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Estrogen Metabolism and Reproduction - is there a Realtionship?

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Estrogen Metabolism and Reproduction – is there a relationship?

M. Rosselli[1,2], R. K. Dubey[1]

The ovarian hormone estradiol importantly participates in the key reproductive processes such as oocyte development, fertilization, embryo implantation and embryo development. Although the biological effects of estradiol are mediated via estrogen receptors (ERs) a or b, recent findings provide evidence that ER-independent actions are also involved. In vivo estradiol is metabolized to multiple biologically active metabolites. Because, catechol-estradiols (e.g. 2-hydroxyestradiol) and methoxyestradiols (e.g. 2-methoxyestradiol), major endogenous metabolites of estradiol with no affinity for ERs are potent signaling molecules, we hypothesize that the sequential conversion of estradiol to catecholestradiols and methoxyestradiols, by cytochrome-P450 (CYP450) and catechol-O-methyltransferase (COMT), respectively, plays a prominent role in regulating the biology and physiology of reproduction. Moreover, abnormalities in estradiol metabolism either genetic or acquired may be importantly associated with reproductive pathologies and infertility. In this review we explore whether endogenous metabolites (catecholestradiols and methoxyestradiols) of estradiol with no affinity for ERs can modulate reproductive function by influencing key cellular processes essential for reproductive success.

Das ovarielle Estradiol ist als wesentliches Schlüsselhormon im Reproduktionsprozeß an Eizellreifung, Befruchtung, embryonaler Implantation und Entwicklung beteiligt. Auch wenn die biologischen Effekte des Estradiols über a- und ß-Rezeptoren (ER) vermittelt stattfinden, geben neuere Forschungsergebnisse Hinweise auf die Beteiligung ER-unabhängiger Prozesse. In vivo wird Estradiol zu zahlreichen biologisch aktiven Metaboliten abgebaut. Da Katecholestradiole (z. B. 2-Hydroxyestradiol) und Methoxyestradiole (z. B. 2-Methoxyestradiol) als wichtige endogene Metabolite des Estradiols ohne Rezeptoraffinität starke Signalmoleküle sind, nahmen wir an, daß die sequentielle Konversion von Estradiol zu Katecholestradiolen und Methoxyestradiolen durch Cytochrom-P450 (CYP 450) bzw. Catechol-O-Methyltransferase (COMT) eine bedeutende Rolle in der Regulation biologischer und physiologischer Reproduktionsvorgänge spielen könnte. Darüber hinaus sind möglicherweise genetisch fixierte oder erworbene Abweichungen des Estradiolmetabolismus mit Fortpflanzungs-Pathologien oder Infertilität eng assoziiert. In diesem Review untersuchen wir, ob endogene Estradiol-Metabolite (Katecholestradiole und Methoxyestradiole) ohne ER-Affinität die Fortpflanzungsfunktion über den Einfluß auf zellulärer Schlüsselprozesse, die essentiell notwendig für eine erfolgreiche Reproduktion sind, modulieren können. ***J Fertil Reprod 2006; 16 (4): 19–23***.

Ovarian hormones play a critical role in facilitating the reproductive process. Although, the ovaries are known to produce several hormones, the cyclic and time-dependent production of estradiol and progesterone is a key factor in fine tuning the reproductive process from oocyte development to fertilization, embryo implantation and embryo development (Figure 1). It is well established that estradiol mediates its pro-reproductive effects via actions on multiple reproductive organs (ovary, oviduct, uterus, placenta formation) as well as biochemical processes. Based on the conventional mechanisms of action, estradiol is thought to bind to estrogen receptors within the reproductive organs and trigger the generation of autocrine and paracrine factors (growth factors and cyokines such as transforming growth factor β, leukemia inhibitory factor, endothelin-1, nitric oxide etc.) which facilitate oocyte development, fertilization, as well as embryo development. Indeed based on this evidence pharmacological fine tuning of estradiol and progesterone levels play a critical role in treating infertile couples undergoing IVF treatment. Although, the conventional mechanisms of estradiol action in reproduction are well studied much less is known about the role of estradiol metabolism in modulating its actions on the reproductive system. Moreover, no scientific explanations are still available in IVF cases where a morphologically perfect embryo fails to implant. In the medical era where multiple diseases are associated with metabolic disorders, it is also possible that the reproductive processes regulated by estradiol are also influenced by estradiol metabolism. The main aim of this brief review is to introduce the readers to the potential role of estradiol metabolism in reproduction.

