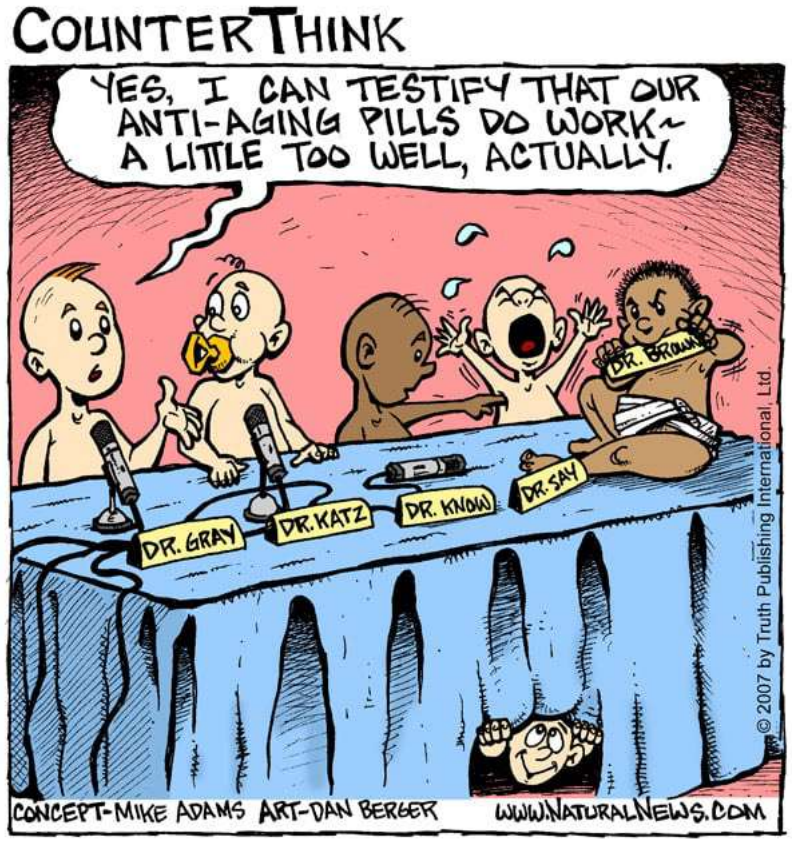
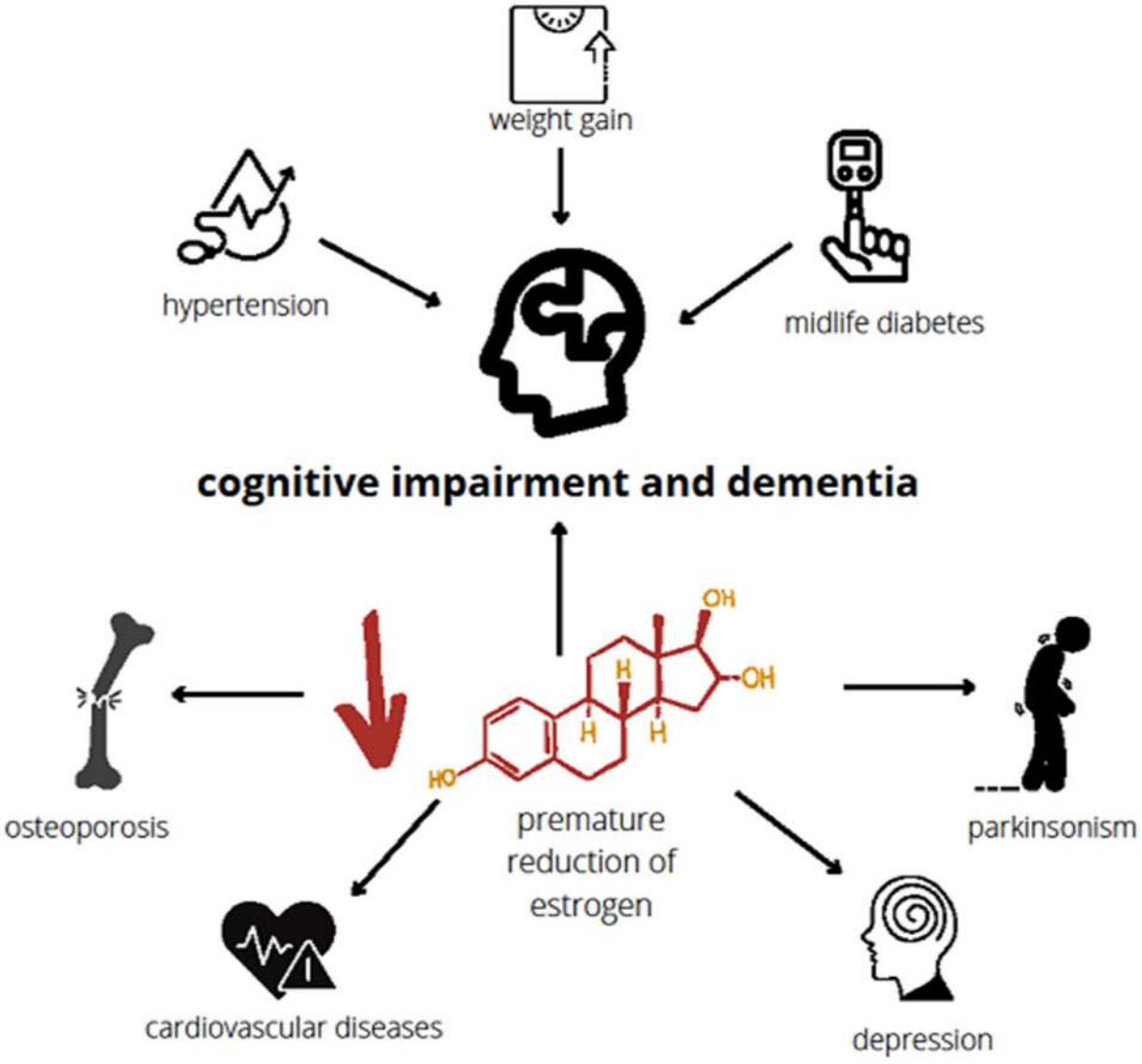


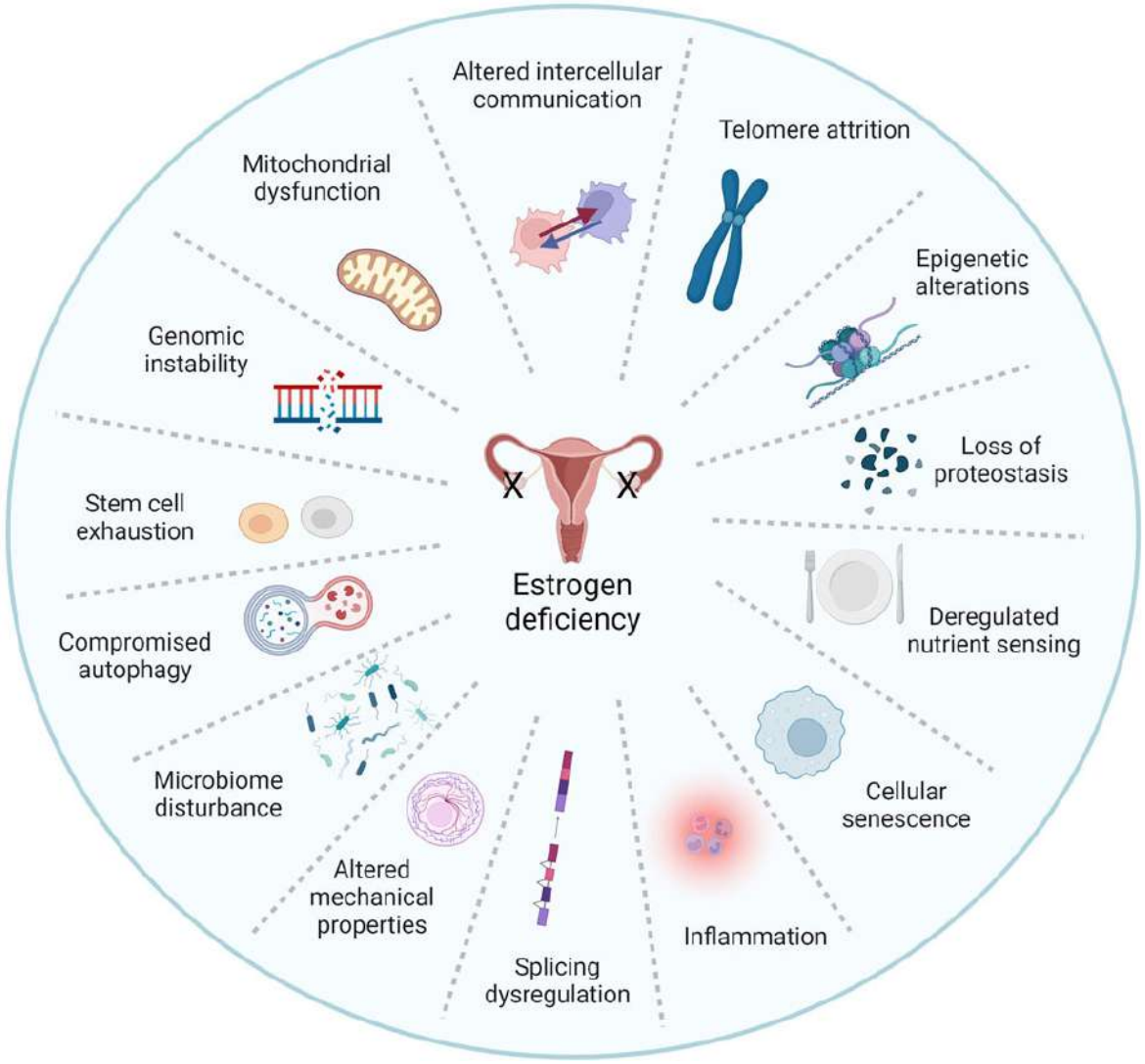
How sexual hormones may slow down aging process after menopause

