Metabolism of Arachidonic Acid via the Lipoxygenase Pathway in Human and Murine Glomeruli*

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Glomeruli isolated from murine and human renal cortex metabolize arachidonic acid to prostaglandins via the cyclooxygenase pathway but whether such glomeruli can also metabolize arachidonic acid via the lipoxygenase pathway is controversial. [1-14C]Arachidonic acid was incubated with glomeruli or glomerular fractions isolated from rat and human renal cortex. The products were extracted, purified by high performance liquid chromatography, and identified by comparison of their retention times with those of authentic 12-hydroxyeicosatetraenoic acid (12-HETE) and 15-hydroxyeicosatetraenoic acid (15-HETE) standards and by gas chromatography-mass spectrometry. At low substrate concentrations, human glomeruli synthesized in equivalent amounts 12- and 15-HETE, whereas rat glomeruli synthesized only 12-HETE and in larger quantities than in man. At higher substrate concentrations, both species synthesized 12- and 15-HETE and the rate of synthesis for both products was higher in human glomeruli. No other HETE was detected in either species. The lipoxygenase products were stored within the glomeruli and recovered almost equally in the 10,000 X g pellet and in the 100,000 X g supernatant of the homogenized glomeruli. The properties of the lipoxygenase system were the following: the enzyme was distributed equally in the membranes and the cytosol; 12-HETE accumulation was linear with time over 15 min; and 12-HETE production correlated linearly with the amount of glomerular protein. 12-Lipoxygenase activity was maximum at pH 7.5 (rat) or 9.0 (human) and at 40–42°C (both species). Km values calculated at low concentrations of substrate (10–200 µM) were for 15-HETE, 125 and 667 µM with murine and human glomeruli, respectively, and for 12-HETE, 44 µM with the glomeruli of both species. This study demonstrates lipoxygenase activity in murine and, for the first time, in human glomeruli. The products of such enzymatic activity, 12- and 15-HETE, may mediate the glomerular inflammatory response in various experimental or spontaneous glomerular diseases.

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§ The abbreviations and trivial names used are: arachidonic acid, 5,8,11,14-eicosatetraenoic acid; PG, prostaglandin; HPLC, high performance liquid chromatography, ETYA, eicosatrayenic acid; GC-MS, gas chromatography-mass spectrometry; HETE, hydroxyeicosatetraenoic acid.

EXPERIMENTAL PROCEDURES

Materials—[1-14C]Arachidonic acid (54 mCi/mmol) was obtained from the Radiochemical Centre (Aeresham, United Kingdom). Arachidonic acid, nordihydroguaiaretic acid, and indomethacin were from Sigma and HPLC grade solvents were from Merck (Darmstadt, West Germany). ETYA was a gift of Roche Pharmaceutical Co. Silicic acid (Silicar CC4) was purchased from Mallinkrodt Chemical. HPLC was performed on a Varian model 5000 chromatograph. An UV detector from Pye Unicam (model LC) was used and radioactivity was monitored by liquid scintillation (Mark II model from Searle) using Picofluor from Packard as scintillator. Gas chromatography-mass spectrometry was performed on a magnetic field mass spectrometer coupled with a computer system (LKB 2091-061, Stockholm, Sweden).

Procedures—Rat glomeruli were isolated as described previously (2). Human glomeruli, obtained from normal renal cortex at the time of nephrectomy for renal tumor (2 patients) and from cadaver kidneys judged to be unsuitable for transplantation (2 patients), were prepared similarly, except for the size of the sieves. In short, minced renal cortex was pressed gently through successive stainless steel sieves. A 105 (rat)- or 180 (man)-µm sieve excluded the tubules and blood vessels. The filtrate was then passed through a 75-µm sieve (both species) which retained the glomeruli and allowed cells and small debris to pass through. Glomeruli were suspended in ice-cold Tris-HCl buffer, pH 7.4, containing 135 mM NaCl, 10 mM KCl, 10 mM sodium ascorbate, and 5 mM glucose (buffer A) and centrifuged at 120 x g for 90 s. The pellet, which consisted of isolated, depaculated glomeruli with less than 2% tubular contamination as demonstrated by light microscopy, was utilized for studies of lipoxygenase activity.

