Maturitas 99 (2017) 1–9

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Regulatory effects of estetrol on the endothelial plasminogen pathway and endothelial cell migration

Maria Magdalena Montt-Guevara, Giulia Palla, Stefania Spina, Guja Bernacchi, Elena Cecchi, Adrian Esteban Campelo, Jorge Eduardo Shortrede, Alessio Canu, Tommaso Simoncini*

Molecular and Cellular Gynecological Endocrinology Laboratory (MCGEL), Department of Clinical and Experimental Medicine, University of Pisa, Pisa, PI, Italy

ARTICLE INFO

Article history:
Received 29 November 2016
Received in revised form 6 February 2017
Accepted 7 February 2017

Keywords:
Estetrol
Estrogen
HUVEC
PAI-1
u-PA
t-PA

ABSTRACT

Background: Estetrol (E4) is a natural estrogen produced solely during human pregnancy. E4 is suitable for clinical use since it acts as a selective estrogen receptor modulator. In clinical trials E4 has been seen to have little or no effect on coagulation. Hence, it is interesting to investigate whether E4 alters endothelial-dependent fibrinolysis.
Objectives: We studied the effects of E4 on the fibrinolytic system and whether this could influence the ability of endothelial cells to migrate. In addition, we compared the effects of E4 with those of 17β-estradiol (E2).
Study design: Human umbilical vein endothelial cells (HUVEC) were obtained from healthy women. Expression of plasminogen-activator inhibitor-1 (PAI-1), urokinase-type plasminogen activator (u-PA) and tissue plasminogen activator (t-PA) proteins was evaluated by Western blot analysis. Endothelial cell migration was studied by razor-scrape horizontal and multiwell insert systems assays.
Results: E4 increased the expression of t-PA, u-PA and PAI-1 in HUVEC, but less so than did equimolar amounts of E2. The effects of E4 on t-PA, u-PA and PAI-1 were mediated by the induction of the early-immediate genes c-Jun and c-Fos. E4 in combination with E2 antagonized the effects induced by pregnancy-like E2 concentrations but did not impair the effects of postmenopausal-like E2 levels. We also found that the increased synthesis of PAI-1, u-PA and t-PA induced by E2 and E4 is important for horizontal and three-dimensional migration of HUVEC.
Conclusions: These results support the hypothesis that E4 acts as an endogenous selective estrogen receptor modulator (SERM), controlling the fibrinolytic system and endothelial cell migration.
© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Estetrol (E4) is a human-specific natural estrogen produced exclusively during pregnancy by the fetal liver. E4 concentrations increase exponentially during pregnancy and peak at term with fetal levels about 10–20 times higher than maternal ones. Soon after delivery, blood levels of E4 become undetectable [1]. The physiological role and mechanisms of action of E4 during pregnancy are still poorly understood.

E4 is an endogenous selective estrogen receptor modulator (SERM), exerting estrogenic actions on the endometrium and the central nervous system but with antagonistic effects on the breast [2].

Based on the available information clinical studies of E4 [3], oral administration has minimal effects on the liver, and surrogate markers of coagulation and fibrinolysis are compatible with a neutral effect on thromboembolic risk. Due to these characteristics, E4 is currently being developed for a number of clinical applications, including contraception and menopausal hormone replacement therapy (HRT) [4,5]. The Women's Health Initiative (WHI) trial showed that oral estrogen plus progestin – an alternative preparation for such applications – may increase the risk of cardiovascular disease (CVD) among postmenopausal women, especially during the first year after the initiation of HRT [6,7].

Plasminogen-activator inhibitor-1 (PAI-1) is one of the primary regulators of the fibrinolytic system *in vivo*, and over-expression of this inhibitor compromises normal fibrin clearance and promotes fibrin deposition and hence thrombotic events [8]. Menopausal estrogen withdrawal is associated with increased blood levels of PAI-1 [9], while a decrease is found with estrogen therapy [10].

* Corresponding author.
E-mail address: tommaso.simoncini@med.unipi.it (T. Simoncini).

http://dx.doi.org/10.1016/j.maturitas.2017.02.005
0378-5122/© 2017 Elsevier B.V. All rights reserved.

