

Radiocontrast Agents Induce Endothelin Release *In Vivo* and *In Vitro*^{1,2}

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ABSTRACT

The intravascular administration of the ionic radiocontrast agent sodium iothalamate (2.9 g of iodine/kg body wt) to rats induced an increase in plasma concentration of immunoreactive endothelin from 21.3 ± 1.2 to 36 ± 3 fmol/mL, preceded by a transient rise in the plasma level of atrial natriuretic peptide and associated with a fall in RBF. Equi-iodine amounts of the nonionic agents ioxaglate and iohexol elicited similar or more marked changes in plasma endothelin, but hypertonic solutions of NaCl, mannitol, or glucose did not. Comparable levels of endothelin produced by infusions of endothelin-1 induced a reduction of up to 29% in RBF. Iothalamate and iohexol stimulated endothelin release from cultured bovine endothelial cells, suggesting a direct effect of ionic and nonionic agents on vascular endothelium. The data invite speculation that under some

circumstances endothelin release might play a role in the circulatory changes caused by these compounds and in the pathogenesis of radiocontrast nephropathy.

Key Words: Endothelin, radiocontrast, iothalamate, iohexol, ioxaglate, atrial natriuretic peptide

Prolonged decreases in RBF and GFR follow radiocontrast administration (1–9). It has been suggested that the reduction in RBF and possible attendant hypoxia, particularly in the outer medullary region of the kidney (10,11) may participate in the pathophysiology of contrast nephropathy (12).

The potent endogenous vasoconstrictor, endothelin, is released from endothelial cells in response to various stimuli (13) and has recently been shown to participate in the renal vasoconstriction induced by cyclosporine (14). In this study, we show that radiological contrast agents release endothelin, both *in vivo*, in intact rats, and *in vitro*, in a preparation of cultured bovine endothelial cells.

METHODS

In Vivo Studies

Male Sprague-Dawley rats (290 to 430 g) were used for all experiments and were fed regular rat chow and water *ad libitum*. Under Inactin anesthesia (100 mg/kg; BYK Gulden, Konstanz, Germany), the right carotid artery or jugular vein and the right femoral artery were cannulated (PE 50; Clay-Adams, Parsippany, NJ) and the rats were put in warmed cabinet (37°C). Various contrast agents and control solutions were injected through the cannulae inserted in the carotid artery or jugular vein over 2 to 3 min. Blood samples (200 μ L) were taken at the end of the injection period for plasma osmolality through the femoral arterial cannulae.

The rats were killed and single end-point blood samples for peptide analysis and plasma osmolality were obtained from the abdominal aorta at various intervals after the administration of the radiocontrast agent. The osmolality of plasma samples and injected solutes was determined with a freezing point osmometer (μ Osmette; Precision Systems, Inc., Natick, MA).

RBF was monitored in a separate set of parallel

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experiments after the i.v. infusion of 80% sodium iothalamate (Angio-Conray; Mallinckrodt, Inc., St. Louis, MO), 6 mL/kg body wt. A pulsed Doppler method was used, with a piezoelectric crystal (VF-1; Valpey-Fisher, Hopkinton, MA) mounted on the left renal artery. These measurements were initiated 20 to 30 min after the abdominal cavity was closed, when blood pressure and RBF had stabilized.

Sequential Effects of Sodium Iothalamate. These experiments were designed to measure levels of endothelin and atrial natriuretic peptide at various intervals after the intra-arterial injection of 80% sodium iothalamate (Angio-Conray; Mallinckrodt, Inc.), 6 mL/kg body wt—the same dose that was studied previously in a model of radiocontrast nephropathy in rats (15). The rats were killed, and blood samples were obtained at baseline or 2, 5, 10, 15, 30, and 60 min after the initiation of contrast injection (four rats in each group).