In additional experiments, three subcellular glomerular fractions (membranes, microsomes, cytosol) were prepared for studies of the localization of lipoxygenase activity and products. Isolated glomeruli were homogenized by sonication (Branson apparatus, 4 X 20 s) in 3 volumes of buffer A and centrifuged at 500 x g for 2 min in order to eliminate glomerular debris. The supernatant was then centrifuged at 10,000 x g for 15 min, and the pellet (including the membranes) saved for further purification. The 10,000 X g supernatant (low speed supernatant) was centrifuged at 100,000 X g for 60 min to prepare microsomes (100,000 X g pellet) and cytosol (100,000 X g supernatant).
The 10,000 X g pellet was resuspended in buffer A, sonicated twice for 20 s, and then recentrifuged at 100,000 X g for 60 min in order to get rid of any trapped cytosol.

Preparation of Authentic Monohydroxysteroycoseicosatetraenoic Acids—5-, 8-, 9-, 11-, 12-, and 15-HETE were prepared from arachidonic acid by reaction with H2O2 in the presence of CuCl2 as described by Boeynaems et al. (8). Their method was modified slightly, the hydroperoxides being reduced with triphenylephosphine at 0 °C for 30 min. The reaction products were submitted to HPLC on a Micropak Si 10 column (30 cm X 4 mm, inner diameter) using the solvent system of Porter et al. (9) (Solvent A, hexane:ethanol:acetic acid, 993:6:1, v/v) at a flow rate of 1.5 ml/min. HETEs were repurified by a second passage through the same column and collected. One aliquot of the fractions containing the separated HETEs was dried under nitrogen and derivatized as methyl esters and trimethylsilyl esters for GC-MS identification. Using this solvent, all the isomers, including 8 and 9 isomers, were resolved. The retention times of 12- and 15-HETE (when submitted to HPLC under the conditions used for purification of the products of conversion of [1-14C]arachidonic acid by isolated glomeruli) were 11 and 13.5 min, respectively. The other isomers were eluted further with the following retention times: 11-HETE, 22 min; 9-HETE, 36 min; 8-HETE, 45.5 min; and 5-HETE, 93 min.

Incubation Conditions and Extraction Procedure—The standard incubation medium (600 μl) was buffer A containing 17 μM [1-14C]arachidonic acid, 5 mM CaCl2, and 40 μM indomethacin. The reaction was initiated by addition of the enzyme (approximately 1 mg of glomerular protein) and, after 15- or 30-min incubation at 37 °C, was stopped by precipitation with 1 ml of cold methanol and centrifugation at 22,000 X g for 2 min. Since it has been demonstrated that arachidonic acid can undergo autoxidation (10), we estimated the nonenzymatic formation of HETEs by incubation of [1-14C]arachidonic acid with either buffer alone (“blank” tube) or glomeruli that had been boiled for 5 min prior to incubation (“inactivated” enzyme preparation). The supernatant was removed and the pellet was re-washed with 1 ml of methanol and respun. The supernatants were then pooled, acidified to pH 3.0-3.5 with 1 M HCl, and added to 6 volumes of diethyl ether and 4 volumes of distilled water. The ether layer was removed and the pooled supernatants extracted again with the same volume of diethyl ether. Both ether layers were pooled and evaporated to dryness under a nitrogen stream.

Column Chromatography—Silicic acid column chromatography was performed in glass columns packed with 0.5 g of silicic acid (Silicar CC4) suspended in Solvent 1 (hexane:diethyl ether, 90:10, v/v), at a solvent flow of 1.5 ml/min. The elution of hydroxy acids was monitored by measurement of UV absorbance at 235 nm. Authentic 12- and 15-HETE standards were added to samples prior to the purification procedure as internal standards. Fractions were collected every minute and 14C radioactivity of each fraction was measured by liquid scintillation counting techniques. The chromatography was usually stopped after 30 min which allowed 12- and 15-HETE to be purified, and the column was washed with a linear gradient of ethanol (0.6 to 10% ethanol in 30 min). As this technique was not suited to the detection of the late-eluting 5-HETE, a different elution system was used in which a second solvent (Solvent B, hexane:ethanol:acetic acid, 899:100:1, v/v), was added. The program was: time zero, 0.8 ml/min, 15% B; time 15 min, 1.5 ml/min, 15% B.

