Effects of Dietary Curcumin on Glutathione S-Transferase and Malondialdehyde-DNA Adducts in Rat Liver and Colon Mucosa: Relationship with Drug Levels

Ricky A. Sharma, Christopher R. Ireson, Richard D. Verschoyle, Kirsti A. Hill, Marion L. Williams, Chiara Leuratti, Margaret M. Manson, Lawrence J. Marnett, William P. Steward, and Andreas Gescher


ABSTRACT
Curcumin prevents colon cancer in rodent models. It inhibits lipid peroxidation and cyclooxygenase-2 (COX-2) expression and induces glutathione S-transferase (GST) enzymes. We tested the hypothesis that 14 days of dietary curcumin (2%) affects biomarkers relevant to cancer chemoprevention in the rat. Levels of inducible COX-2, as reflected by prostaglandin E₂ production by blood leukocytes, were measured ex vivo. Total GST activity and adducts of malondialdehyde with DNA (M₁G), which reflect endogenous lipid peroxidation, were measured in colon mucosa, liver, and blood leukocytes. Curcumin and its metabolites were analyzed by high-performance liquid chromatography in plasma, and its pharmacokinetics were compared following a diet containing 2% curcumin versus intragastric (i.g.) administration of curcumin suspended in an amphiphilic solvent. The curcumin diet did not alter any of the markers in the blood but increased hepatic GST by 16% and decreased colon M₁G levels by 36% when compared with controls. Administration of carbon tetrachloride during the treatment period increased colon M₁G levels, and this increase was prevented by dietary curcumin. Dietary curcumin yielded low drug levels in the plasma, between 0 and 12 nM, whereas tissue concentrations of curcumin in liver and colon mucosa were 0.1–0.9 nmol/g and 0.2–1.8 μmol/g, respectively. In comparison with dietary administration, suspended curcumin given i.g. resulted in more curcumin in the plasma but much less in the colon mucosa. The results show that curcumin mixed with the diet achieves drug levels in the colon and liver sufficient to explain the pharmacological activities observed and suggest that this mode of administration may be preferable for the chemoprevention of colon cancer.

INTRODUCTION
Cancer mortality rates in the developed world have risen throughout most of this century, and it is already the leading cause of death in some Western countries (1, 2). This observation has engendered much research activity aimed at the identification of cancer chemopreventive agents, especially substances derived from the diet (3). Turmeric, the dried ground rhizome of the perennial herb Curcuma longa, is an example of one such agent. This spice is consumed in the diet in quantities up to 4 g/adult/day in some countries (4), which also appear to have low incidence rates of colorectal cancer (1). Turmeric contains curcuminoids and essential oils. Curcumin (diferuloylmethane), a low molecular weight polyphenol and the major curcuminoid in the plant, is regarded as the constituent with the highest biological activity. Curcumin has been shown to inhibit tumor formation in the skin, forestomach, duodenum, and colon of mice and in the tongue, colon, mammary glands, and sebaceous glands of rats (5). Mechanisms by which curcumin causes cancer chemoprevention are thought to involve antioxidation (6), inhibition of kinases (7), interference with the activity of transcription factors such as nuclear factor-κB and activator protein-1 (8), and suppression of expression of the enzyme COX-2 (9).

In a program of preclinical work designed to help optimize the clinical evaluation of curcumin as a colon cancer chemopreventive agent, we tested the hypothesis that curcumin in the diet alters biomarkers of its chemopreventive efficacy. Three biomarkers were selected to represent possible mechanisms of the chemopreventive activity of curcumin in vivo. These were total GST activity, DNA adducts formed by MDA, and inducible COX-2 expression as reflected by PGE₂ production. Induction of GSTs, phase II enzymes that detoxify certain carcinogens, is regarded as a potential mechanism of blockade of the early stages of carcinogenesis (3). Such induction is a property

