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LABORATORY INVESTIGATION

# Renal cortical drug and xenobiotic metabolism following urinary tract obstruction

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**Renal cortical drug and xenobiotic metabolism following urinary tract obstruction.** Renal cortical metabolism of drugs and xenobiotics was assessed with microsomes prepared from normal, contralateral and 4-day postobstructive hydronephrotic kidneys. Microsomal mixed-function oxidase and prostaglandin H synthase systems were determined in control and 3-methylcholanthrene-treated rabbits. Cytochrome P450 content and biphenyl-4-hydroxylase activity but not cytochrome *c* reductase activity were reduced in the hydronephrotic kidney. 3-Methylcholanthrene treatment increased cytochrome P450 content and biphenyl-4-hydroxylase and acetanilide-4-hydroxylase activities in normal, contralateral, and hydronephrotic kidneys. However, even after 3-methylcholanthrene treatment, hydronephrotic kidney cytochrome P450 content and acetanilide-4-hydroxylase activity were not more than 20% of the corresponding normal kidney values. Prostaglandin H synthase metabolism of benzidine was observed in the hydronephrotic kidney but was at the limit of detection in normal or contralateral kidneys with or without 3-methylcholanthrene treatment. Characteristics of benzidine metabolism were consistent with the hydroperoxidase rather than the fatty acid cyclooxygenase activity of prostaglandin H synthase. Therefore, hydronephrosis alters the drug and xenobiotic metabolic profile of the renal cortex from a primarily mixed-function oxidase-dependent system to one with the potential for metabolism by the hydroperoxidase component of prostaglandin H synthase.

**Métabolisme cortical rénal des médicaments et xénobiotiques après obstruction du tractus urinaire.** Le métabolisme cortical rénal de médicaments et de xénobiotiques a été étudié avec des microsomes préparés à partir des reins normaux, controlatérals, et hydronéphrotiques, 4 jours après une obstruction. Les systèmes microsomiaux de fonction oxydase mixte et de prostaglandine H synthétase ont été déterminés chez des lapins contrôles et traités par du 3-méthylcholanthrène. Le contenu en cytochrome P450 et l'activité biphényl-4-hydroxylase, mais non l'activité cytochrome *c* réductase étaient diminués dans le rein hydronéphrotique. Le traitement par le 3-méthylcholanthrène a augmenté le contenu en cytochrome P450 et les activités biphényl-4-hydroxylase et acétanilide-4-hydroxylase chez les reins normaux, controlatérals et hydronéphrotiques. Cependant, même après traitement par le 3-méthylcholanthrène, le contenu en cytochrome P450 du rein hydronéphrotique et son activité acétanilide-4-hydroxylase n'étaient pas de plus de 20% des valeurs dans le rein normaux correspondant. Le métabolisme de la benzidine par la prostaglandine H synthétase était observable dans le rein hydronéphrotique, mais était à la limite de la détection dans les reins normaux ou controlatérals, avec ou sans traitement par le 3-méthylcholanthrène. Les caractéristiques du métabolisme de la benzidine étaient plus compatibles avec l'activité hydroperoxidase qu'avec l'activité cyclooxygénase des acides gras de la prostaglandine H synthétase. Ainsi, l'hydronéphrose altère le profil métabolique des drogues et des xénobiotiques dans le cortex rénal d'un système primitivement dépendant d'une fonction oxydase mixte à un système ayant la capacité de métabolisme par le constituant hydroperoxydase de la prostaglandine H synthétase.

Nephrotoxic reactions account for a large proportion of both acute and chronic renal failures [1–3]. Renal metabolism of drugs and xenobiotics is thought to play an important role in nephrotoxic reactions which require metabolic activation of the parent compound [4, 5]. An example is acetaminophen, which is thought to undergo metabolic activation to elicit its nephrotoxic effects [4, 5]. Oxidative metabolism is a potentially important mechanism for the activation of drugs and xenobiotics to more active toxins and ultimate carcinogens. Previous studies demonstrate two separate pathways for microsomal oxidative metabolism of drugs and xenobiotics in the normal kidney; these two mechanisms exhibit an anatomical separation within the kidney. The cytochrome P450 mixed-function oxidase system predominates in the renal cortex while cooxidation by the hydroperoxidase component of prostaglandin H synthase (PHS) predominates in the renal inner medulla [6–8]. PHS has been shown to metabolize drugs and xenobiotics in intact renal cells [9] and in the whole kidney [10].

