CYP1A2-catalyzed Conversion of Dietary Heterocyclic Amines to Their Proximate Carcinogens Is Their Major Route of Metabolism in Humans

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ABSTRACT

The contribution of CYP1A2 to the metabolism of the dietary heterocyclic amines, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and 2-amino-3,8-dimethylimidazo[4,5-f]quinonoxaline (MeIQx) in vivo in humans, has been determined with furafylline, a highly selective inhibitor of thi enzyme. The inhibitory potential of furafylline in vivo was first assessed by determining its effect on clearance of phenacetin to paracetamol by the model CYPIA2-dependent O-deethylation pathway. Furafylline inhibited this reaction by >99% in all subjects, thus demonstrating its applicability to determining the contribution of CYP1A2 to a given reaction in vivo. A group of 6 healthy male volunteers received either placebo or 125 mg furafylline, in a double-blind balanced crossover design, 2 h prior to consuming a test meal of fried beef containing a known amount of amines. The excretion of PhIP and MeIQx in urine was determined during the subsequent 28 h, using gas chromatography-mass spectrometry. Following furafylline, the excretion of unchanged MeIQx increased 14.3-fold, while that of PhIP increased 4.1-fold (P < 0.01, paired t test). Elimination of both amines was first order and very rapid, with half-lives of <5 h. The elimination rate constants did not change following furafylline, suggesting that total clearance is limited by hepatic blood flow. Because the elimination of the amines was first order, it was possible to calculate the contribution of CYP1A2 to the clearance of the amines. CYP1A2-catalyzed metabolism accounts for 91% of the elimination of ingested MeIQx and 70% of ingested PhIP, most likely via N-hydroxylation.

INTRODUCTION

Although a causal relationship between exposure to the majority of environmental carcinogens and human cancers has yet to be established, it is widely accepted that there is an association between diet and cancer (1) and, more recently, a growing consensus for an association between the consumption of red meat (2), particularly the “doneness” of the meat (3), and some forms of cancer in humans. During the cooking process a number of genotoxic compounds are formed from endogenous constituents of meat (4), and among these are various HA (5, 6). Three of the most abundant amines, PhIP, MeIQx, and DiMeIQx, are imidazoazarenes which are present at levels of 10–50 ng/g for PhIP and 1–2 ng/g cooked beef for MeIQx and DiMeIQx (5–8). Each compound accounts for about 20% of the total mutagenic potential of fried beef (5), and in rodent bioassays, PhIP and MeIQx are carcinogens, inducing tumors in a variety of tissues (9–13), including in the case of PhIP the colon and mammary glands (14). However, little is known about the fate of these compounds in man or the factors affecting it.

In common with other genotoxic carcinogens, cooked meat HA require metabolic activation before they are mutagenic or carcinogenic (15–17). In rodents, there is evidence that the major activating step is N-hydroxylation, catalyzed by members of the polycyclic aromatic hydrocarbon-inducible CYP1A subfamily, CYP1A1 and CYP1A2 (18, 19). It has been widely assumed that the activation of HA in humans also proceeds via N-hydroxylation and that this is catalyzed mainly by CYP1A2 (20–25); however, until recently direct evidence for this was lacking. Studies in vitro have now shown that the oxidation of both PhIP and MeIQx by human liver proceeds almost entirely via N-hydroxylation and that this is catalyzed virtually exclusively by CYP1A2 (24, 25). Clearly, susceptibility to the carcinogenicity of these compounds will, to some extent, depend on the presence and activity of the enzymes responsible for their activation. The expression, activity, and specificity of orthologous forms of P450 are species dependent. Comparison of rat, primate, and human hepatic microsomal fractions reveals that human liver is particularly active in catalyzing HA activation; indeed, the specific reversion rates induced by HA in the Ames/Salmonella assay for rat liver are only comparable to those of human liver after rats are treated with aromatic hydrocarbon inducers (e.g., 3-methylcholanganthrene). CYP1A2 is inducible and exhibits tissue-specific distribution, being confined largely to the liver (26). In rodents, other oxidative pathways, which lead to harmful elimination of HA, compete with the N-hydroxylation pathway (27, 28), whereas from studies in vivo such pathways appear to be of little significance in humans. In addition, the relative risk posed to humans by HA, determined by rodent carcinogenicity studies, is likely to be an underestimate as a consequence of reduced metabolism relative to dose due to saturation of metabolism at high doses (29, 30). Therefore, it is essential to determine the contribution of CYP1A2-catalyzed oxidation to the elimination of these compounds in man, in vivo, at doses encountered on a normal diet.