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3 The abbreviations used are: COX, cyclooxygenase; GST, glutathione S-transferase; MDA, malondialdehyde; PG, prostaglandin; M₁G, malondialdehyde-deoxyguanosine adduct; HPLC, high-performance liquid chromatography; LPS, lipopolysaccharide; CDNB, 1-chloro-2,4-dinitrobenzene as substrate; i.g., intragastric.
of several agents with chemopreventive activity in preclinical models, including curcumin (10) and the broccoli constituent sulforaphane (11). MDA is a naturally occurring product of lipid peroxidation (12), which is also formed during prostaglandin biosynthesis via COX (13), two enzymatic processes that have been implicated in the pathogenesis of a number of cancers, especially colon cancer (14–16). PGE2 is a product of COX-2, the isoenzyme of COX induced during infection, inflammation, and malignant transformation. Inhibition of COX-2 is thought to be an important mechanism of chemoprevention, exhibited by nonsteroidal anti-inflammatory drugs (14) and dietary agents such as curcumin (9). MDA reacts with DNA under physiological conditions to form adducts, predominantly with deoxyguanosine (M1G). Accumulated DNA damage may be important in the etiology of many cancers, and such damage may be reflected by exocyclic DNA adducts such as M1G (17). M1G has been implicated in the induction of G → T transversions by MDA-induced DNA modification (18). M1G levels have been described in malignant and nonmalignant human colon cells in vitro and in leukocytes, pancreas, breast, and liver in healthy volunteers (12); indeed they are comparable with levels of DNA adducts formed by exogenous carcinogens such as polycyclic hydrocarbons.

The ability of curcumin to prevent malignancies in the colorectal tract in rodents has been particularly well documented (7, 19, 20). It has also been shown to inhibit lipid peroxidation (21) and carbon tetrachloride-mediated hepatotoxicity (22, 23). We therefore aimed to test the hypothesis that dietary curcumin affects GST and M1G levels in the intestinal mucosa and prevents increases in M1G levels when lipid peroxidation is induced in this tissue by CCl4. For comparison, levels of GST and M1G were also investigated in liver and blood leukocytes. Because COX-2 is not expressed significantly in normal tissues without provocation, an ex vivo model was used to study its inducibility in peripheral blood indirectly. To be able to rationalize potential pharmacodynamic changes and interpret them in terms of efficacious drug levels, curcumin and its glucuronide or sulfite conjugation products were determined in intestinal mucosa, plasma, and liver. Studies in rodents suggest that curcumin has poor systemic bioavailability when given p.o. and is cleared rapidly from the plasma when administered i.v. (24), but overall the information on its pharmacokinetic behavior is scarce. Whereas in cancer intervention studies using curcumin it has generally been administered mixed in the diet, studies of its pharmacokinetics and metabolism have used i.g. gavage or non-oral routes of administration. In the light of the difficult pharmaceutical properties of curcumin, i.e., its lipophilicity and susceptibility to rapid metabolism, we also tested the hypothesis that drug and metabolite levels after i.g. gavage are representative of those following curcumin ingestion in the diet.

MATERIALS AND METHODS

Reagents. Curcumin was purchased from Apin Chemicals Ltd. (Abingdon, United Kingdom). Analysis by HPLC/mass spectrometry established that the material contained 91% curcumin and 9% desmethoxycurcumin. CCl4, corn oil, glutathione, CDNB, glycerol formal (consisting of 60% 5-hydroxy-1,3-dioxane and 40% 4-hydroxymethyl-1,3-dioxalone) and Cre moporph were purchased from Sigma Chemical Co. (Poole, United Kingdom). Murine M1G monoclonal antibody D10A1 was prepared as described previously (25). Antimurine horseradish peroxidase antibody was purchased from Dako (Ely, United Kingdom). M1G standards were synthesized and characterized as described previously (26).

Treatments. Female F344 rats (6-weeks of age; 160–180 g), obtained from Charles River UK Ltd. (Margate, United Kingdom) had access to water and a standard RMI diet (Special Diet Services) ad libitum. Rats were kept in groups of four per cage at 20°C on a 12-h light/dark cycle. For dietary administration, curcumin and corn oil were mixed with the diet to furnish 2% for each. This level of curcumin in the diet, which rats received for 14 days, has been shown previously to prevent gastrointestinal tract tumors in several rodent models of chemically induced carcinogenesis (5, 10). Control animals received a diet containing corn oil. CCl4 was dissolved in corn oil (2 ml/kg) and administered by i.g. gavage at 0.5 ml/kg on day 10 after commencement of dietary curcumin intake. This dose of CCl4 has been shown previously to raise liver M1G levels (18). Control animals received the equivalent dose of corn oil.

