Celecoxib administration exhibits tissue specific effect on 
$^3$H-benzo(a)pyrene-DNA adduct formation in cigarette smoke inhaling mice

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In the present study, cigarette smoke (CS) exposure significantly enhanced $^3$H-B(a)P-DNA adduct formation in both the pulmonary and hepatic tissues. Mice co-treated with CS and celecoxib (a specific COX-2 inhibitor) exhibited a significant decrease in hepatic carcinogen-DNA adduct formation in comparison to the smoke exposed group, however the lungs of the co-treated animals exhibited a significant increase in carcinogen-DNA adduct formation when compared to the control group and smoke exposed group. CS exposure enhanced the activity of carcinogen activation enzymes in both the tissues and decreased the activity of carcinogen detoxification enzymes in the hepatic tissue only, when compared to the control group. Celecoxib administration to CS inhaling mice modulated the carcinogen biotransformation considerably when compared to the CS exposed group. Celecoxib administration to CS inhaling mice produced a low index of carcinogenesis in the hepatic tissue but increased the index of carcinogenesis in the pulmonary tissue. These observations seem to be critical and tissue specific when related to carcinogenesis.

Keywords: Carcinogen-DNA adduct, Carcinogenesis, Celecoxib, Cigarette smoke, Hepatic, Inhalation, Pulmonary

Epidemiological and experimental studies have shown that smoking plays an important role in the etiology of various sites of human cancer, especially the lungs$^{1,2}$. Cigarette smoke (CS) is a complex mixture of approximately 4700 chemicals, 60 carcinogens, 10 known potent carcinogens, tumor promoters and co-carcinogens$^3$. Of the carcinogens present in CS, especially significant is the polycyclic aromatic hydrocarbon (PAHs) class of carcinogens. PAHs are indirect acting carcinogens that require metabolic transformation to exert their carcinogenic potential$^4$. Benzo(a)pyrene [B(a)P], belongs to the PAH class of carcinogens and is linked to the etiology of human cancers through its presence in CS$^3$, vehicle exhausts, environmental mixtures etc. Upon metabolic activation of B(a)P, the ultimate carcinogen, (±)-anti-BPDE is formed which interacts with and modifies informational molecules such as DNA with potentially mutagenic consequences$^5$.

Metabolic activation of potentially carcinogenic chemicals and the covalent binding of the reactive carcinogen metabolites to DNA forming DNA adducts are considered key events in tumor initiation$^6$. Because DNA adduct formation is considered necessary for carcinogenesis, measurement of carcinogen-DNA adducts provides evidence of molecular dosimetry, genotoxicity and potential cancer risk$^7$. Gangar et al.$^8$ have also employed DNA adduct formation as an index of carcinogenesis initiation in their studies on B(a)P induced fore-stomach tumor genesis.

Several lines of evidence suggest that Cyclooxygenase-2 (COX-2) is an important factor in the etiology of CS related cancer$^9,10$. COX is the key enzyme involved in the conversion of arachidonic acid to prostaglandins (PGs) and other bioactive lipids which are involved in normal physiological functions including the regulation of normal growth responses and also in the process of aberrant cellular growth. COX-1 is constitutively expressed in many tissues and cell types and performs a housekeeping function to synthesize prostaglandins with normal cell regulatory activity. The inducible COX-2 is pro-inflammatory and is induced in response to certain stimuli such as mitogens, cytokines and growth factors$^{11}$. COX-2 also catalyses the conversion of pro-carcinogens to carcinogens$^{12}$ such as conversion of B(a)P to its ultimate carcinogenic form BPDE which is capable of binding to DNA.

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Till now, extensive work has been done in determining the anticancer potential of selective COX-2 inhibitors at the promotional and progression stages of cancer\textsuperscript{13-15}, however the role of COX-2 inhibitors in combating the action of carcinogens at the initiation stage has not been explored much. Therefore, in the present study efforts have been made at exploring the anti-cancer potential of Celecoxib at the initiation stage of carcinogenesis. This has been done by examining the pathway wherein the carcinogens are activated by the action of Phase-I and Phase-II carcinogen biotransformation enzymes resulting in carcinogen-DNA adduct formation which has been taken as an index for the initiation of carcinogenesis.

