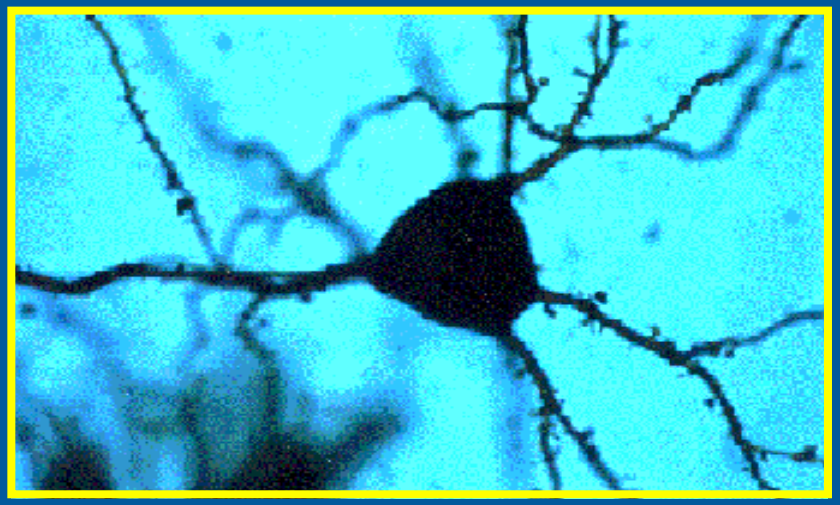
JAGIELLONIAN UNIVERSITY
IN KRAKOW

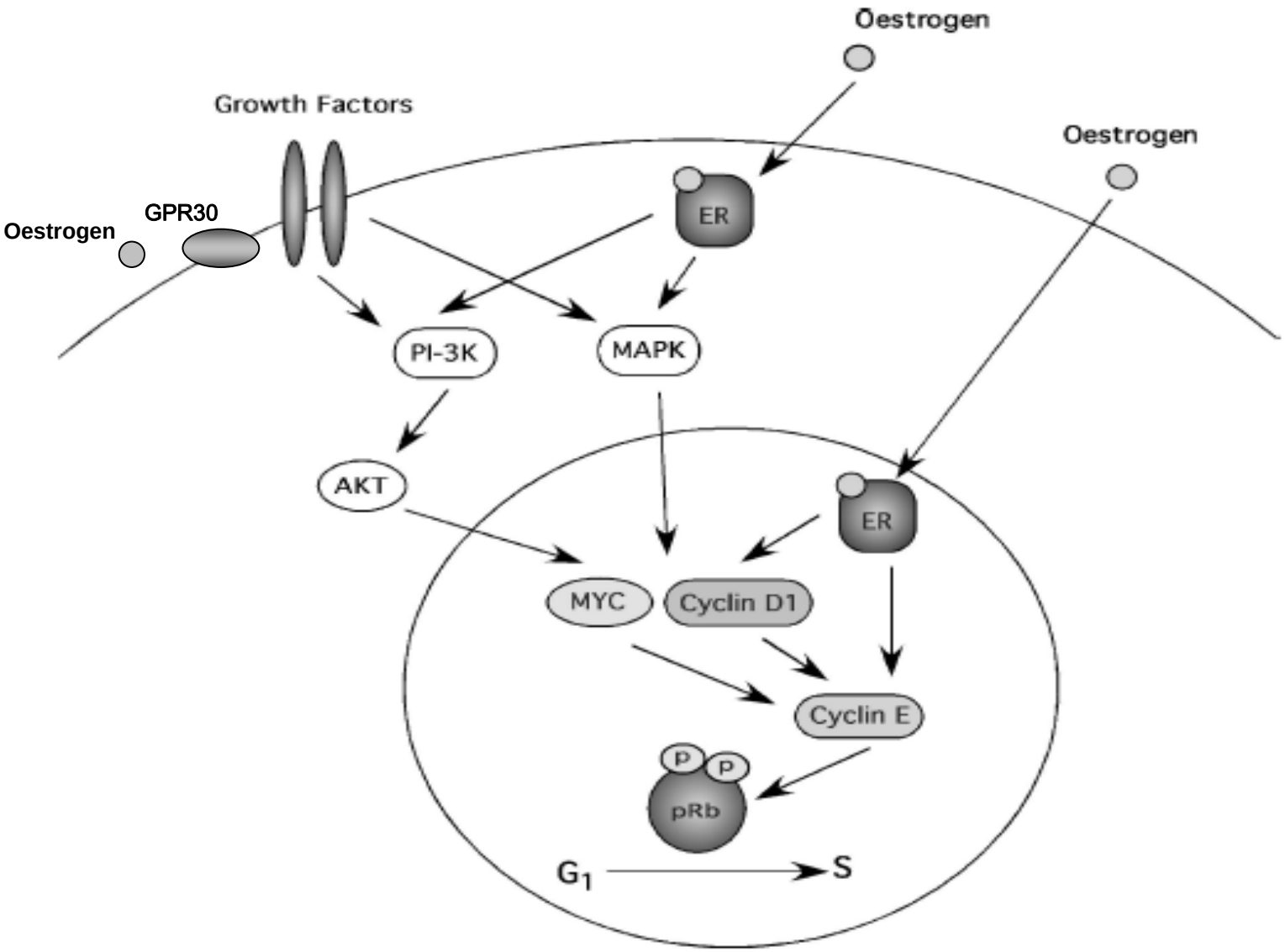


Nuclear receptors

Lecture

Estrogen:
the best for the brain

Cross-talk between growth factor and estrogen pathways



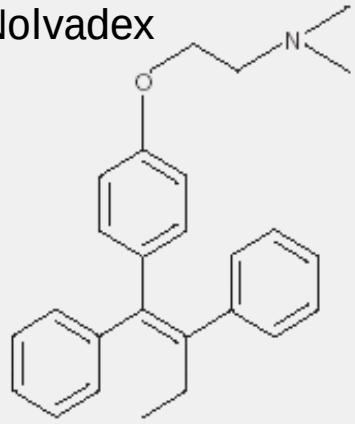
Butt et al. 2005

Tamoxifen – clinical trials

- More than 13 000 women at high risk of breast cancer (before and after menopause) were treated for 5 years with tamoxifen or placebo.

- Tamoxifen **decreased** the risk of breast cancer by 50%.

Nolvadex



Tamoxifen

There were, however, serious side-effects:

- Tendency to increased bone fracture rate

- Increase (2.6 - 4 fold) frequency of **uterus cancer** in postmenopausal women.

In the late 1980s it was recommended as **a drug protecting the women with a high risk of breast cancer, but not in general population** because of the risk of cervical cancer.

Tissue selectivity

- **Ideal profile for SERM**:
(selective estrogen-receptor modulators)

- *Antagonist* **- breast, uterus**

- *Agonist* **- bone, brain, colon, neurons, blood vessels**

SERM - Raloxifene

- Drug similar to tamoxifen, but with **weaker proestrogenic activity in the uterus**, expected to maintains appropriate bone density in the postmenopausal women

- **Efficient chemopreventive drug**: 13 breast cancer cases out of 5129 women in raloxifene group **(0.25%)** versus 27 out of 2576 in placebo group **(1.05%)** in three years - MORE trial.

- Clinical trial to test its effectivity in prevention of **ischemic heart disease** in postmenopausal women - **no positive** but also **no negative effects**.

- Beneficial (applied with estrogens) in protection against osteoporosis.

- In comparison to tamoxifen: **similarly effective** in chemoprevention, but **safer** - less side effects observed in randomized clinical trials.

Evista

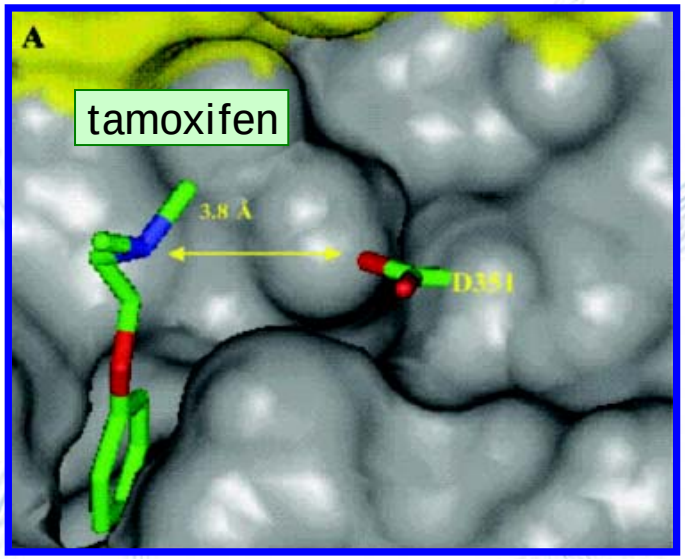
Raloxifene

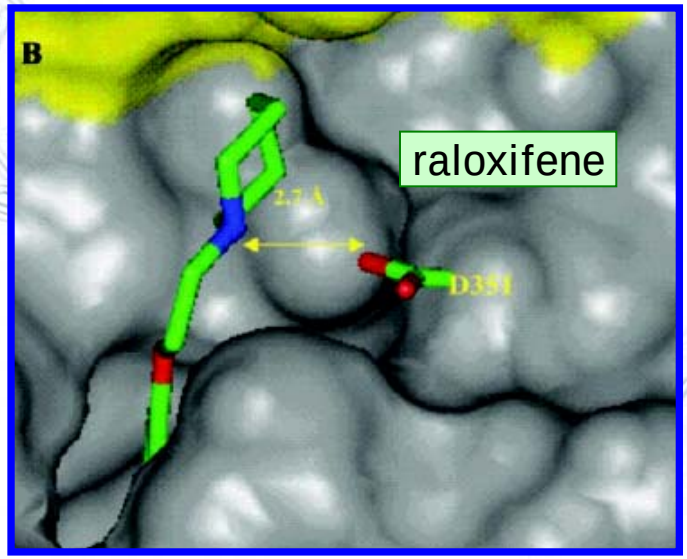
Tissue selectivity

Why does tamoxifen act as proestrogen in uterus, while raloxifene not?

- Side chain of raloxifene is located 1 Å closer to aspartic acid 351 than side chain of tamoxifen in LBD (important for SRC binding).

- If ER undergoes the mutation (D351Y), what happens in some cancers, raloxifene starts to act as estrogen.





Jensen & Jordan, Clin Cancer Res. 2003

Tissue selectivity

- Shape of ER is determined by the nature of the ligand with which it is bound.

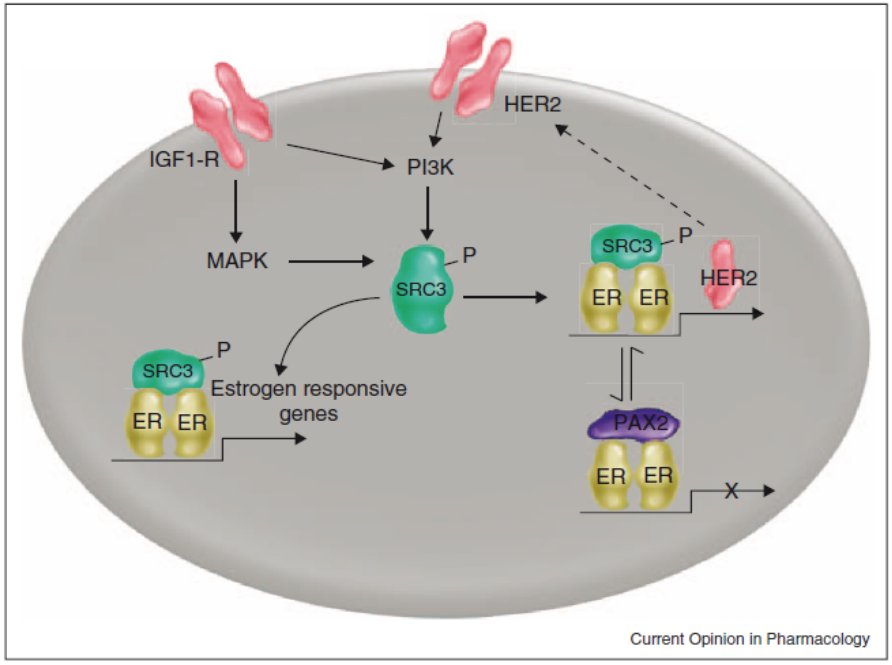
- Receptor conformation regulates the interaction with distinct coregulators.

- The levels of transcriptional coregulators differ between cells.

- ERα and ERβ respond differently to pharmacological agents: whereas tamoxifen inhibits transactivation by ERα, it can function as an ERβ agonist.

- Overexpression of the transcriptional coregulator SRC-1 alone was sufficient to confer upon cells the ability to recognize tamoxifen as an agonist.

- Elevated expression of SRC-1 and/or SRC-3 can be found in a large number of breast cancers.



McDonnell and Wardell, Curr Opinion Pharmacol 2010

SERMS

Raloxifene:

- reduces the risk of invasive breast cancer
- reduces the risk of vertebral fracture
- does not influence the risk of CAD in postmenopausal women
- doubles the risk of venous thromboembolism increasing the risk of stroke

Bazedoxifene:

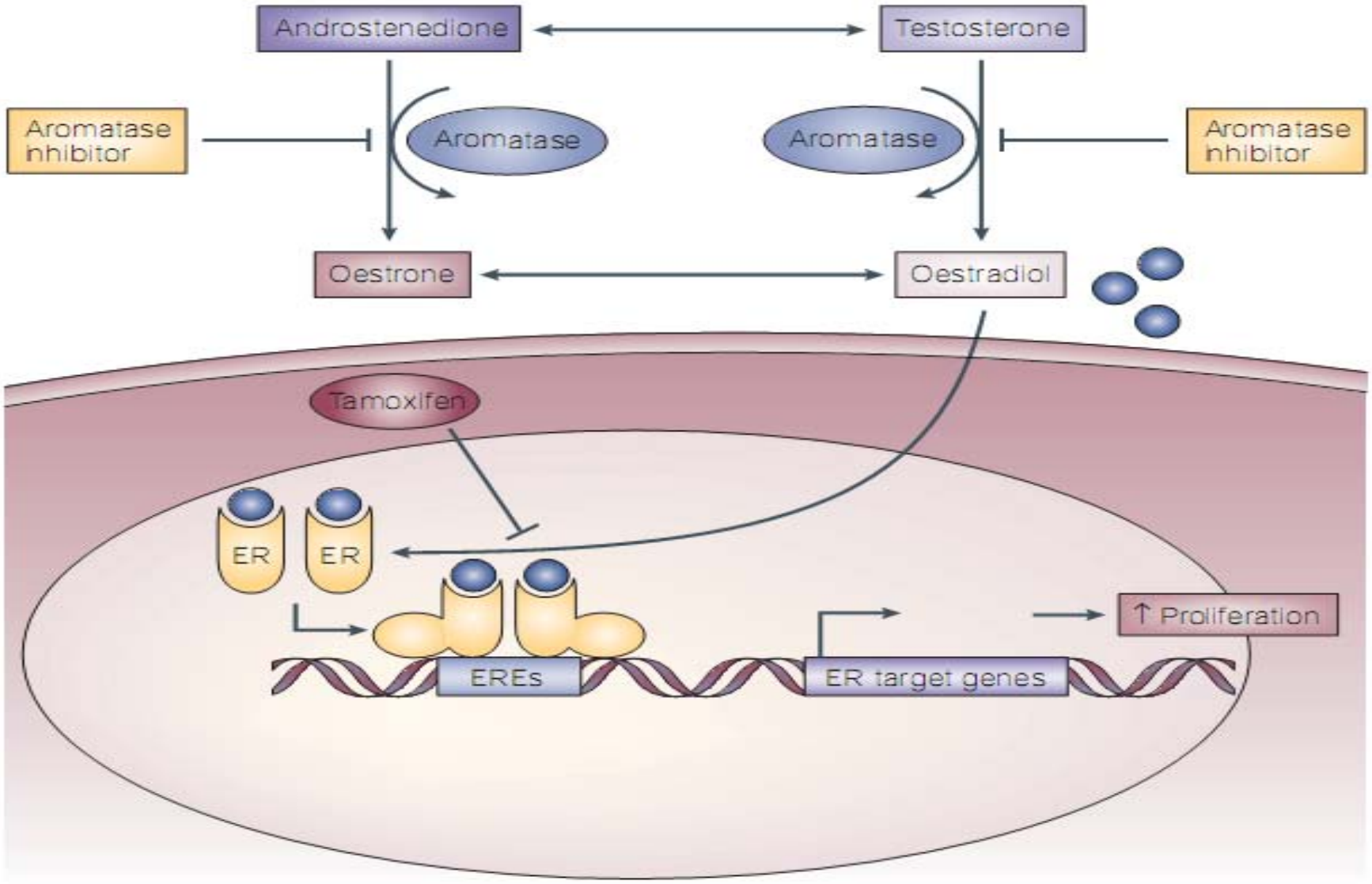
- no adverse effects on endometrium or breast
- reduces the risk of nonvertebral fracture
- increases the risk of venous thromboembolism

Lasofoxifene:

- reduces the risk of breast cancer
- reduces vertebral and nonvertebral fractures
- increases incidence of vaginal bleeding, endometrial thickening and polyps
- reduces the risk of heart disease events, as well as the risk of stroke

Silverman S.L. Curr Osteoporos Rep, 2010.