Recovery of HETEs—Standard 5- or 12-HETE (148 ng) were added to the incubation medium of isolated rat glomeruli with [1-14C]arachidonic acid; extraction and purification were performed as described previously and recovery of 5- or 12-HETE was measured by UV detection at 235 nm. The peak area was read on standard curves established with increasing amounts of the corresponding HETE applied directly to the column. The recoveries of two experiments were 81.6 and 69.6% and 91.2 and 73.8% for 5- and 12-HETE, respectively.

Gas Chromatography-Mass Spectrometry—After purification by HPLC, the products of the enzyme reaction eluting with retention times of 11 and 13 min, respectively, were evaporated under nitrogen and converted to the methyl ester trimethylsilyl ether derivatives for GC-MS studies. The methyl esters were prepared by reacting the dry residues with ethereal diazomethane for 5 min at room temperature. Trimethylsilylation of hydroxy groups was then carried out with N,O-bis(trimethylsilyl) trifluoroacetamide containing 1% trimethylchlorosilane at 60 °C for 30 min. Gas chromatography was performed on high efficiency glass capillary columns (20 m X 0.28 mm, stationary phase OV1, 0.15-μm thick), prepared as described previously (11). The mass spectra were recorded on electron impact at 20 eV with an accelerating voltage of 3.5 kV.

Lipoxigenase activity was expressed as nanograms of 12- or 15-HETE produced/min/mg of glomerular protein. The specific activity of [1-14C]arachidonic acid was used for this calculation with the assumption that the endogenous pool of arachidonic acid was negligible.

Protein concentration was determined according to the method of Lowry et al. (12) with bovine serum albumin as standard.

**Fig. 1. Straight-phase HPLC of [1-14C]arachidonic acid products formed by incubation of glomeruli isolated from human (left) or murine (right) renal cortex.** 1 mg of glomerular protein was incubated for 30 min at 37 °C in the presence of 17 μM [1-14C]arachidonic acid with (●) or without (○) 50 μM ETYA. The peaks corresponding to elution of arachidonic acid (AA) and its identified metabolites (peaks I and II, shaded) and unidentified metabolite (peak III) are indicated by the arrows.
RESULTS

Identification of the Hydroxy Acids Produced by Murine and Human Glomeruli—At low substrate concentration (55 μmol), radiolabeled arachidonic acid was metabolized to several products by the glomeruli isolated from both species. In the presence of indomethacin, an inhibitor of cyclooxygenase, only the less polar products were identified (Fig. 1). The least polar material, which eluted at 5 min, was unreacted arachidonic acid. Additional peaks, composed of distinctly more polar radiolabeled material, then eluted. The elution profile differed between human and murine glomeruli. Three peaks were detected in the extract from human glomeruli. Two peaks (peak I and II) were present in approximately equivalent amounts and had retention times of 11 and 13 min, respectively. A smaller peak (peak III) eluted at 19 min. Rat glomeruli synthesized larger amounts of peak I and an amount of peak III equivalent to that seen with human glomeruli; no radioactivity was detected in the extract from human glomeruli. Two polar radiolabeled material, then eluted. The elution profile differed between human and murine glomeruli. Three peaks (peak I and 11) were present in approximately equivalent amounts.

Localization of the Lipoxygenase Products—When the glomerular suspension was centrifuged for 2 min at 3,000 × g after 30-min incubation with [1-14C]arachidonic acid, the lipoxygenase products were nearly absent from the supernatant as shown in Fig. 2. Even when the pellet was washed with fatty acid-free albumin, 90% of these compounds was recovered in the 3,000 × g pellet. When this glomerular pellet was fractionated further (10,000 × g pellet, 100,000 × g pellet, 100,000 × g supernatant), it appeared that the main product of lipoxygenase activity, 12-HETE, was present in all three fractions, but particularly in the membranes and in the cytosol (Table I).

Localization of Lipoxygenase Activity—Additional experiments were performed to localize glomerular lipoxygenase activity, as distinct from lipoxygenase products. In these studies, each subcellular fraction was incubated for 30 min with [1-14C]arachidonic acid and then extracted and purified for 12-HETE determination. Similar to the location of lipoxygenase products, lipoxygenase activity was located mainly in the membrane and cytosol fractions (Table I).