Materials and Methods

Chemicals—\textsuperscript{3}H-Benzo(a)pyrene \textsuperscript{[3}H-B(a)P\textsuperscript{]} was purchased from BARC, Mumbai, India. 1-chloro-2,4-dinitrobenzene (CDNB), and reduced nicotinamide adenine dinucleotide (NADH) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Capsules containing Celecoxib were obtained from Lupin. The contents of the capsule were reconstituted in carboxymethyl cellulose (CMC) immediately before oral administration to the animals in order to attain the required dose. Filter tipped cigarettes (Four Square) were purchased from the local market. Rest of the chemicals were obtained locally and were of analytical grade.

Animal model and experimental conditions—Male Balb/c mice weighing (25-30 g) were procured from the Central Animal House of Panjab University, Chandigarh. The animals were housed in polypropylene cages bedded with sterilized rice husk. The animals were given free access to clean drinking water (tap water) and standard animal pellet diet (Ashirwad Industries, Kharar, Punjab, India), throughout the experiment and maintained at 21°±1°C, 50-60% RH and a 12:12 hr light and dark cycle. The experimental protocols were approved by the Institutional Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals. The mice were acclimatized to the experimental conditions for 1 week after which various treatments were given.

Treatment of animals—After acclimatization to the experimental conditions for one week the mice were randomly divided into four groups of 6-8 animals each on the basis of the treatment they received. Group I served as the control (sham) and was vehicle treated (carboxy methyl cellulose). In sham exposed group, mice were exposed to fresh air. Group II animals were exposed to cigarette smoke (CS) inhalation for 10 weeks\textsuperscript{16}. Mice in group III were administered celecoxib orally at a dose of 125 mg/kg body weight every alternate day for a period of 8 weeks. Group IV mice were exposed to cigarette smoke inhalation for 10 weeks and co-administered with celecoxib orally at a dose of 125 mg/kg for 8 weeks. The dose of celecoxib was standardized after extensive survey of literature\textsuperscript{17-19}. Celecoxib treatment was started 2 weeks after the initiation of cigarette smoke inhalation. Weekly alterations, if any in the body weights, diet and water consumption were observed for the mice in all the groups throughout the experiment.

Passive cigarette smoke inhalation—Animals (6-8) were exposed (whole-body exposure) at a time to cigarette smoke from five commercially available filter tipped cigarettes in an inhalation apparatus\textsuperscript{16}. The inhalation continued for 60 min every day. The inhalation apparatus consists of a Perspex chamber (8.21 l) with separate inlets for smoke and fresh air. A valve attached at the outlet to a suction pump controlled the air flow (141 cc/min) through the chamber. Each cigarette took approximately 6-8 min to burn completely. After exposure to smoke from each cigarette, mice were exposed to fresh air for 5 min. This procedure has been standardized in such a way that animals inhale cigarette smoke without any visible respiratory stress as is evident from carboxy-hemoglobin (CO-Hb) levels\textsuperscript{20}. It was observed that the CO levels in the control and CS exposed were 1.2±0.8 and 12.2±4.9% saturation of hemoglobin, respectively. No doubt, due to cigarette smoke inhalation there was an increase in CO-Hb levels in the smoke exposed animals as compared to their sham counterparts, the values were found to be within range that have been normally seen in CS smoke exposed animals\textsuperscript{21}. In case of sham exposed group, mice were exposed to fresh air only under similar conditions.

\textsuperscript{3}H-B (a) P-DNA adduct analysis—After completion of the respective treatments, mice from each group were given an intraperitoneal injection of 140 µCi \textsuperscript{3}H-B (a) P/100 g body weight of the mice (specific activity 8000 mCi/mMol). After 12 hrs of \textsuperscript{3}H-B(a)P injection, the mice from all the groups were killed and the pulmonary and hepatic tissues were
obtained and perfused with 0.9% NaCl solution. The tissues were washed and then processed for extraction of DNA as per the standard method of CTAB/NaCl\(^{22}\). The DNA content of the samples was quantified spectrophotometrically and the purity of the extracted DNA was checked by monitoring the \(A_{260}/A_{280}\) ratio. A ratio of \(\geq 1.9\) was taken as an index for DNA purity to be 99%\(^{23}\). For determination of \(^3\)H-B (a)P bound to DNA, \(^3\)H-B(a)P-DNA adducts, aliquots of DNA were transferred to toluene based scintillation fluid and the \(^3\)H activity of the samples along with standards of known \(^3\)H-B(a)P concentration were measured on a \(\beta\)-scintillation counter as described earlier\(^{23}\).

