Estetrol, the first human, physiological Selective Estrogen Receptor Modulator

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Conflict of interest: JMF has received consultancy fees from Mirata E4.

E4: a cooperativity between human fetal, adrenal liver and placenta.

E4 appears very late in evolution.

E4 appears in pregnant monkeys only at the end of pregnancy and reach only 1% of the human levels.

There is a parallel co-evolution between E4 appearance/levels and brain size. Could E4 convey a neuroprotection?
**E4 is the first Human Selective Estrogen Receptor Modulator identified**

E4 acts in a different way than E2, EE and synthetic SERMs.

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**Estetrol in the presence of Estradiol**

Summary of 14 preclinical and 8 clinical studies.

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**E4 displays mixed agonist-antagonist activities: in the brain**

<table>
<thead>
<tr>
<th>Allopregnanolone</th>
<th>β-endorphin</th>
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<tr>
<td><strong>E2+E4</strong> and brain Allopregnanolone</td>
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**E4 displays mixed agonist-antagonist activities: in the breast**

- E4 antagonizes E2 effects in murine mammary glands without changing the structure.
- E4 antagonizes E2 effects in human normal breast cells.

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**Combined endocrine and cell biological effects of estetrol in breast cancer cell lines**

- Allopregnanolone activates ERα in breast cancer cells.
- Estetrol antagonizes E2 effects in breast cancer cells.

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**Estetrol on endothelium**

- NO production
- Endothelial function

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**Estetrol on Endometrium**

- Visible effect on endometrial cells.
- Estradiol and Estetrol effects.

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**Estetrol on Endometrial Vaginal keratinocytes**

- Effects on endometrial cells.
- Estradiol and Estetrol effects.

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**Estetrol on Endothelium**

- High efficiency for VVA atheroma prevention.
- Inhibition of neointima thickening.
- Glucose and lipid metabolism.

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E4 is an antiestrogen on the normal and malignant breast in the presence of Estradiol.

E4 displays mixed agonist-antagonist activities on endothelial cells.

E4 is a pure agonist of ERα, acting in synergy with E2 in endometrium.

E4 prevents atheroma and regulate artergene transcription in synergy with E2.

Are genomic actions the whole story of ERα activation?

E4 is a SERM with modest stimulatory activity compared to E2 to induce stromal epithelial proliferation, genomic actions.

The Nuclear and Membrane forms of the Estrogen Receptor alpha.
Transgenic mice to suppress the nuclear ERα functioning

E2 binds to the nuclear ERα to exert genomic effects

E2 also activates membrane bound ERα: Membrane initiated Signal transduction

E2 activates two types of ERα:

E4 activates the nuclear ERα, but inhibits the membrane ERα pathway

Summary of E4 activities at cellular level
E4 is a SERM able to modulate the nuclear ERα, and is not only devoid of M4S, but also able to antagonize the M4S effects in some tissues, thereby delineating a distinctive profile of ERα activation. Thus, E4 is a natural Selective ER Modulator of human pregnancy that could also be considered for human treatment.

The Membrane bound ERα is essential for ovulation

Abrogation of membrane bound ERα in transgenic C451A mice results in females sterile, with abnormal ovarian follicle populations and increased folliculinizing hormone levels. HCF: hemorrhagic cystic follicles

Vaginal bleeding profile and cycle control

Incidence of scheduled menstruations

Both E4 groups appear to have minor changes on all haemostasis parameters

Estelle®,

Sponsored Symposium: MithraSymposium San Francisco 2014

Estelle: changing hormones in advancing oral contraception
Lee Shulman, MD, Northwestern University, Chicago, Illinois, USA

Estetrol and drospirenone in oral contraception: E4 FREEDOM™ Phase 3b Feacility study design J.M. Foidart MD, PhD

Effects on estrogenic and haemostatic variables of estetrol in combination with Drospirenone C. Muij, Good Biomarker Sciences, Leiden