Menopause Problem Solving pt II

A Biogenetix Clinical Presentation

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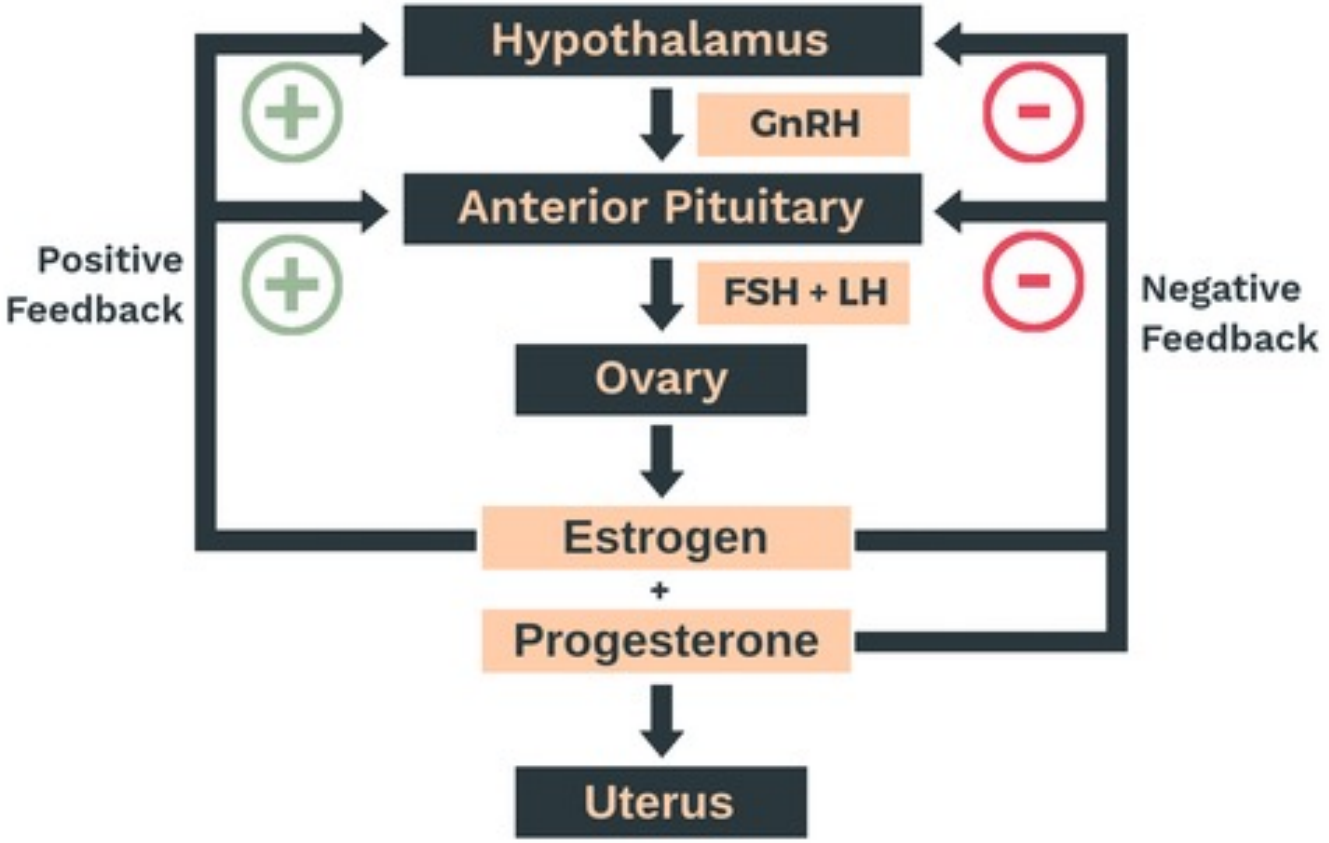
- *Information in this presentation is not intended to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Cycling Female Hormone Pathway

