# Influence of dietary NaCl intake on renin gene expression in the kidneys and adrenal glands of rats

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**Abstract.** The aim of this study was to examine the influence of dietary NaCl intake on renin gene expression in the kidneys and adrenal glands of adult rats. Rats were kept on low (0.02%, w/w), normal (0.6%) or high (4%) NaCl diets and plasma renin activity (PRA) and the relative abundance of renin messenger ribonucleic acid (mRNA) in renal and adrenal tissue were followed for 20 days. In animals on a normal-salt diet PRA and renal renin mRNA levels did not change with time. PRA values in animals on the low-salt diet increased transiently (about threefold) and then declined again during the third week of treatment. Renal renin mRNA levels in these animals paralleled the changes of PRA. Conversely, in the animals kept on a high-salt diet PRA values decreased transiently and renal renin mRNA decreased continuously to about 50% of control values. Arterial blood pressure measured in conscious animals was not significantly influenced by the different salt diets. To establish whether the changes in renin mRNA levels are mediated by renal nerve input, animals on the different diets were also studied after unilateral renal denervation. Renal nerve section led to a 50% decrease of renin mRNA levels in the denervated kidneys in animals kept on the normal-salt diet. In the animals on the low-salt diet renin mRNA rose to similar levels in the denervated to those in the innervated kidney, while in animals receiving a high-salt diet renin mRNA was further decreased in the denervated kidneys. The abundance of renin mRNA in adrenal tissue was low and was estimated to be around 1% of that found in the kidneys. Adrenal renin mRNA levels also increased in animals kept on a low-salt diet and decreased in animals on high-salt diet. Taken together, our findings suggest that renin secretion and renin gene expression are inversely related to salt intake and that the influence of salt diet on these parameters has both transient and constant temporal components. Changes of blood pressure or nerve activity are not likely mediators of the effect of salt intake on renin expression. Since renal and adrenal renin mRNA levels change in parallel in response to alterations of salt intake we hypothesize the existence of a humoral factor that links renin expression to the rate of salt intake.

**Key words:** Juxtaglomerular cells – Renin mRNA – Salt diet – Kidney – Adrenal gland – Plasma renin activity

## Introduction

While the main physiological parameters regulating the release of renin into the circulation have been characterized, the physiological control of the expression of the renin gene is less clear [11]. Although there is no obligatory linkage between renin synthesis and renin secretion at the level of renal juxtaglomerular cells [16] the question is important if those physiological parameters that mainly regulate renin secretion also influence the activity of the renin gene. Among these factors the level of dietary NaCl intake is of particular relevance because, although it is well established that the secretion of renin is inversely related to salt intake [7] in the sense of a negative feedback mechanism, the mechanisms linking renin secretion and salt intake are not well understood.

The influence of dietary salt intake, in particular that of a low-salt diet, on the expression of the renin gene in the kidneys has, so far, almost exclusively been studied using drugs that essentially interfere with the physiological NaCl homeostasis such as loop diuretics [2, 12, 14, 18], converting enzyme inhibitors [18, 22] or steroids [1, 19]. Such pharmacological perturbations of the NaCl homeostasis in combination with NaCl diet may have additional effects of relevance for the renin system such as influence on the macula densa, activation of the autonomic nervous system or changes of blood pressure. It has been found, for instance, that the sodium delivery to the early distal tubule is not changed by a high- or low-sodium diet [26] but is markedly decreased if a low-salt diet is combined with furosemide [6] and is significantly

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increased if a high-salt diet is combined with deoxycorticosterone acetate treatment [25]. Indeed, feeding different salt diets for 5 days without additional pharmacological treatment has been reported not to change renal renin mRNA levels [23], while low- or high-salt feeding in combination with drugs has been demonstrated to increase [2, 12, 14, 18, 19, 22], or decrease [1, 19] renal renin mRNA levels respectively.

In view of these ambiguous findings it is of interest to clarify the primary influence of NaCl intake on renin gene expression by studying the effects of high- and low-salt diet, without additional pharmacological manoeuvres, over a longer period. In particular, we were interested in time-dependent influences of salt intake on renin secretion and on renin gene expression in kidneys and in adrenal glands. These organs have been recognized as relevant sites of renin expression [8, 10, 21]. Moreover, in view of evidence that suggests that renal nerves could mediate the effects of salt intake on renin secretion [20, 26] we examined the role of renal nerves in mediating the influence of salt intake on renin gene expression.

