A novel inbred rat model with inducible hypertension has been generated using a renin transgene under the transcriptional control of the cytochrome P450, Cyp1a1 promoter. The degree and duration of hypertension are regulated tightly by administration of the natural xenobiotic indole-3 carbinol and can be readily reversed. Induction experiments reveal distinct temporal and mechanistic responses to hypertensive injury in different vascular beds, which is indicative of differential susceptibility of organs to a hypertensive stimulus. The mesentery and heart exhibited the greatest sensitivity to damage, and the kidney showed an adaptive response prior to the development of malignant hypertensive injury. Quantitative analysis of morphological changes induced in mesenteric resistance arteries suggest eutrophic remodeling of the vessels. Kinetic evidence suggests that locally activated plasma prorenin may play a critical role in mediating vascular injury. This model will facilitate studies of the cellular and genetic mechanisms underlying vascular injury and repair and provide a basis for the identification of novel therapeutic targets for vascular disease.

Essential hypertension has a complex multifactorial phenotype. Both genetic and environmental factors influence its development, and understanding the pathogenesis of complications such as vascular lesions and end-organ damage may lead to more specific treatment and targeted intervention.

We have identified candidate loci in rats that may contribute to target organ damage and mortality in malignant hypertension (MH), a condition characterized by an accelerated rise in blood pressure, endothelial injury, activation of the renin-angiotensin system, and microangiopathy (1). Several animal models have been generated to investigate the pathophysiology of hypertensive vascular injury. Most animal models of MH to date require surgical or pharmacological intervention to precipitate onset or depend on the constitutive expression of endogenous genes or heterologous transgenes (2–5). In rats doubly transgenic for human renin and angiotensinogen genes, hypertension and fibrinoid vasculitis (5) accompanied by alteration in surface adhesion molecules, proinflammatory cytokines, fibrogenic mediators and leukocyte infiltration (6) have been reported. In most of these models, the onset of disease cannot be determined precisely.

The initiation events of pathological processes can only be studied in an animal model in which hypertension is induced by tightly temporally regulated gene expression. If the onset and level of hypertension can be controlled, then the cellular and molecular events during initiation of the vascular and organ injury can be identified unequivocally. Reversibility of the gene expression provides an opportunity to study the molecular and cellular basis of repair. We therefore have generated inbred transgenic rats with inducible hypertension using the cytochrome P450 promoter, Cyp1a1, to drive expression of the mouse Ren-2 gene. The transgene is expressed primarily in the liver and is rendered inducible by xenobiotics such as indole-3 carbinal (13C) (7, 8), which act via the aryl hydrocarbon receptor (8, 9). 13C is a naturally occurring agent found in cruciferous vegetables that acts as a benign inducer with a short biological half-life.

We demonstrate that transgene expression and hypertension can be regulated in a dose-dependent and reversible manner. Vascular remodeling is observed consistently, and characteristic responses in different vascular beds are seen in the early phase of MH development. The availability of rats with inducible hypertension should provide a basis for detailed studies of the molecular and cellular events occurring during the progression and repair of hypertensive vascular damage.

EXPERIMENTAL PROCEDURES

Animals

Rats were given free access to water and standard commercial rat chow containing 0.32% NaCl (Special Diet Services, Witham, Essex, UK). The breeding, maintenance, and study of animals were performed according to home office regulations.

Generation of Transgenic Rats

The rat Cyp1a1 promoter was isolated by NcoI-SalI double digestion of pAhIR1-LacZ (kindly provided by R. C. Wolf, University of Dundee)
to yield an 11.5-kilobase fragment containing 5'-flanking regions exon 1 and part of exon 2. This was placed upstream of Ren-2 cDNA and an SV40 poly(A) signal in pBluescript SK2+(+) (see Fig. 1a) (10). The injection fragment was excised by NotI-BstXI digestion and was introduced into the Fischer F344 single-cell embryos by microinjection as described (11, 12). Founder mice were identified by Southern blot hybridization after restriction digestion of genomic DNA with EcoRI and hybridization with the Ren2 cDNA probe (Fig. 1b). Animals from line TGR(Cyp1a1Ren2) (formally named TG10) were normotensive by tail-cuff plethysmography and radiotelemetry and were used for detailed study. The remaining lines, which exhibited varying degrees of hypertension in the absence of inducer, were not studied further.

