Renal abnormalities in mutant mice

SIR — On endothelial surfaces throughout the body, angiotensin-converting enzyme (ACE) generates angiotensin II and other peptides which contribute to fluid and electrolyte balance and to the maintenance of blood pressure. ACE is also expressed in tissues from early embryonic stages, including epithelia, where its role is poorly defined. We have been particularly interested in potential roles of ACE in development, because pharmacological blockade in neonatal rats can cause renal abnormalities[1]. Targeted mutation of the ACE gene has recently been shown to reduce blood pressure in heterozygous mice and to produce infertility in homozygous deficient male mice, accompanied by renal cortical atrophy, tubular shrinkage and inflammation[2]. Adult mice of all genotypes appear otherwise outwardly healthy[2].

We used gene targeting designed to preserve expression of the testicular isoform, which is generated from an alternative promoter, to make mice lacking ACE. Homozygous mutants lack ACE in all tissues except the testes. The most notable defect is the inability of homozygous mutant mice to concentrate their urine. Whereas wild-type or heterozygous littermates can concentrate their urine to more than 4,000 mOsm l^{-1} after 2 hours of fluid deprivation, the ACE mutant mice cannot concentrate to more than 820 mOsm l^{-1}. These changes are similar to those seen in neonatal rats treated with ACE inhibitors[1]. The ACE mutant mice are also uraemic, with mean blood urea nitrogen (BUN) of 0.52 mg ml^{-1} at 4 months of age, as opposed to 0.15 mg ml^{-1} in wild-type littermates.

Generation of concentrated urine occurs principally in the loops of Henle and the collecting ducts of the kidney[3]. These sites are clearly disorganized in the mutant mice (see figure): the anatomy of the medulla (which contains the collecting system) and the pelvis (where collecting ducts empty to the ureters) is markedly distorted. The fan-like medullary rays are absent and the triangular pelvis is shrunken and misshapen. Histological section shows the medulla to be compressed by pelvic cystic dilation and medullary cysts. These changes can explain the failure to concentrate the urine. There is no evidence of ureteral obstruction. The kidneys of heterozygous mice appear normal (data not shown). Cortical atrophy, vessel-wall hypertrophy and inflammation noted previously in ACE mutant mice[2] are also present in these ACE mutant mice.

The ACE mutant mice reported here seem to be more sick than the ACE mutant mice reported previously[2], perhaps because of the severity of the renal lesions. Although homozygous mice are born at the predicted 25% rate to heterozygous pairs, most die by the time they are weaned at 3 weeks of age. The only obvious difference between the mutants described in ref. 2 and here is that in our mutants testicular ACE is preserved. We assume that this accounts for the retention of fertility, in contrast to those lacking both isoforms[2]. Presumably, the difference in severity reflects modification by other genes .

ACE inhibitors have been used in antihypertensive therapy since the late 1970s, and can be associated with renal failure in patients with compromised renal blood flow[4]. Recent reports suggest that rats exposed to ACE inhibitors in the neonatal period may suffer renal abnormalities and water wasting, similar to those reported here in the ACE mutant mice[1]. Both angiotensin II and its receptors are present in the developing kidney, and it will be of interest to determine whether the products of ACE activity, which include but are not limited to angiotensin II, act as signalling molecules during assembly of the renal tubules and collecting system.

Medullary cysts, corticotubular atrophy, interstitial inflammation, water wasting and uraemia are characteristics of the nephronophthisis–uraemic medullary cystic disease complex, a group of disorders that cause renal failure in childhood and adolescence[5,6]. In some instances it is familial, but whether any cases reflect ACE deficiency is unknown. This mouse system may offer an opportunity to study progression of this disorder and to examine directed therapies.

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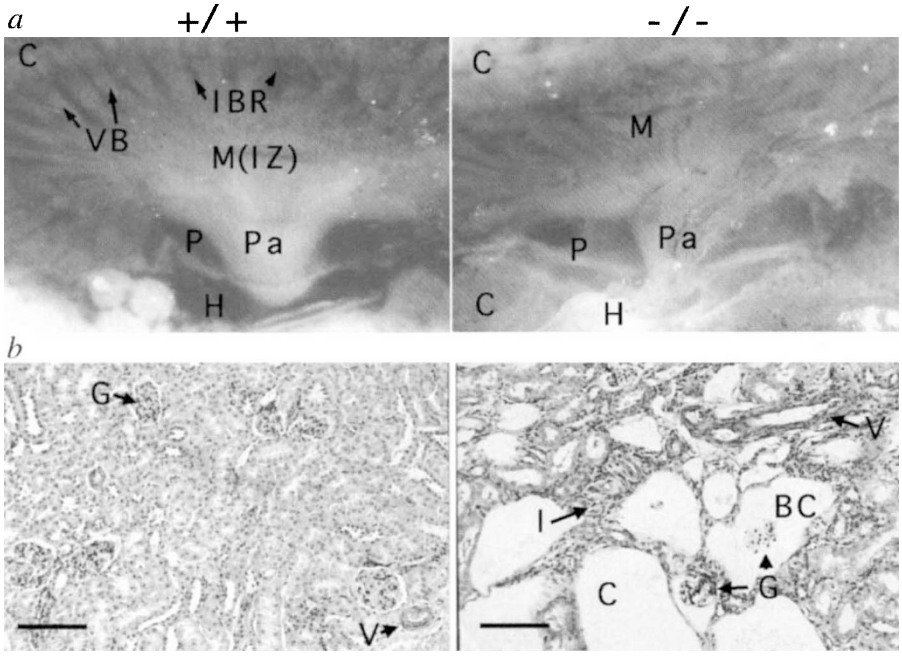

Cystic distortion of the renal pelvis and medulla in ACE mutant mice. *a*, Cut surface of freshly dissected kidneys; *b*, histological sections of adult kidney, stained with haematoxylin and eosin. Left columns are wild-type; right are homozygous ACE mutant mice. In the wild type, the papilla and medulla are well organized, with medullary rays in the outer medulla, whereas in the mutant there is frank disorganization of the medulla, with septate cavernous cystic spaces in the renal pelvis. In addition, the cortex has perivascular and tubulo-interstitial chronic mononuclear inflammatory infiltrates, dilated Bowman's capsules and hypertrophic vessels. C, cortex; H, hilum; IBR, interbundle region; IZ, inner zone of medulla; M, medulla; P, renal pelvis; Pa, papilla; VB, vascular bundles; BC, Bowman's capsule; C, cyst; G, glomerulus; I, inflammatory infiltrate; Scale bar, 100 μm.

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