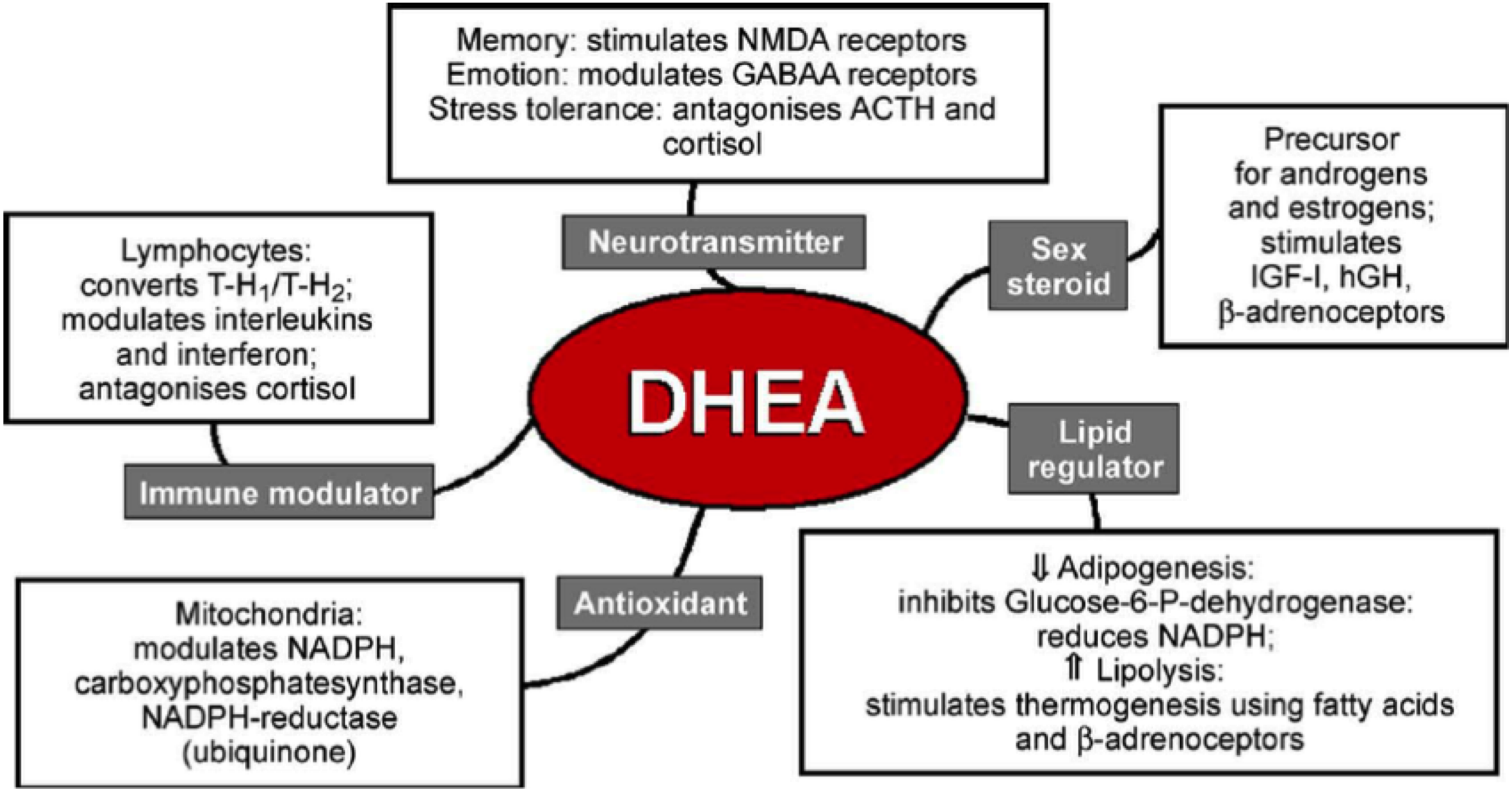
NO increased risks of:

- Breast cancer
- Stroke
- Thromboembolism
- Gallbladder disease

Risk–benefit balance for symptomatic women treated with an opti- mized hormone replacement therapy delivering estradiol by the transdermal route, in combination, if appropriate (women with an intact uterus), with micronized progesterone as the progestogen required for endometrial protec- tion. This ratio remains favorable in asymptomatic women despite the lack of improved quality of life. From L'Hermite (Climacteric 2013;16(Suppl 1):44–53).

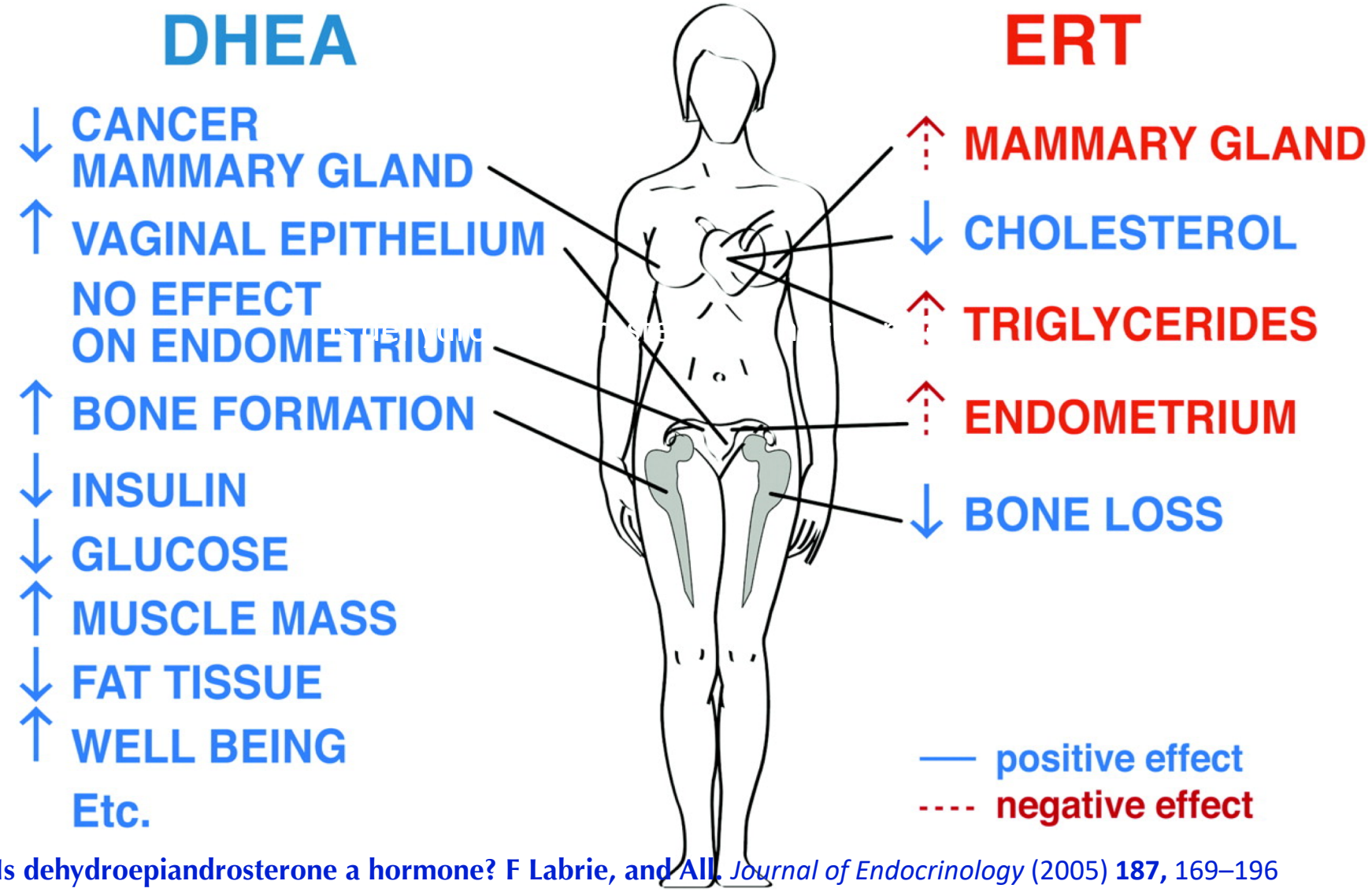
Bioidentical menopausal hormone therapy: registered hormones (non-oral estradiol ± progesterone) are optimal. M. L'Hermite (2017). Climacteric, DOI: 10.1080/13697137.2017.1291607

The effects of oestrogens and their receptors on cardiometabolic health. Eugenia Morselli and All. *Nature Reviews Endocrinology* volume 13, pages 352–364 (2017)


Memory: stimulates NMDA receptors
Emotion: modulates GABAA receptors
Stress tolerance: antagonises ACTH and cortisol
Neurotransmitter
Lymphocytes: converts T-H1/T-H2; modulates interleukins and interferon; antagonises cortisol
Immune modulator
Sex steroid
Precursor for androgens and estrogens; stimulates IGF-I, hGH, β-adrenoceptors
DHEA
Lipid regulator
⇓ Adipogenesis: inhibits Glucose-6-P-dehydrogenase: reduces NADPH;
⇑ Lipolysis: stimulates thermogenesis using fatty acids and β-adrenoceptors
Antioxidant
Mitochondria: modulates NADPH, carboxyphosphatesynthase, NADPH-reductase (ubiquinone)

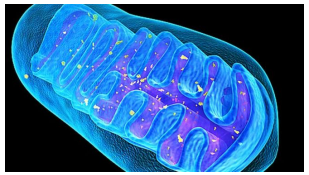
Comparison of the effects of standard ERT (estrogen) and DHEA on parameters of menopause.

Citation: Journal of Endocrinology 187, 2; 10.1677/joe.1.06264

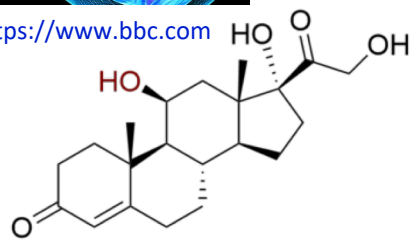


Is dehydroepiandrosterone a hormone? F Labrie, and All. *Journal of Endocrinology* (2005) **187,** 169–196

The effects of DHEA on metabolic functions of adipose tissue.

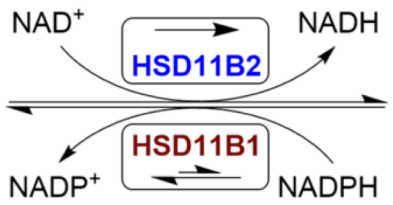


https://www.bbc.com

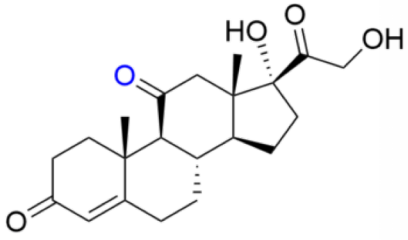


cortisol

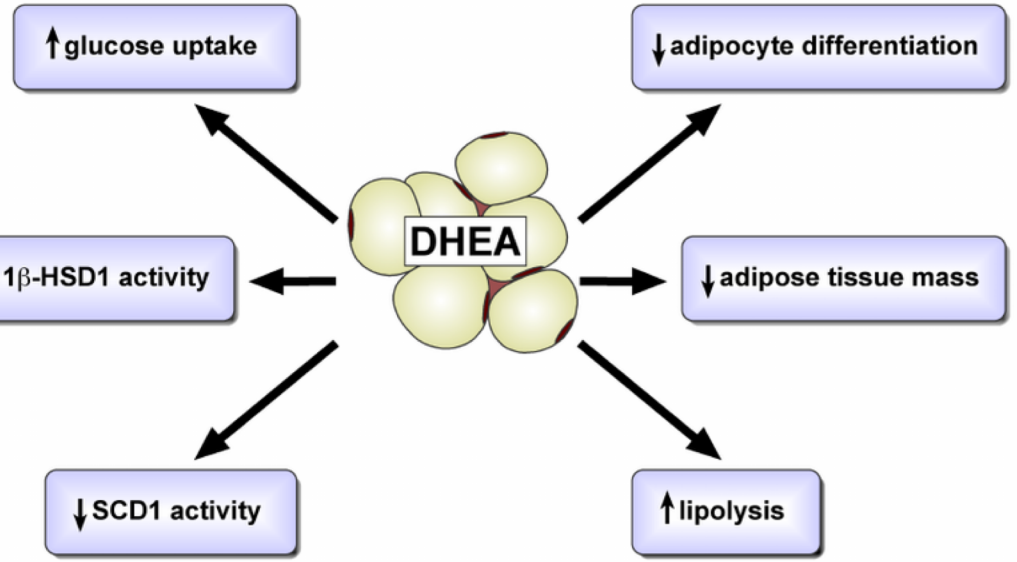
Liver
Adipocytes
CNS

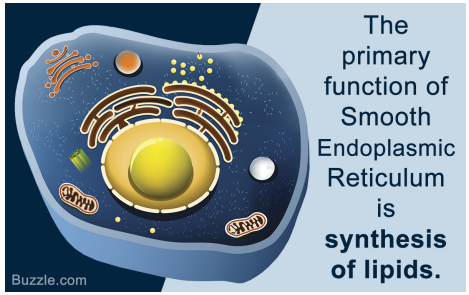


Kidneys

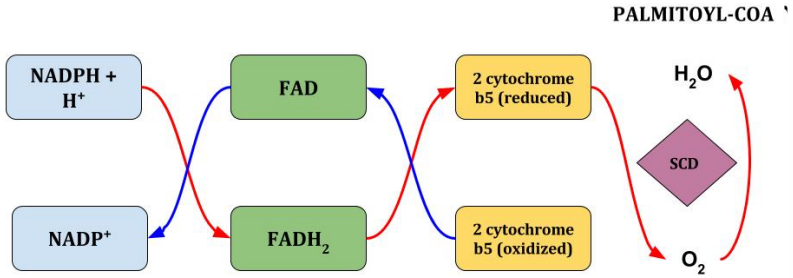


cortisone





https://biologywise.com



Monosaturated fatty acids

Stearoyl-CoA desaturase (Δ-9-desaturase) is an endoplasmic reticulum enzyme that catalyzes the rate-limiting step in the formation of monounsaturated fatty acids (MUFAs), specifically oleate and palmitoleate from stearoyl-CoA and palmitoyl-CoA.

Effects of DHEA on metabolic and endocrine functions of adipose tissue. Joanna Karbowska and All. Literature Review Hormone molecular biology and clinical investigation 14(2):65-74. August 2013

DHEA stimulates NGF and BDNF neurotrophins overexpression and release. It enhances neuronal cell survival, neuronal cell proliferation, and neurite outgrowth via these neurotrophins. If our results could be generalized for human, so formation of new cells in the brain via regenerative pharmacology could be important in treating neurodegenerative diseases such as Alzheimer and Parkinson.

Adv Pharmacol Sci. 2013; 2013: 506191.

DHEA inhibits acute microglia-mediated inflammation

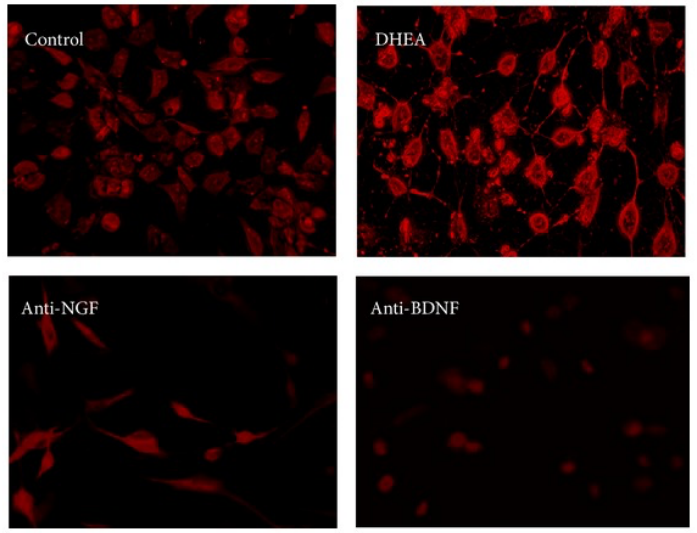
Molecular Psychiatry **volume 23**, pages 1410–1420 (2018)

Decreased dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) concentrations in plasma of Alzheimer's disease (AD) patients

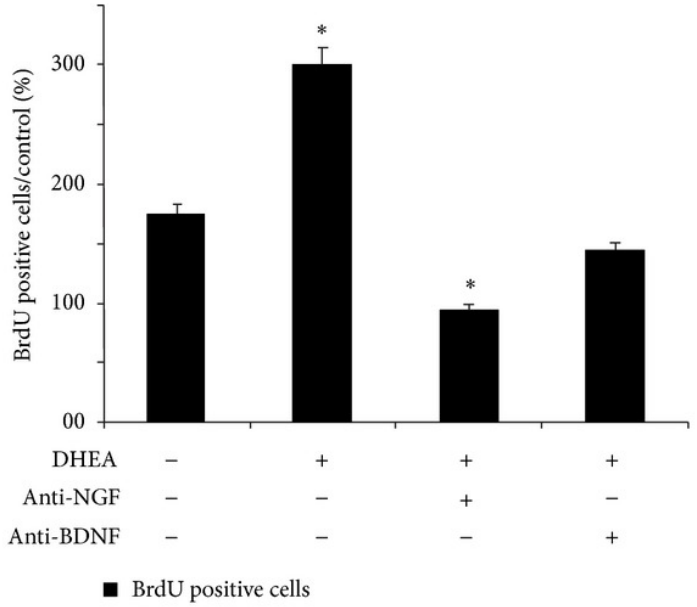
Archives of Gerontology and Geriatrics. Volume 51, Issue 1, July–August 2010, Pages e16-e18

DHEA and DHEAS are multifunctional and exhibit a variety of properties in the CNS, including memory consolidation, neuroprotection.