Transgene Expression

Transgene expression was assessed by Northern blot hybridization analysis using total RNA isolated from frozen tissue by the RNAZOL method (13) and full-length Ren-2 cDNA as a hybridization probe.

Radiotelemetry

Direct blood pressures were monitored by telemetry using a surgically implanted transmitter (Data Sciences International, St. Paul, MN). The signal was decoded using Dataquest IV 2.2 software to give systolic blood pressure, mean blood pressure, diastolic blood pressure, and heart rate data.

Induction of Transgene Expression by Indole-3 Carbinol (I3C)

Single Dose Induction—Blood was collected from adult rats by retro-orbital bleeding under halothane anesthesia. Induction was then initiated by gastric gavage of 150 mg/kg of I3C in sesame oil (50 mg/ml) at day 0 under light halothane anesthesia. The animals were allowed to recover and given free access to standard food and water. At days 1, 3, and 5 after gavage, blood was collected under halothane anesthesia (n = 5, each group), and tissues were collected.

Continuous Induction—Transgenic and nontransgenic animals (10–12 weeks old) were given standard powdered food (Special Diet Services, Witham, Essex, UK) for 24 h before the experiment. I3C (0.3% (w/w)) was then mixed with the rat food (in a small amount of water), and individually caged rats were given ~25 g daily and free access to drinking water. The animals were culled at days 4, 7, and 14 after induction when blood and tissues were collected.

Plasma Collection

Blood was collected by retro-orbital bleeding or cardiac puncture into 0.1 volumes of ice-cold 100 mM EDTA for the renin and aldosterone assays or into 1:40 volume of ice-cold inhibitor mixture (4 mM phenylmethylsulfonyl fluoride, 2.5 µg/ml O-phenanthroline, 0.16 mg/ml captopril, 40 µg/ml pepstatin, 4% p-mercaptoethanol, and 0.25 M sodium EDTA, pH 8.0) for angiotensin II measurement. The samples were centrifuged (100 °C for 6 min), and plasma was snap-frozen and stored at -70 °C prior to assay.

Tissue Homogenates

After perfusion with 0.9% NaCl, the tissues were collected and homogenized in 0.1 M Tris-Cl, pH 7.2, containing 0.1 M phenylmethylsulfonyl fluoride and 5 mM EDTA and centrifuged (100 X g at 4 °C for 10 min) to remove debris and unbroken cells. After further centrifugation (50,000 X g for 30 min) the resultant supernatants were stored at -80 °C prior to renin analysis.

Renin and Prorenin Determination

Active and inactive renin concentrations were determined as described previously (14) after the pretreatment of samples with buffer or trypsin (400 units/ml for plasma and 50 units/ml for tissue), respectively. The samples were incubated with lyophilized renin substrate (80 mg/ml) for 1 h at 37 °C, and the Ang I concentration was then measured by radioimmunoassay (15, 16). For plasma renin concentration, the samples were incubated directly with substrate. Addition of the specific renin inhibitor CH-732 (17) (10 µM, a gift from M. Szeleni, Ferrin Research Institute, Southampton, UK) confirmed the specificity of the reaction. Protein content of the samples was determined using a commercial kit (Bio-Rad).

Specific Immunoprecipitation of Mouse Renin

To determine the percentage of mouse renin present in plasma samples, immunoprecipitation of mouse renin was carried out as described previously (14) using a monoclonal anti-mouse renin antibody (no. 120, provided by M. R. Celio, Universte Perolles, Fribourg, Switzerland) that showed <3% cross-reactivity to purified rat renin. Antibody/renin complexes were precipitated with formalin-fixed Staphylococcus aureus protein A (immunoprecipitation, no. 9321 SB, Life Technologies, Inc.). The renin activities were determined before and after immunoprecipitation.