Aromatase inhibitors



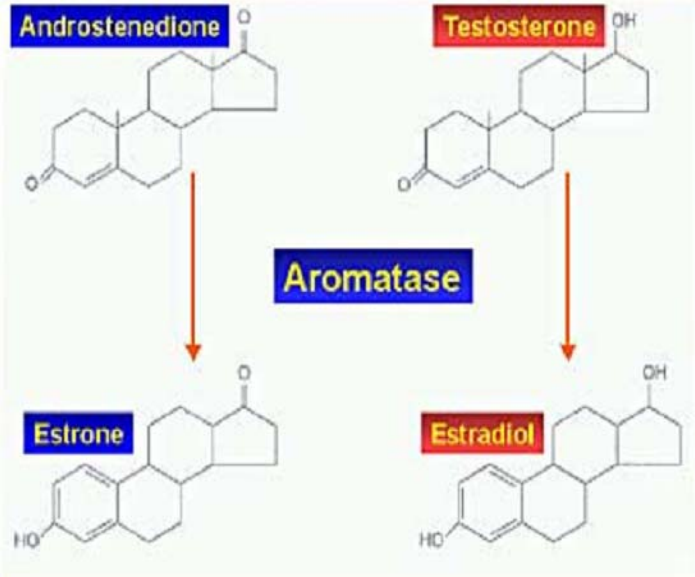
Johnson & Dowsett, Nature Rew. 2003

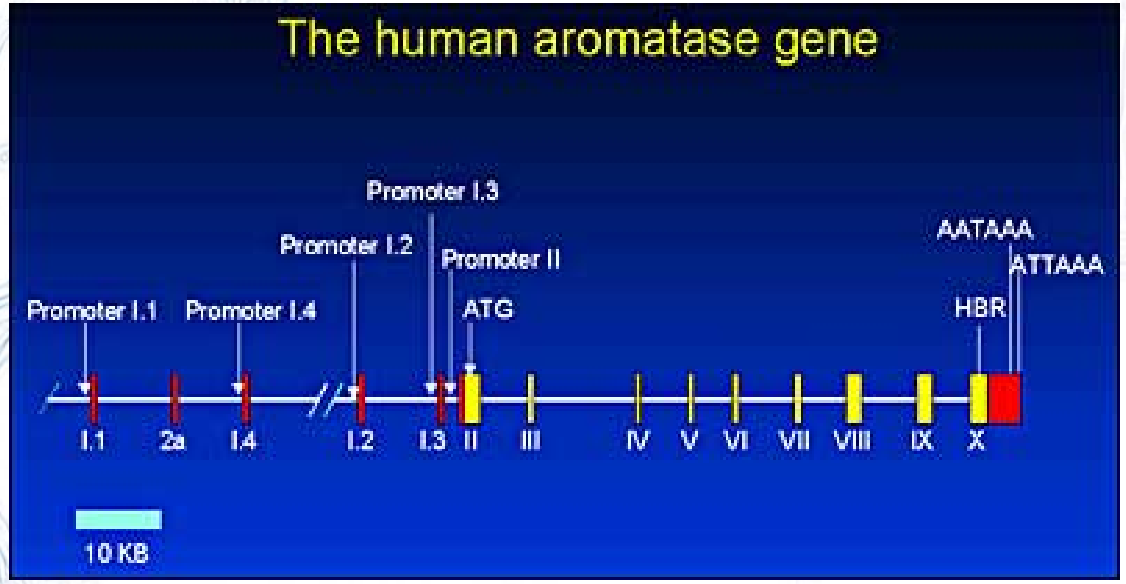
Aromatase inhibitors

- Aromatase (microsomal cytochrome P450) is an enzyme transforming androgens to estrogens

- In human population aromatase is **polymorphic** and it may influence the estrogen level in women.

- Increased expression of aromatase in cancers, results from **usage of different promoter** (instead of promoter which is normally active in adipocytes, active becomes promoter normally active in the ovary).





Aromatase inhibitors – clinical applications

ATAC trial (anastrozole, tamoxifen, or combination tamoxifen and anastrozole)

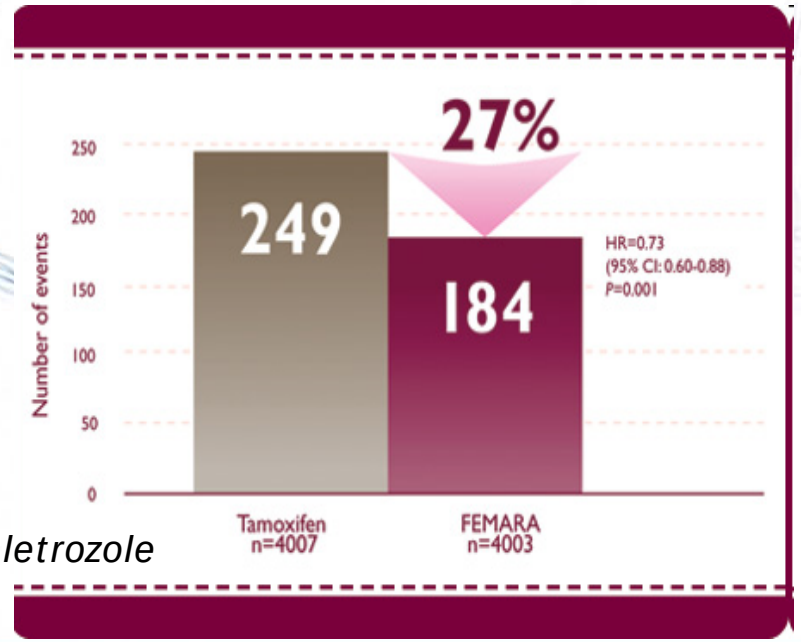
- 9366 postmenopausal patients, with early breast cancer were divided to 3 groups:

  a) tamoxifen (antagonist of ER),
  b) anastrozole (aromatase inhibitor)
  c) combination of both drugs

- comparing to tamoxifen, afer 33 months in patients treated with anastrozole:

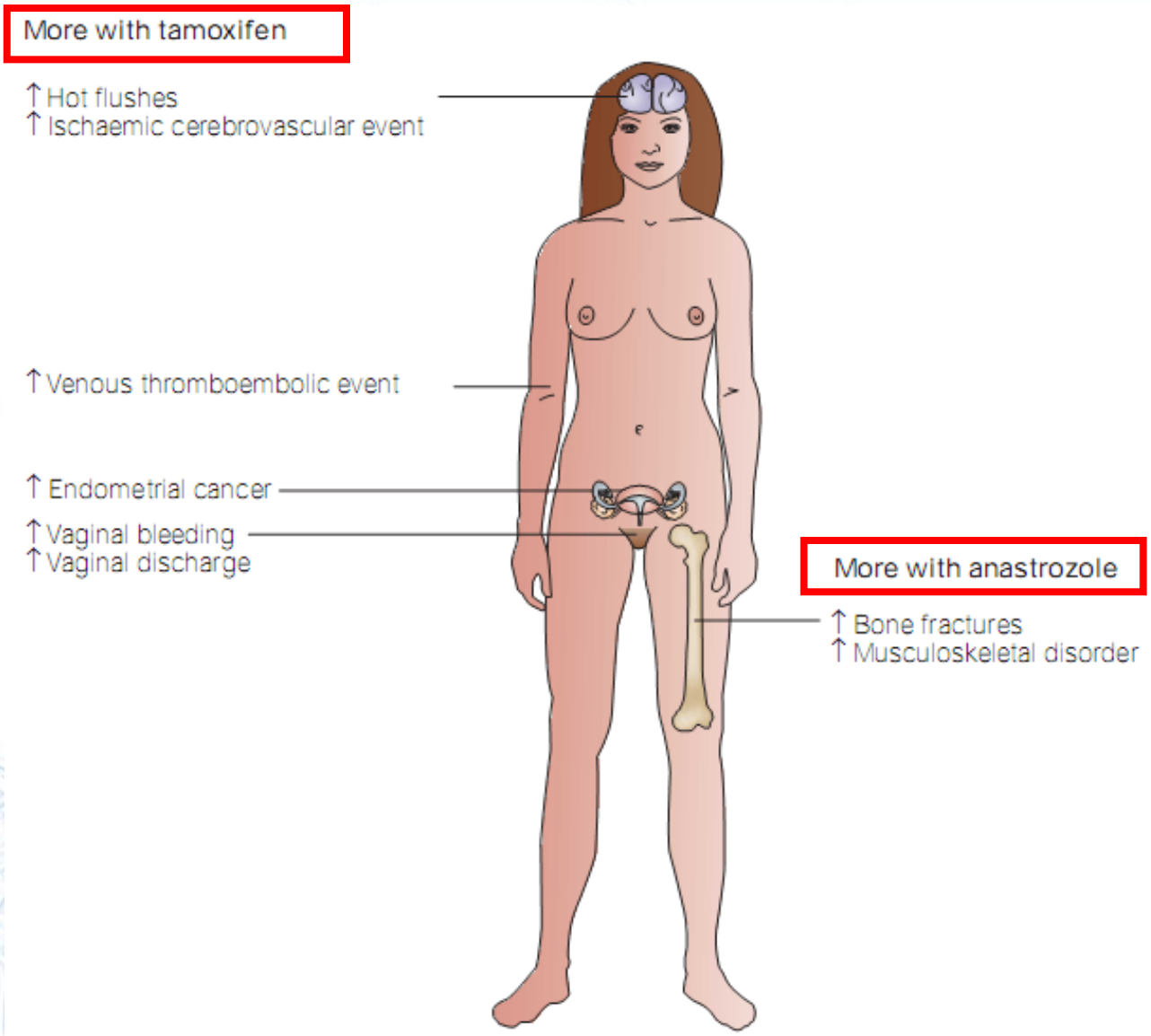
* higher proportion of patients free of disease
* less cases of development of new cancer in the second breast
* less significant side-effects, although higher fracture rate and higher level of bone resorption markers

- combination of both drugs was less effective than anastrozol alone.



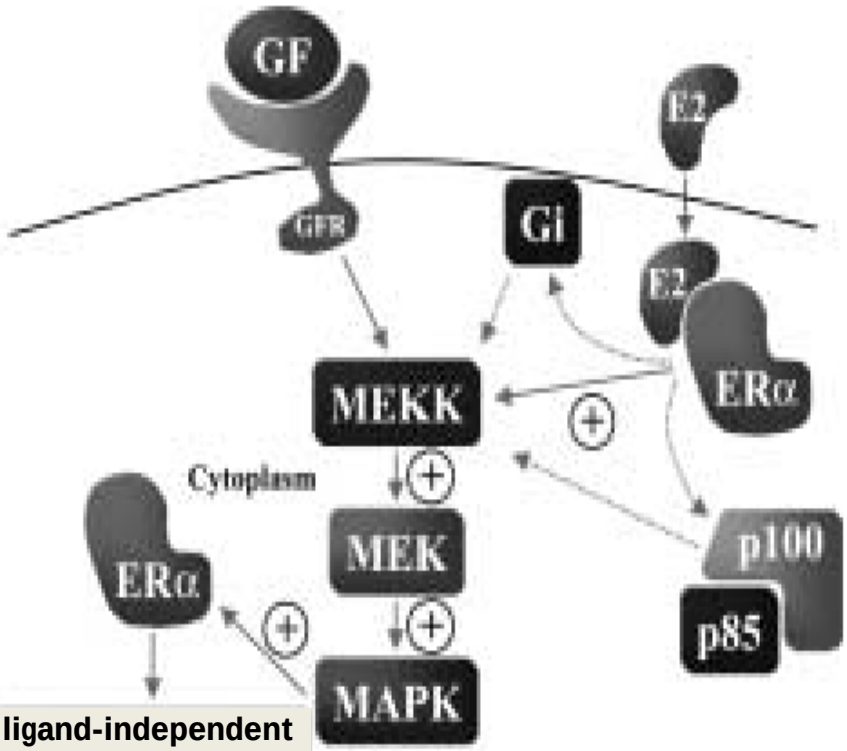
protection against distant metastasis - tamoxifen v. letrozole

