Cyclooxygenase-2 Induction by Paclitaxel, Docetaxel, and Taxane Analogues in Human Monocytes and Murine Macrophages: Structure-Activity Relationships and Their Implications

Pamela B. Cassidy, Philip J. Moos, Robert C. Kelly, and F. A. Fitzpatrick

Departments of Medicinal Chemistry [P. B. C., F. A. F.] and Oncological Science [P. J. M., F. A. F.], Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah 84112-5550, and Pharmacia Research and Development, Kalamazoo, Michigan 49007 [R. C. K.]

ABSTRACT

Paclitaxel and docetaxel can induce pro-inflammatory proteins, typified by cyclooxygenase-2 (prostaglandin H synthase). In some circumstances, this phenomenon may be relevant to the immunomodulatory actions and the adverse effects associated with paclitaxel or docetaxel. Accordingly, we compared a panel of sixteen taxanes, including paclitaxel and docetaxel, for their ability to induce cyclooxygenase-2 in a murine macrophage cell line (RAW 264.7) and in human peripheral blood monocytes. We discovered that the structure-activity relationships governing the induction of cyclooxygenase-2 protein differ markedly between the two species. Of 14 analogues evaluated, only 2 had activity comparable with paclitaxel in RAW 264.7 cells. In contrast, docetaxel and 12 of 14 analogues had activity comparable with paclitaxel in human monocytes. Our results enabled us to predict and subsequently affirm that the major human hepatic metabolite, 6α-hydroxypaclitaxel, would induce cyclooxygenase-2 in human cells but not in murine cells. Our structure-activity data and our experiments with combinations of taxanes suggest a provisional model for cyclooxygenase-2 induction. This model suggests that binding at a high-affinity site on tubulin and stabilization of microtubules is necessary, but not sufficient, for cyclooxygenase-2 induction. Binding at a second, lower-affinity receptor site is also necessary. However, our structure activity data are not fully compatible with two candidate proteins currently proposed as the low-affinity receptor.

INTRODUCTION

The antimitotic taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), are efficacious against a range of solid tumors, particularly carcinomas of the breast and ovary (1–7). Paclitaxel and docetaxel have distinctive pharmacological traits. First, they bind to β tubulin and derange microtubule assembly (8, 9). Stabilization of microtubules with either taxane causes mitotic arrest and apoptosis in vitro (10–12). Second, they act independently of the p53 tumor suppressor in both experimental (12–18) and clinical settings (19–24). Few antineoplastic agents other than taxanes exhibit this favorable trait (25–27). Third, they induce genes encoding TNFα, ILs (28–35), and enzymes such as NO synthase (31, 36–38) and COX-2 (39–41) that generate mediators of inflammation. Gene induction in vitro typically requires 10–30 μM paclitaxel, which is ~1000-fold greater than that required for tubulin polymerization in vitro.

Gene induction by paclitaxel has drawn attention from two different perspectives. Vogel and colleagues (31, 42–47) have pioneered the use of paclitaxel to probe cellular-signaling pathways activated by LPS in murine model systems. In this context, as a research tool, the requirement for 10–30 μM to elicit gene induction and the divergent responsiveness of murine and human macrophages is immaterial. In a second context, investigators have considered induction of cytokines and pro-inflammatory proteins in terms of the pharmacological and toxicological profile of paclitaxel. Its immunomodulatory effects (15, 43, 48) and its adverse reactions profile (1, 2) are compatible with induction of TNFα, IL-1β, IL-8, NO synthase and COX-2. In this context, the requirement for 10–30 μM paclitaxel and docetaxel, the species specificity of the response, and the SARs among different taxanes are material to the interpretation and significance of the results.

Some opinion leaders assert that all paclitaxel effects should be assumed to originate from its microtubule binding activity (49). Certainly, significant clinical benefits from paclitaxel and docetaxel are the result of microtubule stabilization and mitotic arrest within neoplastic cells. However, the assertion that investigations using 10–30 μM paclitaxel cannot be clinically relevant is debatable (49). Plasma concentrations of paclitaxel in the 10–30 μM range are the exception, but they do occur (50–52). For example, plasma C max values equal or exceed 10–30 μM in patients receiving high-dose monotherapy (825 mg paclitaxel/m² infused over 24 h; Ref. 50); in patients who receive infusions of 200–250 mg/m² for 1 h (51); and in patients

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2 To whom requests for reprints should be addressed, at Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope, Salt Lake City, UT 84112-5550. Phone: (801) 581-6204; Fax: (801) 585-0101; E-mail: frank.fitzpatrick@hci.utah.edu.

