Effect of Glucose–Lysine Maillard Reaction Product Fractions on Tissue Xenobiotic Enzyme Systems

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Maillard reaction product (MRP) fractions were prepared from a glucose–lysine (gluc–lys) browning model system by heating 1.0 M solutions of glucose and lysine at 121 °C for 4 h. MRP systems were fractionated into a melanoidin precipitate and a supernatant by the addition of absolute ethanol to a level of 90% volume. The fractions were freeze-dried and called freeze-dried supernatant (FDS) and freeze-dried melanoidin precipitate (FDMP). Chronic animal feeding studies were conducted with the addition of FDS and FDMP to experimental synthetic diets at a 2% level in mice, either B[*a*]P treated or untreated. At 10 weeks, animals were sacrificed and specific xenobiotic metabolizing enzymes [aryl hydrocarbon hydroxylase (AHH), glutathione *S*-transferase (GST), cytochrome b_5, cytochrome P-450, and UDPglucuronyltransferase (UDPGT)] in the liver, lung, kidney, and small intestine microsomes and cytosol samples were measured. There was no adverse effect of the presence of MRP fractions in the diet on body growth of the mice or on the liver, kidney, lung, and intestine weights. Hepatic, kidney, and pulmonary xenobiotic enzyme activities were unchanged in mice fed both MRP fractions. Both FDS and FDMP fractions were found to significantly ($P < 0.05$) reduce the activities of AHH and UDPGT in the small intestine mucosa of mice. In B[*a*]P-treated animals, AHH enzyme activities were increased in hepatic, pulmonary, and kidney tissues. FDS and FDMP fractions had no effect in modifying the enzyme activities in these animals. There were similar increases in AHH and UDPGT activities in the small intestinal mucosa of B[*a*]P-treated animals on FDS and FDMP diets. Our results indicate that the effect of both FDS and FDMP fractions on tissue xenobiotic metabolizing enzymes studied herein was limited to the small intestine.

INTRODUCTION

The Maillard browning reactions occur in food products that have been subjected to thermal treatment such as frying, baking, broiling, roasting, and steam retorting (Powrie *et al.*, 1986). The reactions include the interaction of amino acids with reducing sugars as well as sugar dehydration and fragmentation of the reducing sugars with the formation of aldehydes, ketones, furans, pyrroles, quinolines, and indoles. Many of the Maillard reaction products (MRP) contribute to the odor of the food products. In the final stages of the Maillard browning reactions, brown pigments (melanoidins) are formed through aldol condensations and polymerization of carbonyl compounds (Hodge, 1953; Benzing-Purdie and Ratcliffe, 1986; Powrie *et al.*, 1986). The melanoidins formed in the amino acid–reducing sugar systems have a wide range of molecular weights, ranging from about 290 to 14 200 (Motai, 1974; Benzing-Purdie and Ripmaster, 1983). Observations on the antioxidant activity of Maillard browning reaction products have been reported (Evans *et al.*, 1958), and it is presumed that carboxyl groups which are responsible for the low isoelectric points (pH 2.5) of melanoidin may also contribute to the antioxidant activity (Gomyo and Horikoshi, 1976).

The antinutritional and toxicological effects of dietary Maillard reaction products have been studied extensively in rodents (Lee *et al.*, 1977; Takeuchi *et al.*, 1987; O'Brien and Walker, 1988). Products from model Maillard reaction systems have been shown to induce reverse point mutation in bacteria assays and chromatid breaks and exchanges in cultured mammalian cells (Powrie *et al.*, 1981; Vagnarelli *et al.*, 1991; Kitts *et al.*, *1993*). Antimutagenic properties of MRP have been noted by Chan *et al.* (1982) and Kim *et al.* (1986). The antimutagenic activity of MRP may be attributed to the inhibition of mutagen activation, to the enhanced detoxification of reactive intermediates by modifying phase I and phase II xenobiotic enzyme activities (Pintauro and Lucchina, 1987), or to the adsorption of mutagens by MRP in the intestinal tract (Powrie *et al.*, 1986). Since MRP possess antioxidant properties (Kawashima *et al.*, 1977; Lingnert and Eriksson, 1981), such antioxidant activity may inhibit phase I benzo[*a*]pyrene (B[*a*]P) hydroxylation activity (Rahimtula *et al.*, 1977) and may enhance a detoxifying enzyme system (Bogaards *et al.*, 1990), with the result of reducing mutagenic activity. Although various fractions of MRP in model systems possess antioxidant activity, melanoidins have the greatest antioxidant effect (Yamaguchi *et al.*, 1981). Wu *et al.* (1987) have characterized the paramagnetic signals of