The results of previous studies in vivo have suggested that the methylxanthine derivative, furafylline, inhibits CYP1A2, as shown by a reduction in the clearance of caffeine (31). It was later confirmed in vitro that furafylline is indeed a very potent and specific inhibitor of CYP1A2-catalyzed reactions, such as the N3-demethylation of caffeine in human liver (32). Furafylline is at least 1000-fold more potent than theophylline in human liver (32). Furafylline is at least 1000-fold more potent an inhibitor of CYP1A2 than of any other form of P450 in humans. However, the extent to which furafylline inhibits CYP1A2-mediated metabolism in man in vivo was not known. In this paper, phenacetin, which is a model substrate for CYP1A2 in animals (33) and in man (34), was used to determine quantitatively the extent of furafylline inhibition of CYP1A2 in humans in vivo. Phenacetin is 100% bioavailable but is extensively cleared by hepatic presystemic O-deethyllylation to its major metabolite paracetamol by CYP1A2 (31). Thus, total body clearance after an oral dose represents the intrinsic clear-

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3 The abbreviations used are: HA, heterocyclic amines; MeIQx, 2-amino-3,8-trimethylimidazo[4,5-f]quinonoxaline; furafylline, 1,8-dimethyl-3-(2’-furyl)methylxanthine; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinonoxaline; PhIP,paracetamol, N-(4-hydroxyphenyl)-N,N-dimethyleacetamide; PhIP, N-(4-hydroxyphenyl)-N,N-dimethyleacetamide; phenacetin, 4-ethoxyacetanilide; PNP, 2-amino-1-ethyl-6-phenylimidazo[4,5-b]pyridine; GC-MS, gas chromatography mass spectrometry; AUC, area under the plasma concentration-time curve.
rance, largely by CYP1A2, and as such provides a good measure of the activity of this enzyme. The metabolism of phenacetin in humans, following oral administration, is dose dependent, and in nonsmoking individuals, the intrinsic clearance of phenacetin becomes saturated at subtherapeutic doses of the drug (≤900 mg) (35). Cigarette smoking causes an approximate 3-fold increase in the content of CYP1A2 in human liver (36), with a corresponding increase in the O-deethylation of phenacetin, both in vitro and in vivo in humans. Hence, following the administration of a low dose of phenacetin (~100 mg) to cigarette smokers, CYP1A2-catalyzed oxidation would account for the elimination of essentially all of the drug.

We report the novel use of furafylline as a pharmacological probe to determine the contribution of CYP1A2-dependent activity to the primary metabolism of the dietary mutagens PhIP and MeIQx following consumption of a cooked beef meal in healthy volunteers, using GC-MS analysis of unchanged amines in urine as a measure of their relative clearance (8). This study provides the first quantitative data concerning the primary metabolism of MeIQx and PhIP in humans in vivo.

**MATERIALS AND METHODS**

**Chemicals**

Phenacetin and paracetamol were obtained from BDH (Poole, United Kingdom) and $N$-(4-hydroxyphenyl)trideuteracetamide ($[^{13}C_3]$paracetamol) was synthesized as described elsewhere (37). Type H1 sulfatase was obtained from Sigma Chemical Co., Ltd. (Poole, United Kingdom). Furafylline was obtained from Laboratorios Almirall (Barcelona, Spain).

**Clinical Studies**

Clinical studies were conducted at the Institut Municipal d’Investigació Mèdica (Barcelona, Spain) where Local Ethical Committee approval and written informed consent from each volunteer were obtained before starting.