In the pharmacokinetic study, administration of dietary curcumin was compared with that of an i.g. bolus. For administration by gavage, curcumin was suspended and partially dissolved in a mixture of glycerol formal:cremophore:water (5:2:2), which in preliminary experiments was found to yield a suitable formulation in terms of acceptable viscosity and stability of suspension. This formulation was administered at 500 mg curcumin/kg by i.g. gavage once only or daily for 7 consecutive days. Control animals received the excipient mixture only. Tissue samples were collected 30 min postdose, a time point at which in preliminary experiments curcumin levels had been found to be maximal. For an optimal comparison of this administration mode with dietary curcumin, we exploited the fact that feeding habits of rats are subject to a diurnal cycle with two eating peaks, one of which occurs at around 8:00 p.m. (27). Rats were deprived of food for 6 h, commencing at 1:00 p.m. They then received the curcumin-containing diet for 3 h, coinciding with the eating peak. Subsequently, food was withdrawn for ~30 min, after which blood and tissue samples were collected. This “starvation-refeeding” protocol was performed either in untreated animals or in rats that had received the curcumin diet continually for 7 days.

At the end of the feeding period, or subsequent to i.g. administration, rats were subjected to terminal anesthesia (halothane/nitrous oxide), and blood was removed by cardiac puncture. Blood was placed in heparinized tubes and plasma obtained by centrifugation (1100 × g at 4°C for 25 min). The large intestine was flushed with PBS and dissected out. Cytosol was prepared by standard procedures (28), and blood leukocytes were isolated using Ficoll-Paque Plus (Amersham Pharmacia Biotech, United Kingdom). Murine M1G monoclonal antibody D10A1 was prepared as described previously (25). Antimurine horseradish peroxidase antibody was purchased from Dako (Ely, United Kingdom). M1G standards were synthesized and characterized as described previously (26).

Control animals received the equivalent dose of corn oil.

Biotech, Buckinghamshire, United Kingdom). Histological examination ensured accurate scraping of colonic mucosa only. Blood and tissue samples were protected from light, frozen in liquid nitrogen, and stored at −80°C until pharmacodynamic and pharmacokinetic analyses were performed.

Pharmacodynamic Analyses. Total GST activity of cytosol samples was measured spectrophotometrically using glutathione and CDNB (29). Results were corrected for protein levels using the Bio-Rad protein assay (Bio-Rad, Hemel Hempstead, United Kingdom). Extraction of genomic DNA and analysis of \( M_1 G \) adduct levels by immunoslot blot was performed as described previously (30). Discrepancies in the amount of DNA in each slot were corrected by staining the nitrocellulose filter with propidium iodide and performing UV light densitometry. The detection limit for \( M_1 G \) was five adducts per 10^5 nucleotides. The model for assessing inducibility of COX-2 ex vivo was based on published methods and has been well established in clinical studies as well as preclinical models (31, 32). Aliquots (0.5 ml) of fresh blood were incubated with acetylsalicylic acid (200 μm) for 30 min at 37°C to inactivate platelet COX-1 irreversibly. LPS (10 μg/ml) was added to half the samples and mixed well, and samples were reincubated for 24 h. Plasma was separated by centrifugation and stored at −80°C. PGE_2 in these plasma samples was measured by competitive enzyme immunoassay (Cayman Chemicals, Ann Arbor, MI), with a detection limit of ~30 pg/ml plasma.

