Quelle modulation du Recepteur des Oestrogènes pour quels bénéfices ?

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Pleiotropic effects of estrogens: protective vs harmful

Reproduction / sexual characters
- Breast
- Uterus

Testosterone
- aromatase
- Estradiol (E2)
- ERα
- ERβ

CNS

Immunity

Bone

Cardio-vascular and metabolic homeostasis

Skin
Cardiovascular actions of estrogens (E)

Epidemiological: Sex difference before menopause

Cohort (Nurse’s): Early Menopause No delay

Women Health Initiative: Hysterectomized: E alone

Endogenous E: Protective
Early exogenous E+P: Protective
Delayed E alone: inefficient

No treatment
Hormone treatment
placebo
E alone
50-59 ans
CEE better

60-69 ans

70-79 ans
Placebo better
Question 1: Are estrogens protective against atheroma and their thrombotic complications (acute coronary syndrome)
WHI 2004:
Relative Risk of Coronary Heart Disease of Estrogen alone / placebo

Importance of the timing
Very similar to the Monkey studies (Cardiovasc. Res. 2002)

Estrogen replacement therapy, atherosclerosis, and vascular function

Tomi S. Mikkola, Thomas B. Clarkson

Endogenous E2 “Surgical menopause” Exogenous E2

OVX

Coronary Artery Atherosclerosis Effect (% of Placebo)

1. Healthy Diet → Atherogenic Diet + CEE
   - Premenopausal Years → Postmenopausal Years
   - 70% decrease

2. Atherogenic Diet → Atherogenic Diet + CEE
   - Premenopausal Years → Postmenopausal Years
   - 50% decrease

3. Healthy Diet → Atherogenic Diet No CEE → Healthy Diet + CEE
   - Premenopausal Years → Postmenopausal Years
   - 0% decrease

Delay “=” 6 post-menopausal years for women
Question 1: Are estrogens protective against atheroma and their thrombotic complications (acute coronary syndromes)?

Endogenous and exogenous E are protective early: primary prevention in animal and humans.... but not when delayed or in secondary prevention.

(Reviewed in Lenfant et al. Maturitas 2011)
Question 2: Which estrogen receptor does mediate the vasculoprotective action of estrogen?
Respective roles of each Estrogen Receptors (ER) in the vascular actions of E2?

ERα

ERβ

Pubmed: respective roles of ERα and ERβ unclear

DBD: DNA Binding Domain, LBD: Ligand Binding Domain, AF: Activation Function
Estrogen receptor $\alpha$ mediates most of the protective / beneficial actions of E2 including:
- arteries (atheroma, endothelial healing),
- metabolism (accumulation of adipose tissue, insulino-resistance),
- bone (demineralization, fractures).
- prevention of hot flushes
But also of the undesired / deleterious actions:
- breast and endometrium (increased cancer risk)
- VTE / oral route. Hepatic target
Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis

**BMJ 2008;336;1227-1231**

Marianne Canonico, postdoctoral research fellow,1,2 Geneviève Plu-Bureau, gynaecologist,1,3 Gordon D O Lowe, professor of vascular medicine,4 Pierre-Yves Scarabin, director of research (Inserm)4

<table>
<thead>
<tr>
<th>Observational studies</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
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<tr>
<td><strong>Oral oestrogen</strong></td>
<td></td>
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<tr>
<td>Boston CDSP 1974w21</td>
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<tr>
<td>Daly 1996w1</td>
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<td>Jick 1996w3</td>
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<td>Nurses’ health study 1996w4</td>
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<td>Perez-Gutthann 1997w5</td>
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<td>Smith 2004w9</td>
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<tr>
<td>Douketis 2005w10</td>
<td>1.9 (0.4 to 7.8)</td>
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<tr>
<td>ESTHER 2007w11</td>
<td>4.6 (2.1 to 10.1)</td>
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<td>Pooled odds ratio</td>
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<tr>
<td>Test for homogeneity: $\chi^2 = 14.99$, P=0.03, $I^2 = 53.3%$</td>
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<thead>
<tr>
<th><strong>Transdermal oestrogen</strong></th>
<th>Odds ratio (95% CI)</th>
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<tr>
<td>Daly 1996w1</td>
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<td>Perez-Gutthann 1997w5</td>
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<tr>
<td>Pooled odds ratio</td>
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<tr>
<td>Test for homogeneity: $\chi^2 = 2.92$, P=0.40, $I^2 = 0%$</td>
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Question 3:
Is it possible to uncouple these beneficial actions of estrogens from their deleterious actions?

Already achieved by Selective ER Modulators (SERMs) such as tamoxifen:
- prevents breast cancer
- prevents osteoporosis
but not vasculoprotective nor Type 2 diabetes
Mouse models: Molecular dissection of ERα functions

- **ERα Neo « KO »**
  - 55 kD ERα
  - AF1
  - DBD
  - LBD
  - AF2

- **ERα AF1**
  - 49 kD ERα
  - AF1
  - DBD
  - LBD
  - AF2
Final goal: Uncoupling beneficial/desirable and deleterious actions of ERα .... contribute to the design of SERMs

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<thead>
<tr>
<th>ERα</th>
<th>AF1</th>
<th>AF2</th>
<th>MISS</th>
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</thead>
<tbody>
<tr>
<td>Atheroma (endothelium)</td>
<td>Indep.</td>
<td>Dependent.</td>
<td>?</td>
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<tr>
<td>Obesity/Metab.</td>
<td>Indep.</td>
<td>Dependent.</td>
<td>?</td>
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<tr>
<td>Cortical bone</td>
<td>Indep.</td>
<td>Dependent.</td>
<td>?</td>
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<tr>
<td>Reendothelial.</td>
<td>Indep.</td>
<td>Indep.</td>
<td>Sufficient</td>
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<tr>
<td>Fertility</td>
<td>Dependent</td>
<td>Dependent</td>
<td>?</td>
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<tr>
<td>Uterine growth (endometrium)</td>
<td>Dependent</td>
<td>Dependent</td>
<td>?</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Dependent In vitro (Flouriot et al.)</td>
<td>Dependent</td>
<td>?</td>
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Activation of Discrete ERα Functions => new optimized SERMs

Selective Extra-nuclear ER Activation

Selective AF-2 Activation

Beneficial

Cardiovascular Protection

Obesity, Insulin resistance

Detrimental

Breast Cancer

Reproductive Tract Cancer

Thrombosis

Also?

Osteopenia

Cardiovascular Protection

Obesity, Insulin resistance

Osteopenia
Deleterious

Beneficial

Activation of AF2
and/or MISS

Activation of AF1

Enterolactone (ENL)

Estetrol (E4)