**Study 1: Effects of Furafylline on the O-Deethylation of Phenacetin.**

Eight healthy male volunteers (age, 24.3 ± 1.6 years; weight, 71.6 ± 5.1 kg; mean ± SD) who smoked between 10 and 30 cigarettes/day (median, 18) were asked to refrain from taking any other drugs for at least 7 days before the study and to abstain from alcohol- or xanthine-containing beverages 24 h before beginning the study. At time 0, subjects received a single oral dose of either 125 mg furafylline or placebo in a double-blind balanced crossover design, followed 4 h later by a single oral dose of 100 mg phenacetin. The study was repeated 14 days later when the same subjects received the other treatment. Blood samples from a peripheral vein were collected at frequent intervals for the first 8 h and then less frequently up to 24 h after the dose of furafylline and stored at −20°C until analysis. In addition, all urine was collected at regular intervals during this period, the volume was measured, and 50-ml samples were retained and stored at −20°C.

Partial clearance of phenacetin to paracetamol was calculated only when urine collections were complete.

**Study 2: Effects of Furafylline on Urinary Excretion of Imidazopyrazines following Ingestion of a Cooked Meat Meal.**

Six male volunteers (age, 24.3 ± 3.2 years; weight, 68.9 ± 3.0 kg; mean ± SD; all nonsmokers) received an oral dose of 125 mg furafylline or placebo in a double-blind balanced crossover study and 2 h later were invited to consume a standard cooked beef meal. The two legs of the study were separated by a 14-day washout period. Subjects were requested not to eat red meat/meat products, fish, or fried foods for 24 h before the study or to drink alcohol- or xanthine-containing beverages such as tea, coffee, and cola (there were no other dietary restrictions). On the study day, subjects were requested to fast until the test meal. Before taking furafylline/placebo, subjects were required to void their bladders and to collect a control sample of urine (50 ml). Lean rump beef steak (≈400 g/person) was coarsely minced and molded into 4 equal-sized patties (diameter, ~9 cm; depth, 2 cm). The meat was cooked on a grill hotplate (without added fat or oil) for 10–15 min at 200–250°C until well browned. After the meat was cooked, a portion of each patty was removed and stored at −20°C for subsequent analysis; the remaining meat was consumed. The subjects then consumed the cooked meal together with water (≈400 ml).

the test meal was eaten, subjects were requested not to consume additional food or drink for 6 h and no meat products, fish, or fried foods for 2 days. Urine was collected every 2 h for 12 h and then from 12–24 h and 24–28 h; the volumes were measured and =50-ml samples retained. These were stored at −20°C until analysis.

**Analytical Methods**

**Analysis of Furafylline in Plasma.** Blood samples were taken by venipuncture at appropriate times during the study and transferred to heparinized glass tubes. After the blood was centrifuged, plasma was removed by pipette and stored at −20°C. Plasma samples were then analyzed for furafylline content using the method of Tarus et al. (31, 38).

**Analysis of Phenacetin and Paracetamol in Plasma.** An assay for the simultaneous analysis of phenacetin and paracetamol in plasma using GC-MS has been developed and is reported in detail elsewhere (37). The mass spectrometer was operated in the electron capture negative ion chemical ionization mode with ammonia as the reagent gas. Phenacetin, paracetamol, and the deuterated analogues serving as internal standards were analyzed as their trifluoroacetyl derivatives.

**Analysis of Total Paracetamol in Urine.** The method used to measure paracetamol in urine was a modification of a GC-MS assay originally developed for the analysis of paracetamol in microosomal incubations (39). Each urine sample (20 μl), diluted with deionized water (480 μl), was incubated with a solution of type H1 sulfatase (100 units), which also contained β-gluconuridase (1200 units) in 0.2 M acetate buffer (500 μl, pH 5.5), in a heated water bath at 37°C for 16 h. After this, [3H]paracetamol (1 μg) in methanol (100 μl) was added to each sample and the latter thoroughly mixed by vortex agitation. Samples were then extracted with diethyl ether (8 ml), the ether extracts were evaporated to dryness under nitrogen, and the residues were derivatized as described elsewhere (39). Paracetamol and its deuterated analogue were analyzed as their 3,5-bistrifluoroacetylmethylbenzoyl derivatives, and the mass spectrometer was operated in the electron capture negative ion chemical ionization mode with ammonia as the reagent gas. Quantification was achieved by reference to unextracted standard curves covering a range of 0–1.5 μg paracetamol.

