Methoxyestrogens Exert Feedback Inhibition on Cytochrome P450 1A1 and 1B1

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ABSTRACT

Cytochrome P450 1A1 (CYP1A1) and 1B1 (CYP1B1) catalyze the oxidative metabolism of 17β-estradiol (E2) to catechol estrogens (2-OHE2 and 4-OHE2) and estrogen quinones, which may lead to DNA damage. Catechol-O-methyltransferase catalyzes the methylation of catechol estrogens to methoxyestrogens (2-MeOE2, 2-OH-3-MeOE2, and 4-MeOE2), which simultaneously lowers the potential for DNA damage and increases the concentration of 2-MeOE2, an antiproliferative metabolite. In our study, we showed that CYP1A1 and CYP1B1 recognized as substrates both the parent hormone E2 and the methoxyestrogens. Using purified recombinant enzymes, we demonstrated that CYP1A1 and CYP1B1 O-demethylated the methoxyestrogens to catechol estrogens according to Michaelis-Menten kinetics. Both CYP1A1 and CYP1B1 demethylated 2-MeOE2 and 2-OH-3-MeOE2 to 2-OHE2, whereas CYP1B1 additionally demethylated 4-MeOE2 to 4-OHE2. Because the P450-mediated oxidation of E2 and the O-demethylation of methoxyestrogens both yielded identical catechol estrogens as products, we used deuterated E2 (E2-d4), unlabeled methoxyestrogens, and gas chromatography/mass spectrometry to examine both reactions simultaneously. Kinetic analysis revealed that methoxyestrogens acted as noncompetitive inhibitors of E2 oxidation with Ki ranging from 27 to 153 μM. For both enzymes, the order of inhibition by methoxyestrogens was 2-OH-3-MeOE2 ≥ 2-MeOE2 > 4-MeOE2. Thus, methoxyestrogens exert feedback inhibition on CYP1A1- and CYP1B1-mediated oxidative estrogen metabolism, thereby reducing the potential for estrogen-induced DNA damage.

INTRODUCTION

Estrogens have been implicated in the development of breast cancer by simultaneously stimulating cell proliferation and gene expression via the estrogen receptor and by causing DNA damage via their genotoxic catechol estrogen metabolites (1–3). The two major estrogens, 17β-estradiol (E2) and estrone (E1), are oxidized to the 2-OH and 4-OH catechol estrogens by the enzymes CYP1A1 and CYP1B1 (4–6). These enzymes further oxidize the catechol estrogens to unstable semiquinones and quinones. The estrogen quinones form Michael addition products with deoxynucleosides (7–9). Furthermore, catechol estrogens and their estrogen quinones/semiquinones undergo redox cycling, which results in the production of reactive oxygen species capable of causing oxidative DNA damage (10–12). Thus, P450-mediated estrogen metabolism leads to the formation of both oxidative and estrogen DNA adducts, all of which have been shown to have mutagenic potential (13, 14).

Although the oxidation of catechol estrogens to semiquinones and quinones promotes DNA oxidation and adduct formation, there are two enzyme systems, i.e., catechol-O-methyltransferase and glutathione S-transferases, that prevent this kind of DNA damage by inactivating catechol estrogens and quinones, respectively. COMT, a Phase II enzyme, inactivates 2-OH and 4-OH catechol estrogens by O-methylation, producing the methoxyestrogens 2-MeOE2, 2-OH-3-MeOE2, 4-MeOE2, 2-MeOE1, 2-OH-3-MeOE1, and 4-MeOE1 (15, 16). Thus, COMT reduces the level of catechol estrogens and thereby prevents quinone formation and redox cycling.

Interestingly, 2-MeOE2 is not just a byproduct of estrogen metabolism but is also endowed with anti proliferative activity (17). 2-MeOE2 has been shown to inhibit the proliferation of both hormone-dependent and hormone-independent breast cancer cells (18, 19). Oral administration of 2-MeOE2 (75 mg/kg) for 1 month suppressed the growth of a human breast cancer cell line (estrogen receptor negative) in immunodeficient mice by 60% without toxicity (20). Several synthetic analogues (e.g., 2-methoxyethyl estradiol and 2-ethoxyestradiol) exhibit similar antitumor activity as the endogenous 2-MeOE2 (21, 22). The antiproliferative effect is not limited to breast cancer cells but extends to leukemia, pancreas, and lung cancer cells (23, 24). Human xenograft studies in animal models demonstrated p.o. bioavailability and a high therapeutic index of methoxyestrogens without signs of systemic toxicity. These features and their broad antitumor activity against a variety of tumor cells make methoxyestrogens attractive as potential therapeutic agents (25, 26).