Table I. Composition of Experimental Diets

ingredient	level (%) of ingredient		
	control	FDS	FDMP
casein[a]	20	20	20
corn oil	5	5	5
nonnutritive fiber[b]	5	5	5
mineral mix[c]	3.5	3.5	3.5
vitamin mix[d]	1.0	1.0	1.0
choline bitartate	0.2	0.2	0.2
DL-methionine	0.3	0.3	0.3
cornstarch	14	14	14
sucrose	51	49	49
FDS[e]		2.0	
FDMP[f]			2.0

[a] Approximately 90% protein (Sigma Chemical Co., St. Louis, MO). [b] Alphacel, nonnutritive, bulk (ICN Nutritional Biochemicals, Cleveland, OH), containing finely ground cellulose. [c] AIN mineral mix 76 (ICN Nutritional Biochemicals). [d] AIN vitamin mixture 76 (ICN Nutritional Biochemicals). [e] FDS, freeze-dried supernatant. [f] FDMP, freeze-dried melanoidin precipitate.

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Table II. Effect of Chronic Feeding of Mice with Glucose–Lysine MRP Fractions on Liver Xenobiotic Enzyme Activities[a]

	specific activity or content					
	no B[a]P pretreatment			with B[a] pretreatment		
parameter	C	FDS	FDMP	C	FDS	FDMP
liver wt (g)	1.31 ± 0.7	1.27 ± 0.4	1.26 ± 0.5	1.28 ± 0.3	1.28 ± 0.5	1.28 ± 0.5
% Bwt	5.1	4.7	5.4	5.4	4.9	4.9
AHH	38.7 ± 5.5	34.6 ± 2.1	43.4 ± 7.3	78.4 ± 5.1[b]	86.4 ± 7.1[b]	99.6 ± 10.7[b]
UDPGT	2.08 ± 0.4	2.36 ± 0.2	2.28 ± 0.4	3.33 ± 0.3[b]	3.42 ± 0.1[b]	4.34 ± 0.4[b]
b_5	0.9 ± 0.02	0.6 ± 0.03	0.7 ± 0.03	0.8 ± 0.02	0.9 ± 0.03	0.7 ± 0.03
P-450	0.7 ± 0.06	0.6 ± 0.03	0.9 ± 0.05	0.8 ± 0.04	0.5 ± 0.04	0.9 ± 0.07
GST	243 ± 15.8	223 ± 19.5	250 ± 27.3	289 ± 38.5	253 ± 25	266 ± 9.2

[a] Data represent mean ± SD of 4 groups with 3 pooled animals per group; total is 12 animals/treatment. C, control; FDS, freeze-dried supernatant; FDMP, freeze-dried melanoidin precipitate; B(a)P, benzo[a]pyrene. Animals pretreated with B[a]P received a 50 mg/kg oral dose. Abbreviations: AHH, aryl hydrocarbon hydroxylase [nmol of B[a]P–OH (mg of protein)$^{-1}$ min^{-1}]; UDPGT, glucuronosyl transferase [nmol of naphthyl glucuronide (mg of protein)$^{-1}$ min^{-1}]; cytochrome b_5, [nmol of cytochrome b_5 (mg of protein)$^{-1}$]; P-450, cytochrome P-450 [nmol of P-450 (mg of protein)$^{-1}$]; GST, glutathione S-transferase [nmol of chlorodinitrobenzene conjugate min^{-1} (mg protein)$^{-1}$]. [b] Significantly different from corresponding non-B[a]P-treated animals ($P \leq 0.05$).

melanoidins which have been associated with antioxidant activity (Lingnert and Eriksson, 1981).

This study was designed to determine the effect of MRP fractions in the diet of mice, with and without B[a]P treatment, on the xenobiotic enzyme systems of the liver, kidney, lung, and small intestine tissues. Since polyaromatic hydrocarbons (PAHs) such as B[a]P exemplify xenobiotics that require metabolic transformation and can be detected in significant quantities in foods that have undergone a similar form of heat treatment known to catalyze the production of MRP, the potential toxicological significance of the interaction between B[a]P and MRP was also examined.