Analysis of Curcumin and Its Conjugates. Curcumin and its metabolites were measured as described before (24). Plasma and tissues were extracted with twice the volume of ethyl acetate, and the organic layer was evaporated under nitrogen. Extraction efficiencies from plasma for curcumin, curcumin glucuronide, and curcumin sulfate determined by HPLC (see below) at 0.1 μg/ml were 92 ± 7, 45 ± 10, and 49 ± 9% (mean ± SD, n = 6), respectively; the extraction efficiencies at 40 μg/ml were very similar to these values. Extraction efficiencies from liver and colon mucosal scrapings were not significantly different from those obtained in plasma. The reversed-phase HPLC method for detection and quantitation of curcumin and its conjugates used a Symmetry Shield RP 18 column (150 × 3.9 mm; particle size, 5 μm; Waters) and a Varian Prostar (230 model) solvent delivery system coupled to a UV-visible detector (310 model) and autosampler (model 410). Detection of curcumin, curcumin sulfate, and curcumin glucuronide was achieved at 420 nm. For the detection of products of curcumin reduction, the detector was switched to 280 nm. Detection of curcumin, curcumin sulfate, and curcumin glucuronide was validated using a 0.1 and 40 μg/ml solution yielding intra- and inter-day coefficients of variation of 17 and 13%, and 16 and 19%, respectively (n = 4).

Statistical Evaluation. Results were subjected to ANOVA and Spearman’s test of rank correlation, using Excel and Minitab (both Windows 1997) software packages. Post hoc Fisher’s Least Significant Difference Test was performed.

RESULTS

Pharmacodynamic Effects of Dietary Curcumin. Rats were fed a diet supplemented with 2% curcumin for 2 weeks. On the basis of food consumption, the approximate daily dose ingested was 1.2 g curcumin/kg. Dietary curcumin at this dose did not affect the animals’ body weight gain. Levels of GST activity in the liver of curcumin-fed rats were elevated by 36% over those in control animals (Table 1). GST levels in colon mucosa and lymphocytes were marginally decreased by curcumin; however, this difference was not significant. Levels of \( M_1 G \) adducts in colon mucosa of rats which received curcumin were moderately, but significantly, lower than those in control rats (Fig. 1). M_1 G adduct levels in leukocytes and liver of curcumin-fed rats were also slightly decreased as compared with controls, but these differences were not significant. Treatment of rats with CCl_4 increased levels of \( M_1 G \) adducts in liver and colon mucosa by 49 and 25%, respectively, over control values (Fig. 1). Dietary curcumin attenuated this increase in the liver and completely prevented it in the colon.

To study whether dietary curcumin led to altered COX-2 expression in blood cells, the concentration of PG\( \text{E}_2 \) in plasma was determined after induction with LPS added in vitro. LPS increased blood PG\( \text{E}_2 \) levels ~3-fold, but curcumin feeding failed to interfere with this increase (result not shown).

Levels of Curcumin after Dietary Administration. Plasma, colon mucosa, and liver from rats that had received curcumin in their diet as described above for 2 weeks were analyzed for the presence of curcuminoids. Curcumin and its metabolites, curcumin glucuronide and curcumin sulfate, could not be detected in the plasma obtained by cardiac puncture or from the hepatic portal vein. Levels of curcumin were 1.8 ± 0.8 μmol/g tissue in the colon mucosa and 0.8 ± 0.3 nmol/g in the liver. Curcumin was also present in the feces (8.6 ± 0.6 μmol/g dried feces). Curcumin glucuronide or curcumin sulfate was not detected in either tissues or feces.

Pharmacokinetic Comparison of Modes of Administration. To compare the availability of curcumin admixed with the diet or suspended in an amphiphilic solvent and admis-
that received dietary curcumin (2%) for 14 days; □ and □, animals that received dietary curcumin (2%) for 14 days; □ and □, animals that received carbon tetrachloride (0.5 ml/kg) via the i.g. route on the 10th day of the study diet. Values are means of eight animals; bars, SD. * and **, the difference between control and curcumin-treated animals (*, P < 0.01, by ANOVA) or between animals that received carbon tetrachloride either with or without curcumin (**, P < 0.005, by ANOVA) is significant. For experimental details, see “Materials and Methods.”