However, before progressing to clinical trials, it is important to understand the molecular mechanisms underlying the action of methoxyestrogens.

The inhibitory effect of methoxyestrogens appears to result from several mechanisms that interrupt normal cell function, namely disruption of microtubule function, induction of apoptosis, and inhibition of angiogenesis (27–30). At the present time, only the inhibition of microtubule formation can be explained in molecular terms. Methoxyestrogens bind to β-tubulin and inhibit tubulin polymerization, thereby destabilizing microtubules and arresting mitotic cells (31). In this study, we report another molecular effect of methoxyestrogens of potential importance for extended clinical trials. We show that methoxyestrogens exert feedback inhibition on CYP1A1 and CYP1B1, thereby reducing the oxidative metabolism of E2 to 2-OHE2 and 4-OHE2. Because CYP1A1 and CYP1B1 also play key roles as Phase I enzymes in metabolizing xenobiotic chemicals to procarcinogens in extrahepatic tissues (32), their inhibition by endogenous methoxyestrogens may represent a physiological defense mechanism against carcinogenesis.

MATERIALS AND METHODS

Chemicals. 17 β-estradiol (E2), catechol estrogens (2-OHE2 and 4-OHE2), and methoxyestrogens (2-MeOE2, 2-OH-3-MeOE2, and 4-MeOE2) were obtained from Steraloids (Newport, RI). Deuterated E2 [E2–2,4,16 and 16-d4 (E2-d4)] was obtained from CDN Isotopes (Pointe-Claire, Quebec, Canada).

Recombinant Enzymes. Purified recombinant CYP1B1 and NADPH-P450 reductase were prepared as described previously (6, 33). CYP1A1 was prepared in a manner similar to CYP1B1 (data not shown).

O-Demethylation Assays of Methoxyestrogens. Recombinant CYP1A1 or CYP1B1 (200 pmol) was reconstituted with recombinant NADPH-P450 reductase (400 pmol) and 60 μg of L-α-dilauroyl-sn-glycero-3-phosphocholine in 0.4 ml of 100 mM potassium phosphate buffer (pH 7.4) containing 5 mM glucose 6-phosphate and 1 mM ascorbate. As substrate, each methoxyestrone was added individually (2, 5, 10, 20, 30, and 40 μM), and reactions were...
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RESULTS

CYP1A1 catalyzed the O-demethylation of methoxyestrogens 2-MeOE2 and 2-OH-3-MeOE2 to 2-OHE2 according to Michaelis-Menten kinetics (Fig. 1). The demethylation of 4-MeOE2 was negligible. In contrast, CYP1B1 demethylated 2-MeOE2 and 2-OH-3-MeOE2 to 2-OHE2, as well as 4-MeOE2 to 4-OHE2 (Fig. 2). The reaction kinetics were determined for each enzyme in triplicate at six different concentrations of the respective methoxyestrogen, and the resulting $K_m$ and $k_{cat}$ values are presented in Table 1. The demethylation product of both 2-MeOE2 and 2-OH-3-MeOE2 is 2-OHE2, which is also a product of the CYP1A1- and CYP1B1-catalyzed oxidation of E2. Similarly, demethylation of 4-MeOE2 yields 4-OHE2, which is also produced by CYP1B1-mediated oxidation of E2.