The findings obtained suggest that changes of salt intake lead to inverse changes of both renin secretion rates and of renal and adrenal renin messenger ribonucleic acid levels. Intact renal innervation does not appear to be essential for the influence of salt intake on the expression of the renin gene in the kidney.

## Materials and methods

*Animals.* Male Sprague-Dawley rats (body weights 208 ± 8 g, mean ± SD, obtained from Charles River Wiga, Sulzfeld, Germany) were fed either a low-salt diet (Na 0.14 mg/g, Cl 0.18 mg/g), normal-salt diet (Na 2.5 mg/g, Cl 3.6 mg/g), or high-salt diet (Na 18 mg/g, Cl 28 mg/g) for 20 days. The different salt diets (C1000, C1036, C1051, Altromin, Lage, Germany) and distilled water were available ad lib. After 5, 10, 15 and 20 days feeding, five rats from each dietary group were analysed for plasma renin activity (PRA) and renin mRNA levels. To this end 300 μl blood was sampled for determination of PRA within the first minute after sacrifice by cervical dislocation. The adrenal glands and both kidneys were rapidly removed, snap-frozen in liquid nitrogen and stored at −70°C prior to extraction of total RNA.

*Renal denervation.* A further group of rats (five on each diet) were subjected to left renal denervation after 5 days. Animals were anaesthetized with methohexital (75 mg/kg i. p.) and denervated according to the method of Bello-Reuss et al. [3]. The abdominal wall was opened along the midline and the left renal artery and vein were exposed by carefully retracting the adipose tissue and the peritoneum. Mechanical denervation was carried out using an operation microscope by sectioning any visible nerve fibre penetrating the renal hilus and by stripping the adventitia from the renal artery. To destroy any remaining nerve fibres the artery was painted with a solution of 10% phenol in ethanol. After 5 min exposure to this solution the artery was washed with isotonic saline, the wound closed and the animals allowed to recover. In sham-operated animals, the left artery and vein were exposed as described above, but mechanical denervation and treatment with the phenol solution were omitted. This treatment has recently been shown to cause effective renal denervation [9]. The different salt diets were continued for a further 5 days until sacrifice of the animals.

*Measurement of blood pressure.* In the animals kept on the different salt diets for 10 days a catheter was inserted into the left carotid artery under brief anaesthesia (methohexital, 75 mg/kg) 6 h prior to sacrifice of the animals. Mean arterial blood pressure was monitored in the conscious animals by a Statham transducer connected to the arterial catheter for the 15 min prior to sacrifice.