Congress of the Belgian Society of Aesthetic Medicine 26 and 27 April 2024

Risks following premature reduction in estrogen

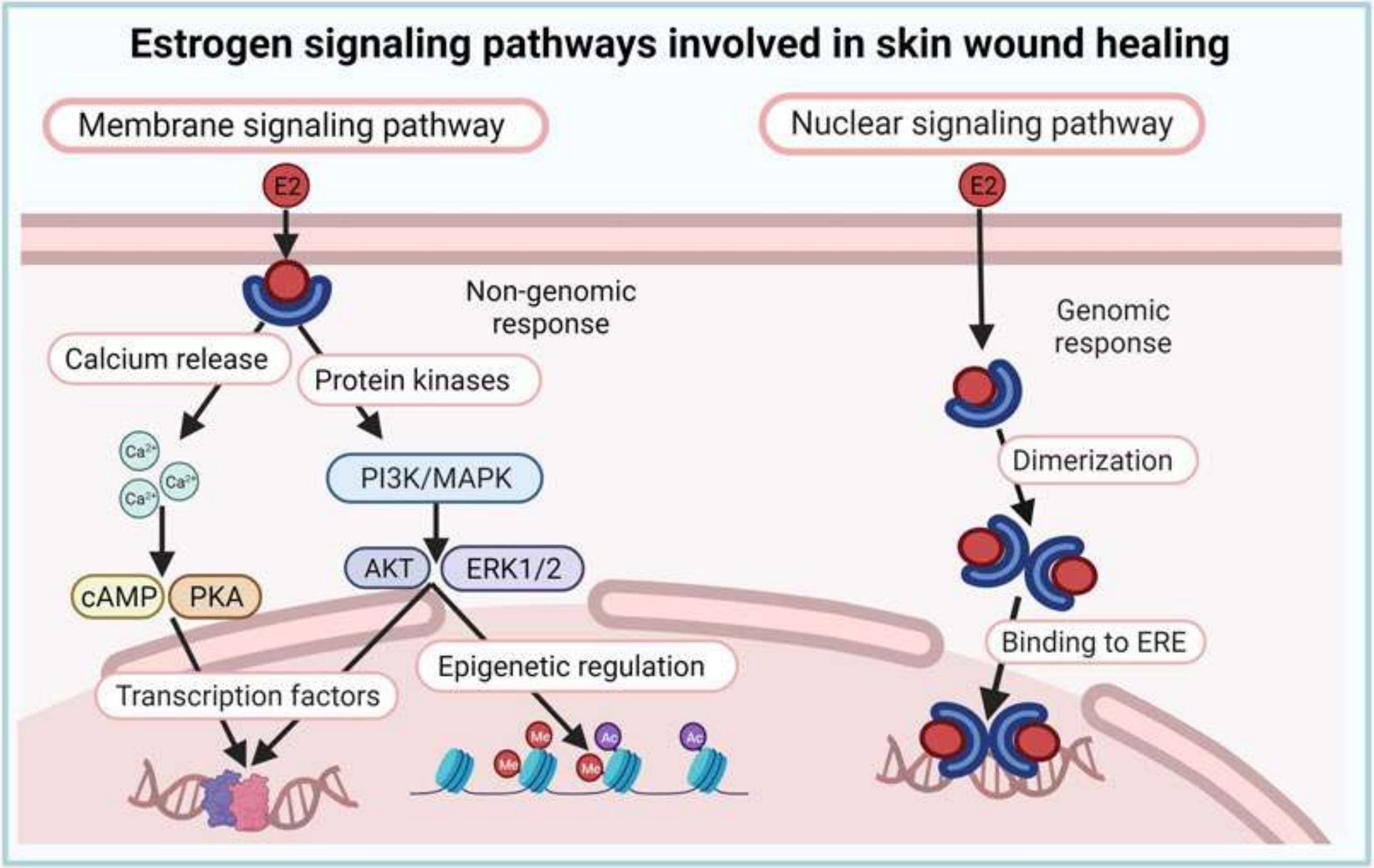


Estrogen was shown to protect against multiple aspects of cellular skin aging

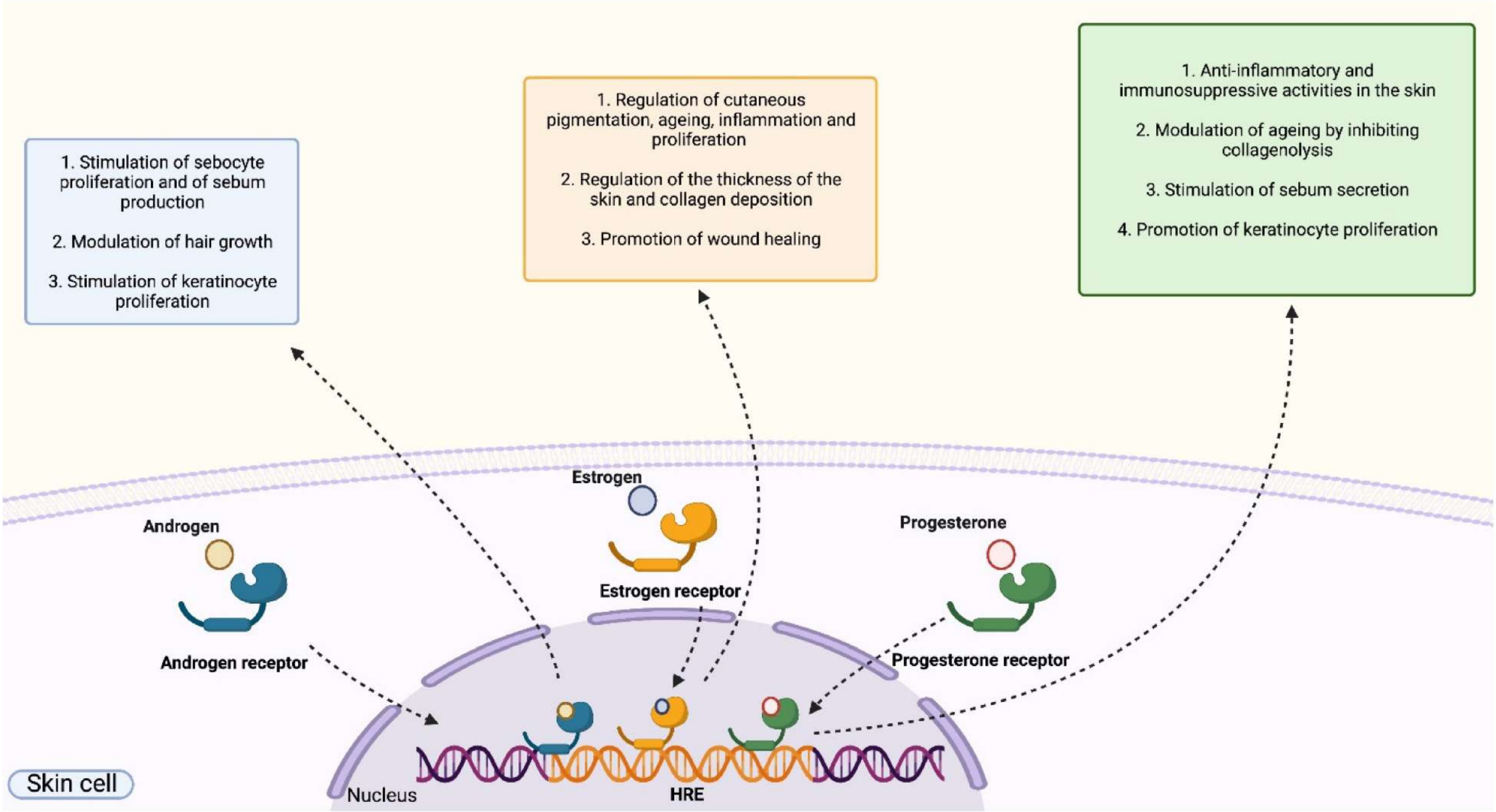


- Estrogen treatment inhibits lipoperoxides and caspase 3 and 8 associated with oxidative stress and apoptosis in aged keratinocytes
- Estrogen also mitigates mitochondrial dysfunction, which is linked to age-related skin deterioration
- Studies also show that estrogen and phytoestrogens influence epigenetic modifications, preserving the integrity of the genome and reducing the accumulation of age-related changes
- Estrogen helps maintain telomere length by regulating telomerase activity, and inhibits cellular senescence, thus preserving cellular function and promoting skin rejuvenation

Targeting estrogen signaling and biosynthesis for aged skin repair. Front. Physiol., 31 October 2023 Sec. Skin Physiology Volume 14 - 2023

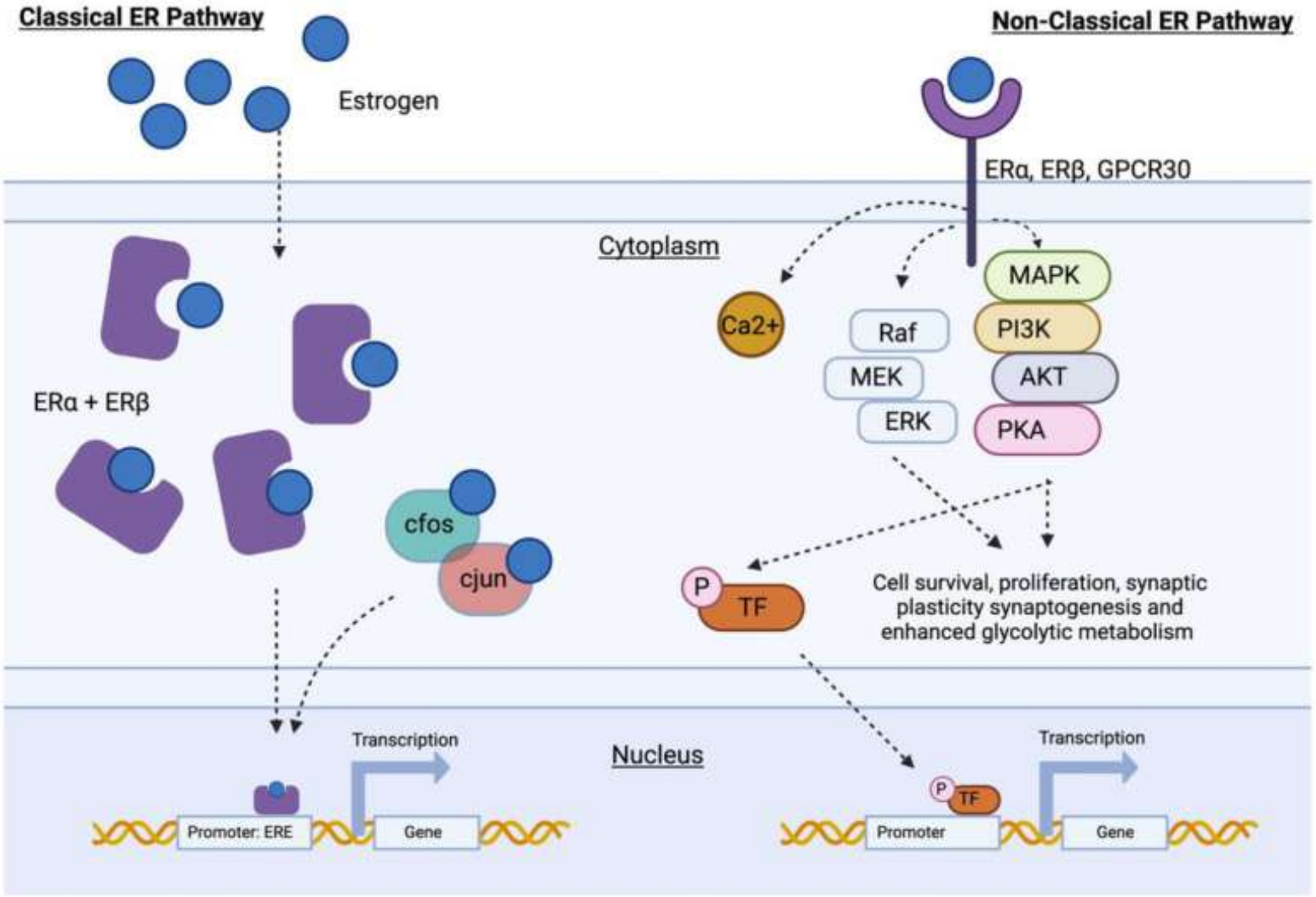


Targeting estrogen signaling and biosynthesis for aged skin repair. Front. Physiol., 31 October 2023 Sec. Skin Physiology Volume 14 - 2023



Unraveling the Role of Sex Hormones on Keratinocyte Functions in Human Inflammatory Skin Diseases. Int. J. Mol. Sci. 2022, 23(6), 3132

Schematic diagram showing the proposed mechanism of classical and non-classical estrogenic action

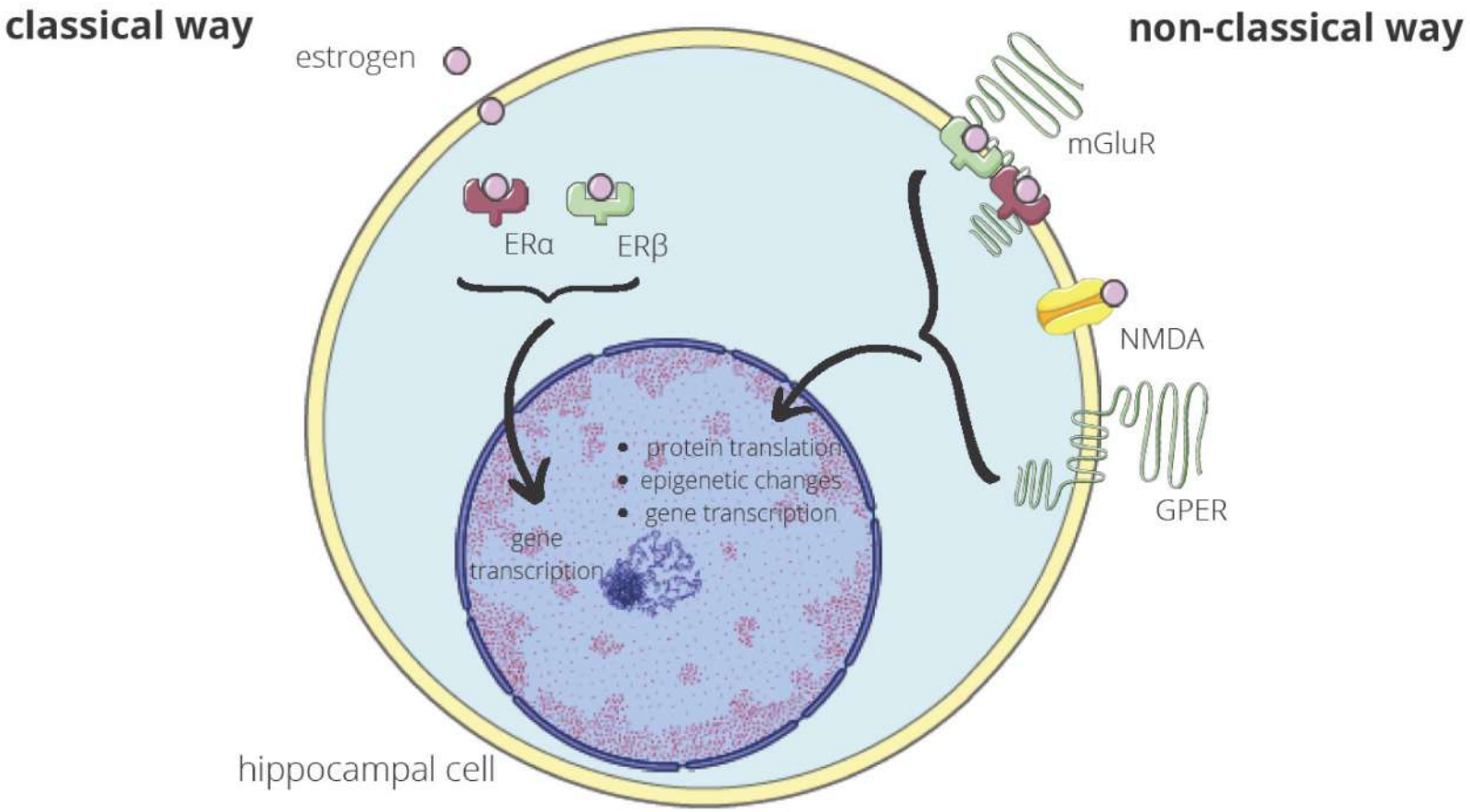


Activation of the classical ER pathway (left) involves nuclear ER found in the cytoplasm directly binding to EREs within target gene promotor regions. Transcription factors, such as c-fos and c-jun, facilitate binding of the nuclear ER to begin gene transcription. The non-classical pathway (right) is facilitated through membrane-bound ER. Upon ligand binding, intracellular protein kinase cascades result in changes to the intracellular environment and activation of independent transcription factors. Abbreviations: ERα: estrogen receptor α; ERβ: estrogen receptor β; ERE: estrogen response element; ERK: extracellular regulated kinase; GPCR30: G protein-coupled receptor 1; MAPK: mitogen-activated protein kinase; PI3K: phosphatidylinositol 3-kinase/Akt signaling; PKA: protein kinase A; Raf/MEK: mitogen-activated ERK kinase signaling; TF: transcription factor.