Urinary tract obstruction is a common clinical problem and is frequently a cause of tubule-interstitial nephritis [11]. In the rabbit, 4 days of ureteral obstruction have been associated with an exaggerated rate of prostaglandin production by the renal cortex, which can be correlated with an increased rate of synthesis of PHS by the ureteral obstructed kidney [12]. The contralateral kidney undergoes increased new protein synthesis associated with compensatory hypertrophy, but there is no evidence that its prostaglandin production increases. The purpose of these experiments is to assess the effect of ureteral obstruction and compensatory hypertrophy on oxidative drug metabolism in cortical microsomes prepared from 4-day postobstructive hydronephrotic (HNK), contralateral (CLK), and normal kidneys (NK).

## Methods

*Materials.* [N-5,6,8,9,11,12,14,15-$^{3}$H]Arachidonic acid (78.2 Ci/mmole), and [U-$^{14}$C]benzidine (25.7 mCi/mmole) were purchased from New England Nuclear Corp., Boston, Massachu-

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setts. Acetanilide (ring-UL-$^{14}$C) (10.5 mCi/mmole) came from California Bionuclear, Sun Valley, California. Scintillation fluid (ACS) was from Amersham, Arlington Heights, Illinois. Nu Chek Prep, Inc., Elysian, Minnesota, supplied the 5,8,11,14-eicosatetraenoic acid (arachidonic acid). Biphenyl and acetylsalicylic acid (aspirin) were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin, 4-hydroxylbiphenyl (p-phenylphenol), acetanilide and 3-methylcholanthrene (3-MC) from Eastman Kodak, Rochester, New York, and acetaminophen (4′-hydroxyacetanilide) from Mallinckrodt, Raleigh, North Carolina. Glucose 6-phosphate (disodium salt), glucose 6-phosphate dehydrogenase (type IV), NADP, NADPH, cytochrome *c* (type III), dithiothreitol, bovine serum albumin, indomethacin, benzidine dihydrochloride, reduced glutathione, 11,14,17-eicosatrienoic acid, 9,12,15-octadecatrienoic acid, sodium salicylate and metyrapone were purchased from Sigma Chemical Co., St. Louis, Missouri. 15-HPETE was synthetized as previously described [13]. $PGE_2$ was a generous gift of The Upjohn Co., Kalamazoo, Michigan. Thin-layer chromatographic plates (Silica Gel $F_{254}$) were obtained from EM Laboratories, Inc., Elmsford, New York. All other chemicals were purchased in the highest possible grade from standard sources.

*Animals and treatment.* New Zealand White male rabbits weighing 1.5 to 2.0 kg were purchased from Eldridge Laboratory Animals, Barnhart, Missouri, housed in a controlled environment and allowed free access to food and water. Complete ureteral obstruction was produced by tying a suture around the left ureter of sodium thiopental anesthetized rabbits. Control and hydronephrotic rabbits were injected with either corn oil or 3-MC, 40 mg/kg in corn oil, i.p., once daily for 3 days [6].

*Preparation of microsomes.* After an overnight fast, control and 4-day ureter-obstructed rabbits were anesthetized with sodium thiopental, 20 mg/kg i.v. [6]. Kidneys and livers were quickly removed and placed in ice-cold 0.9% NaCl. The renal cortex and medulla were separated by careful dissection. Tissue was minced, washed free of hemoglobin, and homogenized with three 15-sec bursts at 30-sec intervals using a Polytron homogenizer in 3 volumes of 0.1 M phosphate buffer (pH 7.8) containing 20% glycerol and $10^{-4}$ M dithiothreitol. The homogenate was centrifuged at $\times$10,000*g* for 15 min and the subsequent supernatant at $\times$100,000*g* for 60 min. Pellets were resuspended in 1.15% KCl and centrifuged at $\times$105,000*g* for 60 min. Microsomal pellets were resuspended in 0.1 M phosphate buffer (pH 7.8) and were stored at −80°C. Protein content was estimated by Lowry's method [14] using bovine serum albumin as a standard.