MATERIALS AND METHODS

Glucose–Lysine Browning Model System Preparation. A 1.0 M D-glucose and 1.0 M L-lysine (reagent grade) aqueous solution was adjusted to pH 9.0 and heated at 121 °C for 4.0 h in an autoclave. The cooled solution was adjusted to pH 7.0, and absolute ethanol was added to a level of 90% by volume. The ethanol reduced the dielectric constant of high molecular weight melanodins and caused aggregation and precipitation (Wu *et al.*, 1987). The ethanol suspension was centrifuged at 5000*g* for 10 min and the supernatant decanted. The supernatant (containing Maillard reaction intermediate compounds and low molecular weight melanoidins) and precipitate (high molecular weight melanoidins) were freeze-dried prior to their addition to the diet.

Animal Experiments. Female BALB/c mice, with initial body weights of 19–21 g (Charles River) were divided into 6 groups, each consisting of 12 mice per group. Three mice of the same group were housed in separate plastic cages with corncob granules as the bedding. One group of animals was divided into three treatments consisting of a control diet and diets containing 2% freeze-dried supernatant (FDS) and 2% freeze-dried melanoidin precipitate (FDMP), respectively. The second group of mice was treated with a single oral dose of B[a]P (50 mg/kg in corn oil) 18 h before sacrifice. Control animals in this treatment group were given corn oil only. The composition of experimental diets is presented in Table I. Animals were fed diets *ad libitum* for a 10-week period. All animals were weighed and sacrificed by cervical dislocation. Liver, lung, and kidney tissues were pooled from three animals, rinsed with cold isotonic KCl, and held at 0 °C before undergoing homogenization in 0.05 M Tris-HCl buffer (pH 7.8) containing 0.25 M sucrose at 0 °C. The small intestines from three animals were washed to remove lumenal contents and the mucosa scraped. The disrupted tissue from the three small intestines was homogenized in ice-cold 0.05 M Tris-HCl buffer (pH 7.8) containing trypsin inhibitor (Sigma; 5 mg/g wet weight intestinal tissue), heparin (3 units/mL), and glycerol (20% v/v). All samples were immediately centrifuged at 10000*g* for 15 min at 4 °C to remove cell debris. Each supernatant was ultracentrifuged at 121000*g* for 1.5 h at 4 °C and the microsomal pellet immediately suspended in 0.1 M phosphate buffer (pH 7.5). The precipitated microsomes and the supernatant cytosol were stored at −70 °C until analyzed.

Enzyme Assays. Cytochrome P-450 was determined from the dithionite-reduced carbon monoxide difference spectra with a molecular extinction coefficient of 91 cm^{-1} mM^{-1} (Omura and Sato, 1964). Cytochrome b_5 was measured from the NADH-reduced difference spectra with 171 cm^{-1} mM^{-1} as the extinction coefficient (Omura and Sato, 1964). Aryl hydrocarbon hydroxylase (AHH) activity was measured by the fluorometric procedure of Nebert and Gelboin (1968). Microsomal UDPglucuronyltransferase (UDPGT) activity was determined by the method of Block and White (1974) using 1-naphthol as the acceptor. Cytosolic glutathione S-transferase (GST) activity was measured according to the method of Habig *et al.* (1974) using 1-chloro-2,4-dinitrobenzene as the substrate. The cytosolic and microsomal protein contents were determined by the modified Lowry procedure (Markwell *et al.*, 1978). For each treatment and control group, all assays were performed in duplicate on the pooled (three mice) samples from each of the four replicate groups of mice. Standard deviations (SD) were calculated between animals within each treatment exposure. Data were analyzed by Student's *t*-test and *P* values obtained in comparison to the control.

RESULTS AND DISCUSSION

Average body weights of mice fed the freeze-dried supernatant (FDS) fraction and the freeze-dried melanoidin (FDMF) were 23.0 ± 0.5 and 26.7 ± 0.6 g, respectively, and similar to the average weight of control animals of 25.4 ± 0.3 g after 10 weeks of feeding. In animals pretreated with B[a]P, the average body weights of animals on diets of FDS and FDMP were 26.8 ± 0.7 and 26.2 ± 0.3 g, respectively, compared to the average weight of 26.8 ± 0.7 g in control animals pretreated with B[a]P. Liver, kidney, intestine, and lung to body weight ratios in animals fed each MRP fraction were similar to those for control animals (Tables II–V). These results are in agreement with other studies on animals fed similar levels of melanoidins (Takeuchi *et al.*, 1987) but contrary to the reported depressed growth of mice fed much higher amounts of melanoidins (Lee *et al.*, 1977; O'Brien and Walker, 1988). Other workers have reported depressed protein digestibility and absorption in rats fed low molecular weight melanoidins (Oste and Sjodin, 1984), whereas the high molecular weight melanoidins had little effect on the growth rate of animals (Olsson *et al.*, 1981).