HRT appears to be a potent and effective therapeutic option for protecting against AD in young women

Is Hormone Replacement Therapy a Risk Factor or a Therapeutic Option for Alzheimer's Disease?. Int J Mol Sci. 2023 Feb; 24(4): 3205. Published online 2023 Feb 6

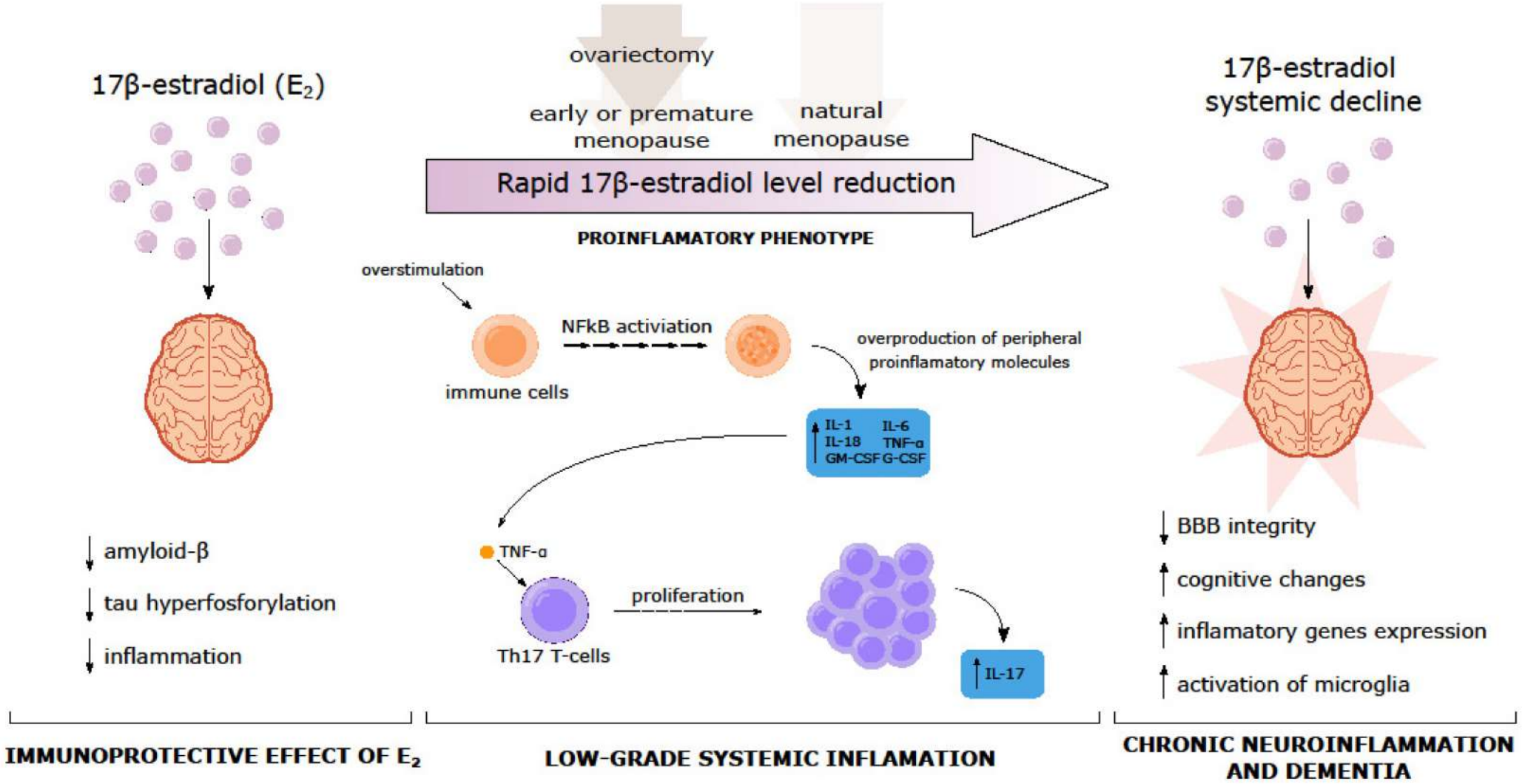
Effect of estrogen on hippocampal cells



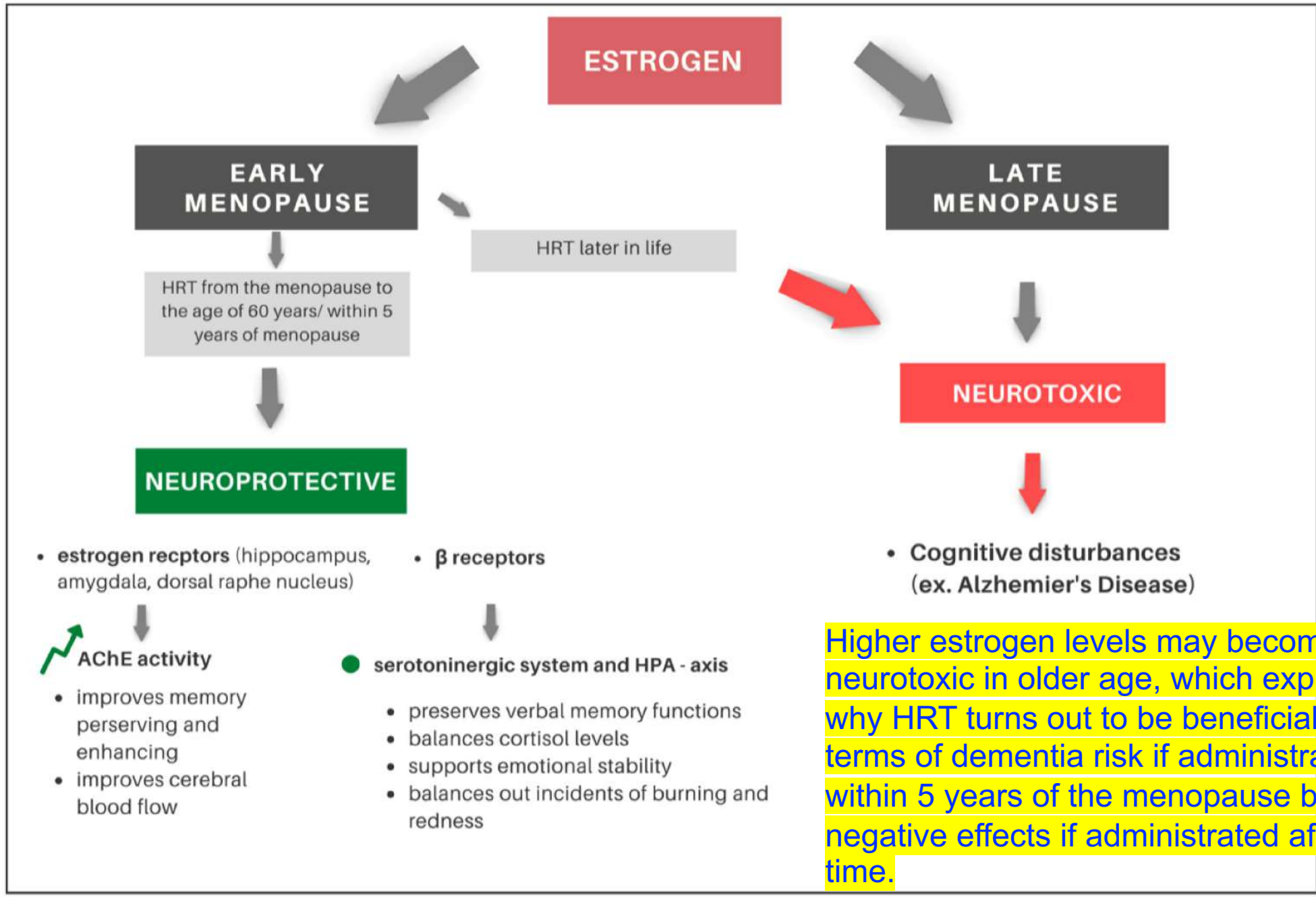
Estrogen interacts with the hippocampal cells through a classical and non-classical way. In the classical one, estrogen binds to ERα and ERβ in the cytoplasm. The estrogen-receptor complexes interact then with the genome, inducing gene transcription. The non-classical way takes place near or in the plasma membrane. Metabotropic glutamate receptor 1a (mGluR1a) is influenced by ERα and ERβ with the bound estrogen, the N-methyl-D-aspartate receptor (NMDA), by estrogen alone and GPER by estrogen indirectly. The receptors induce cell signaling, resulting in protein translation, epigenetic changes, or gene expression. These molecular processes are crucial for memory formation in the hippocampus

Cognitive Decline in Early and Premature Menopause. Int. J. Mol. Sci. 2023. Published: 31 March 2023

Relationship between systemic E2 decline, chronic inflammation, cognitive changes, and dementia

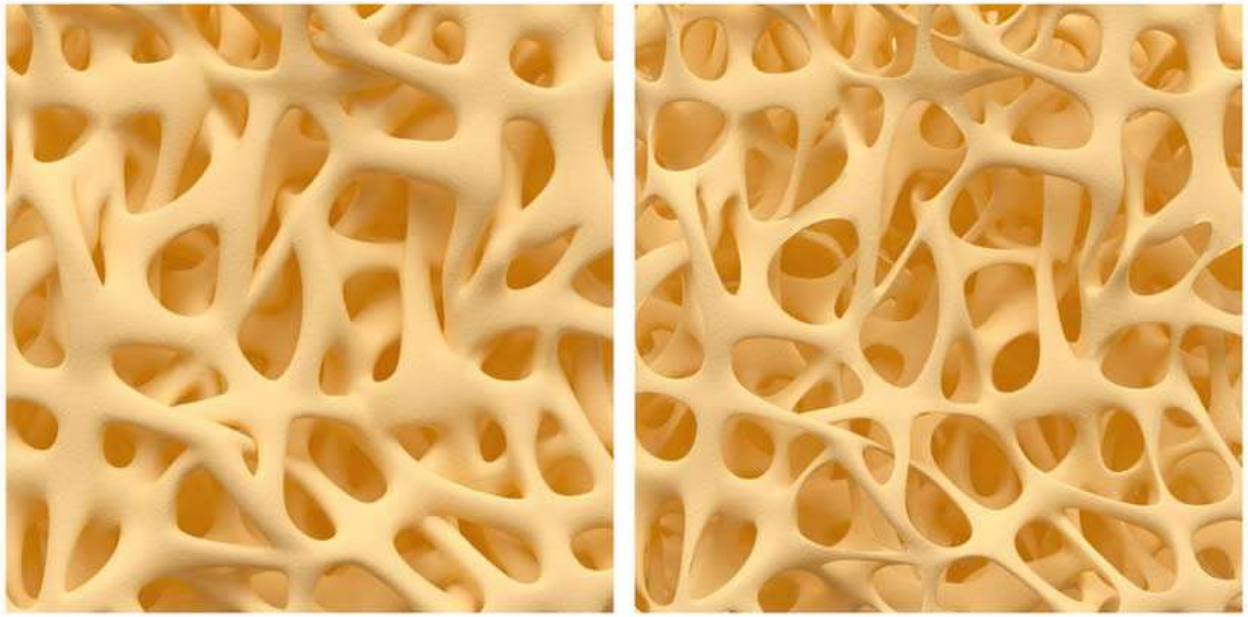


Cognitive Decline in Early and Premature Menopause. Int. J. Mol. Sci. 2023. Published: 31 March 2023

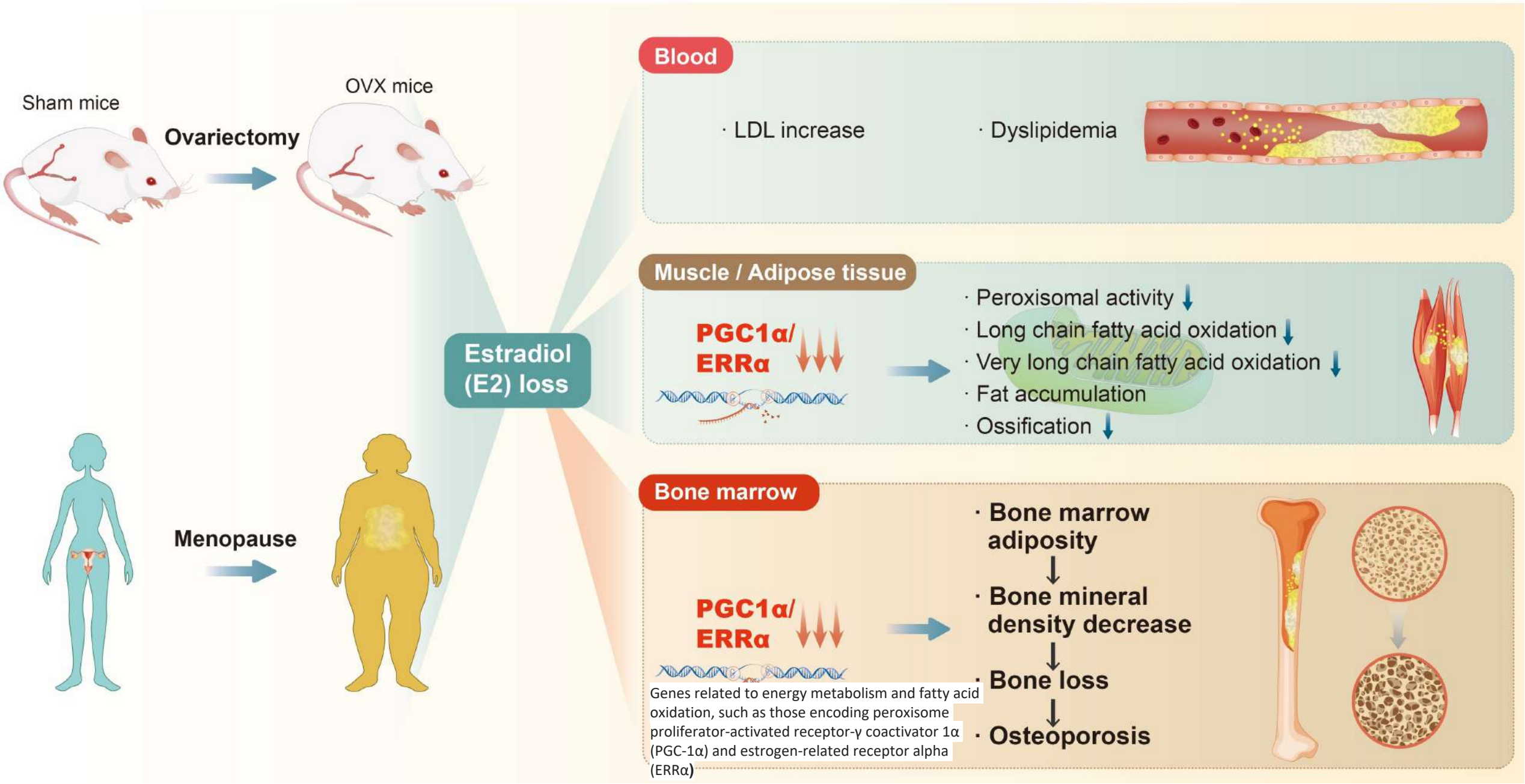


Higher estrogen levels may become neurotoxic in older age, which explains why HRT turns out to be beneficial in terms of dementia risk if administrated within 5 years of the menopause but has negative effects if administrated after that time.