When we realized that CYP1A1 and CYP1B1 recognize both E2 and the methoxyestrogens as substrates, we replaced E2 with E2-d4. The location of the labels permitted the use of GC/MS to simultaneously track the formation of 2-OH and 4-OH catechol estrogens from E2-d4 (i.e., 2-OHE2-d4 and 4-OHE2-d4) and from the nonisotopic methoxyestrogens (i.e., 2-OHE2 and 4-OHE2). At the same time, we replaced E2-d4 as internal standard with E2, which was added after each reaction for accurate quantitation of all metabolites. Fig. 3 shows the comprehensive kinetic analysis of the reaction of CYP1A1 with both 2-MeOE2 and E2-d4. The demethylation of 2-MeOE2 by CYP1A1 exhibited Michaelis-Menten saturation kinetics yielding 2-OHE2 as product. The addition of increasing amounts of E2-d4 led to decreased production of 2-OHE2 (Fig. 3A). At the same time, increasing concentrations of 2-MeOE2 progressively inhibited the formation of 2-OHE2-d4 (Fig. 3B). Fig. 3, C and D shows the complementary analysis using E2-d4 as substrate and 2-MeOE2 as inhibitor. Again, the oxidation of E2-d4 to 2-OHE2-d4 followed Michaelis-Menten kinetics. In the presence of various concentrations of 2-MeOE2, the reaction rates for the oxidation of E2-d4 were inhibited in a concentration-dependent manner, whereas the corresponding $K_m$ values for the E2-d4 substrate were not altered (Fig. 3D).
2-OHE2-d4 (noncompetitive inhibition by 2-MeOE2 of the E2-d4 oxidation to H9262 which ranged from 27 to 153 MeOE2 inhibition of E2-d4 oxidation by methoxy estrogens was 2-OH-3-E2-d4 to 4-OHE2-d4 (Fig. 4, CYP1B1 was even more complex, because the enzyme also oxidized from the other substrate. The analysis of all of the experiments and lists the respective K_i values, K_m (m M) and 4-OHE2-d4 (K_i = 36 ± 3 μM). The same type of analysis was carried out for both enzymes with 2-OH-3-MeOE2 and E2-d4, and for CYP1B1 with 4-MeOE2 and E2-d4, respectively (data not shown). Table 2 summarizes the kinetic analysis of all of the experiments and lists the respective K_i values, which ranged from 27 to 153 μM. For both enzymes, the order of inhibition of E2-d4 oxidation by methoxy estrogens was 2-OH-3-MeOE2 ≥ 2-MeOE2 > 4-MeOE2.

**DISCUSSION**

CYP1A1 and CYP1B1 play key roles in oxidative estrogen metabolism by catalyzing the sequential oxidation of the parent hormones E2 and E1 to their respective catechols and quinones, which may lead to DNA damage. COMT catalyzes the transfer of a methyl group from the donor S-adenosyl-L-methionine to one hydroxyl moiety of a catechol substrate, and the resulting methoxyestrogens constitute physiological end products of the O-methylation reaction (16, 35).

Dixon plot analysis revealed a noncompetitive mode of inhibition (K_i = 88 ± 16 μM). These data indicate that E2-d4 (or E2) and 2-MeOE2 are alternate substrates for CYP1A1, each inhibiting the enzyme in such a way as to decrease the amount of product formed from the other substrate. The analysis of the same reaction with CYP1B1 was even more complex, because the enzyme also oxidized E2-d4 to 4-OHE2-d4 (Fig. 4, A–F). Dixon plot analysis again revealed noncompetitive inhibition by 2-MeOE2 of the E2-d4 oxidation to 2-OHE2-d4 (K_i = 60 ± 5 μM) and 4-OHE2-d4 (K_i = 36 ± 3 μM). The same type of analysis was carried out for both enzymes with 2-Oh-3-MeOE2 and E2-d4 and for CYP1B1 with 4-MeOE2 and E2-d4, respectively (data not shown). Table 2 summarizes the kinetic analysis of all of the experiments and lists the respective K_i values, which ranged from 27 to 153 μM. For both enzymes, the order of inhibition of E2-d4 oxidation by methoxy estrogens was 2-OH-3-MeOE2 ≥ 2-MeOE2 > 4-MeOE2.