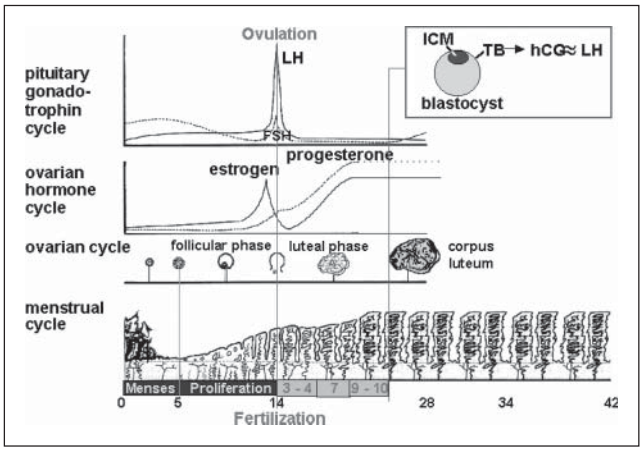

Figure 1. Cartoon depicting the cyclic, time-dependent changes in ovarian hormones during follicular development and early embryo development (ICM, inner cell mass; TB, trophoblast; LH, luteinizing hormone; from http://www.emc.maricopa.edu/faculty/farabee/biobk/BioBookREPROD.html)

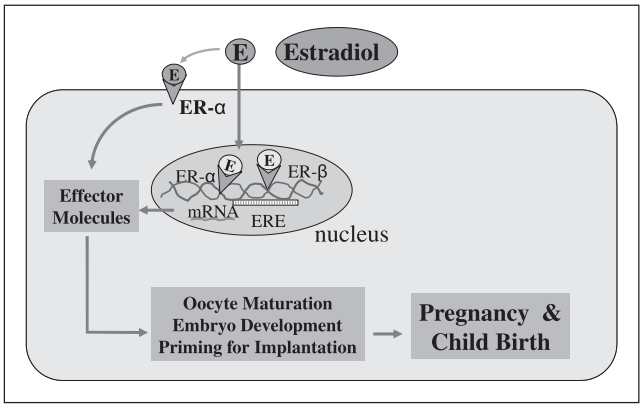

Figure 2. A schematic representation of the conventional mechanism via which estradiol mediates its biologic actions (E, estradiol; ER, estrogen receptor; from Dubey et al, personal communication).

Biological Effects of Estradiol: Potential Role of ER-Dependent and -Independent Mechanisms

Role of ERs: The Conventional Mechanism

It is well established that the biological effects of estradiol

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are mediated by high-affinity intracellular estrogen receptors (ERs) within the target cell. As shown in Figure 2, the nuclear hormone receptor complex binds to chromatin at specific regions of the DNA estrogen response elements (EREs), and this interaction of activated ERs with EREs stimulates or inhibits specific gene expression and protein synthesis. Changes in the generation of intracellular proteins trigger a cascade of events that influences metabolic processes and translates it into cell growth and differentiation. It is well documented that estradiol induces uterine growth (hypertrophy and hyperplasia) and the expression of protooncogenes, which may play a role in estradiol-induced cell growth and proliferation. In uterine cells, treatment with estradiol rapidly increases the steady-state expression of N-myc, c-myc, c-ras, and c-fos mRNA. In addition, ERs increase the synthesis of growth factors such as epidermal growth factor (EGF) and insulin-like growth factor (IGF) and stimulate the levels of growth-promoting peptides that can act in an autocrine fashion to induce cell growth (for details see reviews: [1–3]).

