EFFECTS OF CHINESE, JAPANESE AND WESTERN TEA ON HEPATIC P450 ENZYME ACTIVITIES IN RATS

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SUMMARY

Previous studies have reported that green tea effectively protects against cancers caused by various dietary carcinogens. As P450 enzymes are the major system responsible for the metabolism of many carcinogens, we hypothesise that tea consumption may alter the catalytic activities of P450 enzymes. We conducted this study to screen the effects of four different teas on the activities of P450 enzymes. Tea solutions (2.5%) were prepared by adding boiling water to tea leaves and filtering. Female Wistar rats were divided into five groups (n = 4 each); each had free access to tea solutions while the control group was supplied with water for 4 weeks. Animals were sacrificed and livers were removed for preparation of microsomes.

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Enzyme activities were determined by incubation of liver microsomes with the appropriate CYP substrate. The activity of CYP1A1 in livers from rats receiving Oolong (Chinese) tea (185 ± 63 pmol/mg/min), Japanese green tea (197 ± 22 pmol/mg/min) and Earl Grey tea (228 ± 40 pmol/mg/min) was significantly higher ($p < 0.05$) than in the control group (94 ± 34 pmol/mg/min), whereas no change was observed in the activity of CYP1A2 in any of tested animals. The hepatic activity of CYP2D6 was greater only in rats drinking Earl Grey tea compared to the controls (235 ± 37 vs 161 ± 41 pmol/mg/min, $p < 0.05$). There were also significant increases ($p < 0.05$) in the activity of CYP3A in livers of animals given Oolong tea (653 ± 174 vs 382 ± 114 pmol/mg/min) and Earl Grey tea (751 ± 202 pmol/mg/min), while Jasmine and Japanese green tea had no significant effect. These results indicate that not all types of tea cause alterations in liver CYP enzymes as some elevated activities and some did not. Further studies are needed to determine whether there is a relationship between the effect of tea on CYP activities and anti-carcinogenesis.

KEY WORDS

drug metabolism, cytochrome P450, tea, green tea

INTRODUCTION

Cytochrome P450 (CYP) enzymes, which are mainly found in the liver, are a group of proteins responsible for detoxification of a wide range of foreign compounds, including drugs, environmental pollutants, and cancer-causing agents (carcinogens). The role of CYP enzymes in protecting the body against foreign chemicals is as important as that of antibodies in dealing with invading organisms. Most chemical carcinogens require metabolic activation by CYP enzymes to their genotoxic intermediates /1-4/. In some instances, these activated metabolites are subjected to detoxification by conjugation reactions. Thus, activities or levels of CYP enzymes may be one of the important host factors in determining whether or not exposure to a carcinogen results in cancer /5/. The activities of CYP enzymes can be influenced by many factors including genetic composition of the host, selected medications, and exposure to certain

dietary and environmental chemicals. It has been demonstrated that vegetables, particularly cruciferous ones (cabbage, Brussels sprouts, cauliflower, broccoli, etc.), induce P450 enzymes, namely CYP1A1 and CYP1A2 /6/.

There is increasing awareness that diet may be an important factor in the development and prevention of many common ailments including cardiovascular diseases and cancer. Tea (*Camellia sinensis*) is one of the most ancient and, next to water, the most widely consumed beverage in the world. It is conceivable that water-extractable constituents of tea may modulate the CYP enzymes involved in the activation and detoxification of chemical carcinogens. A number of studies has reported that green tea and its polyphenol extracts effectively protect against cancers caused by various dietary carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons /7-12/. Green tea extract given orally also protected mice from UV-induced skin tumors /13/. Green tea contains at least 10-20% polyphenols. These compounds are powerful antioxidants, capable of scavenging H_2O_2 and superoxide anions, thus preventing H_2O_2- and oxygen free radical-induced cytotoxicity and mutagenicity /14/.