Comparisons With Other Contrast Agents and Cortisol Solutions. Because endothelin levels in rats injected with iothalamate peaked at 10 to 15 min, this set of experiments was designed to compare plasma endothelin at 15 min after the intra-arterial injection of equivalent iodine doses (2.9 g/kg body wt) of ioxaglate (9 mL/kg; Hexabrix 320; Mallinckrodt, Inc.) and iohexol (9.6 mL/kg; Omnipaque 300; Winthrop-Breon Lab., Sterling Drug, Inc., New York, NY). Control groups examined at 15 min were rats injected intra-arterially with 6 mL/kg of 0.85% saline or with hypertonic solutions of saline, glucose, or mannitol (2,590, 2,560 and 1,510 mosM/L, respectively). Also examined at 15 min were rats given iothalamate (6 mL/kg) through the jugular vein (four rats in each experimental group).

Effect of Nephrectomy. In experiments designed to evaluate the contribution of the kidneys to endothelin production and elimination, endothelin levels were measured at 15 min in four rats injected with 6 mL/kg of sodium iothalamate immediately after bilateral nephrectomy through a midabdominal incision. Four sham-operated rats injected with iothalamate and four nephrectomized rats injected with 6 mL/kg of saline served as controls.

Hemodynamic Effects of Low-Dose Endothelin. In order to study the effect of small increases in plasma endothelin upon RBF, endothelin-1 (ET-1; human, porcine; Peninsula Laboratories, Inc., Belmont, CA) was infused through the femoral vein over 20 to 40 min to six rats (245 to 390 g wt), at rates of 2 to 22 pmol/kg/min. The rats were anesthetized with Inactin. RBF was monitored by a pulsed Doppler method with a piezoelectric crystal (VF-1; Valpey-Fisher) mounted on the left renal artery. Each experiment was initiated 20 to 30 min after the closure of the abdominal cavity, when blood pressure and RBF were stabilized. The rat was kept in a heated chamber

and infused with saline (2.2 mL/h). Two to five repeated 0.5-mL blood samples were withdrawn and replaced by saline through the arterial line, at baseline and at intervals during the continuous infusion of endothelin.

In Vitro Studies

Experiments were performed in cultured endothelial cells to evaluate the direct effect of contrast agents and control solutions upon endothelin release.

Cell Preparation. Vascular endothelial cells were scraped from fresh specimens of adult bovine aorta and were seeded on Nunc culture plates coated with human plasma fibronectin (New York Blood Ctr, Inc., New York, NY). Cells were maintained at 37°C in a humidified 5% CO₂ atmosphere in Dulbecco's modified Eagle's medium, supplemented with 25 mM *N*-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid [HEPES] (DMEM-HEPES), 10% calf serum, 5% fetal calf serum, and antibiotics (penicillin [50 U/mL] and streptomycin [50 µg/mL]). They were passaged weekly at a split ratio of 1:3. Confluent, highly organized monolayer cultures, of the 9th to 13th passage were used, 7 to 10 days after seeding, at a density of 1.2×10^6 cells/35-mm dish.

Experimental Design. The regular medium was removed, and the cells were washed twice with phosphate buffered saline (pH 7.4) and reincubated (37°C) with 2 mL of serum-free DMEM-HEPES, containing 0.25% BSA and the various reagents detailed below. Osmolality and immunoreactivity endothelin were determined in the culture medium at 3 h.

At the conclusion of the experiment, cell integrity and viability were confirmed by phase contrast microscopy, carried out immediately and after 24 h of reincubation with DMEM-HEPES containing BSA and antibiotics, and finally by morphological evaluation of methylene blue-stained cells fixed with 1.25% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4).

