Chapter

HYDROXYESTRADIOLS AND METHOXYESTRADIOLS AS ENDOGENOUS FACTORS ASSOCIATED TO PHYSIOLOGICAL AND PHYSIOPATHOLOGICAL CONDITIONS

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ABSTRACT

Estradiol (E_2) is a steroidal hormone generated by the conversion of testosterone via the p450 aromatase enzymatic complex. The E_2 physiological actions are mainly mediated by its interaction with intracellular receptors known as estrogen receptors (ERs). The E_2-ERs complex is able to alter the gene expression in its target cells binding to specific sequences in the DNA. Besides, estrogens can also activate several intracellular signal transduction cascades (e.g. cAMP-PKA, IP3-Ca^{2+}) by non-genomic mechanisms.

Following to exert its biological effects in their target tissues, E_2 must be inactivated and eliminated by the body through its conversion to soluble compounds with a insignificant or very low estrogenic activity. These reactions are accomplished by several enzymatic processes that involve reactions of oxidations and conjugations. The enzymatic modifications that a molecule of E_2 undergoes to be eliminated include sulfonations, O-methylations, hydroxylations and glucurodinations. Even though the conversion of E_2 to inactive or less active metabolites occurs mainly in the liver, it has been reported that some peripheral tissues, including breast, uterus, placenta and brain, express the enzymes required to inactive E_2.

One of the most studied enzymatic pathways that inactive estradiol in peripheral tissues consists in a C-2 hydroxylation, a reaction catalyzed by the enzyme cytochrome p450, isoform 1A1 (CYP1A1), that generates a molecule of 2-hydroxyestradiol ($2OHE_2$) and the C-4 hydroxylation, a reaction catalyzed by the enzyme CYP1B1 that generates 4-hydroxyestradiol ($4OHE_2$). Then, the hydroxyl group previously added is replaced by a methyl group through a conjugation reaction catalyzed by the enzyme Catechol-O-Methyltransferase (COMT), which originates a molecule of 2- methoxyestradiol ($2ME_2$) from $2OHE_2$ and 4-methoxyestradiol ($4ME_2$) from $4OHE_2$.

Recently, it has been demonstrated that hydroxyestradiols and methoxyestradiols are not inactive molecules since several reports have shown that these estradiol metabolites may exert physiological actions in different organs and tissues, while an unbalanced estradiol metabolization to hydroxyestradiols and methoxyestradiols could be the responsible factor of several diseases including cancer and preeclampsia. In this chapter we will review the available literature concerning to the physiological effects that hydroxyestradiols and methoxyestradiols exert in several organs and how an altered production of hydroxyestradiols or methoxyestradiols could have deleterious effects on several biological functions. We will specially discuss the possible physiological and physiopathological effects of $2ME_2$ in female reproductive tissues, where this estradiol metabolite is able to alter the ovum transport and change the gene expression profile. Particularly, we will describe a group of $2ME_2$-induced genes in the mouse uterus that could be useful as biomarkers to elucidate the role of $2ME_2$ in the female reproductive tract.

Keywords: Hydroxyestradiol, Methoxyestradiol, physiology, physiopathology, reproductive tissues, gene expression

INTRODUCTION

Estradiol (E_2) exerts biological actions in several organs, including testis (Carreau et al., 2011), ovary (Drummond and Fuller, 2012), uterus (Groothuis et al, 2007), bone (Khosla et al., 2012), brain (Brown et al., 2009) and in the vascular system (Leung et al., 2007). The mechanisms by which E_2 regulates cell functioning involve its binding to the estrogen receptor α (ERα) and/or β (ERβ), forming a complex that change gene expression (Cheskis et al., 2007). In the last years, it has been also reported that E_2 may alter the functioning of its target cells activating several intracellular signal transduction cascades (e.g. cAMP-PKA, IP3-Ca^{2+}) by non-genomic mechanisms (Raz et al., 2008; Coleman and Smith, 2001).

Following to exert their biological effects, E_2 must be inactivated by its biotransformation to less estrogenic compounds. Four are most known enzymatic modifications that a molecule of E_2 undergoes to be inactivated. These are sulfonations, reactions catalyzed by several estrogen sulfotransferases enzymes; O-methylations, a reaction catalyzed by the enzyme Catechol-O-Methyltransferase; hydroxylations, reactions catalyzed by several cytochrome P450s isoforms enzymes; and glucurodinations, catalyzed by UDP-glucuronosyltransferases enzymes (reviewed in Zhu and Conney, 1998).

Although the conversion of E_2 to inactive metabolites occurs mainly in the liver, some peripheral tissues including breast, uterus, placenta and brain express the enzymes required to inactive estradiol (Tsuchiya et al., 2005). The most studied enzymatic pathways that inactive E_2 consists in the subsequent conversion of E_2 to hydroxyestradiol and then to