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TITLE

SIGNIFICANCE OF ESTRADIOL METABOLITES IN OVARIAN PHYSIOLOGY AND REPRODUCTIVE DYSFUNCTION

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ABSTRACT

Estradiol throughout the reproductive development includes follicle recruitment and dominant follicle selection. E2 exerts diverse biological effects and many of these effects are mediated by intracellular E2R. Interestingly, estrogens are eliminated from the body by metabolic conversion to less active water-soluble EMs by diverse disposition including hydroxylation-glucoronidation-sulfonation and/or methylation. These processes take place in the liver or in selectively extra-hepatic tissues. EMs act through different pathways not associated with activation of classical E2R. Interestingly these metabolites can affect the physiology and pathophysiology of different dysfunction. Consequently we studied of EMs during human luteal phase regression. We emphasize that the human CL produce high levels of E2 during mid luteal phase. The physiological role of luteal E2 is virtually unknown. The CL express CYP450s and COMT, therefore it is plausible that the EM 2-Methoxyestradiol 2-ME could be present in luteal tissue. It is well known that 2-ME produces a significant negative impact on angiogenesis and cell proliferation. Consequently we postulated that 2-ME pathways could play a role in the process of luteolysis. Therefore we measured the levels of 2-ME by HPLC in CL tissue of different ages. The results show a decrease of plasma levels of E2 in association with an increase in luteal late tissue of 2-ME. Simultaneously there was a significant reduction on angiogenic activity of late CL. Physiological doses of 2-ME inhibited basal VEGF production by GC in culture and diminished angiogenic activity. These data suggest the participation of 2-ME in physiologic luteolysis by reducing angiogenesis in non conception cycle. 2-ME did not prevent in vitro HCG stimulation of P4 biosynthesis, providing a new mechanism for CL rescue in the cycle of conception.

INSTITUTE

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