Experimental Groups. Various contrast agents and control hypertonic solutions were added to the medium at final concentrations comparable to estimated plasma levels in the *in vivo* studies. After the addition of radiocontrast agents, the increments of medium osmolality were comparable to those found in the intact rat after injection. Thrombin (10 U/mL) and reagent-free medium served as positive ($N = 8$) and negative ($N = 13$) controls, respectively. The contrast agents tested were sodium iothalamate (20 µL/mL; $N = 11$) and iohexol (32 µL/mL; $N = 6$). These amounts of contrast agents added were calculated to provide a concentration of organically bound iodine in the incubation medium of 9.67 mg/mL. Control hypertonic solutions with an osmolal concentration comparable to that of 20 µL/mL of iothalamate were

also tested by increasing the medium concentration of sodium chloride or glucose by 24.5 and 50 mmol/L, respectively ($N = 7$ for each group). Additional dose-response experiments were carried out to evaluate the relationship of endothelin appearance to progressively increasing concentrations of iohalamate (2, 5, and 10 $\mu\text{L}/\text{mL}$; $N = 7$ for each group).

Assays. Osmolarity and endothelin concentrations were measured in the medium with the added reagents (baseline "blank") and after incubation for 3 h. One-milliliter samples were placed in prechilled tubes and centrifuged, and a 100- μL aliquot of the supernatant was removed for osmolality measurements. EDTA and trasylol were added, and the remainder of the sample was processed as described below.

Endothelin and ANP Measurements

Blood samples were placed into prechilled test tubes containing sodium-EDTA (1.5 mg/mL) and trasylol (400 kallikrein inhibitor units/mL) and immediately centrifuged at 4°C, and the plasma was collected and extracted. Samples of plasma or incubation medium (250 to 1,000 μL) for each peptide were acidified (250 μL of 2 N HCl/mL), extracted over ODS-silica cartridges (Sep-Pak C18; Waters Associates, Milford, MA), washed with a solution of trifluoroacetic acid, and eluted with acetonitrile. Eluates were then lyophilized and stored at -20°C until assayed. RIA for ANP and endothelin were performed with reagents obtained from Amersham, United Kingdom, by a standard double-antibody precipitation technique. ANP measurements were performed as previously described (16). Samples for endothelin were reconstituted in 250 μL of 0.02 M borate assay buffer before the assay. The antibody used was specific for ET-1 and endothelin 2, without cross-reactivity with endothelin 3 or ANP, but with a 38% cross-reactivity with big endothelin. After the addition of antibody and tracer to 100 μL of sample, tubes were incubated at 4°C for 4 days. At the end of that period, 100 μL of goat anti-rabbit antiserum at a dilution of 1:8 and 100 μL of a 1:25 dilution of normal rabbit serum (both produced by Pel-Freez, Rogers, AR) were added and incubation was carried out for an additional 24 h under similar conditions. Bound and free radioactivity were then separated by centrifugation for 30 min at 4°C, with subsequent decantation of the supernatant. Bound radioactivity was determined by counting each tube for 2 min in a gamma scintillation counter. The sensitivity as determined by 50% displacement of trace was approximately 20 fmol/tube. The intra-assay coefficient of variation was 7%, and the interassay coefficient of variation was 15%. Percent recovery of a known amount of ET-1 extracted and lyophilized was $55 \pm 0.4\%$.

In separate experiments, we determined that the addition of iohalamate, iohexol, or ioxaglate to plasma (60 mg of iodine/mL) or of iohalamate or iohexol to cell culture medium (9.67 mg/mL) did not interfere with the binding of labeled endothelin to its antibody in the RIA of endothelin.

Statistics

Descriptive statistics are presented as means \pm SE. A *t* test and analysis of variance (ANOVA) with post-hoc comparisons by the Newman-Keuls test and simple correlations were applied as detailed below. Statistical significance was considered to be present with a *P* value of less than 0.05.