*Determination of preprorenin mRNA.* Total RNA was extracted from half kidneys and both adrenal glands according to the protocol of Chirgwin et al. [5]. Tissue was homogenized in 18 ml guanidine thiocyanate (4 M) containing 0.5% N-dodecyl sarcosinate, 10 mM ethylenediaminetetraacetic acid (EDTA), 25 mM sodium citrate and 700 mM 2-mercaptoethanol with a Polytron homogenizer and RNA was subsequently purified on a caesium chloride gradient by laying the extract onto a cushion of 5.7 M CsCl and 100 mM EDTA and centrifuging for 20 h at 33 000 rpm. After centrifugation RNA pellets were resuspended in 300 μl 10 mM TRIS pH 7.5, 1 mM EDTA containing 0.1% sodium dodecyl sulphate (SDS), precipitated with 3 M sodium acetate (0.1 vol) and ethanol (3 vol) and stored at −70°C prior to analysis. Renin mRNA was measured by RNase protection as described for erythropoietin mRNA [24]. A preprorenin complementary RNA (cRNA) probe containing 296 base pairs of exons I and II, generated from a pSP64 vector carrying a *Pst*I-*Kpn*I restriction fragment of a rat preprorenin complementary deoxyribonucleic acid (cDNA) [4] was generated by transcription with SP6 RNA polymerase (Amersham International, Amersham, UK). Transcripts were continuously labelled with guanosine [α-$^{32}$P]triphosphate (410 Ci/mmol; Amersham International) and purified on a Sephadex G50 spun column. For hybridization, total RNA was dissolved in a buffer containing 80% formamide, 40 mM 1,4-piperazine diethanesulphonic acid (PIPES), 400 mM NaCl, 1 mM EDTA (pH 8). Generally, 20 μg total RNA from kidneys and 80 μg total RNA from adrenal glands were hybridized in a volume of 50 μl at 60°C for 12 h with 5×10$^5$ cpm radiolabelled renin probe. Digestion with RNase A and T1 was carried out at 20°C for 30 min and terminated by incubation with proteinase K (0.1 mg/ml) and SDS (0.4%) at 37°C for 30 min. Protected renin mRNA fragments were purified by phenol/chloroform extraction, ethanol precipitation and subsequent electrophoresis on a denaturing 10% polyacrylamide gel. After autoradiography of the dried gel at −70°C for 1−2 days, bands representing protected renin mRNA fragments from kidneys were excised from the gel and the radioactivity counted in a liquid scintillation counter (1500 Tri-Carb, Packard, Downers Grove, Ill., USA). The amount of radioactivity obtained from each sample of total kidney RNA was expressed relative to an external standard consisting of a 20-μg aliquot of pooled RNA extracted from kidneys of six untreated control animals that was coanalysed on each gel (see Figs. 6, 7, 9). In protection assays for renin mRNA of adrenal glands 0.5 μg or 2.5 μg standard pool was coanalysed and, because of the low abundance of renin mRNA in adrenals (see Results), the duration of autoradiographic exposure was extended to 2−3 weeks. Figure 1 (upper panel) shows an RNase protection assay for renin mRNA performed with different amounts of the standard pool demonstrating linearity of the assay.

*Determination of actin mRNA.* To exclude the possibility of nonspecific influence of salt diet on gene expression in general the abundance of rat cytoplasmatic β-actin mRNA in total RNA isolated from the kidneys was determined by RNase protection assay exactly as described for preprorenin. An actin cRNA probe containing the 76-nucleotide first exon and around 200 base pairs of an adjoining intron was generated by transcription with SP6 polymerase from a pAM19 vector carrying a *Ava*I/*Hin*dIII restriction fragment of actin cDNA [24]. For one assay 2.5 μg RNA was hybridized under the conditions described for the determination of renin mRNA. Figure 1 (lower panel) shows an actin RNase protection assay performed with different amounts of the RNA standard.

*Plasma renin activity.* PRA was determined using a commercially available radioimmunoassay kit for angiotensin I (Sorin, Düsseldorf, Germany).
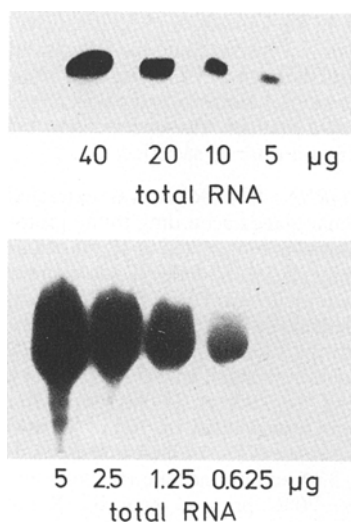
**Fig. 1.** *Upper panel:* autoradiograph of a ribonuclease (RNase) protection assay for renin mRNA using different amounts of renal RNA standard. The radioactivity of the excised bands was 790 cpm, 410 cpm, 220 cpm and 105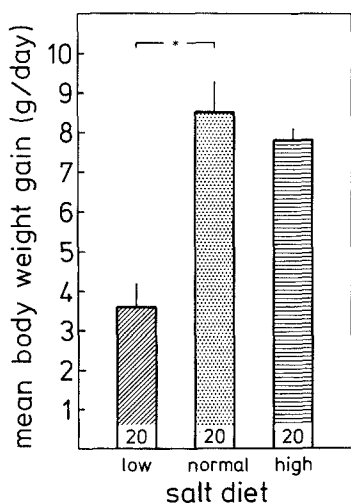 cpm for 40 µg, 20 µg, 10 µg and 5 µg total RNA respectively. *Lower panel:* autoradiograph of an RNase protection assay for $\beta$-actin mRNA using different amounts of total renal RNA standard. The radioactivity of the excised bands was 7000 cpm, 3700 cpm, 1900 cpm and 1000 cpm for 5 µg, 2.5 µg, 1.25 µg and 0.625 µg total RNA respectively