**Table 1. Kinetic parameters for CYP1A1- and CYP1B1-mediated methoxyestrogen metabolism**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>K_m (μM)</th>
<th>k_cat (min⁻¹)</th>
<th>K_cat/K_m (m⁻¹ min⁻¹)</th>
<th>K_m (μM)</th>
<th>k_cat (min⁻¹)</th>
<th>K_cat/K_m (m⁻¹ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-MeOE2</td>
<td>2-OHE2</td>
<td>22 ± 3</td>
<td>0.7 ± 0.1</td>
<td>32 ± 6</td>
<td>28 ± 3</td>
<td>0.4 ± 0.1</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>2-OH-3-MeOE2</td>
<td>2-OHE2</td>
<td>67 ± 16</td>
<td>1.0 ± 0.2</td>
<td>15 ± 5</td>
<td>24 ± 3</td>
<td>2.0 ± 0.1</td>
<td>83 ± 11</td>
</tr>
<tr>
<td>4-MeOE2</td>
<td>4-OHE2</td>
<td></td>
<td></td>
<td></td>
<td>30 ± 3</td>
<td>1.1 ± 0.1</td>
<td>37 ± 6</td>
</tr>
</tbody>
</table>

* Data represent mean ± SE of triplicate assays.
* Reaction insufficient for calculation.

The COMT-mediated formation of methoxyestrogens reduces the concentration of catechol estrogens and thereby the potential for DNA damage. Although the methoxyestrogens are end products of the COMT reaction, we wondered whether CYP1A1 and CYP1B1 would be capable of O-demethylation of methoxyestrogens, in particular, those produced by COMT, i.e., 2-MeOE2, 2-OH-3-MeOE2, and 4-MeOE2 (16). Review of the literature shows that cytochrome P450 enzymes catalyze a variety of reactions, including O-dealkylation (32). Indeed, our results indicate that both CYP1A1 and CYP1B1 demethylate 2-MeOE2 and 2-OH-3-MeOE2 to 2-OHE2, and, in addition, CYP1B1 demethylates 4-MeOE2 to 4-OHE2.

Because CYP1A1 and CYP1B1 are capable of catalyzing both oxidation and O-demethylation reactions, they recognize as substrates both the parent hormone E2 and the methoxyestrogens 2-MeOE2, 2-OH-3-MeOE2, and 4-MeOE2. Kinetic analysis indicates that E2 and the methoxyestrogens are alternate substrates, each catalyzed by the same enzyme, albeit by a different type of reaction. Because they are converted to identical catechol estrogen products, each inhibits formation of 2-OHE2 and 4-OHE2 from the other substrate in a noncompetitive manner. To complicate matters further, because 2-OHE2 and 4-OHE2 are also substrates for CYP1A1 and CYP1B1, we suspect (but do not prove here) that the methoxyestrogens also inhibit oxidation of the catechol estrogens to estrogen semi-quinones and quinones. In an earlier publication, we showed that COMT catalyzes the methylation of catechol estrogens to methoxyestrogens.

![Fig. 3](image-url) Inhibition assay of CYP1A1 with alternate substrates 2-MeOE2 and E2-d4. A and B, demethylation of substrate 2-MeOE2 in the presence of increasing amounts of E2-d4, leading to the formation of 2-OHE2 (A) and 2-OHE2-d4 (B). C and D, oxidation of substrate E2-d4 in the presence of increasing amounts of 2-MeOE2, leading to the formation of 2-OHE2 (C) and 2-OHE2-d4 (D). The reaction conditions are described in "Materials and Methods." Data depict a single assay.
in the following order of product formation: 4-MeOE2 > 2-MeOE2 > 2-OH-3-MeOE2 (16). Interestingly, the results of the present study show the reverse order of inhibitory activity of the methoxyestrogens on E2 oxidation, i.e., 2-OH-3-MeOE2 ≥ 2-MeOE2 > 4-MeOE2.

We are not aware of any data on tissue concentrations of methoxyestrogens. Lymphocytes were shown to accumulate intracellular concentrations of 10^{-6} M under experimental conditions (24). COMT is a ubiquitous, constitutively expressed enzyme expected to produce methoxyestrogens in all tissues, including breast and liver. In a previous study, we showed that COMT is relatively efficient in producing methoxyestrogens with k_{cat}/K_{m} values ranging from 29 to 142 mm^{-1} min^{-1} (16). Moreover, COMT produces six methoxyestrogens (2-MeOE2, 2-OH-3-MeOE2, 4-MeOE2, 2-MeOE1, 2-OH-3-MeOE1, and 4-MeOE1), all of which will act on CYP1A1 and CYP1B1.