3 The abbreviations used are: TNFα; tumor necrosis factor α; COX, cyclooxygenase; IL, interleukin; LPS, lipopolysaccharide; SAR, structure-activity relationship; TBS, Tris (hydroxymethylaminomethane)-buffered saline; HRP, horseradish peroxidase; NO, nitric oxide.
who receive infusions of 90–225 mg/m² for 3 h (52). Notably, hepatic clearance of paclitaxel occurs via a saturable, zero-order process with an estimated Kₘ of ~3 μM. Zero-order elimination kinetics can favor accumulation of paclitaxel in the plasma, particularly in patients with diminished liver function (53). Lastly, we and others recently established that paclitaxel, docetaxel, and other taxanes induce IL-1β and COX-2 in human monocytes (34, 40); IL-8 in human tumors (35); and IL-8 or COX-2 in human tumor cell lines (41). These results dispel the criticism that gene induction by taxanes occurs only in murine macrophages.

Herein, we compared the effect of 16 taxane analogues on COX-2 induction in human peripheral blood monocytes and murine RAW 264.7 macrophage cells, a cell line used frequently to investigate gene induction by taxanes. We report that the SAR governing the induction of COX-2 protein differs markedly between the two species. Human monocytes respond to paclitaxel, docetaxel, and 12 of 14 analogues. In contrast, RAW 264.7 cells respond to paclitaxel and only 2 of 14 analogues. We conclude the following: (a) paclitaxel is a member of a limited group of taxanes useful as a probe for gene induction via the LPS signaling pathway in murine cells; (b) the SAR for gene induction by taxanes in murine cells does not extrapolate readily to human cells. Accordingly, pharmacological or toxicological effects that are attributable to gene induction by taxanes in humans may not occur in mice that receive taxanes; (c) our SAR hypothesis enables predictions that seem relevant to the clinical pharmacology of paclitaxel. Namely, we predicted and affirmed that 6α-hydroxypaclitaxel, a hepatic metabolite of paclitaxel, would induce COX-2 in human monocytes; and (d) experiments with combinations of taxanes support a model in which taxanes bind to two different receptors. We propose that both binding sites might reside on microtubules.

**Isolation of Human Monocytes.** Peripheral blood monocytes were isolated as described previously (57). Briefly, mononuclear leukocytes were separated from the blood of healthy donors by dextran sedimentation, hypotonic lysis of RBCs, and density gradient centrifugation. Monocytes were further purified by countercurrent elutriation. We then suspended 2 × 10⁶ monocytes/ml in RPMI 1640 supplemented with 1% v/v human serum. Cell suspensions contained >95% viable cells as determined by trypan blue-dye exclusion.

**RESULTS**

Fig. 1 shows the concentration dependence for induction of COX-2 protein by paclitaxel in RAW 264.7 cells and human monocytes. RAW 264.7 cells exhibit a concentration dependence with a potency (EC₅₀ = concentration for ½ maximal response) of ~25 μM (Fig. 1A). Monocytes isolated from a single donor showed a similar concentration dependence for induction of COX-2 protein with an EC₅₀ ~35 μM (Fig. 1A). However, we found that responsiveness of monocytes isolated from different donors varied considerably. The concentration dependence for COX-2 induction in monocytes from 11 different donors is shown in Fig. 1B.

We monitored the kinetics of COX-2 protein induction in human monocytes and RAW 264.7 cells, a murine macrophage cell line, to determine how promptly induction occurred and to select a time point for investigating SARs. In human monocytes, COX-2 protein expression rose above the basal level within 1–2 h after exposure to 30 μM paclitaxel (Fig. 2). The response varied from donor to donor, but in all cases, COX-2 levels reached a maximum within 8–12 h. RAW 264.7 murine macrophages responded similarly. COX-2 protein expression rose within 4 h after addition of 30 μM paclitaxel, increased linearly from 4–8 h, and reached an asymptote within 8–12 h (Fig. 2).

In contrast to the similar kinetic and concentration-response profiles for paclitaxel-induced COX-2 expression in...
human and murine cells (Figs. 1 and 2), docetaxel induces COX-2 expression only in human monocytes, and not in RAW 264.7 cells (see Fig. 4; Ref. 40). We investigated a set of 16 taxanes to determine whether this difference extended beyond docetaxel. These analogues, depicted in Fig. 3, contain variations in the N-acyl group attached to the C-13 phenyl isoserine side-chain (compounds 1, 2, 3, and 13), enol-ester linkages to the isoserine side-chain (compounds 6–11), a cyclopropane fused to the C-ring (compounds 6, 7, and 12), C6-C7 double bonds (compounds 10 and 11) and a C-12 hydroxyl group (compound 14).