The functional ERs α and β are expressed in the reproductive organs (ovary, uterus, oviduct etc.), moreover, studies conducted in our laboratory provide evidence that via ERs, estradiol regulates the production of growth regulatory and differentiation factors such as LIF, endothelin, and transforming growth factor-β within the oviduct [4–6]. Whether ER-α and ER-β play a similar or different role in mediating the physiological effects of estradiol remains unclear. However, differential expression of ER-α and ER-β is observed in some tissues, which suggests different physiological roles for these receptors. In this regard, compared with ER-α, high amounts of ER-β mRNA are in fetal ovaries, testes, adrenals, and spleen of the mid-gestational human fetus. Moreover, differential activation by liganded ER-α vs ER-β occurs at the AP-1 site, and xenoestrogens differentially activate EREs when liganded to ER-α vs ER-β. Because, the biologic effects of estradiol correlate with ER expression, any alterations in ER expression could influence its biologic actions (for details see: [1, 7]).

Although the biological effects of estradiol are largely mediated via ERs, however, accumulating evidence suggests that estradiol can also mediate its effects via ER-independent mechanism. In this context estradiol has been shown to induce antioxidant effcts as well as induce NO synthesis, cAMP synthesis [2]. Preliminary findings from our laboratory provide evidence that the stimulatory effects of estradiol on TGF-β synthesis are only partially blocked by the ER antagonist ICI182780, suggesting that the effects were partially ER-independent.

Biological and Pathophysiological Role of Estradiol Metabolism

Although, the biological effects of estradiol are largely ER mediated, estradiol can also mediate other actions via its metabolites. Indeed, as shown in figure 3, endogenous estradiol is metabolized to several biologically active metabolites which can mediate their actions via both ER-dependent and ER-independent mechanisms. Estradiol is eliminated from the body by metabolic conversion by cytochrome P-450 enzymes (CYP450s). Many isoforms of CYP450s exist; however, the isozymes that metabolize steroids such as estradiol are CYP1A1, 1A2, CYP1B1, CYP3A4 [2, 8, 9]. Although most of the metabolites of estradiol are hormonally less active, water soluble, and excreated in the urine, some of the metabolites have significant growth regulatory effects. The importance of estradiol metabolism is illustrated by the findings that inhibition of CYP450 enzymes by cimetidine increases estradiol levels and high doses of cimetidine may cause gynecomastia [10].

In humans, estradiol is largely metabolized within the liver via oxidative metabolism (to form hydroxylated metabolites such as 2- and 4-hydroxyestradiol); glucuronidation (to form glucuronide conjugates); sulfatase action (to form sulfates); esterase action (to form fatty acid esters) ; and O-methylation of catechol estradiols (to form O-methylated catechols). In addition to the liver, cells in several other tissues, including the breast, uterus, kidney and the vasculature, contain CYP450 and metabolize estradiol and its metabolites [8, 9]. Preliminary data from our laboratory provides evidence that the oviduct cells also express CYP450 isozymes 1A1 and 1B1. The metabolism of estradiol locally within a tissue may be of immense importance in mediating several of its physiological as well as pathophysiological effects. Several studies provide evidence that the catechol estradiols can induce biological effects. 2-hydroxyestradiol is a weak ligand for ER and may regulate multiple mechanisms in reproductive tissues, including growth of cancer cells and generation of prostaglandins in the uterus during pregnancy [8, 9]. 2-hydroxyestradiol attenuates catabolism of catecholamines by inhibiting catechol O-methyltransferase activity, and this may modulate the neurophysiological and pharmacological effects of catecholamines within the oviduct. Indeed, norepinephrine has been shown to induce sperm capacitation and oviduct blood flow. Additionally, 2-hydroxyestradiol is a potent antioxidant and thereby protects membrane phospholipids and cells against peroxidation [11].