Plasma Aldosterone, Angiotensin I, and Angiotensin II

Plasma aldosterone was measured by radioimmunoassay after extraction and chromatography as described previously (18). For angiotensin II determinations, the plasma samples were processed by Sep-Pak elution (Walter GmbH, Eschborn, Germany) and were then analyzed by radioimmunoassay for Ang II (19). The cross-reactivity of angiotensin antibodies are as follows: Ang II with Ang I, 0.02%; Ang I with Ang II, <0.01%; and Ang I with angiotensinogen, <0.2%. Ang I was also measured as described previously (34).

Serum Angiotensin-converting Enzyme

Angiotensin-converting enzyme activity was determined as described previously (21) using the substrate Z-Phe-His-Leu (Bachem) with or without captopril or enalaprilat. Subsequent complex formation with Z-His-Leu was measured using a fluorescence spectrometer (RF-1502, Shimadzu).

In Situ Hybridization

In situ hybridizations were performed as described previously (22, 23) with the specificity being verified by parallel incubation with antisense and sense riboprobes on alternate sections. Throughout all experiments the sense probes did not produce any detectable signal.

Pathology

Organs were removed and fixed in 10% formal saline for 24 h and processed to paraffin block, and 4-µm sections were cut and stained using hematoxylin and eosin (H&E), periodic acid-Schiff, and Martius Scarlet Blue (MSB) as reported previously (24).

Quantitative Analysis of Structural Change in Mesenteric Arteries

Mesenteric resistance arteries were mounted on a perfusion myograph and fixed under pressure (calculated from wire myograph experiments at 0.9 liter/min). The arteries were then stained with the nuclear dye, propidium iodide, and morphology was measured with confocal microscopy (514-nm EX, 550-nm EM) and metamorph software (25).

Statistical Analysis

Data are given as mean ± S.E. unless stated otherwise. Differences between groups were evaluated by analysis of variance followed by the post hoc test of Bonferroni. Only p values less than 0.05 were accepted to indicate a significant difference.

RESULTS

Of six transgenic founders identified, TG10 (subsequently named TGR(Cyp1a1Ren2)) and its progeny were normotensive in the absence of inducer, suggesting that the Cyp1a1-Ren2 transgene (Fig. 1a) had integrated into a neutral genomic site. A Y chromosome integration site was suggested by Southern blot hybridization and pedigree analysis (Fig. 1, b and c) and was confirmed by fluorescent in situ hybridization analysis (data not shown).

Continuous Induction—Transgenic and nontransgenic male rats were induced with 0.3% (w/w) dietary I3C for 2 weeks. Severe hypertension (systolic blood pressure = 200 mm Hg) developed in the transgene-positive animals within 1 week of treatment and was sustained throughout the period of administration (Fig. 2a), whereas the nontransgenic controls remained normotensive. Transgenic animals showed clinical signs of severe hypertension including weight loss and polyuria by day 4 of induction, and their condition deteriorated over a 2-week period (average weight loss of 22%). The cessation of I3C administration at days 7 and 14 resulted in the normalization of blood pressure and clinical improvement within 72 h (data not shown).

Increasing plasma prerenin was detectable from 16 h post induction (p < 0.01), whereas the increase in plasma renin concentration (Fig. 2b) occurred 48 h later. After 7 days of
induction all components of the plasma RAS were increased in transgenic animals in comparison to induced nontransgenic controls. Plasma prorenin concentration was increased >200-fold, whereas plasma renin concentration increased 2-fold. Increasing plasma angiotensin II levels were found (day 7, 136.9 ± 13.4 versus 82.9 ± 25.5 ng/ml (p = 0.06, n = 11 and 8); day 14, 657 ± 208 versus 116 ± 117.9 ng/ml (p < 0.05, n = 4 each)), and plasma aldosterone was also higher (day 7, 43.5 ± 7.85 versus 9.7 ± 1.5 ng/100 ml (p = 0.0017, n = 8 and 7)). The immunoprecipitation of renin-2 with mouse renin-specific antibody revealed that the majority of plasma renin was transgene-derived (65.8 ± 18.2% of renin concentration, n = 8) after dietary I3C induction. Because post-induction steady-state levels of renin mRNA were suppressed markedly in the kidneys of induced transgenic and nontransgenic rats (Fig. 2c), these findings confirmed that circulating renin was predominantly extrarenal in origin. The expression of Ren-2 was detected in the liver and small intestine after 14 days of continuous I3C induction but not in the spleen, heart, kidney, lung, adrenal gland, aorta, or skin (data not shown).