We observed differences in the SAR for induction of COX-2 protein in RAW 264.7 cells versus human monocytes. Among 16 taxanes examined, only numbers 8 and 10 induced COX-2 expression in murine cells at a level comparable with paclitaxel (Fig. 4A). As expected, docetaxel was inactive; however, the two most active compounds were close analogues of docetaxel. These analogues both have a t-butyl carbamate as the isoserine N-acyl substituent, as does docetaxel. They both differ from docetaxel at C-10 (acetyl group versus hydroxyl) and at the C-13 isoserine linkage (enol ester versus ester). The murine SAR suggested that these features confer activity on taxanes having the t-butyl carbamate N-acyl group. We noted that compound 7 also has these features but is inactive. We reasoned that this compound may have an altered ring conformation because of its strained, fused cyclopropane ring at C-7, C-8 (60). Paclitaxel analogues (numbers 1, 2, 3, and 13) differ from the parent only at the N-acyl substituent. From these data, we concluded that induction of COX-2 in RAW 264.7 cells by paclitaxel analogues is highly dependent on the nature of this substituent.

In contrast to the murine SAR, only 2 of the 16 taxanes, numbers 2 and 5, failed to induce COX-2 protein expression comparably with paclitaxel in human monocytes (Fig. 4B). Compound 5 differs from paclitaxel only at C-7, where a bulky phenylthio(methoxy) group replaces a hydroxyl substituent. Compound 2 is a member of a diverse series of taxanes (numbers 2, 4, 6, 9, 11, and 12) that have a t-butyl urea as the N-acyl group and a C-10 acetyl substituent. The five active compounds of this series have relatively hydrophobic substituents at C-7. The sole inactive member of the group has a C-7 hydroxyl. The conservative change of C-7 hydroxyl to C-7 fluoro in compound number 4 restores activity. It appears that this series of ureas is sensitive to substitutions at C-7.

The SAR for COX-2 induction in Fig. 4B originated from a human donor who yielded sufficient monocytes to examine all of the taxanes in a single experiment. Fig. 4C illustrates the variability of COX-2 protein induction among four different donors. The rank order of efficacies was constant. For instance, compounds 1, 3, and 13 always induced more COX-2 protein than did paclitaxel. However, the efficacy of individual taxanes, relative to paclitaxel, varied between donors. For example, with monocytes from three separate donors, the response to compound 13 ranged from a 2- to a 5-fold increase in COX-2 relative to paclitaxel.

The taxanes that we examined were similar to paclitaxel in terms of displacement of [3H]paclitaxel from bovine brain microtubules (Table 1). Docetaxel, compound 2, and compound 9...
were more than twice as potent as paclitaxel. Compound 1 was the only analogue less potent than paclitaxel. Although limited in scope, our SAR enables some predictions that are relevant to the pharmacology of paclitaxel in humans. On the basis of the different responses of RAW 264.7 cells and human monocytes to modifications of the taxane ring, we predicted that the major human hepatic metabolite of paclitaxel, \((\text{6})_{12}\) hydroxypaclitaxel, would induce COX-2 in human monocytes but not in RAW 264.7 cells. Results in Fig. 5A affirmed this prediction. With monocytes from three separate donors, COX-2 induction by \(30 \mu M\) \((\text{6})_{12}\)-hydroxypaclitaxel equaled, or exceeded, that induced by \(30 \mu M\) paclitaxel. The time course for COX-2 induction by \(6\alpha\)-hydroxypaclitaxel resembled the time course for paclitaxel (Fig. 5B). Treatment of RAW 264.7 cells with \(30 \mu M\) \(6\alpha\)-hydroxypaclitaxel for 12 h did not result in induction of COX-2 (data not shown).

The divergent SAR for human versus murine cells, and the fact that all of the taxanes examined herein bind to and stabilize microtubules, argues that microtubule stabilization by taxanes is not sufficient for COX-2 induction. If microtubule stabilization by taxanes were sufficient for COX-2 induction, one would expect a uniform response to all taxanes from both species. Nevertheless, microtubule stabilization could be necessary, but not sufficient, for COX-2 induction. This hypothesis implies that taxanes equivaleate with two separate binding partners in cells: (a) microtubules and (b) a receptor associated with COX-2.