Side effects



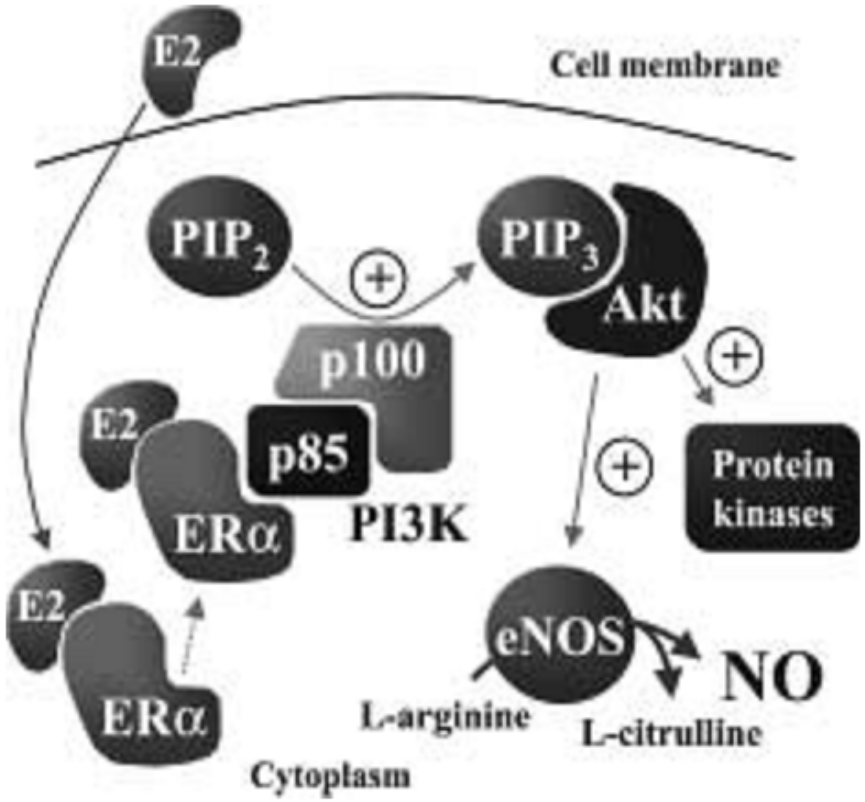
Johnson & Dowsett, Nature Rew. 2003

Cross-talk between growth factor and estrogen pathways



ligand-independent activity

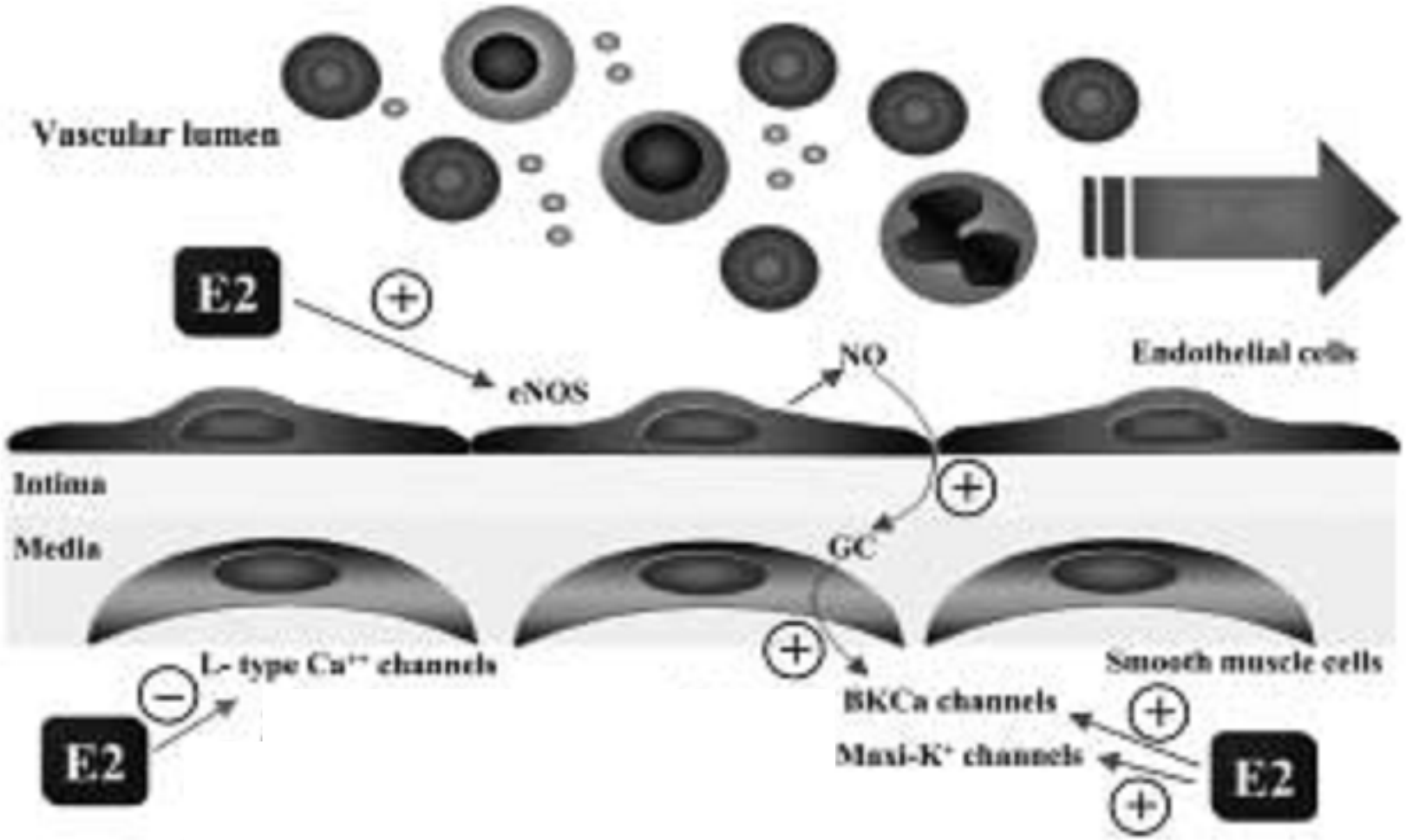
ERs and MAPKs. Binding of growth factors (GF) to the specific membrane receptors induces activation of the MAPK cascade (MEKK → MEK → MAPK). Active MAPK phosphorylates and activates ER independently of the presence of E_2. On the other side, E_2-bound ER triggers the activation of the three-step ERK 1/2 MAPK module. ER activation of MAPK is finely modulated by Gi protein (Gi)-dependent and PI3K (p85/p100)-dependent intracellular pathways.



ER and PI3K. Ligand (E_2)-bound ER interacts with the regulatory subunit (p85) of PI3K (p85/p110). The catalytic subunit (p110) is thus activated, leading to phosphorylation of phosphoinositides (PIP_2, PIP_3) on the D-3 position of the inositol ring. PIP_3 is recognized by specific docking sites on protein kinases, which trigger the activation of protein kinase Akt. Akt regulates, via phosphorylation, several intracellular enzymes (protein kinases), including eNOS, leading to increased NO synthesis.

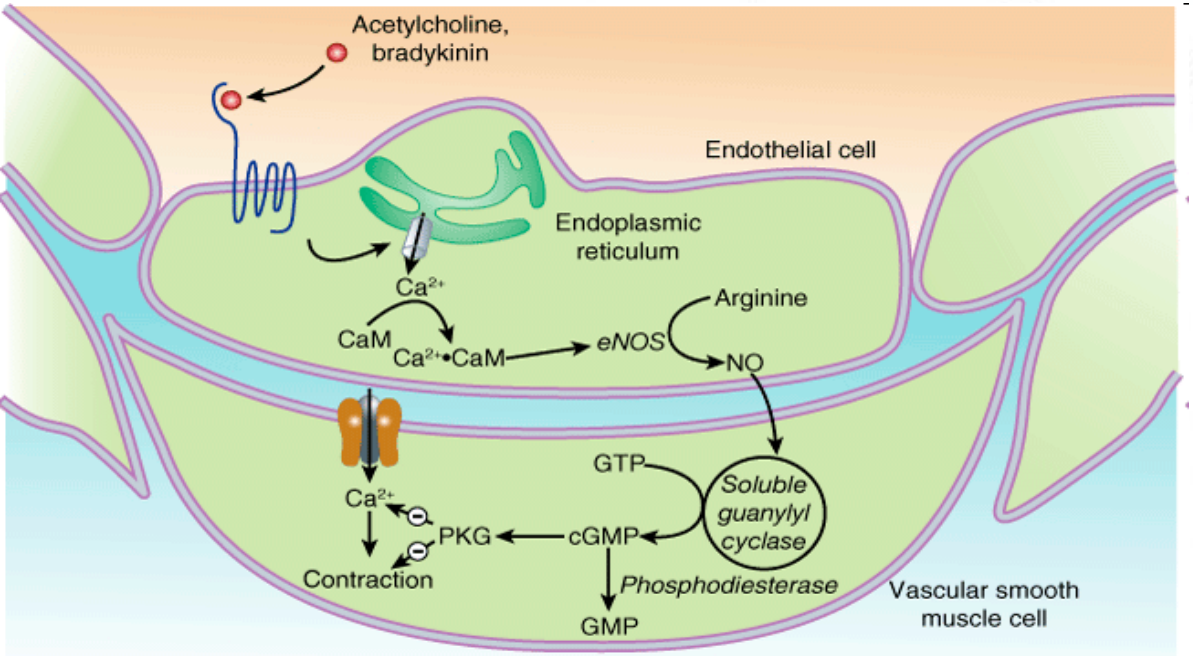
Simoncini et Genatzzani. Eur J Endocrin 2003

Estrogen leads to vasorelaxation



Simoncini et Genatzzani. Eur J Endocrin 2003

Estrogen leads to vasorelaxation



NO a vasodilator.

NO protects against thrombosis and atherogenesis (through the inhibition of proliferation and migration of vascular smooth muscle, and inhibition of platelet aggregation).

NO has an additional inhibitory effect on blood coagulation by **enhancing fibrinolysis**.

NO **reduces endothelial adhesion of monocytes and leukocytes**, due to the inhibitory effect on the expression of adhesion molecules on the endothelial cells.

NO may act as an **antioxidant,** blocking the oxidation of low-density lipoproteins and thus preventing or reducing the formation of foam cells in the vascular wall.

Neuroprotective activity of estrogens

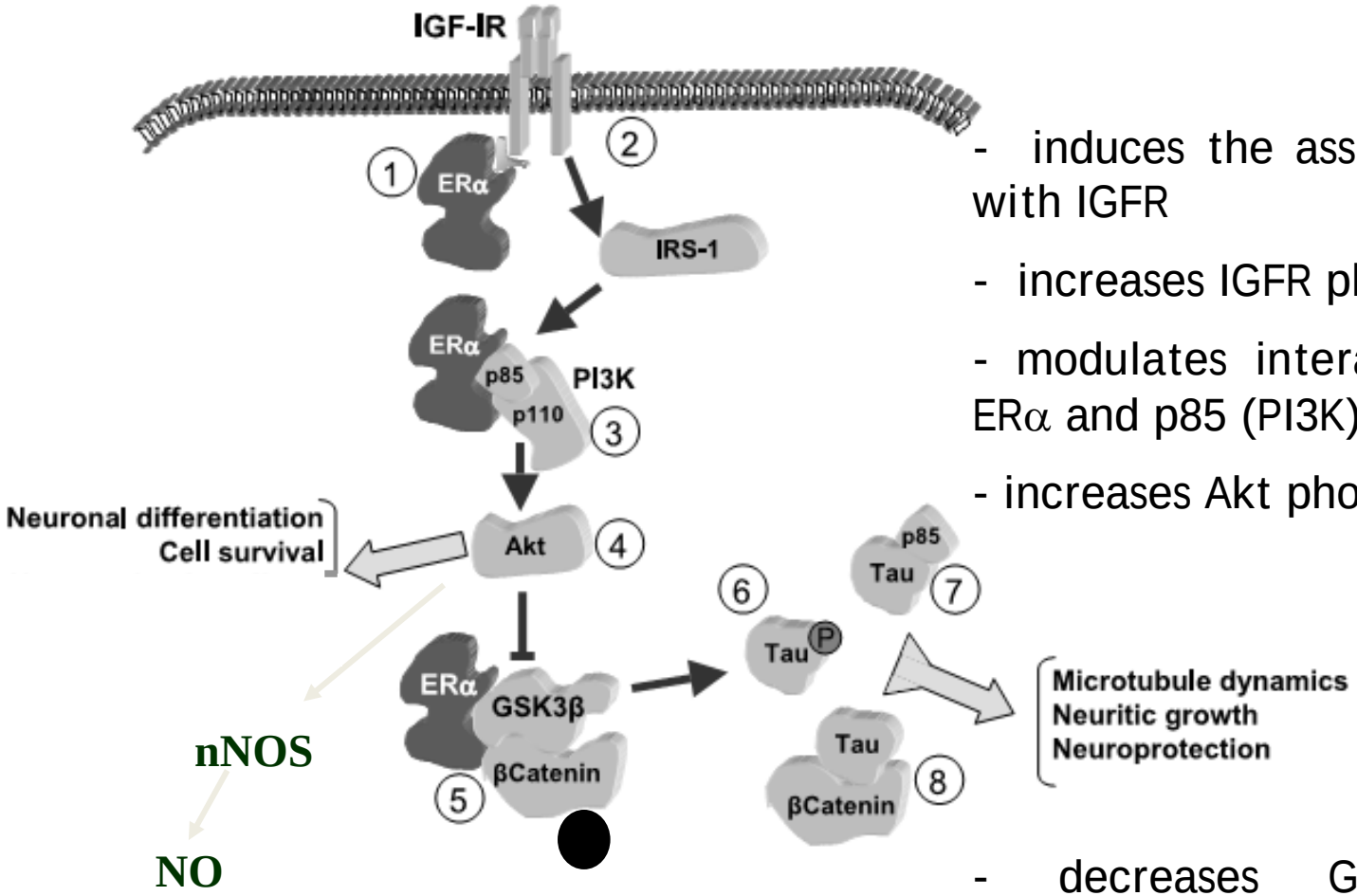
Evidence *in vitro*

* Estrogens *in vitro* upregulate expression of different **neurotrophic factors and their receptors** (e.g. **BDNF** – brain derived neurotrophic factor, **NGF** – neurone growth factor).

* Estrogens increase expression of **structural proteins** of neurons (proteins in neurofilaments and microtubules, **TAU, GAP43** – proteins necessary for growth of axons) and **activation of nNOS**.

* Hyperphosphorylation of TAU leads to TAU dysfunction and is one of the basic pathogenic mechanisms in Alzheimer disease. Both in vitro and in vivo the kinase **which phosphorylates TAU (glycogen kinase 3β, GSK3β) is inhibited by estrogens**.

Estradiol in the brain



- induces the association of ERα with IGFR
- increases IGFR phosphorylation
- modulates interaction between ERα and p85 (PI3K)
- increases Akt phosphorylation
- decreases GSK3β thereby decreases Tau phosphorylation
- increases interaction of p85 and β-catenin with Tau.

Neuroprotective activity of estrogens

Evidence *in vivo*

- Rat **females** are much **less sensitive to brain ischemia**, trauma or some neurotoxins than males. Also in human the **frequency of stroke** and reperfusion injury is **much rarer in premenopausal women** than in men at the same age.

- Expression of aromatase and **production of estrogens** is induced in the glial cells in **response to injuries**.

- Estrogens delivered just before or soon after (up to 3 h) trauma is neuroprotective (data from rats).

- Estrogens reduce reperfusion induced brain injury via:
  * upregulation of Bcl2.
  * upregulation of caspase inhibitors.

} *inhibition of apoptosis*

- Estrogens can act as a neuronal growth factor. Rat female have more new formed neurons in hippocamp than males at the same age.

Neuroprotective effects of estrogens

Clinical and epidemiological evidence

- Neurogenerative diseases have lower frequence, later time of onset, slower progression, and better prognoses in premenopausal women than in men. After menopause these differences disappear.

- Protective effect of estrogens in premenopausal women was proposed in:
    * schizophrenia
    * Alzheimer Disease (AD)
    * Parkinson Disease (PD)
    * Stroke

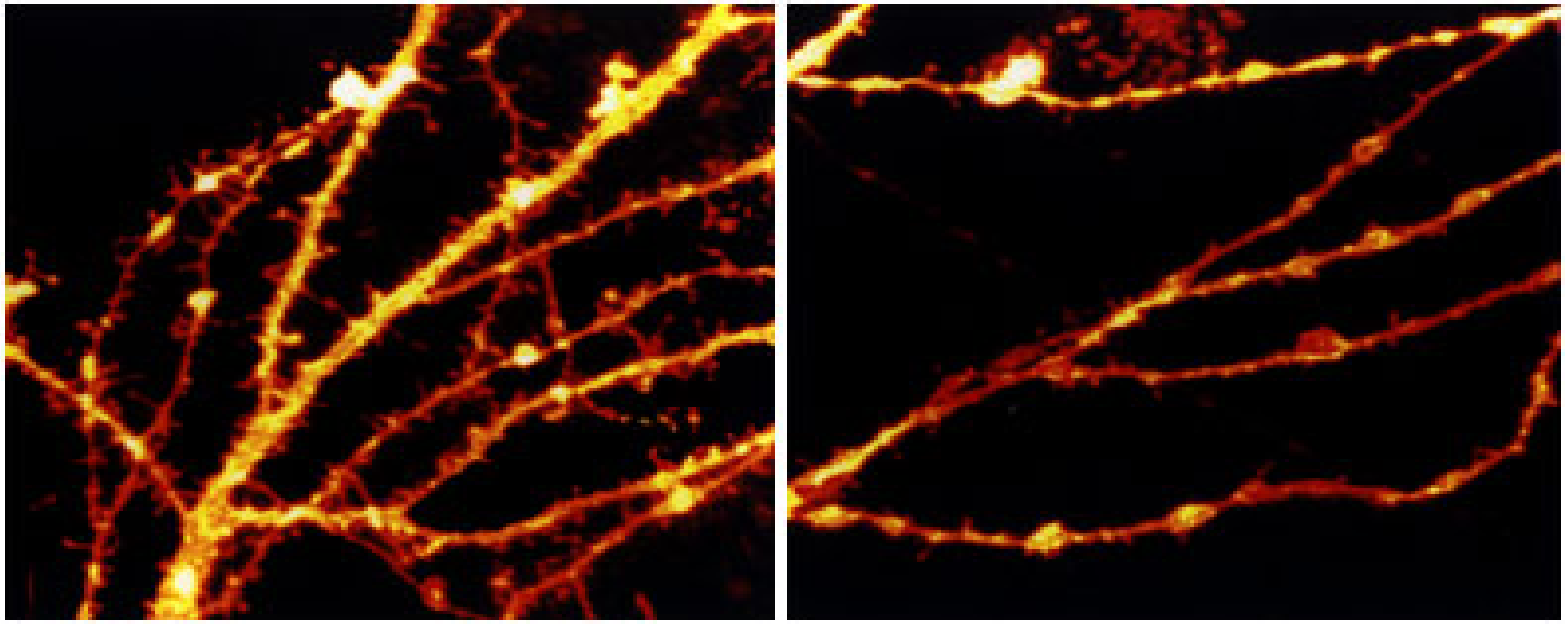
- Decrease in estrogen level leads to decrease in verbal memory

Neuroprotective effects of estrogens

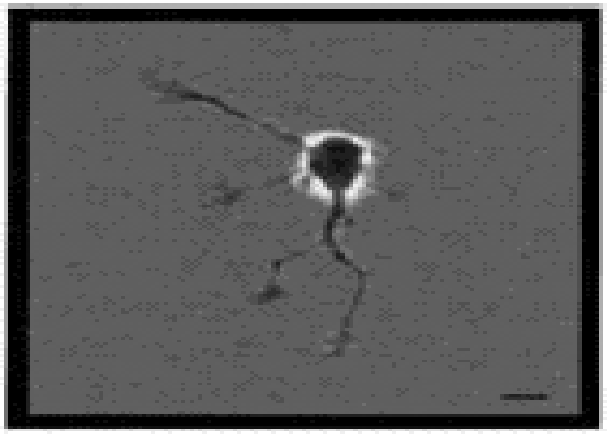
Estrogen's role in memory may be due to its effect on the tiny knobs (spines) that protrude from neuron's dendrites. Spines are formed at the site of connections between neurons.