The effect of RAS activation in the adrenal gland was studied by the in situ hybridization of CYP11B1 and CYP11B2 genes (Fig. 2d). No difference in the hybridization signal of CYP11B1 and CYP11B2 was found between groups prior to induction, but after 14 days it increased the CYP11B2 hybridization signal and higher numbers of expressing cells were observed in the zona glomerulosa of transgenic animals, reflecting the stimulatory effect of angiotensin II on aldosterone synthesis. No difference in CYP11B1 expression, in the zona fasciculata, was observed between induced transgenic and nontransgenic rats.

Pathological changes were observed in transgenic animals induced for 14 days but not in induced controls or transgenic rats prior to induction. A slight medial thickening of renal interlobular arteries and distal tubular hyperplasia was observed in transgenic rats by day 4 of I3C induction, and some showed fibrinoid necrosis (fibrin deposition in the vascular wall and transmural necrosis of vascular smooth muscle cells) of small arteries in the mesentery and heart. By day 7, histological evidence of malignant hypertension was observed throughout the mesenteric and coronary arteries (Fig. 3) with focal fibrinoid necrosis of small arteries. Microinfarction, as evidenced by patchy areas of myocardial necrosis in both the left and right ventricles, was seen with infiltration of inflammatory cells and proliferation of fibroblasts. Despite clear evidence of vascular injury in the mesentery and heart, there was no apparent fibrinoid necrosis in the kidney, although interlobular and arcuate arteries showed medial thickening of the vessel walls (Fig. 3). There was also hyperplasia of distal renal tubules, which might be the result of polyuria, pressure natriuresis, and high aldosterone. No evidence of MH or parenchymal lesions was observed in the brain.

After 14 days of induction, the kidney vessels showed endarteritis obliterans of interlobular arteries and afferent arterioles (Fig. 3). Widespread lesions of MH and tissue injury with chronicity (inflammatory cell and fibroblast proliferation) were observed in the mesentery and heart (Fig. 3). Brain histology was normal with no evidence of brain hemorrhage, infarction, or destructive vessel pathology. Immunohistochemical staining using a human albumin antibody showed a positive signal confined to the intravascular compartment, suggesting vascular integrity (data not shown).

Morphological studies on the mesenteric resistance arteries of the induced hypertensive rats (Fig. 4) revealed an increase in the total number of adventitial cells (p < 0.001) but not in smooth muscle or endothelial cells. There was a statistically significant increase in the media thickness (p < 0.05) and in the media/lumen ratio (p < 0.05). There was a significant increase in the density of adventitial cells (p < 0.01) and a significant decrease in the density of smooth muscle cells in the media (p < 0.05), suggesting that the mesenteric vasculature undergoes eutrophic remodeling. No changes were observed with respect to the width of the vascular wall, the adventitia, the intimal layers, the lumen diameter, or in the wall/lumen ratio.

Short-term Induction—Because I3C has a short biological half-life (26), we evaluated the reversibility of short term I3C induction. Prior to induction there was no difference in systolic blood pressure (as measured by radiotelemetry) between nontransgenic and transgenic animals. The administration of I3C by gastric gavage produced a dose-dependent increase in systolic blood pressure (Fig. 5). At the highest dose administered (150 mg/kg), the blood pressure change was detected by 12 h after induction, reaching the maximum blood pressure of 160 mm Hg by 24 h and returning to normal by 72 h. No clinical symptoms or pathological changes were observed during this short period of induction, and I3C had no effect on blood pressure in nontransgenic rats.

