MENOPAUSE,

BRAIN AGING

and DEPRESSION

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MENOPAUSE, BRAIN AGING and DEPRESSION

I. Generalities

II. The neurobiological mechanism of brain aging

III. Some conditions affect the brain aging process

- Insulin and brain
- Schizophrenia
- Decreased glutathion
- Menopause and decreased Estrogen

IV. Depression

V. Slowing down brain aging and decreasing depression

Generalities

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- Human lifespan in the world has increased considerably.
- According to WHO, by the year 2050, people > **60 years of age** will increase up to **22%, nearly 2 billion people** (compared with 12% and 900 million people - 2015).

➢ Increased lifespan ⟹ increased frequency of diseases:

- cognitive impairment (Alzheimer's disease),
- other diseases associated with blood vessels, bones, joints ...

⟹ **reduced quality of life.**

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- In Vietnam, the population over 65 years of age has been increasing, approximately 11 million people in 2016, estimated approximately 18 million people in 2022 and 22 million people in 2030.

- **The average menopausal age of Vietnamese women is 48 – 51** *(Vinh et al. 1997; Đuc et al, 2001)*

- **75% of Vietnamese women experience discomfort symptoms** (vasomotor, psycho-neurological, osteoarthritic, urogenital) **and postmenopausal diseases** such as cardiovascular disease, osteoporosis, geriatric dementia

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- It is needed to *understand the neurobiological mechanism* of brain aging in order to be able to prevent, slow down and reduce the negative effects of aging as well as to find appropriate therapeutic methods for the population who is getting older!

- **Urgency**: Preventing factors causing diseases for the elderly and slowing down brain aging, helping the elderly can maintain

HEALTHY LIFE AND MENTAL CLARITY

The neurobiological mechanism of brain aging

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The neurobiological mechanism of brain aging:

- Unknown,
- The hippocampal region contains **neural stem cells**
  → *can produce new neurons*, even in adults.
- A mitotic checkpoint kinase - **BubR1**, presents in the dental gyrus of hippocampus
  - is an important regulatory factor **in neurogenesis in the hippocampal region**
  - regulates the function of myelin in the axon, **neurotransmission**
  - **decreased considerably with age.**

Syed Mohammed Qasim Hussaini and Mi-Hyeon Jang AGING 2017, Vol 9, No 9

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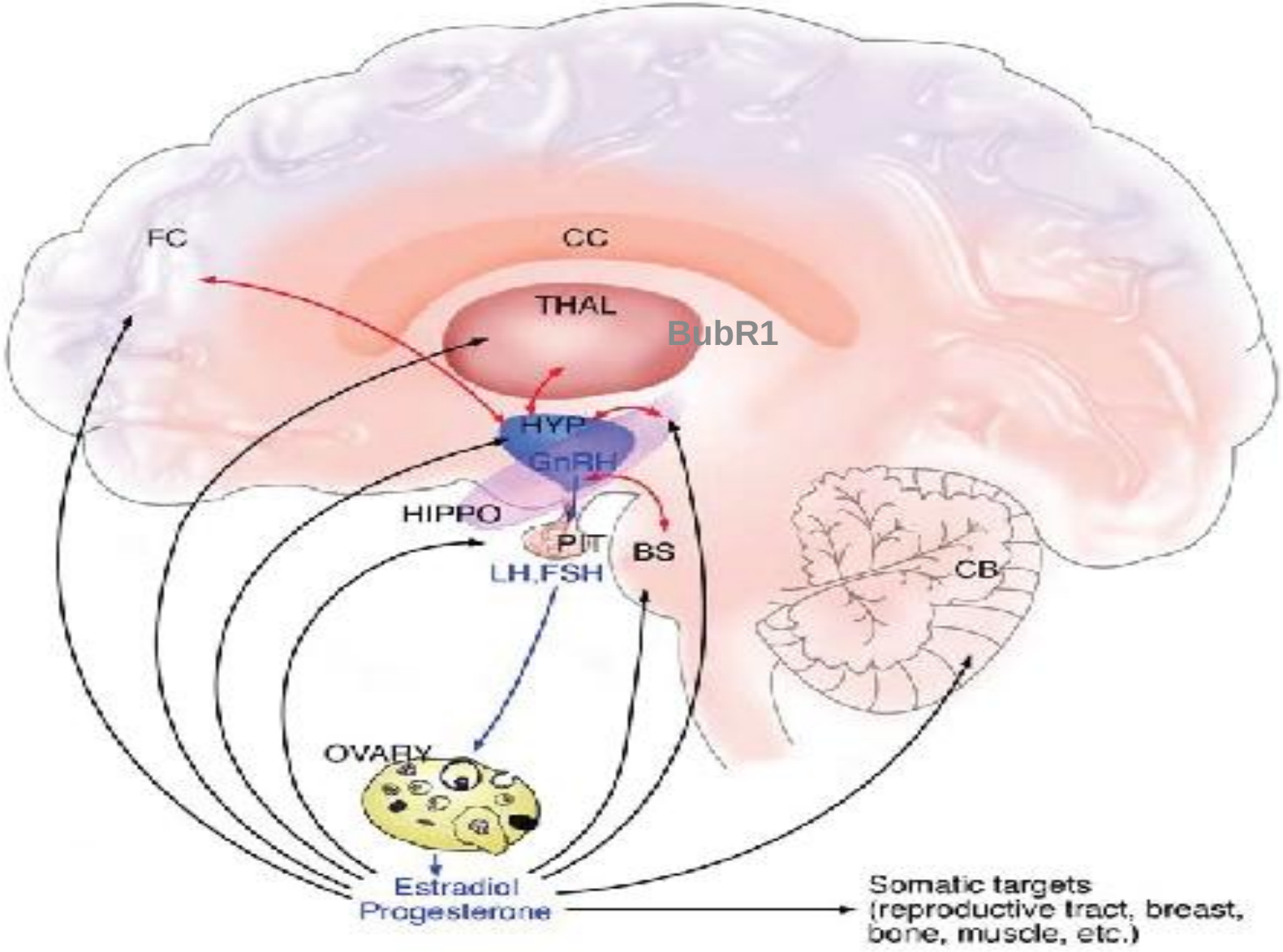
Frontal lobes, *hippocampal region and brain stem (BS) region* (which contain the nervous stem cells (NSCs)) are affected by BubR1, resulting in changes in many fields of the body's activity such as reproductive, cardiovascular, osteoarthritic, psychoneurological ...

Hippocampus plays a role in memory formation, learning and emotion regulation, hippocampal damage will affect these activities.


FC
CC
THAL
BubR1
HYP
GnRH
HIPPO
PIT
LH,FSH
BS
CB
OVARY
Estradiol
Progesterone
Somatic targets
(reproductive tract, breast,
bone, muscle, etc.)

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The neurobiological mechanism of brain aging:

- Through experiments: not only due to reduced ovarian reserve leading to menopause,
- ***Impaired hypothalamus-pituitary-ovary axis***

  menopause
- In the hypothalamus: Many factors cause changes in GnRH amount including ***Glutamate***.
- Glutamate and its receptors affect the GnRH-producing cells in the hypothalamus, which alter the amount of GnRH.

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Decreased *GnRH* leads to decreased BubR1, thereby decreased production, neuronal activity and decreased neurotransmission, leading to brain aging.

The consequences of brain aging are not only in the ovaries, pituitary and hypothalamus but brain aging also ***affects the whole-brain activity*** via ***the Estrogens receptors in the brain.***

Some conditions affect the brain aging process

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- Many studies showed that:

  - The elderly often has peripheral insulin resistance

  - When there is an insulin resistance in the brain, the rate of mental and cognition impairment increases.

So what is the role of insulin for brain aging phenomenon?

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- Insulin is very important in brain physiology *(Dorn & cs. 1983).*
- Insulin is a large molecule peptide that can not penetrate the vascular walls of the brain.
- However, in the cerebrospinal fluid, insulin is present in large amounts.

