Renal endothelin and hypertension

SIR — Kurihara *et al.*[1], in their paper on the production of mice deficient for the gene for endothelin-1 (ET-1), report one result of great interest to those in the field of human hypertension. In their heterozygote ET-$1^{+/-}$ mice, reductions in plasma and lung tissue levels of the mature peptide were confirmed, but this was accompanied by increased blood pressure. This hypertension was observed in both conscious and anaesthetized mice, and was not associated with any change in responsiveness to exogenous ET-1, or to inhibition of nitric oxide synthase. Some of the vascular mechanisms by which deficiency of ET-1 during ontogeny could cause hypertension have been discussed by Kurihara *et al.*[1] and by Vanhoutte in an accompanying News and Views article[2].

We would like to suggest a different mechanism based on the emerging role of the renal ET-1 system in blood pressure regulation. Kitamura *et al.*[3] reported reduced tissue levels of ET-1 in kidneys of spontaneously hypertensive rats. Others[4] have confirmed this observation. We recently reported markedly reduced urinary levels of ET-1 in patients with essential hypertension, especially in a subgroup whose blood pressure was sensitive to salt loading[5]. Decreased urinary levels of ET-1 are found in women with either pre-eclampsia or hypertension during pregnancy[6]. Because ET-1 is synthesized in the kidney, excreted in the urine, and not filtered from the plasma[7], low urinary ET-1 could reflect a reduced rate of renal synthesis of ET-1.

The common denominator of all these studies, in both experimental animals and in humans, is an association between reduced renal ET-1 generation and elevated blood pressure. Because the accumulating evidence suggests that the physiological autocrine/paracrine function of ET-1 in the kidney is natriuresis and diuresis[8], it is conceivable that renal deficiency of the peptide causes sodium and water retention and salt sensitivity, and thereby volume-overload hypertension.

These observations suggest that either an absolute or relative deficiency of renal ET-1 may be a causative mechanism for the development and/or maintenance of human essential hypertension. Further studies should clarify the role of the renal ET-1 system in the physiological regulation of blood pressure, to identify those patients with hypertension associated with low urinary ET-1, and to explore specific diagnostic and therapeutic options.

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MAEMURA *ET AL.* REPLY — Hoffman *et al.* suggest that elevated blood pressure in ET-$1^{+/-}$ heterozygous mice[1] may be caused by the impairment of sodium and water handling. To test this hypothesis, we fed 8–12-week-old male heterozygous and wild-type mice with a normal chow containing 0.2% NaCl in metabolic cages and measured several parameters relating to renal function and volume homeostasis. Under these conditions, the blood pressure of ET-$1^{+/-}$ mice was significantly higher than that of wild-type mice[1]. Circulating plasma volume was also determined using ^{125}I-labelled albumin[9]. In ET-$1^{+/-}$ mice, kidney ET-1 levels were half those in ET-$1^{+/+}$ wild-type mice (see table). There was no difference between heterozygous and wild-type mice in the other parameters examined (table). In particular, the absence of any difference in serum sodium concentration, urine sodium output or circulating plasma volume argues against the idea that the elevated blood pressure in ET-$1^{+/-}$ mice is associated with increased sodium retention and volume expansion. Thus, we believe that factors other than volume overload due to sodium retention are responsible for blood pressure elevation in ET-$1^{+/-}$ mice.

These results do not exclude a physiological role of ET-1 in renal water and sodium handling for the following reasons. First, the diuretic and natriuretic effects of ET-1 could be negated by an opposite effect on renal fluid absorption[10]. Second, the presence of impaired renal function and salt-sensitivity in ET-$1^{+/-}$mice can be manifested only by experiments using high salt loading[11]. In young Dahl salt-sensitive rats, for example, a low salt diet does not cause sodium retention, volume overload and high blood pressure, but a high salt diet does[12]. Third, any local effect in organs such as the kidney might be obscured in ET-1-deficient mice because their phenotype represents a net effect of systemic decrease in ET-1 production. Furthermore, a decrease in diuresis and natriuresis, if it occurs, may be compensated by other systems such as the renin–angiotensin system through possible feedback mechanisms in ET-$1^{+/-}$ mice. Such a problem is a general limitation on the interpretation of the physiological consequences in transgenic mice in which vasoactive substances have been 'knocked out'. We agree that further examination of physiological changes under various conditions is necessary to elucidate the precise mechanism of blood pressure elevation in ET-$1^{+/-}$ mice and to clarify the role of ET-1 in various organs.

COMPARISON OF RENAL PARAMETERS BETWEEN ET-$1^{+/-}$ HETEROZYGOUS AND ET-$1^{+/+}$ WILD-TYPE MICE

	Wild-type	Heterozygote
Renal ET-1 content	2.3 ± 0.4	1.2 ± 0.1*
(pg per mg protein)	(*n*=13)	(*n*=16)
Blood urea nitrogen	26.6 ± 1.7	27.3 ± 1.0
(mg per dl)	(*n*=12)	(*n*=14)
Serum creatinine	0.30 ± 0.03	0.29 ± 0.02
(mEq per l)	(*n*=19)	(*n*=22)
Serum Na	150 ±1	151 ± 1
(mEq per l)	(*n*=12)	(*n*=10)
uNa/uCr	0.24 ± 0.03	0.24 ± 0.02
(mEq Na per mg creatinine)	(*n*=6)	(*n*=6)
Plasma volume	51.8 ± 2.5	51.4 ± 1.6
(μl per g body weight)	(*n*=7)	(*n*=12)

uNa/uCr, urinary sodium excretion divided by urinary creatinine excretion; *$P<0.05$ versus wild type. Data are presented as mean ± s.e.m.

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1. Kurihara K *et al. Nature* **368**, 703–710 (1994).
2. Vanhoutte, P. M. *Nature* **368**, 693–694 (1994).
3. Kitamura, K. *et al. Biochem. biophys. Res. Commun.* **162**, 38–44 (1989).
4. Hughes, A. K. *et al. Hypertension* **20**, 666–673 (1992).
5. Hoffman, A. *et al. Kidney Int.* **45**, 556–560 (1994).
6. Wang, M. *et al. Am. J. Hypertension* **7**, 308–313 (1994).
7. Abassi, Z. A. *et al. Hypertension* **20**, 89–95 (1992).
8. Hoffman, A. *et al. Eur. J. Pharmac.* **182**, 603–606 (1990).
9. Crispell, K. R., Porter, B. & Nieset, R. T. *J. clin. Invest.* **29**, 513–516 (1950).
10. Garcia, N. H. & Garvin, G. L. *J. clin. Invest.* **93**, 2572–2577 (1994).
11. Campese, V. M. *Hypertension* **23**, 531–550 (1994).
12. Simchon, S., Manger, W. M. & Brown, T. W. *Hypertension* **17**, 1063–1071 (1991).