As CYP enzymes are the major system responsible for the metabolism of many carcinogens, we hypothesise that tea consumption may alter the catalytic activities of CYP enzymes in producing its cancer protective effect. Therefore, we conducted this study to screen the effects of Chinese, Japanese and Western teas (Chinese jasmine, Oolong, Japanese green tea and Earl Grey tea) on the activities of CYP enzymes.

MATERIALS AND METHODS

Chemicals

NADPH, sodium dithionite, sodium dodecylsulphate, phenacetin, acetaminophen (paracetamol) and quinine hydrochloride were purchased from Sigma Chemical Co. (St Louis, MO, USA). Debrisoquine and 4-hydroxydebrisoquine were kindly donated by Roche (Auckland, New Zealand). Guanoxan hemisulphate was supplied by Pfizer (Auckland, New Zealand). 3-Hydroxyquinine was a gift from Dr. P Winstanley, University of Liverpool, UK. HPLC-grade acetonitrile

and methanol were obtained from the Fisher Scientific Co. (Springfield, NJ, USA).

Treatment of rats with tea

The study was approved by the University of Otago Animal Ethics Committee, Dunedin, New Zealand. Female Wistar rats (8 weeks old) were used. They were kept on a 12-h light, 12-h dark cycle and had free access to a commercial rodent diet (F49, Reliance Stock Food Co., Dunedin, New Zealand). The animals were housed two per cage with wire lids. They were divided into five groups of four rats each. The control group received water and the experimental groups were maintained on 2.5% (w/v) tea solutions for 4 weeks as the sole source of fluid. Tea samples tested were Chinese jasmine, Oolong, Japanese green tea and Earl Grey tea. They were purchased from a local supermarket of Asian groceries in Dunedin, New Zealand. The tea solutions were prepared by adding boiling water (400 ml) to tea leaves (10 g) and left to stand for 10 min. The solutions were filtered and transferred into glass water feeding bottles protected from light by covering with aluminium foil.

Preparation of liver microsomes

After 4 weeks of pretreatment, rats were sacrificed and the livers were excised and rinsed in 0.9% (w/v) NaCl solution. The liver tissues were homogenized in 3 weight volumes of ice-cold phosphate buffer (pH 7.4). Liver microsomes were prepared by differential ultracentrifugation as previously described /15/. The microsomal pellet was resuspended in a volume of 0.25 M phosphate buffer (pH 7.4) containing 20% (v/v) glycerol. Samples were either assayed fresh or frozen immediately at -84°C in aliquots with a protein concentration of 9-24 mg/ml. Content of microsomal protein was determined by the method of Lowry *et al.* /16/ with serum bovine albumin as standard. Cytochrome P450 content was measured based on the method previously described /17/ using microsomal protein concentration of 1 mg/ml in phosphate buffer (pH 7.4).

CYP enzyme assays

In all enzyme assays, each microsomal sample was performed in duplicate. Phenacetin *O*-deethylase (CYP1A1) activity was determined as described by Boobis *et al.* /15/ using a high concentration (300 μM) of phenacetin and 1 mM NADPH in 1 ml final volume with 0.1 M phosphate buffer (pH 7.4). The reaction was initiated by addition of NADPH. After incubating the mixture for 15 min at 37°C, the reaction was terminated by adding 270 μl of NaOH. The reaction mixture was extracted with chloroform and subsequently with diethyl ether as previously described /18/. Formation of the metabolite acetaminophen (paracetamol) was determined by a specific HPLC assay /18/ with slight modification in which the mobile phase was modified to consist of 12% methanol and 88% HPLC water.

Phenacetin *O*-deethylase (CYP1A2) activity was assayed in exactly the same manner as mentioned above, except that the substrate (phenacetin) concentration used was 3 μM, approaching the mean K_m value reported for the high activity (CYP1A2) enzyme responsible for phenacetin *O*-deethylation /15/.