**Biochemical parameters**—After completion of the respective treatments the mice were sacrificed by cervical dislocation under ether anaesthesia. The pulmonary and hepatic tissues were obtained and perfused with cold normal saline (0.9% NaCl solution), blotted and then weighed carefully. The hepatic and pulmonary tissues were homogenized in 100 mM potassium phosphate buffer (pH 7.4) containing 150 mM KCl to obtain 25% homogenate (w/v). Aliquots of 25% homogenate were kept at 4°C and post mitochondrial fraction at 10,000 g for 30 min was prepared for the estimation of Cytochrome P\(_{450}\) and Cytochrome b\(_5\). Remaining homogenate was diluted with potassium phosphate buffer to obtain 10% homogenate (w/v). The 10% homogenate was subjected to cold centrifuge at 10,000 g for 30 min and the supernatant (post mitochondrial fraction) thus obtained was used for various biochemical estimations.

Cytochrome P\(_{450}\) (cyt. P\(_{450}\)) and Cytochrome b\(_5\) (cyt.b\(_5\)): The cyt. P\(_{450}\) content was determined using the carbon monoxide difference spectra (409-490 nm) of dithionate reduced samples as per the method of Omura and Sato\(^{24}\) using an absorption coefficient of 91 mM\(^{-1}\) cm\(^{-1}\). The cyt. b\(_5\) content was determined by recording the difference spectrum (409-424 nm) of NADH reduced versus air saturated samples by the method of Omura and Sato\(^{25}\). The molar extinction coefficient of the difference spectrum of cytochrome b\(_5\) was taken as 185 mM\(^{-1}\) cm\(^{-1}\). The amount of cyt. P\(_{450}\) and cyt. b\(_5\) were expressed as nmol/mg of protein.

Glutathione-S-transferase (GST): GST activity was determined spectrophotometrically according to the procedure described by Habig et al\(^{26}\). The reaction mixture (3 ml) contained 2.7 ml of 100 mM potassium phosphate buffer (pH 6.5), 0.1 ml of 30 mM CDNB and 0.1 ml of 30 mM GSH. After pre-incubating the reaction mixture at 37°C for 2 min, the reaction was started by the addition of an appropriate amount of the supernatant. The absorbance was followed for 3 min at 340 nm. The specific activity of GST was expressed as \(\mu\)mol of GSH-CDNB conjugates formed/min/mg protein using an extinction coefficient of 9.6 mM\(^{-1}\) cm\(^{-1}\).

Protein estimation: The protein contents of various samples were estimated by the method of Lowry et al.\(^{27}\) using BSA as a standard.

**Statistical analysis**—The data are expressed as mean ± SD. Statistical significance was analysed by one-way ANOVA followed by Student’s Newman Keul Test. For body weight analysis, data was analyzed using Student’s paired \(t\)-test.

**Results**

The mice were observed for changes in body weight, diet and water consumption throughout the experiment. Non-significant changes were observed in the diet and water consumption by the mice in all the groups studied (data not shown). Also, non-significant changes were observed in the final body weight of the groups studied when compared with their respective initial body weight (Table 1).

**\(^3\)H-B(a)P-DNA adduct formation** (Fig. 1)—The 10 week CS exposure caused a significant increase in the hepatic (130.0±27.1 to 260.0±15.8 fmoles/mg of DNA) and pulmonary (110.0±16.3 to 190.0±39.3 fmoles/mg of DNA) \(^3\)H-B(a)P-DNA adduct formation when compared to the control group. Celecoxib administration to the CS exposed animals caused a significant decrease (260.0±15.8 to 94.50±2.04 fmoles/mg of DNA) in the hepatic \(^3\)H-B(a)P-DNA adduct formation when compared with the control group. Celecoxib administration to the CS exposed animals caused a significant decrease (260.0±15.8 to 94.50±2.04 fmoles/mg of DNA) in the hepatic \(^3\)H-B(a)P-DNA adduct formation when compared to the CS exposed group. However, in the pulmonary tissue the conjunctive treatment of CS plus celecoxib, exhibited a significant increase in the adduct formation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial body weight</th>
<th>Final body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28.3±1.8</td>
<td>30.3±1.4</td>
</tr>
<tr>
<td>Smoke</td>
<td>29.7±1.4</td>
<td>28.3±1.4</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>28.7±1.5</td>
<td>29.8±1.4</td>
</tr>
<tr>
<td>Smoke+celecoxib</td>
<td>29.0±1.9</td>
<td>29.0±1.5</td>
</tr>
</tbody>
</table>

Data were analysed using Student’s paired \(t\)-test.
formation when compared to their control group (314.0±24.1 to 110.0±16.3 fmoles/mg of DNA) and only CS exposed group (314.0±24.1 to 190.0±39.3 fmoles/mg of DNA). Celecoxib per se group exhibited non-significant increase in the hepatic and pulmonary DNA adduct formation when compared to the control group.