Investigations of the therapeutic potential of methoxyestrogens have shown that the antiproliferative effect of 2-MeOE2 is concentration dependent. At nano and micromolar concentrations, 2-MeOE2 caused disruption of microtubule function, induction of apoptosis, and inhibition of angiogenesis (24, 28–30). At millimolar concentrations, 2-MeOE2 caused chromosome breaks and aneuploidy (36). Clearly, the micromolar concentrations of methoxyestrogens shown to exert feedback inhibition in the present study indicate that CYP1A1 and CYP1B1 are valid molecular targets of methoxyestrogens in therapeutic trials.

There are other endogenous and exogenous compounds capable of inhibiting reactions catalyzed by members of the CYP1 family, e.g., arachidonic acid, retinoids, and cholecalciferol inhibited the CYP1A1-dependent O-deethylation of 7-ethoxycoumarin (37). Several natural and synthetic xenobiotics (e.g., resveratrol, hesperetin, homoeriodictyol, 7-hydroxyflavone, rhapontigenin, and TMS) have

Table 2  Inhibitory effect of methoxyestrogens on CYP1A1- and CYP1B1-mediated E2 metabolism

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>2-MeOE2 k_i (µM)</th>
<th>2-OH-3-MeOE2 k_i (µM)</th>
<th>4-MeOE2 k_i (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1 2-OH2</td>
<td>88 ± 16</td>
<td>69 ± 5</td>
<td>b</td>
</tr>
<tr>
<td>CYP1B1 2-OH2</td>
<td>60 ± 5</td>
<td>27 ± 6</td>
<td>153 ± 13</td>
</tr>
<tr>
<td>4-OH2</td>
<td>36 ± 3</td>
<td>24 ± 3</td>
<td>149 ± 15</td>
</tr>
</tbody>
</table>

a Data represent mean ± SE of three assays for each methoxyestrogen.
b Reaction insufficient for calculation.
also been shown to inhibit the enzymatic activity of CYP1 family members (38–40). Hydroxy and/or methoxy substitutions at the 3′ and 4′ positions in flavonoids conferred selectivity for CYP1 inhibition (39), e.g., the flavonone homoeriodictyol selectively inhibited CYP1B1 but not CYP1A1 and CYP1A2. Hesperetin was O-demethylated at the 4′ position by both CYP1A1 and CYP1B1 to the corresponding 4′-hydroxylated flavonoid, eriodictyol, which was then further metabolized by the same enzymes. Glycosides of these flavonoids are major constituents of citrus fruits. Hesperidin (hesperetin-7-rutinoside) is the major flavonoid in orange juice, whereas eriocitrin (eriodictyol-7-rutinoside) is the major flavonoid of lemon and lime juices (41). Considering the possible role of CYP1B1 in activating carcinogens and the apparent selectivity of hesperetin and homoeriodictyol as inhibitors of this enzyme, these dietary compounds may protect against the development of certain cancers. The synthetic TMS exhibited 50-fold selectivity for CYP1B1 over CYP1A1 and 500-fold selectivity for CYP1B1 over CYP1A2. In particular, TMS strongly inhibited 2- and 4-hydroxylation of E2 by CYP1B1 with a K_i of 3 nm (40). By decreasing the CYP1B1-mediated production of carcinogetic estrogen metabolites, agents such as TMS may be beneficial in breast cancer prevention. On the other hand, several anticancer drugs were also shown to inhibit CYP1B1 activity. Using the ethoxyresorufin O-deethylase assay, paclitaxel, doxorubicin, and tamoxifen yielded K_i values 31.6, 2.6, and 5 μM, respectively (42).