International Review of Neurobiology. Volume 46, 2001, Pages 379-397



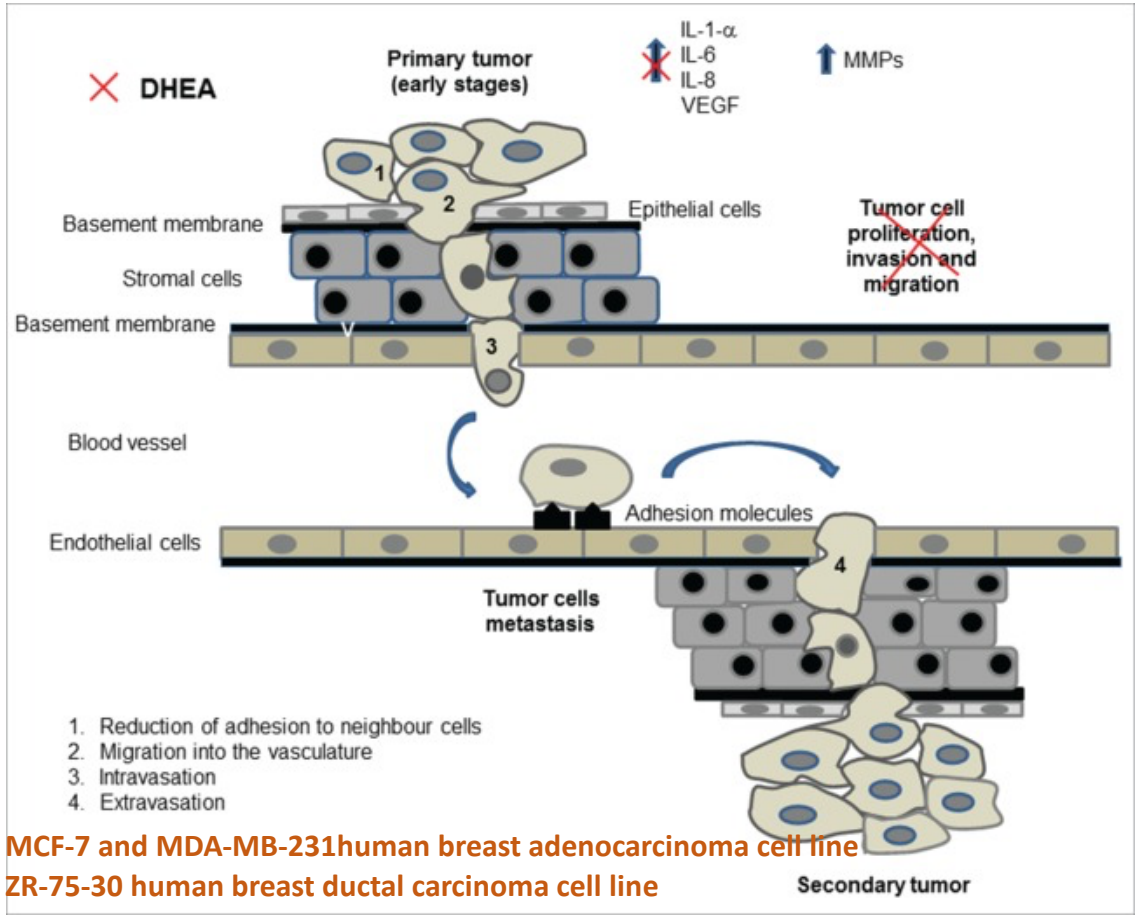
(a)



(b)

DHEA inhibits acute microglia-mediated inflammation through activation of the TrkA-Akt1/2-CREB-Jmjd3 pathway. Alexaki and All. *Molecular Psychiatry* **volume 23**, pages 1410–1420 (2018)

Breast cancer



MCF-7 and MDA-MB-231human breast adenocarcinoma cell line
ZR-75-30 human breast ductal carcinoma cell line

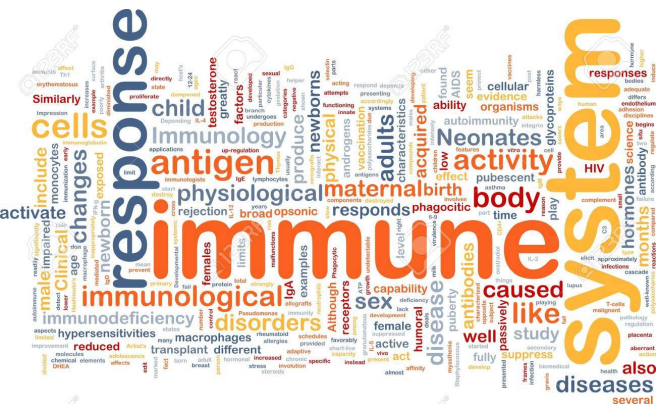
https://www.health24.com/Medical/Breast

The mechanism of DHEA actions against breast cancer involves the inhibition of cell proliferation and the suppression of migration, indicating that DHEA could be useful in the treatment of breast cancer.

MCF-7 cells were the most responsive to the exposure to DHEA, whereas ZR-75-30 cells responded less to this hormone, suggesting that DHEA could be used in the treatment of breast cancer in early stages.

Eur J Pharmacol. 2011 Jun 25;660(2-3):268-74.

Dehydroepiandrosterone inhibits events related with the metastatic process in breast tumor cell lines. Rebeca López-Marure, and All. Cancer Biol Ther. 2016; 17(9): 915–924.



DHEA has significant immune modulatory function, exhibiting both immune stimulatory and anti-glucocorticoid effects.

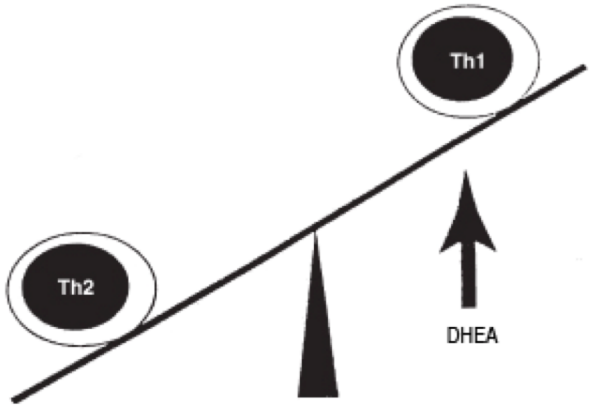
Evidence from the study of immune cells is now accumulating to suggest a role for DHEA in regulating human immunity. This ability to regulate immune function has raised interest in the therapeutic potential of DHEA as a treatment for the immunological abnormalities that arise in subjects with low circulating levels of this hormone. This has included attempts at reversing the impaired immune response of older individuals to vaccination and restoring immune regulation in patients with chronic autoimmune disease.

Most importantly, no significant adverse or negative side effects of DHEA were reported in clinical studies of men and women.

The Journal of Steroid Biochemistry and Molecular Biology. Volume 120, Issues 2–3, 31 May 2010, Pages 127-136

Autoimmune disease	Immunologic mediator	Female Patients, %
Hashimoto thyroiditis	TH2	95
Sjögren syndrome	TH2	94
Addison disease	Unknown	93
Scleroderma	TH2	92
Systemic lupus erythematosus	TH2	89
Primary biliary cirrhosis	TH1	89
Graves disease	TH2	88
Rheumatoid arthritis	TH1	75
Myasthenia gravis	Unknown	73
Polymyositis/dermatomyositis	Unknown	67
Multiple sclerosis	TH1	64
Vtiligo	TH1	52
Type 1 diabetes mellitus	TH1	48

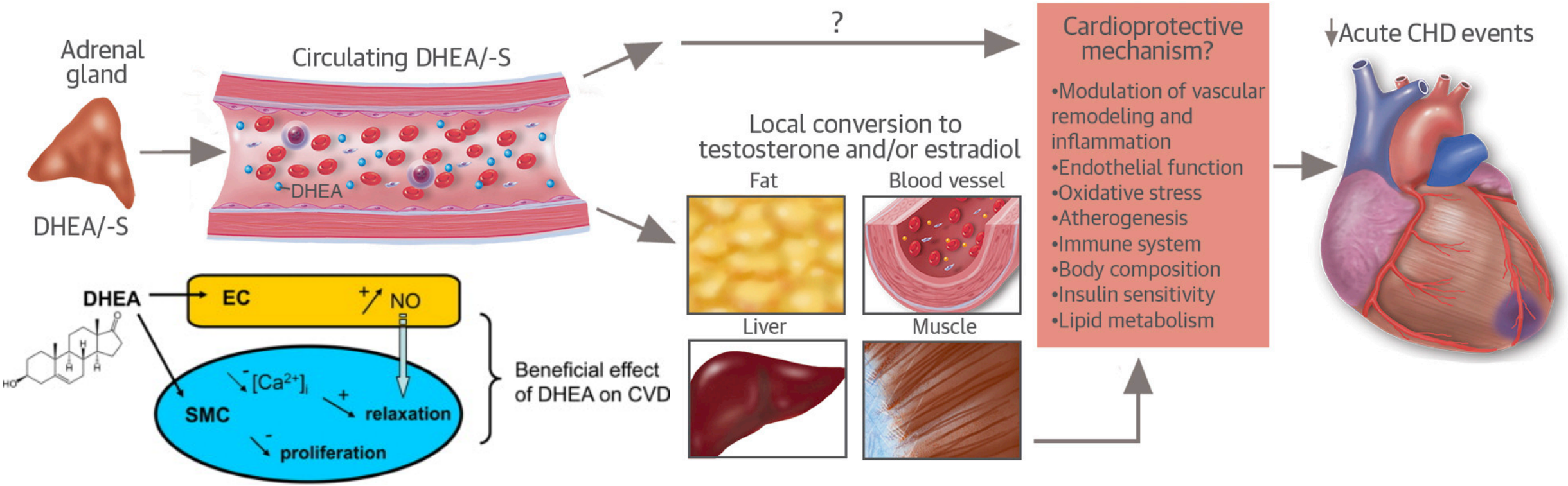
* Adapted from Ref. 3



DHEA, represents a pivotal up-regulator of Th1 immune response.

The Th1-Promoting Effects of Dehydroepiandrosterone Can Provide an Explanation for the Stronger Th1-Immune Response of Women Mohammad Reza Namazi.
Iranian journal of allergy, asthma, and immunology 8(1):65-9 · April 2009

Low serum levels of DHEA and its sulfate predict an increased risk of CHD, but not CBD, events in elderly men.

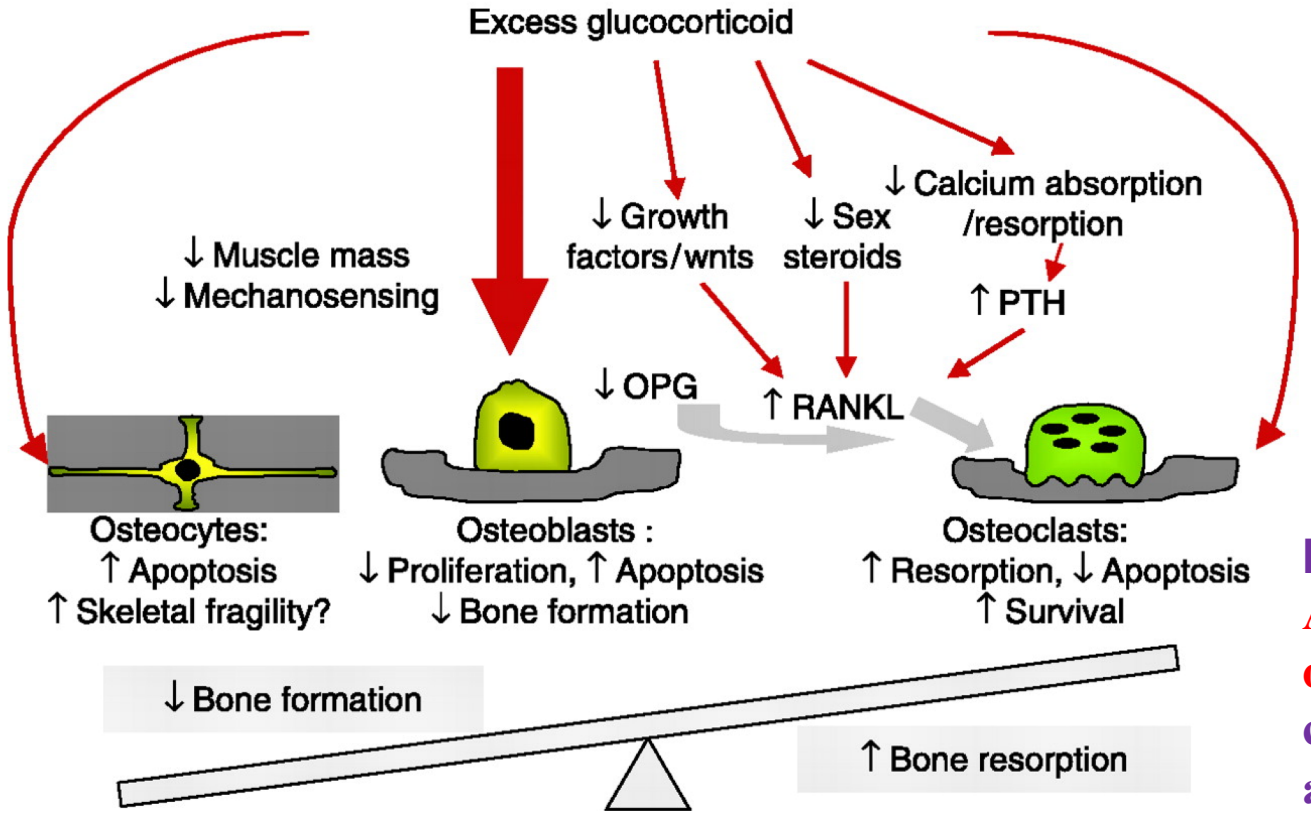


Biochemical Pharmacology. Volume 85, Issue 6, 15 March 2013, Pages 718-726

Possible Mechanisms for Adrenal-Derived DHEA/-S to Reduce Risk of CHD Events

Dehydroepiandrosterone and its Sulfate Predict the 5-Year Risk of Coronary Heart Disease Events in Elderly Men. ÅsaTivesten, and All. Journal of the American College of Cardiology. Volume 64, Issue 17, 28 October 2014, Pages 1801-181

Sex-specific effects of dehydroepiandrosterone (DHEA) on bone mineral density and body composition: A pooled analysis of four clinical trials. Jankowski CM and All. Clin Endocrinol (Oxf). 2019 Feb;90(2):293-300



Bone loss in inflammatory disorders. R Hardy and All. Research Article. Journal of Endocrinology Volume 201: Issue 3 : **Page(s):** 309–320. 2009

DHEA therapy may be an effective approach for preserving bone and muscle mass in women.