Estrogen resulted in a two-fold increase of the number of spines in rat embryo brain cells compared to those without the supplements of estrogen.

with estrogen **without estrogen**



Effect of estrogen on hippocampal neurons in vitro



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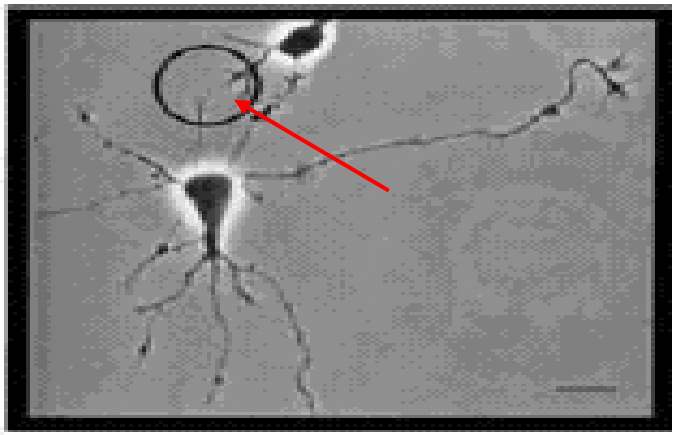
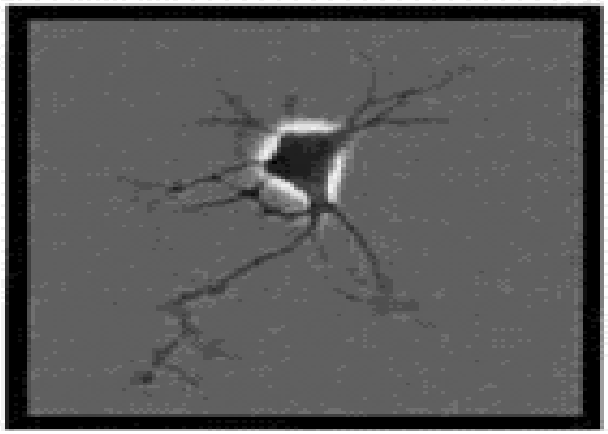
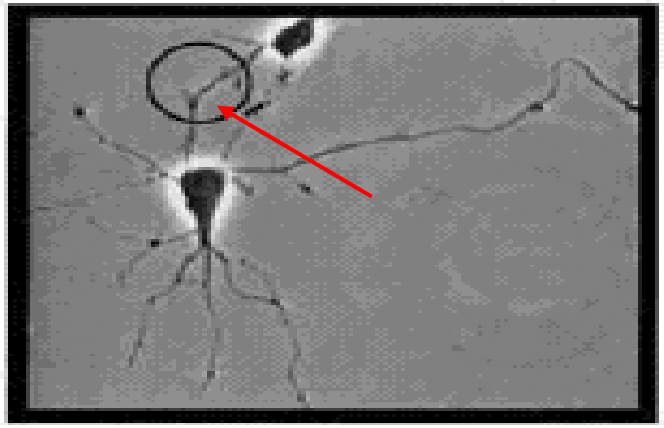


Prior to CEE



Following 24 hr CEE exposure



Following 1 hr CEE exposure

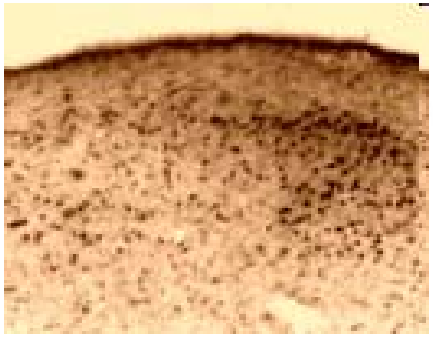
CEE- conjugated equine estrogen (used in HRT)

R.D. Brinton et al. / Neurobiology of Aging 21 (2000) 475–496

Mechanism of neuroprotective activity of estrogens

Genomic (classical) pathway:

ERα - amygdala



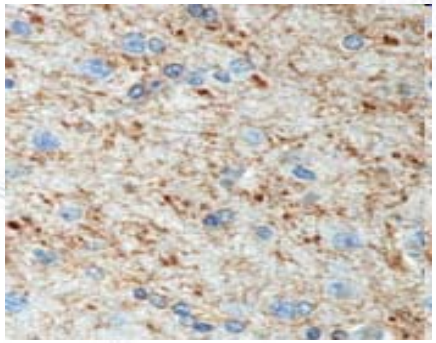
* Slow - effects after several hours

* Mediated by ERα and ERβ

* Erα and ERβ are expressed and coexpressed in different cells of central and peripheral nervous system. Possibly both are involved in neuroprotection.

* Genes with ER response elements in the promoter:
  # **oxitocine** (peptide hormone),
  # **apoE** (neuroregeneration, clearence of β-amyloid)
  # **somatostatin** (peptide hormone)
  # **BDNF, NGF, and their receptors**
  # **TGFα** (transforming growth factor-α)
  # **IGF-I** (anti-apoptotic protein)
  # **BCL-2** (anti-apoptotic protein)
  # **choline acetyltransferase (produces ACh)**
  # **tyrosine hydroxylase (produces dopamine)**

ERβ - cortex

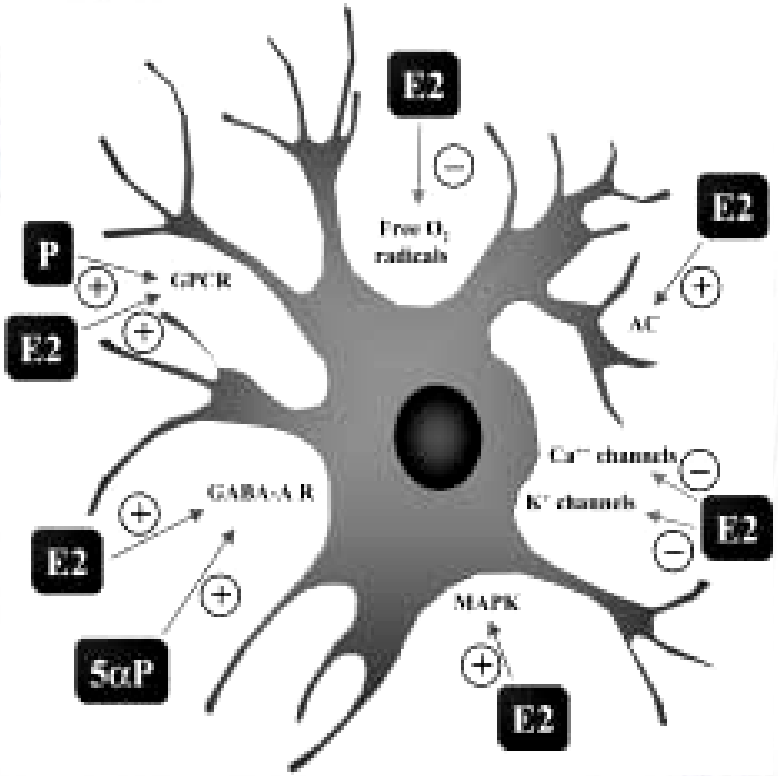


Mechanism of neuroprotective activity of estrogens

Non-genomic pathway (influence on other signal transduction pathways):

* Can be very fast – effects after minutes.

* Can be mediated by:
  # activation of adenylyl cyclase, elevation of **cAMP**, induction of **PKA, CREB**, and **AP-1**
  # elevation of Ca^{2+} and stimulation of **PLC**
  # activation of **PI3K** and **Akt** kinases (ERα may directly bind to PI3K).
  # activation of **ERK1/2**
  # activation of **Src** kinase (and thereby MAP kinases).



* Activation of **PI3K and Akt kinase** increase activity of **nNOS and eNOS** (neuronal and endothelial nitric oxide synthase): mechanisms of neuro- and cardioprotection.

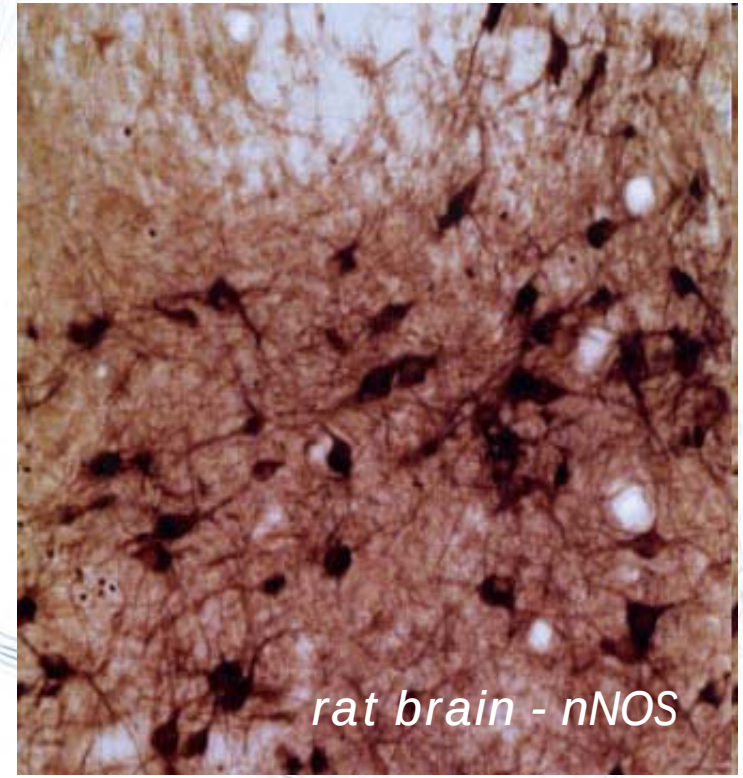
* **Inhibition of NFκB** attenuates inflammatory response

NO in peripheral nervous system

- NO acts as a mediator in nonadrenergic, noncholinergic (NANC) neurons.
- NO is a major mediator of penile erection.

NO in the central nervous system:

- NO is an important **neurotransmitter**. Unlike classic transmitters NO is not stored, but **synthesized on demand** and diffuses to neighboring cells. NO synthesis is induced at postsynaptic sites in neurons, most commonly upon activation of glutamate receptor, which results in calcium influx and activation of nNOS.



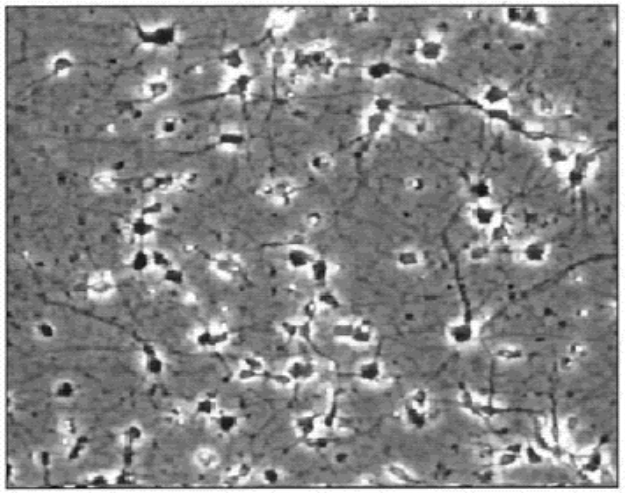
- NO synthesized postsynaptically may function as a **retrograde messenger**.

- NO plays a major role in the regulation of synaptic plasticity, the process of synapse strengthening that underlies **learning and memory**.

http://www.abcam.co.jp/ps/datasheet/images/ab6175_1.jpg

Protective effect of CEE against glutamate-induced toxicity

(Hippocampal neurons cultured *in vitro*)



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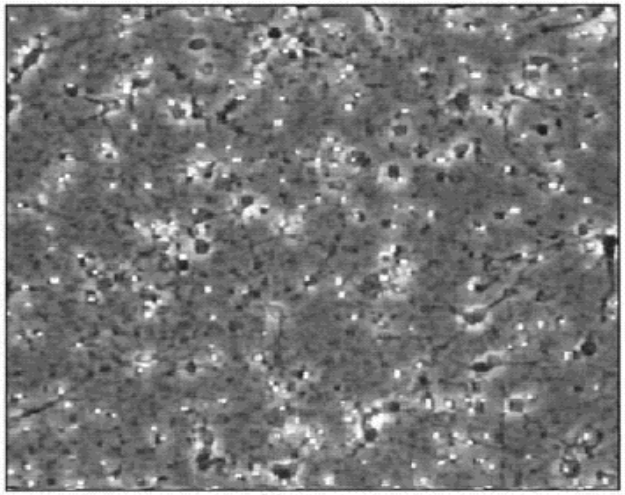
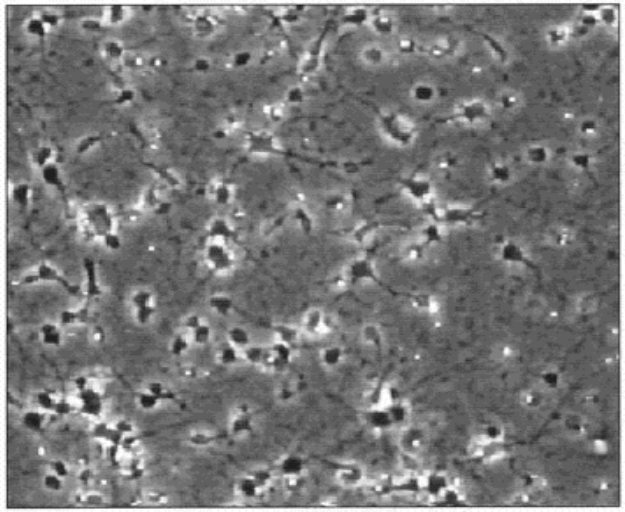
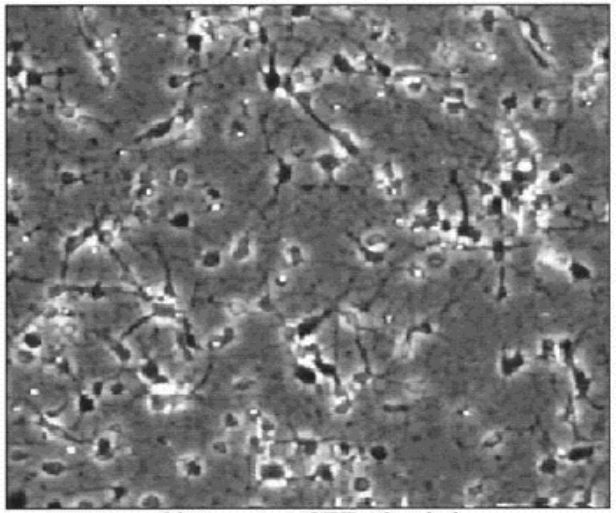


Glutamate



Glutamate + CEE 0.1ng/ml



Glutamate + CEE 10ng/ml

plating the cells

↓ 4 days

supplementation with CEE

↓ 4 days

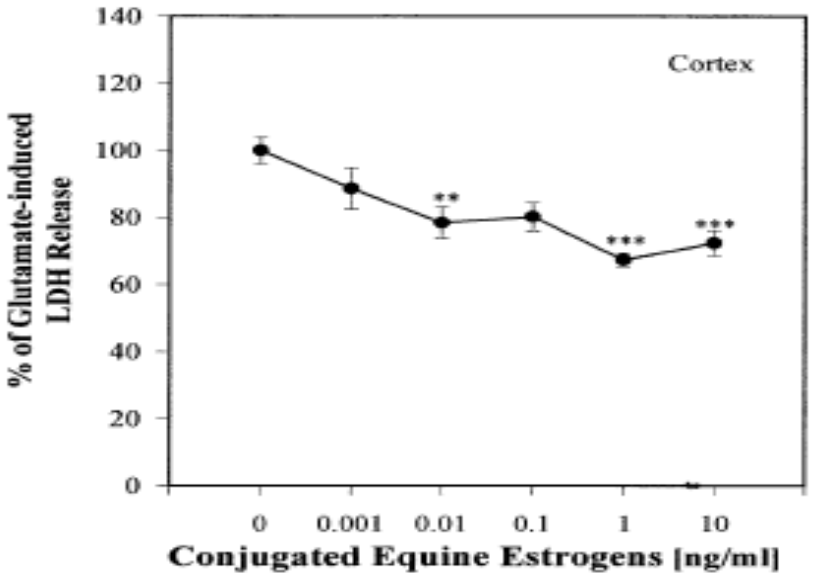
exposure to glutamate (5 min)