Day 12-14



Most of cycle

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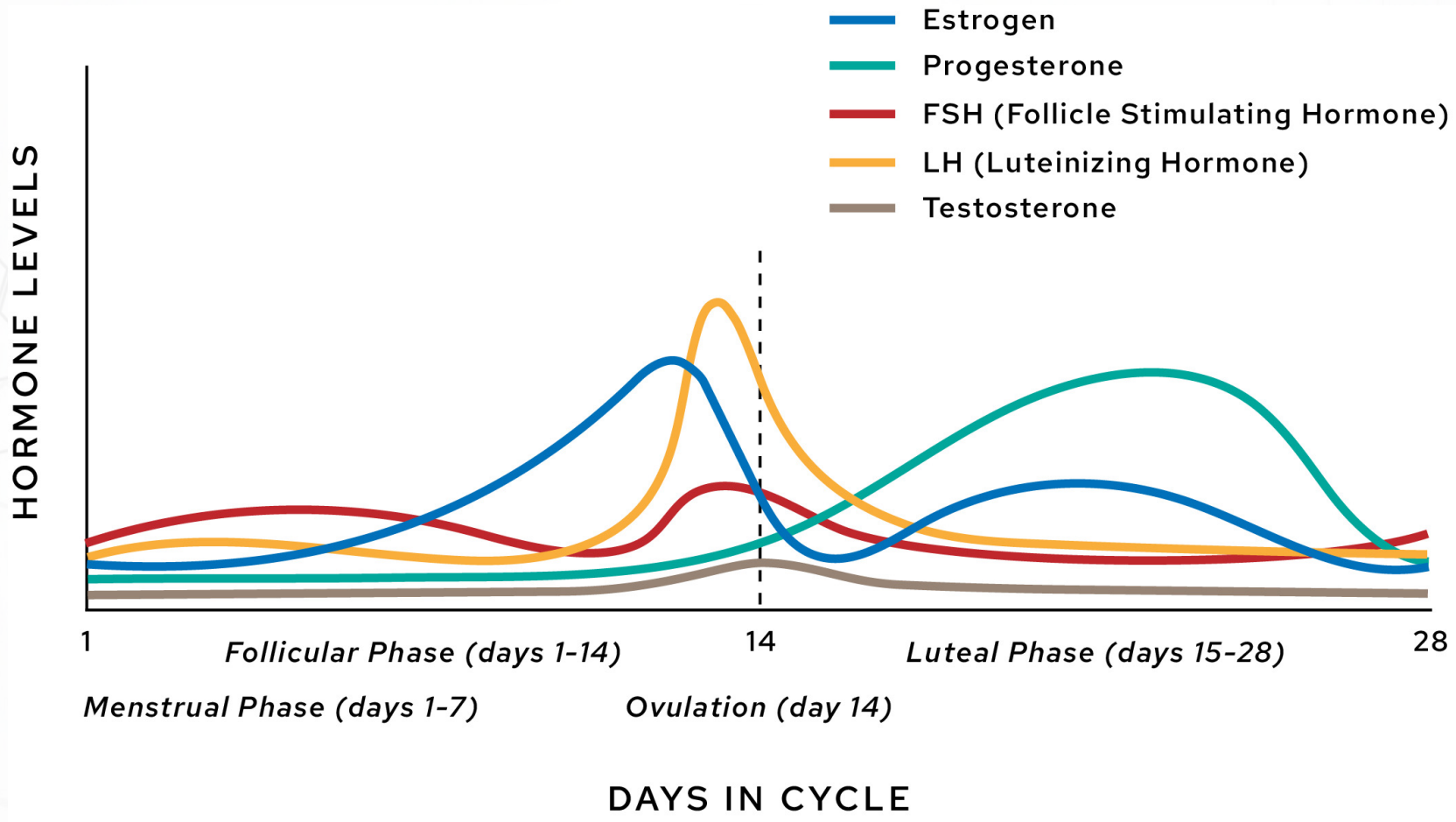
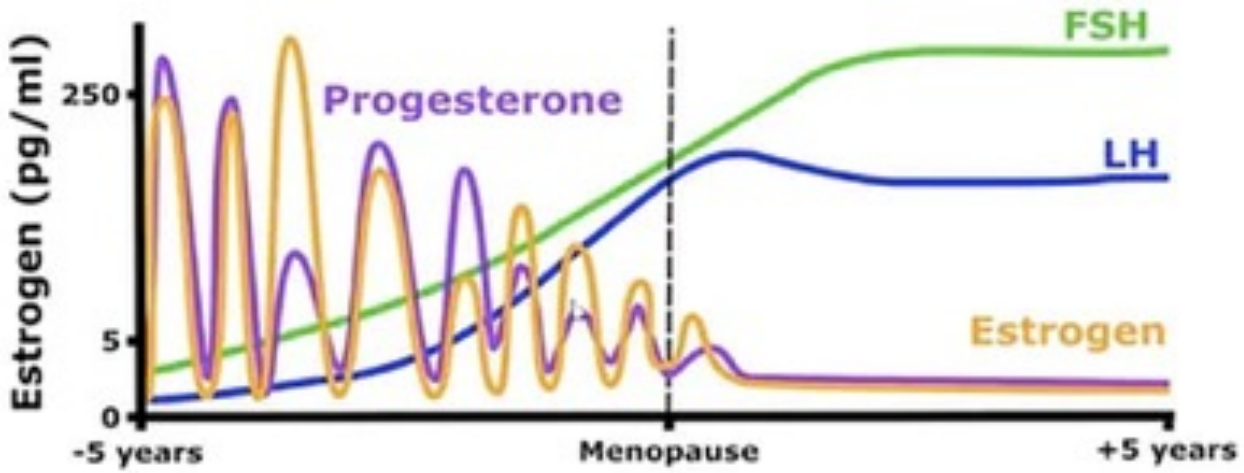