The presence of two MRP fractions in diets of mice had little effect on liver microsomal protein content and AHH and UDPGT enzyme activities (Table II). Pintauro and Lucchina (1987) have reported significant increased hepatic AHH activity in animals fed Maillard brown egg albumin. This effect was not observed in animals fed hydrolyzed Maillard browned egg albumin. These workers attributed the different effects of the hydrolyzed and unhydrolyzed brown albumin to the breakdown of Maillard

Table III. Effect of Chronic Feeding of Mice with Glucose–Lysine MRP Fractions on Kidney Xenobiotic Enzyme Activities[a]

	specific activity or content					
	no B[a]P pretreatment			with B[a]P pretreatment		
parameter	C	FDS	FDMP	C	FDS	FDMP
kidney wt (g)	0.33 ± 0.7	0.30 ± 0.4	0.30 ± 0.2	0.32 ± 0.07	0.32 ± 0.04	0.32 ± 0.07
% Bwt	1.29	1.12	1.30	1.35	1.19	1.14
AHH	3.6 ± 1.4	1.5 ± 0.4	3.1 ± 0.8	8.1 ± 1.7[b]	8.7 ± 1.9[b]	13.0 ± 4.6[b]
UDPGT	2.6 ± 0.7	2.0 ± 2.0	2.0 ± 0.4	1.6 ± 0.8	2.5 ± 0.4	1.7 ± 0.4
GST	38.6 ± 4.4	27.9 ± 7.5	34.0 ± 3.3	44.9 ± 6.3	39.5 ± 4.1	36.6 ± 9.2

[a] Data represent mean ± SD of 4 groups with 3 pooled animals per group; total is 12 animals/treatment. C, control; FDS, freeze-dried supernatant; FDMP, freeze-dried melanoidin precipitate; B[a]P, benzo[a]pyrene. Animal pretreated with B[a]P received a 50 mg/kg oral dose. Abbreviations: AHH, aryl hydrocarbon hydroxylase [pmol of B[a]P–OH min^{-1} (mg of protein)$^{-1}$]; UDPGT, glucuronosyl transferase [nmol of naphthyl glucuronide min^{-1} (mg of protein)$^{-1}$]; GST, glutathione *S*-transferase [nmol of chlorodinitrobenzene conjugate min^{-1} (mg of protein)$^{-1}$]. [b] Significantly different from corresponding non-B[a]P-treated animals ($P \leq 0.05$).

Table IV. Effect of Chronic Feeding of Mice with Glucose–Lysine MRP Fractions on Lung Xenobiotic Enzyme Activities[a]

	specific activity or content					
	no B[a]P pretreatment			with B[a]P pretreatment		
parameter	C	FDS	FDMP	C	FDS	FDMP
lung wt (g)	0.23 ± 0.02	0.23 ± 0.02	0.26 ± 0.03	0.28 ± 0.03	0.25 ± 0.02	0.25 ± 0.03
% Bwt	0.91	1.0	0.97	1.02	1.05	0.95
AHH	23.7 ± 3.4	29.5 ± 6.3	33.1 ± 8.8	98.3 ± 11.2[b]	134.7 ± 29[b]	86.0 ± 14.0[b]
UDPGT	6.7 ± 0.9	4.0 ± 1.4	6.0 ± 1.5	8.6 ± 2.8	6.9 ± 0.4	5.7 ± 0.8
GST	25.7 ± 5.6	23.9 ± 4.4	31.0 ± 5.6	32.9 ± 7.4	28.5 ± 4.5	36.5 ± 5.92

[a] Data represent mean ± SD of 4 groups with 3 pooled animals per group; total is 12 animals/treatment. C, contro; FDS, freeze-dried supernatant, FDMP, freeze-dried melanoidin precipitate; B[a]P, benzo[a]pyrene. Animal pretreated with B[a]P received a 50 mg/kg oral dose. Abbreviations: AHH, aryl hydrocarbon hydroxylase [pmol of B[a]P–OH min^{-1} (mg of protein)$^{-1}$]; UDPGT, glucuronosyl transferase [nmol of naphthyl glucuronide min^{-1} (mg of protein)$^{-1}$]; GST, glutathione *S*-transferase [nmol of chlorodinitrobenzene conjugate min^{-1} (mg of protein)$^{-1}$]. [b] Significantly different from corresponding non-B[a]P-treated animals ($P < 0.05$).