Northern blot and RNase protection analyses of liver total RNA failed to detect Ren-2 mRNA before induction. Expression was detected 24 h after induction (150 mg/kg), but Ren-2 mRNA was again undetectable after 72 h (data not shown). The highly significant increase in plasma prorenin at 24 h declined
by day 3 and dropped to baseline by day 5, concomitant with the change in blood pressure (Fig. 6). Detailed studies during the first 24-h period revealed that plasma prorenin was increased significantly within 6 h (51.2 ± 4.6 ng Ang I/ml/hr (0 h); 244.4 ± 35.5 (6 h); 1121.3 ± 221.2 (12 h); 1065.6 ± 118.9 (18 h); n = 6 each). There was no statistically significant change in plasma RAS in either transgenic or nontransgenic animals after single bolus induction. However, both prorenin and renin concentrations were increased significantly in transgenic liver and heart tissue homogenates after 24 h (Fig. 7).

**DISCUSSION**

Only one founder of six was found to be normotensive in the absence of the inducer, suggesting that the transgene is sensitive to its site of insertion and is prone to leakiness. Because the transgene was integrated on the Y chromosome in line TGR(Cyp1a1Ren2), it precludes the study of hypertension in females, but nevertheless the model has wide applicability. Hypertension is induced rapidly in a dose-dependent manner as a consequence of transgene expression and can be reversed in the absence of sustained induction. Ren-2 gene expression was detected in liver within 24 h of but not prior to I3C induction. Noninduced transgenic animals are indistinguishable from Fischer F344 controls with respect to plasma renin concentration, angiotensin concentration, blood pressure, and adrenal aldosterone synthase expression. A continuous dietary administration of I3C resulted in sustained hypertension, high circulating renin-angiotensin-aldosterone activity, and clinical manifestations of malignant hypertension including polyuria and weight loss (a consequence of salt and water depletion). The immunoprecipitation of mouse renin indicated that the high plasma renin concentration was primarily transgene-derived, whereas in situ hybridization revealed suppression of kidney renin mRNA in the induced transgenic animals (presumably as a result of negative feedback (27)), confirming that the kidney was not the source of high circulating renin.

Short-term kinetics studies of plasma and tissue RAS suggest that prorenin uptake and activation by tissues may be implicated in the development of hypertension. During short-term induction plasma prorenin was induced >20-fold without any change in plasma renin levels, suggesting that prorenin is not activated in plasma. However, in the liver and heart, active renin accounted for 30 and 37% of the total renin concentration, respectively.

The increase in transgene-derived plasma renin found during continuous dietary induction also followed a significantly earlier rise in plasma prorenin, again suggesting uptake and proteolytic activation of mouse prorenin in tissues (10) and subsequent redistribution in the circulation rather than plasma activation.

Physiological consequences of RAS activation include up-regulation of aldosterone synthase in the adrenal cortex and increased aldosterone production, which might contribute to vascular injury independent of the effects of blood pressure (28). Prorenin may also have vasculotoxic effects independent of blood pressure elevation as suggested previously (29), and...
The effects of increased angiotensin II on cell growth and extracellular matrix formation may determine the extent of adaptive processes of vascular and tissue injury.

Adaptive changes in blood vessels and histopathology characteristic of malignant hypertensive vascular injury were observed in the induced transgenic rats with continuous dietary I3C. Pathological examination in various tissues demonstrated differential susceptibility to vascular injury from malignant hypertension. Despite exposure to the same level of hypertension and circulating hormonal levels, the mesentery and heart were primarily the affected organs accompanied to a lesser extent by the kidney, in which medial thickening of arteriolar walls developed after 4 days of induction, but the vascular structural adaptation of malignant nephrosclerosis (proliferative endarteritis of interlobular arteries and fibrinoid necrosis of arterioles) only became apparent after day 7. This sequential pattern of vascular pathology in kidney was also observed in the nonclipped kidney of experimental two-kidney one-clip hypertension. Cerebral blood vessels were affected minimally, and there was no evidence of plasma exudation or cerebral edema.