**Analysis of MeIQx, DiMeIQx, and PhIP in Cooked Meat and Urine.** Methods for the analysis of MeIQx, DiMeIQx, and PhIP in cooked meat and urine using GC-MS have been described and are reported in detail elsewhere (8). Stable isotope-labeled analogues of MeIQx and PhIP were used as internal standards, and the mass spectrometer was operated in the electron capture negative ion chemical ionization mode with ammonia as the reagent gas. The amines were chromatographed as their di-3,5-bistrifluoroacetylmethylbenzoyl derivatifs, and all three compounds could be measured in a single chromatographic run.

**Expression of Results and Statistical Analysis.** Total body clearance (CL) of phenacetin was calculated from the relationship:

\[
CL = \frac{F \cdot \text{Dose}}{AUC_{\infty}}
\]

where F is the fraction of the dose absorbed (which is complete and therefore = 1), and AUC is calculated by the trapezoidal rule from 0 to 20 h after administration of phenacetin, with extrapolation to infinity.

Partial clearance to paracetamol was estimated from the relationship:

\[
CL_{\text{par}} = CL \times P_{\text{par}}
\]

where \( P_{\text{par}} \) is the fraction of the dose excreted in the urine from 0–20 h as paracetamol and its conjugates. It was assumed that excretion was complete at 20 h.

The amounts of PhIP and MeIQx ingested and excreted by each individual were calculated using the data for the meat and urine samples for that individual, and then urinary amine excretion was expressed as a percentage of the estimated ingested dose of amine. The elimination rate constants for the amines were determined by nonlinear iterative regression analysis of plots of the excretion rates of the amines against the midpoint of the collection intervals. Half-lives were obtained from the expression 0.693/k, where k is the elimination rate constant. Statistical analysis was performed using Statgraphics (version 5) statistical software package (STSC Inc., Rockville, MD).
RESULTS AND DISCUSSION

Following administration of furafylline, plasma levels of the inhibitor increased to >2.3 \( \mu \)g/ml in all subjects (range, 2.4–4.1 \( \mu \)g/ml) within 15 min and remained >1.6 \( \mu \)g/ml in all subjects throughout the 24-h duration of the study (Fig. 1a). The half-life of furafylline was 42.7 ± 14.5 h (mean ± SD, data not shown) and is in agreement with previous observations (31). Hence, throughout the study, the plasma concentration of furafylline was at least 10-fold greater than its \( K_i \) for inhibition of phenacetin \( O \)-deethylation to paracetamol, as determined in vitro with human hepatic microsomal fraction (\( K_i = 0.18 \mu \)g/ml) (32). Following administration of furafylline, the mean peak plasma concentrations of phenacetin were almost 100-fold greater than those following placebo, whereas the time to peak was ≈2 h later (Fig. 1b). The AUC for phenacetin increased >200-fold following the administration of furafylline, from 14.2 ± 8.7 ng/ml/h on placebo to 3490 ± 2410 ng/ml/h (mean ± SD, Table 1). As expected, following placebo administration, the total body clearance of phenacetin was very high (178 ± 118 liters/min, mean ± SD), because all of the subjects were cigarette smokers. Following treatment with furafylline, phenacetin clearance was markedly reduced in all subjects, to less than hepatic blood flow in most subjects (0.82 ± 0.83 liters/min), and was only 0.52 ± 0.35% of the control value (Table 1). The partial clearance to paracetamol showed a corresponding decrease. Because the recovery of phenacetin as paracetamol (free and conjugated) in the plasma and urine did not change following furafylline treatment (data not shown), the effect of the xanthine must have been on metabolism rather than absorption. Hence, in humans in vivo furafylline inhibits 99.5% of CYP1A2-dependent activity, consistent with results in vitro, demonstrating the utility of the xanthine as a specific probe with which to determine the contribution of CYP1A2 to the metabolism of drugs/chemicals of toxicological interest in vivo in humans.