Table V. Effect of Chronic Feeding of Mice with Glucose–Lysine MRP Fractions on Intestine Xenobiotic Enzymatic Activities[a]

	specific activity or content					
	no B[a]P pretreatment			with B[a]P pretreatment		
parameter	C	FDS	FDMP	C	FDS	FDMP
SI (g)	1.15 ± 0.4	1.33 ± 0.9	1.34 ± 0.8	1.29 ± 0.9	1.32 ± 0.6	1.35 ± 0.6
% Bwt	4.5	5.6	5.8	4.9	5.1	5.1
AHH	18.6 ± 0.5	5.6 ± 0.4[c]	8.1 ± 0.8[c]	28.1 ± 1.4[b]	16.4 ± 1.7[b,c]	19.9 ± 0.7[b,c]
UDPGT	13.1 ± 1.4	8.1 ± 1.2[c]	7.8 ± 1.4[c]	16.3 ± 2.3	14.7 ± 0.7[b]	13.8 ± 1.3[b]
P-450	23.8 ± 7.8	14.9 ± 5.9	17.5 ± 9.0	41.7 ± 19	19.7 ± 8.9	15.9 ± 7.41
GST	26.6 ± 5.8	17.9 ± 2.5	19.0 ± 3.3	28.9 ± 8.5	26.5 ± 5.0	31.6 ± 4.9

[a] Data represent mean ± SD of 4 groups with 3 pooled animals per group; total is 12 animals/treatment. SI, small intestine; C, control; FDS, freeze-dried supernatant; FDMP, freeze-dried melanoidin precipitate; B[a]P, benzo[a]pyrene. Animals pretreated with B[a]P received a 50 mg/kg oral dose. Abbreviations: AHH, aryl hydrocarbon hydroxylase [nmol of B[a]P–OH (mg of protein)$^{-1}$ min^{-1}]; UDPGT, glucuronosyl transferase [nmol of naphthyl glucuronide (mg of protein)$^{-1}$ min^{-1}]; P-450, pmol (mg of protein)$^{-1}$; GST, glutathione *S*-transferase [nmol of chlorodinitrobenzene conjugate min^{-1} (mg of protein)$^{-1}$]. [b] Significantly different from corresponding non-B[a]P-treated animals ($P < 0.05$). [c] Significantly different from corresponding treatment control animals.

reaction products to intermediates with potentially different affinities to stimulate xenobiotic enzyme activity.

Insignificant changes in kidney (Table III) and lung (Table IV) xenobiotic enzyme activities were observed in mice fed either one of the MRP fractions. Other workers have shown only a small degree of accumulation of low molecular weight melanoidin in kidneys (Nair *et al.*, 1981; Takeuchi *et al.*, 1987), thus suggesting that the lack of a potential effect of melanoidins on xenobiotic enzyme activity in the kidney was limited by the amount of melanoidin deposited in this organ. In previous studies, pulmonary AHH activity has been shown to be reduced in mice fed dietary phenolic compounds with antioxidant activity, such as ellagic acid (Das *et al.*, 1985). A similar effect was not obtained with either the FDS or FDMP fraction in this study. The fact that melanoidin fractions had no effect on lung xenobiotic activity in both B[a]P-treated and untreated mice is again likely due to the lack of uptake by lung tissues (Nair *et al.*, 1981).

A significant ($P < 0.05$) reduction in intestinal mucosal AHH and UDPGT enzyme activities was observed in animals fed either the FDS or FDMP fraction (Table V). The action of MRP fractions to decrease the specific intestinal xenobiotic enzyme activities, not observed in other tissues, could be attributed to its limited absorption from the intestine. Nondialyzable melanoidins are excreted to a large extent in the fecal matter (Takeuchi *et al.*, 1987; O'Brien and Morrissey, 1989) because of the existence of a melanoidin gel that is formed under the low pH levels of the stomach contents and the effect of microbial action in the intestine (Gomyo and Miura, 1986).