Key questions are :

(a) the extent to which longer duration DHEA can attenuate the loss of bone and muscle in women,

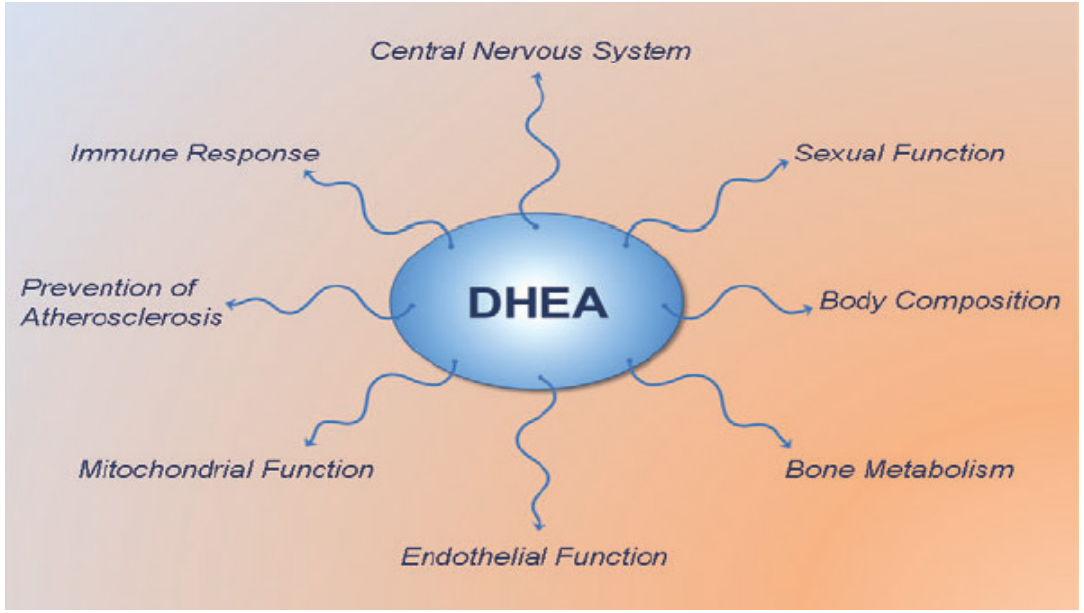
(b) whether DHEA has a more favourable benefit-to-risk profile for women than oestrogen therapy.

IGF-1, IGFBP-3 and IGF-1/IGFBP-3

A significant increase in IGF-1 and the IGF-1/IGFBP-3 ratio over time was observed in women on DHEA treatment as compared to placebo ($p<0.001$ for both). Both IGF-1 levels and the IGF-1/IGFBP-3 ratio increased by more than 20% and these increases were maintained throughout the 12 month treatment. treatment status in men (Table 2).

Osteoporos Int. 2008 May; 19(5): 699–707.

Why should we prescribe DHEA

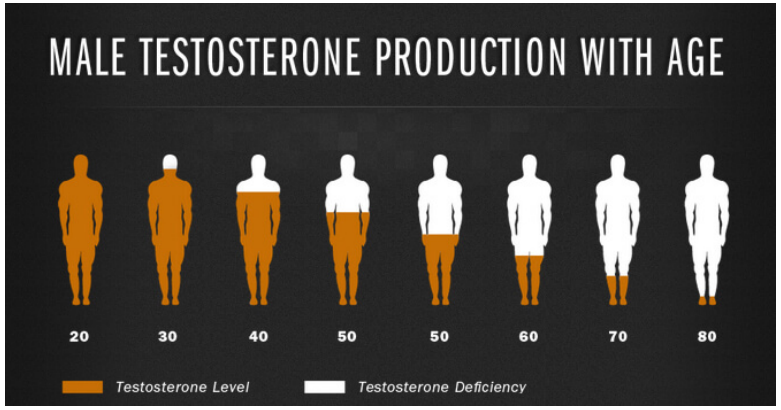


1. DHEA modulates endothelial function
2. Reduces inflammation
3. Improves insulin sensitivity
4. Blood flow.
5. Cellular immunity
6. Body composition
7. Bone metabolism
8. Sexual function
9. Physical strength in frailty
10. Provides neuroprotection
11. Improves cognitive function, and memory enhancement.

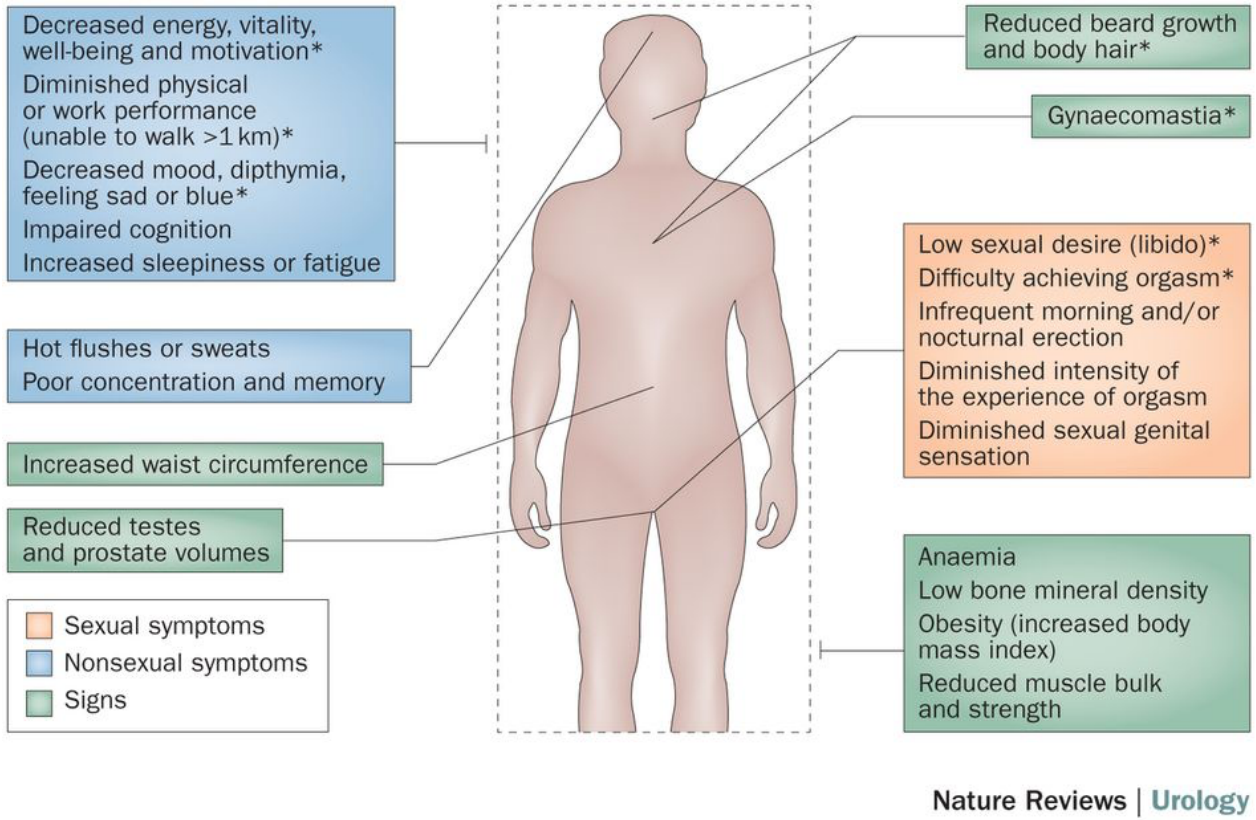
DHEA possesses pleiotropic effects and reduced levels of DHEA and DHEA-S may be associated with a host of pathologies

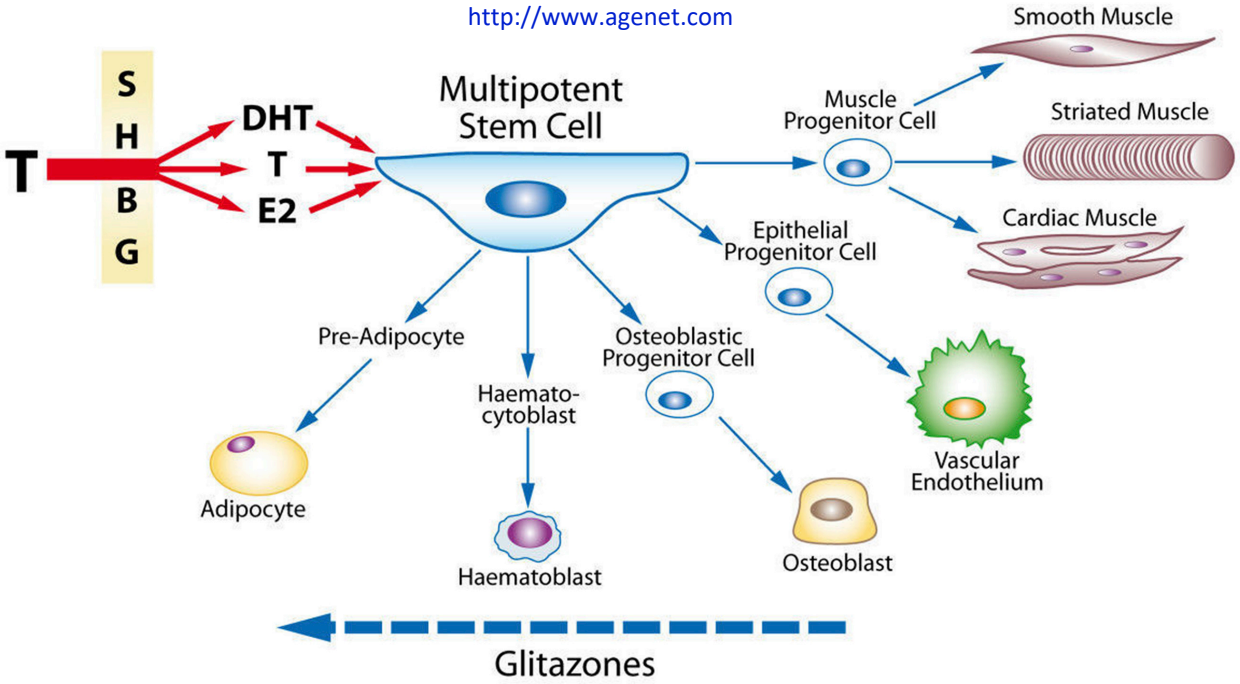
Low Testosterone

https://bodymedia.com



http://www.agenet.com





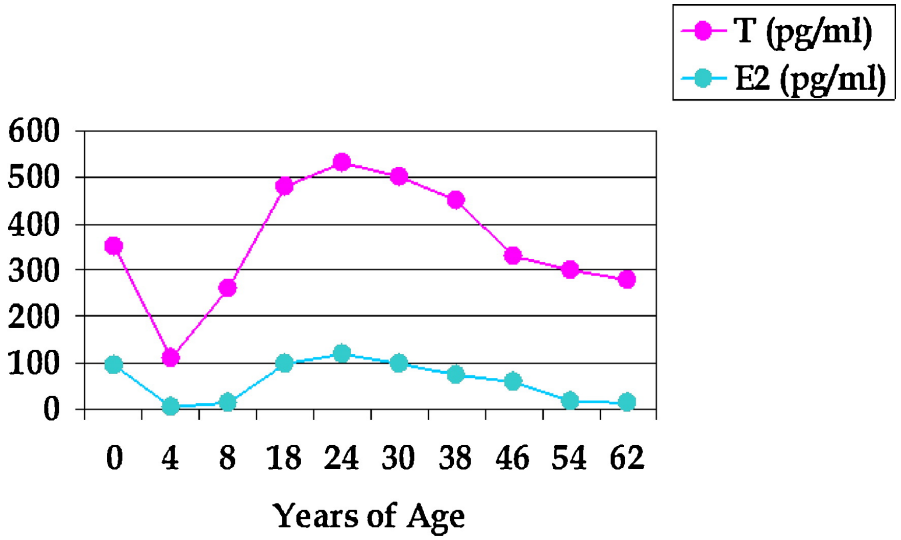
Testosterone, directly or through conversion to 5α-dihydrotestosterone or estradiol, modulates multipotent stem cell metabolism and function to promote differentiation to progenitor cells for muscle, endothelium, bone, and red blood cells.

The practical management of testosterone deficiency in men. Antonio Aversa & Abraham Morgentaler*Nature Reviews Urology* volume 12, pages 641–650 (2015)

Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency. Sexual Medicine Reviews. Volume 6, Issue 1, January 2018, Pages 86-10

Testosterone therapy in women: Myths and misconceptions.

Rebecca Glaser and All. Maturitas. Volume 74, Issue 3, March 2013, Pages 230-234



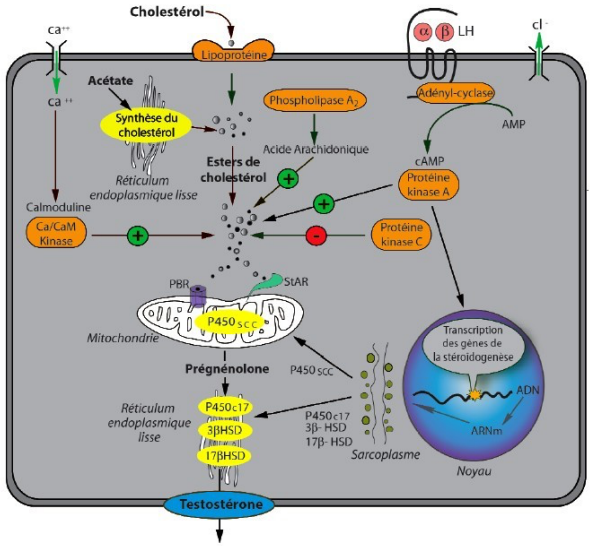


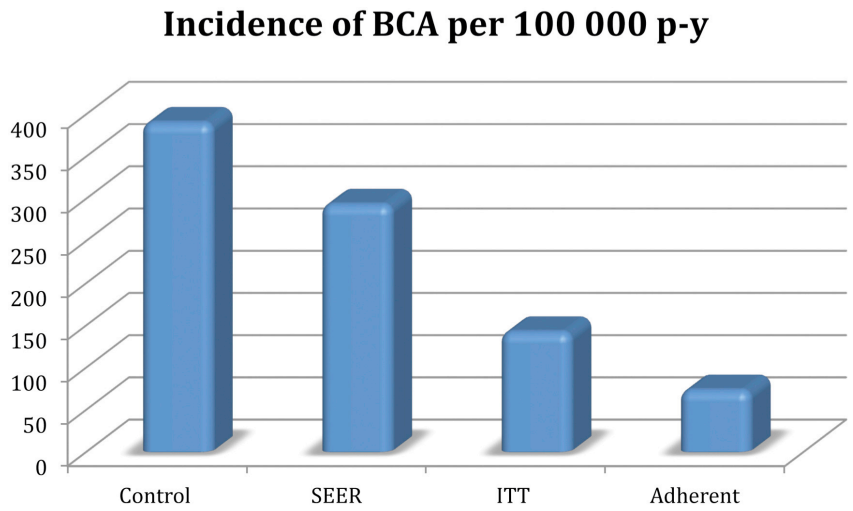
Figure 1 : Régulation de la stéroïdogenèse dans la cellule de Leydig

Testosterone (T) is the most abundant biologically active female hormone, T is essential for physical and mental health in women, T is not masculinizing, T does not cause hoarseness, T increases scalp hair growth, T is cardiac protective, parenteral T does not adversely affect the liver or increase clotting factors, T is mood stabilizing and does not increase aggression, T is breast protective, and the safety of T therapy in women is under research and being established.

Abandoning myths, misconceptions and unfounded concerns about T and T therapy in women will enable physicians to provide evidenced based recommendations and appropriate therapy.