*Cytochrome P450 content.* Microsomal cytochrome P450 content was determined by the method of Omura and Sato [15]. An extinction coefficient of 91 $mM^{-1}$ $cm^{-1}$ for the carbon monoxide difference spectrum of reduced microsomes ($E_{450}$-$E_{490}$) was used.

*Biphenyl-4-hydroxylase activity.* Enzyme activity was determined by the method of Creaven, Parke, and Williams [16] as modified by Atlas and Nebert [17]. Assays were done at a microsomal protein concentration of 3.0 mg/ml and results are expressed as picomoles of 4-hydroxybiphenyl produced per minute per milligrams of microsomal protein. Blank values (no regenerating system) were subtracted from all samples. Fluorescent measurements were performed with spectrophotofluorometer (Model J4-8960, Aminco-Bowman, Silver Springs, Maryland) with 1 $cm^2$ quartz cuvettes, and a xenon lamp light source. Excitation and emission wavelengths were 311 and 400 nm, respectively, and were uncorrected instrumental values. Because previous studies have demonstrated that biphenyl-2-hydroxylase activity is negligible in rabbit kidney microsomes [18], only biphenyl-4-hydroxylase activity was determined.

*Acetanilide hydroxylase activity.* Enzyme activity was measured according to Daly [19] and Atlas and Nebert [17] with the following modifications: Total reaction volume of 0.1 ml contained 0.25 mM $^{14}$C-acetanilide, 0.65 mg microsomal protein, and a regenerating system consisting of 8.75 mM glucose-6-phosphate, 0.75 mM NADP, and 0.0125 U glucose-6-phosphate dehydrogenase. Reaction was stopped with 0.01 ml 2 M citric acid, and 3 mM 4′-hydroxyacetanilide. Samples were extracted twice with 1 ml of ethyl acetate, dried with sodium sulfate, and evaporated to dryness under $N_2$. Residues were dissolved in 0.05 ml acetone and applied to thin-layer chromatographic plates. $R_f$'s for acetanilide and 4′-hydroxyacetanilide were 0.34 and 0.11, respectively. After ultraviolet visualization, spots were scraped into scintillation vials; the radioactivity was assessed with a liquid scintillation counter (Beckman 6800, Beckman Instruments, Fullerton, California). Hydroxylase activity was completely inhibited by metyrapone. Blank values (no regenerating system) were subtracted from all samples. Results are expressed as picomoles of 4′-hydroxyacetanilide produced per minute per milligram of microsomal protein.

*Cytochrome c reductase activity.* Enzyme activity was assayed according to Williams and Kamin [20], using a molar absorbancy index of 21.0 $\times$ $10^6$ $cm^2$ $mole^{-1}$ [21].

*Determination of $^{14}$C-benzidine binding.* Reaction mixtures contained 0.5 to 0.9 mg/ml microsomal protein, 0.1 M phosphate buffer (pH 7.8), 0.07 mM $^{14}$C-benzidine, either 0.1 mM arachidonic acid or other substrates as indicated, and various inhibitors in a final volume of 0.1 ml [22]. Inhibitors were preincubated with microsomes for 5 min at room temperature. Incubations at 37°C for 10 min were started by the addition of substrate. The reaction was stopped by the addition of unlabeled benzidine to a concentration of 0.75 mM, followed by 1 ml of ethyl acetate, as previously described [22]. The organic layer was removed after centrifugation at $\times$1,500*g* for 10 min. Following three ethyl acetate extractions, the aqueous phase was adjusted to 0.3 M TCA and centrifuged at $\times$2,500*g* for 10 min. The aqueous layer was saved, and the resulting precipitate was washed with 1 ml of 0.3 M TCA followed by centrifugation until the radioactivity of the supernatant was similar to the background. The original aqueous layer was combined with subsequent washes and the radioactivity was assessed to determine aqueous, non-TCA-precipitable metabolism. The pellet was dissolved in 0.4 ml of 1 N NaOH at 60°C for 30 min, diluted to 0.8 ml with distilled water, aliquoted, and analyzed for aqueous TCA-precipitable material. Blank values were obtained with heated microsomes and were not different from samples incubated without arachidonic acid. Blank values were subtracted from experimental values. Metabolism is expressed as pmoles/mg protein/min.