The amounts (ng/g) of PhlP, MelQx, and DiMelQx present in all cooked beef samples were: PhlP, 21.5 ± 3.4; MelQx, 1.9 ± 0.2; and DiMelQx, 0.5 ± 0.1 (mean ± SEM; \( n = 12 \) test meals). There were no significant variations in the total amounts of amines in cooked meat ingested following placebo and furafylline treatments (\( P > 0.05, \) paired Student’s \( t \) test). The data for the meat content of MelQx and DiMelQx are consistent with those reported previously, as was the ratio of MelQx:DiMelQx (3:1) (8). Although the levels of PhlP were slightly higher than those observed previously (21.5 of 16.4 ng/g cooked meat), this was not significant (\( P > 0.2, \) unpaired Student’s \( t \) test).

The relative clearances of PhlP, MelQx, and DiMelQx were assessed from the percentages of ingested amines excreted unchanged in the urine. No PhlP, MelQx, or DiMelQx could be detected in control urine samples collected from volunteers before taking furafylline or placebo, following abstention from meat and fish products for 24 h. We have previously shown that virtually all urinary excretion of unchanged PhlP and MelQx normally occurs within 8 h of ingestion (8). To allow for possible prolongation of urinary elimination of unchanged dietary amines following furafylline treatment, urine was collected for 28 h after consumption of the test meal. During this period there was no change in mean diurnal fluctuation of urinary pH or specific gravity following treatment with furafylline compared with placebo (data not shown). Following treatment with placebo, all unchanged MelQx was eliminated within 8 h in all subjects but one, and PhlP elimination was complete within 12 h, whereas DiMelQx could not be detected (Fig. 2), thus confirming our previous observations (8).

Following furafylline treatment, mean levels of unchanged MelQx and PhlP in urine peaked at 8 h. PhlP was detectable until 24 h, and MelQx was detectable until 28 h (Fig. 2). However, as with placebo, no DiMelQx could be detected in any of the urine collections. The urinary excretion of MelQx and PhlP, expressed as a percentage of the estimated dose ingested, for each subject is shown in Table 2. Subjects treated with placebo excreted 2.6 ± 1.3% (average ± SD) of the MelQx and 1.2 ± 0.8% of the PhlP as unchanged amine in the urine during the entire collection period (Fig. 3), which is in agreement with our previous data (8). Following treatment with furafylline, the amount of unchanged amine excreted in urine increased in all subjects, to 31.2 ± 14.8% for MelQx (\( P < 0.01, \) Student’s \( t \) test, 95% confidence limit) and 4.2 ± 2.1% for PhlP (\( P < 0.01 \)).
These results represent an average 14.3-fold increase in the urinary excretion of MelQx and a 4.1-fold increase of PhlP following treatment with furafylline and show that CYP1A2 plays a significant role in the primary oxidative metabolism of MelQx and PhlP in humans. Plots of the urinary excretion rates of MelQx and PhlP against the midpoints of the collection intervals were monoexponential following placebo treatment and, in all of the subjects, following furafylline (data not shown). Hence, the elimination of the amines is first order.