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- 3 supplies of insulin for cerebrospinal fluid ***(CSF)***:

- Insulin is delivered to the central nervous system (CNS) ***mediated by insulin binding transporter receptors (GLUT-4),***

- insulin ***penetrates through the vascular wall of the ventricle*** because the capillaries of this area are particularly porous,

- the ability of **insulin to be synthesized and released just in the brain**, by neurons and astrocytes.

Diehi T, Mullins R, Kapogiannis D. Transl Resb2017;183:26-40
Akintola AA, van Heemst D. Front Endocrinol (Lausanne) 2015;6:13

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- **Insulin receptors (IRs)** are distributed throughout the brain, particularly in the hippocampus, hypothalamus, olfactory center, cerebellum, amygdala, and cerebral cortex.
- IRs are distributed throughout the brain so, insulin has many functions in the brain.
- Brain IRs differ from peripheral IRs: the molecular weight is smaller and IRs may be exposed to increased serum insulin without reducing the number of receptors.

Diehi T, Mullins R, Kapogiannis D. Transl Resb2017;183:26-40
Akintola AA, van Heemst D. Front Endocrinol (Lausanne) 2015;6:13

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- **Brain insulin has effects:**

- protection of neurons,
- enhancement of glucose infiltration through neurons through the "insulin-sensitive glucose transporter" - named GLUT-4, presents largely in the hippocampus, cerebellum and hypothalamus.
- it can control emotions, affect cognition, learning and memory by increasing glucose metabolism in neurons

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- **Insulin and brain aging physiology in normal people**

- Frolich et al (cadaver biopsy): aging ⟹ decreases insulin and binding ability to IRs in the cortex.

- this condition is more severe if there were insulin resistance and previously increased serum insulin.

- the cerebrospinal fluid ***(CSF)/serum insulin ratio*** also demonstrates the decreased insulin passing through the blood vessel walls of the brain (decreased GLUT-4).

- **glucose metabolism in the brain decreases, beginning the brain aging process**

- **Insulin and brain aging physiology in patients with Alzheimer's disease:**

- Diabetes: risk of Alzheimer's disease increases 50 - 60%.

- Type 2 diabetes + Alzheimer's disease (AD): Amyloid-β plaque raises considerably compared to non diabetes

↓

increasing cerebral atherosclerosis

↓

increasing cerebral infarction

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Studies proved that:

- Insulin is present in large quantities and plays an important role in brain metabolism.
- Age increases insulin resistance, decreases glucose metabolism in the brain, increases inflammation, increases amyloid-β plaque resulting in atherosclerosis and cerebrovascular accident.
- Tye 2 diabetes increases disorders of insulin and glucose metabolism in the brain,

brain aging is a partial consequence from glucose metabolism disorders

Schizophrenia and brain aging:

Joanne Voisey et al. had two studies on the epigenetics of brain aging phenomenon in schizophrenic patients (1 small study with n = 48 and 1 study with n = 392) and showed that:

- DNA methylation of the frontal lobe is closely correlated with age, but
- ***Not different in normal or schizophrenic people.***

Joanne Voisey et al *npj Schizophrenia (2017)3:26; doi:10.1038/$41537-017-0026-4*

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Glutathion and brain aging

- **Oxidation stress** is a sign of brain aging. Many antioxidants are expected to protect the brain from degeneration
- **Glutathion is a strong antioxidant** (α-l-glutamyl-l-cysteine-nylglycine, GSH) that helps to balance the brain.
- Study on **GSH quantification** in the cadaver biopsy of 74 persons aged from 1 day to 99 years showed that :

➢ GSH in children and the elderly 76 - 99 years: similar, low.

➢ GSH in adults: high in the caudal cortex, frontal lobe, cerebellum

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GSH in the brain:

- Slows down in the brain aging process after being adult, the lowest in the brain of the elderly with brain aging, and
- High in young adults, without brain aging

Is **decreased Glutathion** the expression of brain aging?

Can Glutathion be used to slow down the brain aging process?

Junchao Tong et al Free Radical Biology and Medicie – 0891-5849/© 2016 Elsevier Inc.

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- **Impaired Estrogen leading to hippocampal damage in menopausal mice:**

Yan Yan, Liang Cheng – Harbin University (China) conducted experimental study in menopausal female mice:

- **Impaired E2** → - mitochondria damage to the DG area
  - hippocampal damage, increased lipofuscin plaque and destroyed microtubules
- **E2 subcutaneous injection** of 3.5 μg/kg every 3 days for 2 months in 6-month-old female mice, can **prevent**:

  - mitochondria damage, lipofuscin plaque,
  - but the axonal microtubules (neuron signaling) in the hippocampal region are still damaged