*Metabolism of $^3$H-arachidonic acid.* Reaction mixtures contained 0.3 to 0.6 mg/ml microsomal protein, 0.1 M phosphate buffer (pH 7.8), 1.0 mM glutathione, and 0.1 mM $^3$H-arachidonic acid in a final volume of 0.1 ml [23]. The reaction was started by the addition of arachidonic acid, incubated at 37°C for 10 min and stopped by the addition of hydrochloric acid. Samples adjusted to pH 3 to 3.5 were extracted with ethyl acetate and

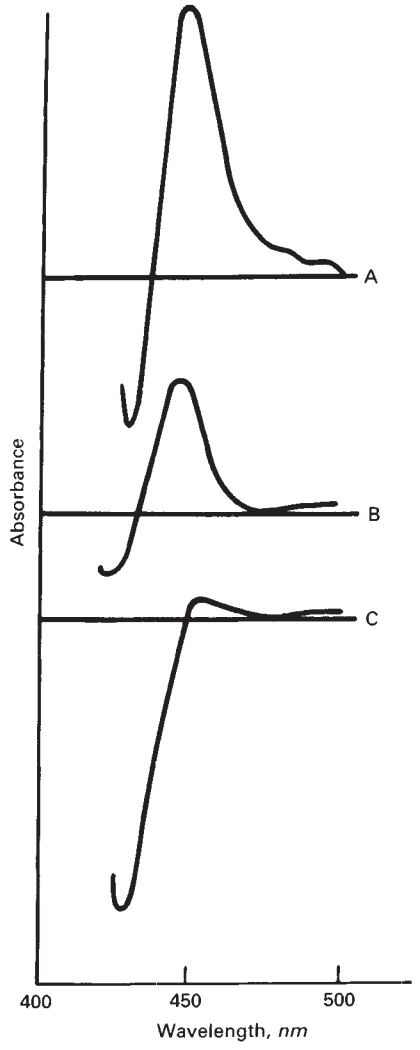


**Fig. 1.** *Cytochrome P450 spectra of microsomes prepared from normal* **(A)**, *contralateral* **(B)**, *and hydronephrotic* **(C)** *kidney cortex.* Difference spectra were obtained with dithionite-reduced, carbon monoxide-treated microsomes.

evaporated to dryness under nitrogen gas. Samples were applied to silica gel $F_{254}$ plates and developed with a solvent system containing chloroform:methanol:acetic acid (90:5:5). Radioactivity was determined with a radiochromatogram scanner (Series 7320, Packard Instruments, United Technology, Downers Grove, Illinois). Arachidonic acid and prostaglandin standards were visualized with iodine vapors.

## Results

Cytochrome P450 difference spectra of cortical microsomes prepared from NK, CLK, and HNK are illustrated in Figure 1. NK and CLK spectra were similar. The difference spectrum observed with HNK was at the limit of detection, even when measured at 5 mg/ml of microsomal protein.

To further assess differences in the renal cortical mixed-function oxidase system, normal and hydronephrotic rabbits were treated with 3-MC (Table 1). 3-MC treatment elicited a significant increase in cytochrome P450 content in NK, CLK, and HNK. However, the cytochrome P450 content in HNK cortex, even after 3-MC was still barely detectible. Cytochrome *c* reductase, another component of the mixed-function oxidase system, was similar in NK, CLK, and HNK cortex with control or 3-MC-treated rabbits.