Subcellular localization of the 12-lipoxygenase product and 12-lipoxygenase activity

Estimation of distribution of the major lipoxygenase product, 12-HETE, was made after incubation of intact glomeruli with [1-14C]arachidonic acid, whereas estimation of the distribution of 12-lipoxygenase activity was made by incubation of [1-14C]arachidonic acid with subcellular fractions that had been prepared prior to incubation. Results correspond to two experiments for each study.

| Subcellular Fraction | 12-HETE Distribution | Distribution of 12-Lipoxygenase Activity |
|----------------------|-----------------------|----------------------------------------|
| Membranes            | 37.2                  | 36.7                                   |
| (10,000 × g pellet)  | 44.6                  | 40.3                                   |
| Microsomes           | 11.5                  | 6.7                                    |
| (100,000 × g pellet) | 5.2                   | 27.9                                   |
| Cytosol              | 51.3                  | 56.6                                   |
| (100,000 × g supernatant) | 50.2           | 31.8                                   |
Glomerular Lipoxygenase

Fig. 3. 12-HETE synthesis by isolated glomeruli plotted as a function of time (a), glomerular protein (b), temperature (c), and pH (d). ○ and ●, human and murine glomeruli, respectively; △, the results obtained in the presence of 50 μM ETYA during the time course study. In b, c, and d incubations were carried out for 15 min.

Fig. 4. Rate of synthesis of 12- (left) or 15- (right) HETE as a function of the concentration of arachidonate in the presence of murine (●) or human (○) isolated glomeruli. Logarithmic scales are used for the abscissa of the figures (full range of arachidonate concentrations). Normal scales are used for the abscissa of the insets (lower arachidonate concentrations). Incubation was carried out for 15 min.

General Properties of the Glomerular Lipoxygenase System—In these studies only 12-HETE, which was found to be the main product of lipoxygenase activity in both species, was measured. The formation of 12-HETE by rat glomeruli was dependent on time and the amount of enzyme added. The time course of the reaction was linear for 15 min at 37 °C. Formation of 12-HETE reached a plateau after 30-min incubation and was inhibited completely by addition of ETYA (Fig. 3a). There was a linear relationship between the rate of 12-HETE synthesis by rat glomeruli and the amount of glomerular protein from 0 to 1.5 mg (r = 0.93, p < 0.05) (Fig. 3b). This allowed expression of the results in relation to the protein concentration. Lipoxygenase activity was also temperature- and pH-dependent in the glomeruli of both species. Lipoxygenase activity increased progressively from 0 to 40 °C (Fig. 3c). The loss of activity at 50 °C was nil or very small. Nonenzymatic formation of 12-HETE was estimated at three temperatures (24, 37, and 42 °C) using boiled glomeruli. Rates of production were close to the blank value and did not vary with changes in temperature. Lipoxygenase activity of rat glomeruli was the greatest at pH 7.3 and decreased rapidly at more alkaline pH, whereas that present in human glomeruli was maximum at pH 8.5-9.0 (Fig. 3d). Glomerular lipoxygenase activity was not affected by variations in extracellular calcium concentration between 0 and 10 mM. Addition of the calcium ionophore A 23187 also did not produce any effect.