**Fig. 3** Chemical structures of taxanes.
induction (Fig. 6A). Saturation of microtubule-binding sites with a taxane analogue that does not induce COX-2 (e.g., docetaxel in RAW 264.7 cells) should shift the equilibrium binding of paclitaxel toward the second receptor, with a corresponding increase in the rate or the amount of COX-2 induction. To test this prediction, we incubated RAW 264.7 cells for 1 h with 30 μM docetaxel or DMSO; then we added 20 μM paclitaxel and monitored COX-2 induction. Docetaxel, alone for 24 h, did not induce COX-2 in RAW 264.7 cells. DMSO vehicle alone for 1 h, then combined with paclitaxel for 24 h induced COX-2. Docetaxel for 1 h, then combined with paclitaxel for 24 h, induced appreciably more COX-2 than did the paclitaxel alone (Fig. 6B). These differences in the rates and amounts of COX-2 induction conform to the model depicted in Fig. 6A. We obtained similar results with another inactive taxane, compound 2, substituted for docetaxel. RAW 264.7 cells, treated for 1 h with 20 μM compound 2, then 12 h with 10 μM paclitaxel, produced eight times more COX-2 than did cells treated for 1 h with DMSO vehicle and then for 12 h with 10 μM paclitaxel (data not shown).

We performed the above experiment with combinations of paclitaxel and compound 2 in human monocytes (Fig. 7). We treated cells with 30 μM compound 2 for 1 h followed by paclitaxel at either 15 μM or 30 μM for 12 h. The 30-μM compound-2 treatment resulted in a small but detectable increase in COX-2 when compared with vehicle alone. Induction of COX-2 protein by a combination of the two taxanes exceeded the sum of COX-2 protein induction by either agent alone. The amount of COX-2 induced by treatment with 15 μM paclitaxel plus 30 μM compound 2 was >2 × the amount induced by 15 μM paclitaxel alone.

### Table 1

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<th>Compound</th>
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<th>Relative potency</th>
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<tr>
<td>Docetaxel</td>
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<tr>
<td>1</td>
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*ND, not determined.

**Fig. 5** Effect of 6α-hydroxypaclitaxel, the human hepatic metabolite of paclitaxel, on COX-2 protein induction by human monocytes. A, the immunochemical analysis of COX-2 protein in monocytes incubated at 37°C for 12 h with 30 μM 6α-hydroxypaclitaxel (6-OH Px), 30 μM paclitaxel (Px), or DMSO vehicle. COX-2 protein induction by 6α-hydroxy paclitaxel was 1.6 ×, 7 ×, and 3 × that by paclitaxel in monocytes from three separate human donors. B, time course of COX-2 protein induction by human monocytes (■) incubated at 37°C with 30 μM 6α-hydroxypaclitaxel.
μM paclitaxel, alone, plus the amount induced by compound 2, alone. The amount of COX-2 induced by treatment with 30 μM paclitaxel plus 30 μM compound 2 was >3 times the sum of COX-2 induced by either agent alone.

DISCUSSION

Human monocytes produce COX-2 in response to treatment with a wide variety of taxanes. In this investigation, 12 of 14 paclitaxel analogues induce the expression of COX-2 with efficacies greater than or equal to that of paclitaxel. These analogues possess modifications of the β-phenyl isoserine chain: the position of the olefin in the A-ring; and substituents at C-6, C-7, or C-8. There are no other SAR studies directly comparable with ours. However, Watson et al. (35) reported that paclitaxel, docetaxel, and 8 of 10 analogues with modifications at the C1-C4 positions induced IL-8 in human ovarian OVCA 420 cells. The only changes that abolished activity were scission of the D-ring oxetane and elimination of the β-phenyl isoserine side chain (35). Thus, other types of human cells tolerate many taxane structures without impairing cytokine induction.

The SAR for COX-2 induction in human monocytes and IL-8 induction in OVCA 420 cells (35) prompted us to predict that paclitaxel metabolites might retain the ability to induce COX-2. We confirmed this prediction with the observation that 6α-hydroxypaclitaxel, a hepatic metabolite of paclitaxel, does induce COX-2 in human monocytes. It is likely that the plasma concentrations of paclitaxel plus its metabolite reach levels sufficient to induce inflammatory proteins in some circumstances (Table 2) and (61). This discovery fortifies the rationale for assessing selective COX-2 inhibitors to manage certain adverse effects of paclitaxel. Such trials are under way.4

It will be interesting to see whether taxanes have improved

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4 Andrew Dannenberg, personal communication.
antitumor efficacy when coadministered with COX-2 inhibitors. William et al. (62) have reported that solid human tumors grow more slowly when implanted in mice lacking both alleles of COX-2, compared with mice lacking both alleles of COX-1 or with wild-type mice. Pharmacological inhibition of COX-2 activity, coincident with its induction by paclitaxel, might confer a similar benefit by reducing formation of COX-2 products like prostaglandin E₂ that promote angiogenesis (63), antagonize apoptosis (64), and inhibit cell-mediated antitumor immune responses. In other words, COX-2 induction by taxanes may be limiting their efficacy. Notably, the use of selective COX-2 inhibitors in combination with paclitaxel would leave the induction of IL-8 and other cytokines intact. IL-8 reportedly stimulates neutrophil infiltration and reduces growth in human ovarian tumors (33). Other cytokines that are induced by paclitaxel include GM-CSF and IP-10, which also have antitumor effects through the immune system or by inhibiting tumor angiogenesis (65).