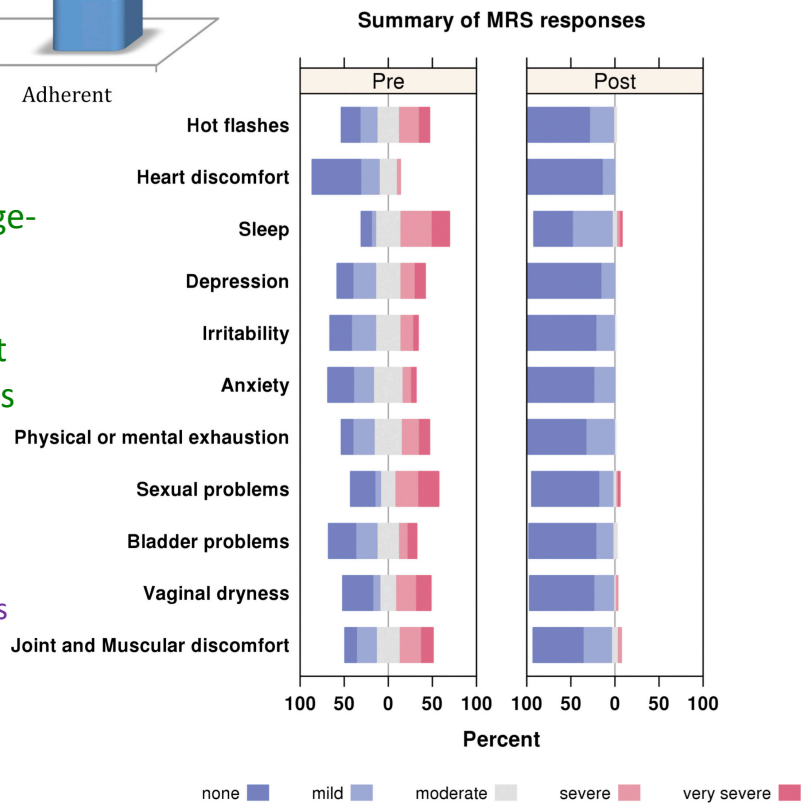
Testosterone and breast cancer prevention

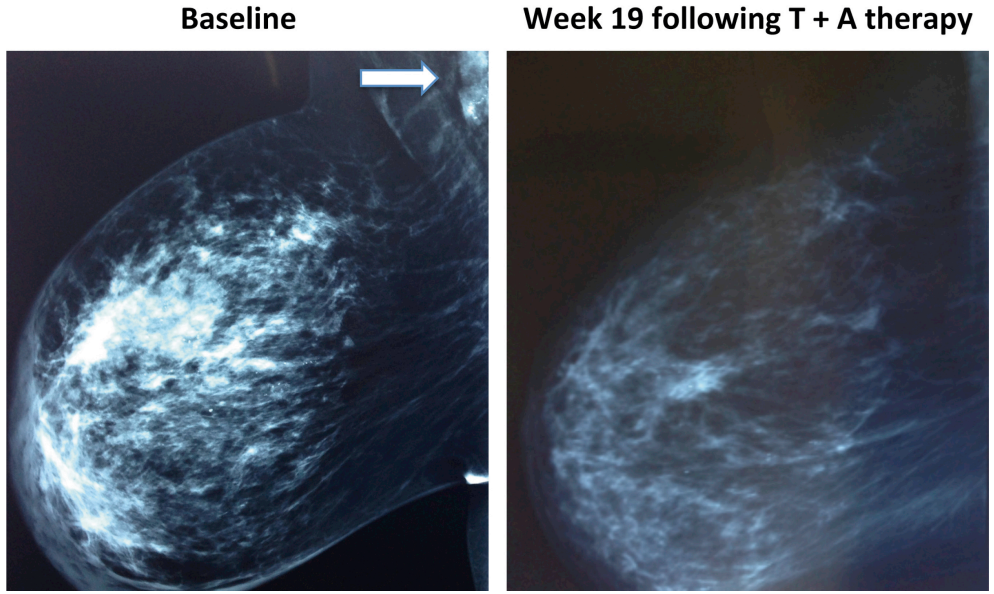
R.Glase and All. Maturitas. Volume 82, Issue 3, November 2015, Pages 291-295



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)

SEER :Surveillance Epidemiology and End Results

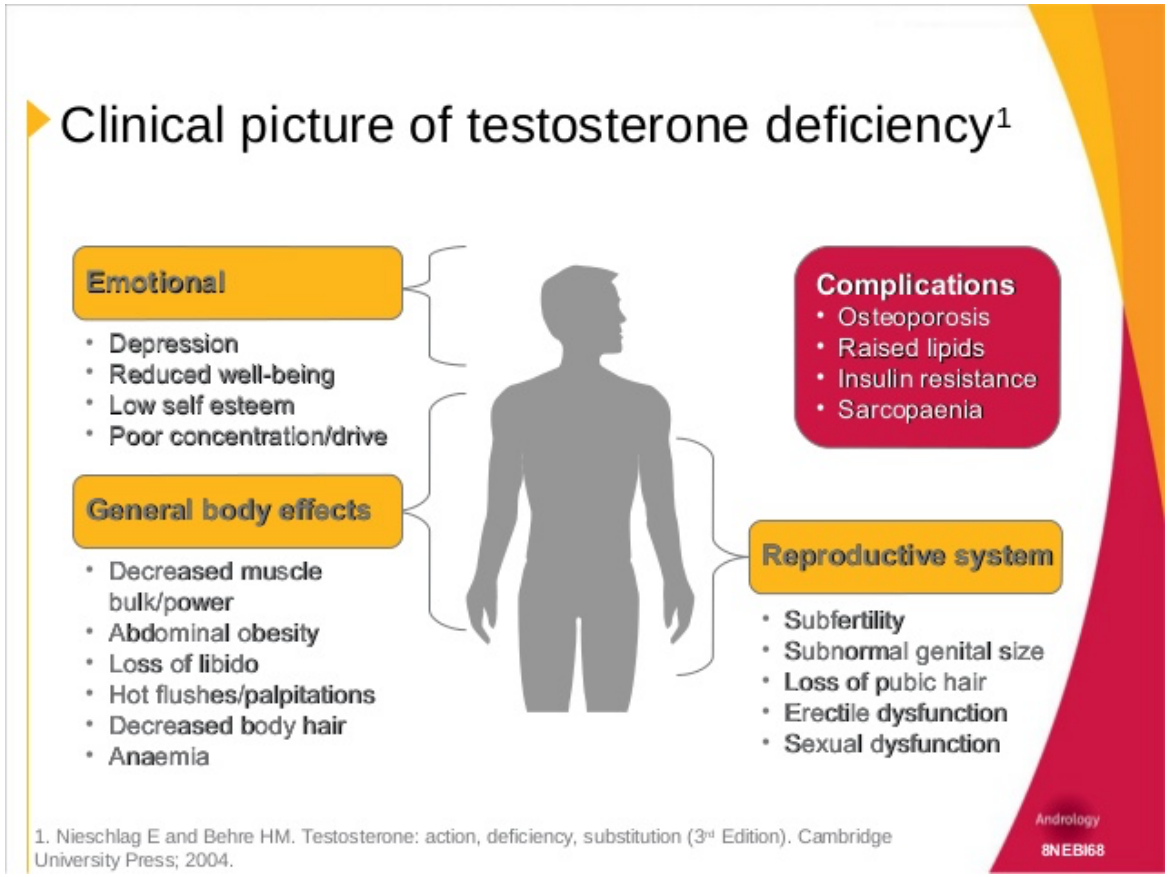




Comparison mammography, right medial lateral oblique view at baseline (left) and at follow up (right), week 19 following neoadjuvant, intramammary T + A therapy of infiltrating lobular, hormone receptor positive BCA (ER+, PR+, AR+). Note the significant reduction in tumor size and absence of previously palpable axillary lymph nodes. (Previously unpublished images, Glaser, Dimitrakakis).

Summary of distribution of severity scores in each of the 11 'Menopausal Rating Scale' categories pre- and post-therapy with T + A subcutaneous implants in BCA survivors demonstrating significant improvement in quality of life for all symptom categories

Quality of Life and Sexual Function Benefits of Long-Term Testosterone Treatment: Longitudinal Results From the Registry of Hypogonadism in Men (RHYME). Rosen RC and All. J Sex Med. 2017 Sep;14(9):1104-1115.



https://www.slideshare.net/PeninsulaEndocrine/hypogonadism-and-testosterone-replacement

TRT-related benefits in QOL and sexual function are well maintained for up to 36 months after initiation of treatment.

We confirmed the broad and sustained benefits of TRT across major QOL dimensions, including sexual, somatic, and psychological health, which were sustained over 36 months in our treatment cohort.

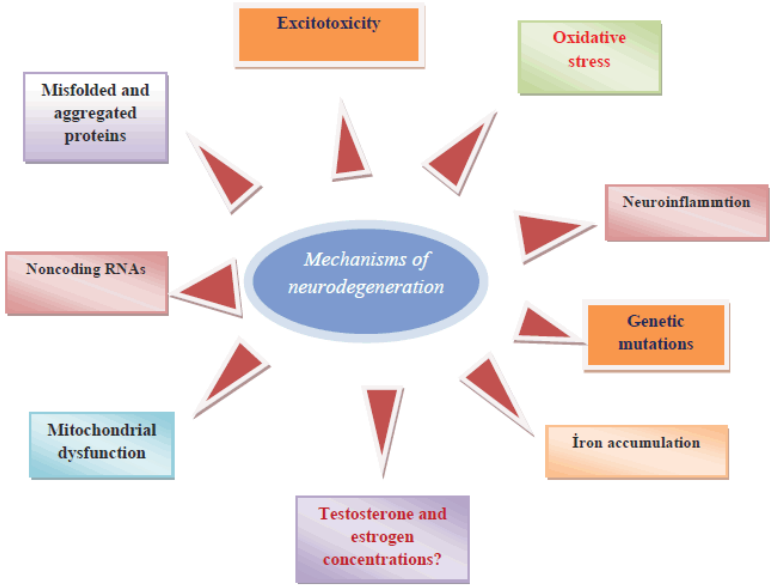


Figure 2: Different biological processes which are involved in the development of neurodegeneration.

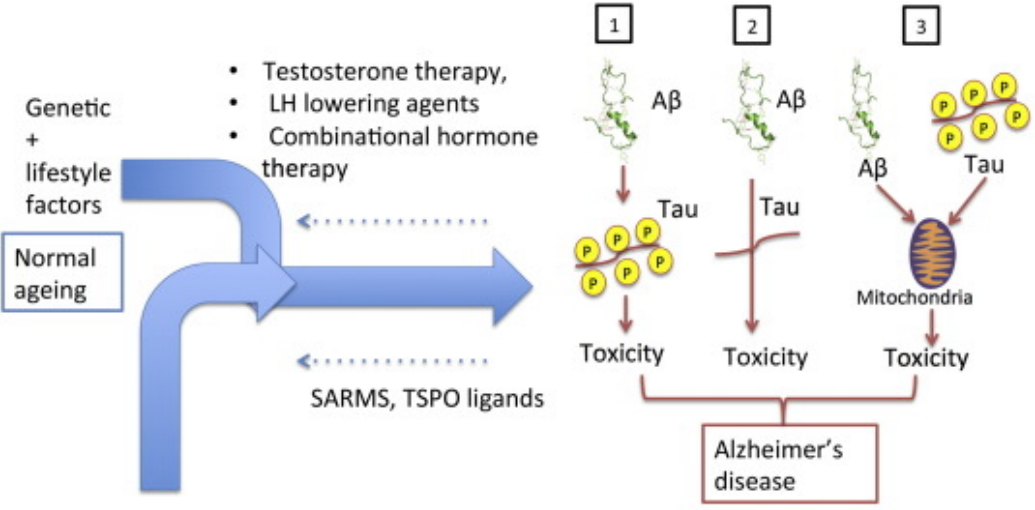
The free form of testosterone can pass the bloodbrain barrier and stimulate the differentiation of neurons and neurite outgrowth increase.

Age-related deficiency of testosterone might increase the neurodegeneration and lead to diseases such as AD and PD.

Testosterone replacement therapy might be useful under low oxidative stress conditions.

It has been reported that the levels of testosterone is low in PD and other neurodegenerative diseases.

Is testosterone perspective available for neurodegenerative diseases? Orcun Avsar. Neuropsychiatry Review Article - (2018) Volume 8, Issue 5

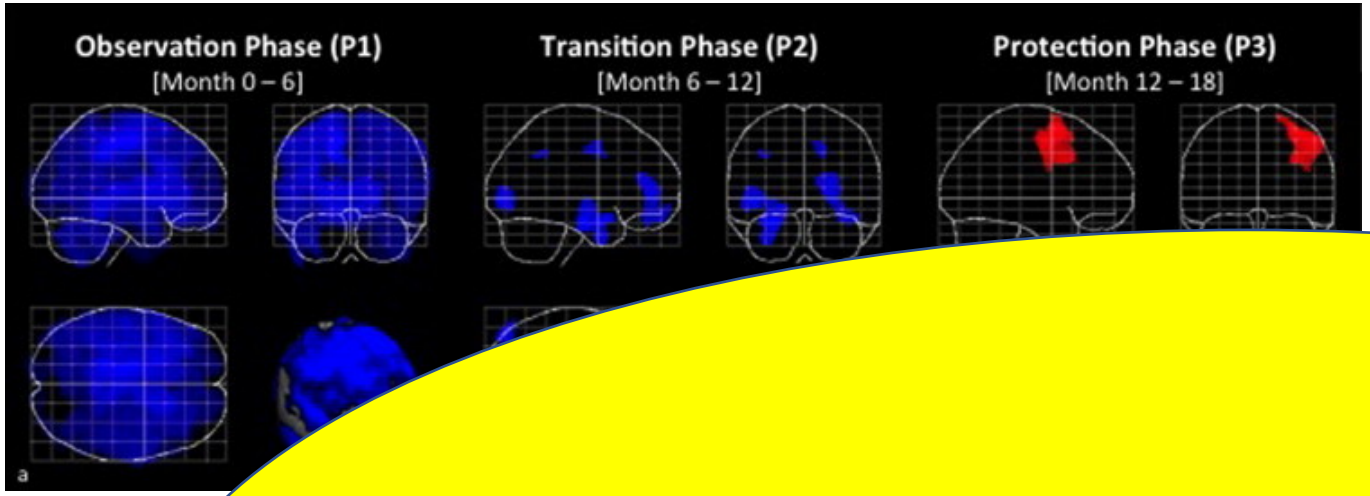


Highlights

- **Testosterone and luteinizing hormone (LH) have roles in Alzheimer's disease (AD) pathogenesis.**
- **Testosterone and LH modulate beta amyloid accumulation in the brain.**
- **These hormones are currently being target for AD therapeutics.**

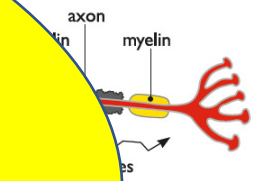
The impact of luteinizing hormone and testosterone on beta amyloid (Aβ) accumulation: Animal and human clinical studies. GiuseppeVerdile and Coll. ScienceDirect Hormones and Behavior. Volume 76, November 2015, Pages 81-90

without treatment for 6 months Androgel 10%



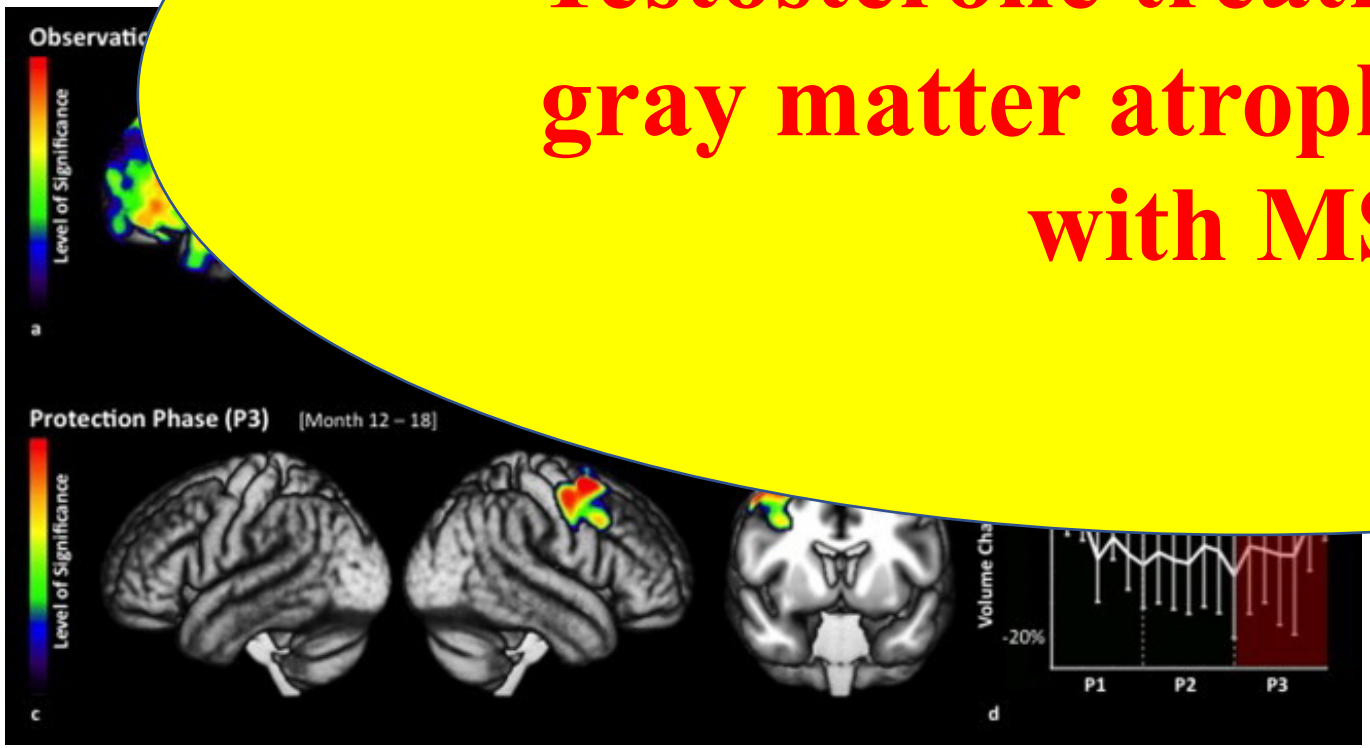
Regional gray matter volume increase in testosterone treated men with MS. (a) Significant gray matter changes during the observation phase, (b) the transition phase, and (c) the protection phase, threshold at $p \leq 0.05$, FWE-corrected for multiple comparisons. Displayed are intensity projections superimposed onto the SPM standard rendering onto the mean template. in red. Note the significant gray ignificant gray