Cognitive Decline in Early and Premature Menopause. Int. J. Mol. Sci. 2023. Published: 31 March 2023

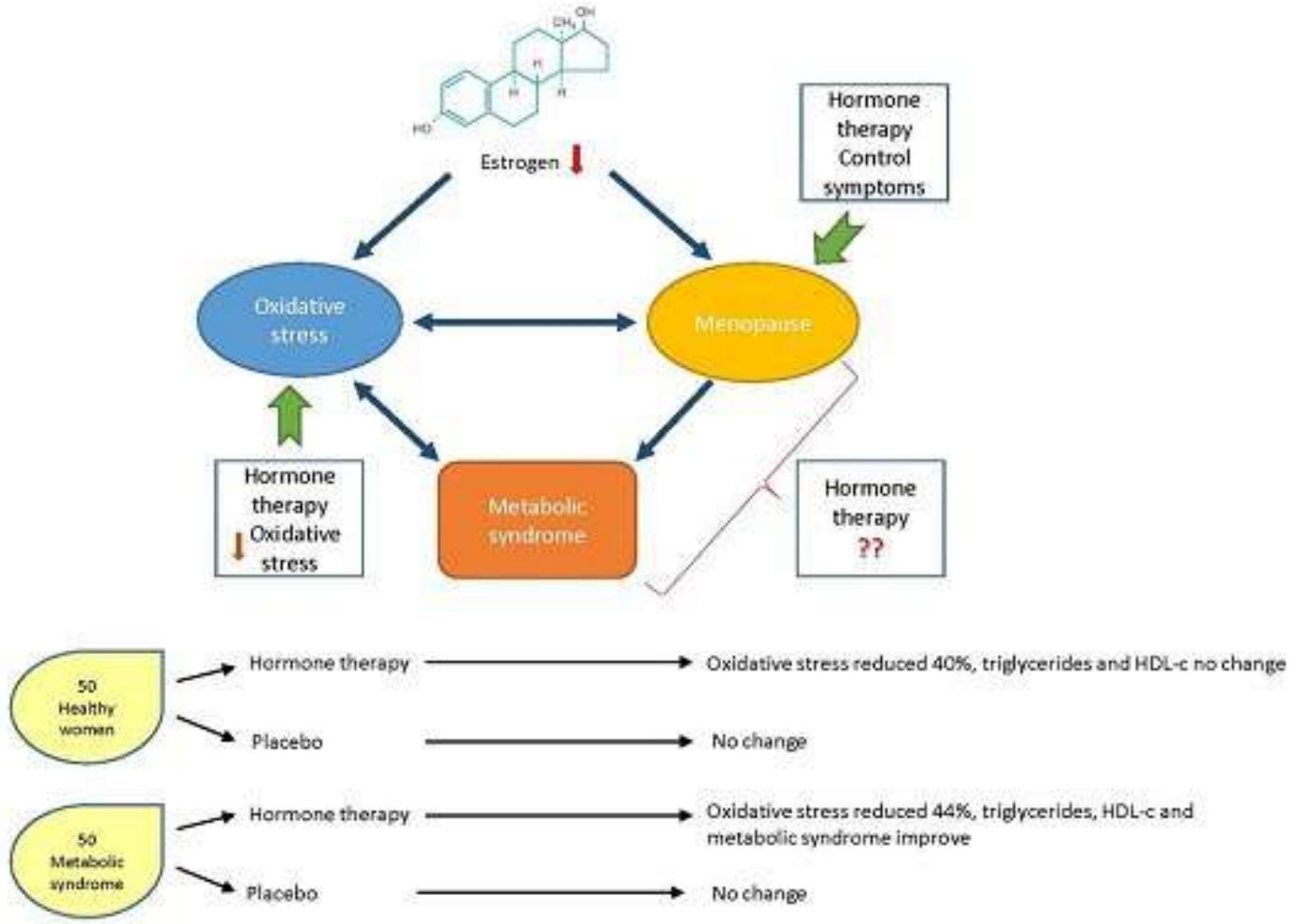


normal osteoporosis



Common Regulators of Lipid Metabolism and Bone Marrow Adiposity in Postmenopausal Women. Pharmaceuticals 2023, 16(2). Published: 20 February 2023

HT improves the lipid and oxidative alterations that occur in MetS in postmenopausal women, supporting the proposal that HT has an antioxidant effect, thus could be used as a complementary treatment option for improve MetS and OS: option for improve MetS and OS.

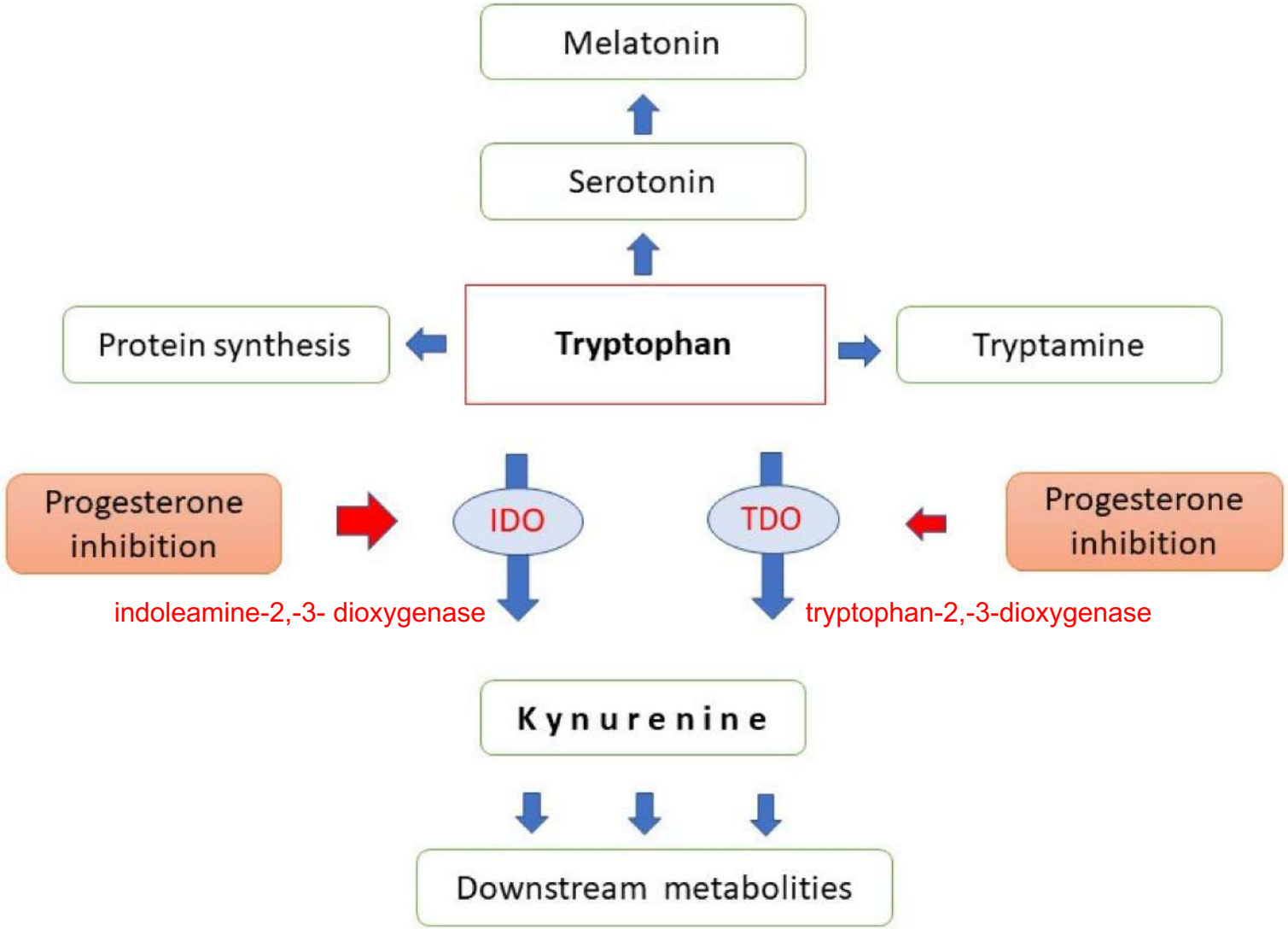


Hormone therapy (estradiol valerate & medroxiprogesterone) improves oxidative stress in postmenopausal women with metabolic syndrome to 6 months follow up

The characteristic metabolic changes of MetS worsen due to the endocrine changes that occur during aging, particularly in women after menopause. In this regard, it has been reported that as a result of the decrease in estrogen level, an increase in abdominal adiposity and a decrease in energy expenditure occurs; this causes an increase in the cholesterol and TG concentration, in addition to a significant increase in glucose and insulin concentrations, which may explain the increased frequency of MetS and the risk of cardiovascular disease and death during the post-menopausal period.

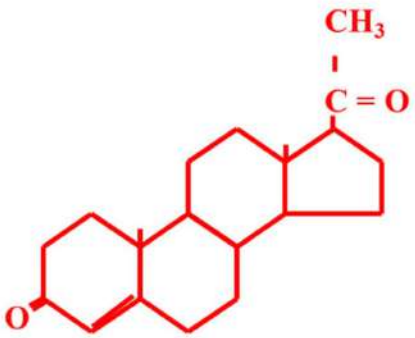
Effects of Hormone Therapy on Oxidative Stress in Postmenopausal Women with Metabolic Syndrome. Int. J. Mol. Sci. 2016, 17(9), 1388

Major pathways of tryptophan metabolism



Key to Life: Physiological Role and Clinical Implications of Progesterone. Int. J. Mol. Sci. 2021, 22(20), 11039

Is progesterone really a key to life?



Progesterone

Progesterone is a key to:
Reproduction
Birth control
Female and male secondary sexual characteristics
Salt and water balance, regulation of blood pressure
Stress adaptation
Thermoregulation
Protection against tumors
Neurogenesis and neuroprotection

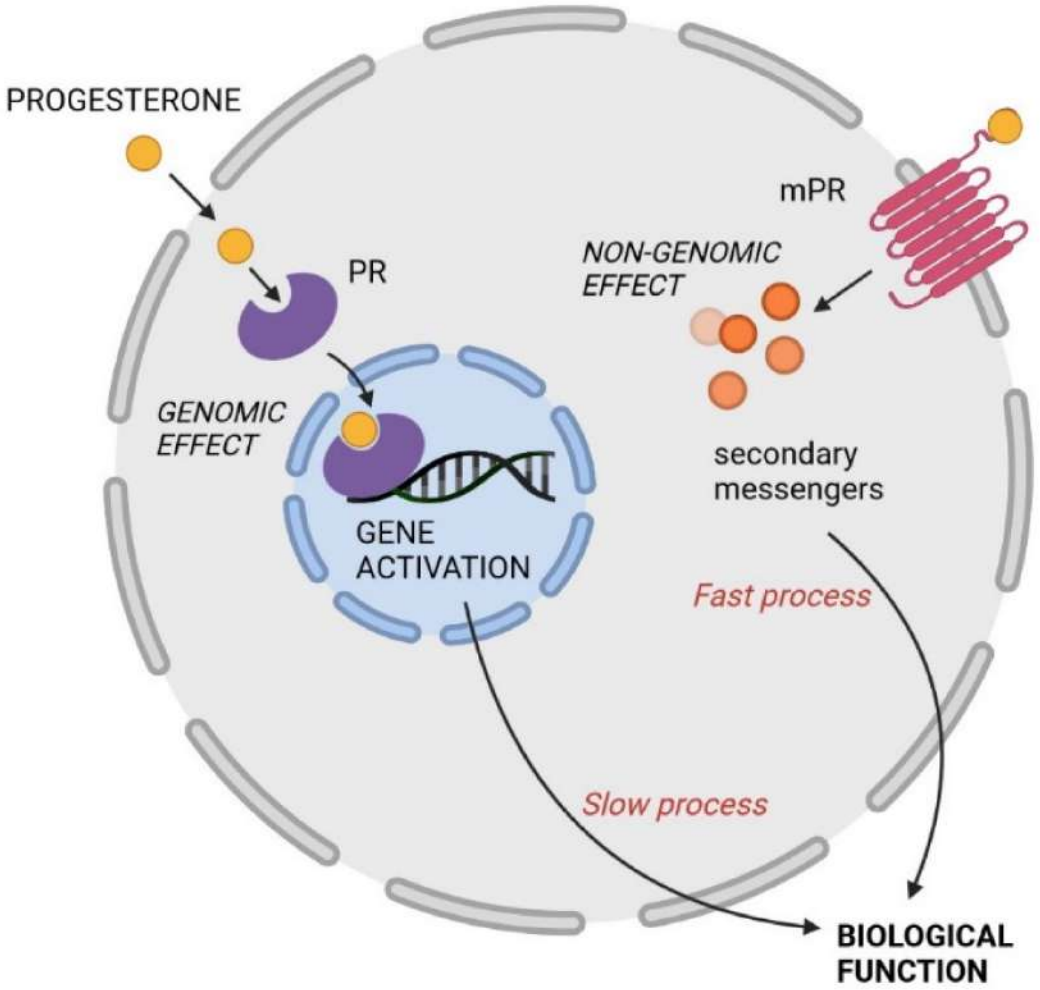
- Progesterone is an essential steroidogenetic precursor of other gonadal and non-gonadal hormones such as aldosterone, cortisol, estradiol and testosterone. These hormones are responsible for innumerable functions such as sodium conservation in the kidney, regulation of blood pressure, response to stress and low blood-glucose concentration, development of female and male secondary sexual characteristics.