**Fig. 2.** Averaged daily body weight gains of rats kept on low-, normal- or high-salt diet for 5, 10, 15 and 20 days. The values were calculated by dividing the individual body weight gains during the experimental periods by the number of days of experiment. Data are means ± SEM from 20 animals in each dietary group. * $P < 0.05$

*Statistics.* Analysis of variance and students's paired and unpaired $t$-tests were used for intra- and interindividual comparisons. $P < 0.05$ was considered significant.

## Results

The influence of the sodium diets on weight gain of the rats is shown in Fig. 2. Rats on the low-salt diet gained
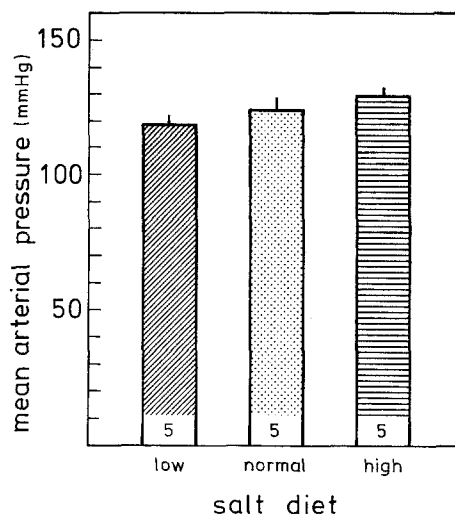


**Fig. 3.** Mean arterial pressure in conscious rats kept on low-, normal- or high-salt diet for 10 days. Data are means ± SEM ($n = 5$ for each group)
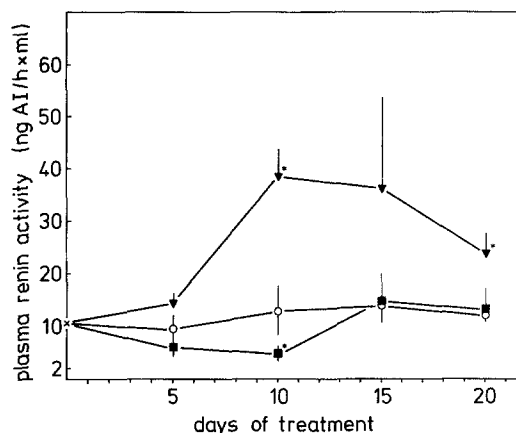


**Fig. 4.** Plasma renin activities in rats on low- (▼), normal- (○) or high-salt (■) diet. Data are means ± SEM ($n = 5$ each day and diet). * $P < 0.05$ compared to normal-salt diet. AI, angiotensin I

significantly less weight than those on the normal diet, whereas the high-salt diet had no influence on body weight gain. The different sodium chloride diets had no significant effects on the blood pressure measured in conscious rats on day 10 (Fig. 3).

Differences in the salt content of diets led to significant changes in PRA after 5 days on the diets (Fig. 4). On the low-salt diet PRA increased transiently and reached a maximum after 10 days, when PRA values were 3-fold higher than those in animals kept on the normal-salt diet. High-salt feeding, on the other hand, led to a transient decrease of PRA values to approximately 50% of the control values during the first 10 days of feeding (Fig. 4). PRA values in the high-salt group were not different from those in the normal group after 15 days whilst those in the low-salt group, although declining, were still significantly elevated at 20 days.