- Are neuronal axons **destroyed by** ↑ **ROS ??**

Oncotarget, 2017, Vol. 8, (No 13), pp: 21892-21902

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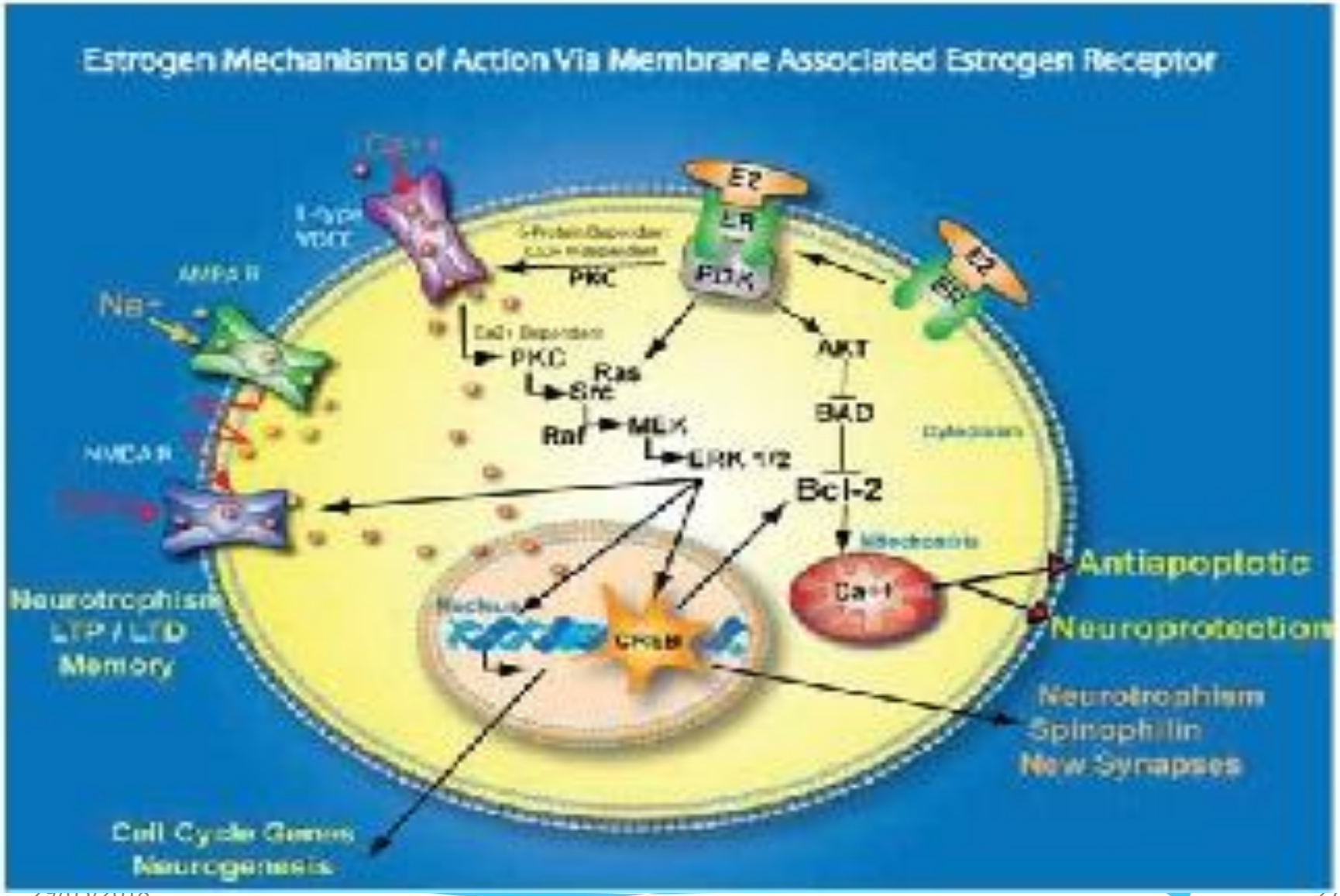
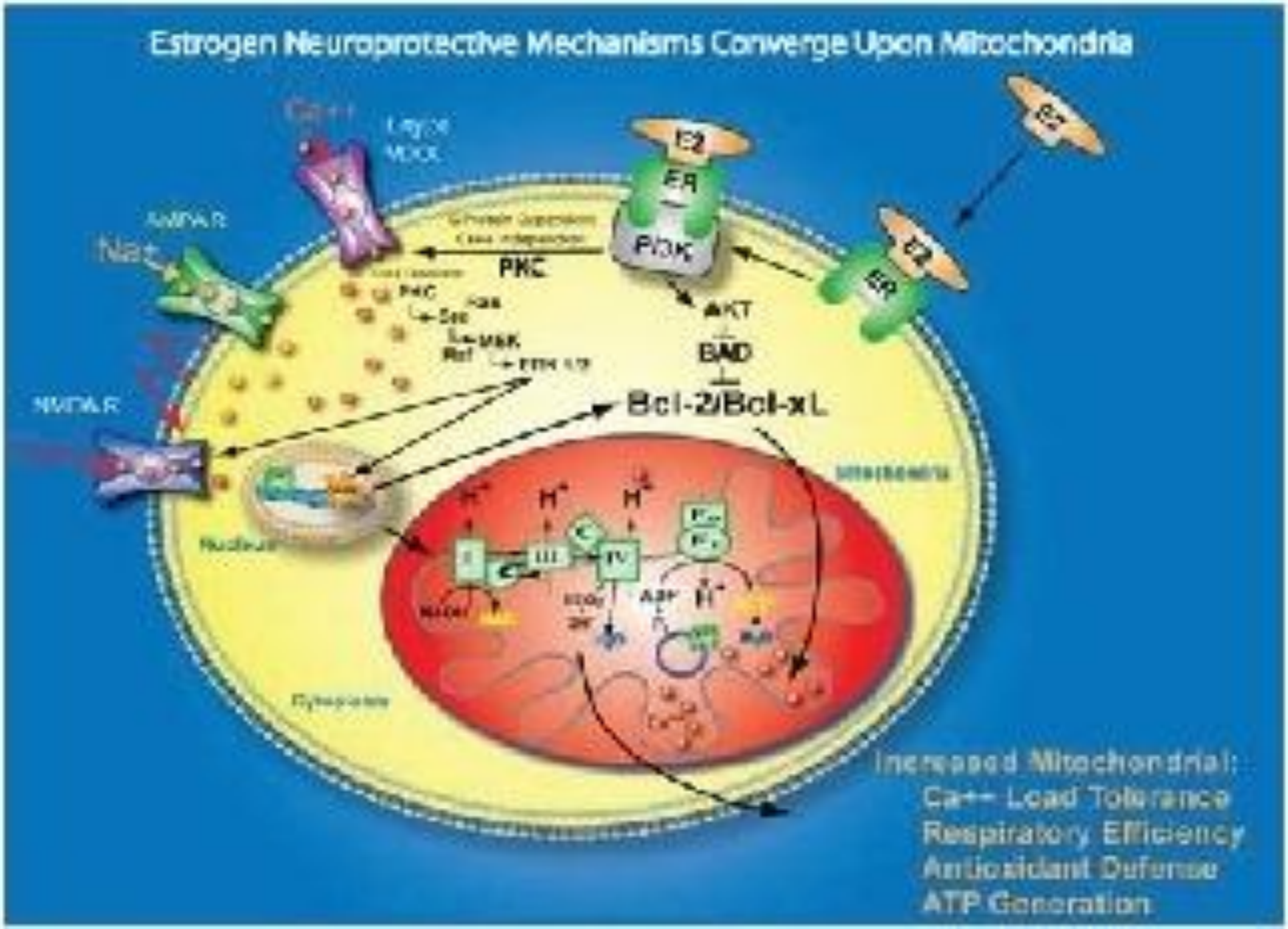
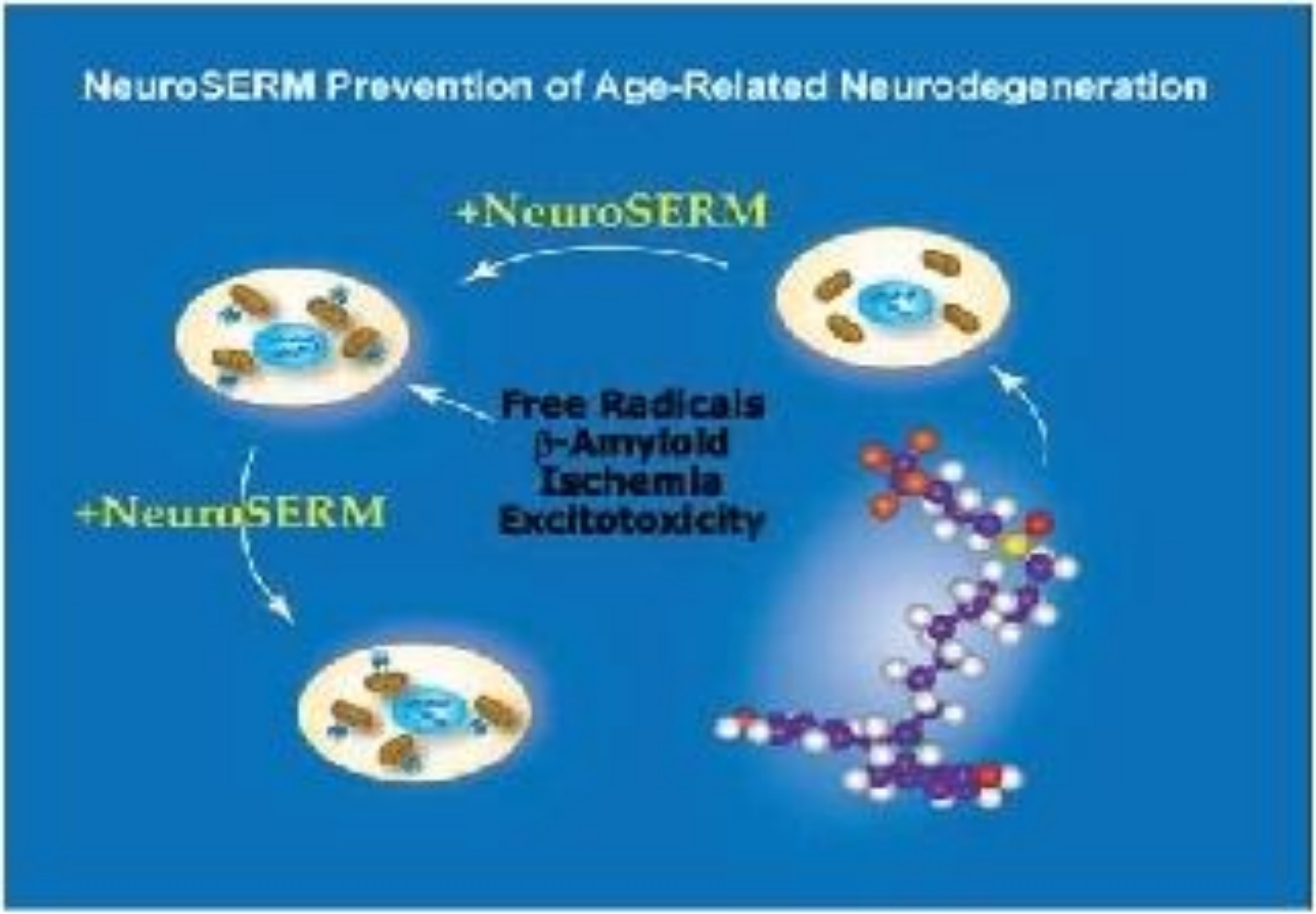
Mechanism of action of Estrogen on neurons:

- Regulation of Ca^{2+} stabilization in mitochondria,
- Neuronal plasmid protection so that they it does not contain too much Ca^{2+}
- Mitochondria can breathe, without injury, neurones are protected.