RESULTS

Effects of Iohalamate in Intact Rats

A rise in plasma endothelin was noted after the injection of 6 mL/kg of sodium iohalamate. The plasma concentration almost doubled (from 21.3 ± 1.2 to 36.2 ± 2.6 fmol/mL) during the first 10 to 15 min ($P < 0.01$; ANOVA), and elevated concentrations were significantly sustained for as long as 30 min after the administration of the contrast agent. Intravenous and intra-arterial injections of iohalamate produced comparable increases in plasma endothelin at 15 min (to 38 ± 3.2 and 35 ± 2.7 fmol/mL, respectively), and these results were therefore pooled for further comparisons.

Prior nephrectomy did not alter the response of plasma endothelin to iohalamate. Fifteen minutes after its administration, the concentration of plasma endothelin in bilaterally nephrectomized rats (39.5 ± 3.6) was not different from that in sham-operated rats (36.2 ± 3.1). Plasma endothelin did not rise in nephrectomized rats injected with 0.9% saline (13.7 ± 2.6 ; $P < 0.01$ versus the other two groups by ANOVA).

Plasma ANP concentrations rose abruptly after iohalamate injection, from 194 ± 12 to $1,500 \pm 57$ pmol/L, with the highest values noted at 5 min. At 15 min, the ANP concentration had fallen substantially, to 555 ± 30 pmol/L, although plasma levels were still slightly elevated above baseline at 60 min.

The abrupt rises in osmolality and plasma ANP were associated with an initial fall in arterial blood pressure, which returned to baseline as plasma ANP started to decline and endothelin levels rose to their maximum. In three rats, the initial decrement in blood pressure was attenuated by pretreatment with indomethacin (10 mg/kg) (Sigma Chemical Co., St. Louis, MO) and 1-*N*-monomethylarginine (15 mg/kg) (Calbiochem Corporation, La Jolla, CA), suggesting the contribution of other endogenous vasodilators to this early transient hypotension.

As shown in Figure 1, an initial increase in total RBF (of 34% at 2 min), coinciding with the decrease in blood pressure and the rise in plasma ANP, was succeeded by a gradual decline that reached its lowest point at 10 min ($83 \pm 7\%$ of baseline). The recovery of RBF to baseline levels proceeded slowly over the

next 35 min, with further increase later on. These findings confirm earlier observations of an initial abrupt decrease in peripheral and renal vascular resistance when radiocontrast agents are injected, followed by sustained renal vascular constriction (1–9).