The influence of salt diet on renin mRNA levels was determined using a sensitive RNase protection assay with total RNA prepared from kidneys and adrenal
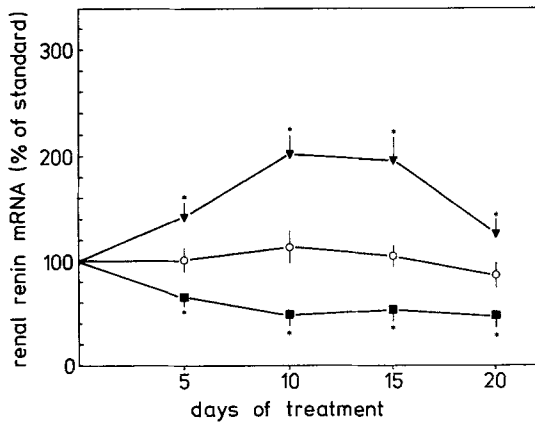
**Fig. 5.** Renal renin mRNA levels expressed in relation to an external standard (20-µg aliquot of total RNA from control animals) in rats on low- (▼), normal- (○) or high-salt (■) diet. RNA was extracted from the left kidneys. Data are means ± SEM ($n = 5$ each day and diet). * $P < 0.05$ compared to normal salt diet
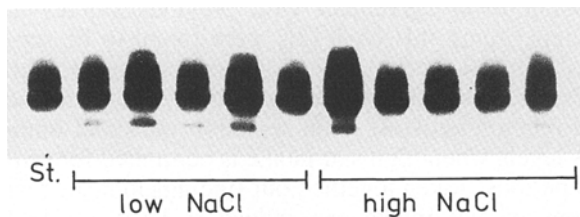


**Fig. 6.** Autoradiographs of RNase protection assays for $\beta$-actin mRNA with total RNA isolated from the left kidneys of individual rats kept on low- ($n = 5$) or high-salt ($n = 5$) diet for 10 days; 2.5 µg total RNA was analysed in each assay. *St.*, 2.5 µg RNA standard taken from an RNA pool isolated from the kidneys of six normal rats
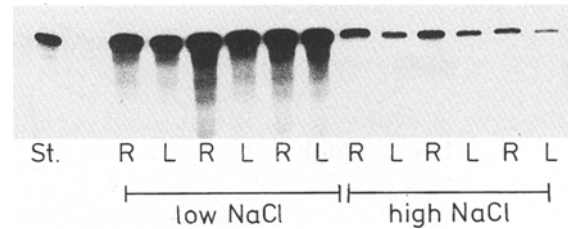


**Fig. 7.** Autoradiograph of RNase protection assays for renin mRNA with total RNA isolated from the individual kidneys of unilaterally denervated rats kept on low- ($n = 3$) and high-salt ($n = 3$) diet. *L*, left (denervated); *R*, right (intact) kidney; 20 µg total RNA was analysed in each assay. *St.*, 20 µg RNA standard
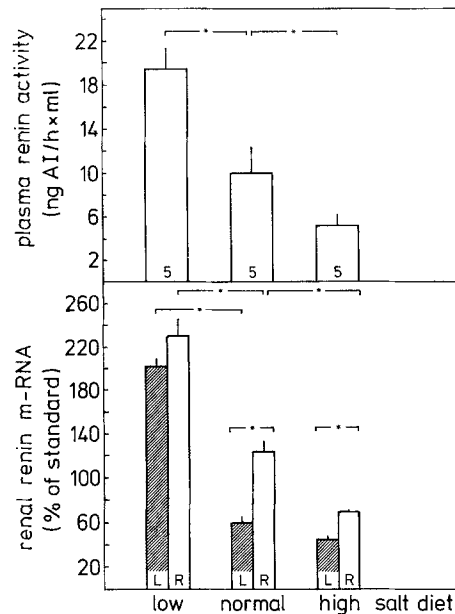


**Fig. 8.** *Upper panel:* plasma renin activities in unilaterally (left side) denervated rats kept on low-, normal- or high-salt diet for 10 days. Data are means ± SEM ($n = 5$ each group). *AI*, angiotensin I. *Lower panel:* renal renin mRNA levels expressed as percentage of the standard RNA in unilaterally (left side) denervated rats kept on low-, normal- or high-salt diet for 10 days. *L*, left (denervated); *R*, right (intact) kidney. Data are means ± SEM ($n = 5$ each group). * $P < 0.05$

glands. Renal renin mRNA levels in rats kept on the low-sodium diet had increased after 5 days, reaching maximum values that were about 100% higher than those of controls after the first week, and then declining (Fig. 5). The high-salt diet, on the other hand, led to a permanent decrease in renal renin mRNA levels that had reached about 50% of the respective controls after the first week of feeding (Fig. 5). For comparison and to exclude non-specific influences on gene expression, the abundance of rat cytoplasmic $\beta$-actin mRNA levels in the RNA preparations assayed for renin mRNA was analysed. No difference in the abundance of renal actin mRNA was found in animals kept on low- or high-salt diet for 10 days (Fig. 6) when compared with animals on normal salt diet.