https://www.palmhealth.com/wp-content/uploads/2023/09/Female-Hormones.jpg

HORMONAL FLUCTUATIONS

In the years before and after menopause.



Chidi-Ogbolu N and Baar K (2019) Effect of Estrogen on Musculoskeletal Performance and Injury Risk. Front. Physiol. 9:1834.

> Eur Rev Med Pharmacol Sci. 2022 Apr;26(8):2975-2989. doi: 10.26355/eurrev_202204_28629.

Unopposed estrogens: current and future perspectives

M Montanino Oliva [1], R Gambioli, G Forte, G Porcaro, C Aragona, V Unfer

Affiliations + expand

Estrogens and progestogens act on female reproductive tissues in opposite ways. As they counteract each other actions, the correct balance between these two classes of hormones is pivotal to avoid dangerous states. Unopposed estrogens occur when progestogen levels do not balance estrogens, primarily deriving from overproduction of estrogens via aromatase enzyme. In the endometrium, unopposed estrogens induce proliferative or invasive phenomena, which represent the first step toward different diseases. These pathologies include endometrial hyperplasia, endometrial polyps, endometriosis and adenomyosis. Endometrial hyperplasia and polyps are proliferative pathologies, while endometriosis and adenomyosis are characterized by the invasion of other tissues by endometrial cells. Current pharmacological treatments include Gonadotropin-Releasing-Hormone analogs, aromatase inhibitors and progestogens, either alone or in combination with estrogens. As these drugs usually lead to burdensome undesired effects, researchers seek to find new therapeutical molecules. Recent literature highlights the positive effects of metformin, an insulin sensitizing drug that reduces the insulin proliferative stimulus on the endometrium. d-chiro-inositol is an insulin second messenger with insulin sensitizing and mimetic properties, recently described as an aromatase down-regulator. Based on current evidence, d-chiro-inositol may be useful to treat the pathologies responsive to unopposed estrogens.

What causes high estrogen levels?

Your estrogen levels may be high because:

- Your body is making too much estrogen.
- You're getting too much estrogen in the medicine you're taking.
- Your body's not breaking down estrogen and removing it from your body as it should.

A variety of factors can contribute to high estrogen, including:

- **Medications:** Hormone therapy to boost low estrogen levels may cause your levels to become too high at first. It may take some time to get the dosage right. (high-dose oral contraceptives/birth control pills)
- **Body fat:** Fat tissue (adipose tissue) secretes estrogen. Having a high percentage of body fat can lead to high estrogen levels.
- **Stress:** Your body produces the hormone cortisol in response to stress. Producing high amounts of cortisol in response to stress can deplete your body's ability to produce progesterone. The estrogen in your body is left unchecked by progesterone.

https://my.clevelandclinic.org/health/diseases/22363-high-estrogen

- **Alcohol:** Drinking too much alcohol can increase your estrogen levels and reduce your body's ability to break down (metabolize) estrogen.
- **Liver problems:** Your liver breaks down estrogen and eliminates it from your body. If your liver's not functioning correctly, too much estrogen can accumulate. Too few digestive enzymes, too much bad gut bacteria (dysbiosis), low magnesium levels and too little fiber in your diet can prevent your liver from removing excess estrogen.
- **Synthetic xenoestrogens:** Synthetic xenoestrogens are chemicals found in the environment that act like estrogen once they're inside your body. They can increase your estrogen levels. Xenoestrogens include bisphenol A (BPA) and phthalates. Both of these chemicals are used in various plastics. Xenoestrogens can also be found in pesticides, household cleaning products and some soaps and shampoos.

https://my.clevelandclinic.org/health/diseases/22363-high-estrogen

Review > Cardiol Clin. 1986 Feb;4(1):145-52.