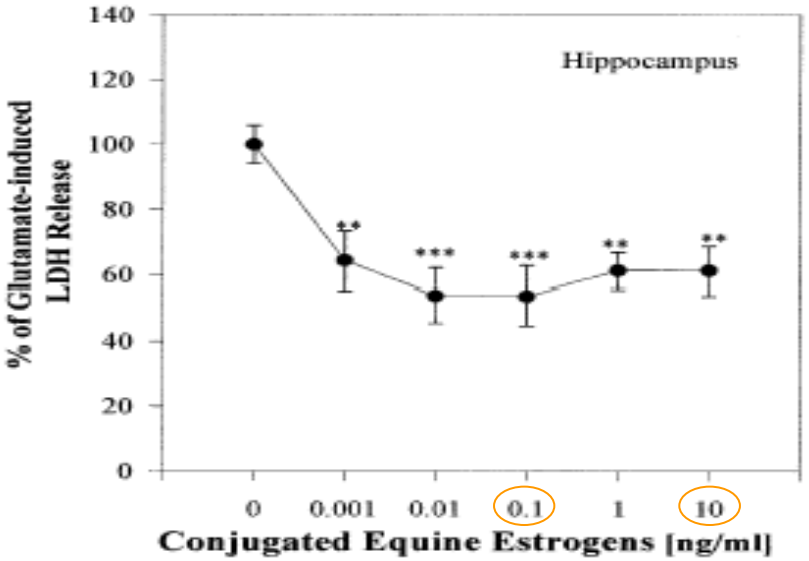
↓ 24 h

analysis

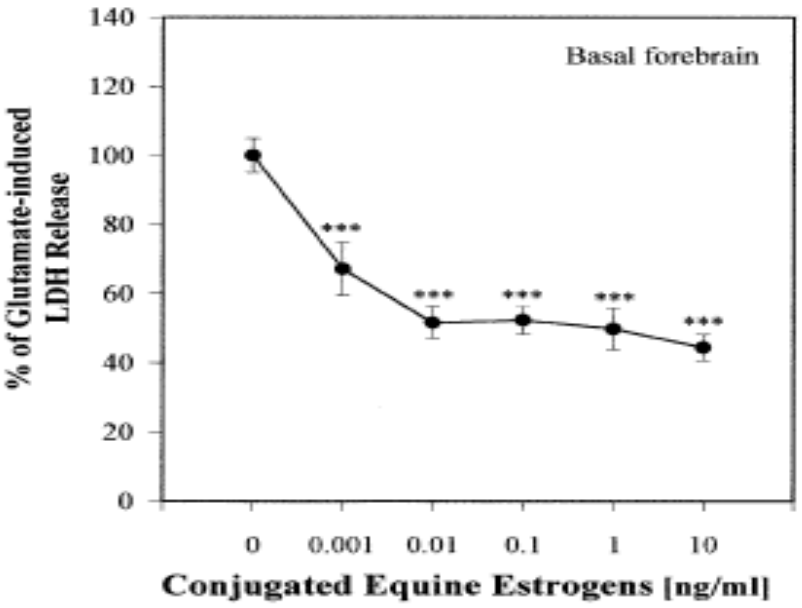
R.D. Brinton et al. / Neurobiology of Aging 21 (2000) 475–496

Protective effect of CEE against glutamate-induced toxicity





neurons cultured *in vitro*



R.D. Brinton et al. / Neurobiology of Aging 21 (2000) 475–496

Neuroprotective activity of estrogens

Antioxidative activity:

* Estrogen has similar activity to vitamin E and may inhibit lipid peroxidation. This effect is independent of ER.

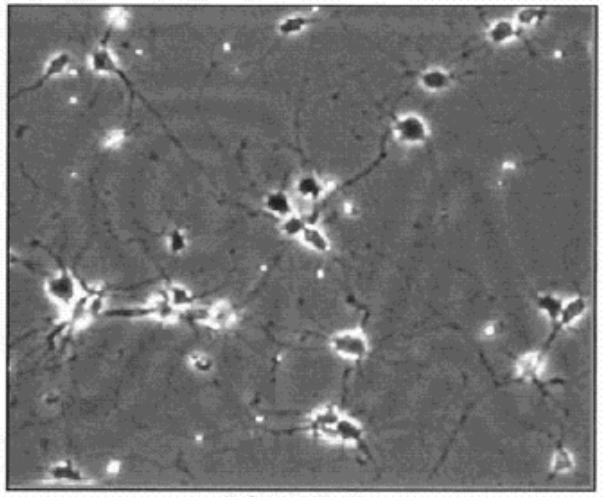
* Estrogens protect neurons against O_2^-, H_2O_2, and $HO^\bullet$.

* Effective concentrations of estrogens to obtain antioxidative effect are within micromolar range, much above physiological concentrations. However, although usually the level of estrogens can reach only low nanomolar levels, local accumulation to micromolar concentrations cannot be excluded.

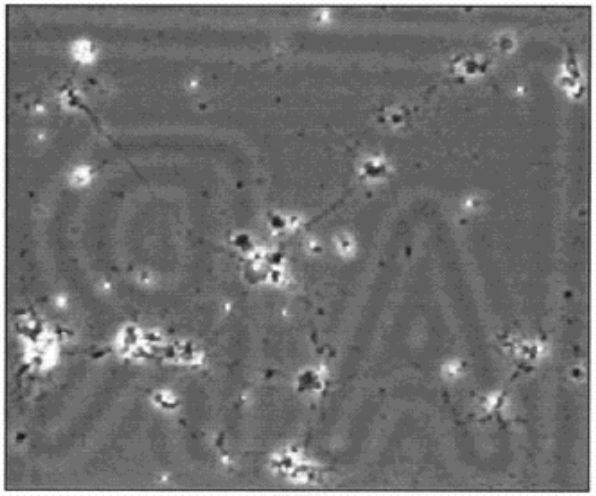
* Effective concentration of estrogens may be much lower (within physiological range), e.g. in the presence of glutathione.

Protective effect of CEE against H_2O_2-induced toxicity

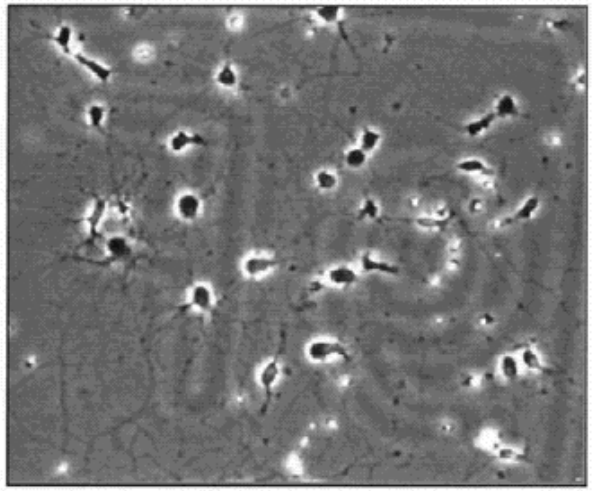
(Hippocampal neurons cultured *in vitro*)



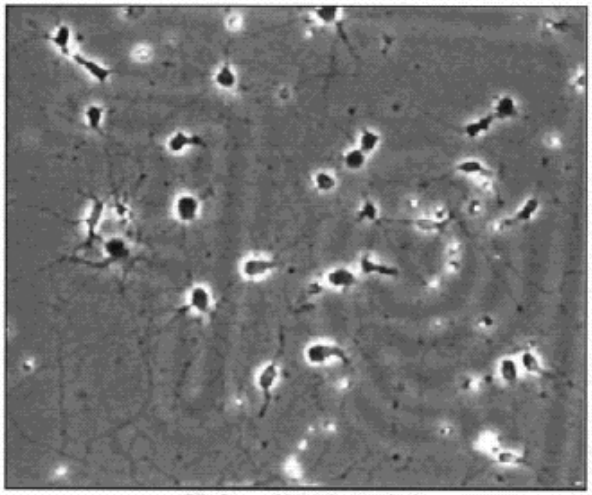
Prior to H_2O_2



H_2O_2



Prior to H_2O_2



H_2O_2 + CEE 0.1ng/ml

plating the cells

↓ 4 days

supplementation with CEE

↓ 4 days

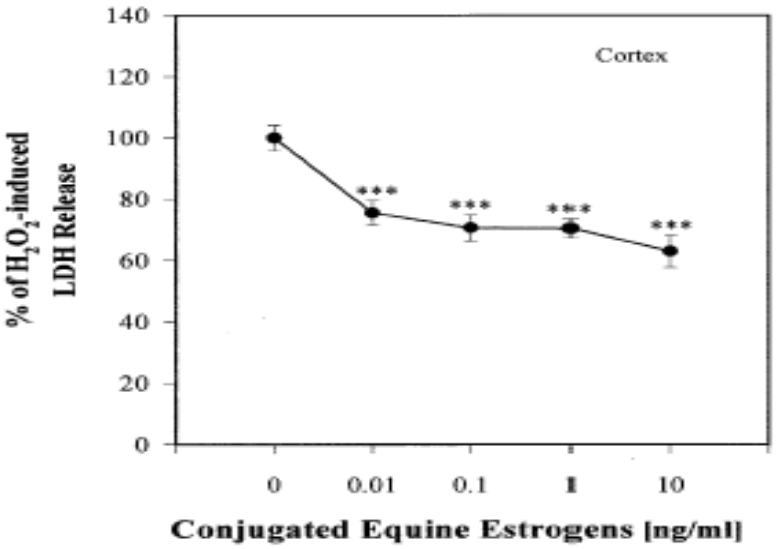
exposure to H_2O_2 (20 min)

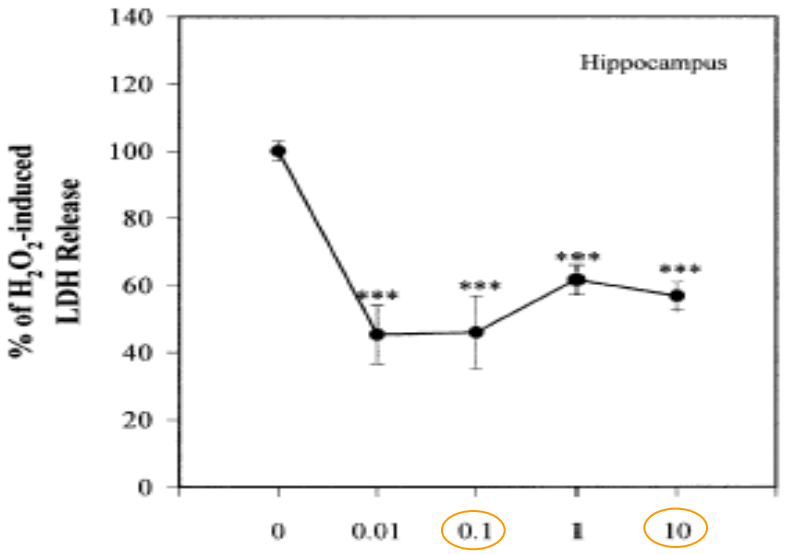
↓ 24 h

analysis

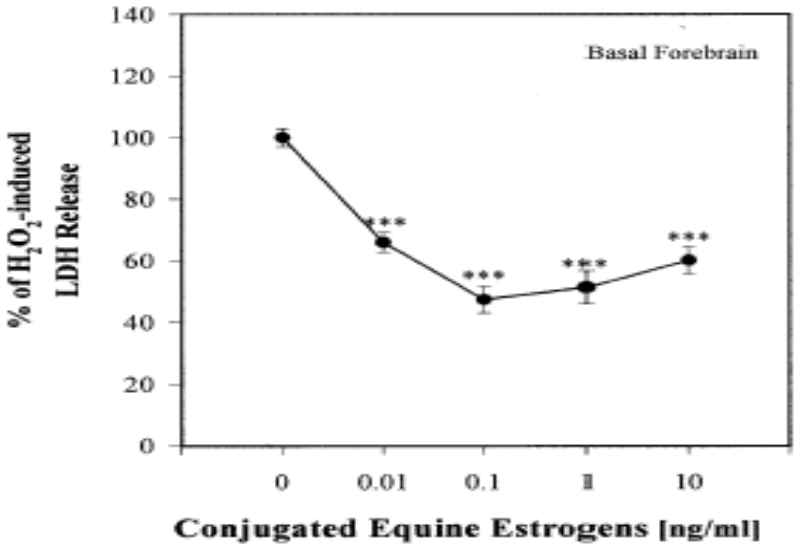
R.D. Brinton et al. / Neurobiology of Aging 21 (2000) 475–496

Protective effect of CEE against H_2O_2-induced toxicity



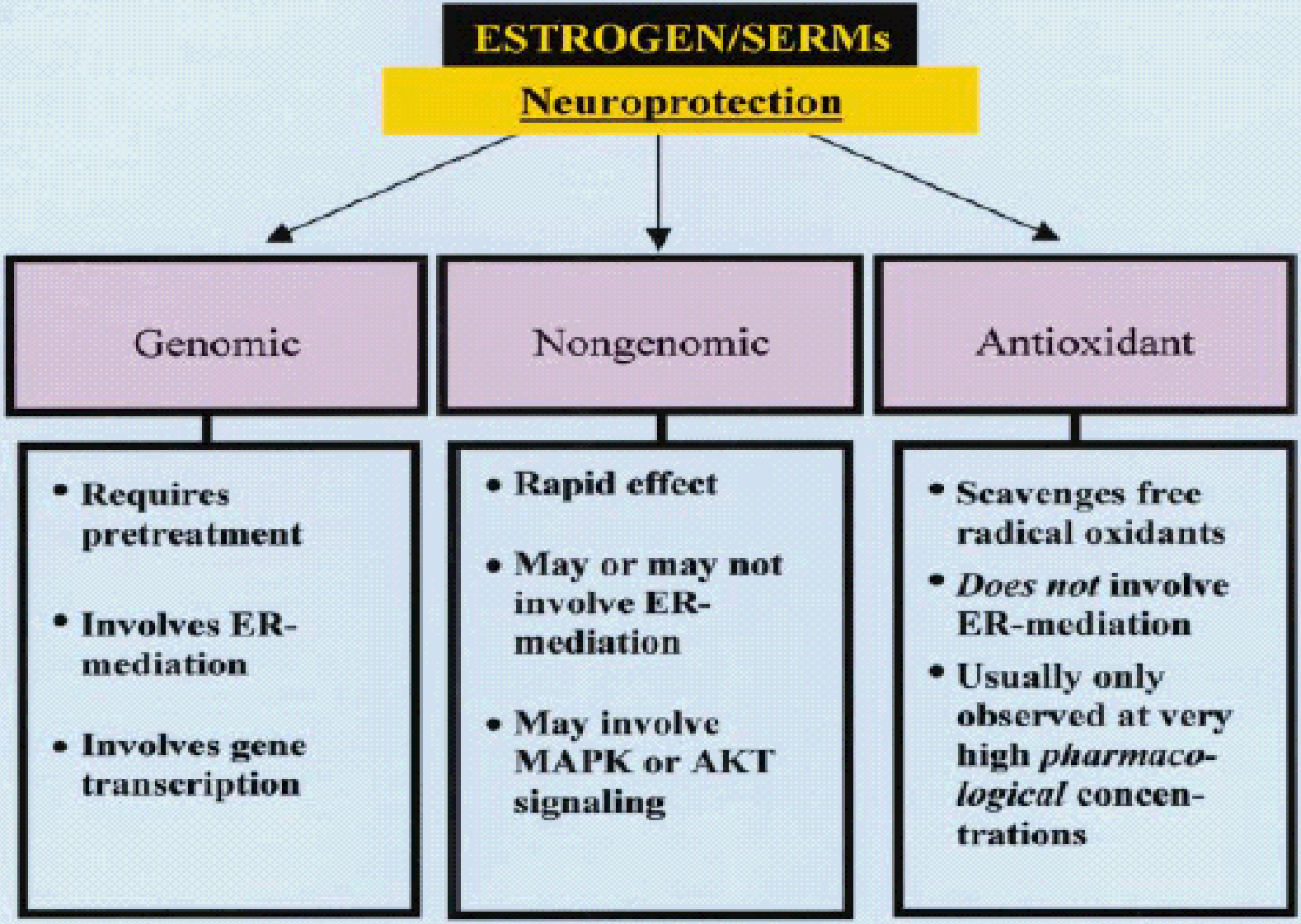


neurons cultured *in vitro*



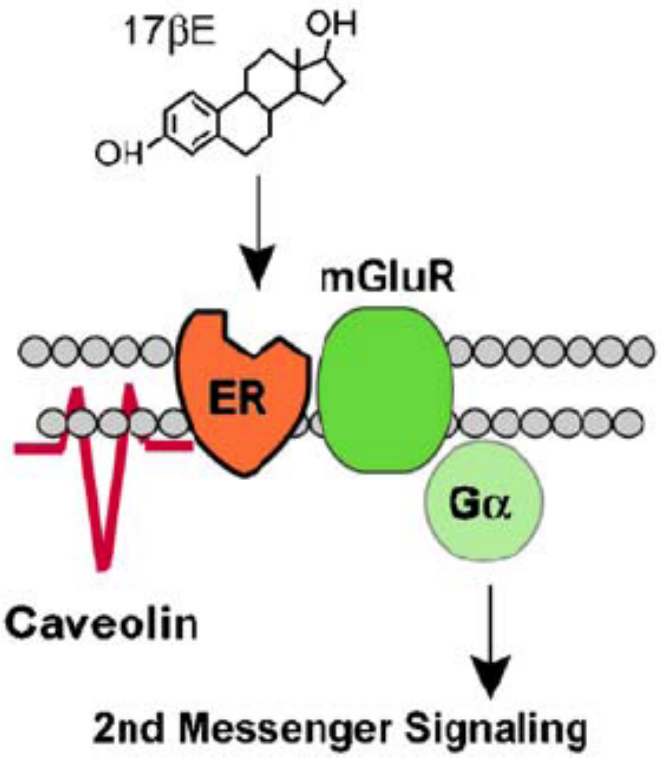
R.D. Brinton et al. / Neurobiology of Aging 21 (2000) 475–496