The mixed-function oxidase enzymes biphenyl-4-hydroxylase and acetanilide hydroxylase were also evaluated (Table 1). There was approximately three times as much biphenyl-4-hydroxylase activity in NK or CLK compared to HNK. Following 3-MC treatment, enzymatic activity increased in all three tissues to the extent that the rate of biphenyl metabolism was similar in NK, CLK, and HNK. Acetanilide hydroxylase activity was only observed following 3-MC treatment; this activity in HNK was approximately 20% that observed in NK.

The prostaglandin H synthase system was assessed as an alternative pathway for the renal cortical metabolism of drugs and xenobiotics (Fig. 2). Prostaglandin H synthase activates benzidine to a cation-free radical intermediate, which binds nucleophilic sites on protein and nucleic acids [24]. Therefore, the binding of benzidine to protein is an index of metabolism by prostaglandin H synthase. Benzidine binding to TCA-precipitable material was at the limit of detection with NK or CLK microsomes. Significant binding was observed in HNK with or without 3-MC treatment. Requirements for benzidine binding with HNK microsomes were further investigated (Table 2). Arachidonic acid elicited a dose-dependent increase in benzidine metabolism. Neither 11,14,17-eicosatrienoic acid, 9,12,15-octadecatrienoic acid, $PGE_2$, or NADPH elicited metabolism of benzidine, while metabolism was observed with 15-HPETE. Arachidonic acid-mediated metabolism was inhibited by aspirin, indomethacin, and meclofenamic acid but not by salicylate or metyrapone. Glutathione increased the ratio of aqueous non-TCA-precipitable to aqueous TCA-precipitable material. Arachidonic acid metabolism by cortical microsomes prepared from HNK and CLK was determined (Fig. 3). Significant metabolism of arachidonic acid was observed with HNK but not CLK microsomes.

## Discussion

These results indicate specific differences in the profiles of oxidative drug and xenobiotic metabolism between renal cortical microsomes prepared from HNK and either CLK or NK. There was a loss of cytochrome P450 content and biphenyl-4-hydroxylase activity in the hydronephrotic cortex. Microsomal cytochrome *c* reductase activity was similar in all three preparations. Because the synthesis and degradation of cytochrome P450 and hydroxylases are through a different pathway than cytochrome *c* reductase, the reduction of the former but not the latter during hydronephrosis suggests that the loss in activity was not due to reduced recovery of microsomes. Therefore, 4-day unilateral ureter obstruction reduces the capacity of the kidney to metabolize drugs and xenobiotics by the microsomal mixed-function oxidase system.

There was less renal mixed-function oxidase activity in the HNK compared to NK or CLK even after 3-MC treatment. However, biphenyl-4-hydroxylase activity was similar in NK, HNK, and CLK after 3-MC treatment. Both cytochrome P450 content and acetanilide-4-hydroxylase in HNK were increased by 3-MC but neither parameter was more than 20% of the corresponding values in NK. The reason for this differential effect of 3-MC is not entirely clear. The mixed-function oxidase

**Table 1.** Renal cortical cytochrome P450 content, NADPH-cytochrome *c* reductase and mixed-function oxidase activities from control and 3-methylcholanthrene-treated rabbits[a]

| Type of kidney | Cytochrome P450 content[b] | | NADPH-cytochrome *c* reductase[c] | | Biphenyl-4-hydroxylase[d] | | Acetanilide hydroxylase[e] | |
|---|---|---|---|---|---|---|---|---|
| | Control | Treated | Control | Treated | Control | Treated | Control | Treated |
| Normal | 0.09 ± 0.01 | 0.15 ± 0.01 | 25 ± 2 | 18 ± 2 | 11 ± 1 | 25 ± 2 | ND | 23 ± 2 |
| Hydronephrotic | ND | 0.03 ± 0.004 | 23 ± 3 | 27 ± 2 | 3 ± 0.5 | 29 ± 3 | ND | 5 ± 1 |
| Contralateral | 0.06 ± 0.004 | 0.16 ± 0.01 | 27 ± 1 | 26 ± 2 | 10 ± 1 | 31 ± 3 | ND | 30 ± 3 |

Abbreviation: ND, not detectable.
[a] The values represent mean ± SE; $N = 3$ to 4.
[b] The values represent nanomoles of cytochrome P450 per milligram of microsomal protein.
[c] The values represent micromoles of cytochrome *c* reduced per milligram of microsomal protein per minute.
[d] The values represent picomoles of 4-hydroxybiphenyl formed per milligram of microsomal protein per minute.
[e] The values represent picomoles of 4′-hydroxyacetanilide formed per milligram of microsomal protein per minute.