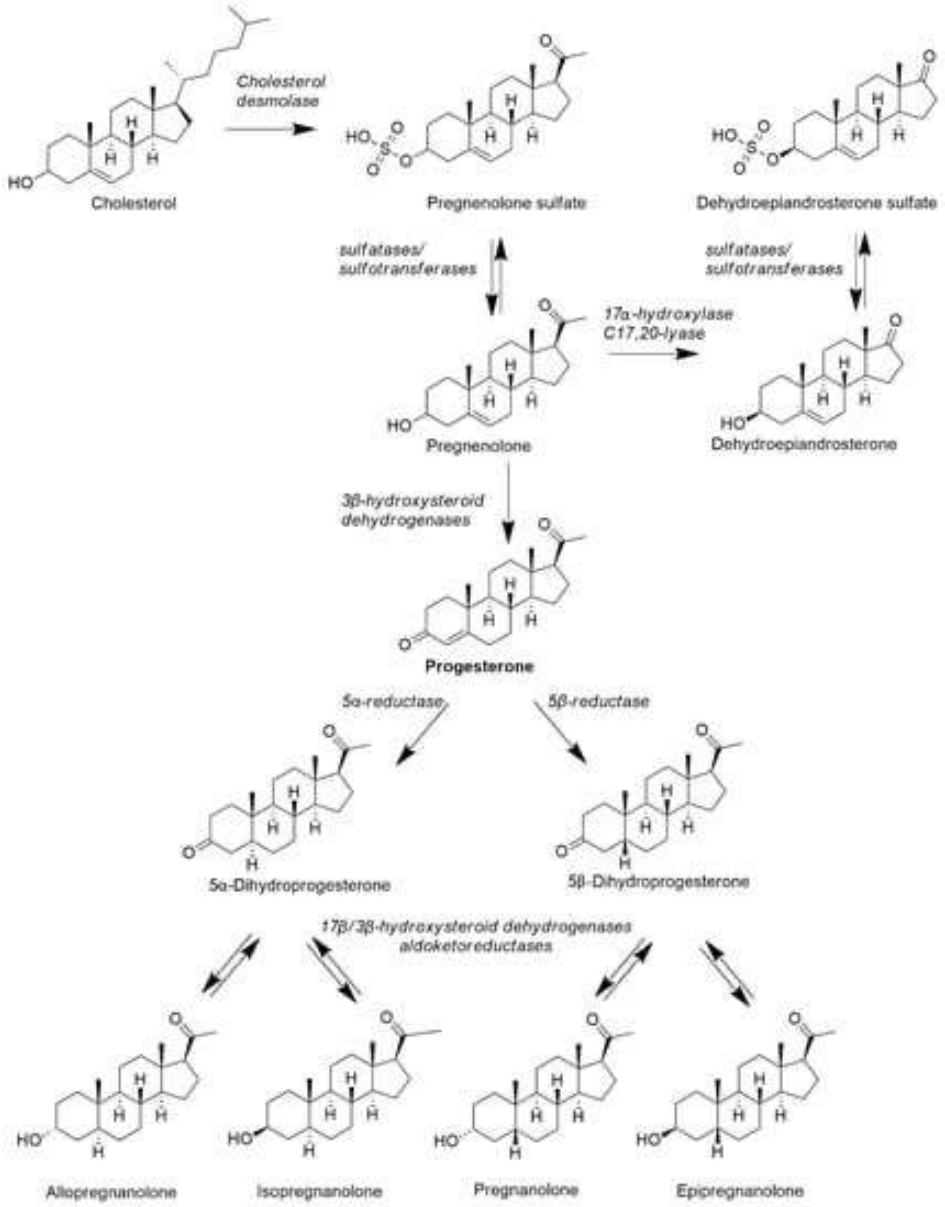
- Progesterone also plays an important role in the nervous system. Its neurogenic effect is essential for normal brain development in fetuses, while the neuroprotective effect of progesterone improves the patient's survival after traumatic brain injury.

- Progesterone has an important role in immune response and also in the prevention and treatment of various cancers.

Key to Life: Physiological Role and Clinical Implications of Progesterone. Int. J. Mol. Sci. 2021, 22(20), 11039

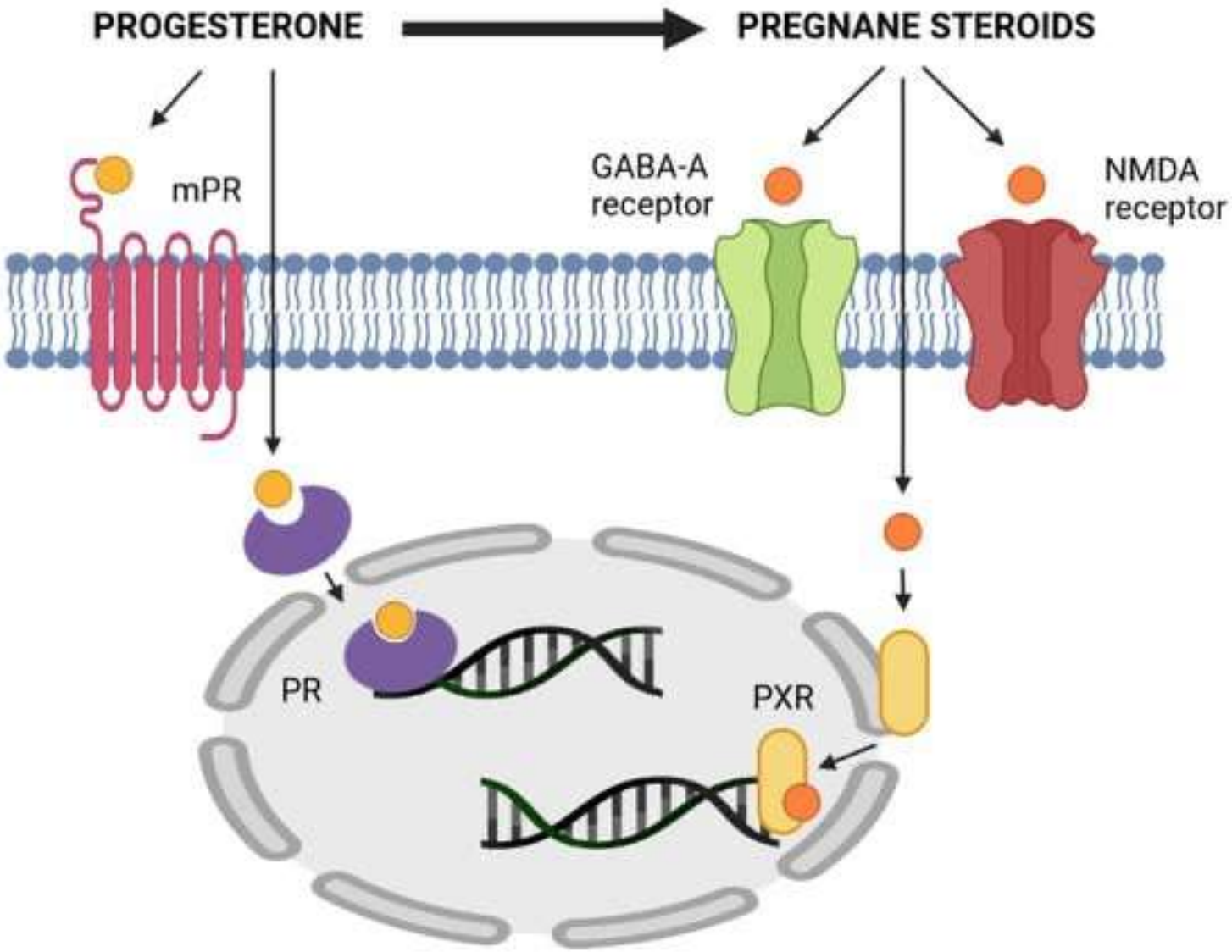
The steroidogenic pathway leading to progesterone and its neuroactive metabolites (pregnane steroids)





Progesterone: A Steroid with Wide Range of Effects in Physiology as Well as Human Medicine. Int. J. Mol. Sci. 2022, 23(14), 7989

The action on progesterone and its neuroactive metabolites



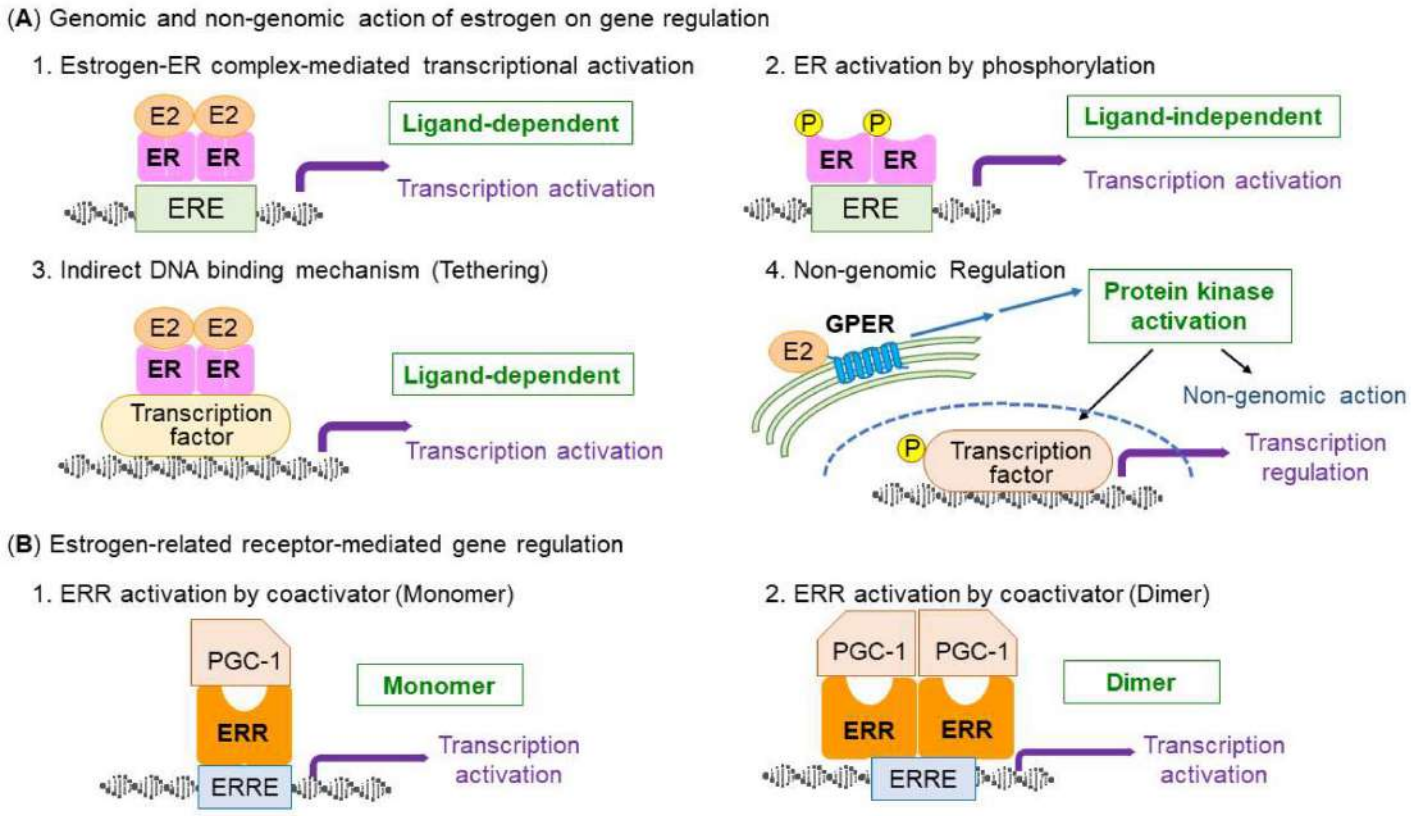
For the positive modulation of $GABA_A$-r, allopregnanolone and isopregnanolone are positive modulators of $GABA_A$-r . These substances act by increasing the frequency and opening time of the chloride channels that are associated with $GABA_A$-r. The influx of chloride into nerve cells causes a decrease in their activity. In general, they are thus neuroinhibitors and exhibit sedative, hypnotic, anesthetic, anxiolytic and anticonvulsant properties.

Pregnanolone and epipregnanolone) and conjugates of all pregnane steroids [31] act as negative $GABA_A$-r modulators and thus activate neurons.

Positive modulators of NMDA-r increase the influx of calcium ions into the cell and thus cause neuroactivation, while negative modulators act oppositely. Positive modulators of NMDA-r are polar conjugates of 5α-pregnane isomers (sulphates) [**102**], while negative modulators of NMDA-r are polar conjugates of 3β-pregnane isomers allopregnanolone and isopregnanolone.

Progesterone: A Steroid with Wide Range of Effects in Physiology as Well as Human Medicine. Int. J. Mol. Sci. 2022, 23(14), 7989

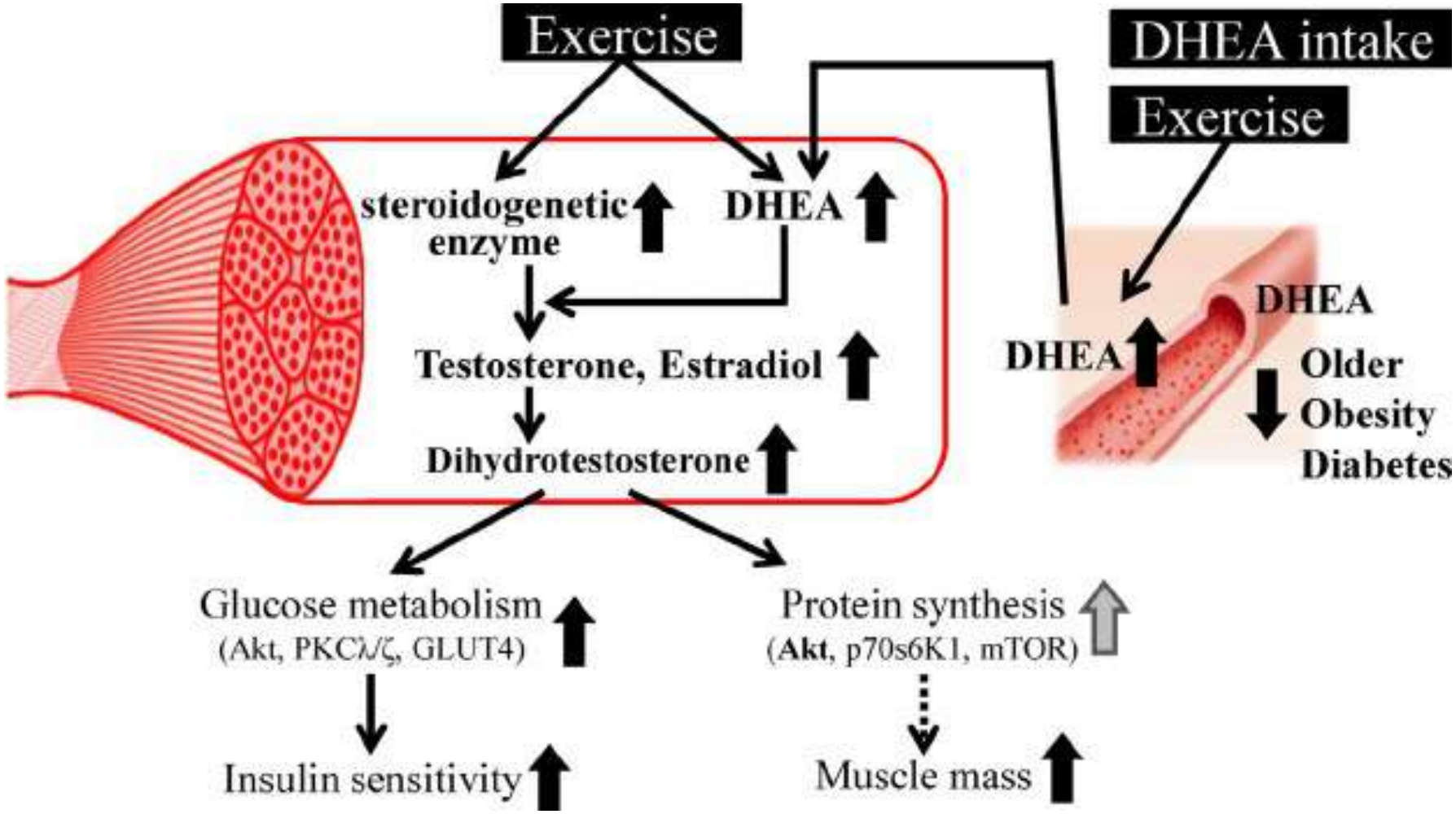
Classical nuclear estrogen receptors (ERs) and membrane-type G protein-coupled estrogen receptor (GPER)



Classical nuclear estrogen receptors (ERs) and membrane-type G protein-coupled estrogen receptor (GPER). (A) Endogenous estrogens, including 17β-estradiol (E2), bind to two types of nuclear ERs (i.e., ERα, ERβ) or membrane-type GPER, which is predominately localized to the intracellular membranes. Estrogen activates nuclear ERs, inducing the dimerization of the receptors and binding of receptors to estrogen responsive elements (EREs) in the genome. Alternatively, ERs bind with other classes of transcription factors through protein–protein interactions and the complexes bind to the genome. GPER stimulates the activation of protein kinases (i.e., MAPK and PI3K/Akt), which mediates nongenomic actions of estrogen and contributes to transcription factor regulation. (B) Schematic model for transcriptional regulation by ERRs and its coactivator PGC-1. ERRs preferentially bind to estrogen-related receptor responsive elements (ERREs) in the genome as a monomer or a dimer. PGC-1 is a necessary coactivator for the activation of ERR transcription activity.