The adverse effects of hormonal therapy

T L Bush

PMID: 3518931

Estrogen therapy must be cycled with progestin therapy in women with intact uteri in order to prevent uterine cancer. However, these women cannot be expected to benefit (with regard to cardiovascular disease) from any estrogen-induced changes in the lipoprotein profile, as progestins will either negate or overwhelm any estrogen effects. However, such women will definitely benefit from estrogen's effects with regard to menopausal symptoms and bone loss. These clearly beneficial effects of estrogen-progestin therapy are not outweighed by any known risks. However, in women without uteri (approximately 30 per cent of women), unopposed estrogen therapy in the menopause may protect against cardiovascular disease, as well as have beneficial effects on bone metabolism and menopausal symptoms. In this special case, the beneficial effects of unopposed estrogen therapy clearly outweigh any known risk.


CHEVROLET
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Conservative Care Questions Checklist:

1. Do you have hormone symptoms?
2. What are the current hormone levels? (blood, saliva, urine)
3. Pathologically low levels of hormone? (low body fat, terrible adrenals, hx of amenorrhea…)
4. Are receptor sites in play? (normal estrogens, excess body fat, etc.)
5. Does the patient have all their parts?
6. What does nutrition look like? (SAD, vegetarian/vegan, Paleo)
7. What does thyroid function look like?
8. What does GB/Liver complex function look like?

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Menopause Hot Flashes and Molecular Mechanisms Modulated by Food-Derived Nutrients

Ewa Forma,[1,*] Karina Urbańska,[2] and Magdalena Bryś[1]

Nancy King Reame, Academic Editor

The causes of vasomotor symptoms, including hot flashes, are not fully understood, may be related to molecular factors, and have a polygenic architecture. Nutrients and bioactive molecules supplied to the body with food are metabolized using various enzymatic pathways. They can induce molecular cell signaling pathways and, consequently, activate effector proteins that modulate processes related to hot flashes in menopausal women. In this review, we analyzed the literature data from the last 5 years, especially regarding genome-wide association study (GWAS) analysis, and selected molecular factors and cell signaling pathways that may potentially be related to hot flashes in women. These are the kisspeptin-GnRH pathway, adipocyte-derived hormones, aryl hydrocarbon receptor signaling, catechol estrogens and estrogen sulfotransferase, inflammatory and oxidative stress biomarkers, and glucose availability. Then, single compounds or groups of food ingredients were selected that, according to experimental data, influence the course of the discussed molecular pathways and thus can be considered as potential natural therapeutic agents to effectively reduce the troublesome symptoms of menopause in women.

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One of the well-known classic symptoms of the menopausal transition is hot flashes. Hot flashes are vasomotor symptoms, which occur in more than 75% of menopausal women [2,6,7,8]. The medium duration of hot flashes is approximately four years, with some lasting as long as 20–30 years [2,9,10]. Hot flashes are described as transitory episodes of heat sensations, flushing and excessive sweating in the face and chest. The sensation lasts from 2 to 4 min and is associated with palpitation, anxiety, irritability, and night sweats. The frequency of hot flash episodes varies from occasional attacks in a week or day to at least one every hour [2,8,10,11]. Hot flashes are often associated with impairments in quality of life, loss of productivity, depressed mood, embarrassment, fatigue, anxiety, sleep disturbance, and possibly even poorer memory function and social isolation [4,7,12]. The physiological and molecular mechanism of hot flashes is still incompletely known. Hot flashes during menopause are based on complex endocrine, neuroendocrine and epigenetic mechanisms [13]. The hot flashes are triggered by a small elevation in core body temperature, which causes activation of the sympathetic nervous system by peripheral vasodilation and increased activity of sweat glands. This mechanism may be associated with the response of the hypothalamus to decreased estrogen levels and modulation of the neurotransmitter activity (serotonin and noradrenaline) [4].