John H. Morrison et al. The Journal of Neuroscience, Oct 11, 2006. 26(41):10332-10348


Estrogen Mechanisms of Action Via Membrane Associated Estrogen Receptor
E2
ER
PI3K
PKC
PKC
Ras
Src
Raf
MEK
ERK 1/2
AKT
BAD
Bcl-2
Ca++
Antiapoptotic
Neuroprotection
Neurotrophism
LTP / LTD
Memory
Neurotrophism
Spinophilin
New Synapses
Cell Cycle Genes
Neurogenesis


Estrogen Neuroprotective Mechanisms Converge Upon Mitochondria
E2
ER
PI3K
PKC
AKT
BAD
Bcl-2/Bcl-xL
Nucleus
Increased Mitochondrial:
Ca++ Load Tolerance
Respiratory Efficiency
Antioxidant Defense
ATP Generation


NeuroSERM Prevention of Age-Related Neurodegeneration
+NeuroSERM
Free Radicals
β-Amyloid
Ischemia
Excitotoxicity
+NeuroSERM

Menopause and Depression

The progressive stages of menopause

- Transition period: 10 – 15 years
- Perimenopause: early, middle and late
- **Menopause**
- **Postmenopause**

MENOPAUSE and DEPRESSION

Menopausal transitional period lasts, 10 to 15 years before the last menstrual period.

- Hormones steroides *oscillate a lot*
- Early transition period**: Ovarian inhibin decreases**

  → GnRH increases → FSH increases → E2

  E2 +
- Late transition period: no or low ovulation PRG decrease, with up/down levels

menopause**, *Estrogen and PRG oscillate***

Depression occurs in the high transtion period with the hormonal oscillation

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- Not all menopausal women are depressed: ***Menopause is not a direct cause of depression***

- Many studies (Avis et al. 2001): ***Depression does not only occur in people with a history of disease.***

- Depression can lead to:
  - reduce the quality of life of the postmenopausal woman and her family.
  - many diseases associated with it (cardiovascular disease, metabolic diseases ...)

John H. Morrison, Roberta D. Brinton et al. The Journal of Neuroscience, October 11 2006* 26(41): 10332 - 10348

Long-term consequences after removal of two ovaries on brain aging

Mayo Clinic studied in

- 1,252 women with removal of one ovary,
- 1,075 women with removal of two ovaries before signs of menopause,
- 2,368 women without ovarian removal.

These women were monitored for 25 – 30 years to see:

- cardiovascular disease rate
- Parkinson disease rate
- cognitive impairment rate
- depression rate

W A Rocca et al. Women's Health 2009 January; 5(1):39-48. doi:10.2217/17455057

The rate of cognitive impairment *after early removal of two ovaries, before menopause age and/or before 45 years of age.*

- Overall rate of cognitive impairment for all patients:

  HR 1.33; CI 95% 0.98 – 1.81; ***P = 0.07***

- Cognitive impairment rate (patients < 43 years of age):

  HR 1.74; CI 95% 0.97 – 3.14; ***P = 0.06***

- Cognitive impairment rate (patients < 49 years of age), no estrogen therapy to at least 50 years of age:

  HR 1.89; CI 95% 1.27 – 2.83; ***P = 0.002***

The rate of anxiety, depression after surgical removal of two ovaries

(Patients < 50 years of age, have not yet had these symptoms before surgery)

- Depression rate:

  HR 1.54; CI 95% 1.04 – 2.26; ***P = 0.01***

- Anxiety rate:

  HR 2.29; KTC 95% 1.33 – 3.95; ***P = 0.01***

W A Rocca et al. Women's Health 2009 January; 5(1):39-48. doi:10.2217/17455057

Nathorst-Boos et al studid in 101 women with hysterectomy,

- 35 kept the two ovaries,
- 33 + resected both ovaries and did not use estrogen after surgery
- 33 + resected both ovaries and used estrogen after surgery

The study team reported ***a considerably increase in the rate of anxiety and depression in patients with removal of uterus + two ovaries without use of estrogen*** after surgery.

Nathorst-Boos J, von Schoultz B, Carlstrom K.
J Psychosom Obstet Gynaecol PubMed: 8142982

Can brain aging be slowed down?

1. Avoid or treat diabetes early and effectively
2. Can some substances such as glutathion, glutamate be used early to reduce stress oxidation?
3. Family's care, exercise, proper nutrition, good family and social relationships are key factors to keep balance in life, stress avoiding as a measure for slowing down brain aging

Can brain aging be slowed down?

4. Experimental study of Anusha J. et al. in the United States proved:

- E + P supported the elimination of amyloid-β toxic substance from the brain.
- Particularly, the authors found that the higher activity of insulin in the brain, the lower level of amyloid-β.

Anusha Jayaraman et al.
Endocrinology. 2012 Nov; 153(11): 5467–5479. PMCID: PMC3473201

Can brain aging be slowed down?

HRT should be considered as first-line therapy for depression and neurasthenia symptoms in perimenopausal women.

Transdermal estrogens are safer than oral estrogens in that they cause less venous thrombosis and are more effective in the treatment of perimenopausal depression and neurasthenia.

«*HRT should be considered as first line therapy for perimenopausal depression.*

Transdermal estrogens are safer than oral estrogens in that they do not carry any extra risk of thrombosis and also have been reported as more effective in the treatment of depression».

Can brain aging be slowed down?

Beneficial effects of early HRT in older age women:

There is a need for more well-designed observational studies to eliminate important variables that may cause bias of results on how early HRT use that affect dementia risk in women with early natural menopause, including women with premature ovarian insufficiency

«*Beneficial effects of early HRT on dementia risk in older age women*
There is a need for good-quality observational studies controlling for the effect of important confounders on how early HRT use affects dementia risk in women with early natural menopause, including women with premature ovarian insufficiency».

Có thể làm châm LHNB?

The potential for estrogens in preventing Alzheimer's disease and vascular dementia

James W. Simpkins, Evelyn Perez, Xiaofei Wang, ShaoHua Yang, Yi Wen and Meharvan Singh

Therapeutic Advances in Neurological Disorders
(2009) 2(1) 31–49
DOI: 10.1177/1756285608100427

«...Estrogens have been studied extensively for the prevention of Alzheimer's disease. Estrogens have been proven to protect the nervous system..., decrease the formation of beta-amyloid. .»

Estrogens are the best-studied class of drugs for potential use in the prevention of Alzheimer's disease (AD). These steroids have been shown to be potent neuroprotectants both in vitro and in vivo, and to exert effects that are consistent with their potential use in prevention of AD. These include the prevention of the processing of amyloid precursor protein (APP) into beta-amyloid (A), the reduction in tau hyperphosphorylation, and the elimination of catastrophic attempts at neuronal mitosis

Published in final edited form as:
Menopause. 2013 June ; 20(6): 695–709. doi:10.1097/GME.0b013e3182960cf8.