Debrisoquine 4-hydroxylase (CYP2D) activity was performed as described previously /19/ using 1 mM debrisoquine as the substrate. After incubating the mixtures, the reaction was stopped by adding 200 μl of NaOH. Formation of the metabolite, 4-hydroxydebrisoquine, was monitored by an HPLC method /20/.

Quinine was used as a marker for determining CYP3A activity according to a previously described procedure /21/. Briefly, the reaction mixture (0.5 ml) containing 30 μM quinine, NADPH, and rat liver microsomes (0.5 mg protein/ml) was incubated at 37°C for 12 min. The reaction was stopped by the addition of cold methanol (1 ml). The substrate concentration used is approximately the K_m value obtained in female Wistar rats /21/. Formation of metabolite 3-hydroxyquinine was measured by a specific HPLC method /22/.

Statistical analysis

Results are reported as means ± SD. Differences between groups were evaluated using one-way analysis of variance (ANOVA), followed by Dunnett's test for pair-wise comparison. A p value of less than 0.05 was considered statistically significant.

RESULTS

There was no difference in the amount of water or tea solutions consumed by rats among the control and test groups, each rat drinking approximately 20-23 ml per day. Body weight gain over the 4-week period was similar in all groups studied, even though those drinking jasmine and Oolong tea weighed slightly more than the control group at the end of week 4 (Table 1). There were no differences in the liver weights relative to their body weights (as % body weight) of the rats among all the groups (Table 2). There was no statistically significant difference in total P450 content among the five groups studied.

The activity of CYP1A1 was significantly greater ($p < 0.05$) in the rats drinking Oolong (Chinese), Japanese green tea or Earl Grey tea as compared to the control group (Table 2). There was no significant difference between these three groups in the activity of CYP1A1. CYP1A1 activity was increased by 97%, 110% and 143%, respectively, compared to the control group. Treatment with Chinese jasmine tea for 4 weeks did not cause a significant increase in the activity of CYP1A1. In contrast, the activity of CYP1A2 (the high affinity isoform for phenacetin) was not changed by any of these treatments with different tea solutions.

Treatment of rats with Earl Grey tea for 4 weeks caused a significant ($p < 0.05$) increase in CYP2D activity as measured by debrisoquine 4-hydroxylation (Table 2). No significant change in the activity of CYP2D was observed with the other teas tested. A considerabe increase in CYP3A activity, 71% and 97%, respectively ($p < 0.05$), was observed in rats drinking Oolong or Earl Grey tea (Table 2). The same period of treatment with either jasmine or Japanese green tea had no influence on the activity of CYP3A.

DISCUSSION

Tea is the second most consumed beverage around the world, after water. Black tea is the most prevalent (80%) and is the most popular tea in Western countries. Oolong tea is less frequently consumed (<2%) whereas green tea is the most popular in China, Japan, North Africa, and the Middle East. Green tea represents approximately 20% of worldwide tea consumption /8,11/. Many studies have shown that the consumption of tea and its polyphenols can afford prevention

TABLE 1

Effects of tea consumption on body weight gain in female Wistar rats

Weeks of drinking	Body weight (g)				
	Control (water)	Jasmine tea	Oolong tea	Japanese green tea	Earl Grey tea
0	173 ± 6	182 ± 7	179 ± 9	175 ± 11	176 ± 8
1	189 ± 6	195 ± 4	196 ± 5	190 ± 7	185 ± 9
2	199 ± 6	205 ± 9	209 ± 5	200 ± 8	200 ± 11
3	212 ± 7	221 ± 6	226 ± 8	219 ± 7	214 ± 6
4	216 ± 8	235 ± 7*	235 ± 7*	228 ± 6	219 ± 9

Data given as means ± SD from groups of four rats receiving water (control) or 2.5% tea solutions.
* Significantly different from controls ($p < 0.05$).