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4. Adipocyte-Derived Hormones

Go to:

In the hypothalamus, signals are exchanged between the nervous and endocrine systems, and this system of signals is created by hormones circulating in the body. Under the influence of stimuli from the hypothalamus, the pituitary gland produces hormones that regulate the functioning of other endocrine glands. In this way, changes in their secretion may influence abnormal eating behavior. The most important hormones responsible for nutritional processes are leptin, resistin, ghrelin, and insulin. Leptin is produced mainly by adipose tissue cells, and it is secreted from adipose tissue under the influence of insulin, in the period after food consumption, when the elevated glucose concentration is lowered by insulin to the physiological level. The most important target site of leptin's action is the hunger and satiety center in the hypothalamus. There, the receptors react with leptin, as a result of which neurons stop producing the neurotransmitter, neuropeptide Y, which is an appetite stimulator. In this way, the desire to eat is inhibited. Leptin accelerates metabolism, inhibits the deposition of fat tissue, and activates its breakdown. Because the amount of leptin produced depends on the amount of fat tissue in the body, chronically elevated leptin levels in the blood are observed in overweight or obese people. In this case, the cells of the hypothalamus "get used to" the constantly elevated level of this hormone and eventually stop responding to it. This means that despite the body's energy needs being met, the feeling of hunger and appetite is not suppressed after eating a meal [38]. As shown by Karim et al., higher ghrelin concentrations are positively correlated with a greater likelihood of hot flashes in women in the early and late postmenopausal period [39]. Based on their research, Sau et al. suggest a relationship between hot flashes and the occurrence of metabolic syndrome in women aged 40–65 [12]. Also, Kazama et al. showed that the fat mass index was positively associated with severe hot flashes, whereas the lean mass index was negatively correlated [40].

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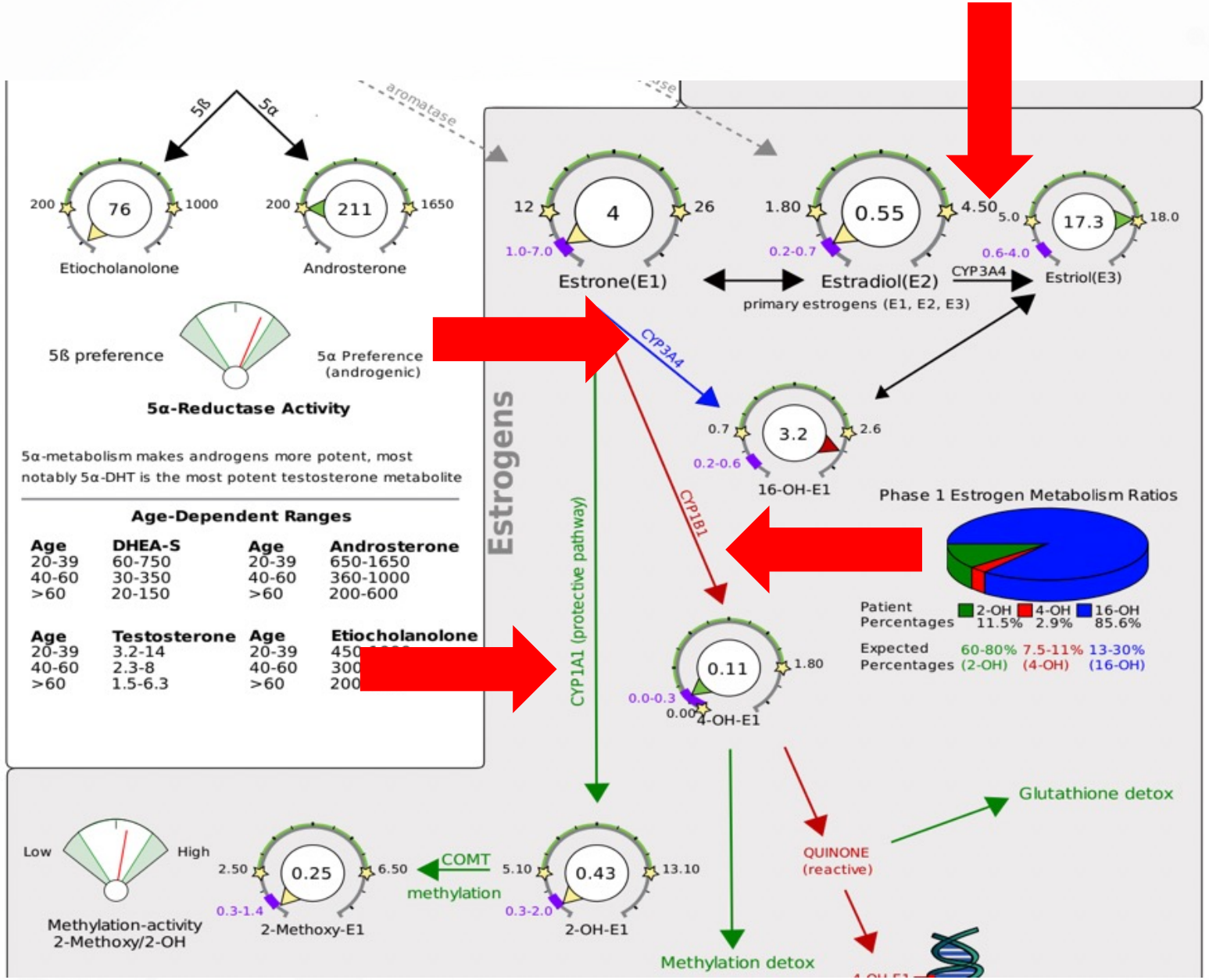
Variations in sex steroid metabolism genes such as CYP1B1 may occur. The function of CYP1B1 is to convert 17β-estradiol into 2-hydroextradiol-17β, which changes the balance of estradiol as the main female sex hormone. Fluctuations in estradiol levels occurring during menopause are associated with the etiology of hot flashes [15]. It has been shown that the AHR-ARNT complex (AHR nuclear translocator) binds to the xenobiotic response element (XRE) in regulatory genes, inducing specific gene expression of enzymes such as CYP1A1, CYP1A2 and CYP1B1 [54]. The association between some nutrients and CYP1B1 action is described by Shah et al. (2019) [54]. The article considers such compounds as apigenin, luteolin, quercetin, scutellarein, kaempferol, taxifolin, indole-3-carbinol, folic acid, piceatannol and compounds contained in flaxseed, green tea extracts and olive oil. Furthermore, in silico studies have shown a potential relationship between cytochrome P450 enzymes (CYP1A1 and CYP1B1) and the flavonoids isorhamnetin and pedalitin present in food [55].

