Comparison of Estradiol and Estetrol on Estrogen Receptor alpha signaling

Anne Gallez, Céline Gérard, Silvia Blacher, Irina Primac, Jean-Michel Foidart, Christel Péqueux

Context: Estetrol (E4) is a natural estrogen produced by the human fetal liver during pregnancy. However, the physiological roles of E4 during pregnancy remain unknown. Several evidences highlight that E4 is a promising compound for clinical applications in estrogen-sensitive tissues, since it elicits a high binding specificity for both estrogen receptors, ERα and ERβ. E4 treatments in rodents and women revealed that it shares with Estradiol (E2) and Estriol (E3) several estrogen-like effects on numerous tissues such as brain preventing hot flushes, endothelium protecting from atheroma, bone preventing osteoporosis or vaginal epithelium avoiding vaginal dryness. E4 has also characteristics distinctive from other estrogens, which makes it an appropriate compound to be used for menopause hormone treatment (MHT) or combined oral contraceptive (COC) in women. Nevertheless, it remains essential to document the molecular and cellular mode of action of E4 and to compare it to E2, especially regarding its impact on ERα signaling that relays most of the physiological effects of estrogens.

Objective: The aim of this study was to compare E4 and E2 on several steps of ERα signaling.

Results: The ERα signaling relies on two main pathways: 1) the genomic/nuclear pathway that is associated to the direct ability of ERα to bind to specific DNA sites to modulate the expression of target genes, 2) the rapid/non-genomic/membrane-initiated steroid signaling (MISS) that is related to the activation of the membrane form of ERα. In this study, we compared how E2 and E4 modulate these two pathways. To specifically study the genomic pathway we evaluated the ability of E2 and E4 to induce the phosphorylation of ERα, one of the first step of ERα activation, to bind to DNA estrogen responsive element (ERE) and to induce the expression of genes (PR, pS2) specifically related to the genomic pathway. The activation of the MISS pathway was studied by measuring the interaction between ERα and Src, the initiating step of the MISS effects. Induction of specific genes of the MISS pathway (PMAIP1, TSKU, HSPB8) were also evaluated. Finally, we compared the broad transcriptomic impact of E2 and E4.

Conclusions: This study provides a comprehensive comparison of the impact of E4 and E2 on ERα signaling. This allows a better understanding of the specificity of E4 action on several estrogen-sensitive tissues.