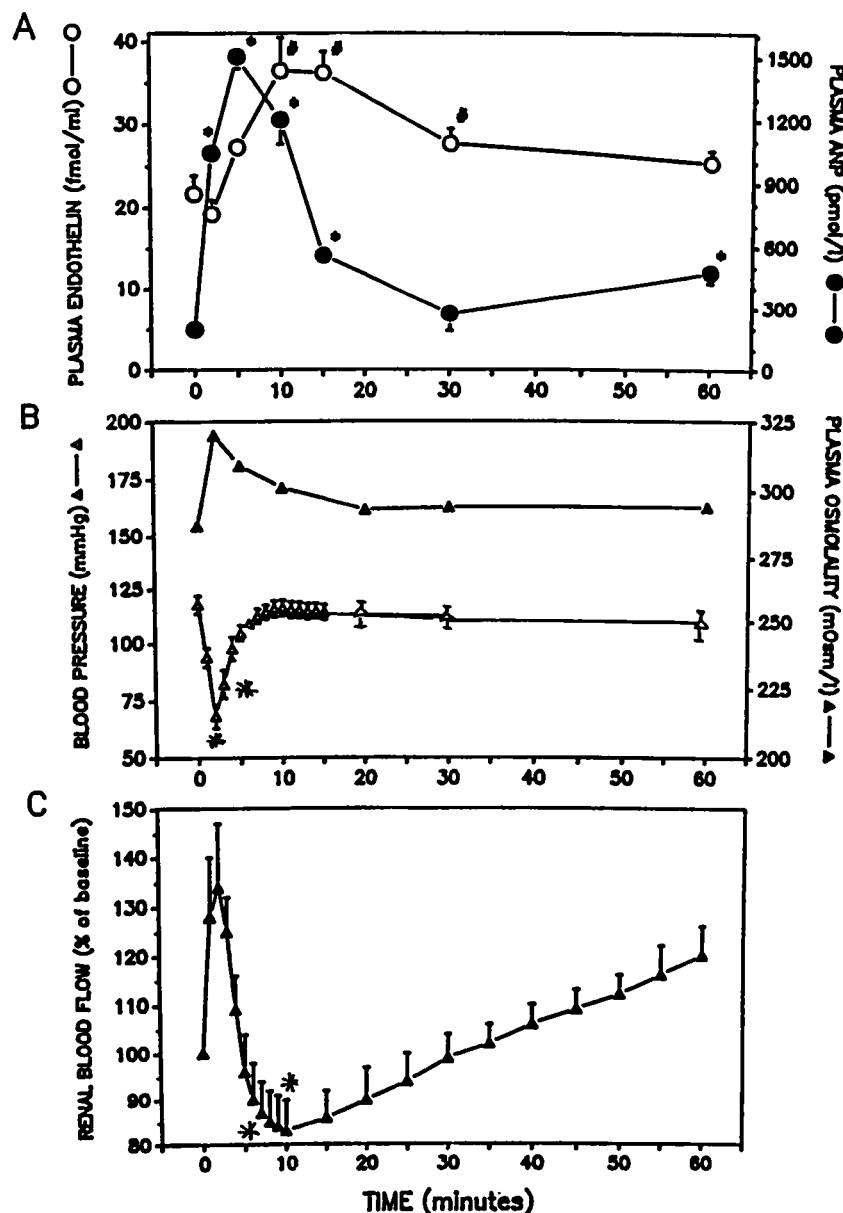


Figure 1. Changes in plasma endothelin and ANP levels (A) and in mean blood pressure and plasma osmolality (B) in rats sacrificed at various intervals after the injection of 6 mL/kg of 80% sodium iohalamate. Each point represents four or eight measurements (panels A and B, respectively) with the exception of peptide levels at 15 min (eight experiments). Changes in RBF were recorded in four rats in a separate set of experiments conducted under similar conditions (C). Note the early transient increase in ANP, as compared with the more delayed and sustained response of endothelin. (* $P < 0.01$ versus baseline; # $P < 0.01$ versus baseline and 2 min; one-way ANOVA). Peak and nadir changes in RBF, blood pressure measurements at 1 to 5 min, and postinjection plasma osmolality over the first 10 min are all significantly different from baseline ($P < 0.01$; one-way ANOVA). The standard error bars for plasma osmolality are smaller than the symbol size.

Effects of Other Contrast Agents and Control Solutions

Equi-iodine injections of ioxaglate and iohexol also elicited a rise in plasma endothelin at 15 min that exceeded those seen in the rats given iothalamate (Table 1) ($P < 0.01$; ANOVA).

Comparable osmotic loads of hypertonic solutions of sodium chloride, glucose, and mannitol did not produce elevated concentrations of plasma endothelin. The rise in plasma endothelin was not correlated with postinjection plasma osmolality.

Effect of Exogenous Endothelin on RBF

Plasma concentrations of immunoreactive endothelin ranging from 20 to 71 fmol/mL, comparable to those measured after radiocontrast injection, were produced by infusing ET-1 at rates varying from 2 to 22 pmol/kg/min. Increases of this magnitude in plasma endothelin produced distinct reductions of up to 29% in RBF (Figure 2).

Effect of Radiocontrast Agents on Endothelin Release From Cultured Endothelial Cells

Radiocontrast agents induced the appearance of endothelin in the medium bathing a preparation of cultured bovine endothelial cells, in a way reminiscent of their effects *in vivo*. The increase in endothelin release (2.5 to 4 times the control values) from cells exposed to iothalamate and iohexol was more

pronounced than that of cells exposed to thrombin, a known stimulant of endothelin release. High osmotic concentrations of hypertonic saline and glucose did not augment the release of endothelin by cultured cells (Table 2).