(DUTCH will show correlation)


5ß
5α
aromatase
200
76
1000
Etiocholanolone
200
211
1650
Androsterone
5ß preference
5α Preference
(androgenic)
5α-Reductase Activity
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
Age-Dependent Ranges
Age DHEA-S
20-39 60-750
40-60 30-350
>60 20-150
Age Androsterone
20-39 650-1650
40-60 360-1000
>60 200-600
Age Testosterone
20-39 3.2-14
40-60 2.3-8
>60 1.5-6.3
Age Etiocholanolone
20-39 450
40-60 300
>60 200
Estrogens
12
4
26
1.0-7.0
Estrone(E1)
1.80
0.55
4.50
0.2-0.7
Estradiol(E2)
CYP3A4
5.0
17.3
18.0
0.6-4.0
Estriol(E3)
primary estrogens (E1, E2, E3)
CYP3A4
0.7
3.2
2.6
0.2-0.6
16-OH-E1
CYP1B1
Phase 1 Estrogen Metabolism Ratios
Patient Percentages
2-OH 11.5%
4-OH 2.9%
16-OH 85.6%
Expected Percentages
60-80% (2-OH)
7.5-11% (4-OH)
13-30% (16-OH)
CYP1A1 (protective pathway)
0.11
1.80
0.0-0.3
0.00
4-OH-E1
Glutathione detox
QUINONE
(reactive)
Low
High
Methylation-activity
2-Methoxy/2-OH
2.50
0.25
6.50
0.3-1.4
2-Methoxy-E1
COMT
methylation
5.10
0.43
13.10
0.3-2.0
2-OH-E1
Methylation detox

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Nancy King Reame, Academic Editor

6. Catechol Estrogens and Estrogen Sulfotransferase

Go to: ▸

Estrogen conjugates are formed by biotransformation from both endogenous and exogenous estrogens. Conjugated estrogens do not have the ability to activate ER receptors and therefore do not initiate cell signal transmission. The most active catechol estrogen (CE) conjugative pathway is methylation. CE methylation is catalyzed by catechol-O-methyltransferase (COMT), which catalyzes the transfer of methyl groups from S-adenosyl methionine to the hydroxyl groups of several catechol substrates, including the catechol estrogens [56].

Some phenolic compounds acting as substrates for catechol-O- methyltransferase (COMT)-catalyzed O-methylation can also operate as COMT inhibitors, impeding the O-methylation of a variety of catechol substrates. These compounds are present, among others, in coffee, tea and extra virgin olive oil [53,54].