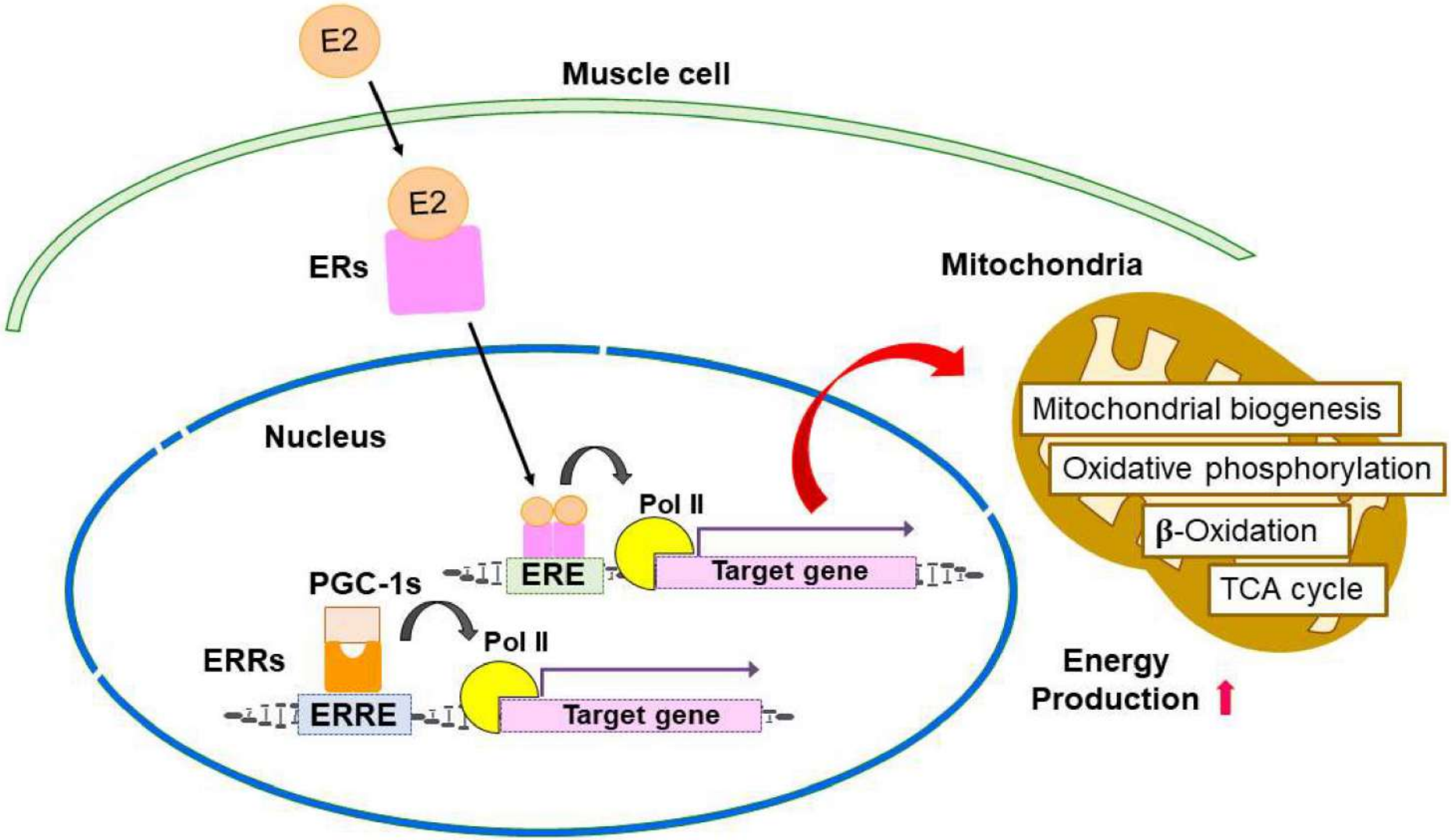
Roles of Estrogen, Estrogen Receptors, and Estrogen-Related Receptors in Skeletal Muscle: Regulation of Mitochondrial Function. Int. J. Mol. Sci. 2023, 24(3), 1853

Schematic illustration of the effect of exercise on muscle steroidogenesis, potentially resulting in prevention and treatment of life-related diseases



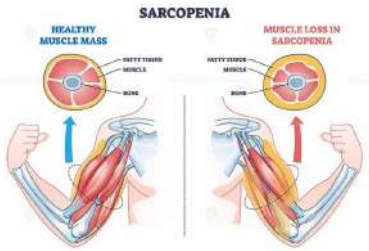
Exercise and sex steroid hormones in skeletal muscle. April 2014. The Journal of Steroid Biochemistry and Molecular Biology 145

ERs and ERRs regulate muscle functions and mitochondrial metabolism



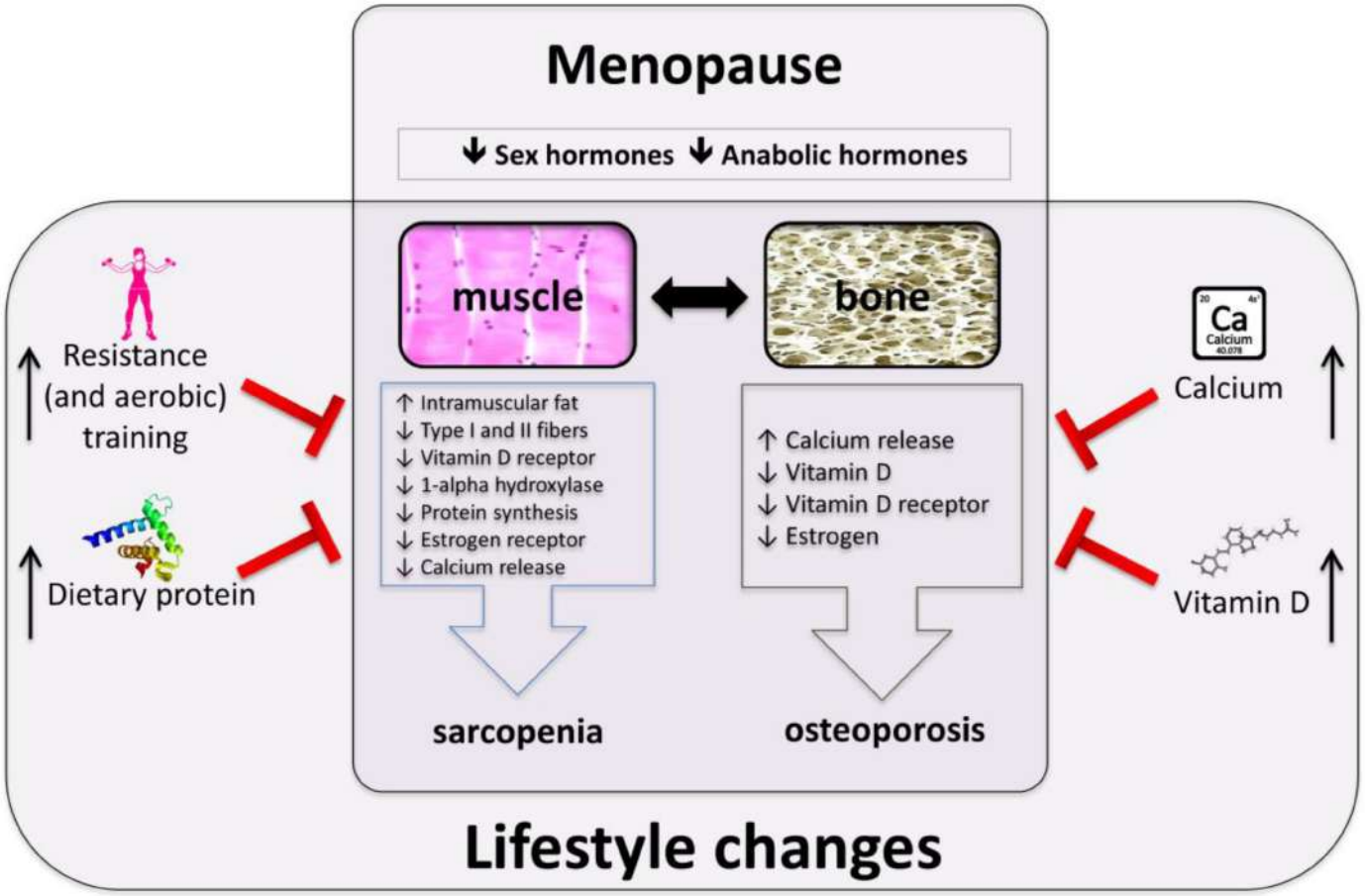
Roles of Estrogen, Estrogen Receptors, and Estrogen-Related Receptors in Skeletal Muscle: Regulation of Mitochondrial Function. Int. J. Mol. Sci. 2023, 24(3), 1853

Decreased Neuromuscular Function and Muscle Quality along with Increased Systemic Inflammation and Muscle Proteolysis Occurring in the Presence of Decreased Estradiol and Protein Intake in Early to Intermediate Post-Menopausal Women



Menopause causes a reduction in estradiol (E2) and may be associated with neuromuscular degeneration. Compared to pre-menopausal (PRE-M) women, this study sought to determine dietary protein intake and whether lower levels of circulating E2 in post-menopausal women (POST-M) were occurring alongside increased levels of biomarkers of axonal and neuromuscular junction degeneration (NMJ), inflammation, muscle protein degradation, and reduced indices of muscle quality and performance. Employing a cross-sectional design, PRE-M (n = 6) and POST-M (n = 6) dietary analysis data were collected and participants then donated a blood and urine sample followed by assessments for body composition, motor unit activation, and muscle performance. Independent group t-tests were performed to determine differences between groups ($p \leq 0.05$). In POST-M women, E2, motor unit activity, muscle quality, and muscle performance were significantly less than those for PRE-M women; however, the levels of c-terminal fragment of agrin, tumor necrosis factor-α, and urinary titin were significantly greater ($p < 0.05$). POST-M women were also shown to be ingesting fewer total calories and less protein than PRE-M ($p < 0.05$). Reduced E2 and dietary protein intake in POST-M women occurs in conjunction with increased levels of biomarkers of NMJ degradation, inflammation, and muscle proteolysis, which may be associated with reduced motor unit activation and muscle quality.

Nutrients 2024, 16(2), 197; https://doi.org/10.3390/nu16020197 Published: 7 January 2024



Because muscle tissue is important not only for locomotion, but also for thermoregulation and whole-body metabolism, the menopause-related reductions in muscle mass may represent the onset of widespread negative effects on women's health.