The Critical Window Hypothesis of Hormone Therapy and Cognition: A Scientific Update on Clinical Studies

Pauline M. Maki, PhD
Departments of Psychiatry and Psychology University of Illinois at Chicago Chicago, IL 60612

«... Considering the use of HRT (17β-estradiol) for menopausal women to improve mood, alleviate anxiety and make them understand that SSRIs or SSRNs do not reduce low mood in menopausal women who have not had Alzheimer's disease...»

Consider HRT to alleviate low mood that arises as a result of the menopause.
1.4.6 Consider CBT to alleviate low mood or anxiety that arise as a result of the menopause.
1.4.7 Ensure that menopausal women and healthcare professionals involved in their care understand that there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression (see the NICE guideline ondepression in adults).

Có thể làm chậm LHNB?

NIH Public Access
Author Manuscript
Menopause. Author manuscript; available in PMC 2014 June 01.

Published in final edited form as:
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The Critical Window Hypothesis of Hormone Therapy and Cognition: A Scientific Update on Clinical Studies

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... For hysterectomized women, general opinion in the literature is advocating the use of estrogen alone to avoid cognitive impairment. ... it is especially important for women who have two ovaries removed before menopause...».

... «For hysterectomized women, the literature provides tentative support for beneficial cognitive effects with estrogen alone. Such treatment might be especially important for women who have their ovaries removed before the natural onset of the menopause»

Có thể làm chậm LHNB?

OPEN ACCESS Freely available online

PLOS | ONE

Prospective Randomized Trial to Assess Effects of Continuing Hormone Therapy on Cerebral Function in Postmenopausal Women at Risk for Dementia

Natalie L. Rasgon[1]*, Cheri L. Geist[2], Heather A. Kenna[1], Tonita E. Wroolie[1], Katherine E. Williams[1], Daniel H. S. Silverman[2]

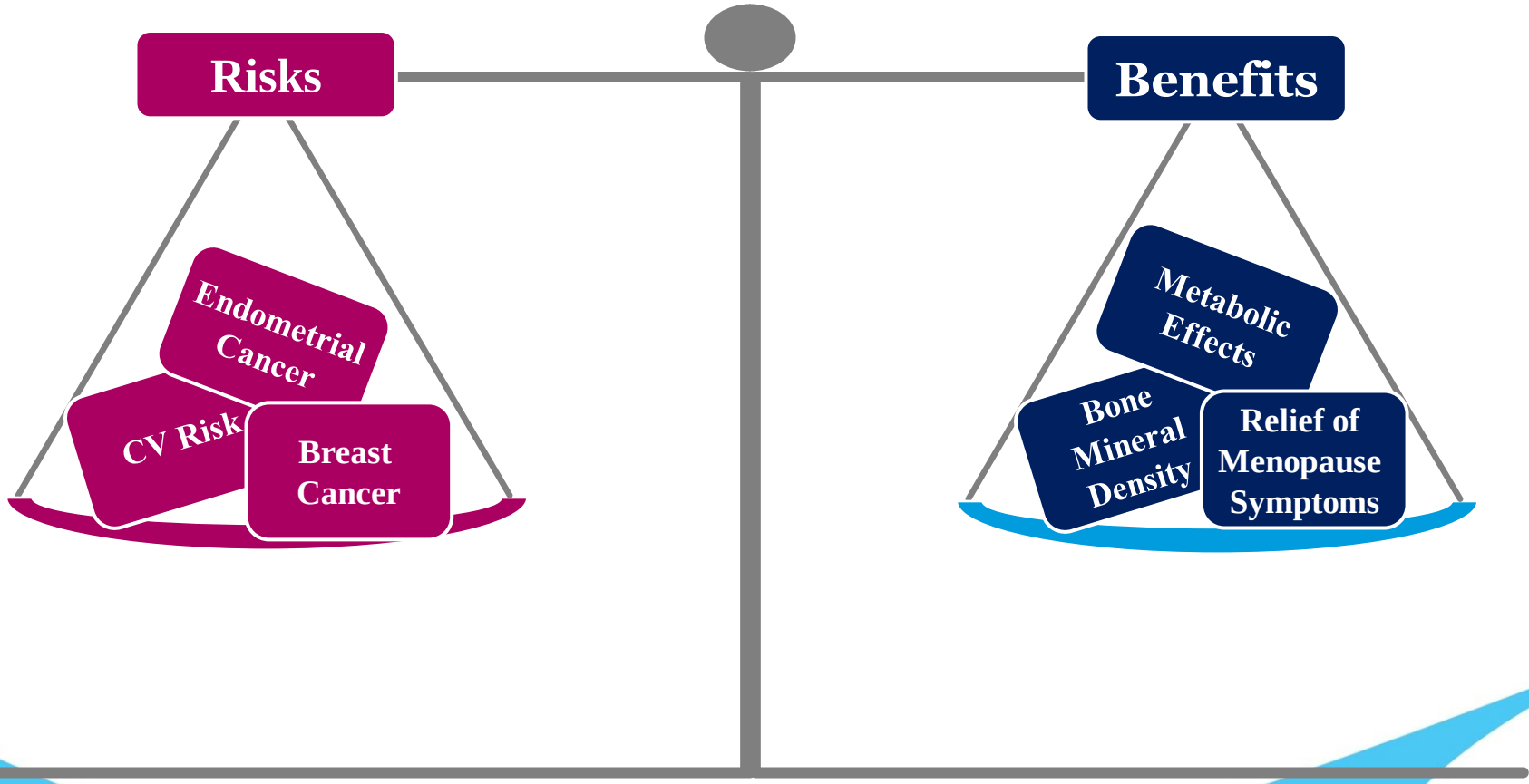
«...Preserved metabolism for the posterior cingulate in menopausal women who continued use of 17β-estradiol suggests that 17β-estradiol alone may slow the onset of Alzheimer's disease symptoms...»

«Preserved metabolism for the posterior cingulate in only those women who continued use of unopposed 17b-E suggests that HT with **17b-E alone may be a viable means to slow the onset of AD symptoms.** These findings lead to the conclusion that **the strongest neuroprotection of the precuneus/posterior cingulate area is afforded by unopposed 17b-E**, and that including progesterone in HT mitigates the benefits conferred by estrogen». treatment.

But, are there concerns about the use of hormone replacement therapy (HRT)????

1. **Breast cancer**
2. Other types of cancer
3. Cardiovascular diseases ...

HORMONE REPLACEMENT THERAPY (HRT) AND BREAST CANCER



National Institute for Health and Care Excellence (NICE). http://www.nice.org.uk/guidance/ng23. Accessed 1 April 2016;
De Villiers TJ and et al. *Climacteric* 2013;16:316–337

BREAST CANCER RISK FACTORS

Hormone Related Indicators of the Risk of Breast Cancer[1,2]

Relative Risk <2.0	• Use of oral contraceptives (OCs) (RR 1.1–1.2) • Estrogen use (RR 1.2–1.4) • Estrogen-Progestin use (RR 1.3–1.4) • No breast-feeding* (RR 1.4) • No children (RR 1.4) • Menarche <12 years (RR 1.3–1.5) • Menopause ≥ 55 years (RR 1.2–2.0)
Relative Risk 2.0–4.0	• Family history of breast cancer (RR 1.8–3.6) • First child ≥ 30 years (RR 1.7–3.5) • Increased bone density (RR 2.7–3.5)
Relative Risk >4.0	• Increased serum estradiol concentration (RR 1.8–5.0) • Increased breast density (RR 6.0)