In view of evidence suggesting that renal nerves are involved in the effect of salt intake on renin secretion [20, 26] rats were unilaterally denervated and fed the low-, normal- or high-salt diet for 10 days and the abundance of renin mRNA was determined separately for the denervated and the innervated kidneys of each animal; individual examples are shown in Fig. 7. Figure 8 shows that in animals on the normal-salt diet unilateral denervation depressed renin mRNA levels in the denervated kidneys (115 ± 20% intact kidney compared to 58 ± 5% denervated kidney). Renin mRNA levels in the

contralateral kidneys were not significantly different from those in sham-operated rats (data not shown). In rats on the low-salt diet renin mRNA increased similarly in the both denervated (200 ± 5%) and innervated (228 ± 20%) kidneys, abolishing "side differences" in renin gene expression (Figs. 7, 8). In rats on the high-salt diet, on the other hand, renin mRNA levels were decreased both in the denervated (42 ± 3%) and in the innervated (70 ± 2%) kidneys; the difference between the denervated and intact kidneys remained significant. The pattern of the response of renal renin mRNA to changes in salt intake was thus not basically different in the denervated compared with the intact kidney. PRA in the unilaterally denervated animals showed the same pattern as in non-operated animals (day 10, Fig. 4) and sham-operated animals (data not shown).

To establish whether the influence of salt intake on renin gene expression is restricted to the kidneys or is a
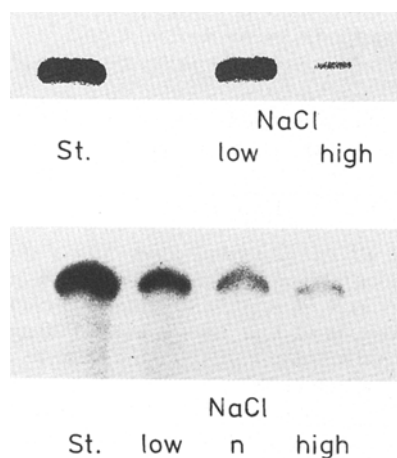
**Fig. 9.** *Upper panel:* renin RNase protection assays of 80 µg total RNA isolated from the adrenal glands of rats kept on low- or high-salt diet for 10 days. *St.*, standard (0.5 µg total renal RNA). Adrenal RNA was pooled from four rats from each experimental group, combining 20 µg each of adrenal RNA isolated from both adrenals of one animal. *Lower panel:* renin RNase protection assays as described above with total adrenal RNA isolated from rats kept on low-, normal- (*n*) or high-salt diet for 15 days

more general phenomenon, we analysed renin mRNA levels in the adrenal glands. In pilot experiments the abundance of adrenal renin mRNA was found to be low compared with that in the kidneys. We therefore pooled 20 µg each of total adrenal RNA from four animals from each of the three experimental groups for assay of renin mRNA. As shown in Fig. 9 (lower panel), 80 µg total RNA from adrenal glands produced a much weaker hybridization signal than did 2.5 µg renal RNA; both samples were prepared from animals on a normal-salt diet. From this comparison we estimate that the abundance of renin mRNA in the adrenal glands is about 1% of that in normal rat kidneys. Nonetheless, an obvious difference in adrenal renin mRNA levels between animals on low- or high-salt diet was visible after 10 (Fig. 9, upper panel) and 15 (Fig. 9, lower panel) days of feeding. Similar to the changes in renal renin mRNA, adrenal renin mRNA increased in animals on the low-salt diet and decreased in rats on the high-salt diet. Adrenal actin mRNA levels did not differ with diet (not shown).