In contrast to all of the preceding inhibitors, methoxyestrogens appear to be unique because they exert feedback inhibition of CYP1A1 and CYP1B1. Other P450 enzymes known to oxidize estrogens to catechol estrogens, such as the liver-specific CYP1A2 and CYP3A4, may also be subject to feedback inhibition by methoxyestrogens. In fact, CYP1A2 has been shown to demethylate methoxyresorufin as efficiently as CYP1A1 (39). These results suggest that methoxyestrogens cause feedback inhibition of both extrahepatic and hepatic P450 enzymes, an important consideration for clinical trials of methoxyestrogens as potential p.o. therapeutic agents. The feedback inhibition described in this study may contribute to the understanding of some unexplained results recently reported by Lavigne et al. (43). These authors examined the effect of estrogen metabolism on oxidative DNA damage (8-oxo-dG) in 2,3,7,8-tetrachlorodibenzo-p-dioxin-treated MCF-7 cells exposed to E2 and Ro41–0960, a specific inhibitor of COMT. Administration of the COMT inhibitor blocked 2-MeOE2 formation and, at the same time, increased 2-OH2 and 8-oxo-dG levels. In the presence of COMT inhibition, increased oxidative DNA damage was detected in MCF-7 cells exposed to as low as 0.1 μM E2, whereas in the absence of COMT inhibition, no increase in 8-oxo-dG was detected at E2 concentrations ≤ 10 μM. These results demonstrate that COMT activity is protective against oxidative DNA damage associated with catechol estrogen metabolites. When COMT activity and methoxy estrogens were absent, the authors observed a linear relation between 2-OH2 plus 4-OH2 and 8-oxo-dG levels. However, this relationship did not hold under experimental conditions that allowed limited formation of methoxyestrogens, i.e., 8-oxo-dG levels were less than expected for a given concentration of 2-OH2 plus 4-OH2 in the presence of 2-MeOE2. On the basis of our results, it would appear that 2-MeOE2 exerts feedback inhibition in MCF-7 cells of CYP1-mediated E2 metabolism, resulting in reduced 8-oxo-dG formation.

In summary, we present data that require a revision of the existing view of oxidative estrogen metabolism (Fig. 5). Instead of simply being end products of the COMT reaction, we find that methoxyestrogens can regulate the oxidative estrogen metabolism pathway by exerting feedback inhibition on CYP1A1 and CYP1B1. Several points are noteworthy about the observed feedback regulation. First, CYP1A1 and CYP1B1 generate catechol estrogen substrates for COMT, and at the same time, they compete with COMT by converting the catechol estrogens to estrogen quinones. In turn, the methoxyestrogens generated by COMT are alternate substrates for CYP1A1 and CYP1B1 and inhibit oxidation of the parent hormone E2 (most likely the catechol estrogens as well) by CYP1A1 and CYP1B1. Second, the inhibition occurs at a strategic point in the pathway where it branches into 2-OH and 4-OH catechol estrogens. This may be important in view of the apparent difference in carcinogenicity of 2-OH and 4-OH catechol estrogens (44, 45). Third, all three products of the COMT-mediated reaction (i.e., 2-MeOE2, 2-OH-3-MeOE2, and 4-MeOE2) act as inhibitors, thereby maximizing the feedback regulation. Although not examined in this study, we expect that the methoxyestrogens produced by COMT from E1 (i.e., 2-MeOE1, 2-OH-3-MeOE1, and 4-MeOE1; Ref. 16) similarly act as inhibitors, thereby doubling the number of physiologically inhibiting substrates. Fourth, the feedback regulation occurs at the step in the pathway preceding the conversion to estrogen semiquinones and quinones, thereby reducing the formation of reactive oxygen species during semiquinone-quione redox cycling and the potential for estrogen-induced DNA damage. Fifth, we see the joint involvement of enzymes categorized as Phase I (CYP1A1 and CYP1B1) and Phase II (COMT) in a biologically important feedback loop. Because CYP1A1 and CYP1B1 play key roles as Phase I enzymes in metabolizing various xenobiotic chemicals to procarcinogens in extrahepatic tissues (32), their inhibition by endogenous methoxyestrogens may represent a physiological defense mechanism against carcinogenesis. CYP1A1 and CYP1B1 are highly inducible by numerous xenobiotics (46, 47), and the associated multifold increase in enzyme action may be attenuated by the methoxyestrogen feedback inhibition produced by the constitutively expressed COMT. Finally, our data add to a better understanding of the mode of action of 2-MeOE2, which is currently undergoing preclinical trials as a therapeutic agent (25, 26).

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