Table 2 Curcumin and curcumin conjugates in the plasma of rats that received curcumin in the diet or by the i.g. route

<table>
<thead>
<tr>
<th>Dosing schedule</th>
<th>Curcumin (nmol/ml)</th>
<th>Curcumin glucuronide (nmol/ml)</th>
<th>Curcumin sulfate (nmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short feeding</td>
<td>&lt;10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Single i.g.</td>
<td>30 ± 9</td>
<td>56 ± 36</td>
<td>134 ± 100</td>
</tr>
<tr>
<td>7-day feeding</td>
<td>12 ± 5</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Repeated i.g.</td>
<td>65 ± 28</td>
<td>638 ± 146</td>
<td>360 ± 160</td>
</tr>
</tbody>
</table>

<sup>a</sup> Rats received curcumin as an i.g. bolus (500 mg/kg) once (“Single i.g.”) or daily for 7 consecutive days (“Repeated i.g.”), or with the diet (2%) for 3 h after a period of starvation (“Short feeding”), or after a starvation-refeeding regimen after unlimited access to a curcumin-containing diet for 7 days (“7-day feeding”). The dose of curcumin when given with the diet, as calculated by weighing food removal, was between 200 and 400 mg/kg. For details of curcumin administration and its measurement, see “Materials and Methods.”

<sup>b</sup> Values are mean ± SD from three to four animals.

DISCUSSION

The results of this study allow two conclusions that may help to optimize clinical trials of curcumin as a cancer chemopreventive agent: (a) the bioavailability of curcumin in blood and tissues is dramatically affected by the way in which it is p.o. administered; and (b) colon mucosa and liver are pharmacological targets of dietary curcumin.

The first conclusion is based on the observed differences in levels of curcumin and its conjugates in plasma and tissues after the two administration modes. Dietary curcumin elicited concentrations of the drug in the colon mucosa of between 0.3 and 1.8 µmol/g, whereas plasma levels were around the limit of detection. Curcumin suspended in a solvent mixture and given by i.g. bolus furnished levels of drug in the plasma that were 3–6-fold higher than those seen after dietary administration. Curcumin metabolites were detectable in the plasma only after i.g. administration. Conversely, colon mucosal levels of curcumin after i.g. bolus were only a fraction of those observed after dietary administration.

Curcumin exerts its effects on growth, COX-2 expression,
and transcription factor activity in cells in vitro at concentrations of 5 μM or above (9). The colon mucosal level of curcumin after 14 days feeding observed in this study, 1.8 μmol/g, is more than 300-fold higher than the minimal concentration shown to be active in vitro. This result demonstrates that dietary administration of curcumin can produce pharmacologically relevant drug concentrations in colon mucosa. Although the dose used in this study, 2% in the diet, has been used frequently in rodent intervention studies (5, 10, 33), it is at least 10 times higher than the highest estimated daily human intake of curcumin as a dietary constituent (4) and does not reflect normal dietary use. In recent intervention studies, dietary levels of 0.2 and 0.1% curcumin have been demonstrated to protect rodents from colon cancer induced by azoxymethane (7, 19, 20) and to reduce polyp numbers in the Min mouse (34), a model of the genetic defect found in human familial adenomatous polyposis. Our results therefore intimate that dietary curcumin at doses considerably lower than those used here might yield pharmacologically efficacious levels in the colon mucosa and perhaps also in the liver.

Intriguingly, curcumin glucuronide and curcumin sulfate were not detected in plasma or tissues after its administration in the diet, whereas they were the major drug-derived species present in the plasma after i.g. administration. In a recent report, a small amount of a curcumin reduction product, tetrahydrocurcumin, was found in plasma samples from rats fed a curcumin-containing diet (1%) subsequent to treatment of plasma with enzymes that hydrolyze xenobiotic glucuronides and sulfates (35). In contrast, products of curcumin reduction were not unequivocally detected in plasma after dietary curcumin given for 14 days in the experiments described here, although hexahydrocurcumin and hexahydrocurcinol were identified by mass spectrometry in the bile. Overall, this part of the study suggests that the pharmacokinetic behavior of curcumin after administration of an i.g. bolus of curcumin in suspension is clearly unrepresentative of that of curcumin mixed into the diet. This finding is important because, although in intervention studies curcumin is generally given as a constituent of the diet, studies of its pharmacokinetics and metabolism have been performed mostly with the drug formulated in suspension, using DMSO, aqueous carboxymethyl cellulose solution, or arachis oil as solvents, and administered as an i.g. bolus or via the i.p. route (36–39). The results presented here suggest that should oral curcumin be advocated in the chemoprevention of malignancies remote from the liver or gastrointestinal tract, improvement of its oral bioavailability might be necessary, perhaps by formulating it as a solution.