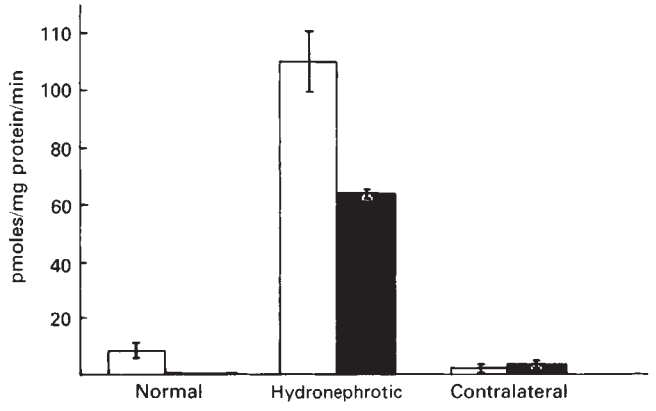


**Fig. 2.** *Arachidonic acid-dependent metabolism of $^{14}$C-benzidine by cortical microsomes prepared from control □ and 3-methylcholanthrene-treated ■ rabbits.*

**Table 2.** Requirements for benzidine metabolism by microsomes prepared from control hydronephrotic kidney cortex[a]

| Additions | Concentration mM | N | Aqueous, TCA precipitable | Aqueous, non-TCA precipitable |
|---|---|---|---|---|
| | | | *pmoles/mg protein/min* | |
| Experiment 1[b] | | | | |
| None | | 7 | ND | ND |
| Arachidonic acid | 0.1 | 7 | 94 ± 4 | 27 ± 1 |
| | 0.05 | 4 | 51 ± 5 | 16 ± 1 |
| 11,14,17-Eicosatrienoic acid | 0.1 | 4 | 9 ± 1 | ND |
| 9,12,15-Octadecatrienoic acid | 0.1 | 3 | ND | ND |
| $PGE_2$ | 0.1 | 3 | ND | ND |
| NADPH | 1.0 | 3 | ND | ND |
| 15-HPETE | 0.05 | 4 | 90 ± 4 | 23 ± 2 |
| Experiment 2[c] | | | | |
| Arachidonic acid | 0.15 | 7 | 120 ± 8 | 11 ± 1 |
| + Aspirin | 2.0 | 4 | 2 ± 0.6 | ND |
| + Salicylate | 2.0 | 4 | 116 ± 20 | ND |
| + Indomethacin | 0.1 | 3 | ND | ND |
| + Meclofenamic acid | 0.15 | 4 | ND | ND |
| + Metyrapone | 1.0 | 3 | 136 ± 14 | 23 ± 3 |
| + Glutathione | 1.0 | 3 | 16 ± 1 | 74 ± 5 |

Abbreviations: ND, not detected; *N*, number of experiments.
[a] The incubations contained microsomal protein, 0.1 M phosphate buffer, 0.09 mM benzidine, and 0.0012 mM methemoglobin.
[b] In experiment 1, reactions were initiated by the addition of the indicated substrate.
[c] In experiment 2, test agents were preincubated with reaction mixtures for 2 min before the addition of the arachidonic acid substrate.

system is not uniformly distributed within the renal cortex, but rather appears to be primarily located in the $S_2$ and $S_3$ segments of the proximal tubule [25, 26] and, to a lesser extent, in the renal endothelium [25]. In addition, the distribution of cytochrome P450 isozymes appears to be unique, with Forms 2 and 3 localized in the proximal tubule and Forms 4 and 6 in the renal endothelium [25]. This differential distribution could explain why there is a differential response to 3-MC treatment if certain cells are damaged more than others by hydronephrosis.