Similar to 2-hydroxyestradiol, 4-hydroxyestradiol induces several important biological effects. Even though it is not the dominant metabolite formed by the liver, 4-hydroxyestradiol is a major metabolite formed in some extrahepatic tissues such as rat pituitary and human myometrial, myoma, and breast tissue, as well as kidney and vasculature tissue. In contrast to estradiol, 4-hydroxyestradiol binds with low affinity to ER; however, its dissociation rate from the receptor is much lower than that observed for estradiol. 4-hydroxyestradiol has been shown to induce kidney tumors growth in Syrian hamsters and uterotrophic effects in rats [12]. 4-hydroxyestradiol also prevents inactivation of cate-

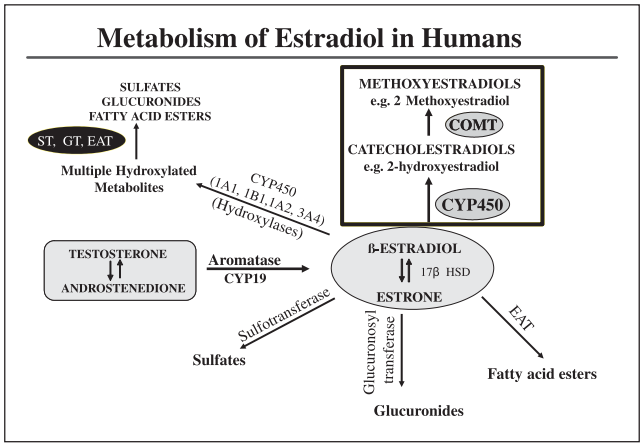

Figure 3. Schematic representation of the key pathways involved in the metabolism of estradiol. The sequential conversion of estradiol to hydroxyestradiol (catecholestradiol) and methoxyestradiol by cytochrome-P450 (CYP450) and catechol-O-methyltransferase (COMT) is an important pathway. Both the hydroxyestradiol and methoxyestradiol can induce biological activity via ER-independent pathway (from Dubey et al, personal communication).

cholamines by inhibiting catechol O-methyltransferase activity [12] and may help in the norepinephrine-induced sperm capacitation process.

In contrast to 2-hydroxyestradiol, 4-hydroxyestradiol induces carcinogenic effects [8, 9]. In fact, recent studies provide evidence for reduced 2-hydroxylation and increased 4-hydroxylation of estradiol in subjects with cancer, suggesting that 2-hydroxyestradiol or its methylated metabolite (2-methoxyestradiol) may be anticarcinogenic, whereas 4-hydroxyestradiol and its metabolite 4-methoxyestradiol may be carcinogenic. Because abnormal growth of cells is a hallmark for both ectopic-pregnancy and endometriosis, it is feasible that the catechol metabolites of estradiol may also play an important role in regulating cell growth within the oviduct. Because, the CYP450s responsible for metabolizing estradiol are expressed in the oviduct, it is plausible that 2-hydroxyestradiol formed locally may influence sperm motility as well as the fertilization process (for details see: [8, 9, 12]).

In vivo the catechol estradiols are rapidly methylated by the ubiquitous enzyme COMT to form methoxyestradiols. The metabolite 2-methoxyestradiol has no binding affinity for ERs and is a potent inhibitor of cell growth. Within the breast, uterus, prostate and several other organs 2-methoxyestradiol has been shown to induce anti-carcinogenic effects. Based on its interaction with tubulin, it is classified as along with taxol and colchicine, potent inhibitors of cell growth. Because, the oviduct cells express both CYP450 and COMT, we hypothesize that estradiol can be converted to methoxyestradiol locally within the oviduct. Whether 2-methoxyestradiol plays a role in the pathophysiology of oviduct function and fertilization is not known. Based on the fact that under basal conditions the CYP450 activity (CYP1A1 and CYP1B1) is not highly expressed, hence the local levels of 2-methoxyestradiol would be low and would not interfere with sperm motility and embryo development. Because, 2-methoxyestradiol has been shown to decrease superoxide dismutase activity and act as an antioxidant, low concentrations may protect and enhance sperm function as well as embryo development. However, under pathological conditions where the CYP450 activity is induced, the local formation of 2-methoxyestradiol within the oviduct may interfere with the fertilization process and inhibit both sperm motility and embryo development. This contention is based on the fact that 2-methoxyestradiol concentration-dependently inhibits cell-migration, tubulin polymerization and cell division [8, 9, 12].

Can Metabolism of Estradiol to Methoxyestradiol Influence Reproductive Process?