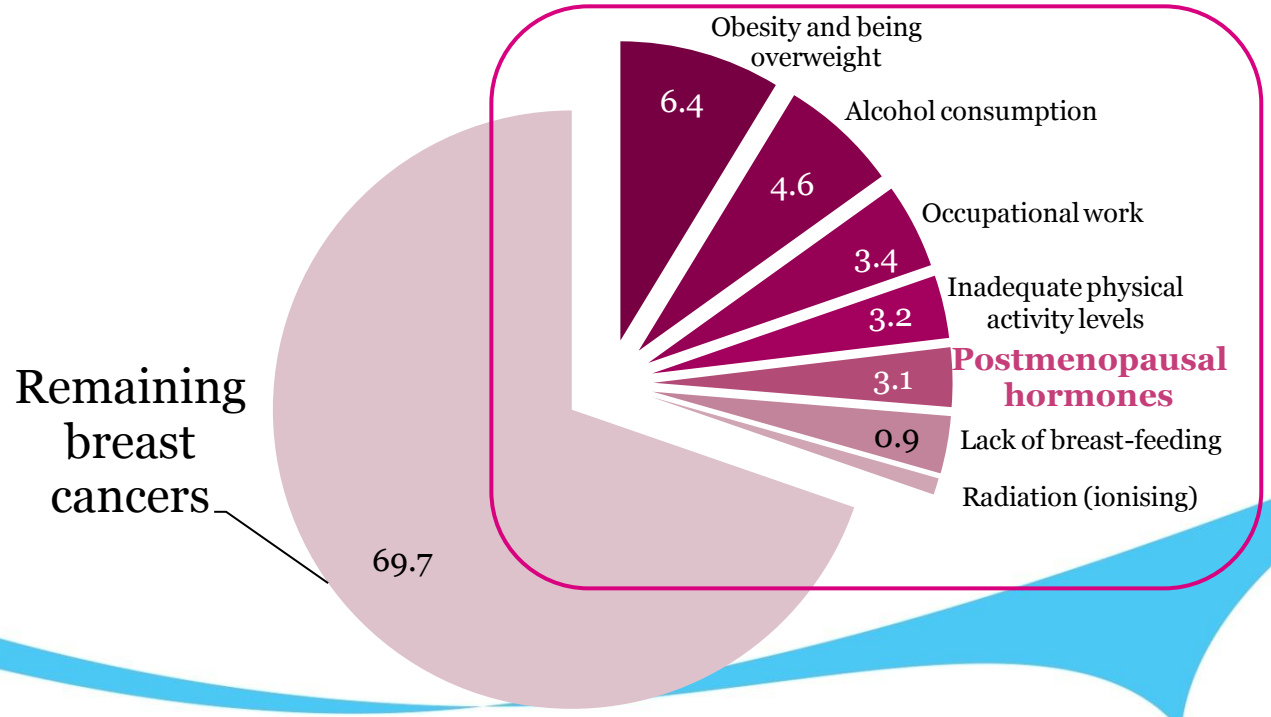
* High-risk group defined as no breastfeeding and low-risk group as breastfeeding ≥16 months
Relative risk (RR) calculated with the low-risk group as the reference group

1. Clemons M, Goss P. *N Engl J Med* 2001;344(4):276–85; 2. Singletary SE. *Ann Surg* 2003;237(4):474–482

Breast cancer and lifestyle factors

OVERALL POPULATION RISK (POPULATION ATTRIBUTABLE FRACTION)

Approximately 30% of breast cancers diagnosed in the UK in 2010 were estimated to be attributed to lifestyle and environmental factors

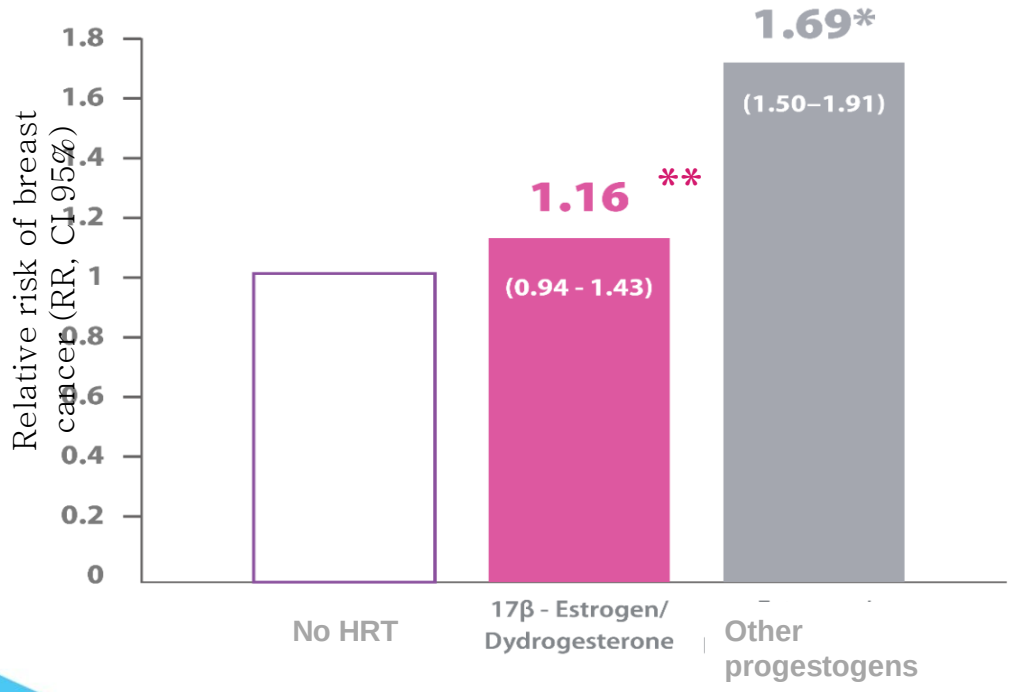


Parkin DM and et al. *Br J Cancer* 2011;105:S77–S81

Does any HRT increase the risk of breast cancer ???

Risk of breast cancer –not all HRTs have the same efficacy

17β - Estradiol/Dydrogesterone did not increase the risk of breast cancer versus no HRT or use of other HRT.



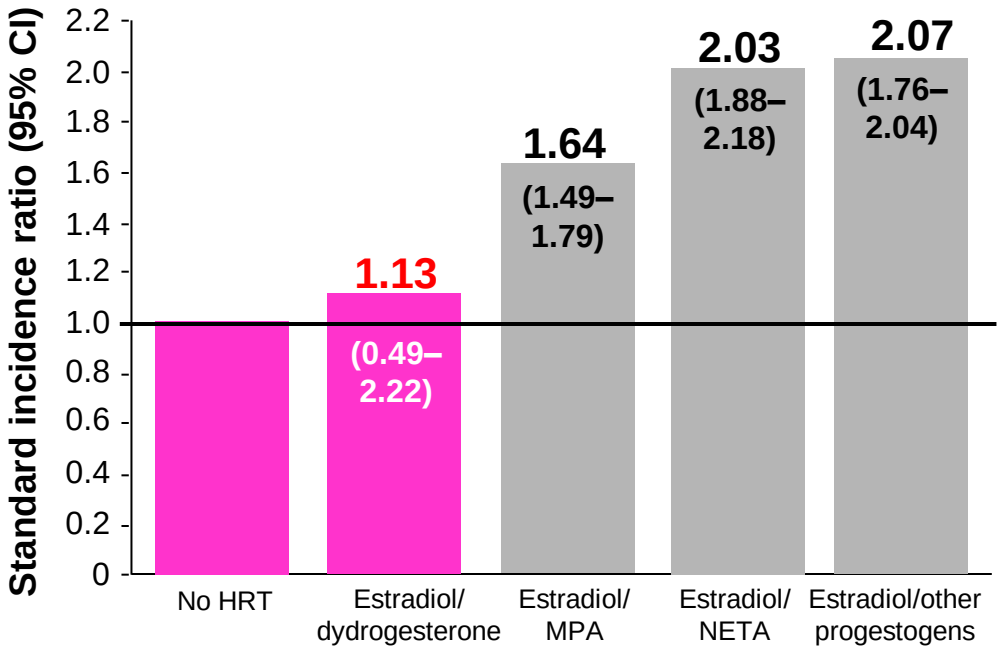
*p< 0.001 vs. other groups
**p = 0.16 vs No HRT