When the concentration of sodium iothalamate in the culture medium was systematically altered, the release of endothelin correlated with iodine dose ($r = 0.63$; $P < 0.0003$), reaching a plateau at iodine levels above 2.5 mg/mL (Figure 3).

DISCUSSION

The intravascular administration of the radiocontrast agents iothalamate, ioxaglate, and iohexol to rats produced a substantial rise in the plasma concentration of immunoreactive endothelin, with peak values attained by 10 to 15 min after the injection. Although all agents were hypertonic to plasma, the trigger for endothelin release did not appear to be hypertonicity, because hyperosmotic solutions of glucose, sodium chloride, and mannitol did not evoke a rise in plasma endothelin. The effect was elicited by an ionic, "low osmolar" agent (ioxaglate), a nonionic agent (iohexol), and an ionic "high osmolar" agent (iothalamate), in amounts comparable to those sometimes employed for extensive angiographic examinations in patients.

The increase in plasma endothelin produced by radiocontrast agents in intact rats is likely to result from an interaction of these organic iodine compounds with vascular endothelium, because endothelin release from bovine aortic epithelial cells in culture could be stimulated directly by radiocontrast

TABLE 1. Plasma endothelin: *in vivo* studies^a

Experimental Group (No. of rats)	Plasma Endothelin (fmol/mL)	Plasma Osmolality (mosM/kg)
Saline (4)	17.3 ± 1.4	286 ± 2
Iothalamate (8)	36.2 ± 2.6 ^b	320 ± 2 ^{c,d}
Ioxaglate (4)	59.3 ± 5 ^e	303 ± 3 ^c
Iohexol (4)	74.7 ± 9.8 ^e	304 ± 3 ^c
Hypertonic NaCl (4)	19.7 ± 2.5	327 ± 2 ^{c,d}
Hypertonic Glucose (4)	24.3 ± 2.2	319 ± 2 ^{c,d}
Hypertonic Mannitol (4)	26.3 ± 4.8	306 ± 3 ^c

^a Plasma levels of endothelin were obtained 15 min after the injection of contrast agents or control solutions to anesthetized rats. Plasma osmolality was measured at 2 min, immediately after solute injection. The injection solutions include iothalamate, ioxaglate, and iohexol (2.9 g of iodine/kg) or 6 mL/kg of 0.85% saline, hypertonic saline (2.590 mosM/kg), glucose (2.560 mosM/kg), or mannitol (1.510 mosM/kg). One-way ANOVA was used to estimate statistical significance.

^b $P < 0.01$ versus baseline endothelin levels (Figure 1) and versus saline by *t* test.

^c $P < 0.01$ versus saline.

^d $P < 0.01$ versus low osmolar contrast agents and mannitol.

^e $P < 0.01$ versus other groups (except between each other).

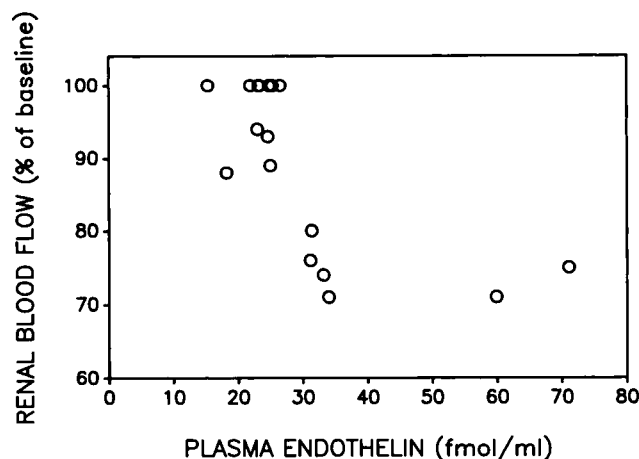


Figure 2. Relationship between plasma endothelin and the reduction of RBF in six rats continuously infused with increasing doses of endothelin (2 to 22 pmol/kg/min). In two animals, data consist of 4 to 5 repeated measurements of plasma endothelin per animal taken before and during the infusion.

