The best for the brain

Estrogens
- Tamoxifen is used as a competitive antagonist of ER.

- After binding tamoxifen, ER may dimerize and bind to consensus sequence. Changed conformation of such a complex changes interaction with corepressors and coactivators, when compared with estrogen-ligated receptor.

- Effects of tamoxifen can be tissue-specific. In some tissues (uterus) the drug behaves as partial agonist. Therefore its effectivity is limited.

- Tamoxifen does not decrease the expression of PR (and even can increase it).

- Patients suffering from cancer lacking ER do not respond to treatment with tamoxifen.

- Many cancers after temporary improvement acquire resistance to tamoxifen and starts to growth again.
Tissue Selectivity

- Ideal Profile for SERM
  (selective estrogen-receptor modulators)

- **Antagonist** - breast, uterus
- **Agonist** - bone, brain, colon, neurons, blood vessels
- 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 was designed 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.

Similarly effective in chemoprevention, but safer - less side effects observed in randomized clinical trials.
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
Mechanism of action of aromatase inhibitors and tamoxifen. Oestradiol binds to the oestrogen receptor (ER), leading to dimerization, conformational change and binding to oestrogen response elements (EREs) upstream of oestrogen-responsive genes including those responsible for proliferation. Tamoxifen competes with oestradiol for ER binding whereas aromatase inhibitors reduce the synthesis of oestrogens from their androgenic precursors.
- 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

- Aromatase inhibitors may be steroid or non-steroid compounds.

  * **Steroid inhibitors** (e.g. exemestane) are derivatives of androstenedione (aromatase substrate) and act as competitive inhibitors.

  * **Non-steroid inhibitors** (np. letrozole, anastrozole) bind through nitrogen atom to iron atom in heme group in aromatase.

- First drugs were not fully specific and because of side effects could not be used in a fully efficient doses because of serious side effects. Many aromatase inhibitors (drugs of the I and II generations) introduced to the market at the beginning 1990s have been withdrawn.

- Drugs of the third generation (e.g. letrozole) can be applied in doses which in postmenopausal women almost completely inhibit aromatase (99%) and do not produce side effects apart of those resulting from inhibition of hormone synthesis.
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, after 33 months in patients treated with anastrozole was demonstrated:
  * much higher proportion of patients free of disease
  * significantly 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 anastrozole alone.

Aromatase inhibitors – clinical applications

protection against distant metastasis - tamoxifen v. letrozole
Summary

- Aromatase inhibitors act through pure oestrogen deprivation to achieve an endocrine response in oestrogen receptor (ER)-positive breast cancer.
- Both experimental and clinical data now confirm that aromatase inhibitors achieve greater responses compared with the non-steroidal ER antagonist tamoxifen. This difference might be related to the partial agonist effects of tamoxifen, which can limit its clinical effectiveness.
- Aromatase activity in peripheral tissues and local malignant and normal breast tissue supplies breast cancer cells with the oestrogen that stimulates cancer growth. The molecular control of this process in breast cancer seems to involve increased COX2 expression.
- High plasma oestradiol levels are now known to be associated with an increased risk of breast cancer in postmenopausal women. So, use of aromatase inhibitors might provide a novel prevention strategy in the future.
- Clinical trials have confirmed that aromatase inhibitors are more effective and better tolerated than tamoxifen in postmenopausal women with early or advanced ER-positive breast cancer. As such, aromatase inhibitors are set to replace tamoxifen as the standard of care for these patients.
- In ER-positive breast carcinomas that co-express the growth-factor receptors EGFR and/or ERBB2, oestrogen deprivation might be more effective than tamoxifen at inhibiting tumour growth. This is consistent with emerging data that confirm cross-talk between growth-factor-receptor and steroid-receptor pathways that leads to tamoxifen resistance as a result of an increased agonist response.
- Acquisition of resistance during long-term oestrogen deprivation might also involve cross-talk pathways. ER expression might be increased in these cells, with receptors becoming activated and hypersensitive to low residual levels of oestradiol. Strategies to prevent this occurring with various signal-transduction inhibitors and oestrogen-receptor downregulators are now being tested.
Side effects of anastrozole compared with tamoxifen. The most significant adverse effects of anastrozole and tamoxifen on normal tissues in postmenopausal women with breast cancer that were recorded as pre-specified events in the ATAC trial.