80,377 women for 8.1 years

A prospective cohort study in 80,377 menopause women for 8.1 years **- E3N French**

1. *Adapted from research of Fournier A et al. Breast Cancer Res Treat 2008;107:103–11;*

No breast cancer risk increase versus no HRT



50,210 women for **5** years

N = 50,210 women > 50 years; 5-year treatment duration

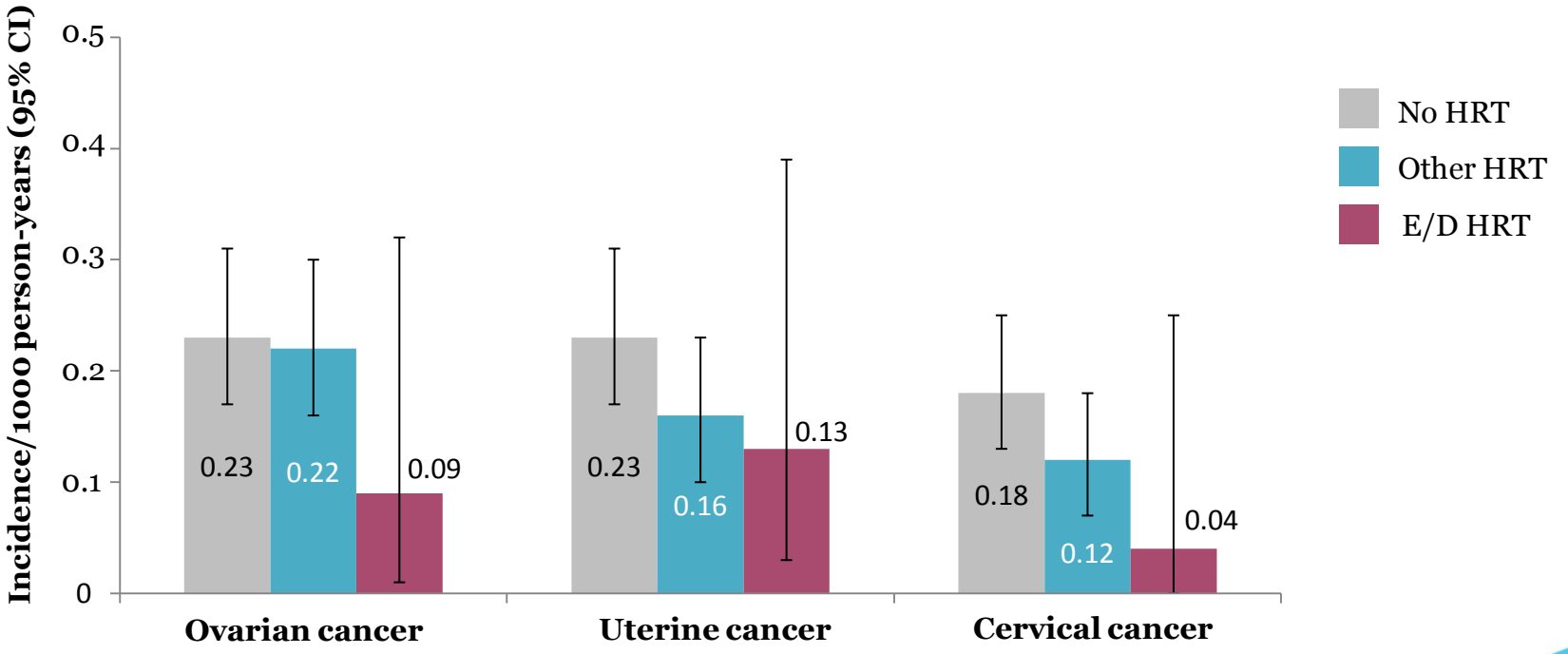
Not statistically significantly different from risk without HRT

Significantly different from the risk without HRT ($p < 0.001$ for all breast cancers; $p = 0.05$ for subtype)

Lyytinen H et al. Obst Gyn 2009;113:65–73.

GYNECOLOGICAL RISK WITH E/D (17β-estradiol/ dydrogesterone) SIMILAR TO NON-USERS OF HRT

Case-control analysis from UK-based General Practice Research Data N=69, 412



- **E/D use for several months to a few years was not associated with a risk of gynecological cancers *versus* no HRT or use of other HRT**

Schneider C and et al. *Climacteric* 2009;12:514–524

2016 International Menopause Society recommendation and 2017 Vietnam National Standard Guidelines

International Menopause Society
Promoting education and research on midlife women's health

Updated 2016 International Menopause Society recommendation on menopausal hormone therapy and preventive strategies for midlife health

BỘ Y TẾ
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HƯỚNG DẪN QUỐC GIA
về các dịch vụ chăm sóc sức khỏe sinh sản

(Ban hành kèm theo Quyết định số 4128/QĐ-BYT ngày 29/7/2016 của Bộ trưởng Bộ Y tế)

Hà Nội, 2016

"Hormone replacement therapy (HRT) is still **THE MOST EFFECTIVE THERAPY** for vasomotor symptoms"

"Compared to synthetic progestogens **DYDROGESTERONE** minimize the risk of breast cancer"

The Vietnam National Guidelines:

- *Progestogens:*

+ Nếu còn tử cung, thì phải sử dụng progestogen kèm theo estrogen. Progestogen có nhiều dạng như kết hợp với estrogen trong mỗi viên nội tiết (Femoston:17 β-estradiol 1mg/dydrogesterone 5 mg), hoặc viên Dydrogesterone riêng lẻ (Duphaston 10 mg), hoặc progesterone dạng mịn (Utrogestan, Progendo, Cyclogest 200 mg). Một số tác dụng phụ của progestogen là căng đau vú, phù, trầm cảm hoặc nhẹ hơn, buồn bã, cáu gắt, bứt rứt.

HOW IS HORMONE REPLACEMENT THERAPY (HRT) USED?

~~Uterus~~

Continuous Estrogen

Estrogen

No tablet break
No bleeding as no uterus

Uterus

Cyclic HRT

Estrogen

Progestogen

7-day tablet break

Day 7 — Day 14

Sequential therapy with tablet break
Regular bleeding at end of cycle

Continuous Sequential HRT

Estrogen

Progestogen

Day 14

Sequential therapy without tablet break
Regular bleeding at end of cycle

(Continuous Combined HRT

Estrogen

Progestogen

Combined therapy without tablet break
No bleeding at end of cycle

Besides estrogen, phytoestrogens or some other functional foods have been confirmed that they have beneficial effects in slowing down brain aging or depression, anxiety because only very low dose of estrogen is required.

Rubio J, Caldas M et al., conducted experimental study of Maca plant (Lepidium meyenii) in Peru and showed that, in addition to the effect of the hypothalamic-pituitary-ovary axis regulation, the Maca extract has effect of reducing neurasthenia and enhancing learning ability.

Valiero LG Jr, Gonzales GF *(Toxicol Rev 2005;24☹1):11-35)* studied and proved that Lepidium meyenii is not toxic to humans.