Effect of Substrate Concentration on Lipoxygenase Activity—Whether 12- and 15-lipoxygenase activities were dependent on the concentration of arachidonate was studied with both murine and human glomeruli. The shapes of the velocity versus substrate concentration curves (Fig. 4) suggested a complex enzyme system. The rate of synthesis of 12- and 15-HETE increased progressively with increasing concentrations of arachidonate in the range between 6 and 2000 μM. 12-HETE was the main product synthesized at low concentrations of substrate (10-200 μM) in rat glomeruli. Its rate of synthesis under the same conditions was less in human glomeruli. The shapes of the velocity versus substrate concentration curves (Fig. 4) suggested a complex enzyme system. The rate of synthesis of 12- and 15-HETE increased progressively with increasing concentrations of arachidonate in the range between 6 and 2000 μM. 12-HETE was the main product synthesized at low concentrations of substrate (10-200 μM) in rat glomeruli. Its rate of synthesis under the same conditions was less in human glomeruli. The shapes of the velocity versus substrate concentration curves (Fig. 4) suggested a complex enzyme system. The rate of synthesis of 12- and 15-HETE increased progressively with increasing concentrations of arachidonate in the range between 6 and 2000 μM. 12-HETE was the main product synthesized at low concentrations of substrate (10-200 μM) in rat glomeruli. Its rate of synthesis under the same conditions was less in human glomeruli. The shapes of the velocity versus substrate concentration curves (Fig. 4) suggested a complex enzyme system. The rate of synthesis of 12- and 15-HETE increased progressively with increasing concentrations of arachidonate in the range between 6 and 2000 μM. 12-HETE was the main product synthesized at low concentrations of substrate (10-200 μM) in rat glomeruli. Its rate of synthesis under the same conditions was less in human glomeruli.
synthesis became predominant reaching levels 2-3 times that of 12-HETE. $K_m$ and $V_{max}$ values were derived from Lineweaver-Burk plots using the data obtained at low concentrations of substrate, which are generally considered to be the more physiologic (Fig. 5). $K_m$ values were 125 and 667 $\mu M$ with murine and human glomeruli, respectively, for 15-HETE and 44 $\mu M$ with the glomeruli of both species for 12-HETE. $V_{max}$ values were 0.125 and 2.0 pmol/min/mg for 15-HETE and 0.43, and 1.25 pmol/min/mg for 12-HETE with human and murine glomeruli, respectively.

**DISCUSSION**

The results of the present study demonstrate, for the first time, the presence of both 12- and 15-lipoxygenase activity in glomeruli isolated from human renal cortex and confirm the recently reported observation of 12-lipoxygenase activity in glomeruli isolated from the rat (7). Such formation of 12- and 15-HETE by glomeruli resulted from an enzymatic process since boiled glomeruli or glomeruli incubated in the presence of 12-HETE is not produced HETEs in an amount greater than the blank value. Furthermore, since the hydroxy derivatives of arachidonic acid were identified, these results imply the presence, within the glomeruli, of another enzyme which transforms 12- and 15-hydroperoxy derivatives, the direct products of lipoxygenase, into the corresponding HETEs. The presence of such a hydroperoxy eicosatetraenoic acid peroxidase activity has been described recently in the human platelet (13).

In contrast to our results in glomeruli isolated from human and rat kidneys and those of Jim et al. (7) using glomeruli from rat, Winokurt and Morrison (5) and Oliw et al. (6) failed to find evidence for lipoxygenase activity in preparations of whole cortex obtained from rabbits, although Winokurt and Morrison did find 12- and 15-HETE production by a crude enzyme preparation from rabbit kidney medulla (5). Working on the 100,000 x g cortical supernatant, they concluded that the compounds observed were formed by the cytochrome P-450-linked monoxygenase system. It should be pointed out that in both studies, the pellet of the first low speed centrifugation (10,000-17,000 x g) which contained the glomeruli was discarded. It is thus very likely that they excluded the main cortical source of lipoxygenase. In our study, as shown in Fig. 2, 12-HETE was present nearly entirely in the pellet (3,000 x g) containing the glomeruli and in only a very small concentration in the incubation medium. Further fractionation indicated that this lipoxygenase product was almost equally distributed in the membranes and the cytosol (Table I). This finding differs completely from what we observed previously with glomerular prostaglandins (2) which were not stored but released immediately from the cells into the incubation medium. Thus, extraction was performed with the whole glomerular suspension in agreement with the studies utilizing intact cells such as polymorphonuclear leucocytes (14, 15) or peritoneal macrophages (16).

Similar to the location of the lipoxygenase products, lipoxygenase activity was distributed almost equally in the membranes and the cytosol. A smaller fraction was found in the microsomes (Table I). Such a particulate localization was also observed in human platelets by Ho et al. (17). Our findings of significant amounts of lipoxygenase activity in cytosol are also in agreement with those of Siegel et al. (13) in the human platelet and with those of Winokurt and Morrison (5) in medullae of rabbit kidneys.