TABLE 2. Release of endothelin from cultured endothelial cells^a

Treatment	No. of Cultures	Endothelin Release Per Hour (fmol/1.2 × 10 ⁶ cells)	Osmolal Increment (mosM/kg)
Control	13	45.5 ± 5.9	4 ± 1
Thrombin	8	94.8 ± 10.3	10 ± 1
Iothalamate	11	116.1 ± 14.9 ^b	41 ± 2 ^{c,d}
Iohexol	6	176.2 ± 40.6 ^e	19 ± 1 ^c
Hypertonic Saline	4	37.6 ± 8.5	40 ± 3 ^{c,d}
Hypertonic Glucose	4	38.5 ± 8.2	35 ± 2 ^{c,d}

^a Endothelin release from cultured bovine aortic endothelial cells incubated for 3 h in serum-free DMEM-HEPES. Control values are compared with those obtained after adding thrombin (10 μ L/mL) or iothalamate or iohexol (9.67 mg of organically bound iodine/mL) or after increasing the medium osmolality with sodium chloride or glucose. Mean endothelin release per hour is presented. The osmolal increment refers to the increase in medium osmolality produced by the addition of reagents, measured at 3 h, as compared with the osmolality of the initial control medium (one-way ANOVA). Thrombin-stimulated endothelin release fell short of statistical significance by ANOVA ($P < 0.1$ versus control), probably as a result of cell injury, noted in this group only.

^b $P < 0.05$ versus control, hypertonic saline, and glucose.

^c $P < 0.01$ versus control.

^d $P < 0.01$ versus iohexol.

^e $P < 0.01$ versus control, hypertonic saline, and glucose.

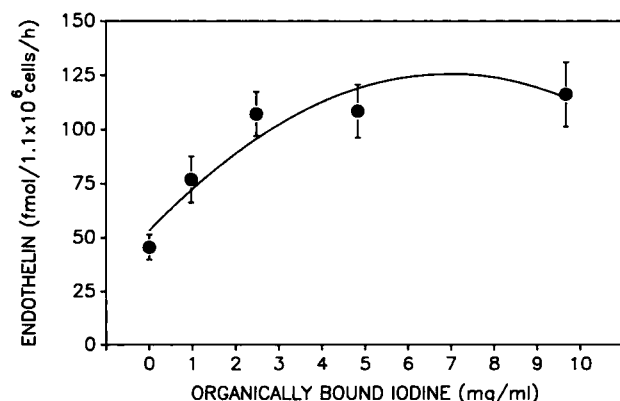


Figure 3. Endothelin release from cultured bovine endothelial cells exposed to various concentrations of sodium iohalamate over 3 h. Mean endothelin release per hour correlates with the medium content of the organically bound iodine ($r = 0.63$; $P < 0.0003$). The dose-response regression curve plateaus at iodine concentrations above 2.5 mg/mL.

agents. Other mechanisms such as radiocontrast-induced thrombin generation (17), release of vasopressin (18), or local hypoxia (19, 20) might also stimulate endothelin release *in vivo*.