Our second conclusion is borne out by the findings that dietary curcumin elevated hepatic GST levels, reduced colon mucosal M1 G adduct levels, and decreased the elevation of M1 G adduct levels elicited by a powerful lipid peroxidative stimulus in the liver and colon mucosa. These potentially beneficial effects correlated with curcumin levels of 1.8 μmol/g in the colon mucosa and 0.8 mmol/g in liver. The high concentrations of curcumin in the colon mucosa described here are consistent with the outcome of intervention studies in preclinical rodent models of colon cancer (7, 19, 20, 34). Although the decrease in M1 G levels in colon mucosa was modest, it underlines in principle that curcumin supplementation of the diet can achieve drug concentrations sufficient to decrease levels of DNA adducts formed as a corollary of lipid peroxidation. Curcumin glucuronide and curcumin sulfate were not found in liver or colon mucosa after dietary administration of curcumin, strongly suggesting that parent curcumin rather than either conjugate affects GST activities and M1 G adduct levels in vivo.

The levels of M1 G adducts in rat liver measured here were approximately three times higher than those described previously in Sprague Dawley rats and are more analogous to background levels found in normal human liver (18). Differences may be related to the age, sex, and strain of the animals used, or fat composition of the diets used. M1 G adduct levels in rat leukocytes and colon mucosa have not been documented previously. CCl4 has been shown to increase MDA and M1 G adduct levels in rat liver (18), and increases in hepatic MDA levels have been attenuated by feeding rats 100 mg/kg curcumin for 4 weeks (23). The results described here extend these findings, because they show that CCl4 also engenders M1 G adducts in the colon mucosa, and that this increase can be prevented by dietary curcumin. These findings are pertinent in the light of a recent study in which oxidative DNA damage linked to lipid peroxidation was detected in biopsies from normal human colon (40). The M1 G-lowering effect of curcumin provides a tentative rationale for the regular use of dietary curcumin in the protection of the colon mucosa against oxidative damage, perhaps in premalignant conditions such as ulcerative colitis.

Liver GST activity was raised over controls after curcumin ingestion in the diet. The effects of curcumin on GST and its expression are complex and may involve competitive enzyme inhibition (41) as well as indirect enzyme induction (42). Our finding that 14 days of dietary curcumin induces GST activity in the liver is consistent with an earlier study of the same dose of curcumin in diet and water fed to 8-week-old mice (10). Similarly, mice that received curcumin dissolved in aqueous sodium carboxymethylcellulose via i.g. gavage for 15 days at a dose approximately one-fifth of that used here were found to have significantly higher GST levels in liver compared with controls (41). In contrast, in a more recent study of 8-week-old Sprague Dawley rats, curcumin dissolved in corn oil given daily for 14 days via the i.g. route at various doses failed to induce hepatic GST at doses >6% of the dietary dose used here (43). This discrepancy may relate to differences between the studies in rodent species and strain, age of the animals, dose of curcumin, and its route of administration. Compatible with earlier rodent studies of dietary curcumin (10, 44), we failed to detect any significant alteration in GST activity in the colonic mucosa.

In cells in vitro, we have shown previously that curcumin inhibits COX-2 expression by a mechanism involving interference with nuclear factor-κB activation and inhibition of the IκB kinase complex (9). In the study described here, PGF2α production induced ex vivo as an indicator of leukocyte COX-2 activity was not affected by dietary curcumin. The fact that curcumin administered in the diet did not affect COX-2 inducibility, GST activity, or M1 G levels in rat blood leukocytes is consistent with the finding that this mode of administration furnished extremely low levels of parent curcumin in the plasma.
In conclusion, the results presented above show that dietary administration of curcumin to rats produces pharmacologically active levels of unmetabolized curcumin in the colon mucosa and liver, capable of decreasing M}\textsubscript{G}G levels and elevating GST activity. These effects may contribute to cancer chemoprevention. The results also suggest that dietary adixture may be the preferable mode of administration for curcumin in the chemoprevention of colon cancer. The chemopreventive efficacy of oral curcumin in the colorectum and the liver merits clinical evaluation.

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