Neuron in MS



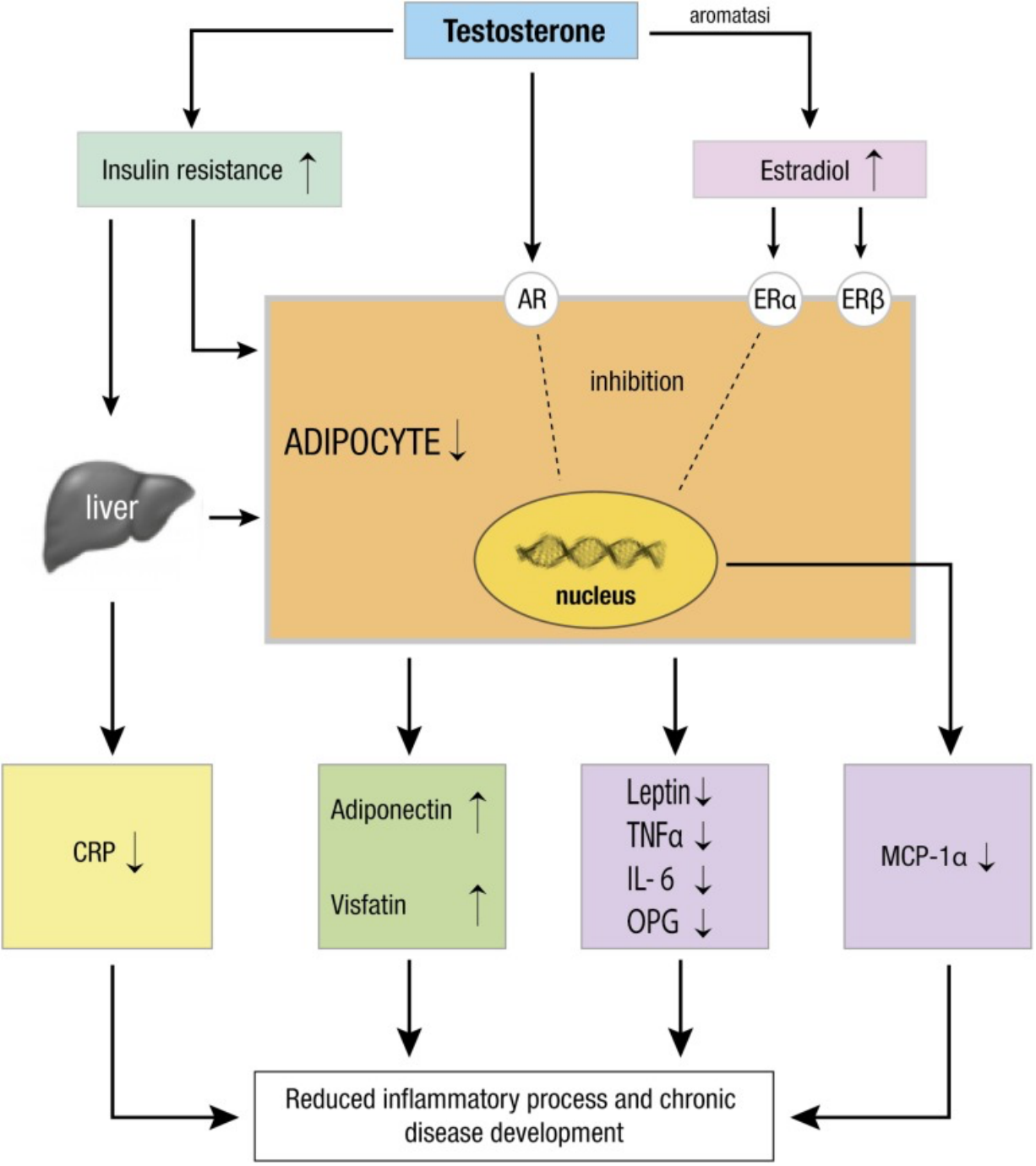
In the prote es

Testosterone treatment reverse gray matter atrophy associated with MS.



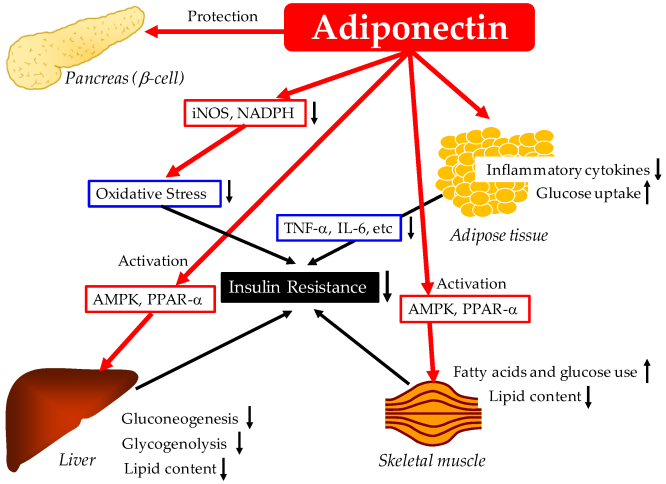
05, FWE-
GM
e arrested
M decrease was
). (c) Regional GM
hase. Heat maps visualize regional
vel of significance. (d) In this cluster, testosterone treatment resulted in a GM increase during the protection phase (P3), which locally reversed the GM loss observed before treatment (P1).

Neuroprotective effects of testosterone treatment in men with multiple sclerosis. Florian Kurth, and All. Neuroimage Clin. 2014; 4: 454–460

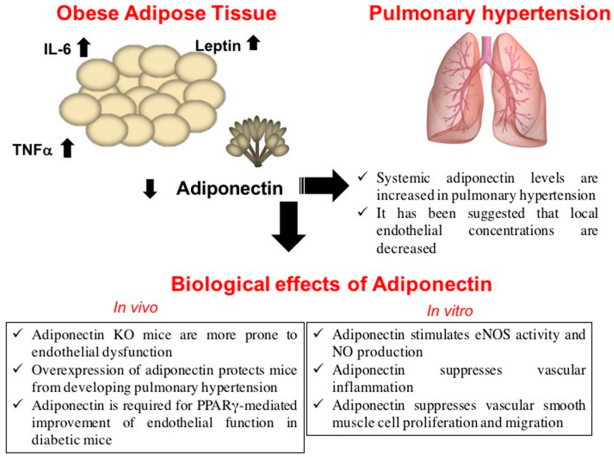


T exerts its anti-inflammatory activity through different mechanisms. Firstly, T inhibits body fat expansion and reduces adipocytes size and metabolism. After its aromatization in estradiol, T can activate AR and ER*α*and ER*β*, which contribute to adipocytes regulation decreasing the release of adipokines (leptin, IL-6, TNF-*α*, OPG, MCP-1*α*) and improving adiponectin and visfatin production, which possess an anti-inflammatory effect. Furthermore, T improves insulin activity and reduces the CRP from the liver.

Altogether, it results in a reduction of inflammation and development of chronic disease.

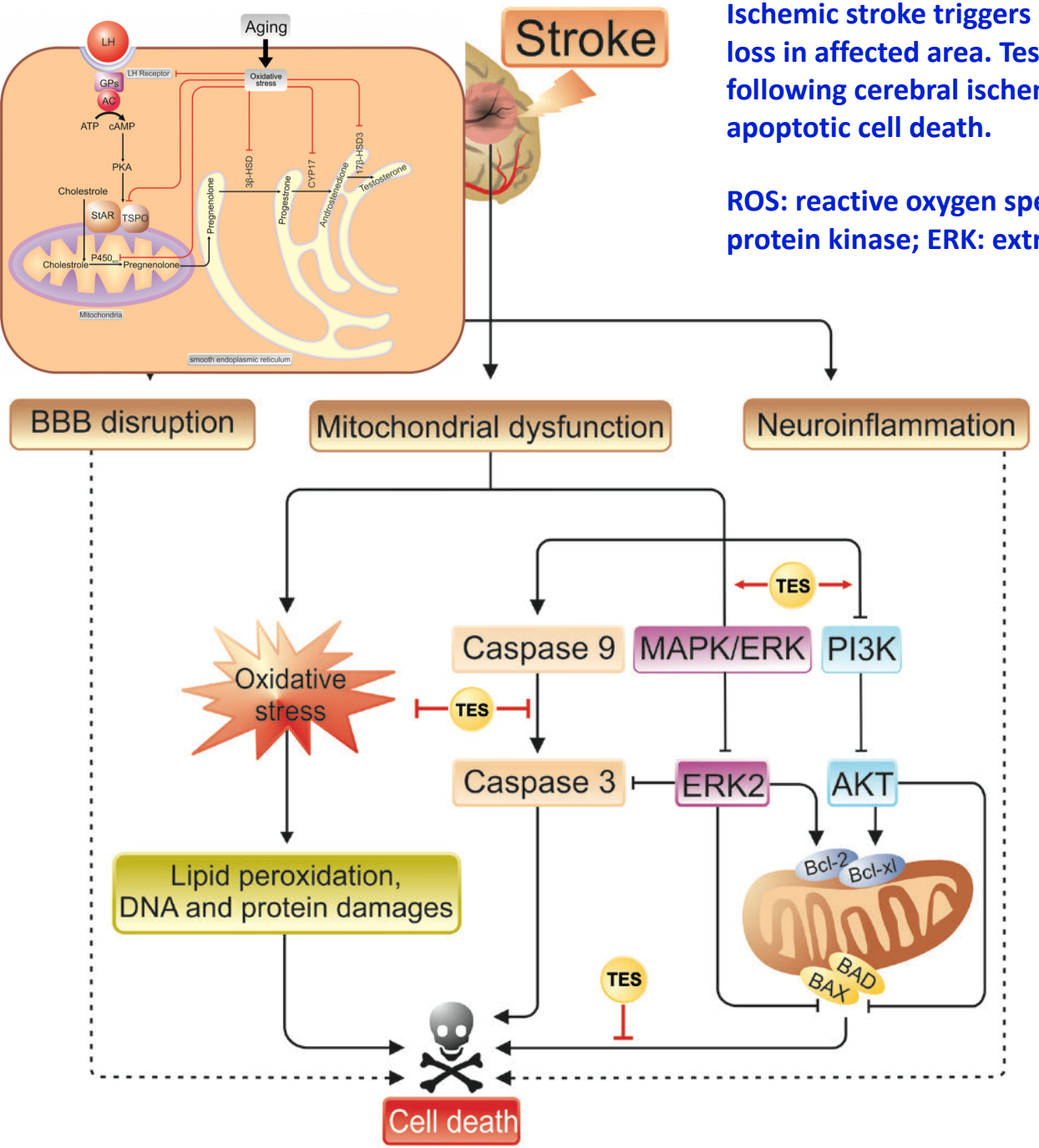


Int. J. Mol. Sci. **2019**, *20*(5), 1190



Int. J. Mol. Sci. **2019**, *20*(4), 912

The Anti-Inflammatory Effects of Testosterone. Bianchi VE and All. J Endocr Soc. 2018 Oct 22;3(1):91-107

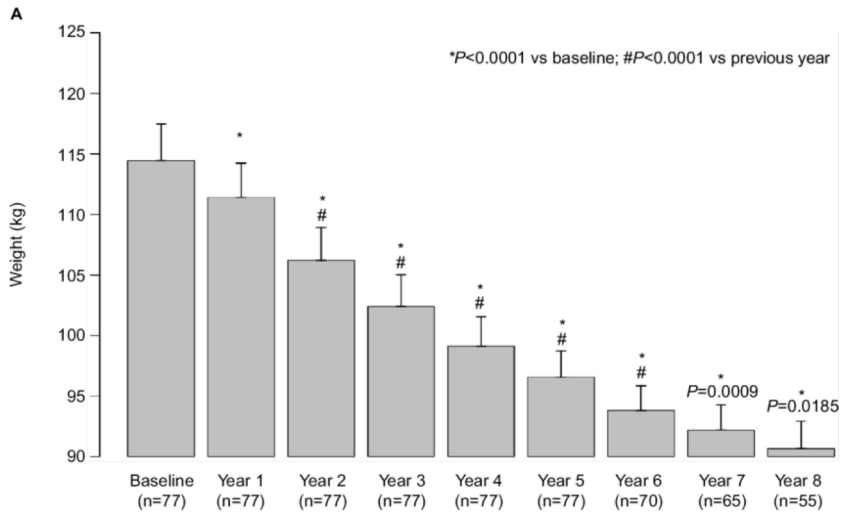


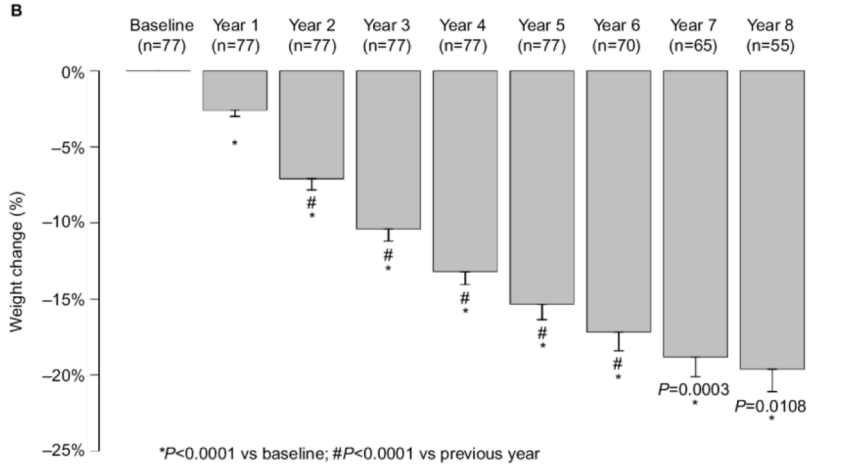
Ischemic stroke triggers cascades of complex events resulting in the neuronal loss in affected area. Testosterone induces neuroprotection in the neuronal cell following cerebral ischemia through inhibition of oxidative stress and blocking apoptotic cell death.

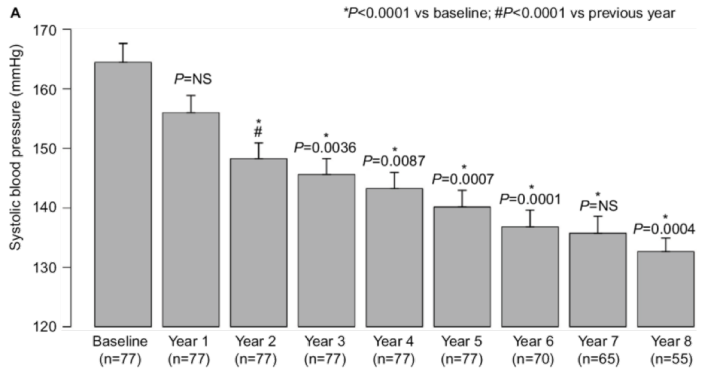
ROS: reactive oxygen species; TES: testosterone; MAPK: mitogen-activated protein kinase; ERK: extracellular signal- regulated protein kinase.