Potential Impact of Estradiol Metabolism on Oocyte Development

It is well established that follicular development is positively supported by the dynamic changes in the microcirculation within the ovary. Indeed, cyclic changes in the microcirculation i.e. angiogenesis and regression of the micro-vessels, is known to actively occur and support follicular development. Because, 2-methoxyestradiol is a potent inhibitor of angiogenesis (inhibits endothelial cell proliferation) it is feasible that increased generation of 2-methoxyestradiol, locally within the ovary may inhibit the cyclic angiogenesis process, thereby limiting the supply of nutrients and hampering follicular development. In the same vein, it is important to note that intracellular tubulin reorganization plays a key role in oocyte development (Figure 4). Because, similar to taxol, 2-methoxyestradiol is known to interfere with the tubulin polymerization process [12], increased metabolism of estradiol to 2-methoxyestradiol within the ovary may negatively influence oocyte development. Since 2-methoxyestradiol is known to induce apoptosis [12], its increased generation may induce deleterious effects on the oocyte resulting in cell (oocyte) death. Taken together the above evidence suggests that abnormal (increased) local metabolism of estradiol to 2-methoxyestradiol can negatively influence follicular development and may be associated with the pathophysiology of female infertility.

Potential Impact of Estradiol Metabolism on Fertilization and Embryo Development

The mammalian oviduct plays an important role in the reproductive process by not only acting as a conduit for the gametes and embryos, but also providing the ideal environment for the fertilization process and for the development of the embryo. Oviduct-derived factors regulate the rhythmic contraction and ciliary movement within the lumen of the oviduct. Moreover, oviductal factors are involved in the capacitation process and ample evidence suggests that factors generated within the oviduct i.e. maternal in origin, regulate the process for early embryo development and are probably involved in early embryo-gene expression. Considering the key role of the oviduct in the fertilization process, abnormalities caused by exogenous or endogenous factors can lead to infertility by directly or indirectly influencing either: oocyte viability, fertilization early development of the embryo tubal contractility, sperm viability, sperm motility, sperm capacitation process and transport function. The fact that tubal dysfunction is one of the major causes for human infertility highlights the importance of elucidating the mechanisms regulating oviduct function.

Numerous studies provide evidence that 2-methoxyestradiol is a potent inhibitor of cell growth. It has been shown that 2-methoxyestradiol inhibits the proliferation of cancer cells from multiple tissues (breast, prostate, uterine etc. [8, 9]). Consistent with these findings we have shown that 2-methoxyestradiol inhibits the proliferation of MCF-7 cells in a concentration-dependent fashion. Because the epithelial cells within the oviduct and uterine are phenotypically similar we hypothesize that pathological increases in 2-hy-

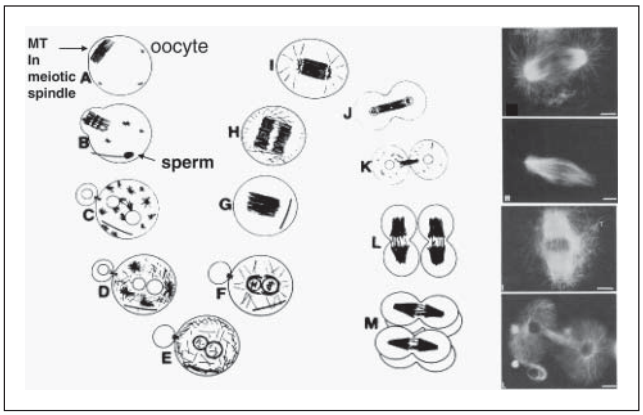

Figure 4. Schematic representation of the dynamic changes in the microtubule (MT) assembly within the oocyte (A) from fertilization (B) to embryo development (C–M). Photomicrographs on the right show changes in tubulin dynamics following immunostaining (Modified from: Schatten G, Simerly C, Schatten H. Microtubule configuration during fertilization, mitosis, development in the mouse and the requirement for egg mediated motility during mammalian fertilization. Proc Natl Acad Sci 1985; 82: 4152–6.)

droxyestradiol and 2-methoxyestradiol can inhibit growth of oviduct cells. Indeed, we have shown 2-hydroxyestradiol and 2-methoxyestradiol are potent inhibitors of smooth muscle cell growth and migration [11–13]. As shown in figure 4, the process of cell division and migration is tightly regulated by tubulin, which alters its configuration in a dynamic fashion. Because, similar to taxol and colchicine, 2-methoxyestradiol binds to tubulin and can interfere with its polymerization or depolymerization (Figure 5), we hypothesize that exposure of proliferating cells to 2-methoxyestradiol would inhibit cell proliferation. Because, 2-hydroxyestradiol and 2-methoxyestradiol block cell migration, they may also influence the spermatozoa and adversely influence their motility as well as the fertilization process. Finally, 2-hydroxy- and 2-methoxyestradiol may negatively influence the growth of embryo. Because the early stages of embryo development occur within the oviduct the local production of 2-hydroxyestradiol and 2-methoxyestradiol may be of great importance. Indeed, recent studies conducted by Lattanza et al [14] and our laboratory have shown that 2-methoxyestradiol can block the development of early embryos and induce apoptosis (Figure 5).

The above findings provide evidence that 2-methoxyestradiol, an endogenous metabolite of estradiol can negatively influence the reproductive process at multiple levels. Although, circulating metabolites are active and can possibly influence oviduct function, however, it is the local conversion of estradiol to hydroxy- and methoxyestradiols that may be an important prerequisite for these deleterious actions to occur. Because, sequential actions of CYP450 and COMT are responsible for converting estradiol to hydroxy- and methoxyestradiols, respectively, we conducted preliminary studies to evaluate whether oviduct cells express these enzymes. Our data provides evidence that oviduct cells are well endowed with the enzymes (CYP450 and COMT) responsible for the sequential conversion of estradiol to hydroxyestradiol and methoxyestradiol. It should be pointed out that low/physiological levels of 2-methoxyestradiol is not biologically active and is rapidly eliminated. Hence, pathological conditions resulting in increased metabolism of estradiol to 2-methoxyestradiol would induce deleterious effects on the reproductive system.

Potential Impact of Estradiol Metabolism on Embryo Implantation

Similar to the oviduct, the enzymes responsible for the sequential conversion of estradiol to 2-methoxyestradiol are expressed in the uterus. Since the implantation of the embryo within the uterus is a dynamic process which involves cell proliferation at the site of embryo implantation and placenta development, factors that can inhibit cell growth may induce deleterious actions on this process. We have previously shown that 2-methoxyestradiol is a potent inhibitor of cell proliferation [12, 13], hence, increased production of 2-methoxyestradiol within the uterine may inhibit embryo implantation as well as placenta development.

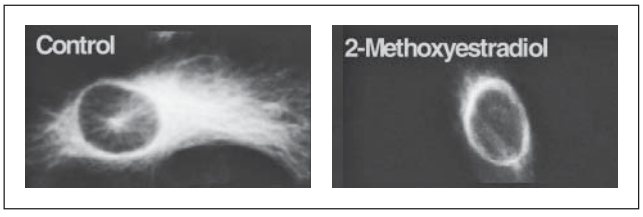

Figure 5 depicts the inhibitory effects of 2-methoxyestradiol on tubulin polymerization in cultured cells (from Dubey et al, personal communication).

Moreover, since 2-methoxyestradiol is known to induce COX-2 expression [13], increased generation of 2-methoxyestradiol may result in proinflammatory actions within the uterus and may negatively influence embryo implantation which could potentially result in abortion. Taken together the above facts suggest that abnormal metabolism of estradiol to methoxyestradiol may negatively influence embryo implantation and could be associated with abortions. In this context it is interesting to note that progesterone which facilitates the implantation process and rises during the implantation period, is a competitive inhibitor for the metabolism of estradiol to hydroxyestradiol, a precursor of 2-methoxyestradiol. This suggests that progesterone may facilitate embryo implantation by limiting the local conversion of estradiol to 2-methoxyestradiol. This also suggests that inhibitors of estradiol metabolism may be of important therapeutic use to prevent against abortions following embryo transfers.

Exogenous Factors Associated With Infertility and Estrogen Metabolism

The potential pathological effects hypothesized above may be of particular importance in infertility associated with exposure to environmental chemicals/estrogens. It is well established that exposure to dioxin and polychlorinated biphenyls (PCBs) causes reproductive disorders including infertility. Because dioxin and some of the PCBs have little or no affinity for ERs their endocrine disruptive effects are largely ER-independent. It has been hypothesized that the disruptive effects of these agents may be due to their influence on estradiol metabolism. Indeed, dioxin, coplanar PCBs are ligands for aryl hydrocarbon receptor (AhR; also called dioxin receptor), which is a ligand-activated helix-loop-helix protein that heterodimerizes with a nuclear translocatory protein (ARNT) and moves from the cytoplasm to the nucleus. The heteromeric complex acts as a signal transducer and transcription factor for target genes, including CYP450 (1A1, 1A2, 1B1), detoxifying phase II enzymes, and growth regulatory genes involved in cell proliferation, differentiation and inflammation [3]. Because exposure to environmental chemicals like dioxin and coplanar PCBs would induce CYP450 activity, this would result in increased formation of 2-hydroxyestradiol and 2-methoxyestradiol. Also, due to the close proximity of the oviduct to the ovary, it would be exposed to high levels of estradiol and hence form large amounts of 2-hydroxyestradiol and 2-methoxyestradiol. The increased formation of 2-methoxyestradiol would in-turn induce deleterious effects within the oviduct and inhibit sperm motility as well as block embryo development. In contrast to xenoestrogens, phytoestrogens do not induce deleterious effects on the reproductive system. It is feasible that in contrast to xenoestrogens, the phytoestrogens do not activate CYP450 mediated estradiol metabolism, thereby limiting 2-methoxyestradiol formation.

Another important factor associated with infertility is smoking. It has been shown that hydrocarbons generated from cigarette smoking are potent inducers of CYP450 enzymes responsible for the metabolism of estradiol to the 2-methoxyestradiol precursor hydroxyestradiol. Hence it is feasible that the increased metabolism of estradiol within the ovary, oviduct and uterus is in part responsible for the infertility observed in smoking women.

The fact that estradiol is largely metabolized to 2-hydroxyestradiol by CYP1A1 and the constitutive expression of this

enzyme is low suggests that under normal conditions, the local production of these inhibitory metabolites is very low and would not influence cell growth. However, based on the fact that CYP1A1 is activated by environmental chemicals such as dioxin and coplanar PCBs, known to induce reproductive disorders, we hypothesize that increased production of 2-hydroxyestradiol and 2-methoxyestradiol within the female reproductive system contributes to the reproductive disorders (infertility, abortion etc) associated with exposure to several environmental chemicals/estrogens.

Finally, exposure to chemicals such as dioxin, which stimulate CYP450 activity, is associated with endometriosis. Because, in contrast to 2-hydroxyestradiol and 2-methoxyestradiol, 4-hydroxy- and methoxyestradiol stimulate growth of cancer cells, it could be hypothesized that abnormal growth associated with endometriosis is regulated by the ratio between 2- and 4-methoxyestradiol formation. Moreover, increased formation of 4-hydroxy- and methoxyestradiol and decreased formation of 2-hydroxy- and 2-methoxyestradiol, locally within the oviduct may contribute to he abnormal growth leading to endometriosis.

Conclusion and Future Perspective

The above findings provide convincing evidence that endogenous metabolites of estradiol are biologically active molecules that can interfere with key processes associated with reproduction. The fact that methoxyestradiols are potent inhibitors of cell growth and early embryo development suggests that increased production of 2-methoxyestradiol locally within the ovary, oviduct or uterus can induce deleterious effects on the reproductive process and may be associated with infertility. Establishing methods to accurately monitor 2-methoxyestradiol levels may be helpful in defining the success of embryo development and implantation in IVF. Moreover, agents that inhibit estradiol metabolism or agents that bind to 2-methoxyestradiol and render it inactive may be of therapeutic importance in treating infertility associated with increased metabolism of estradiol.

Acknowledgements

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