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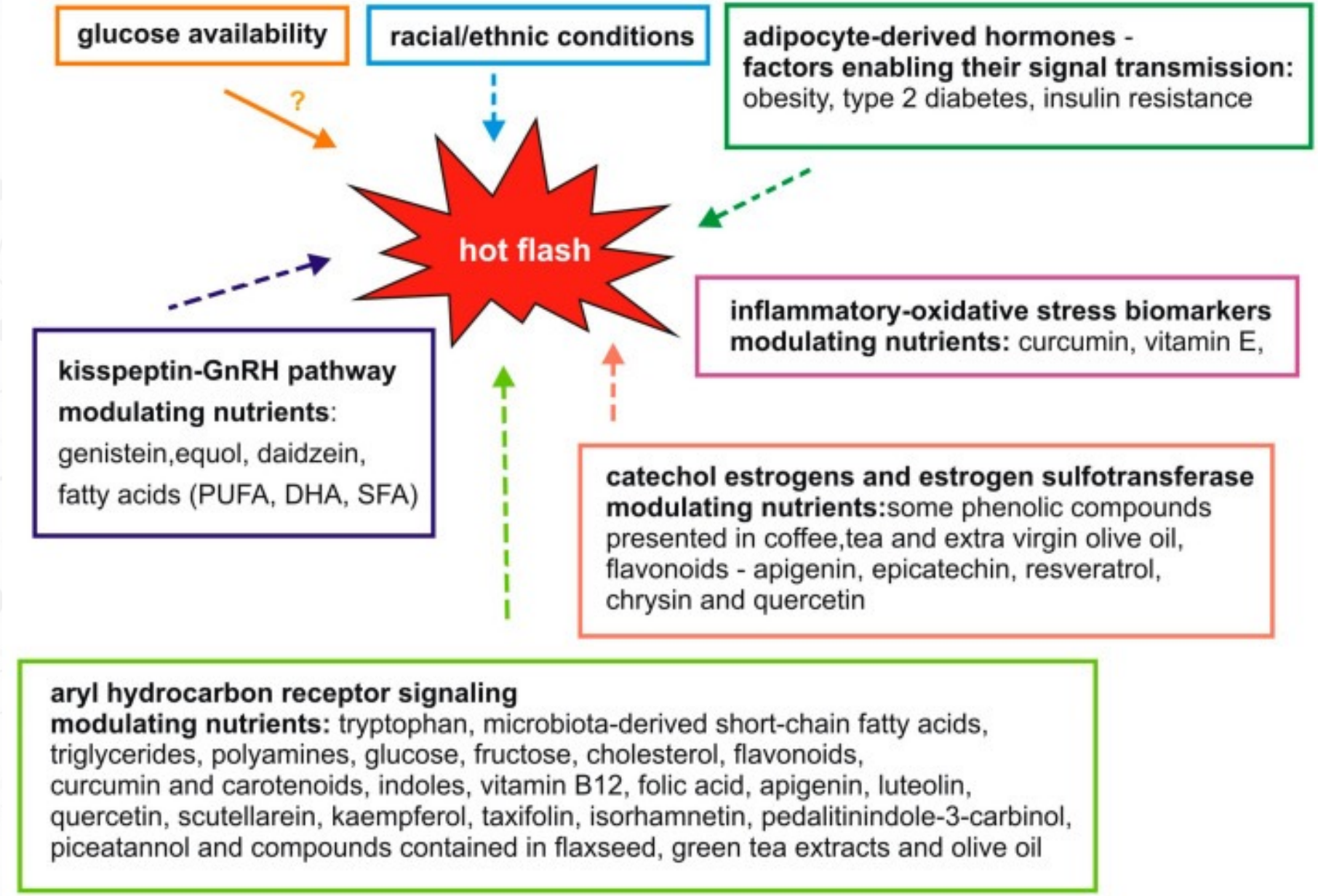
8. Glucose Availability

Go to:

Information on the relationship between blood glucose levels and hot flashes is sparse and dates back more than a decade. Nevertheless, due to the significant share of glucose in the diet, they seem very important and worth presenting.

In his review article, Dormire (2009) presents the hypothesis that hot flashes are an indicator of transient glucose deficiencies in the central nervous system, secondary to reduced estrogen stimulation of glucose transporter 1 (GLUT 1). Low estrogen levels that occur during menopause result in reduced glucose availability in neuroendothelial cells in ovariectomized rats. As has been shown in studies in animal models, hot flashes can be triggered by stimuli that, for example, lower blood glucose levels or block the ability of brain cells to use glucose. According to the current literature data, research on the molecular pathways of glucose transport mediated by GLUT receptors and their involvement in generating hot flashes was not continued [59].