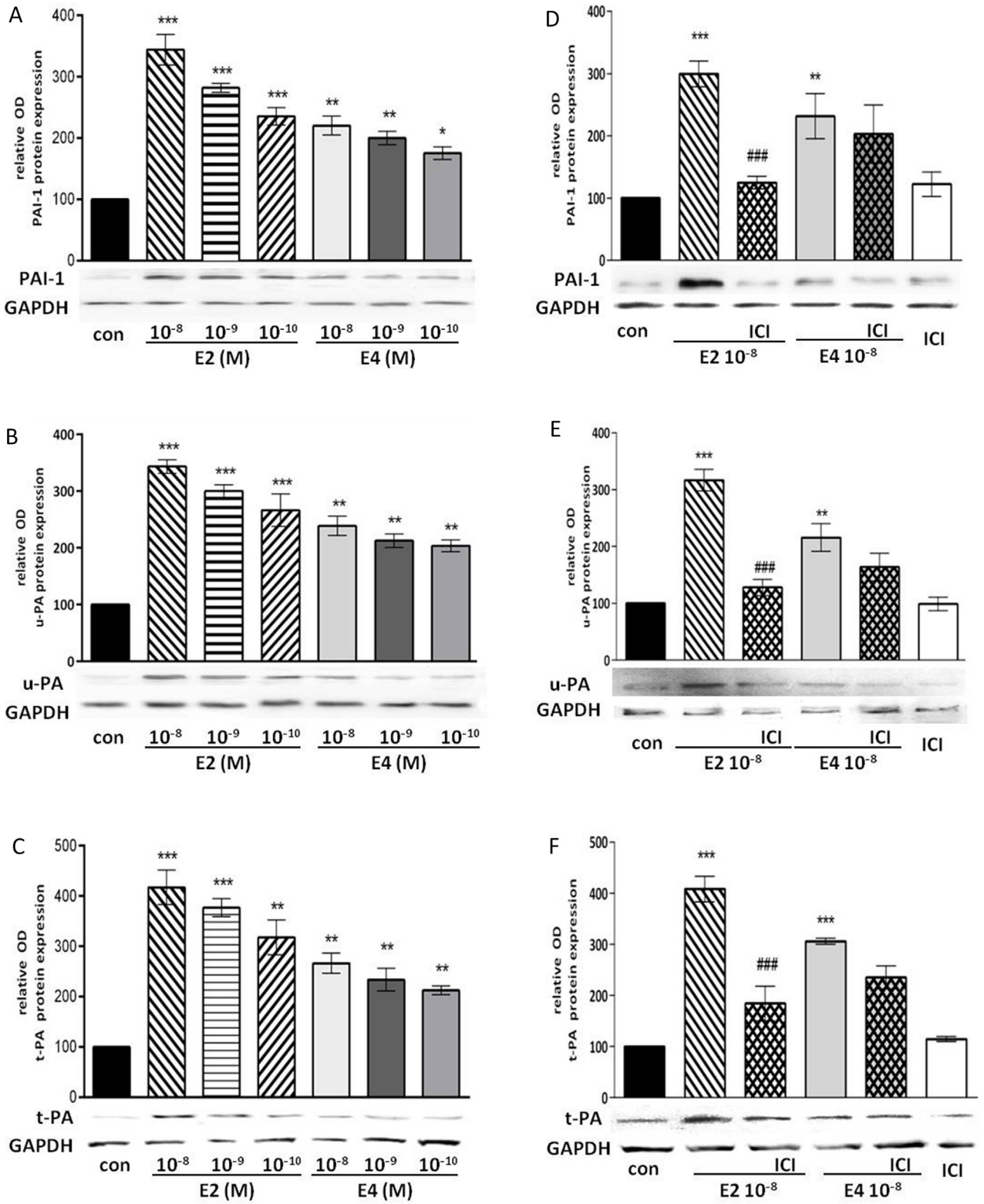

Fig. 1. E4 increases expression of PAI-1, u-PA and t-PA in human endothelial cells. HUVEC were treated during 24 h with vehicle (con) or increasing doses of E2 or E4 (A–C) in the presence or absence of ICI (D–F). Cell lysates were analyses by Western blotting for PAI-1, u-PA and t-PA. Quantitative bar graphs are expressed as mean ± SEM (upper panel) of three independent experiments and representative blots are shown (lower panel). The significance of the observed effects was evaluated using one-way ANOVA followed by Tukey's multiple comparisons post-test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. con) (###$p < 0.001$ vs. E2).

These changes have been interpreted as potential reasons for the beneficial vascular effects of endogenous estrogens in fertile women. Additionally, estrogen receptor (ER) agonists are known to control endothelial cell migration and the proteolytic activity of PAI-1, urokinase-type plasminogen activator (u-PA) and tissue plasminogen activator (t-PA) [11,12].

In human endothelial cells, E4 mimics the effects of 17β-estradiol (E2), enhancing nitric oxide (NO) synthesis when provided

Download English Version:

https://daneshyari.com/en/article/5503513

Download Persian Version:

https://daneshyari.com/article/5503513

Daneshyari.com