TABLE 2

Effects of tea consumption on hepatic drug metabolism parameters in female Wistar rats

	Control (water)	Jasmine tea	Oolong tea	Japanese green tea	Earl Grey tea
Liver weight (% body wt)	4.1 ± 0.2	4.3 ± 0.3 (105%) [#]	4.3 ± 0.2 (105%)	4.6 ± 0.3 (112%)	4.6 ± 0.1 (112%)
P450 content (nmol/mg protein)	0.27 ± 0.09	0.18 ± 0.09 (67%)	0.38 ± 0.19 (141%)	0.39 ± 0.18 (144%)	0.46 ± 0.22 (170%)
Phenacetin O deethylase activity (pmol/mg/min):					
CYP1A1	94 ± 34	163 ± 30 (173%)	185 ± 63* (197%)	197 ± 22* (210%)	228 ± 40* (243%)
CYP1A2	89 ± 31	105 ± 24 (118%)	103 ± 42 (116%)	111 ± 42 (125%)	126 ± 10 (142%)
Debrisoquine 4-hydroxylase activity (pmol/mg/min):					
CYP2D	161 ± 41	155 ± 41 (96%)	173 ± 40 (107%)	169 ± 18 (105%)	235 ± 37* (146%)
Quinine 3-hydroxylase activity (pmol/mg/min):					
CYP3A	382 ± 114	338 ± 93 (88%)	653 ± 174* (171%)	287 ± 40 (75%)	751 ± 202* (197%)

Results given as means ± SD of four determinations (n = 4), each derived from a different animal.

[#] Value in parentheses represents the percentage of the corresponding control value.

* Significantly different from the control group ($p < 0.05$).

against cancer and coronary heart diseases, but the evidence obtained from the epidemiological studies is not conclusive /11,12/. Because of this potential benefit, defining the mechanisms of the biological effects of tea is important.

It is well recognised that modulation of drug metabolizing enzyme activity by dietary components may be important in terms of human health, as this can both activate and deactivate a wide range of xenobiotics. The diet may contain many chemicals that can antagonize the effects of chemical carcinogens. One of the mechanisms could be by modulating the enzyme systems involved in the activation and detoxification of chemical carcinogens. Most of the chemical carcinogens are not reactive themselves and require metabolic activation by a variety of enzymes responsible for drug metabolism to exert their genotoxicity. The CYP system is one of the major sets of enzymes involved in the activation of carcinogens /2-4/. There is some evidence relating to metabolic enzyme modulation by green tea and black tea in various rodent models /11,12,23,24/.

In the current study, a marked induction of hepatic metabolism of phenacetin to acetaminophen (paracetamol), mediated by CYP1A1, was observed in rats given three different kinds of teas, Oolong tea, Japanese green tea and Earl Grey tea, whereas the activity of CYP1A2 was not significantly altered by 4-week treatment with all teas studied. Our results with CYP1A1 are in agreement with previous results reported by other investigators. Exposure of rats to green tea has shown to increase the level and activity of CYP1A /25/. Pretreatment of rats with green and black teas caused significant induction of CYP1A2, CYP1A1, CYP2B and CYP4A1 /12,23,26/. Liver microsomal preparations from rats pretreated with tea were much more effective than controls in converting the carcinogen, 2-amino 3-methyl imidazole quinoline (IQ), to mutagenic intermediates in the Ames test /25/. Induction of Phase I and II enzymes was observed in livers of F344 rats receiving 2% solution of green or black tea for 6 weeks. Activity of CYP1A1, CYP1A2, CYP2B1 and UDP glucuronosyl transferase was increased significantly but glutathione transferase was not /25,27,28/. After 4 weeks treatment with green and black teas, activity of CYP1A1 and CYP1A2 was markedly increased /29/. As caffeine is also present in tea even though tea contains less caffeine than coffee /8,11,26/, its effect on CYP activity was previously investigated. Pretreatment of rats with caffeine solution as the sole