Estrogens, through their direct action on various nervous systems, bidirectionally modulate cognitive functions, which require an energy load on the brain and, at the same time, an adequate supply of metabolic substrates, such as glucose, lactates, and ketones, to function efficiently [60,61,62]. Reduced estrogen levels during menopause are probably associated with a deficit in glucose availability, which in turn leads to dysregulation of energy homeostasis and increases the risk of nervous disorders. As demonstrated in a mouse model of Alzheimer's disease, ovariectomy resulted in reduced glucose uptake by the central nervous system and a shift in the bioenergetic profile in the hippocampus to one that favors reduced glucose utilization and increased lactate and ketone utilization [63].



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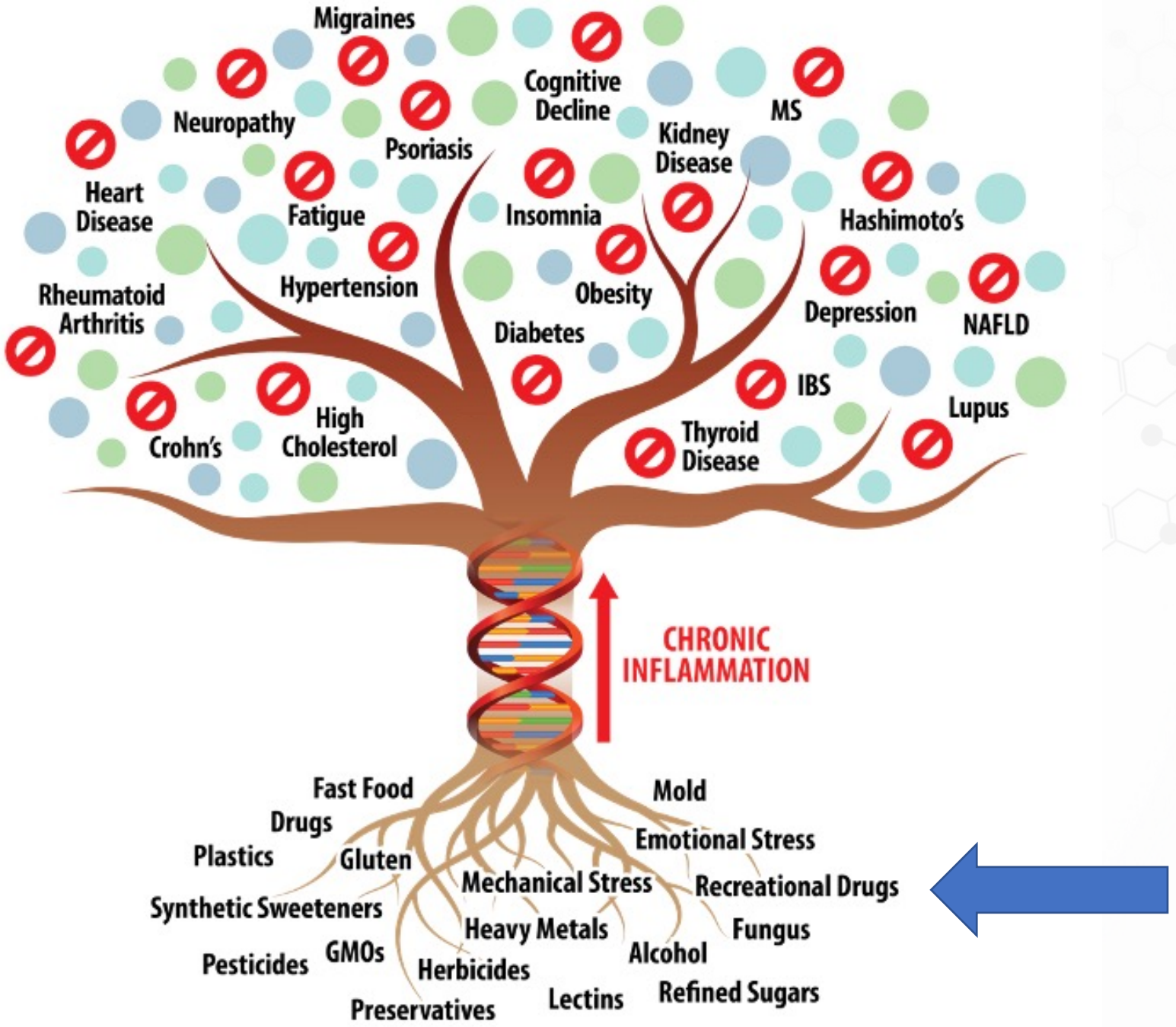
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives