Abstract

Catechol estrogens (2- or 4-hydroxyestradiol and 2- or 4-hydroxyestrone) are chemically reactive estrogen metabolites that are O-methylated to less polar monomethyl ethers by catechol-O-methyltransferase, an enzyme present in many tissues such as the liver, kidney, brain, placenta, uterus, and mammary gland. In the present report, we review recent studies on the antitumorigenic and antiangiogenic effects of exogenously administered 2-methoxyestradiol in vitro and in vivo. We also discuss data that suggest that endogenous formation of 2-methoxyestradiol (and its 2-hydroxyestradiol precursor) may have a protective effect on estrogen-induced cancers in target organs. Although the molecular mechanism of action of 2-methoxyestradiol is not clear, we suggest that some unique effects of 2-methoxyestradiol may be mediated by a specific intracellular effector or receptor that is refractory to the parent hormone, estradiol. Additional research is needed to identify factors that regulate the metabolic formation and disposition of 2-methoxyestradiol in liver and in target cells and to evaluate the effects of modulating 2-methoxyestradiol formation on estrogen-induced carcinogenesis.

Introduction

Chronic administration of estrogens (such as estradiol and estrone) results in tumor formation in target organs in several animal models (1–7). Estrogens have also been increasingly implicated as an important etiological factor in the causation of certain types of human cancer (8–16). Chronic administration of estrogens to postmenopausal women is strongly associated with an increased risk of endometrial cancer (8–12). Although the relationship between estrogen and breast cancer is not as strong as between estrogen and endometrial cancer, there is mounting evidence associating elevated breast cancer risk with an increased total life-time exposure to estrogens (13–16). Epidemiological studies indicate an increased risk of breast cancer in women with: (a) high serum levels of estrogens (comparison of women in the United States with those in Japan and China); (b) prolonged exposure to estrogens (due to early menarche and late menopause or long-term use of estrogen supplements); and (c) obesity (a cause of increased formation of estrogen by enzymatic aromatization of androgens in adipose cells) (reviewed in Refs. 15 and 16). Although the mechanism of estrogen-induced carcinogenesis is still not clear, it is thought that the superpotent mitogenic action of estrogenic hormones (5, 14, 17–21), together with the potential genotoxicity of reactive estrogen metabolites (e.g., 4- and 16α-hydroxylated estrogens; see Refs. 6 and 22–32), may play important roles in the induction of estrogen-associated cancers in target organs of animals and humans.

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Estradiol or estrone can be hydroxylated at various positions by NADPH-dependent cytochrome P450 enzymes present in liver and extrahepatic target cells (reviewed in Refs. 33 and 34). The chemically reactive catechol estrogens (2- or 4-hydroxyestradiol and 2- or 4-hydroxyestrone) can be metabolically O-methylated to monomethyl ethers (structures shown in Fig. 1) by COMT, an enzyme present in large amounts in many organs and cells such as liver, kidney, brain, placenta, uterus, mammary gland, and RBCs (35–42). Because of the ubiquitous distribution of COMT activity in mammalian tissues (35–42) and the very rapid metabolic O-methylation of catechol estrogens as demonstrated both in vitro and in vivo (42–46), large amounts of monomethylated estrogen metabolites are produced. A previous study reported that blood concentrations of unconjugated and conjugated 2-methoxyestrone are approximately 4000 and 6000 pg/ml, respectively, in pregnant women (47, 48), which are over 50-fold higher than the concentration of estradiol. Interestingly, 2-methoxyestradiol and 2-methoxyestrone have higher binding affinities for the sex hormone-binding globulin in blood than does estradiol (48), which may be an important factor (in addition to rapid metabolic formation of methoxyestrogens) that contributes to their high circulating levels.

Most studies showed that methylated catechol estrogens have little or no binding affinities for the classical estrogen receptor (<0.1% compared with estradiol), and they lack estrogenic activity in the uterus (43, 49, 50). An important question is why animals and humans make large amount of hormonally inactive yet highly lipophilic estrogen metabolites that probably have much longer half-lives than estradiol? Studies on the chemical reactivity and potential genotoxicity of catechol estrogens (23, 25–27, 29–32) have led to the suggestion that metabolic O-methylation may be a rapid inactivation/detoxification pathway for these estrogen-derived catechols, as is known for catecholamines. However, there are several studies indicating that 2-methoxyestradiol may not be just an inactive metabolite of estradiol but may have unique biological activities that are not shared with estradiol, 2-hydroxyestradiol, or 4-methoxyestradiol (51–57).

In this report, we review data that point to the hypothesis that endogenously formed 2-methoxyestradiol may have a unique protective role against estrogen-induced carcinogenesis in estrogen target organs. We also propose that some unique actions of 2-methoxyestradiol may be mediated by a specific but unidentified intracellular receptor or effector that is refractory to the parent hormone, estradiol.

Inhibitory Effect of 2-Methoxyestradiol on the Growth of Tumor Cells in Vitro and in Vivo

2-Methoxyestradiol inhibits the proliferation of many human cancer cell lines in vitro (54, 55, 57–61). Human breast cancer cell lines were particularly sensitive to the cytotoxic effect of 2-methoxyestradiol and several synthetic analogues irrespective of the estrogen receptor status of the cell lines studied (58). An earlier study showed that the inhibitory effect of 2-methoxyestradiol (at a 10 μM concentr-
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Estradiol and its metabolites are known to play a role in breast cancer development. Among these metabolites, 2-methoxyestradiol is particularly interesting due to its inhibitory effect on angiogenesis and tumor growth.

**Mechanism of Action**

2-Methoxyestradiol has been shown to inhibit the proliferation of breast cancer cells such as MCF-7 and MDA-MB-231. This effect is mainly due to its ability to inhibit the activity of catechol-O-methyltransferase (COMT), an enzyme that catalyzes the O-methylation of catechol derivatives. By inhibiting COMT, 2-methoxyestradiol prevents the conversion of estradiol to its inactive metabolite, 2-hydroxyestradiol.

**Clinical Relevance**

The inhibitory effect of 2-methoxyestradiol on angiogenesis and tumor growth in vitro and in vivo has been demonstrated in various models. This includes inhibition of tumor growth in animal models, such as Meth-A sarcoma and B16 melanoma in C3H mice, and inhibition of the growth of human breast cancer cells, including MCF-7 and Hela cells.

**Comparison with Estradiol**

While estradiol is a potent estrogen, its metabolites, particularly 2-methoxyestradiol, show specific inhibitory effects. Unlike estradiol, which is known to have both pro- and anti-angiogenic effects, 2-methoxyestradiol is primarily an antiangiogenic agent.

**Future Directions**

Further studies are needed to elucidate the exact mechanisms by which 2-methoxyestradiol exerts its inhibitory effects. Understanding these mechanisms could lead to the development of new therapeutic strategies for breast cancer treatment.
and form reactive quinone/semiquinone intermediates (23, 25, 69), which is believed to contribute to diethylstilbestrol-induced carcinogenesis. In addition, it was observed that 7,12-dimethylbenz[a]anthracene-induced mammary tumors in rats (70) and azoxymethanol-induced colonic neoplasms in mice (71) were not increased (but significantly decreased) by chronic cotreatment with quercetin. The inhibitory effects of quercetin on 2-methoxyestradiol formation in vitro and in vivo, and its stimulatory effect on estradiol-induced carcinogenesis but not diethylstilbestrol-, 7,12-dimethylbenz[a]anthracene-, or azoxymethane-induced carcinogenesis (described above) are consistent with the concept that selective stimulation of estradiol-induced carcinogenesis by quercetin is caused by a reduced formation of the antituurnorigenic 2-methoxyestradiol.

In accord with the inhibitory effect of dietary catechols such as quercetin and fisetin on COMT-catalyzed O-methylation of catechol estrogens (64, 65), endogenous catechols may also exert an inhibitory effect on the O-methylation of catechol estrogens. Recent studies have shown that very high concentrations of endogenous catecholamines (substrates and inhibitors of catechol estrogen O-methylation) are present in male Syrian hamster kidney, CD-1 mouse uterus, and Fisher-344 rat pituitary (72), three target organs that develop estrogen-induced tumors (1, 2, 4). The concentrations of catecholamines in these target tissues are up to 50-fold higher than those in nontarget tissues of these animals or in tissues of other strains or species (72). Because catecholamines inhibit the enzymatic O-methylation of catechol estrogens in vitro at physiologically relevant concentrations (72), we believe that high tissue concentrations of catecholamines may inhibit the metabolic formation of 2-methoxyestradiol in addition to elevating the concentrations of reactive catechol estrogens in target organs.

Earlier studies in female C3H/He mice showed that increased levels of environmental or manipulative stress markedly increased the incidence of spontaneous mammary cancers (73). Interestingly, epidemiological studies in humans suggest a positive relationship between the degree of sustained emotional stress and the risk for developing breast cancer (74–76). Because studies in animals and humans both indicate that an increased level of stress is accompanied by an increased release of endogenous catecholamines, we suggest a unifying hypothesis that sustained stress increases the levels of catecholamines, which then inhibit the enzymatic O-methylation of catechol estrogens, resulting in decreased formation of estradiol and increased accumulation of reactive catechol intermediates in target tissues. This hypothesis is in accord with data indicating an association of sustained emotional or environmental stress with an increased breast cancer risk. Decreased immune system function with sustained stress has also been postulated to play a role in the increased breast cancer risk observed (77, 78).

Several early studies noted marked person-to-person variations in the COMT activity in RBCs (79–81). Additional studies showed that the distribution of COMT activity in an American population has a polymorphic bimodal pattern (82–84). Genetic analysis revealed that human COMT is encoded by a single gene (a wild-type and a variant allele), and approximately one-fourth of the Caucasians studied inherited a variant allele encoding a low activity form of the enzyme (82, 85–90). We anticipate that individuals who inherit the low activity form of the COMT gene will be at increased risk for estrogen-associated breast cancer due to decreased formation of the antituurnorigenic 2-methoxyestradiol and increased accumulation of reactive catechol estrogens (particularly 4-hydroxyestradiol, which is hormonally active and is carcinogenic). A recent study by Lavigne et al. (91) indicated that postmenopausal women with a variant allele coding for a low activity form of the COMT have an increased risk (odds ratio, 2.18) for developing breast cancer compared with women with a normal allele. This observation is consistent with the proposed antituurnorigenic role of 2-methoxyestradiol and the carcinogenic role of 4-hydroxyestradiol in human mammary carcinogenesis. It will be of interest in future studies to determine the COMT enzyme activity and levels of 2-methoxyestradiol and 4-hydroxyestradiol in the breast of the same subjects and to correlate these parameters with the breast cancer risk in women with a normal versus a variant allele of the COMT gene.

Increased Formation of 2-Hydroxyestradiol and 2-Methoxyestradiol Is Associated with a Decreased Risk of Estrogen-induced Cancers

The data discussed above suggest that decreased formation of 2-methoxyestradiol is associated with increased formation of estradiol-induced tumors. There are also data (discussed below) suggesting that increased formation of 2-hydroxyestradiol and 2-hydroxyestrone (products of estrogen 2-hydroxylation metabolism), which subsequently leads to elevated formation of 2-methoxyestradiol and 2-methoxyestrone by COMT, is associated with a decreased risk of estrogen-associated tumors in target organs.

The formation of spontaneous mammary tumors in female C3H/OuJ mice, spontaneous uterine tumors in Oncomice or in Donryu rats, and chemically induced mammary tumors in Sprague Dawley rats is dependent on the presence of endogenous estrogens (5, 92–94). Studies during the past several years have shown that chronic treatment of animals with indole-3-carbinol stimulates the 2-hydroxylation of estradiol (95–97), and this treatment is associated with decreases in spontaneous mammary tumorigenesis in C3H/OuJ mice (95, 96), spontaneous uterine tumorigenesis in Oncomice (98) or Donryu rats (99), and chemically induced mammary tumorigenesis in Sprague Dawley rats (100). Recent studies in our laboratory showed that chronic administration of 0.05% sodium phenobartil in the drinking water to female C3H/OuJ mice for 16 months very strongly inhibited the formation of spontaneous mammary tumors, and this inhibitory effect of phenobarbital was accompanied by a manyfold increase in liver microsomal 2-hydroxylation of estradiol with little or no increase in estradiol 4- or 16a-hydroxylation.5

Earlier studies in humans showed that cigarette smokers have enhanced 2-hydroxylation of estradiol in vivo (101–103) and somewhat lower serum and urinary levels of estradiol and estrone (104–106). This stimulatory effect of cigarette smoking on estrogen 2-hydroxylation was associated with a decreased risk of uterine endometrial cancer (in addition to an increased incidence of osteoporosis) in female cigarette smokers (107–109).

Human cytochrome P450 1A1 as well as other P450 isozymes (e.g., 1A2 and 3A4) possess strong catalytic activity for estrogen 2-hydroxylation (33, 34). A recent preliminary study suggested that individuals with an MspI polymorphism in the CYPIA1 gene had a low basal level of estrogen 2-hydroxylation, and treatment of these individuals with indole-3-carbinol failed to induce estradiol 2-hydroxylation (110). Research on a possibly increased risk of breast cancer in Caucasian women or in African-American women with polymorphisms in the CYPIA1 gene has resulted in inconsistent conclusions (111, 112).

It was recently reported that African-American women have a lower rate of estradiol 2-hydroxylation than American Caucasian women (113, 114). It is not known whether this difference in estrogen 2-hydroxylation contributes to the higher breast cancer mortality rate observed in African-American women than in American Caucasian women (115). The relative roles of genetic and environmental factors.

5 Unpublished data.
in explaining these differences in estrogen metabolism in African-American and Caucasian-American women have not been explored.

Consistent with observations associating high levels of estrogen 2-hydroxylation with a reduced cancer risk in animals and humans, earlier studies with a commonly used hamster kidney tumor model showed that 2-hydroxyestradiol and 2-hydroxyestrone are devoid of carcinogenic activity at dose levels where estradiol or 4-hydroxyestradiol gives rise to a 100% tumor incidence (63, 66). The lack of carcinogenic activity of 2-hydroxylated estrogen metabolites is not completely understood. Although earlier studies suggested that 2- and 4-hydroxyestradiol have similar chemical reactivity and genotoxicity when tested in vitro (23, 25, 26), 2-hydroxyestradiol appears to have a faster rate of metabolism by COMT-catalyzed O-methylation (44, 72), a more rapid metabolic clearance in vivo (116, 117), and a weaker hormonal activity in estrogen target organs (118–126) than 4-hydroxyestradiol. Moreover, the COMT-catalyzed O-methylation of 4-hydroxyestradiol is inhibited by 2-hydroxyestradiol, whereas the O-methylation of 2-hydroxyestradiol is not inhibited by 4-hydroxyestradiol (44). It is likely that 4-hydroxyestradiol may accumulate in target cells because of inhibition of its O-methylation. Finally, the presence of increased amounts of 2-hydroxylated estrogens will subsequently lead to increased formation of 2-methoxyestradiol, and the formation of this cytostatic and antiangiogenic metabolite may be an important reason for the lack of carcinogenicity of 2-hydroxylated estrogens in animals and for the reduced cancer risk in animals and humans associated with high levels of estrogen 2-hydroxylation. This concept is illustrated in Fig. 2.

High levels of estradiol are present in estrogen target tissues, and cancerous breast tissue contains particularly high levels of estradiol and estrone (127, 128). Many breast cancers also contain high levels of enzymes that catalyze the formation of catechol estrogens from estradiol or estrone (129–133) as well as the subsequent O-methylation of the catechol metabolites (39, 40). It is expected that large amounts of 2-methoxyestradiol will be produced in these target tissues. Because cultured human breast cancer cells (regardless of their estrogen receptor status) are particularly sensitive to growth inhibition by 2-methoxyestradiol (58), increased formation of 2-methoxyestradiol by the breast is likely to be an important endogenous factor that suppresses the development of estrogen-associated mammary cancers. There is a need to enhance our understanding of person-to-person differences in the formation of 2-methoxyestradiol and of factors that influence the formation of 2-methoxyestradiol in normal human breast and in breast cancers. Selectively enhancing the endogenous formation of 2-methoxyestradiol in target cells may represent a new approach for the prevention and treatment of mammary cancers.

Potential Physiological Functions of 2-Methoxyestrone

Although very high concentrations of 2-methoxyestrone are present in the human circulation, this estrone metabolite only has about 1% of the growth-inhibitory potency of 2-methoxyestradiol in cultured blood-vessel endothelial cells or fibroblasts (57). Because 17ß-HSD is a group of intracellular isozymes catalyzing interconversions between estradiol and estrone (134, 135), it is expected that this enzyme will also catalyze interconversions between 2-methoxyestradiol and 2-methoxyestrone (Fig. 3). Accordingly, it is likely that 2-methoxyestrone is an immediate metabolic precursor of 2-methoxyestradiol.

17ß-HSD activity has a cell-specific localization (such as in the secretory glandular epithelium and proliferative endometrium of the uterus; Ref. 136), and this enzyme activity is regulated by certain hormones during different stages of the normal menstrual cycle (137).
The uterine 17β-HSD (type II) predominantly catalyzes the 17β-oxidative conversion of estradiol to estrone (anticipated conversion of 2-methoxyestradiol to 2-methoxyestrone; Refs. 134 and 138), whereas the 17β-HSD (type I) present in breast tumors predominantly catalyzes the 17β-reductive conversion of estrone to estradiol (anticipated conversion of 2-methoxyestrone to 2-methoxyestradiol; Refs. 139 and 140). It is noteworthy that the 17β-reductive activity of 17β-HSD is higher in mammary tumors than in normal breast that does not contain malignant cells (141–143). This increased 17β-HSD (reductive activity) in mammary cancer cells not only provides these cells with a favorable estrogenic environment for growth due to increased conversion of estrone to estradiol but may also increase the formation of the antitumorogenic 2-methoxyestradiol from 2-methoxyestrone. The amount of 2-methoxyestradiol formed in situ from 2-methoxyestrone would depend on the availability of 2-methoxyestrone and the level of 17β-HSD (reductive activity) in target cells.

Although long-term exposure to exogenously administered estradiol or estrone has been shown in several animal models to induce tumors in their target organs (1–7), surprisingly the very large amount of endogenous estrogens present during human full-term pregnancy is associated with a decrease in the risk of human uterine and mammary cancers (144–147). It is possible that endogenous substances that are produced during pregnancy possess protective activity against estrogen-dependent tumor formation. Previous studies suggest that progesterone may be one of the inhibitory substances in animals and possibly also in humans (148–151). Because human placenta produces large amounts of estradiol and estrone, and this organ also contains high estrogen 2-hydroxylase and COMT activity, it is expected that large amounts of 2-methoxyestradiols will be produced by the placenta. Consistent with these observations, a previous study (47) reported that the blood concentration of unconjugated plus conjugated 2-methoxyestrone was ~10,000 pg/ml in pregnant women. Although the level of 2-methoxyestradiol was not reported, it is likely that substantial amounts are formed from 2-methoxyestrone in target cells by the action of the reductive 17β-HSD. The potent growth-inhibitory and antiangiogenic activity of 2-methoxyestradiol may protect against estrogen-induced carcinogenesis in target organs during human pregnancy. It will be of considerable interest to test this hypothesis.

**Importance of 2-Methoxyestradiol for Understanding the Physiological Significance of the Estrogen 2-16α-Hydroxylation Ratio**

Bradlow, Fishman, and their colleagues (98, 152–154) proposed that the extent of estrogen 16α-hydroxylation or the ratio of estrogen 2- to 16α-hydroxylation is an important biomarker for the risk of breast cancer in animals and humans. The core of their hypothesis is that the products of the 16α-hydroxylation pathway (hormonally active 16α-hydroxyestrone and 16α-hydroxyestradiol) are carcinogenic, whereas the products of the 2-hydroxylation pathway (hormonally weak 2-hydroxyestrone and 2-hydroxyestradiol) are not carcinogenic. According to this hypothesis, the beneficial effect of increased estrogen 2-hydroxylation is because it decreases the pool of endogenous parent estrogen and thereby reduces the formation of 16α-hydroxyestrone and 16α-hydroxyestradiol. 16α-Hydroxyestrone, which is not only hormonally active but also chemically reactive (28, 152, 153, 155), may play a role in estrogen-induced mammary cancer. The concept of 16α-hydroxylated estrogens as an important etiological factor in hormonal carcinogenesis, however, is weakened by the very low carcinogenic activity of 16α-hydroxyestrone and 16α-hydroxyestradiol (estriol) relative to estradiol or 4-hydroxyestradiol (63, 156). Moreover, some studies suggest that estrogen 16α-hydroxylation is not markedly different among women with different risks for mammary cancer (114, 155, 157–159). To accommodate the 16α-hydroxylation hypothesis with these experimental observations, emphasis has been shifted to the ratios of estrogen 2- to 16α-hydroxylation as a biomarker for breast cancer risk (98, 152, 153, 155). This shift in emphasis tends to decrease the importance of the absolute extent of estrogen 16α-hydroxylation.

The recent findings of potent antitumorogenic activity for 2-methoxyestradiol suggest a new explanation for the inverse relationship observed previously between the ratios of estrogen 2- to 16α-hydroxylation and breast cancer risk. We believe a major reason that enhanced 2-hydroxylation of estradiol is associated with decreased mammary carcinogenesis is because enhanced 2-hydroxylation increases the formation of 2-methoxyestradiol, and this compound is a potent antitumorogenic metabolite of estradiol (illustrated in Fig. 2).

**Possible Mechanisms of Action of 2-Methoxyestradiol**

The mechanism for the growth-inhibitory and antiangiogenic effects of 2-methoxyestradiol is not known. Observations indicating the ability of 2-methoxyestradiol to induce abnormal spindle formation in cultured cells (54), to interact with tubulin at the colchicine binding site (56), and to inhibit tubulin polymerization (56, 61) have led to the suggestion that the antitubulin activity of 2-methoxyestradiol may contribute in an important way to its cytotoxic effect. It should be noted, however, that the concentration of 2-methoxyestradiol or some of its synthetic analogues required for inhibition of tubulin polymerization or colchicine binding to tubulin in vitro is considerably higher (low μM range) than that required for inhibiting the growth of many different types of cancer cells in culture (10–100 nM; Refs. 56, 58, 59, and 61). It is noteworthy that a recent study showed that 2-methoxyestradiol at concentrations sufficient for causing complete metaphase arrest in cultured cells does not inhibit the formation of mitotic spindles (160).
In cultured H460 or A549 human lung cancer cells (both of which contain the wild-type p53 gene), treatment with 5 μM 2-methoxyestradiol increases the wild-type p53 protein levels and induces apoptosis (161). However, 2-methoxyestradiol at the same concentration does not induce apoptosis in human lung cancer cells, either without the wild-type p53 gene or with a mutated p53 gene (161). These results suggest that 2-methoxyestradiol at relatively high concentrations may activate the wild-type p53-mediated apoptosis.