Furthermore, these data show that furafylline does not affect the renal clearance of the amines and that this is not urine flow dependent. Therefore, it was possible to calculate the quantitative contribution of CYP1A2-catalyzed activity, putatively N-hydroxylation, to the elimination of MelQx and PhlP. When elimination is first order, the renal clearance of a compound equals the ratio of the amount excreted at infinity to the AUC. Hence, the fraction of the dose eliminated at infinity represents the ratio of the renal clearance to the total clearance. If the renal clearance does not change, as appears to be the case with MelQx and PhlP, the increase in the fraction of the dose excreted unchanged is inversely proportional to the decrease in the total clearance. For MelQx, the amount of amine excreted unchanged in the urine following furafylline administration increases by 14.3 ± 6.9-fold (mean ± SD). It is assumed that this reflects a corresponding increase in the AUC, then the clearance of MelQx by the inhibitable pathway must be 90.8 ± 5.7% of the total clearance (values were calculated for each subject and then averaged) in the absence of furafylline. But it is known that 2.6 ± 1.3% of the dose is eliminated via the kidneys, so that only 6.6 ± 5.7% of the dose is normally eliminated by other routes of metabolism, most likely via conjugation (29, 30). For PhlP, the increase in excretion of unchanged amine following furafylline treatment is 4.1 ± 2.2-fold, which corresponds to a reduction in clearance by 69.9 ± 14.7%, which again reflects the normal contribution of the CYP1A2-catalyzed pathway to the elimination of this compound. Other routes of metabolism, most likely conjugation, would then account for 28.9 ± 14.7% of PhlP elimination (including

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1.2% via renal excretion). From the elimination rate plots it can be estimated that the half-life of MelQx is normally 3.4 h, and this shows very little change following furafylline (3.1 h). Similarly, the half-life of PhIP following furafylline (4.6 h) is not very different from that following placebo (3.6 h). These short half-lives are consistent with the rapid elimination of the amines in the urine. The data also suggest that the elimination of both MelQx and PhIP is limited by hepatic blood flow.

From studies conducted in vitro it is known that the oxidation of MelQx and PhIP by human hepatic microsomal fractions results predominantly (>90%) in the formation of the respective N-hydroxy-amine. This reaction is catalyzed almost entirely by CYP1A2. In the present paper we have described a novel approach to defining the role of this enzyme in the elimination of these two potential human dietary carcinogens in vivo. The data show that both MelQx and PhIP are subject to extensive N-hydroxylation, accounting for an average of >90% of the elimination of MelQx and 70% of the elimination of PhIP. The lack of effect of furafylline on the half-lives of the amines suggests that metabolism is largely presystemic. CYP1A2 is largely a hepatic specific enzyme. Hence, activation of both PhIP and MelQx must occur predominantly in the liver, although this does not exclude a low level of local activation, particularly where forms of P450 such as CYP1A1 are induced by, for example, cigarette smoking.

N-hydroxy PhIP is a direct-acting mutagen (27), whereas N-hydroxy MelQx requires further metabolism, e.g., O-acetylation, before it is mutagenic. Nevertheless, further metabolism of N-hydroxy PhIP increases its mutagenicity considerably. Previous studies have shown that human liver and colon preparations are both able to catalyze the O-acetylation of hydroxylamines to their ultimate genotoxic forms in vitro (20). Unlike the situation in rodents, in humans in vivo almost all of the ingested dose of MelQx and a large proportion of ingested PhIP is converted to a form suitable for further metabolism to the ultimate carcinogenic species. The results of the present study suggest that the activity of CYP1A2 may be a major susceptibility factor in human diet-associated cancers of the colon and possibly of other tissues such as the breast.

MelQx and PhIP are the most abundant bacterial mutagens formed during the cooking of beef, on the basis of mass and specific retention rate (5). In view of the significant association between eating cooked meat and the occurrence of a number of tumor types in humans, particularly of the colon (2), this would suggest that these amines may play an important role in diet-related carcinogenesis in humans. If this is the case, efforts must be made to coordinate strategies which reduce exposure to dietary heterocyclic amines, such as through the use of alternative cooking methods (e.g., microwave cooking), dietary intervention (e.g., increasing consumption of fiber and antioxidants), or simply by reducing the amount of meat consumed in our diet. If, however, it is shown that neither PhIP nor MelQx plays a significant role in human diet-related carcinogenesis, then the validity of risk assessment based on the relationship we assume to exist between mutagenicity and carcinogenicity, as defined by the use of short-term mutagenicity tests and rodent bioassays to identify potential human carcinogens, will need complete reevaluation.

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CYP1A2-catalyzed Conversion of Dietary Heterocyclic Amines to Their Proximate Carcinogens Is Their Major Route of Metabolism in Humans


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