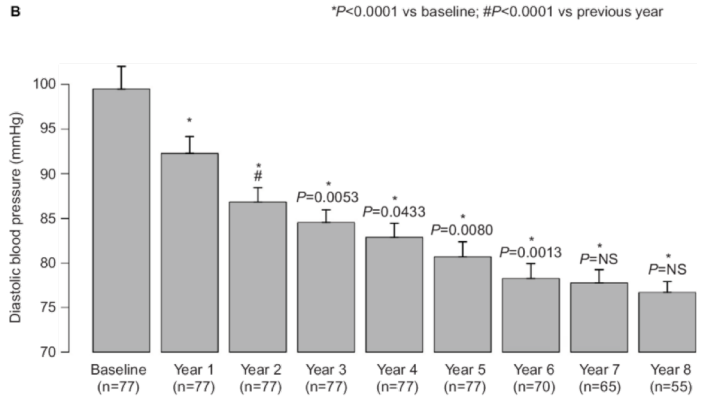
TES neuroprotection against stroke in aging appears to be mediated by several mechanisms including inhibition of production of oxidant molecules, enhancing the enzymatic antioxidant capacity of the brain, activation of PI3K/AKT pathway and enhancing cell survival, inhibition of pro-apoptotic protein through AR- dependent MAPK/ERK pathway, as well as improvement of brain neuronal and BBB integrities.

These mechanisms may propose future therapeutic strategies to improve the quality of life and decrease androgen-related health problems in the aging population.



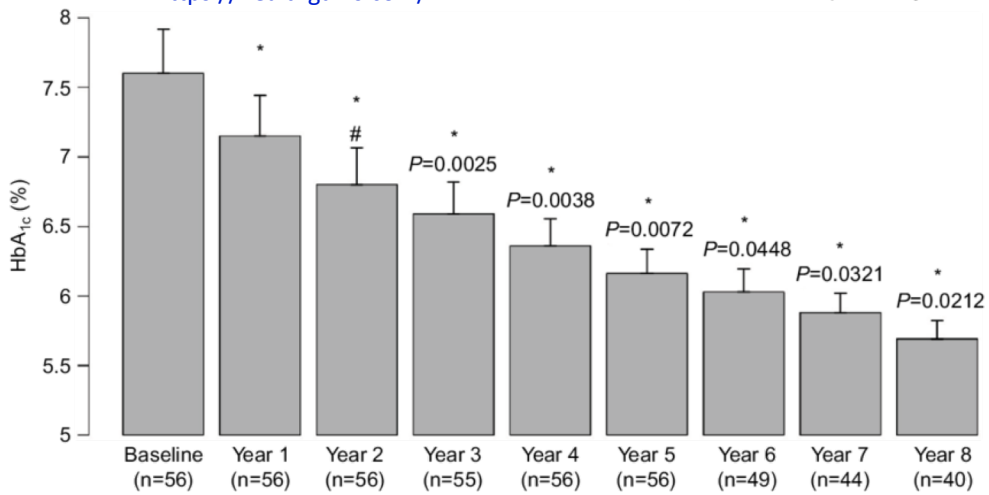






https://www.kingsbergmedical.com/side-effects-of-low-testosterone-treatment/

https://healthgains.com/



Long-term TTh in men with hypogonadism and a history of CVD appears to be an effective approach to achieve sustained improvements in anthropometric parameters and cardiometabolic function, with no reported increases in CVD events.

The fact that none of these high-risk patients had another CV event may suggest that TTh can have beneficial effects in men with a history of CVD, provided comprehensive secondary prevention therapy is already in place.

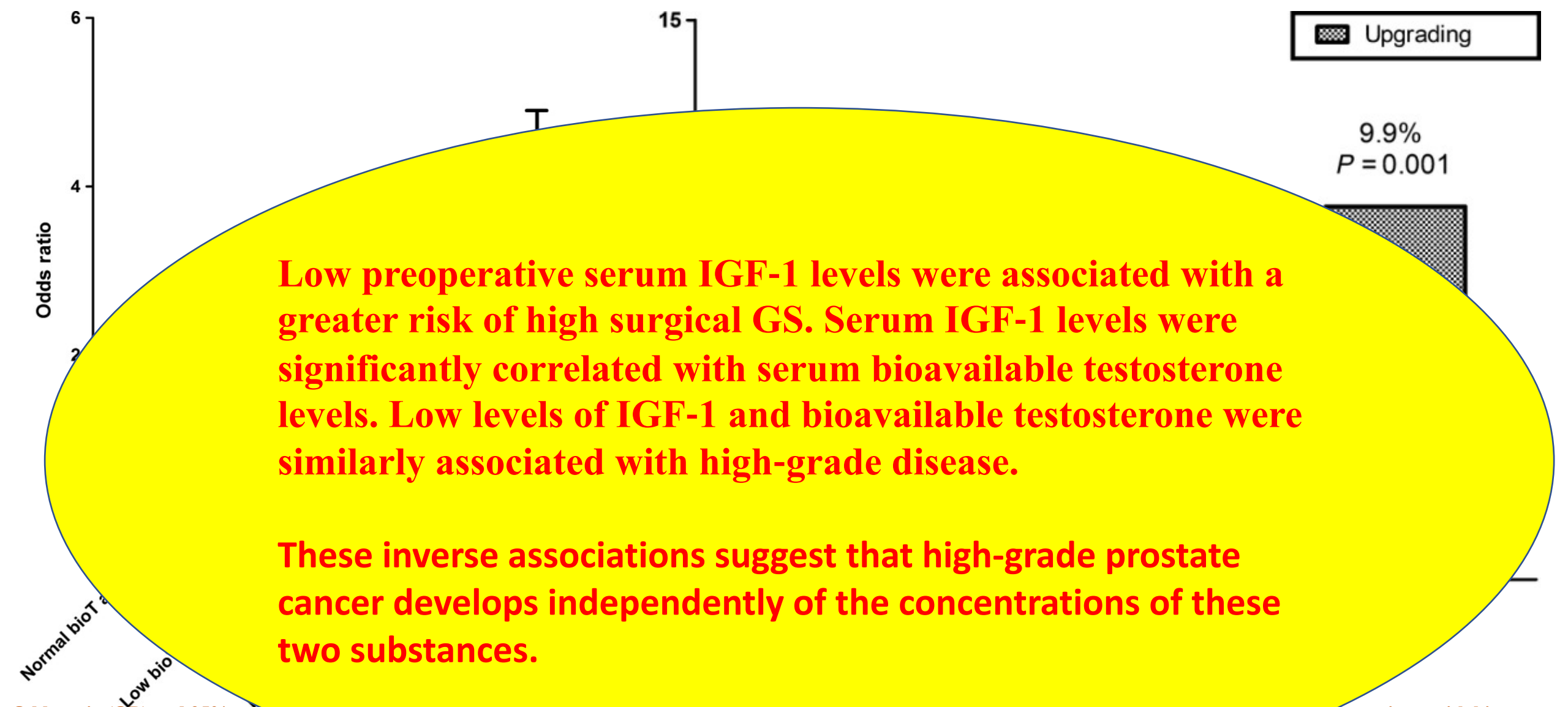
Men with testosterone deficiency and a history of cardiovascular diseases benefit from long-term testosterone therapy: Observational, Real-life data from a registry study. Saad Farid and Col. Vascular Health and Risk Management 12(Issue 1):251 · June 2016

Cardiovascular benefits and risks of testosterone replacement therapy in hypogonadal men with type 2 diabetes mellitus and/or the metabolic syndrome: a systematic review.

LE MINH QUANG, ATUL KALHAN. THE BRITISH JOURNAL OF DIABETES Vol 18, No 4 (2018)

https://www.mybeautygym.com/how-are-fast-food-and-obesity-related/

Our retrospective and systematic review of the literature suggests an increased risk of all-cause mortality and CV events in men with low endogenous T levels.[53-55] An extensive analysis of published data (available on 30 June 2016) from RCTs and non-RCTs is supportive of the protective effect of TRT on all-cause mortality and Major Adverse Cardiacs Events in hypogonadal men with T2DM and/or Metabolic syndrome. However, caution needs to be exercised while considering TRT in elderly men with co-morbidities. There is also a need for larger double-blind RCTs to evaluate the long-term outcome of TRT in hypogonadal men.



Low preoperative serum IGF-1 levels were associated with a greater risk of high surgical GS. Serum IGF-1 levels were significantly correlated with serum bioavailable testosterone levels. Low levels of IGF-1 and bioavailable testosterone were similarly associated with high-grade disease.

These inverse associations suggest that high-grade prostate cancer develops independently of the concentrations of these two substances.

Odds ratio (OR) and 95% confi… among patients with biopsy according to serum levels of bioavailab… available testosterone (bioT) and (IGF)-1. The OR for high surgical Gleason score… actual prevalence of upgrading was 1.066-4.897) in patients with low bioT (≤0.85 ng/mL) and lo… had a low bioT (≤0.85 ng/mL; 9.3% or 5/54) or followed by when one of bioT (OR = 1.968; 95% CI, 1.045-3.704) or IGF-1 (OR … level (≤116.0 ng/mL; 9.9% or 12/121) than in patients who had normal bioT 95% CI, 1.442-3.371) was low and IGF-1 levels (2.6% or 8/307)

Association between serum levels of insulin-like growth factor-1, bioavailable testosterone, and pathologic Gleason score. Myong Kim and Coll. Cancer Med. 2018 Aug; 7(8): 4170–4180

Curr Urol Rep. 2018 Jun 30;19(8):67. doi: 10.1007/s11934-018-0812-1.

The Role of Testosterone Therapy in the Setting of Prostate Cancer.

Rodriguez KM[1], Pastuszak AW[2,3], Khera M[4].

Author information

Abstract

PURPOSE OF REVIEW:

The role of testosterone in the development of prostate cancer and the safety of testosterone therapy (TTh) after prostate cancer treatment, or in the setting of active surveillance, remains controversial. There are many concerns about using TTh in men, particularly those with a history of prostate cancer, ranging from a possible increased risk of cardiovascular disease to cancer progression or recurrence. With many prostate cancer patients living longer, and hypogonadism having significant morbidity, much care must go into the decision to treat. **Here, we review the literature investigating the effects of testosterone on the prostate as well as the efficacy and safety of exogenous testosterone in men with a history of prostate cancer.**

RECENT FINDINGS:

The improvement in quality of life with TTh is well studied and understood, while the argument for significantly increased risk of cancer or other adverse effects is much less robust. Neither increased rates of prostate cancer, cancer recurrence, or cardiovascular risk have been well established. In men with high-risk prostate cancer, evidence in the setting of TTh is very limited, and TTh should be used with caution. **The fears of TTh causing or worsening prostate cancer do not appear to be well supported by available data.** Though more studies are needed to definitively determine the safety of TTh in men with prostate cancer, consideration should be given to treatment of hypogonadal men with a history of CaP

Testosterone Therapy on Active Surveillance and Following Definitive Treatment for Prostate Cancer.

Vishnukamal Golla and Alan L. Kaplan Curr Urol Rep. 2017; 18(7): 49.

Summary of critical literature for testosterone therapy and prostate cancer

Author	Year	Study design	Patient no.	Treatment type	Results
Calof [15]	2005	Meta-analysis	644	None	Prostate cancer, PSA > 4 ng/mL, and biopsies were higher in the T group than the placebo group.
Sarosdy [24]	2007	Retrospective case study	31	Brachytherapy	No recurrence or progression of prostate cancer (PSA < 1 in all patients)
Shabsigh [16]	2009	Systematic review	2292	Multiple	T therapy did not increase prostate cancer risk or increase Gleason grade in treated vs. untreated men. No consistent effect on PSA
Morgentaler [5]	2011	Retrospective case series	13	Active surveillance	No change in PSA or prostate volume with an increase in mean serum total testosterone. Biopsy in one man and a prostatectomy in another showed no progression or distant disease.
Patuszak [26]	2013	Retrospective case series	13	Radiation therapy	Median f/u of 29.7 months after starting testosterone resulted in large increase in testosterone with no significant increase in PSA. No cancer recurrences in follow-up
Patuszak [22]	2013	Retrospective case series	10	Radical prostatectomy	Median f/u of 27.5 months, significant increases in testosterone and PSA in both high-risk and non-high-risk prostate cancer groups. The reference group had more frequent referrals to radiation oncology or subsequent salvage therapy. There was a significantly increased number of T3b tumors in the reference group vs. testosterone group.
Ory [17]	2015	Retrospective review	82	Active surveillance	PSA increased in patients on active surveillance in this cohort, but no patients were upgraded to a higher Gleason grade on subsequent biopsies.
Millar [27••]	2016	Survey	57	None	The survey showed that 65% of sample of Canadian urologists believe that testosterone therapy is a safe practice. The majority feel that testosterone is safe in post surgical patients; 10–12% fewer are comfortable doing the same in radiated patients. And 20–30% fewer are comfortable with patients on active surveillance.

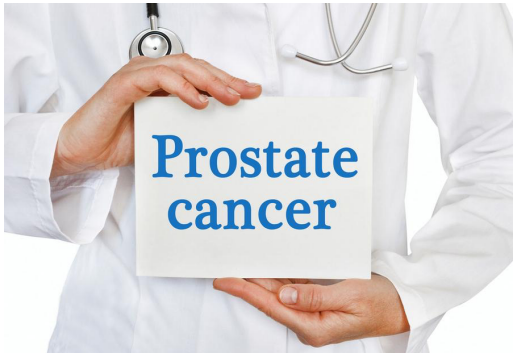
The importance of negative effects of testosterone deficiency on health and health-related quality of life measures has pushed urologists to re-evaluate the role testosterone plays in prostate cancer.

This led to a paradigm shift that testosterone therapy might in fact be a viable option for a select group of men with testosterone deficiency and a concurrent diagnosis of prostate cancer.

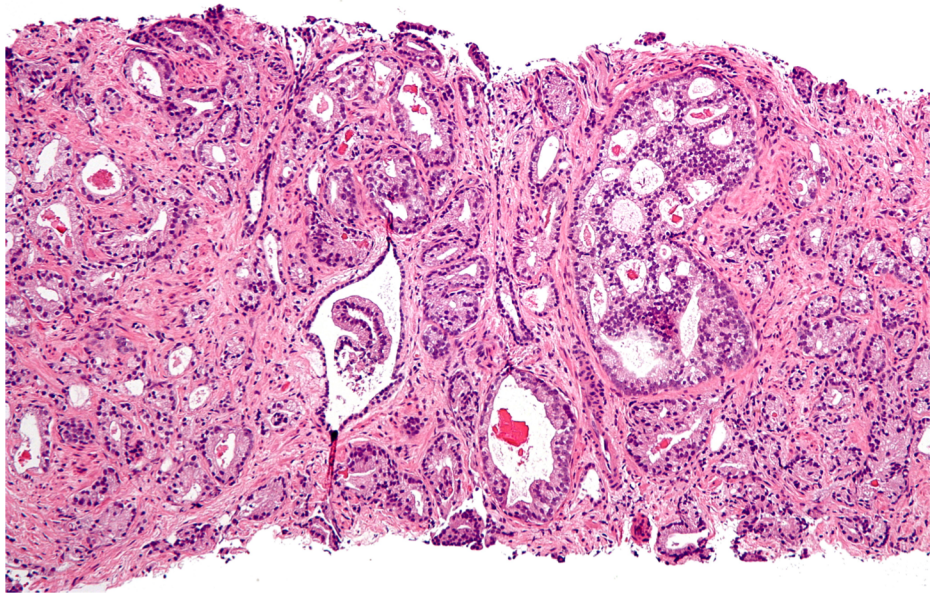
A large body of evidence in the literature has shown that testosterone deficiency has a significant detrimental effect on health and quality of life that can be mitigated with testosterone therapy. The studies discussed in this review including single- and multi-institution case series, retrospective reviews, and population-based studies have not found a higher than expected risk of prostate cancer progression or recurrence in testosterone-deficient men who received testosterone and were previously treated for prostate cancer (radiotherapy or surgical excision).

Shifting the Paradigm of Testosterone Replacement Therapy in Prostate Cancer.

Michael A. Bell and Coll. World J Mens Health. 2018 May; 36(2): 103–109.



https://www.hopkinsmedicine.org/



Par Nephron — Travail personnel, CC BY-SA 3.0,
https://commons.wikimedia.org/w/index.php?curid=10613950

Recent academic endeavors have shifted the paradigm of TRT being a contraindication in prostate cancer to becoming a viable option for select patients with symptomatic hypogonadism.