Cytochrome P<sub>450</sub> (Table 2)—CS exposure caused a significant increase in the hepatic (1.2 folds) and pulmonary (1.16 folds) cyt.P<sub>450</sub> levels when compared with the control group. Celecoxib administration to CS inhaling mice caused a significant decrease in the hepatic (1.5 folds) and pulmonary (1.55 folds) cyt.P<sub>450</sub> level when compared to the group exposed to CS only. A significant increase in the hepatic cyt.P<sub>450</sub> level and a non-significant increase in pulmonary cyt.P<sub>450</sub> level was observed in the celecoxib per se group when compared to the control group.

Cytochrome b<sub>5</sub> (Table 2)—The 10 week exposure to CS caused a significant increase in the hepatic (7 folds) and pulmonary (4.3 folds) cyt.b<sub>5</sub> content when compared to the control group. In the conjunctive treatment group a significant increase (1.83 folds) in the hepatic cyt.b<sub>5</sub> content was observed when compared to the group exposed to CS only. There was no significant difference in the pulmonary cyt. b<sub>5</sub> content of the conjunctive treatment group and CS exposed group. In the celecoxib per se group, no significant change was observed in the hepatic and pulmonary cyt. b<sub>5</sub> levels when compared to the control group.

Glutathione-S-transferase (Table 2)—CS exposure caused a significant decrease (1.3 folds) in the hepatic GST levels when compared to the control group. Non significant change was observed in the hepatic GST levels of the co-treated group and the CS exposed group. The 10 week CS exposure was unable to alter the pulmonary GST levels when compared to the control group. Celecoxib administration to CS inhaling mice caused a significant increase (1.3 folds) in the pulmonary GST activity when compared to the

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Table 2—Modulatory effects of CS, celecoxib and co-treatment of CS and celecoxib on hepatic and pulmonary phase-1 and phase-2 xenobiotic transformation enzymes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Smoke</th>
<th>Celecoxib</th>
<th>Smoke + celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyt P&lt;sub&gt;450&lt;/sub&gt;*</td>
<td>Hepatic</td>
<td>0.100 ± 0.01</td>
<td>0.120 ± 0.003&lt;sup&gt;a2&lt;/sup&gt;</td>
<td>0.110 ± 0.004&lt;sup&gt;a2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.106 ± 0.01</td>
<td>0.124 ± 0.003&lt;sup&gt;a3&lt;/sup&gt;</td>
<td>0.112 ± 0.004&lt;sup&gt;a3&lt;/sup&gt;</td>
<td>0.080 ± 0.008&lt;sup&gt;b3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyt b&lt;sub&gt;5&lt;/sub&gt;*</td>
<td>Hepatic</td>
<td>0.010 ±0.004</td>
<td>0.071±0.007&lt;sup&gt;a2&lt;/sup&gt;</td>
<td>0.010 ±0.001&lt;sup&gt;b2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.017 ±0.004</td>
<td>0.074±0.007&lt;sup&gt;a1&lt;/sup&gt;</td>
<td>0.016±0.001&lt;sup&gt;b2&lt;/sup&gt;</td>
<td>0.136 ±0.027&lt;sup&gt;a1&lt;/sup&gt;</td>
</tr>
<tr>
<td>GST†</td>
<td>Hepatic</td>
<td>7.70 ± 0.13</td>
<td>5.69 ± 0.17&lt;sup&gt;a2&lt;/sup&gt;</td>
<td>6.64 ± 0.15</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.18 ± 0.06</td>
<td>1.08 ± 0.03</td>
<td>0.660 ± 0.12&lt;sup&gt;a1&lt;/sup&gt;</td>
<td>1.49 ± 0.22&lt;sup&gt;b1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data were analyzed using one-way ANOVA followed by Students-Newman Keul Test. P values: <sup>a1</sup><i>p</i><0.05; <sup>a2</sup><i>p</i><0.01; <sup>a3</sup><i>p</i><0.001 significant as compared to control group, <sup>b1</sup><i>p</i><0.05; <sup>b2</sup><i>p</i><0.01; <sup>b3</sup><i>p</i><0.001 significant as compared to control group.