As shown in Figure 1, plasma levels of endothelin measured 1 h after the injection of radiocontrast had

returned toward baseline. These endothelin levels are unlikely to cause protracted renal failure (unless recruitment of endothelin receptors had occurred, as was recently observed with cyclosporine [21]). In fact, rats injected with high doses of iohalamate do not develop nephropathy unless simultaneously treated with salt depletion and indomethacin (15). On the other hand, that such increases in circulating endothelin may have hemodynamic consequences is suggested by the decrease in RBF that accompanied similar concentrations of plasma endothelin produced by infusing exogenous ET into rats. These findings were not unexpected, because comparable levels of plasma endothelin also increased renal vascular resistance in dogs (22), anesthetized pigs (23), and isolated rat kidneys (24), whereas suppressor doses of endothelin have been found to reduce RBF in rats (25). Endothelin release might therefore contribute to some extent to the transient intrarenal vasoconstriction commonly induced by radiocontrast agents. Injections of exogenous ANP prevent the reduction in RBF normally elicited by radiocontrast in dogs, which is also accompanied by a rise in plasma endothelin (26). Contrast-induced renal vasoconstriction might therefore be ameliorated in part by the concomitant secretion of endogenous ANP, such as is seen in these experiments.

Could endothelin contribute to the pathogenesis of radiocontrast nephropathy? Recent work has demonstrated acute regional hypoxic tubular injury as early as 60 min after radiocontrast administration (27). The distribution of this injury follows intrarenal gradients of oxygenation, suggesting focal hypoxia as an important factor in the pathogenesis of this syndrome (15, 27). After the injection of contrast agents, direct measurements of tissue oxygen tension in the kidneys of intact rats demonstrate a sharp decline in outer medullary oxygenation from baseline low levels of P_{O_2} (27). Hypoxic outer medullary injury in isolated perfused rat kidneys is augmented by the addition of radiocontrast agents to the recirculating perfusate (15,28). In experimental animals, radiocontrast agents cause significant damage only in states associated with renal hypoperfusion, such as pretreatment with indomethacin, salt depletion, or angiotensin II (15,28,29); renal ischemia (30); or heart failure (31). This suggests that under some circumstances radiocontrast agents may adversely affect the balance of intrarenal oxygenation, normally determined by the interplay of several vasoactive agents (32). The inhibition of the formation of the endothelial-derived relaxing factor nitric oxide greatly exacerbates the nephrotoxicity of radiocontrast material (33). Perhaps endothelin released at a critical time (and possibly at a critical site) could likewise contribute to radiocontrast-induced hypoxic intrarenal damage in suitably conditioned subjects. Direct testing of

this hypothesis must await the use of specific endothelin antagonists or antiendothelin antibodies to prevent radiocontrast-induced renal damage.

Our observations in nephrectomized rats suggest that a major contribution to the increase in endothelin in peripheral plasma is from extrarenal sources. It is of interest, however, that within the kidney, mRNA for endothelin is localized chiefly in the vasa recta of the medulla (34), although endothelin is also formed in glomeruli (35), mesangial cells (36), and medullary tubules (37–39). Receptors for endothelin are found in high concentration in the medullary vasa recta (34,40) as well as in glomerular capillaries (40,41). The stimulation of endothelin release from intrarenal sites by radiocontrast agents might thus be expected to produce vasoconstriction selectively affecting the renal medullary circulation and the glomeruli, conceivably exacerbating medullary hypoxia by a local action, without necessarily contributing to the concomitant rise in endothelin levels in the systemic circulation.

The mechanism by which radiocontrast agents elicit the release of endothelin from endothelial cells remains to be elucidated. Although production of endothelin is constitutive in cultured endothelial and mesangial cells (13,36,41), previous studies suggest that its release is regulated primarily at the level of mRNA transcription (13,42,43). Nevertheless, the early increase in plasma endothelin, noted in our experiments *in vivo* within 15 min, is in agreement with that from other studies, indicating rapid endothelin release *in vivo* induced by endotoxin (44) and cyclosporine (14), and suggests the presence of post-transcriptional regulation of endothelin production or release (45).

In summary, the intravascular administration of ionic and nonionic radiocontrast agents to rats induces an increase in plasma immunoreactive endothelin. Sodium iohalamate and iohexol directly stimulate the release of endothelin from cultured bovine endothelial cells. These observations suggest that under some circumstances, endothelin might play a role in the pathogenesis of radiocontrast nephropathy.

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