Increased synthesis of prostaglandins is a unique characteristic of the HNK and has been correlated with increased synthesis of PHS. Increased prostaglandin synthesis is not observed in renal medullary tissue following unilateral obstruction. Increased cortical prostaglandin synthesis has been associated with increased proliferation and/or infiltration of fibroblasts and macrophages within the renal cortex [27]. As shown in Figure 3, the HNK synthesizes significantly more prostaglandins and thromboxanes from arachidonic acid than CLK.

The prostaglandin hydroperoxidase activity of PHS is responsible for the metabolism of certain drugs and xenobiotics. In view of the decreased mixed-function oxidase activity and the increased rate of prostaglandin synthesis observed in the HNK, the PHS system was assessed and compared to the mixed-function oxidase system. Benzidine was metabolized by HNK cortex but was at the limit of detection in NK or CLK. Benzidine metabolism was initiated by specific fatty acid substrates, arachidonic acid [28], and was prevented by specific inhibitors of PHS, that is, aspirin, indomethacin, and meclofenamic acid [29]. Salicylate, the deacetylated aspirin analogue, and metyrapone, a mixed-function oxidase inhibitor, did not alter arachidonic acid-dependent metabolism of benzidine. Effects of glutathione were consistent with previous studies which suggested the formation of a glutathione-benzidine conjugate [22]. Glutathione is thought to be important in the in vivo inactivation of renal toxins [4, 5]. The 15-hydroperoxy analogue of arachidonic acid (15-HPETE) initiated benzidine metabolism which was not inhibited by aspirin (not shown). These results are consistent with the hydroperoxidase rather than the fatty cyclooxygenase activity of PHS catalyzing the metabolism of benzidine in HNK.

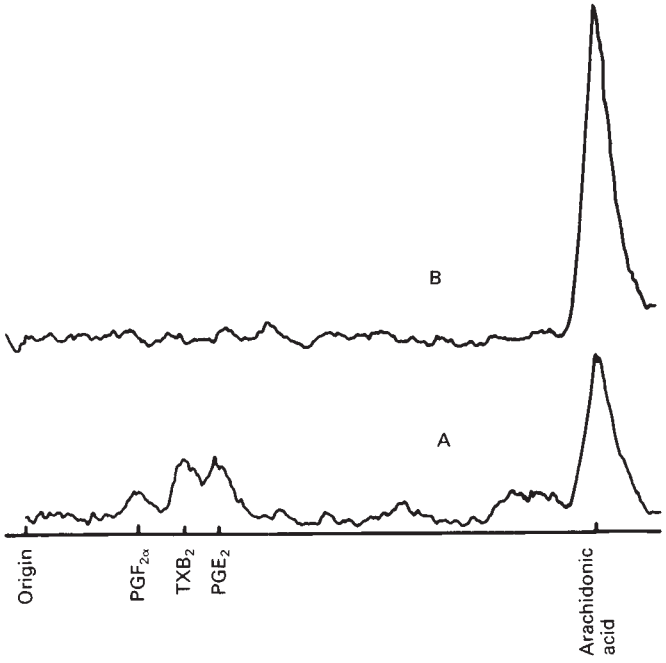


**Fig. 3.** *Thin-layer chromatographic radioscan of $^3$H-arachidonic acid metabolism by microsomes prepared from hydronephrotic* (**A**) *and contralateral* (**B**) *kidney.*