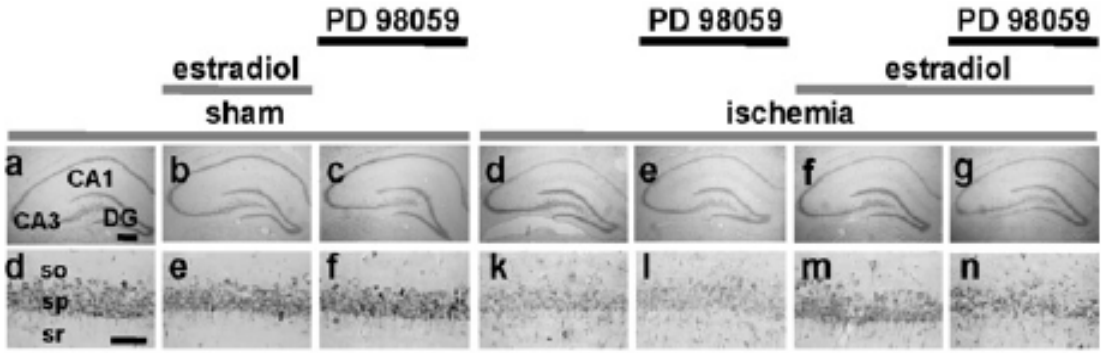
Possible Mechanisms of Estrogen/SERM Neuroprotection

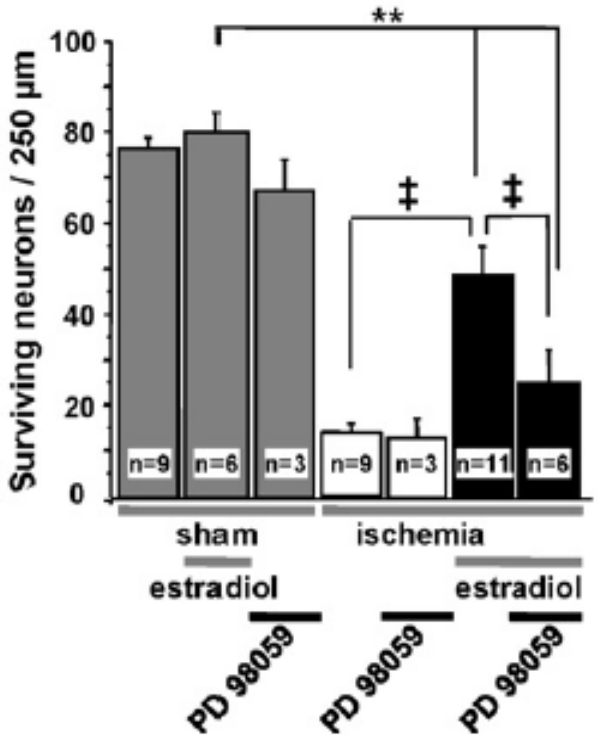


Dhandapani KM and Brann DW Biol Reprod 2002.

ER activation of mGluR signaling







Micevych and Mermelstein, Mol Neurobiol, 2008; Lebesgue et al. Steroids 2009.

Menopause

*** Menopause is associated with an increase in various risk factors for stroke.**

*** Menopausal transition is associated with:**

- increase in abdominal obesity and body-mass index

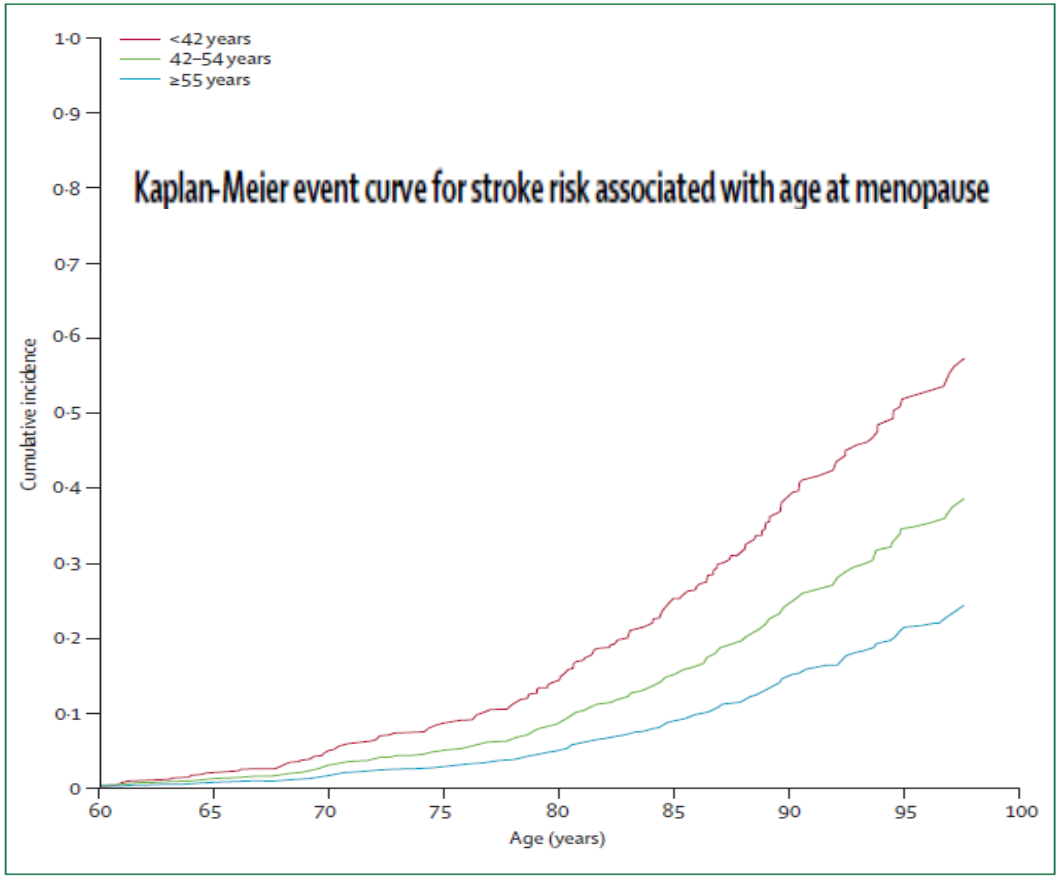
- increase in triglycerides,

- increase in total cholesterol and LDL cholesterol,

- decrease in HDL cholesterol,

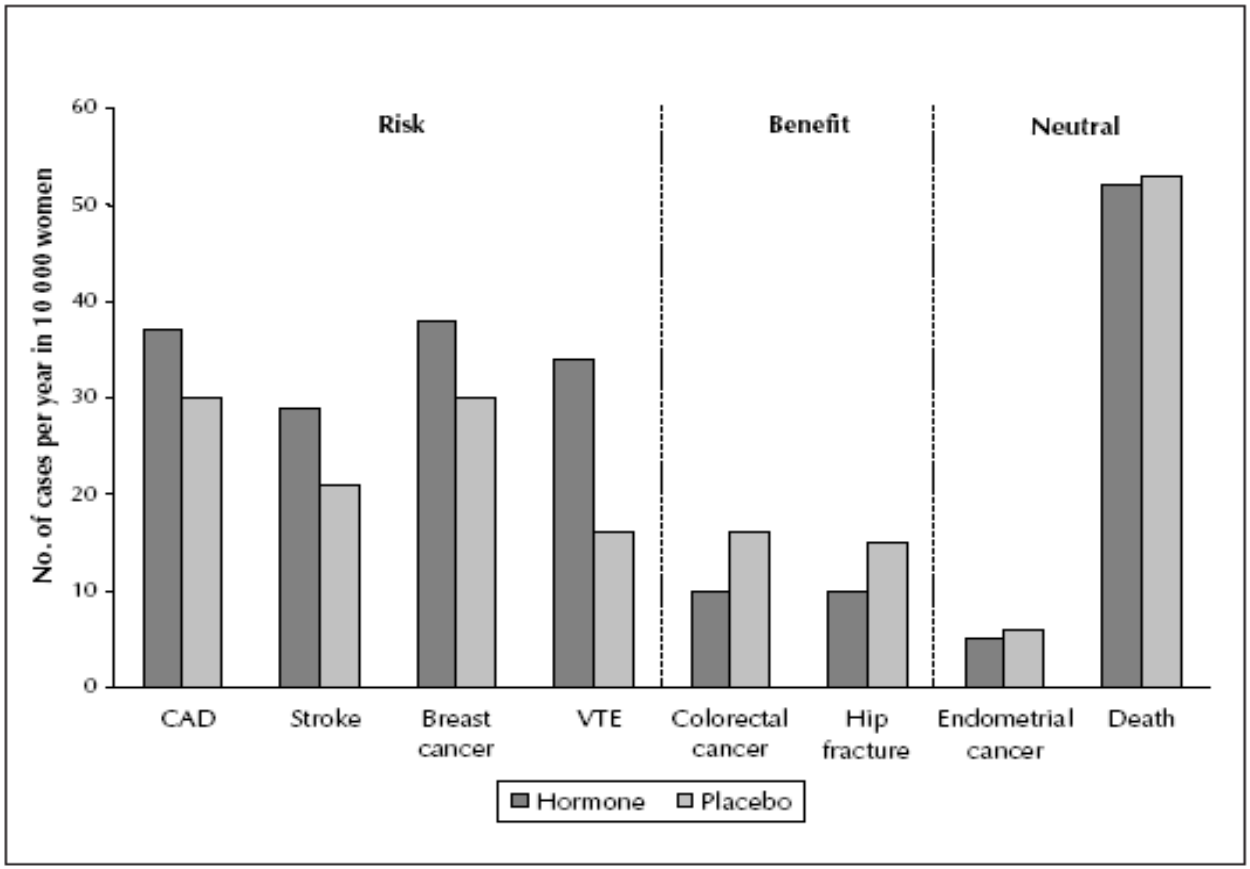
- increase in fasting glucose and other measures of insulin resistance,

- increased blood pressure



Lysabeth and Bushnell, Lancet Neurol 2012

Hormon replacement therapy



CAD – coronary artery disease; **VTE** – venous thromboenbolism

WHI trial

Participants had a 23% increase in cardiovascular disease

(37 vs. 30 cases per 10,000 persons/years)

0.37% v 0.30%

and a 38% increase in strokes

(29 vs. 21 cases per 10,000 persons/years).

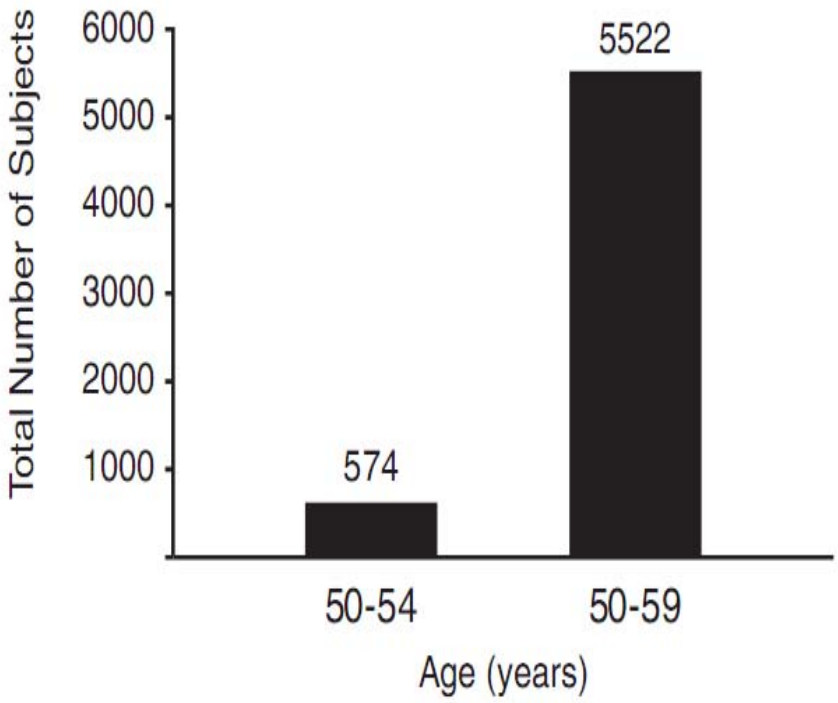
0.29% v 0.21%

Recent data suggest decreased risk of Alzheimer disease (by 67%) and other forms of dementia as well as preservation of cognitive function in women subjected to a long-term HRT (not conlusively confirmed).

WHI - not easy for interpretation (?)

- The mean age in WHI study: it was 63 years in the E+P subgroup.

- The WHI subjects started the hormone therapy at an average of 12 years postmenopause.



- WHI studies combined a small (less than 20% of the study population) healthy group of patients in their early 50s at the start of the study with a much larger study group of patients in their late 50s to late 70s, many of whom have had advanced subclinical disease.

- In the E+P arm of WHI study, only 33% of hormone-treated and control subjects were 50 to 59 years old, and only 16% to 17% were within 5 years of menopause at the time of enrollment

Nodis HN. Clin Obstet Gynecol 2009.

Number of events per 10,000 women per year of CEE therapy compared to placebo in the Women's Health Initiative Estrogen Trial by age at baseline

Nodis HN. Clin Obstet Gynecol 2009.

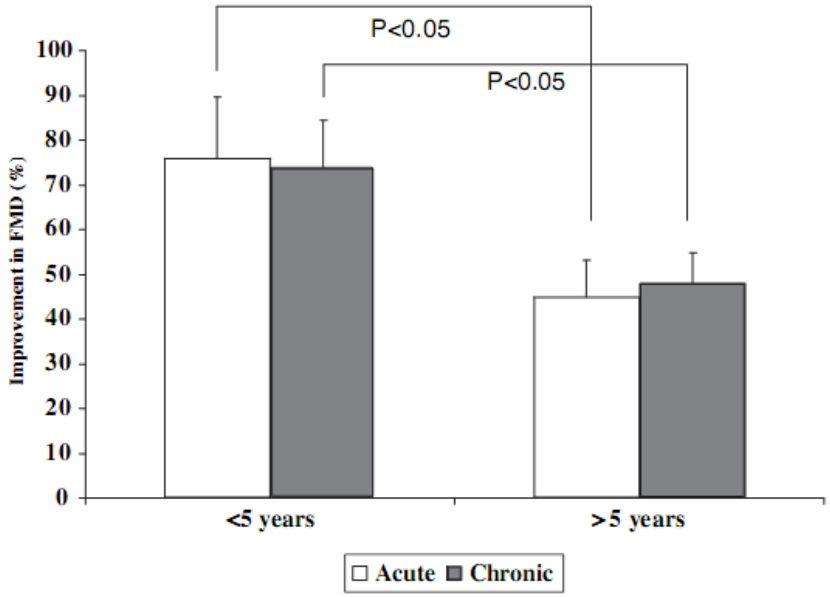


Figure 1. Improvement in FMD after acute and chronic estradiol administration in exogenous estrogen naïve. FMD improved significantly more ($P<0.05$) in women <5 years since menopause than in women >5 years since menopause.