More with tamoxifen

- Hot flushes
- Ischaemic cerebrovascular event

More with anastrozole

- Venous thromboembolic event
- Endometrial cancer
- Vaginal bleeding
- Vaginal discharge

- Bone fractures
- Musculoskeletal disorder
Cross-talk between growth factor and estrogen pathways
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 E₂. On the other side, E₂-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 (E₂)-bound ER interacts with the regulatory subunit (p85) of PI3K (p85/p110). The catalytic subunit (p110) is thus activated, leading to phosphorylation of phosphoinositides (PIP₂, PIP₃) on the D-3 position of the inositol ring. PIP₃ 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.
Estrogen leads to vasorelaxation
NO has a significant effect on vascular smooth muscle tone and blood pressure - it is 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 may have an additional inhibitory effect on blood coagulation by enhancing fibrinolysis.

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

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 effects 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 βcatenin with Tau.
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) after trauma is neuroprotective (data from rats).

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

\[
\text{inhibition of apoptosis}
\]

- 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

- Decrease in estrogen level leads to decrease in verbal memory

- Neurogenerative diseases have lower frequency, 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

- Possibly, low levels of estrogen can be a risk factor in AD, while high expression of one of ERβ isoform may play a protective role. Data, however, are still not conclusive.
Estrogen's role in memory may be due to its effect on the tiny knobs called spines that protrude from a neuron's dendrites. Spines are formed at the site of connections between neurons. The images demonstrate that 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.
Effect of estrogen on hippocampal neurons in vitro

CEE- conjugated equine estrogen (used in HRT)
Mechanisms of neuroprotective activity of estrogens:

Genomic (classical) pathway:

* Slow - effects after several hours

* Mediated by ERα and ERβ

* ER are expressed in different cells of central and peripheral nervous system. In the brain, in many cell types both types of receptors are coexpressed. Possibly both are involved in neuroprotection.

* Genes with ER response elements in the promoter:
  # oxitocine (peptide hormone), apoE (neuroregeneration, clearance 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)
Non-genomic pathway (influence on other signal transduction pathways):

* Can be very fast – effects after minutes.

* mediated by:
  # activation of adenylyl cyclase, elevation of cAMP, induction of PKA, CREB, and AP-1
  # elevation of Ca\(^{2+}\) and stymulacja PLC
  # activation of PI3K and Akt kinases (ER\(\alpha\) may directly bind to PI3K).
  # activation of ERK1/2 (survival signaling).
  # 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) – it can be one of the mechanisms of neuro- and cardioprotection.

* Inhibition of **NF\(\kappa\)B** attenuates inflammatory response
**NO in the central nervous system:**

- NO is an important neurotransmitter. Unlike classic transmitters NO is not stored, but synthesized on demand and immediately 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.
Neuroprotective effect of CEE against glutamate-induced toxicity
(Hippocampal neurons cultured in vitro)

- Plating the cells
- 4 days
- Supplementation with CEE
- 4 days
- Exposure to glutamate (5 min)
- 24 h
- Analysis
Neuroprotective effect of CEE against glutamate-induced toxicity
**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$^-$.

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

* Noteworthy, effective concentration of estrogens may be much lower (within physiological range), e.g. in the presence of glutathione.
Neuroprotective effect of CEE against $\text{H}_2\text{O}_2$-induced toxicity
(Hippocampal neurons cultured in vitro)

- Plating the cells
- 4 days
- Supplementation with CEE
- 4 days
- Exposure to $\text{H}_2\text{O}_2$ (20 min)
- 24 h
- Analysis
Neuroprotective effect of CEE against $\text{H}_2\text{O}_2$-induced toxicity
Possible Mechanisms of Estrogen/SERM Neuroprotection

**ESTROGEN/SERMS**

**Neuroprotection**

- Genomic
  - Requires pretreatment
  - Involves ER-mediation
  - Involves gene transcription
- Nongenomic
  - Rapid effect
  - May or may not involve ER-mediation
  - May involve MAPK or AKT signaling
- Antioxidant
  - Seavenges free radical oxidants
  - *Does not involve ER-mediation*
  - Usually only observed at very high pharmacological concentrations

*Dhandapani KM and Brann DW Biol Reprod 2002.*
Amyloid precursor protein cleavage by β- and γ-secretases leads to the production of amyloid-β, the primary component of senile plaques in AD.