Treatment of MCF-7 human breast cancer cells with a low concentration (10 nm) of 2-methoxyestradiol caused marked changes (an increase or decrease) in the intracellular cyclic AMP concentration depending on the phase of the cell cycle, whereas 10 nm estradiol or 2-hydroxyestradiol had little or no effect (55). This change of cyclic AMP levels during 2-methoxyestradiol treatment was accompanied by marked changes in the phosphorylation patterns of various cellular proteins (55). A recent report indicated that treatment of MCF-7 cells with 10 nm 2-methoxyestradiol selectively altered the expression of several kinases involved in cell cycle control (162, 163). These biochemical responses to very low concentrations of 2-methoxyestradiol may be physiologically important, but more studies are needed.

The high specificity and high potency of 2-methoxyestradiol as an inhibitor of angiogenesis and tumor cell growth are of great interest and have led us to suggest that some of the unique effects of 2-methoxyestradiol may be mediated by a specific receptor or intracellular effector (such as a transcriptional factor or an enzyme) that is refractory to estradiol. Candidate receptors for 2-methoxyestradiol include: (a) the so-called nuclear type II estrogen binding sites, which have a low apparent binding affinity for estradiol (164–166) and functionally may mediate a growth-inhibitory effect in estrogen-sensitive cells (167); (b) one or more of the multiple variants of the classical estrogen receptor, which are present in some estrogen target tissues or cells (168, 169); (c) a novel estrogen receptor that was recently found to be expressed in rat prostate and ovary (170); and (d) certain member(s) of the nuclear orphan receptor family (171, 172).

Whatever the structural identity of the putative intracellular effector or receptor for 2-methoxyestradiol, we believe that the interaction of 2-methoxyestradiol with its specific effector or receptor in target cells is an initial step leading to the expression of its growth-inhibitory effects in sensitive cells. An understanding of the mechanism of action of 2-methoxyestradiol should greatly enhance our understanding of its unique physiological and antitumorigenic functions.

Concluding Remarks

We have described recent studies on the antitumorigenic and antiangiogenic effects of exogenously administered 2-methoxyestradiol in vitro and in vivo. We have also discussed data which suggest that endogenously formed 2-methoxyestradiol may have a protective effect against estrogen-induced cancers in target organs. Although the molecular mechanisms of action of 2-methoxyestradiol are not known, a hypothesis is proposed that some unique effects of 2-methoxyestradiol may be mediated by its interaction with a specific cellular receptor or effector that is refractory to estradiol.

Although the data reviewed here collectively suggest that 2-methoxyestradiol may be an important endogenously formed estrogen metabolite that protects cells from estrogen-induced carcinogenesis, it should be pointed out that there are still many important unresolved questions about this estradiol metabolite that require more research. It will be important to find out: (a) the concentrations of endogenously formed 2-methoxyestradiol in the circulation and in estrogen target tissues or cells under different physiological or pathophysiological conditions; (b) the effective circulating or intracellular concentrations of 2-methoxyestradiol that are needed to exert an antitumorigenic effect; (c) target cells that are particularly sensitive to growth inhibition by 2-methoxyestradiol; (d) endogenous and exogenous factors that regulate the metabolic formation and disposition of 2-methoxyestradiol in liver and in estrogen target cells; and (e) the molecular mechanism(s) underlying the growth-inhibitory and antiangiogenic actions of 2-methoxyestradiol. Studies in these and related areas will not only greatly enhance our understanding of the physiological roles of 2-methoxyestradiol, a nonpolar estradiol metabolite formed in large amounts in liver and in estrogen target cells, but these studies may also offer novel mechanistic insights and strategies for the prevention and treatment of estrogen-associated cancers.

References

2-METHOXYESTRADIOL AS AN INHIBITOR OF BREAST CANCER


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2-METHOXYESTRADIOL AS AN INHIBITOR OF BREAST CANCER


Is 2-Methoxyestradiol an Endogenous Estrogen Metabolite That Inhibits Mammary Carcinogenesis?

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