Differential susceptibility to hypertensive vascular injury may reflect the distinctly different structural and functional properties of blood vessels in the brain and the kidney, which play a protective role in both vital organs in response to high pressure. In addition to the metabolic and/or myogenic mechanisms of autoregulation seen in most tissues of the body, the kidney is protected by tubuloglomerular feedback, where a flow-dependent increase in NaCl concentration at the macula densa elicits a vasoconstriction of smooth muscle cells at the vascular pole of the associated glomerulus. Capillaries in the brain are less permeable than those in almost any other organ.

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**Fig. 3.** Kidneys from induced Tg− (A) and uninduced Tg+ (B, day 0) show normal glomeruli (g) tubules (t), interlobular artery (ia), and afferent arteriole (aa). C, by day 7 of I3C induction, the interlobular artery shows luminal reduction and medial thickening of the wall. D, after 14 days there is evidence of malignant vascular injury with fibrinoid necrosis (fn) and endarteritis obliterans (eo). Hearts from induced Tg− (E) and uninduced Tg+ (F) with normal bundles of cardiac myocytes (cm) and coronary arterioles (ca) are shown. G, by day 7 of I3C induction, severe cardiac pathology, with fibrinoid necrosis (fn) of coronary arterioles and myocardial microinfarction (mi), occurs. H, after 14 days, early organization (org) of microinfarct with inflammatory infiltrate and fibroblast proliferation. The mesenteric artery (ma) histology of induced Tg− (I) and uninduced Tg+ (J, day 0) is normal. K, by day 7 of I3C induction, endarteritis obliterans (eo) affects peripheral mesenteric arteries and fibrinoid necrosis of arterioles is seen at bowel wall (data not shown). L, after 14 days, continuing fibrinoid necrosis of arterioles (fn) at serosal surface of intestine and early organization (org) with inflammatory infiltrate and elsewhere fibroblast proliferation.

**Fig. 4.** Morphometric analysis of mesenteric resistance arterioles determined by confocal microscopy. a, a significant increase in media thickness (but not of total wall, adventitial, or intimal layers) is seen between Tg− and Tg+ rats after induction (p < 0.05). b, a significant increase in the media/lumen ratio (p < 0.05) but not in the wall/lumen ratio is seen. c, a significant increase in total cell number (p < 0.05) and particularly adventitial cell number is seen (p < 0.001) but not in smooth muscle cells. d, cell density in the adventitia increased significantly (p < 0.01), whereas medial smooth muscle cell (SMC) density decreased significantly (p < 0.05).
tissue of the body (33), because the membranes of the adjacent endothelial cells form tight junctions (the blood-brain barrier). The “glial feet,” which support the capillaries on all sides, prevent overdistension in the event of high blood pressure and protect against transudation of fluid into the brain.

Quantitative analysis of structural changes in resistance mesenteric arteries revealed a eutropic remodeling of the vessels consistent with the characteristic cellular changes found in mesenteric arteries from the genetic hypertensive spontaneously hypertensive stroke-prone rat (20) and basilar arteries following drug-induced hypertension (L-nitro arginine methyl ester) in Wistar Kyoto rats (25). Given that different arteries were quantified in the three studies, there are clear similarities regarding the increase in number and density of adventitial cells and a reduction in the density of smooth muscle cells in the medial layer. However, spontaneously hypertensive stroke-prone rat vessels showed inward hypertrophic remodeling (i.e. an increase in tissue volume), whereas in the basilar arteries there was a reduction in the number of smooth muscle cells.

The inducible hypertensive rats provide a unique model in which malignant hypertension and hypertensive end-organ damage can be investigated systematically. Control of the onset, level, and duration of hypertension requires no surgical manipulation and minimal physiological disturbance. Increased blood pressure causes clear, reproducible, differential tissue modifications and can be tightly regulated. This allows precise investigation of the initiating events in the development of vascular lesions, of the cellular and molecular basis of vascular remodeling in both mild and severe hypertension and, because of its reversibility, the mechanisms of vascular repair.

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Controlled Hypertension, a Transgenic Toggle Switch Reveals Differential Mechanisms Underlying Vascular Disease
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