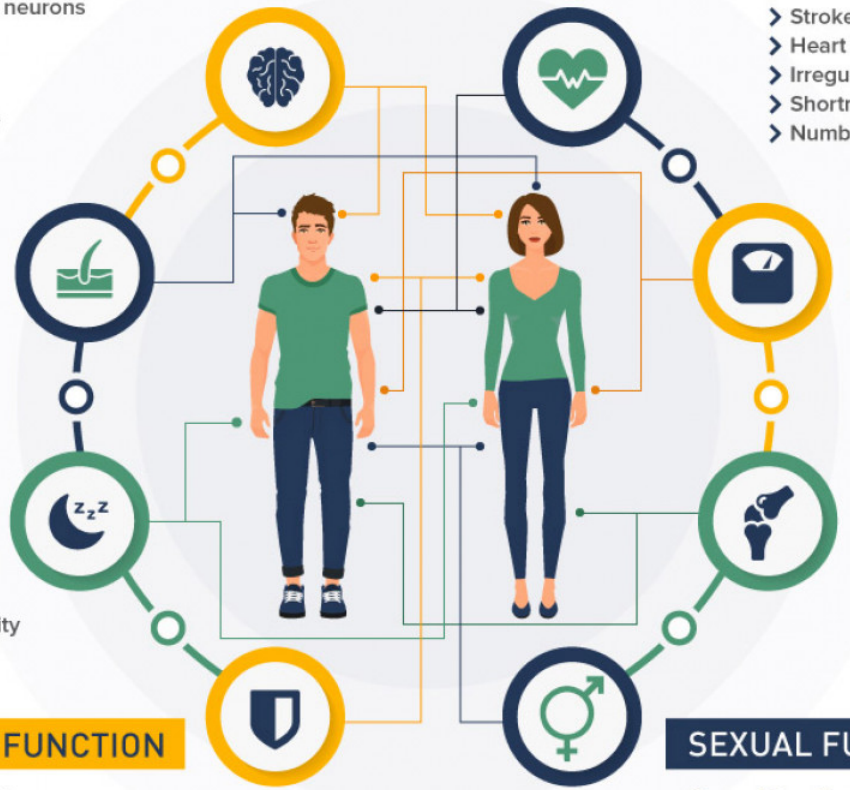
Current data suggest that TRT can cautiously be offered to carefully selected men treated with curative intent for low- and intermediate-risk prostate cancer, who have no evidence of disease recurrence.

More urologists, are becoming comfortable prescribing TRT for these men as well as those on active surveillance for low-risk prostate cancer.

Improving QOL in patients is an important aspect of prostate cancer survivorship, and therefore treatment should be considered for men suffering from TD.

Further multi-center, randomized, placebo-controlled trials are necessary to make a definitive statement on clinical safety.

HUMAN GROWTH HORMONE BENEFITS



BRAIN FUNCTION

- Memory
- Dendritic formation of cortical neurons
- Cognitive function
- Improved mental function
- Alertness
- Motivation and Work Capacity
- Prevents Alzheimer's disease
- Concentration

HEART

- HGH enhances Cardiac Functions
- Stroke
- Heart Attack
- Irregular Heartbeat
- Shortness of Breath
- Numbness

SKIN & HAIR

Positive Results

- Thicker hair
- Growth in areas where hair was lost
- Increased collagen
- Skin thickening
- Smoother, firmer skin
- Of wrinkles, fine lines, and cellulite
- Decreased sagging

BODY FAT

- HGH accelerates metabolism

SLEEP

- HGH Improves Your Sleep Quality

BONE DENSITY

- Reduced Risk of Osteoporosis
- HGH Increase Bone Healing

IMMUNE FUNCTION

- Stimulates bacteria fighting macrophages
- Increase production of T-cell and Interleukin2
- Increases erythropoiesis
- Increases maturation of neutrophils
- Increases and intensifies the production of new red blood cells
- Increases production of white blood cells that fight disease

SEXUAL FUNCTION

Sexual function in men

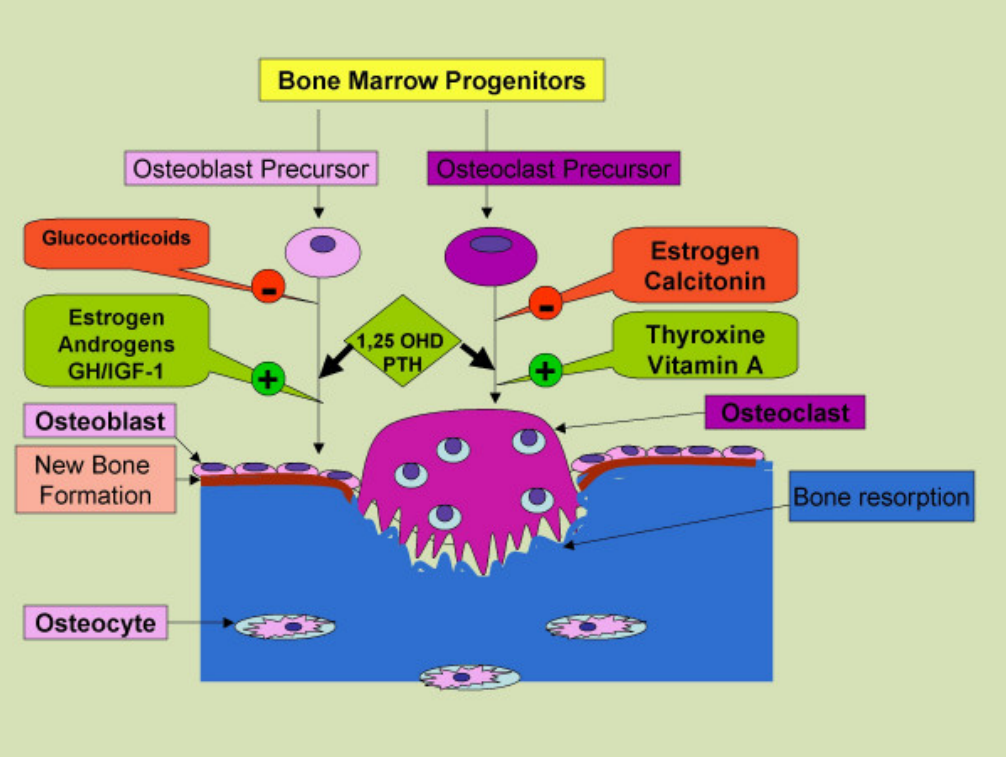
- Increased desire
- Faster arousal times
- Stronger erections
- Longer lasting stamina
- Increased pleasure

Sexual function in women

- Increased vaginal lubrication
- Heightened arousal
- Stronger desire
- Improved endurance
- Multiple orgasms

NATIONAL HRT

https://visual.ly/community/Infographics/health/human-growth-hormone-benefits



https://www.researchgate.net/figure/Development-of-osteoblasts-and-osteoclasts-from-bone-marrow-progenitors-Factors_fig1_6834713

Our meta-analysis suggested that growth hormone replacement therapy could have beneficial influence on bone mineral density in growth hormone deficient adults, but, in some subject populations, the influence was not evident.

Effects of Growth Hormone Replacement Therapy on Bone Mineral Density in Growth Hormone Deficient Adults: A Meta-Analysis. Peng Xue, and All. International Journal of Endocrinology Volume 2013, Article ID 216107, 13 pages http://dx.doi.org/10.1155/2013/216107Research Article

Administration of rhGH led to a significant increase in lumbar spine (LS) and femoral neck (FN) BMD in randomized/controlled studies of more than 1 year.

Positive association between the BMD change and treatment duration

This meta-analysis suggests a beneficial effect of rhGH replacement on BMD in adults with GH deficiency. This effect is affected by gender, age, and treatment duration. Larger studies are needed to evaluate the effect of rhGH on fracture risk.

In a subgroup analysis, the increase in LS and FN BMD was significant in men but not in women.

Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis.
Barake M and All. J Clin Endocrinol Metab. 2014 Mar;99(3):852-60

Long-term benefits and risks of growth hormone replacement therapy in adult patients with growth hormone deficiency.

Patient Data	Benefits	Risks or Drawbacks
Body composition	Reduction in fat mass Increase in lean mass Increase in muscle strength	Increase in BMI Increased waist circumference Increase of waist-hip index
Bone metabolism	Increase in bone mineral density	Effect on the incidence of fractures not clearly shown
Health-related quality of life	Improvement in quality of life questionnaires Greater benefit in patients with low quality of life at baseline	No improvement in all dimensions Probable absence of effect in patients with normal quality of life
Cardiovascular risk markers	Increase in HDL-chol Reduction of total and LDL-chol Diastolic blood pressure reduction Reduction of CRP Reduction of carotid intima-media thickness	Reduced insulin sensitivity Increase in fasting glucose and insulin Trend to the increase in the prevalence of metabolic syndrome Increase in lipoprotein (a)
Cardiovascular disease	Reduction in the incidence rate of myocardial infarction	Trend to increase in cerebrovascular disease
Neoplasms	No increase in the rate of recurrence or progression of hypothalamic-pituitary tumors No increase in overall risk of neoplasia in adults with GHD	Tendency to increase risk of second malignancy in childhood cancer survivors treated with GH in childhood There are subgroups with increased risk of certain neoplasia in adults who were treated with GH in childhood
Mortality	Tendency to decrease the global and cardiovascular mortality of hypopituitarism	Persistence of higher mortality than the general population in some studies

Abbreviations: BMI, body mass index; chol, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein; GHD, deficiency of growth hormone.

There are no well-conducted prospective studies on the effect of age on the benefits and risks of GH replacement. In a systematic review of eleven studies in patients older than 60, treatment with GH decreased total and low density lipoprotein cholesterol levels, but did not alter high density lipoprotein or triglyceride levels. In addition, GH did not affect body mass index, blood pressure, or bone mineral density but decreased waist circumference, increased lean body mass, and decreased total fat mass. GH replacement consistently improved QoL.

Treatment with Growth Hormone for Adults with Growth Hormone Deficiency Syndrome: Benefits and Risks. Juan J. Díez and All. Int J Mol Sci. 2018 Mar; 19(3): 893.

Clinical abnormalities in hypopituitary adult patients with growth hormone deficiency (AGHD).

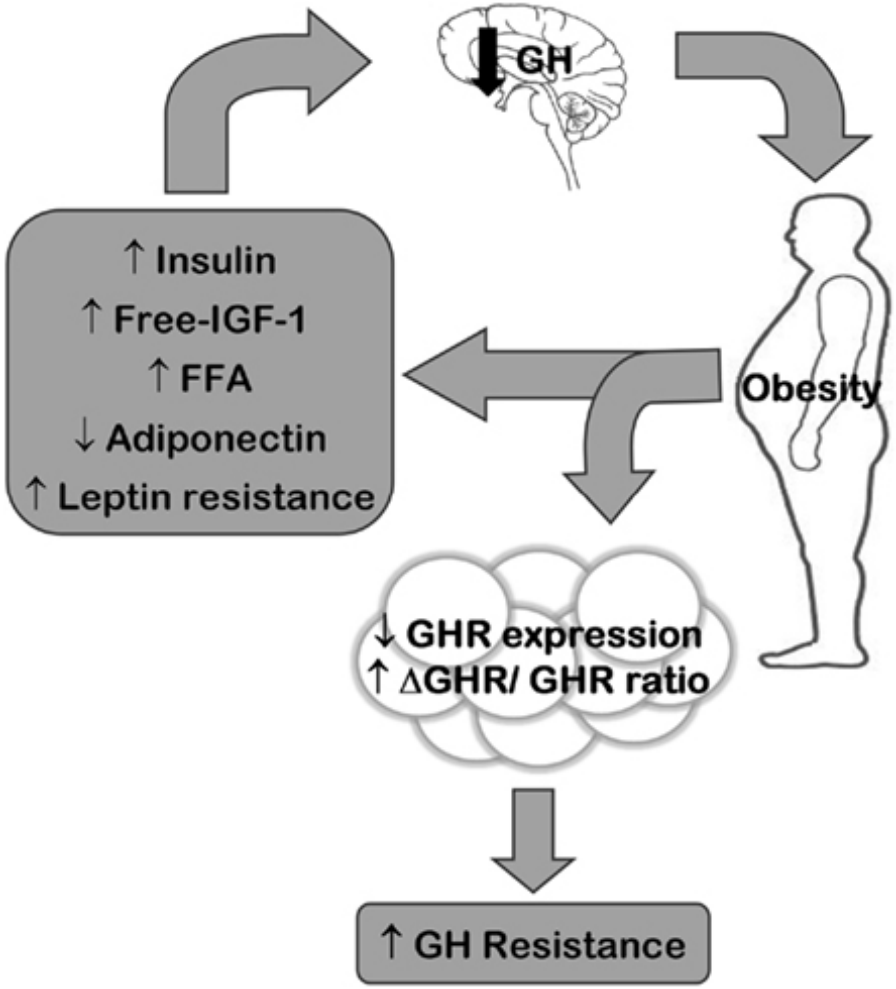
Clinical abnormalities	Effect of growth hormone deficiency
Impairment of cognitive and psycho-social functions (poor quality of life)	Fatigue (low energy, reduced vitality) Low self-esteem Bad mood Reduced concentration Reduced memory Increased sick days Greater social isolation
Altered physical capacity	Reduced muscular strength Reduced maximum oxygen uptake Impaired cardiac function Hypohydrosis
Presence of cardiovascular risk factors	Dyslipidemia Insulin resistance (visceral obesity) Abnormal fibrinolytic activity Increased pro-inflammatory markers Increased intimal media thickening

What is well recognized is that GH therapy can correct or improve clinical abnormalities seen in patients with AGHD, resulting in beneficial effects on body composition, skeletal integrity, exercise capacity, QoL, and cardiovascular risk factors.

Observational studies with at least 7 years of follow-up have demonstrated that many clinical benefits of GH therapy in patients with AGHD are sustained in the long term with a low prevalence of serious adverse events and complications.

Update on GH therapy in adults. Cesar Luiz Boguszewski, and All. Published online 2017 Nov 16. doi: 10.12688/f1000research.12057.1

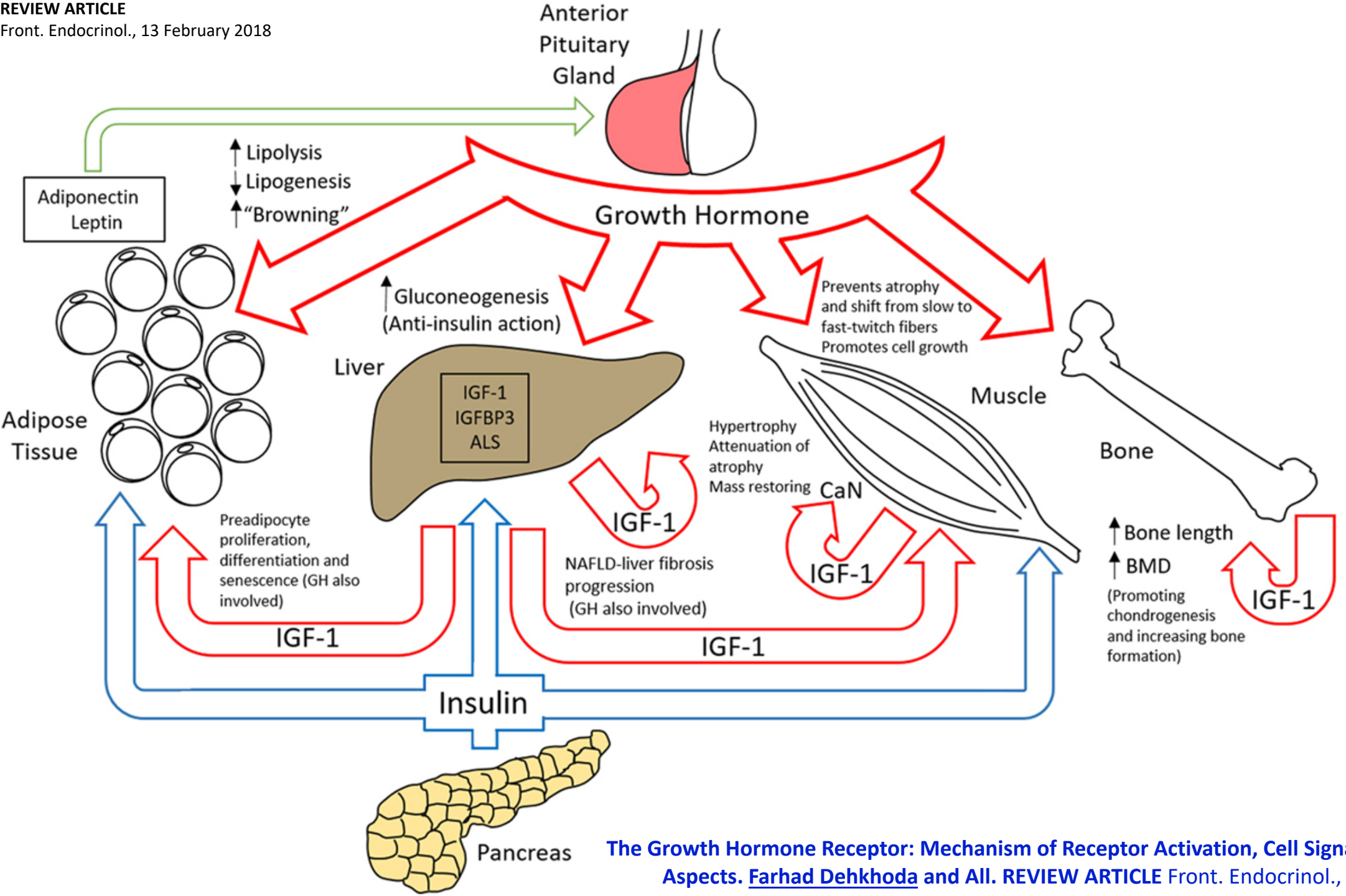
Decreased GH action in obesity may in itself contribute to the associated metabolic abnormalities.