source of drinking fluid for 21 days caused a significant increase in methoxyresorufin-*O*-deethylase (CYP1A) activity similar to that observed with 2% tea solutions, while decaffeinated green tea did not /26/. These results suggested that previous reports of CYP1A induction could be due to the effect of caffeine and not due to tea polyphenols. Some contradictory results have been reported. For instance, when green tea fractions were added to rat liver microsomes, inhibition of several enzymes, such as ethoxyresorufin-*O*-deethylase, 7-ethoxycoumarin-*O*-deethylase and arylhydrocarbon hydroxylase, was observed /23/. These enzymes are involved in reactions catalyzed by CYP1A. Treatment with (-)-epigallocatechin gallate, the major and putative active component of green tea, inhibited both CYP1A and CYP2B1 /30/. It is possible that the contradictory results in effect of tea preparations on CYP activity may be related to the relative contents of caffeine and polyphenols in tea leaves. CYP1A plays an important role in the activation of aromatic and heterocyclic amine precarcinogens, including food mutagens, such as 2-amino-3-methylimidazo[4,5]quinoline and 2-amino-1-methyl-6-phenylimidazo-[4,5] pyridine /26/. The results of increased activity of CYP1A1 by tea consumption found in this study may suggest that tea may enhance the activation of chemical carcinogens which rely on this CPY isozyme for their activation. However, the reactive intermediate formed can be subsequently detoxified by Phase II conjugation reactions, including glucuronidation, sulfation and glutathione conjugation. Tea may enhance activity of the Phase II conjugating enzymes or involve scavenging of reactive oxygen species by virtue of its antioxidant properties /10,14,31/. Green tea contains a wide variety of polyphenols that can function as scavengers of reactive oxygen species /31/. At tissue levels at which CYP1A is induced, the scavenging of reactive metabolites may predominate over the enhanced oxidative activity. Moreover, tea may owe its anti-carcinogenic potential, at least in part, to its ability to modulate the initiation stage of chemical carcinogenesis by affecting the enzymes that catalyze the activation and detoxification processes. The inhibition of metabolic activation of procarcinogens catalyzed by CYP enzymes by green tea may be one of the mechanisms of anti-carcinogenic effect /32/. It could be envisaged that the mutagenic and carcinogenic process, and the ultimate risk of developing a chemically-induced cancer, lie in the delicate balance

between Phase I carcinogen activating enzymes and Phase II detoxifying enzymes.

The CYP3A enzymes activate dietary pro-carcinogens such as aflatoxin B1, suggesting a possible role in cancer prevention for compounds that inhibit CYP3A activity /33/. Inhibition of CYP3A was not seen in rats treated with any of the tea preparations studied. Some tea preparations caused an increase in activity of CYP3A, i.e. consumption of Oolong tea and Earl Grey tea produced a significant increase in the activity of CYP3A. This finding is in contrast with previous studies in which treatment with green and black tea in rats did not change the activity of CYP3A /27,29/. Moreover, catachins, major polyphenolic constituents of green tea, were shown to inhibit midazolam hydroxylation mediated by CYP3A4 in human liver microsomes /32/. The discrepancy in the results could be due to the different types of tea used, and the content of tea polyphenols could be different depending on location and season of harvesting the tea leaves /8,32/.

This study has shown that different teas produced different effects on CYP activity. For example, CYP1A1 was induced by treatment with Oolong tea, Japanese green tea and Earl Grey tea, whereas jasmine tea had no effect. With respect to CYP3A, its activity was significantly increased by Oolong tea and Earl Grey tea but not by jasmine tea and Japanese green tea. The difference in their effects on CYP enzyme activity could be related to the relative content of tea polyphenols and caffeine in tea leaves which could be influenced by geographical location or harvesting season of the tea leaves.

In summary, the present study has shown that tea consumption can alter the activity of CYP enzymes in rats, but not all kinds of tea produce this effect. Further studies are needed to identify the active constituents in these teas, and to define the relationship between the effect of tea on CYP activities and anti-carcinogenesis. In addition, more definitive epidemiology studies on the effects of tea on human cancer are needed.

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