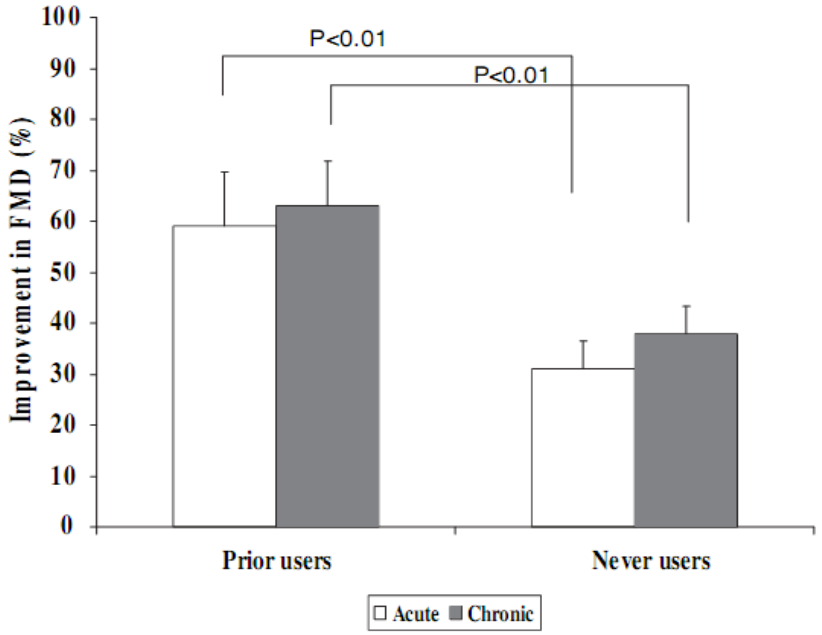


Figure 2. Improvement in FMD after acute and chronic estradiol administration in women >5 years since menopause. FMD improved significantly more ($P<0.01$) in those women who had received estrogens in the past than in those who exogenous estrogen naïve.

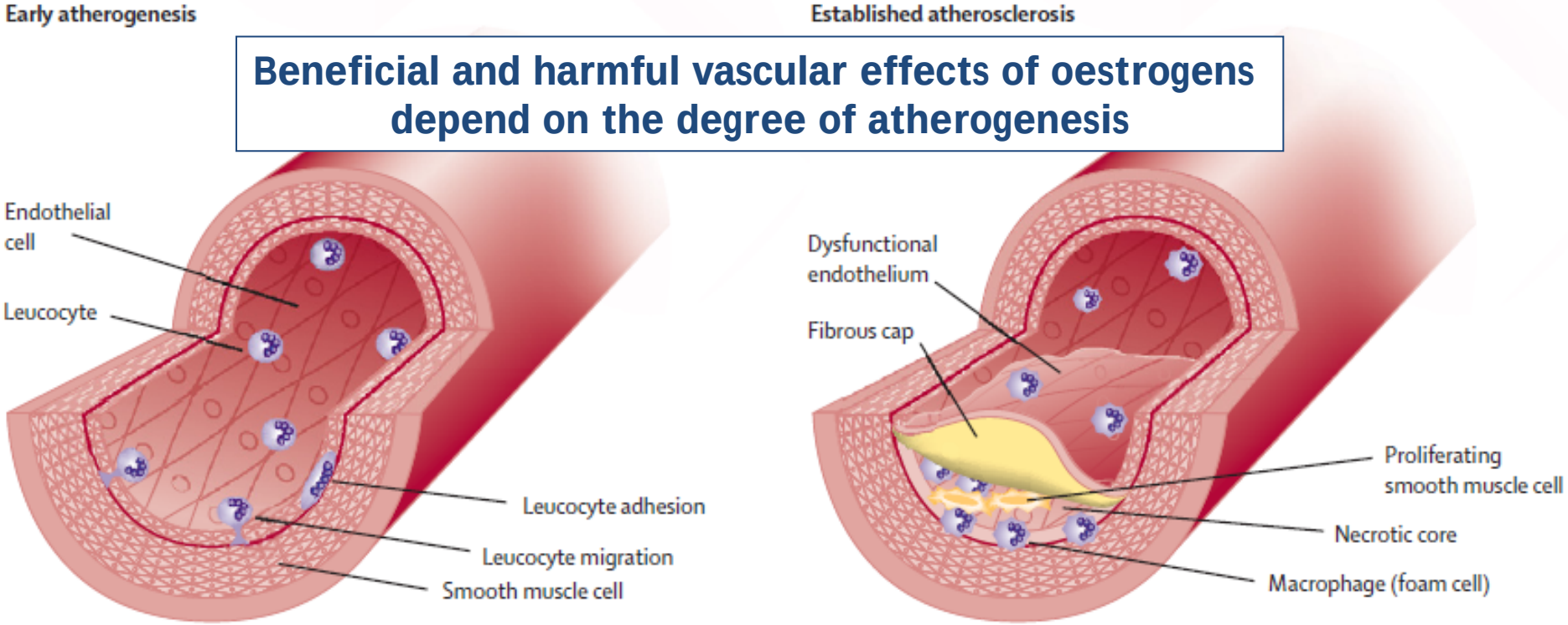
The risks associated with estrogen alone appear to be negligible (supported by ~40 studies that also indicate that initiation of **HT early** in the postmenopausal period and continued for a prolonged period of time results in a significant **reduction of total mortality and CHD**).

The **window of opportunity** for maximal expression of the beneficial effects of HT on CHD appears to be initiation of **HT within 6 years of menopause** and/or by 60 years of age and continued for 6 years or more.

Vitale et al. ATVB 2008, Nodis HN. Clin Obstet Gynecol 2009.

Hormon replacement therapy

Beneficial and harmful vascular effects of oestrogens depend on the degree of atherogenesis



Beneficial effects of HRT

↑Vasodilation
↑Nitric oxide
↓Endothelin
↑COX-2

↓Inflammatory activation
↑Nitric oxide
↓CAMs
↓MCP-1, TNF-α

↓Lesion progression
↑Nitric oxide
↓Inflammatory cell adhesion
↓LDL oxidation/binding
↓Platelet activation
↓VSMC proliferation

Harmful effects of HRT

↓ER expression, function

↓Vasodilation

↑Inflammatory activation

↑Plaque instability
↑MMP
↑Neovascularisation

Lysabeth and Bushnell, Lancet Neurol 2012

Phytoestrogens

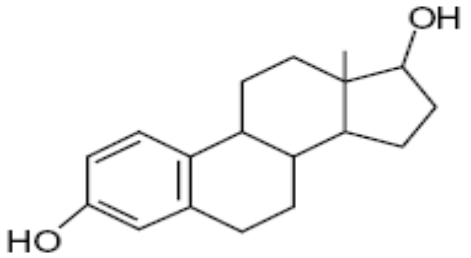
- **Phytoestrogens are non-steroid polyphenols present in many plants, including edible plants.**

- **Plants produce phytoestrogens e.g. as chemoatractants for Rhizobium, as the protective compounts against bacteria and fungi, and as repellents against plant-eating animals.**

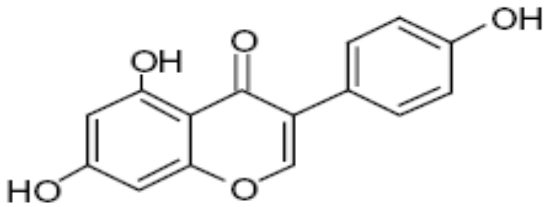
- **Isoflavonoids (one of four classes of phyto-estrogens) activate ER *in vitro*,**

- **Their activity is, however, very different ranging usually from 1/1000 to 1/500 of estradiol activity.**

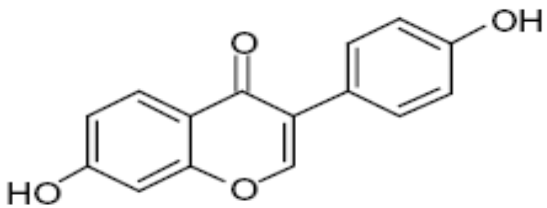
17β-Estradiol



Genistein



Daidzein



Genistein

- Partial agonist of ER with 30 x higher affinity to ERβ than to ERα.

- Inverted correlation between genistein concentration in the blood and frequency of breast cancer, cardiovascular diseases, and osteoporosis were reported.

- Proposed as an alternative of supplementary hormone therapy, as menopause disorders are less pronounced in the countries with a high consumption of soya (hot flushes: 80% in Europe, 18% in China, where the bigger problems are headache and backache). In Chinese medicine, to relieve these symptoms, the plants reach in phytoestrogens are recommended.

- Some data suggest that soya-reach diet may decrease the hot flushes, but doses required are very high.

- Clinical trials **did not** confirmed any beneficial effects of soya.

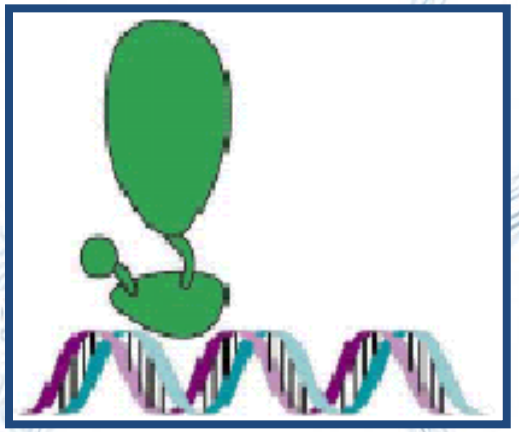
Genistein is an inhibitor of tyrosine kinases

ERR - estrogen related receptor

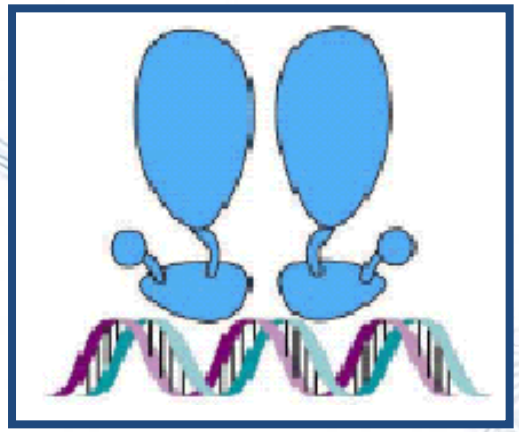
- Still orphans, but waiting for adoption (perhaps will be adopted soon).

- ERR family, closely related to estrogen receptors (ER), contains three similar members: ERRα, ERRβ (KO in embryos - lethal), ERRγ.

- ERRs bind to DNA as **monomers** *(then recognize the same sequence as SF-1 orphan nuclear receptor, steroidogenic factor-1)* or as **homodimers** *(then recognize estrogen receptor response element)*. In the cytoplasm they are connected to Hsp90.



SF1-responsive element



ER-responsive element

ERR - estrogen related receptor

- Perhaps *in vivo* they can be constitutively active, as even without any ligand they can interact with coativators.

- Homodimers may recognize estrogen responsive elements (67% aminoacid similarity in DBD). Therefore they can possibly target all genes regulated by estrogens.

- ERR **cannot bind estrogens** *in vitro*, despite some homology in LBD (35% aminoacid similarity).

ERR - estrogen related receptor

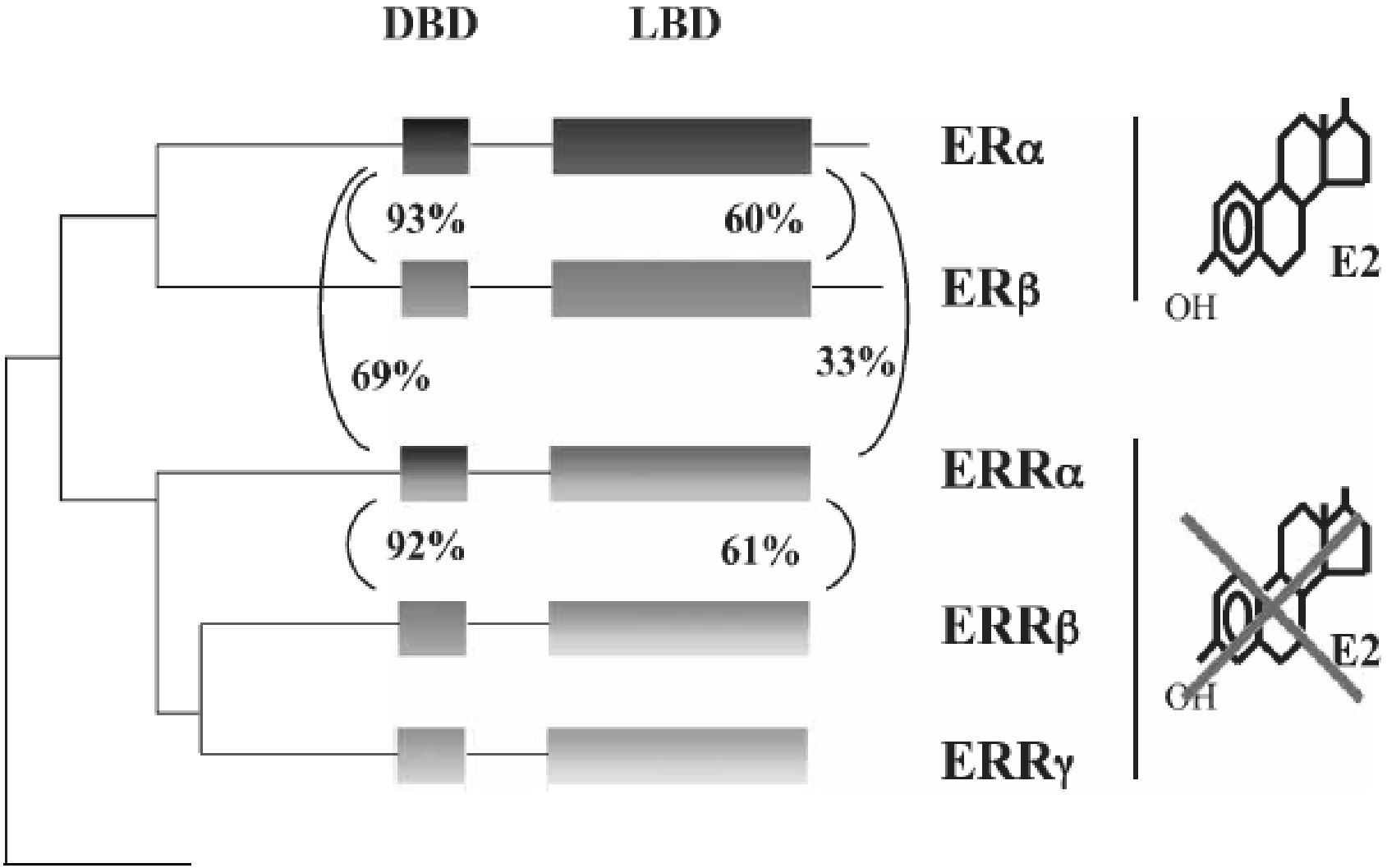
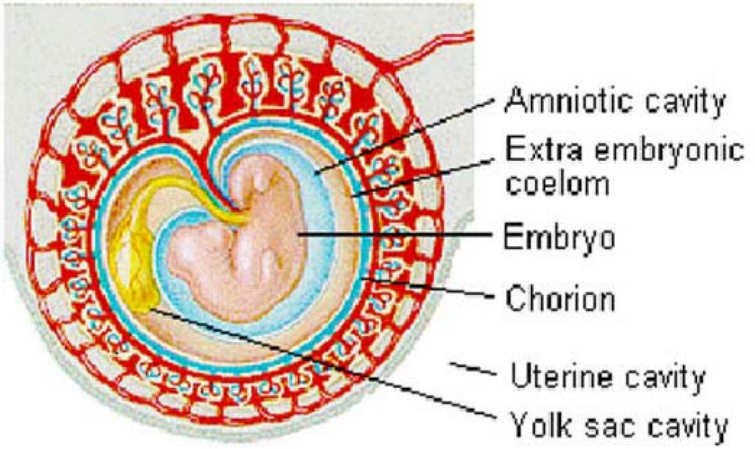


Figure 1 The ER/ERR subfamily A schematic representation of the two mouse ERs and the three mouse ERRs is displayed. Percentage of sequence identity within the DBD and the LBD is indicated.

Expression of ERR

- **ERRα expression is found in embryo in:**

  * trophoblast,
  * visceral yolk sac,
  * primitive heart
  * neural tube
  * bones



- **ERRα in adults:**

  * ubiquitously

- **ERRβ in embryo**:

  * early chorion - play a role in early placenta formation

- **ERRγ in embryo**:

  * brain and also kidney, lung, liver

- **ERRγ in adults**:

  * brain, spinal cords, and also lung, bone marrow, adrenal and thyroid glands etc.

Function of ERR

- ERR play a role in **bone** formation:

  * They are expressed in ossification zones of embryo and up-regulates the expression of the osteopontin gene.

  * They play a role in osteoprogenitor cell proliferation and differentiation.

- In **adipose tissues**, ERR participate in the control of energy expenditure and fat metabolism through the regulation of the expression of the MCAD (medium chain acyl CoA dehydrogenase) gene.

- In the **central nervous system**, ERR are highly expressed but their role is still unknown.