The decrease in intestinal AHH activity corresponding to no change in GST activity and a decline in UDPGT conjugating activity suggests that the presence of polymeric brownish pigments in the diet may have reduced the production of potential electrophilic compounds, but at the expense of lowering the host's ability to detoxify xenobiotics. Cytosolic GST activity is an important detoxifying phase II enzyme system and associated with anticarcinogenic effects in the small intestine (Bogaards *et al.*, 1990). It is not known to what extent the lower intestinal AHH and UDPGT activities are related to

changes in mucosal morphology and undernutrition of enterocytes, reflected in various forms of intestinal disorders (Hoensch *et al.*, 1979). Animals fed melanoidins have been shown to exhibit changes in intestinal morphology (Gomyo and Miura, 1986; O'Brien and Walker, 1988) which could feasibly affect xenobiotic enzymes or associated availability of cofactors that are contained in the surface of mucosal crypt cells.

The oral administration of B[*a*]P to mice resulted in significant increases in AHH activity in liver (Table II), kidney (Table III), lung (Table IV), and intestine (Table V). With the exception of the small intestine, dietary intake of both MRP fractions had no significant effect in lowering AHH activity. The lack of effect of MRP fractions to modulate the increased xenobiotic enzyme activity induced by B[*a*]P in the said tissues does not support the thought that carbonyl groups present on melanoidin compounds are antimutagenic when in the presence of B[*a*]P (Chan *et al.*, 1981; Kim *et al.*, 1986). Our results, however, make it possible to exclude a role for MRP including melanoidins in enhancing the metabolic activation of B[*a*]P in these vital organs.

Previous studies have demonstrated the effect of a number of dietary antioxidants on B[*a*]P hydroxylation enzyme activity, the *in vitro* conversion to mutagenic substances in hepatic tissues (Rahimtula *et al.*, 1977) and *in vivo* inhibition of B[*a*]P-induced neoplasia of the forestomach in mice (Wattenberg, 1972). Antioxidants, such as butylated hydroxyanisole and propylgallate, are classified as free radical terminators that interfere with metabolic activation of the precarcinogen or its binding of carcinogen to DNA. Xenobiotic compounds, including carcinogens, are metabolically activated by free radical reactions by P-450 isoenzyme components of the monooxygenase enzyme system (Nebert and Gelboin, 1968; Pelkononen and Nebert, 1982). Melanoidin fractions have been found to have antioxidant properties (Yamaguchi *et al.*, 1981; Lingnert *et al.*, 1983). With paramagnetic resonance spectrometry, it has been shown that similar melanoidin fractions derived from a gluc–lys model system, used in this study, possessed stable free radicals (Wu *et al.*, 1987). Taken together, this suggests that the reported antioxidant properties of different melanoidin fractions may have a potential anticarcinogenic property by inhibiting cytochrome P-450 enzymes. The data in the present study indicate that although the oral feeding of MRP fractions had no appreciable effect on hepatic, kidney, pulmonary, or intestinal P-450 activity, there was a significant effect in reducing the AHH activity in the small intestine of B[*a*]P-pretreated and normo-treated animals. The fact that AHH is predominantly dependent on cytochrome P-448 indicates that MRP fractions may have altered intestinal cytochrome P-450 isoenzyme composition. Additional studies are required to measure the effect of MRP fractions on B[*a*]P excretion patterns to confirm the noted changes observed with intestinal xenobiotic enzyme activities.

CONCLUSION

In this study, the effect of two MRP fractions on individual toxin metabolizing enzymes was examined in both B[*a*]P-treated and untreated mice. B[*a*]P was chosen as the xenobiotic agent because it requires metabolic transformation (Pelkononen and Nebert, 1982) prior to eliciting a potential carcinogenic response. Moreover, B[*a*]P can be detected in significant quantities in foods which have undergone a similar form of heat treatment known to catalyze the production of MRP. Thus, the interaction between B[*a*]P and MRP may have significant toxicological importance. The physiological effect of MRP in modifying AHH activity in particular was found only in the small intestinal mucosa of mice. Our observations lend support to the theory that MRP including melanoidins may provide some degree of bioactivity *in vivo*, which may contribute to a natural chemotherapeutic property important for protection against chemical carcinogens present in the gastrointestinal tract.

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