The results of our studies indicate that important differences, both qualitative and quantitative, exist between species (human versus rat), with respect to the type of lipoxygenase activity that is present predominantly. At low substrate concentrations, human glomeruli synthesized in equivalent amounts 12- and 15-HETE, whereas rat glomeruli synthesized more 12-HETE but no 15-HETE. At higher substrate concentrations both species synthesized 12- and 15-HETE, but the rate of synthesis for both products was higher in human glomeruli. The observation that 12-HETE is the predominant product in the rat in our studies accords with the results of Jim et al. (7). However, our results appear to differ from those of these authors in that we failed to find evidence of other lipoxygenase products whereas they found a small quantity of 8- and/or 9-HETE. These differences may be due in part to the fact that their study was performed under stimulated conditions (in the presence of the ionophore A 23187) and may also reflect differences in substrate concentration or the specific activity of the isotope employed. However, we failed to observe an effect of the ionophore or of a change in extracellular calcium concentrations in our studies.

Which lipoxygenase is present predominantly may also depend on the tissue studied. 12-HETE is predominant in human platelets (13, 17), whereas 15-HETE is observed in reticulocytes (18) and leukocytes (14); 5-HETE, which is the source of leukotrienes, is also found in leukocytes (15). Inasmuch as we found that 12-HETE was the major product of the lipoxygenase pathway in glomeruli isolated from both species studied, we analyzed the characteristics of the 12-lipoxygenase system in more detail. 12-Lipoxygenase activity was stable at high temperatures (38-50 °C), a finding that differs from the observation of Ho et al. (17) in which the same enzyme purified from human platelets lost 50% activity at 50 °C. We also found a marked difference between the pH dependence of human and murine glomerular 12-lipoxygenase.

![Lineweaver-Burk transformation of the data shown in the insets in Fig. 4. The reciprocal of the rate of synthesis of 12- (left) or 15- (right) HETE is plotted as a function of the reciprocal of substrate concentration. Correlation coefficients corresponding to the linear regression of these data are given. Incubation was carried out for 15 min.](http://www.jbc.org/content/journal/jbc/258/7/4329.full.html)
Siegel et al. (13) concluded that, in human platelets, 12-lipoxygenase was active over a broad range of pH with an optimum at 6.0. The characteristics of the lipoxygenase derived from glomeruli isolated from the rat are different from those of cyclooxygenase present in the same preparation since the latter enzyme is most active at 30–37 °C (2) and at pH values between 8.0 and 9.0.2 12-HETE production was linear over 15 min as observed by Ho et al. (17) with the 12-lipoxygenase from human platelets. The $K_v$ values of human and murine lipoxygenases were estimated only at low concentrations of substrate and were found to be close to 40 μM. This is half the value observed at similar concentrations of arachidonate by Siegel et al. (13) for the human platelet 12-lipoxygenase. In contrast, 15-HETE is inactive on leucocyte chemotaxis (21). The differences in synthetic rates of these two compounds by both species (human and mouse) were found to be close to 40 μM at low concentrations of substrate. This value is less than those we have observed with both human and murine glomeruli.

Products of lipoxygenase activity may have several physiologic effects. 12-HETE stimulates chemotactic and chemoattractant responses as well as the hexose monophosphate shunt (19) and lysosomal enzyme release (20) in polymorphonuclear leukocytes. In contrast, 15-HETE is inactive on leucocyte chemotaxis (21). The differences in synthetic rates of these two compounds by both species (human versus rat) is difficult to correlate with differences in glomerular physiology. Since it has been shown that 15-HETE inhibits the 12-lipoxygenase of platelets (22), glomerular formation of 15-HETE may represent an intracellular regulatory mechanism. 15-HETE is also the source of a particular leukotriene pathway including a 14,15-oxido analogue of leukotriene A₄ and its two derivatives: 8,15-leukotriene B₄ and 14,15-leukotriene B₅ (23, 24) whose biological activities remain to be defined. 12- and 15-HETE are also strong immunosuppressors capable of inhibiting red blood cell rosette formation and concanavalin-induced blast transformation of leukocytes (25). Thus, these two lipoxygenase-derived products may play a role as mediators of the inflammatory response of the glomerulus both in experimental models of glomerulonephritis and in human renal diseases.

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