Spires and Hyman 2005
The neuropathological steps of Alzheimer’s disease

- **Amyloid deposition**
  - Abnormal APP metabolism
  - β-amyloid deposition
  - β-amyloid plaques

- **Increased Inflammation**
  - Activated microglia and astrocytes
  - Cytokines & Chemokines

- **Tauopathy**
  - Abnormal tau phosphorylation
  - Formation of paired helical filaments
  - Neurofibrillary tangles

- **Loss of synapses and neurons**

- **Neurotransmitter disturbance**

- **Alzheimer’s disease**

*Jacobsen et al. 2005*
Neuroprotective effect of CEE against β-amyloid-induced toxicity

(Hippocampal neurons cultured in vitro)

- Plating the cells
- Supplementation with CEE
- Exposure to β-amyloid
- Analysis

Control

β-Amyloid

β-Amyloid + CEE 0.1 ng/ml

β-Amyloid + CEE 10 ng/ml

R.D. Brinton et al. / Neurobiology of Aging 21 (2000) 475–496
Neuroprotective effect of CEE against β-amyloid-induced toxicity

(Hippocampal neurons cultured in vitro)
Isoflavonoids (one of four classes of phytoestrogens) activate ER in vitro,

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

- Plants produce phytoestrogens e.g. as chemoattractants for Rhizobium, as the protective compounds against bacteria and fungi, and as a repellent against plant-eating animals.

- Isoflavonoids (one of four classes of phytoestrogens) activate ER in vitro,

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

- Partial agonist of ER with 30 x higher affinity to ERβ than to ERα.
- Reversed correlation between genistein concentration in the blood and frequency of breast cancer, cardiovascular diseases, menopause disorders 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). In China and Japan 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 it recognizes estrogen receptor response element). In the cytoplasm they are connected to Hsp90.
ERR - estrogen related receptor

• **ERR generally repress transcription of target genes, but they can also activate transcription.**

• Perhaps in vivo they can be constitutively active, as even without any ligand they can interact with coactivators.

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

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

• They were shown to modulate the expression of genes regulated by estrogen receptors in bones and breast tissues.
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 and then in brain and spinal cord
  - bones

- **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 the mouse embryo and up-regulates the expression of the osteopontin gene.

  * They play a role in *in vitro* 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, bind to ERRα, ERRβ, and ERRγ)
  * 4-hydroxytamoxifen (4-OHT, binds to ERRβ and ERRγ) repress their constitutive transcriptional activity. Raloxifem does not bind to ERR.

• These 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.
ERR and breast cancer

ERRα (P = 0.10)  

ERRβ (P = 0.22)  

ERRγ (P = 0.001)
**ER and ERR ligands**

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<th>4-OHT</th>
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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, it should be noted that 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 activator peptide in vitro.

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

• It could be suggested that some of the antitumor effects of TAM might be mediated by ERR.
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.
Phytoestrogens and ERRs

%Luciferase activity

DMSO  Biochanin A  Genistein  Daidzein  6,3',4'-tri-hydroxyflavone

10 µM  10 µM  10 µM  10 µM

Genistein

Luciferase activity (RLU)

0, 1, 5, 10, 20 [µM]
• 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.

• Altogether, these finding have raised the possibility that the ERRs might directly and indirectly modulate the estrogenic response.
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 conclusively confirmed).

**Fig. 3: Effect of HRT on cardiovascular and noncardiovascular outcomes among healthy postmenopausal women in the Women’s Health Initiative trial.**

Outcomes are grouped according to whether HRT had a negative or positive effect, or no effect, compared with placebo. [Source: WHI HRT Update — 2002, National Heart, Lung, and Blood Institute (National Institutes of Health, US Department of Health and Human Services), Bethesda, Md. (available www.nhlbi.nih.gov/health/women/upd2002.htm [accessed 2003 Mar 19]).

**WHI trial**
Participants had a 23% increase in cardiovascular disease

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

0.34% v 0.30%

and a 38% increase in strokes

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

0.29% v 0.21%
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 (in clinical practice: supplementation in the perimenopausal and early postmenopausal periods).

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 can be assumed to 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.

Number of Events per 10,000 Women per Year of Conjugated Equine Estrogen Therapy Compared to Placebo in the Women's Health Initiative Estrogen Trial by Age at Baseline

The risks associated with estrogen alone appear to be quite negligible (supported by approximately 40 observational 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
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

Slides can be found in the library and at the Heme Oxygenase Fan Club page:

https://biotka.mol.uj.edu.pl/~hemeoxygenase