Unlike human monocytes, murine RAW 264.7 cells did not tolerate much diversity in the taxane structures that confer COX-2 induction; only 2 of 14 analogues were active in our investigation. Burkhardt et al. (30) observed a similarly restricted response for TNFα induction in RAW 264.7 cells. Of 11 compounds examined, including docetaxel, only paclitaxel and its 7-acetyl analogue induced TNFα expression (30). Likewise, Kirikae observed that taxane-induced TNFα and NO production in murine peritoneal macrophages was very sensitive to changes at the C-3′-N position (36, 37). Among a group of 12 paclitaxel analogues consisting of 11 aryl-substituted benzamides and the C-3′-(p-phenyl)phenylacetamide, only 6 compounds retained the ability to stimulate production of TNFα and NO in murine macrophages. The six active analogues had relatively minor substitutions on the benzamide ring (4-methyl-, 4-fluoro-, 2,4-difluoro-, 4-chloro-, 4-methoxy-, and 4-ethyl-). Paclitaxel analogues having acyl modifications at C-7 have recently been restricted response for TNFα induction in RAW 264.7 cells. Of 11 compounds examined, including docetaxel, only paclitaxel and its 7-acetyl analogue induced TNFα expression (30). However, they observed antagonism of NO induction by taxane analogues, which indicated that taxanes can be agonists, antagonists, or partial agonists (38) gene induction, raising a concern that COX-2 induction might involve interaction of taxanes with receptors other than the current candidates.

The results from our experiments with combinations of taxanes support a model (Fig. 6) in which taxanes equilibrate between a high-affinity receptor on microtubules and another, lower-affinity receptor. The former accounts for microtubule stabilization; the latter accounts for COX-2 induction. Occupancy of the high-affinity binding sites on microtubules with a taxane analogue that binds selectively to these sites shifts the equilibrium binding of paclitaxel toward the site responsible for gene induction. Results by Kirakae et al. (37) also fit a model analogous to that depicted in Fig. 6. However, they observed antagonism of NO induction by taxane analogues, which indicated that taxanes can be agonists, antagonists, or partial agonists at the low-affinity site responsible for gene induction.

When paclitaxel binds to microtubules stoichiometrically (i.e., >5 μM paclitaxel), the phosphorylation, composition, and subcellular trafficking of microtubule-associated protein complexes, such as mitogen-activated protein kinases (41, 72) and K-Ras (73), are affected. These changes perturb the signal cascades that govern membrane-to-nuclear signaling and the induction of COX-2 as well as other proteins. It is possible that the species-specific SAR that we observe arises from differential effects on microtubule-associated proteins and their downstream kinases.

In considering what second process might participate in gene induction, we draw attention to investigations on microtubule assembly dynamics and the stoichiometry of paclitaxel binding to microtubules (59, 74). Derry et al. (59) have established that paclitaxel binds at two distinct sites on microtubules; one of high affinity on the interior region of the microtubules, and another of lower affinity at the microtubule ends. Using a different approach Carlier and Pantaloni (74) also concluded that microtubule ends have a distinctive, low-affinity binding
site for paclitaxel. It is noteworthy that vinblastine, which causes COX-2 induction in human cells (41), suppresses microtubule dynamics with a very steep concentration dependence by binding to a few sites at microtubule ends (10).

We speculate that a low-affinity binding site at microtubule ends might be the second receptor responsible for COX-2 induction by taxanes (Fig. 6). We base our speculation on the following: (a) the experimental evidence for two distinct paclitaxel binding sites on microtubules, one of high affinity and one of much lower affinity, (59, 74) the latter possibly at microtubule ends; and (b) the fact that occupancy of both high- and low-affinity sites, perturbations in the composition and distribution of microtubule associated proteins, and COX-2 induction, all occur when paclitaxel concentrations exceed 5–10 μM. We are using this explicit model to guide our ongoing studies of the remarkable clinical efficacies and deleterious side effects of the taxanes.

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