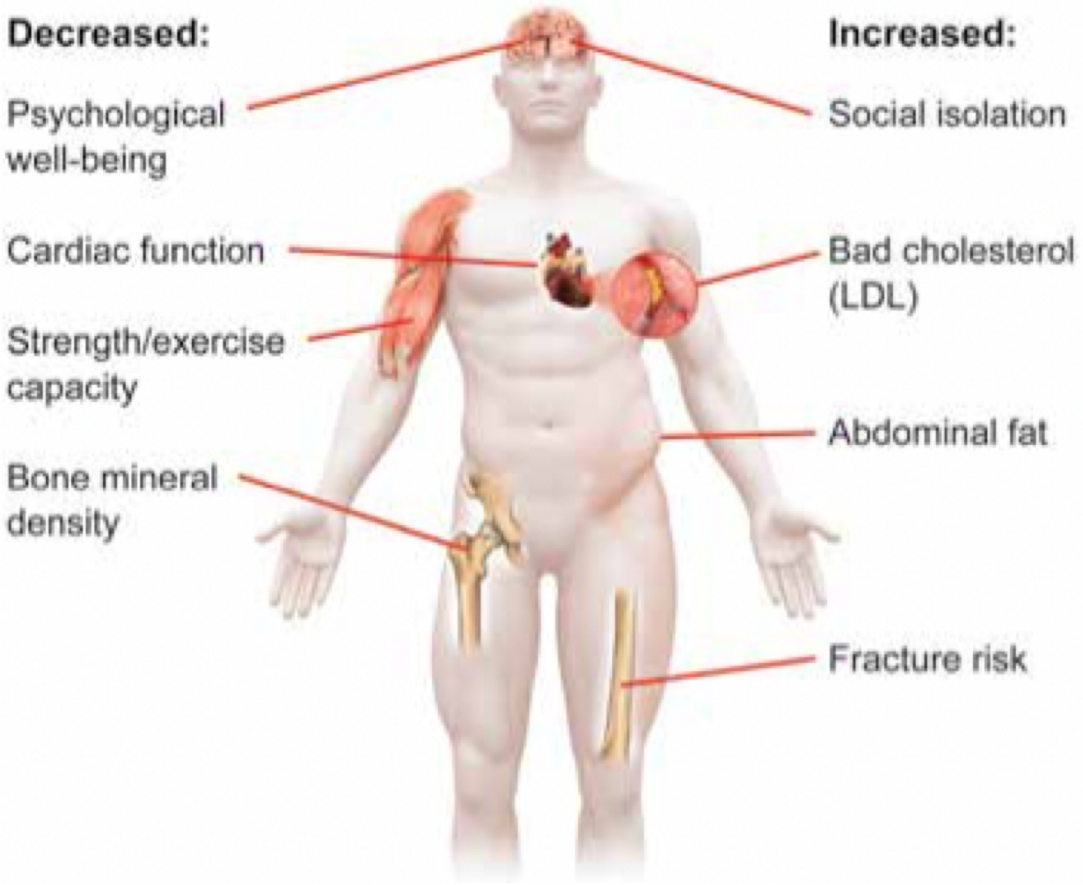
Possible mechanisms mediating reduced GH action in obesity.

Obesity-induced hyperinsulinemia, hypoadiponectinemia, leptin resistance, and increased bioactive insulin-like growth factor-1 (IGF-1) and free fatty acid (FFA) levels could suppress GH secretion from the pituitary by various mechanisms. Reduced GH secretion further increases fat accumulation and, thus exacerbates the obesity condition. Moreover, reduced GH receptor (GHR) expression and increased expression of truncated GHR (ΔGHR) in the adipose tissue results in a GH-resistant state that also contributes to the complications associated with obesity.

The intricate role of growth hormone in metabolism. Archana Vijayakumar and All. REVIEW ARTICLE Front. Endocrinol., 27 September 2011



The Growth Hormone Receptor: Mechanism of Receptor Activation, Cell Signaling, and Physiological Aspects. Farhad Dehkhoda and All. REVIEW ARTICLE Front. Endocrinol., 13 February 2018



GH levels decrease with age. This decrease may be so important that insulin growth factor-1 (IGF-1) levels found in elderly individuals are as low as those encountered in adult patients with established GH deficiency.

GH decrease combined with the fact that frailty and aging share several characteristics with GH deficiency encountered in younger adults (increase of fat mass and decrease of lean mass, cognitive impairment, psychological difficulties, dry and thin skin, and impaired cardiac capacity) have made it rather popular in antiaging medicine.

As a matter of fact, both too high and too low levels of GH and IGF-1 seem to be associated with reduced longevity in humans.

Off-label use of hormones as an antiaging strategy: a review. Nikolaos Samaras. Clin Interv Aging. 2014; 9: 1175–1186

The syndrome of AGHD is increasingly recognized as a cause of fatigue, dysthymia, and increased mortality as a result of dyslipidemia.

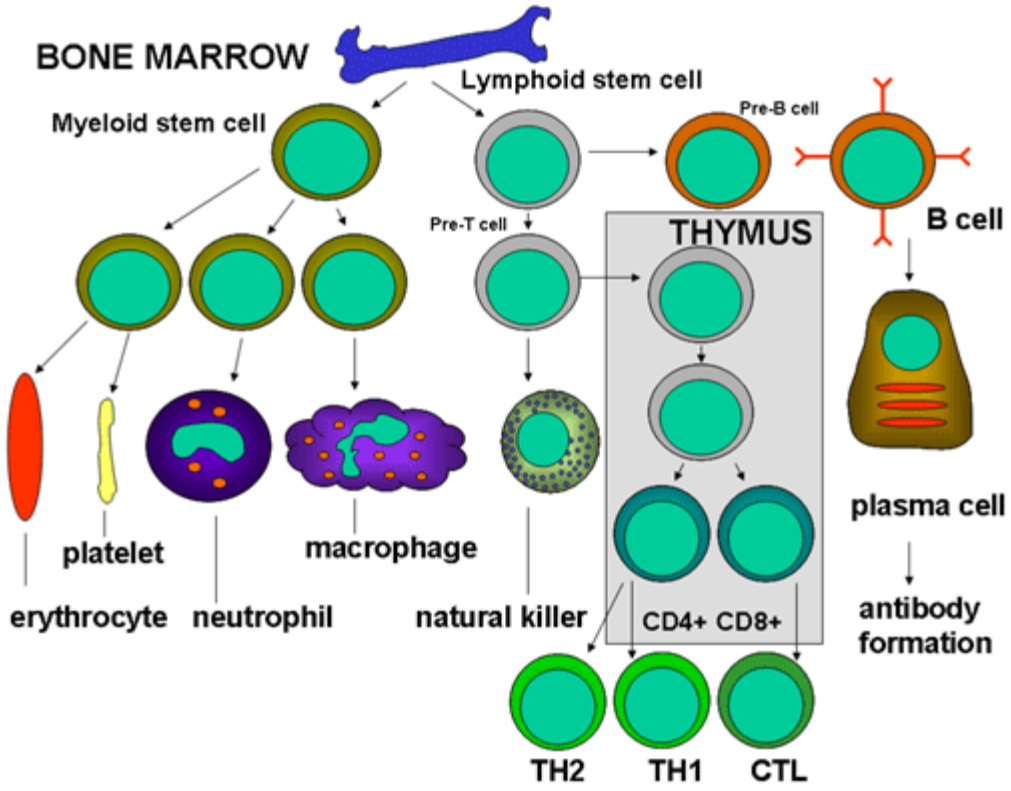
Clinical features of adult GH deficiency	Improved by GH replacement
Increased abdominal fat	Yes
Reduced muscle mass and strength	Yes
Reduced cardiac capacity	Yes
Reduced blood volume	Yes
Cold intolerance	Probably
Impaired exercise capacity	Yes
Thin, dry skin	Yes
Reduced sweating	Yes
Reduced bone mineral density	Yes (delayed effect after 1 year)
Psychosocial dysfunction	Yes
Atherogenic lipid profile	Probably
Increased atherosclerosis	Not known
Reduced life expectancy	Not known

GH—growth hormone.

Stimulation of protein synthesi
Mobilization of stored fat
Retention of sodium, phosphate, and water
Maintains blood glucose by suppressing insulin
Inhibits proteolysis
Inhibits apoptosis
Enhances the effects of stimulating hormones such as TSH and ACTH
Stimulates differentiation and proliferation of chondrocytes
Stimulates the differentiation and proliferation of muscle cells
Increases glomerular filtration rate
Decreases blood glucose
Stimulates wound healing

TSH—thyroid-stimulating hormone; ACTH—adrenocorticotropic hormone.

Current Pain and Headache Reports 9(5):331-8 · November 2005

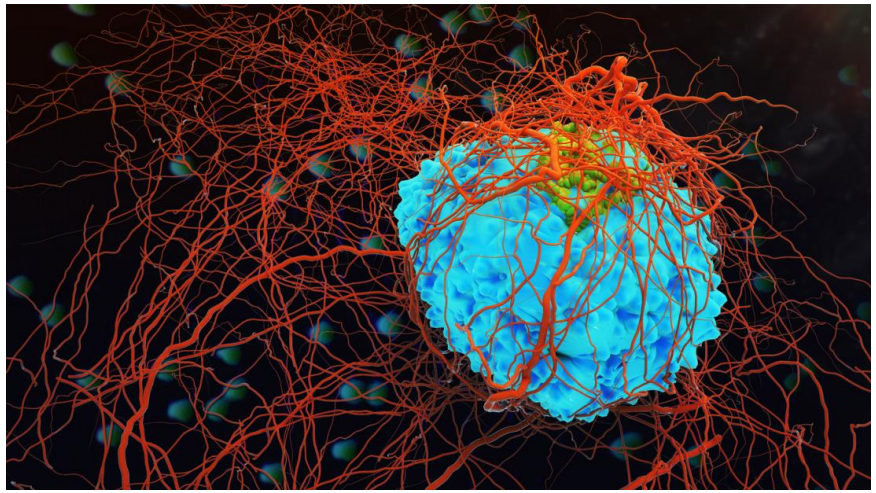


http://www.microbiologybook.org/French-immuno/immchapter1.htm

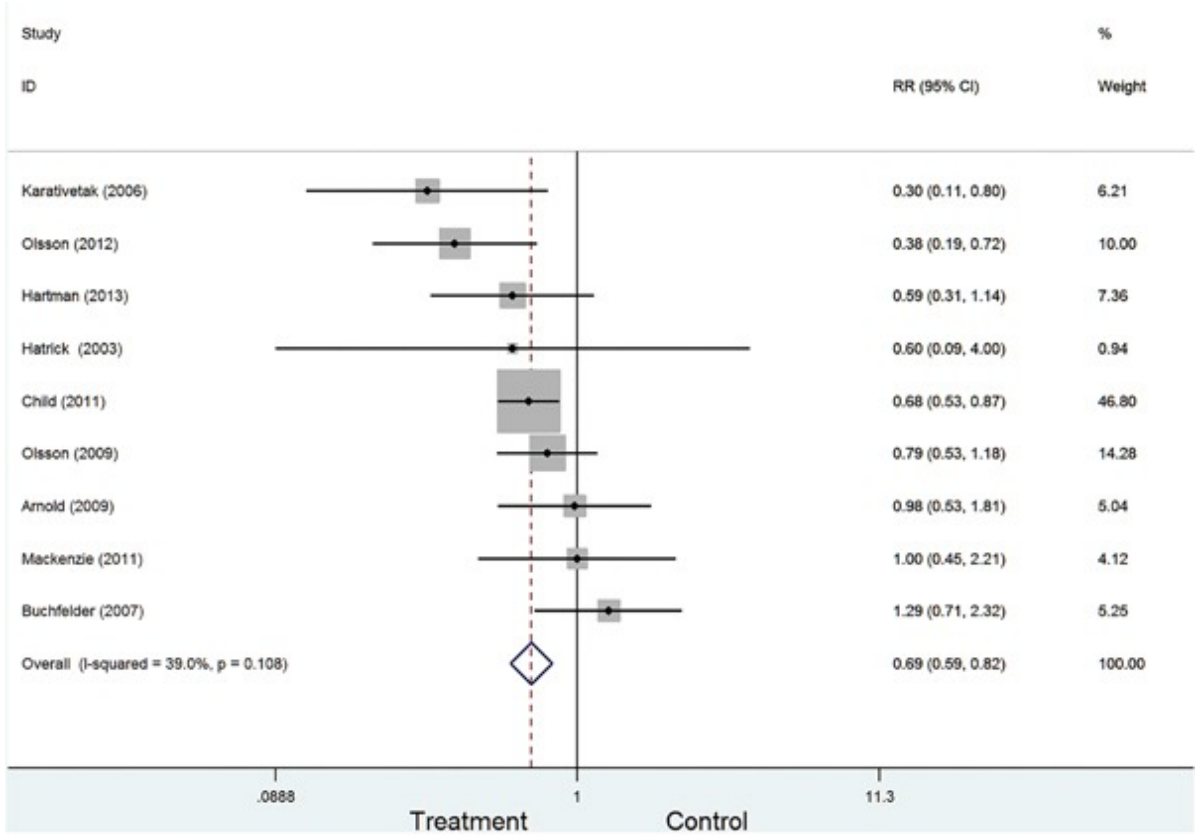
It is well known that lymphoid organs such the thymus, the spleen and peripheral blood produce growth hormone (GH) and GH receptor is expressed on different subpopulations of lymphocytes. Many in vitro and in animal studies demonstrate an important role of GH in immunoregulation. GH stimulates T and B cells proliferation and immunoglobulin synthesis, enhances the maturation of myeloid progenitor cells and is also able to modulate cytokine response.

Literature Review. Effect of growth hormone (GH) on the immune system. Pediatric endocrinology reviews: PER 1 Suppl 3(Suppl 3):490-5 · September 2004

Growth hormone replacement therapy reduces risk of cancer in adult with growth hormone deficiency: A meta-analysis. Zhanzhan Li, and All. Oncotarget. 2016 Dec 6; 7(49): 81862–81869.



No increase in the risk for cancer with GH supplementation has been reported in young patients with overt deficiency. In older patients with age-related GH deficiency, short-term clinical trials observed no increase of cancer incidence or deaths, but no data exist for long-term treatments.



Forest plot for GH replacement therapy for cancer risk in adult with GHD

In conclusion, our results suggest that growth hormone replacement therapy reduces risk of cancer in adult with growth hormone deficiency. Future study with more long-term follow-up are needed to explore the association between GHRT and recurrence of cancer or other types of tumor.

Oncotarget. 2016 Dec 6; 7(49): 81862–81869.

Off-label use of hormones as an antiaging strategy: a review. Nikolaos Samaras. Clin Interv Aging. 2014; 9: 1175–1186

THANK YOU FOR LISTENING

ANY QUESTION???