Units: *nanomoles / mg of protein; †umoles of CDNB-GST conjugate formed/min/mg of protein
CS group. In the celecoxib per se group, a significant decrease was observed in the pulmonary GST activity when compared to the control group. Non-significant change was observed in the hepatic GST activity of the celecoxib per se group when compared to the control group.

Discussion

B(a)P, a major component of CS is a well-known carcinogenic PAH. It is a pro-carcinogen and requires metabolic activation to form reactive intermediates (the ultimate carcinogens such as 7,8-dihydroxy-9,10-oxy-7,8,9,10-tetrahydroxy benzo(a)pyrene) through the action of microsomal mixed function oxidases. These reactive carcinogenic intermediates bind with DNA leading to the formation of DNA adducts. DNA adduct formation is a critical step in the carcinogenic cascade of a carcinogen. It is well established that the degree of carcinogenicity is directly proportional to the extent of DNA adduct formation. Carcinogen-DNA adduct formation results from the complex processes of carcinogen absorption, activation and detoxification as well as DNA repair and tissue turnover. Carcinogen-DNA adduct formation constitutes biologically effective dose resulting from carcinogen exposure. Therefore, in the present study, the extent of DNA adduct formation has been taken as an index for the initiation of carcinogenesis.

Since COX-2 over-expression is a cardinal feature in the process of tumorigenesis, the COX pathway represents a reasonable target for therapeutic intervention. The potency of COX-2 inhibitors such as non-steroidal anti-inflammatory drugs in vivo can be attributed to the inhibition of this enzyme in tumor and stromal cells, resulting in anti-proliferative, pro-apoptotic, and anti-angiogenic activities within the tumor and in stromal cells. COX-2 inhibitors also act as blockers of carcinogen biotransformation mediated by phase-I and phase-II enzymes and also by inhibiting the carcinogen activation mediated by the COX-2 enzyme itself. Therefore, it is speculated that COX-2 inhibition can decrease the incidence of carcinogenesis by affecting the initiation, promotional and progression stages of tumor formation.

In the present study, CS exposure for 10 weeks caused a significant increase in the 3H-B(a)P-DNA adduct formation in the hepatic and pulmonary tissues of mice when compared to the control group. Erika et al. have demonstrated the formation of DNA adducts in tumor, normal peripheral lung and bronchus, and peripheral blood lymphocytes from smoking and non-smoking lung cancer patients. An increase in the DNA adduct formation in the pulmonary tissue of CS inhaling has been reported. Celecoxib administration to CS inhaling mice significantly decreased DNA adduct formation in the hepatic tissue and enhanced DNA adduct formation in the pulmonary tissue when compared to the group exposed to CS only.

The activation of a xenobiotic depends on the metabolic capacity of the corresponding tissues, which should be considered while considering the extent of DNA adduct formation. Cytochrome P450 is an important constituent of phase I enzymes and plays a major role in the metabolism of exogenous/endogenous substrates. Induction of phase I enzymes is considered to be a potential risk factor because many of the phase I reactions such as hydroxylation, epoxidation etc leads to the activation of pro-carcinogens to their ultimate carcinogenic form which is rendered suitable for interaction with nucleophilic sites in DNA. Cytochrome b5 is another heme-protein found in the endoplasmic reticulum of eukaryotic cells and has been known to augment some P450 monooxygenase reactions.

In the present study, exposure to CS caused a significant increase in the cyt. P450 and cyt. b5 content in the hepatic and pulmonary tissues of mice when compared to the control group. In the conjunctive treatment group, a significant decrease in the hepatic and pulmonary cyt. P450 content was observed when compared to the group exposed to CS only. In the co-treated group, a significant increase in hepatic cyt. b5 level was observed when compared to the group exposed to CS only. Non-significant increase was observed in the pulmonary cyt.b5 level of the co-treated group and CS exposed group. CS has been reported to contain numerous CYP450 inducers. Nishikawa et al. have shown that CS exposure induces hepatic CYP enzymes especially CYP1A2 in both rats and hamsters. Decrease in the level of cyt. P450 in the liver and lungs of animals following the administration of NSAIDs such as diclofenac and naproxen has been reported. Fracasso et al. have reported a fall in the level of CYP450 in the liver of rats after they were treated with indomethacin.