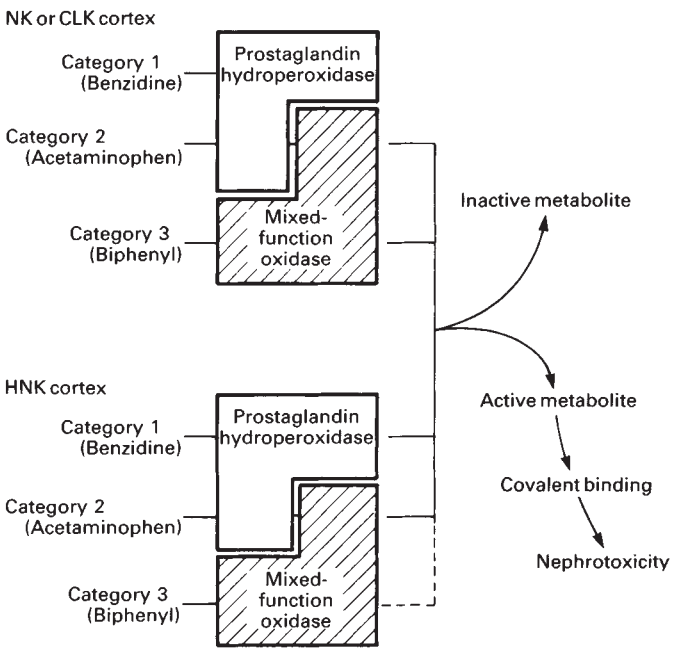


**Fig. 4.** *Proposed model to explain renal cortical oxidative metabolism in normal* (NK), *contralateral* (CLK), *and hydronephrotic* (HNK) *kidneys. Solid lines* indicate major routes of metabolism and *dashed lines* indicate reduced routes of metabolism.

PHS-catalyzed metabolism of benzidine, a nephrotoxin and urinary tract carcinogen [30], may be a unique characteristic of this enzyme. Benzidine is not metabolized by the mixed-function oxidase system but this enzyme system will metabolize the acetylated derivatives of benzidine [31, 32]. PHS has been shown to activate benzidine to a cation-free radical which binds tissue nucleophiles such as protein, t-RNA, and DNA [24, 33]. Nephrotoxins and renal carcinogens are thought to elicit their toxic effects by binding such nucleophiles. Several other urinary tract carcinogens and nephrotoxins besides benzidine are metabolized by PHS. These include acetaminophen [23, 34, 35], 3-hydroxymethyl-1-[(3-(5-nitro-2-furyl)-allydidene)amino]-hydantoin [36], diethylstilbestrol [8], 2-naphthylamine [37], 4-aminobiphenyl [37], 2-aminofluorene [37], and *p*-phenetidine [37]. Except for 3-hydroxymethyl-1-[(3-(5-nitro-2-furyl)-allydidene)amino]-hydantoin, all these compounds have been shown to be activated by PHS to bind tissue nucleophiles. Immunohistofluorescence studies of subcellular localization have demonstrated that PHS is associated with the endoplasmic reticulum and nuclear membrane [38]. This subcellular localization would make both the cytoplasm and nucleus of cells susceptible to cooxidative damage.

Hydronephrosis alters the drug and xenobiotic metabolic profile of the renal cortex. A model describing these alterations is illustrated in Figure 4. Three categories of compounds are envisioned: one in which metabolism only occurs by PHS (that is, benzidine), a second in which both PHS and mixed-function oxidase are metabolically active (that is, acetaminophen), and a third in which only mixed-function oxidase is active (that is, biphenyl). It has been recently shown that acetaminophen is metabolized by both the mixed-function oxidase and PHS systems [4, 35]. In contrast, biphenyl is metabolized by the mixed-function oxidase system [16, 17] but not by PHS (not shown). In NK and CLK, drugs and xenobiotics can only be metabolized by the mixed-function oxidase system (categories 2 and 3). In HNK, drugs and xenobiotics can be metabolized by both the mixed-function oxidase and PHS systems (categories 1, 2, and 3). However, metabolism by the mixed-function oxidase system in HNK is significantly reduced. 3-MC treatment can restore a certain amount of the latter. The HNK is capable of metabolizing certain chemicals not possible in the NK or CLK. Nephrotoxicity is thought to be initiated by the metabolic formation of activated compounds which bind tissue nucleophiles. Alteration of the drug and xenobiotic metabolic profile in HNK may have profound effects on renal cortical function and may contribute to the progressive deterioration observed in hydronephrosis.

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