## Discussion

The aim of this study was to examine the influence of dietary salt intake on the secretion of renin and the expression of the renin gene in adult rats. Our findings suggest that changes of dietary salt intake lead to proportional and inverse changes of both renin secretion rates and kidney mRNA levels (Figs. 4, 5). In contrast to a previous study [23], renal renin mRNA changed within 5 days after the salt intake was changed (Fig. 5). The magnitude of changes of plasma renin activity observed in this study agree with a previous investigation [26] but both these and the changes of renin mRNA were markedly less pronounced than in previous studies in

which animals were additionally treated with furosemide, captopril or deoxycorticosterone acetate [2, 12, 14, 19, 22]. In these investigations 3- to 8-fold increases of renin mRNA levels and 3- to 46-fold increases in PRA have been reported. In this study we found that salt restriction alone led to a transient and proportional 2-fold increase of PRA and or renal mRNA levels (Figs. 3, 4). The discrepancies between the present study and those studies cited above may reasonably be ascribed to the additional pharmacological interventions in those studies.

The transience of the responses of PRA and renal mRNA levels to low salt intake could indicate that under such circumstances additional sodium saving mechanisms become operative and lead to a relief of the renin system. More difficult to explain is the dissociation between renin secretion and renal renin gene expression, which occurred after 2 weeks of feeding the high-salt diet. While PRA had returned to control values at that time, renin mRNA levels remained suppressed. The latter finding is in agreement with previous studies in which renal renin mRNA levels were found to be suppressed 2 and 4 weeks after high-salt feeding [1, 19]. Our results thus suggest that there is a change in the normal relation between renin secretion rates and renin mRNA levels when high salt intake is continued for prolonged periods. Taken together, our findings indicate that variations of salt intake can induce at least a 4-fold change of renin gene expression in the kidney of rats.

The mechanisms adapting renin gene expression to salt intake are, as yet, unknown. Possible mediating mechanisms include changes in blood pressure, macula densa function, renal nerve activity or humoral factors. In accord with a previous study [26] there were no consistent changes of blood pressure in the rats on the different salt diets. Thus a contribution of arterial pressure to the influence of salt intake on renin gene expression appears to be unlikely. Two arguments suggest that the same is true for the macula densa. First, altered salt intake alone does not influence the sodium chloride delivery to the early distal tubule [26]. The latter is considered to be the relevant parameter for the macula densa mechanism [17]. Secondly, it has been demonstrated recently that salt restriction leads to an increase of renin mRNA levels in hydronephrotic kidneys (in which all tubular structures are destroyed) [2]. Renal nerves have also been suggested as the mediators of the influence of salt intake on renin secretion [20, 26]. Successful renal denervation in this series of experiments may be suggested by the observation that, in animals on normal diet, denervation caused renin mRNA levels to fall to 50% of the contralateral value, a finding in harmony with recent observations made by others [27] and ourselves (Holmer et al., unpublished observations) indicating that the renal nerves indeed play a role in the basal expression of the renin gene. Our findings, however, suggest that renal nerves do not mediate the salt-intake-dependent changes in renin mRNA levels (Fig. 8).

A humoral factor mediating the influence of salt intake on renal renin gene expression may thus be inferred. Indeed, the suggestion that the effect of salt intake on

renin secretion is somehow related to the release of vasopressin [15] was made 12 years ago. The inference of a humoral factor linking renal renin gene expression to salt intake is strongly supported by the observation that not only renal, but also adrenal renin gene expression is similarly sensitive to salt intake (Fig. 9). Our observations in normal rats agree with, and thus confirm, the recent report on an influence of salt intake on adrenal renin gene expression in Dahl salt-sensitive and Dahl salt-resistant rats [13]. Several studies have recently demonstrated that the adrenal glands are a relevant site of renin gene expression [8, 10, 21]. Moreover, it has been estimated that the abundance of renin mRNA in adrenal glands of normal rats is approximately 10% of that found in the kidneys [8]. Our findings suggest an even lower abundance of renin mRNA in the adrenal glands (approximately 1% of that in the kidneys). Whether this discrepancy is due to the different rat strains used, to a different prestimulation of adrenal renin gene expression or to the different methods used for renin mRNA quantification is not yet clear.

In summary, our findings suggest that the level of salt intake determines the production or the release of a humoral factor that effectively controls renin gene expression. Its mode of action, its nature and its site of origin remain to be clarified in future studies.

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