Katerina Valentova, Jitka Ulrichova *(Biomed papers 14/(2), 119-130 (2003)* conducted fundamental studies and clinical experiments and showed that:

- Maca has been used as food and folk medicine in Peru for centuries, and more recently, has been popular in South America, North America, Europe.
- Lepidium meyenii in Maca plant can be *used as an adjuvant for treatment*:
  - infertility,
  - premenstrual symptoms,
  - depression, neurasthenia
  - and osteoporosis

- ***Maca – Lepidium Meyenii***:

- This is a herb, commonly known as Peruvian Ginseng, has effect of **increasing strength, endurance and helping the body to adapt to external environment.** It is used by people **to treat anemia, infertility and used for sport athletes and for patients with decreased sexual activity.**
- It has been studied abroad and in Vietnam and recognized that **having effect to regulate receptors of male and female sex hormones.** Lepidium Meyenii extracts contain estrogen, which may have a hormone supplement effect for women at the age of menopause.
- **Four studies of Lepidium Meyenii were analyzed and showed that the use of Lepidium Meyenii improved the Greene Climacteric index and the Kupperman index of quality of life.**

Isoflavones extracted from soy bean

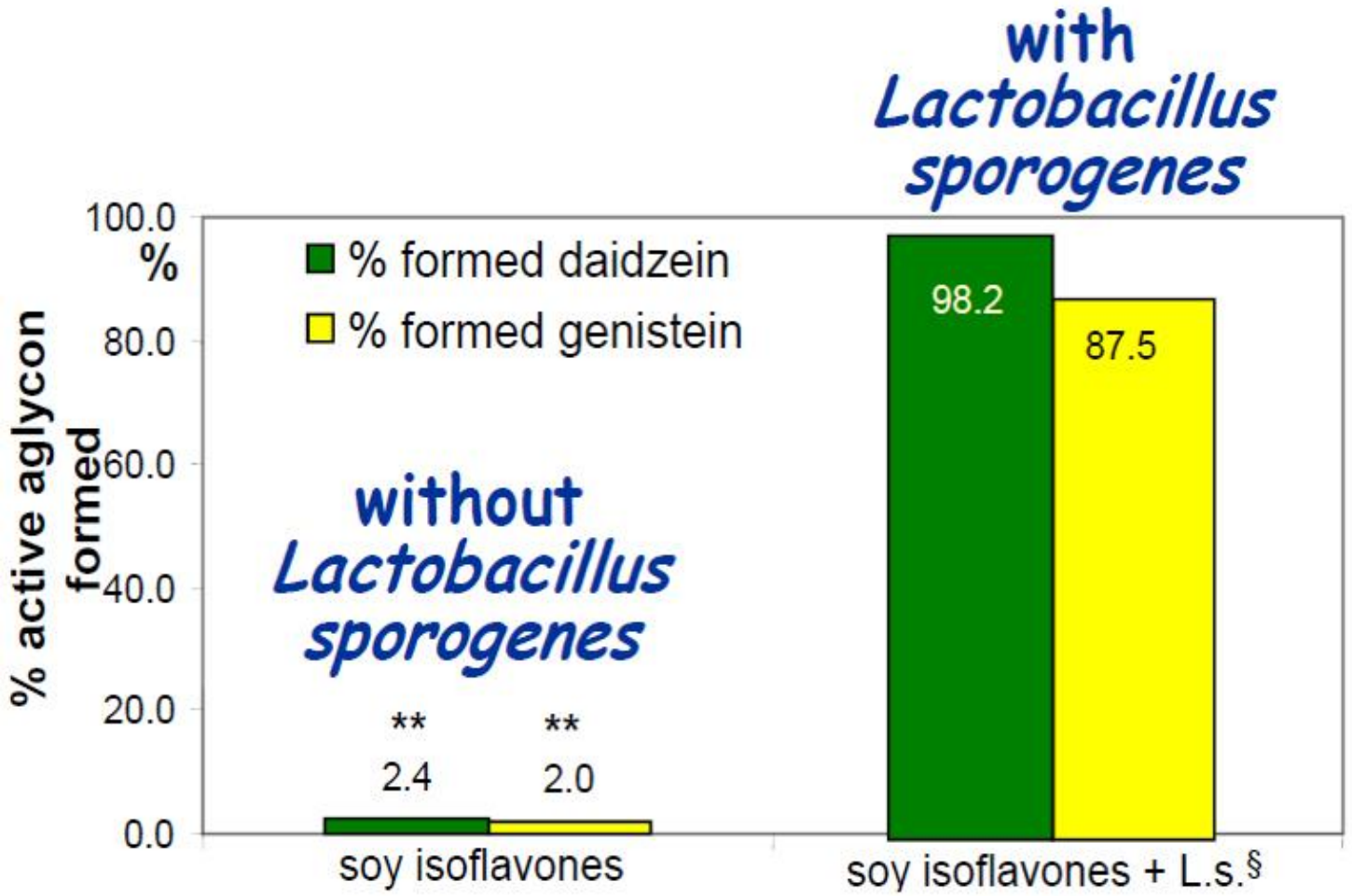
Isoflavones in soy beans are often referred to as herbal estrogen - phytoestrogen because isoflavones bind to both estrogen receptors, though it is weak.

A pooled analysis of 13 studies with 602 women used # 6 - 12 months with isoflavones and 594 with placebo, showed a reduction in menopausal symptoms (mean reduction of -20.62 with 95% CI (-28.38) - (-12.86)).

Mechanism of action:

- **genistein and daidzein aglycone from isoflavones are absorbed through intestine**
- ***Daidzein is converted by a type of enterobacteria into 2 types of equol*: R(+) equol and S(-)-equol are the same as estrogen but rate of binding to globulin is less (45 – 50%).**
- ***The bioavailability of isoflavones depends on whether the intestinal tract with enterobacteria produce S(-)equol or not.***

Lactobacillus sporogenes converts isoflavones into active forms



** p< 0.01 vs Estromineral

Arcoraci V 2005

Estromineral contains soy isoflavones and Lactobacillus sporogenes, along with Calcium and Vitamin D3, Equisetum extract of Equisetum debile Roxb., is a fully natural treatment for menopause.

- **Isoflavones and metabolites *effectively alleviate menopausal symptoms.***
- **Isoflavones do not cause endometrial thickening, acting is only *1 part of million of estradiol on endometrium.***
- **Isoflavones do not change breast tissue cells.**
- **An appropriate study is required, at least for 24 months, to see the effect of isoflavones on bone.**

- ***Soy bean isoflavones*** **can be used with** ***a starting dose of 50 mg or more daily, continuously for 12 weeks*****.**
- **It is possible to give orally** ***3 g of soy bean sprout powder daily*** **to have enough of the above dose.**
- **It is needed** ***to continuously monitor*** **to detect undesirable effects**
- **If** ***after 12 weeks but the symptoms did not decrease, it must be changed to other treatment.***

Summary

1. Increased number of menopause women, increased patients with neurodegenerative diseases (brain aging, Alzheimer ...), increased depression.

2. It is needed to improve quality of life for menopause women, not only without physical diseases but also protection of intellectual capacity, communication...

3. The brain aging mechanism is being explored, it is still much complex. There is a detail bringing a hope: the hippocampus is the place where new neurons can be produced even in older people.

Can brain aging be slowed down?

4. Attention should be paid to mental health care, stress reduction, prevention and treatment of early metabolic diseases.

5. Estrogen, especially 17β-estradiol, can be used as soon as in the menopausal transition period to protect brain, neurons and transmitting nerves.

6. Some functional foods have good effects for the brain, slowing down brain aging, alleviating depression and anxiety such as phytoestrogens or Lepidium Meyenii.

CONCLUSIONS

- **Meet patient first time:**
  - **Examining carefully medical history, previous history, functional symptoms**
  - **Noting delicate symptoms: urinary incontinence, painful and burning intercourse, frequent urination - especially at night**
- **Treatment consideration:**
  - **<u>Determination</u>: importance and impact level on quality of life, risk when treatment with MHT, full explanation of benefits and side effects; advice on lifestyle change, nutrition, exercise, non-hormone therapy**
  - **Treatment decision is based on effect extent of symptoms**

Moderate/ severe → **MHT**

(Lowest effective dose - less side effects – 5 years)

Individualization

Considering risk-benefit → **Follow up**

Mild → **Lifestyle change**

Exercise

Non-hormone therapy

Early menopause Premature ovarian failure → **Hormone supplement:**

Early

Higher dose than standard dose

SINCERELY THANKS