Muscle and Bone Health in Postmenopausal Women: Role of Protein and Vitamin D Supplementation Combined with Exercise Training. Nutrients 2018, 10(8), 1103

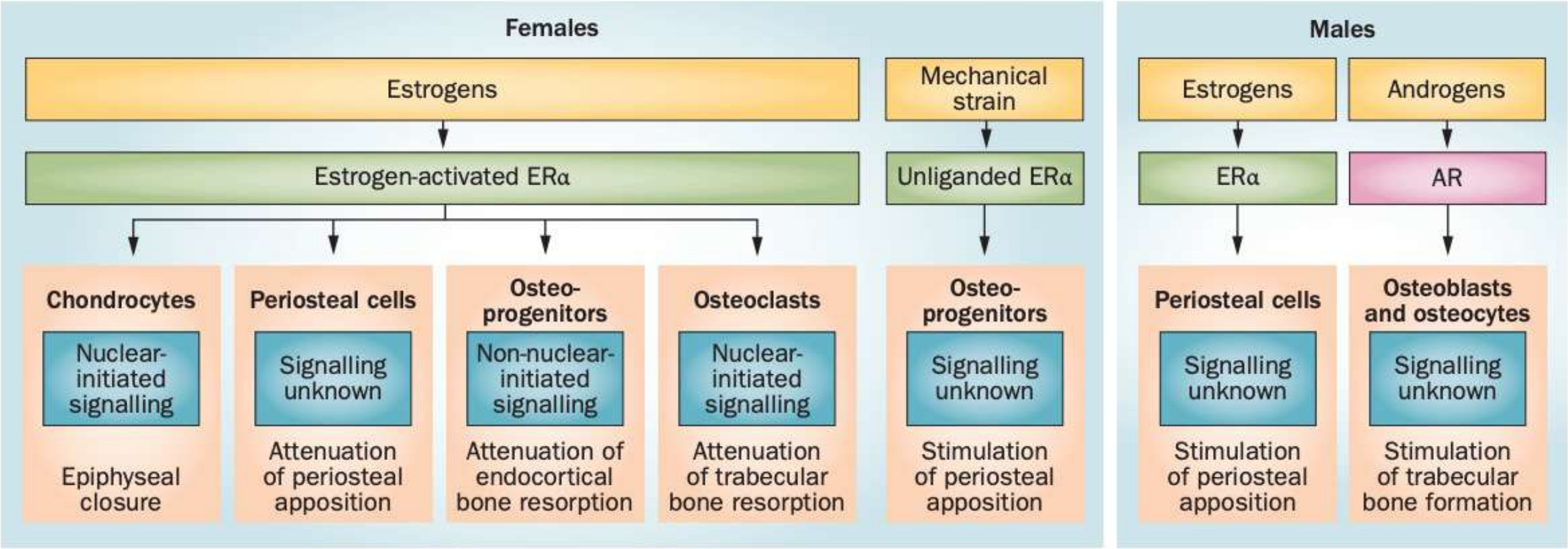
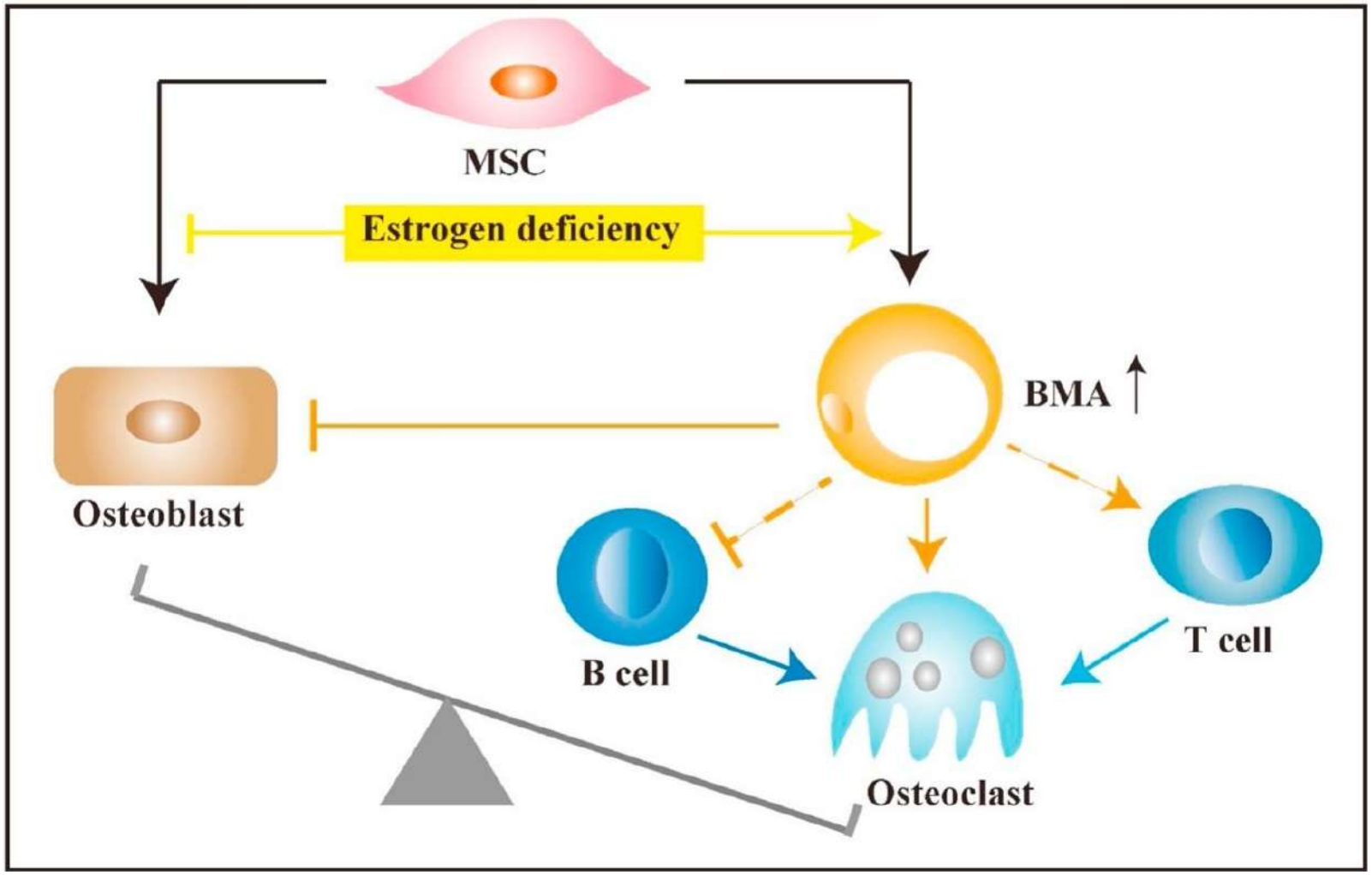


Figure 3 | Function and signalling mechanisms of ERα and AR in female and male mammals. Effects on different cell types were determined using mouse models of cell-specific deletions. Non-nuclear-initiated signalling mechanisms were elucidated using cascade-selective estrogenic compounds.

The role of estrogen and androgen receptors in bone health and disease. Nature Reviews Endocrinology volume 9, pages699–712 (2013)

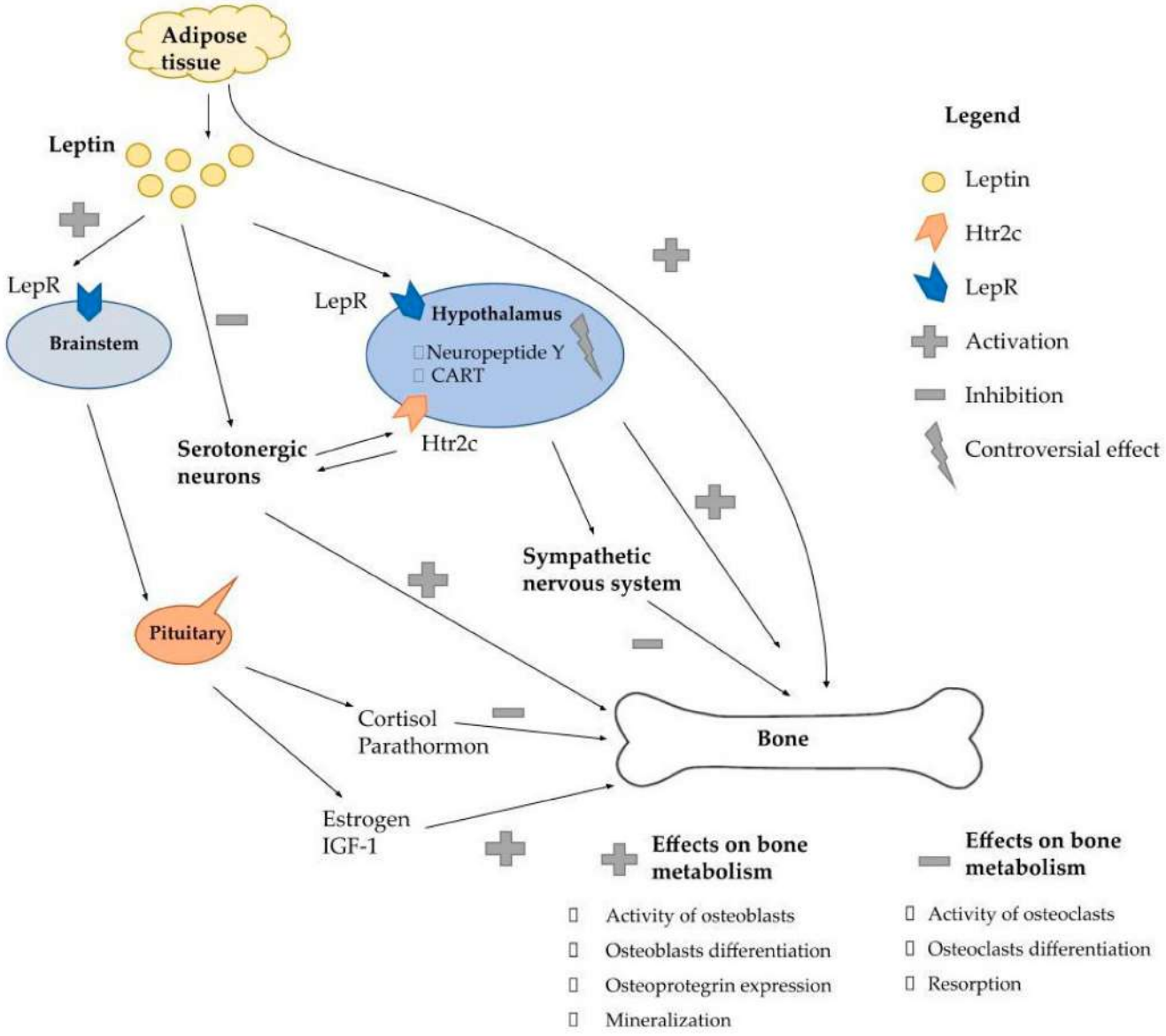
Abnormal expansion of marrow adipose tissue (MAT) plays a crucial role in the onset and progression of PMOP

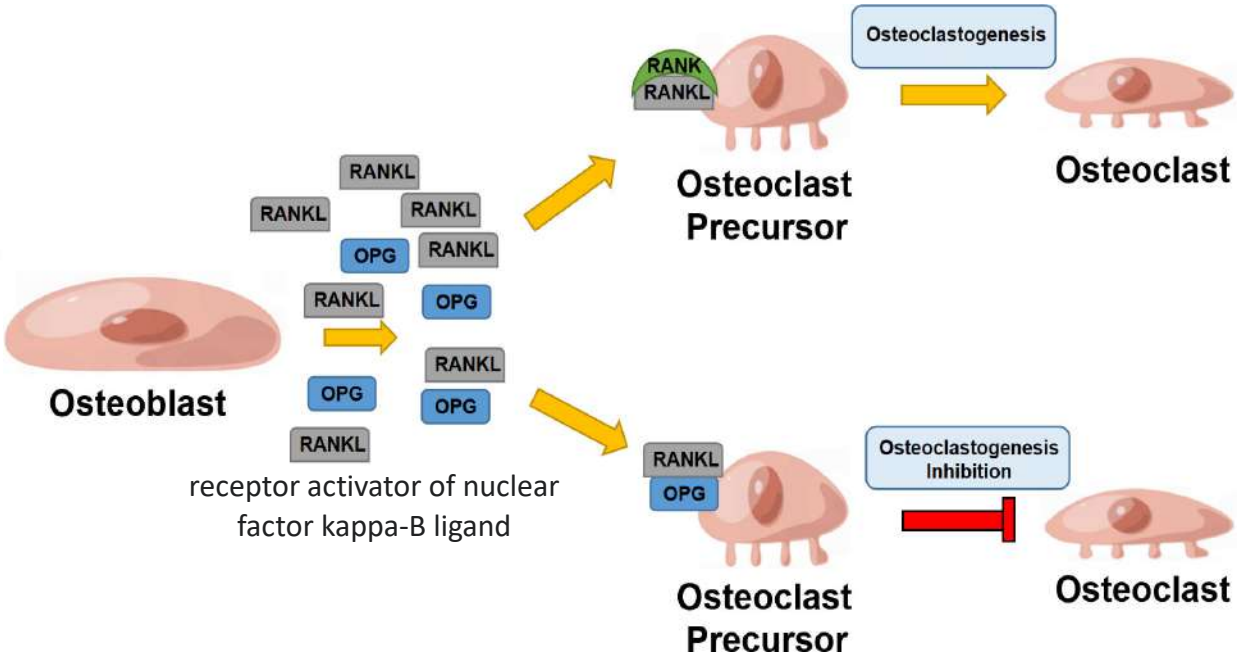


MAT expansion induced by estrogen withdrawal has been recognized to exert dual effects involving the inhibition of bone formation and the promotion of bone resorption, which disrupts skeletal homeostasis and leads to bone loss. Furthermore, MAT as an endocrine organ can affect bone remodeling through both its intrinsic properties and indirect regulation of hematopoiesis.

MAT directly affects bone remodeling by its intrinsic properties as well as its secretion of adipokines and cytokines. It also indirectly influences bone mass via the negative regulation of hematopoiesis.