GST is a major phase II carcinogen biotransformation enzyme that catalyses the conjugation of a variety of endogenous and
exogenous compounds with the non-protein thiol, glutathione. A number of toxic electrophilic xenobiotics are conjugated to glutathione and rendered inactive. If the toxic xenobiotics are not conjugated to GSH they become free to attack the cellular macromolecules such as DNA, RNA and protein. The role of GSH in GST mediated conjugation/ detoxification of xenobiotic metabolites is most important in modulating the process of initiation of chemical carcinogenesis. A significant decrease in the hepatic GST activity and non-significant decrease in pulmonary GST activity was observed on exposure to CS when compared to the control group. Celecoxib administration to CS inhaling mice caused a significant increase in the pulmonary GST and non-significant increase in hepatic GST activity when compared with the group exposed to CS only. There is a strong relationship between the depletion of GST and the increase in cancer susceptibility. Gangar et al. have reported a significant decrease in the GST activity of hepatic tissue of skin tumor bearing mice induced by the application of PAHs. Eke and Iscan have reported a decrease in hepatic and pulmonary GST activity in rats after exposure to smoke of cigarette with low tar content. Esther et al. have reported an increase in GST levels in the rat digestive tract after they were treated with NSAIDs.

It is evident from the present results that CS exposure enhanced the activity of carcinogen activation enzymes and decreased the activity of carcinogen detoxification enzymes, which manifests itself in the enhanced DNA adduct formation in both the hepatic and pulmonary tissues of the CS exposed animals. In the conjunctive treated group celecoxib administration to CS inhaling mice exhibits a tissue specific effect on the DNA adduct formation. Animals of the co-treatment group have lower levels of hepatic and pulmonary CYP450 in comparison to the animals exposed to CS only, which suggests decreased activation of pro-carcinogen to the ultimate carcinogen. Hence, celecoxib may have acted as a blocker in the initiation of carcinogenesis since it depresses the metabolism of the pro-carcinogen to the ultimate carcinogen thereby reducing the amount of reactive metabolite available for reacting with the target cellular macromolecules such as DNA, RNA and protein. In the pulmonary tissue, an increase in DNA adduct formation in the co-treatment group was unanticipated because celecoxib administration to CS inhaling mice shifts the balance towards carcinogen detoxification.

Since, CS induces the expression of COX-2, which has been known to activate carcinogens, it is possible that celecoxib administration could not effectively repress COX-2 in the lung and hence prevent the increase in DNA adduct formation despite the fall in carcinogen activation enzymes and an increase in detoxification enzymes. COX-2 catalyses the conversion of pro-carcinogens to carcinogens especially in organs with low cyt.P concentration such as bladder and lung. Its cyclooxygenase activity oxygenates polyunsaturated fatty acids to hydroperoxy endoperoxides, and its peroxidase activity reduces the hydroperoxy group to hydroxy groups with the subsequent formation of peroxy radicals. These cyclooxygenase-formed peroxy radicals are capable of adding an oxygen molecule across the isolated C9-C10 double bond of B (a)P-7,8-diol forming B(a)P-7,8-diol-9,10-oxide.

The tissue distribution and mechanisms of oxidation of COX-2 are distinct from those exhibited by the principal drug metabolizing enzyme in animal tissue, CYP450. Therefore, PGH synthase (COX-2) serves as an alternative metabolic activation enzyme to the P450 isozymes in tissues such as the lung. There appears little chance that COX-2 plays a major role in systemic drug metabolism; but may be involved in tissue specific pathology to certain toxins or carcinogens. Many other stimuli present in the pulmonary microenvironment that are associated with the risk of lung cancer development can also induce the COX-2 expression in amount considerably higher than the amount present in other tissues such as liver.

Therefore, use of COX-2 inhibitors such as celecoxib by smokers would modulate carcinogen biotransformation, effectively reducing the carcinogen activation and enhancing carcinogen detoxification. This by any chance should not be ascertained for a decrease in the index of carcinogenesis because in the present investigation DNA adduct formation has been observed to increase in the pulmonary tissue. These results seem to be tissue specific and critical in context to CS associated carcinogenesis and therefore, need to be further looked into.

References