- ERR is mainly expressed during **early embryonic development** where they are necessary for proper trophoblastic cell proliferation and differentiation.

Ligands of ERR

- No natural ligands are known so far.

- Synthetic ligands:

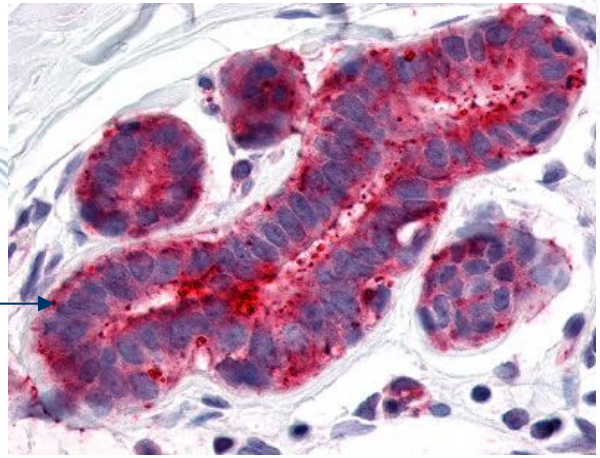
  * Diethylstilbestrol (DES, binds to ERRα, ERRβ, and ERRγ) represses activity of ERRs.

  * 4-hydroxytamoxifen (4-OHT, binds to ERRβ and ERRγ) represses their constitutive transcriptional activity. Raloxifene does not bind to ERR.

- Both drug molecules have a long history of use in women's health, through their opposing effects on the activity of the classical ER.

- It has been suggested that ERR regulators may be used for treatment of breast cancer.

breast epithelium stained for ERRγ



Diethylstilbestrol (DES)

- DES, a synthetic estrogen, was widely used between the 1940s and the 1970s to prevent spontaneous abortion in women. However, **patients exposed** ***in utero*** **to high doses of DES** have a range of gynecological troubles, including a **higher incidence of vaginal cancers** and **malformations of the reproductive tract**.

- DES is a potent **estrogen receptor agonist**, it can therefore be intuitively thought to act through ER and mimic the broad spectrum of E2 action. Recent data evidence that DES also **represses the molecular activities of ERRs**.

- However, the DES concentration necessary to achieve a half-maximal inhibition of ERR activities is much higher compared with its ER-activating potential.

Tamoxifen (TAM) and 4-OH tamoxifen (4-OHT)

- TAM and 4-OHT are selective **ER modulator**, and as such displays **estrogenic or antiestrogenic actions** according to the target tissue. In particular, TAM acts as an estrogen antagonist in the mammary gland and is clinically used for the treatment of breast cancer.

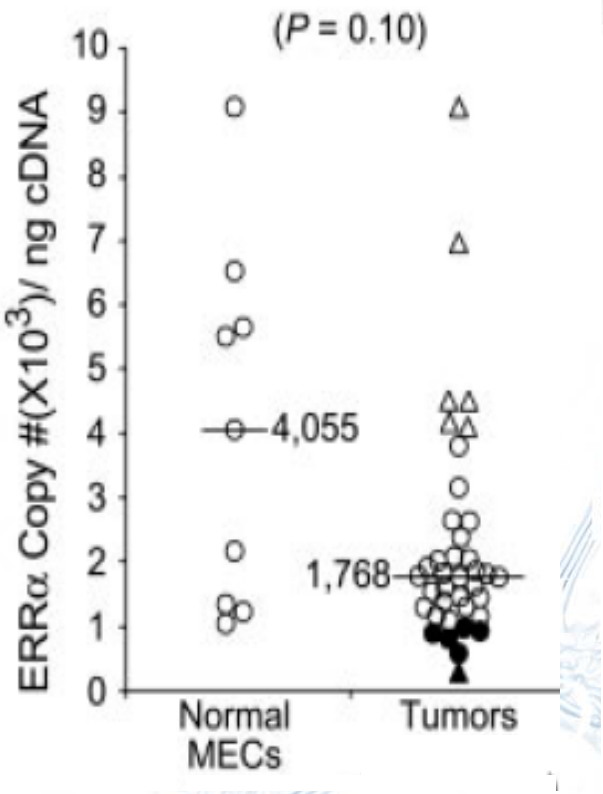
- TAM and 4-OHT **disrupt the interactions between ERR and a SRC-1 coactivator** peptide *in vitro*.

- Much higher concentrations (but still pharmacologically relevant) are necessary to obtain inhibition of ERR than ER.

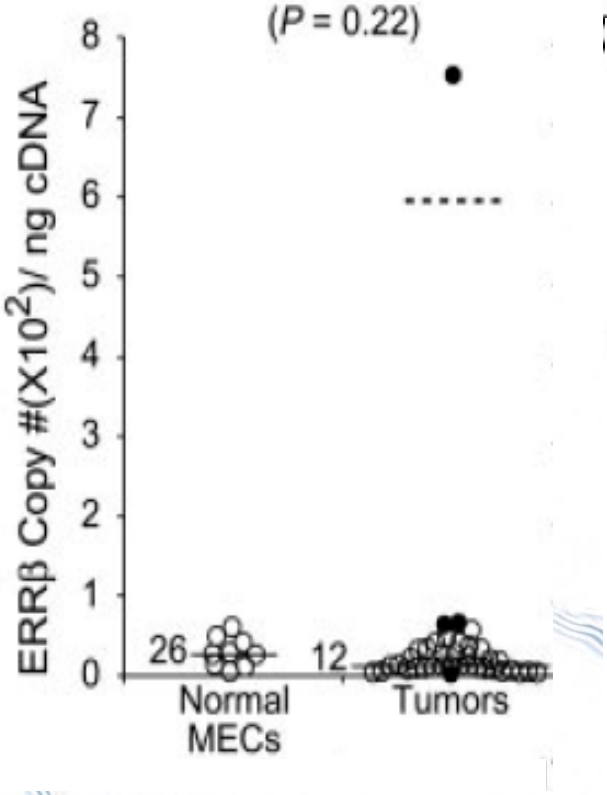
- Some of the antitumor effects of TAM might be mediated by ERR.

ERR and breast cancer

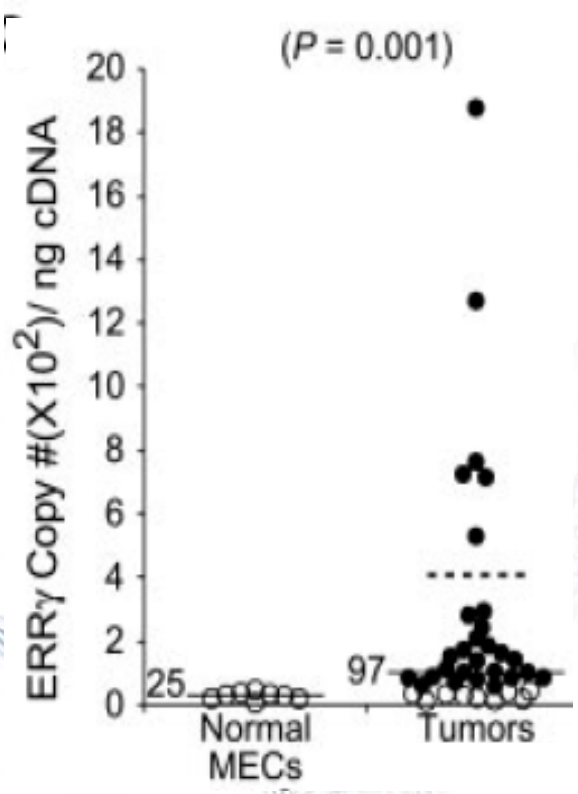
ERRα

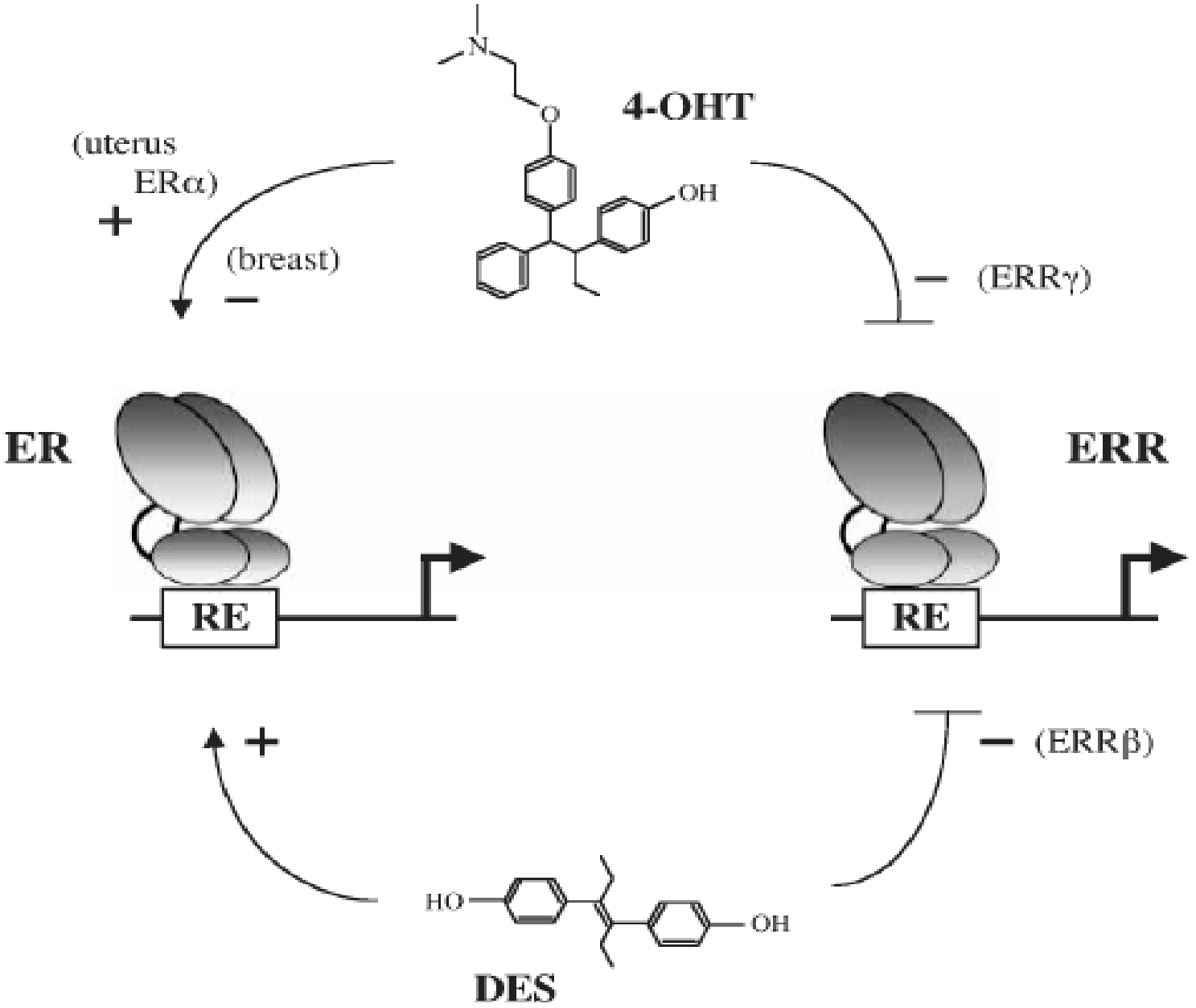


ERRβ



ERRγ



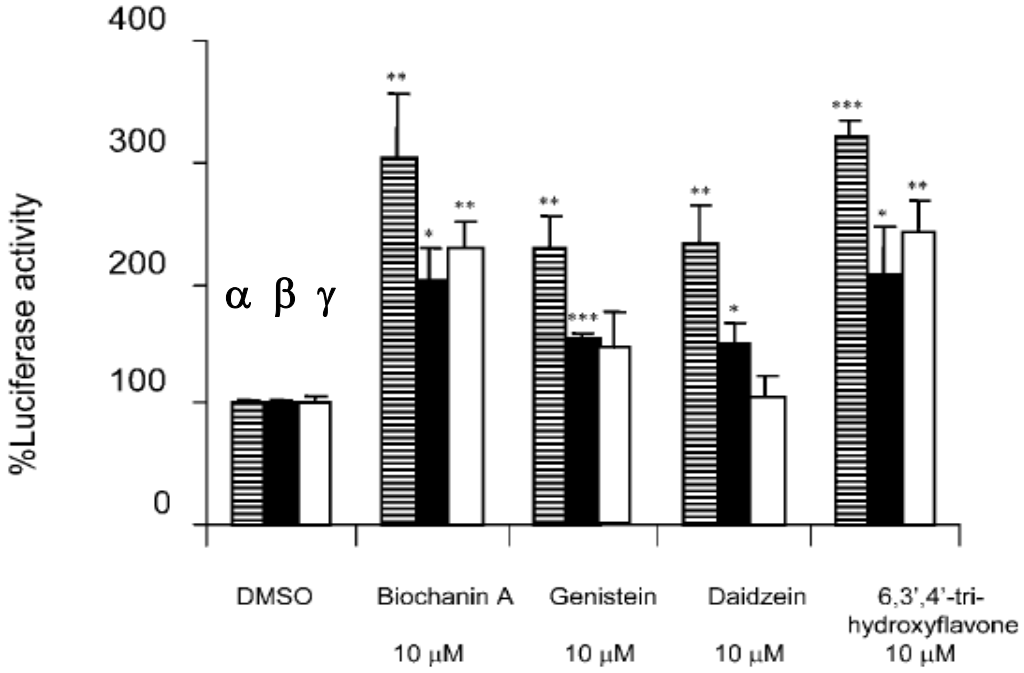


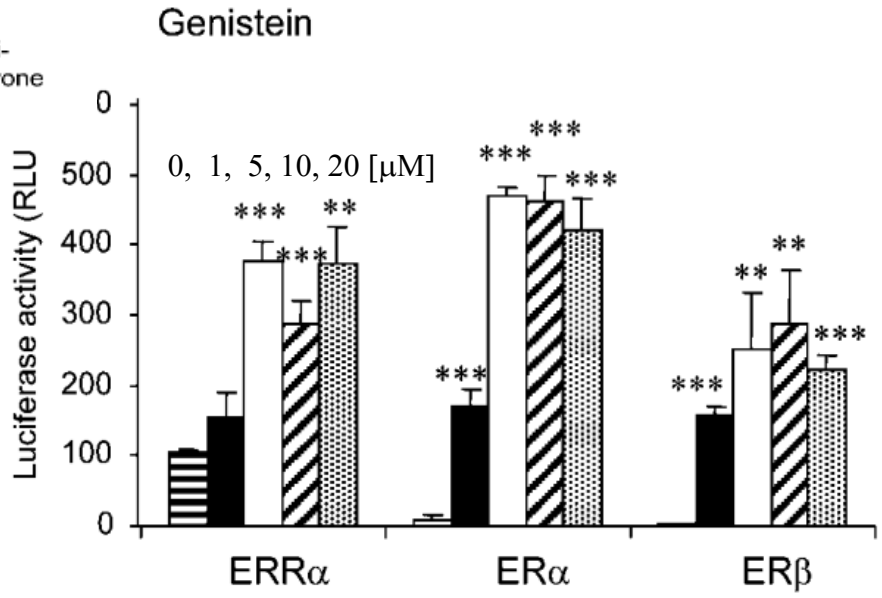
Contrasting effects of SERMs on ERs and ERRs. 4-OHT activates ERα in the uterus and bone, but acts as an estrogen antagonist in breast. 4-OHT also deactivates ERRγ. DES is a potent ER agonist and inhibits ERRβ's transcriptional activities.
RE: response element.

ER and ERR ligands

	ESTRADIOL	DES	4-OHT	RALOXIFENE
ERα	Agonist	Agonist	Antagonist / Agonist	Antagonist
ERβ	Agonist	Agonist	Antagonist / Agonist	Antagonist
ERRβ	—	Antagonist	Antagonist	—
ERRγ	—	Antagonist	Antagonist	—

Phytoestrogens and ERRs





Suetsugi et al. Mol Canc Res 2003

ER and ERR interaction

- **ERRs and ERs share common transcriptional target genes**, such as lactoferrin, or osteopontin, on which they can either synergize or compete with one another.

- Human **ERR interact with human ER** at least *in vitro* through protein–protein contacts, what possibly increases activity of ER.

- The **aromatase gene**, encoding the enzyme catalyzing the conversion of androgens to estrogens, **is a positive transcriptional target of ERR.**

ERRs might directly and indirectly modulate the estrogenic response.

Thank you and see you next week…

What would be profitable to remember in June:

- **Role of ER in neuroprotection**

- **Ligands for ERR**

-**ER and ERR interactions**