The relationship between bone marrow adipose tissue and bone metabolism in postmenopausal osteoporosis. ELSEVIER Cytokine & Growth Factor Reviews Volume 52, April 2020, Pages 88-98

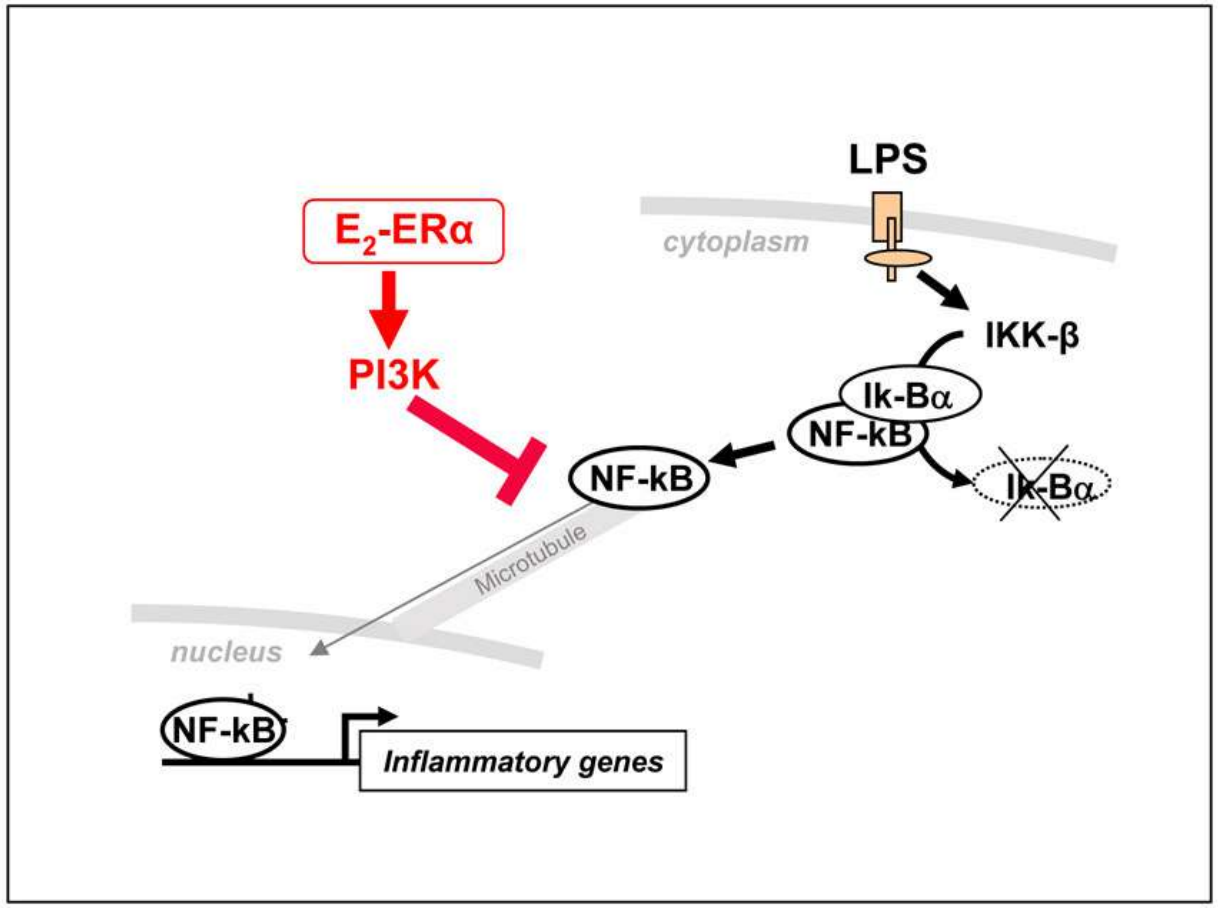




The osteoblast secretes the RANKL protein that binds to the RANK receptor, allowing the maturation of the osteoclast ; the osteoblasts also secrete osteoprotegerin , preventing the binding of RANKL to RANK and inhibiting the maturation of the osteoclast.

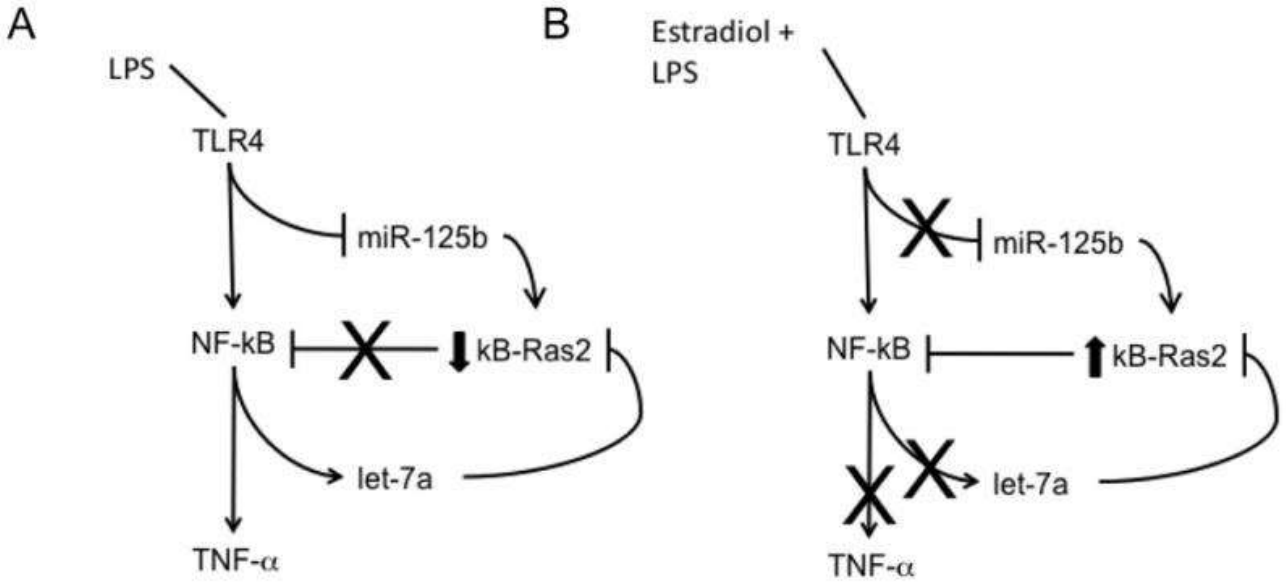
Bones and Hormones: Interaction between Hormones of the Hypothalamus, Pituitary, Adipose Tissue and Bone. Int. J. Mol. Sci. 2023, 24(7), 6840

Schematic representation of the mechanism of action of estradiol in microglia

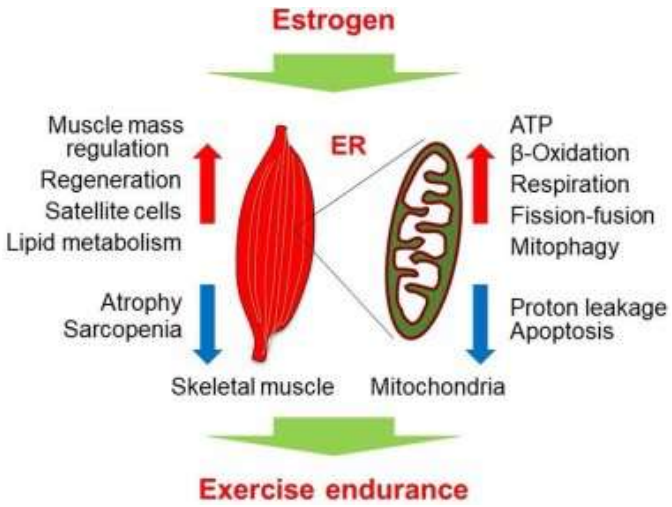


Front Neuroendocrinol. 2008 Oct; 29(4): 507–519.

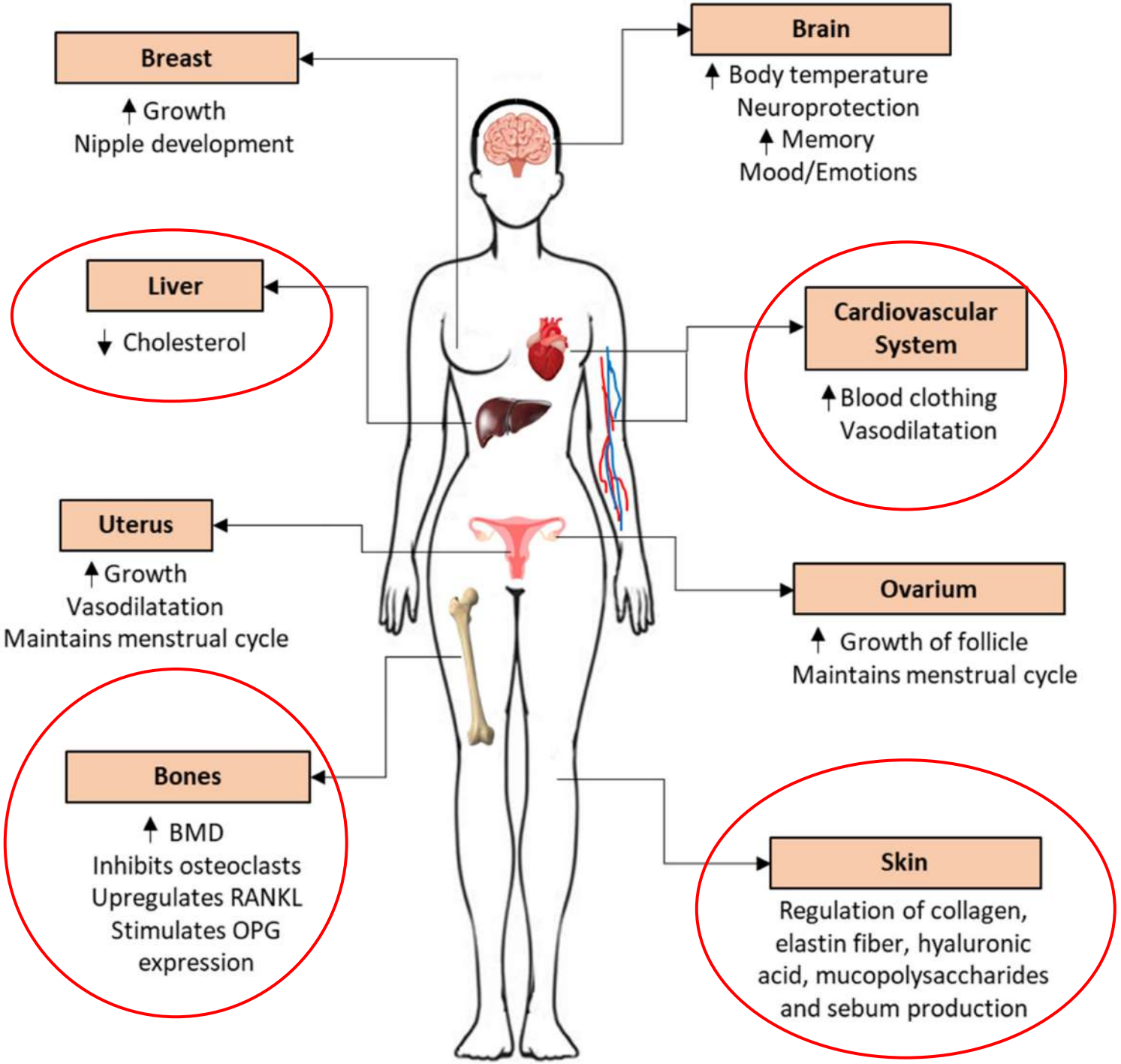
Proposed mechanism of estradiol regulation of NF-κB signaling in primary human macrophages



J Immunol. 2010 May 1; 184(9): 5029–5037



The Journal of Steroid Biochemistry and Molecular Biology
Volume 191, July 2019, 105375



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

Central nervous system

↑ Mood

↓ Anxiety

↓Depression

↑ Cognitive function

↑ Sexual function

Neuro protective

Skin

↑ Sebum production

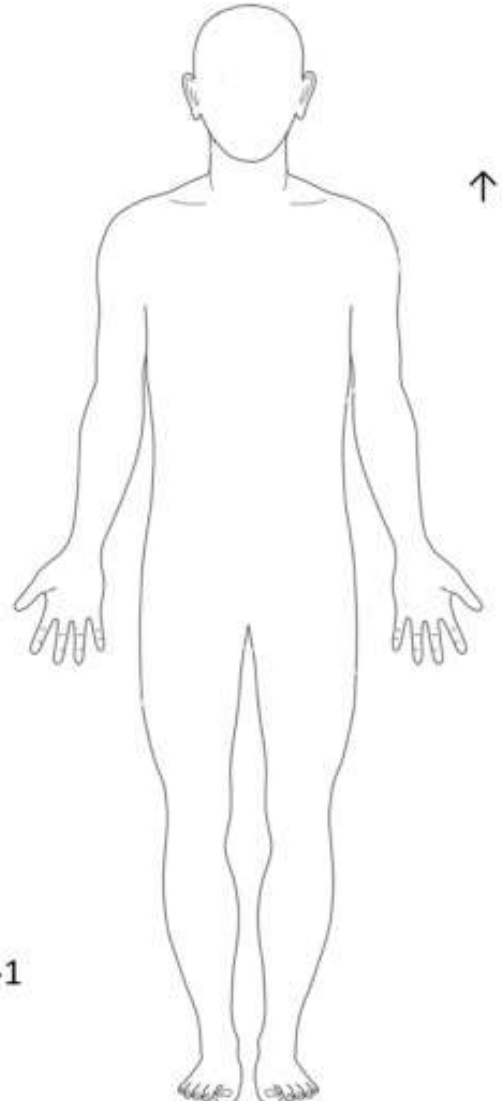
↑ Acne

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

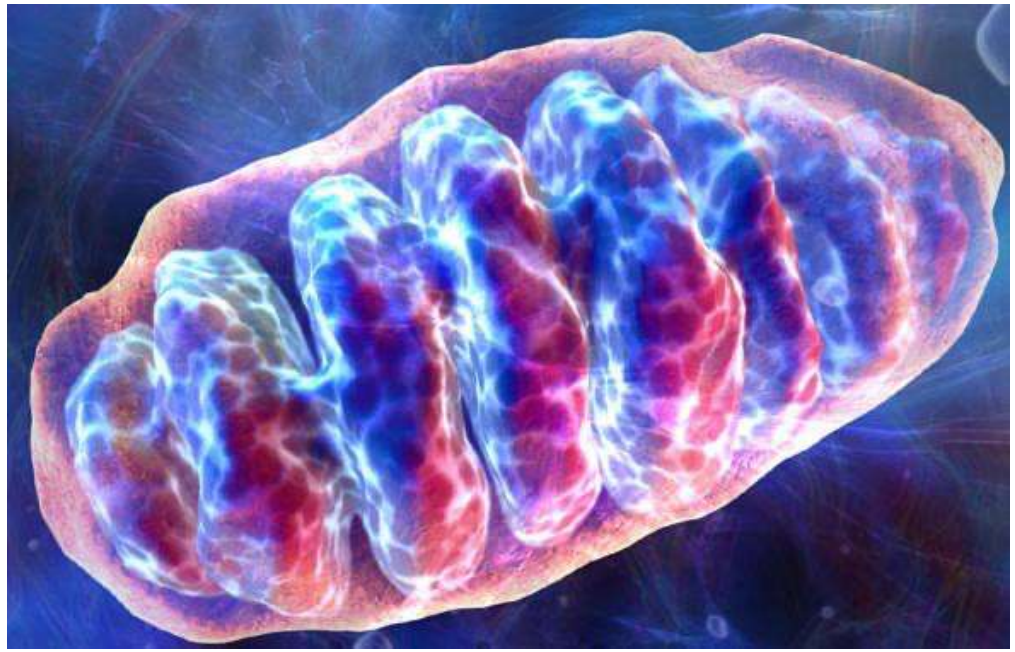
↓ Menopausal thermoregulation disturbances

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

Take Home Messages

How sexual hormones may slow down aging process after menopause

- Anti NFKB decreasing inflammation which is link to civilization diseases
- Mitochondria : oxydative stress, biogeneis, phosphorilation oxydative, B oxydation, energy production.




Thank you for your
attention !
Any questions ?