Paper

Renal Haemodynamics are not Related to Genotypes in Offspring of Parents with Essential Hypertension

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Abstract

Introduction. The pathogenesis of essential hypertension (EH) has a major genetic component and is associated with renal abnormalities. Normotensive offspring of hypertensive parents are likely to develop EH and are a suitable population for identifying possible relations between genetic and renal abnormalities.

Methods. We investigated if renin-angiotensin-aldosterone system associated genotypes (angiotensinogen [M235T] and ACE [I/D]) are related to blood pressure (BP), renal haemodynamics and sodium excretion in sex and age-matched (18–35 years) healthy Caucasian offspring of either two parents with EH (n=101, EH-offspring) or two normotensive parents (n=50, controls). The alpha-adducin polymorphism (G460W) was also investigated.

Results. Compared to controls, BP, heart rate, renal vascular resistance (RVR) and urinary sodium excretion were, respectively, 5%, 7%, 15% and 20% higher in EH-offspring. In controls, the TT-genotype of the M235T angiotensinogen polymorphism was associated with higher BP and higher plasma angiotensinogen. By contrast, in EH-offspring the TT-genotype was associated with lower BP and unchanged plasma angiotensinogen. Plasma angiotensinogen correlated positively with BP in EH-offspring, with a similar tendency (p=0.08) in controls. The distributions of the three candidate polymorphisms were similar in EH-offspring and controls. There were no associations between any of the polymorphisms and any of the renal parameters measured.

Conclusion. The markedly greater RVR, proportionally larger than the greater BP, supports a role for RVR in the pathogenesis of EH. The lack of association between the candidate polymorphisms and the investigated parameters, even in this homogenous and for hypertension strongly predisposed group, suggests that the polymorphisms investigated do not play important roles in the pathogenesis of hypertension.

Introduction

The risk of developing essential hypertension (EH) is increased for offspring of parents who have EH, suggesting a strong genetic component is involved. However, despite intensive efforts, the genetic basis is unknown. The multifactorial nature of hypertension and the complex regulation of the blood pressure (BP) has suggested[1-3] that it would be advantageous to correlate genotypes with intermediate biologically plausible phenotypes. Such an intermediate phenotype could involve renal abnormalities. Evidence for the kidney being important in the pathogenesis of hypertension comes from kidney transplant studies in animals[4] and clinical observations of kidney transplanted patients.[5] Additionally, in young persons, whose parents have EH,[6] renal vascular resistance (RVR) is increased, in agreement with animal experimental studies.[7]

Several genetic polymorphisms have been identified that in some populations are associated with increased BP. Particular focus has been placed on genes of the renin-angiotensin-aldosterone system (RAAS), namely polymorphisms in the angiotensinogen gene (M235T)[8] and the angiotensin-converting enzyme (ACE) gene (insertion/deletion in intron 16).[9,10] Recently, the alpha-adducin gene (G460W),[11] which probably affects BP through the control of renal sodium excretion, has also been recognised.[12] Many hundreds of papers have been published on these genotypes, with extremely variable results. The variability may be due to the heterogeneous nature of the populations studied, and the large preponderance of individuals who are not disposed to hypertension. However, there are few papers concerning offspring of hypertensive individuals,[13-15] of whom half of the individuals may be expected to develop essential hypertension.[16] These individuals should therefore *a priori* be particularly suitable for demonstrating genes coding for hypertension if these have any importance.

The present study takes advantage of the 'Danish Hypertension Prevention Project'[17] that has identified young Caucasian persons for whom both parents had essential hypertension. Our hypothesis was that in these hypertension-predisposed persons BP and renal haemodynamics would be related to some or all of the above-mentioned polymorphisms.

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Methods

Study Population

As a part of the 'Danish Hypertension Prevention Project'[17] we compared subjects who had either two hypertensive or two normotensive parents, selected as follows.

Subjects with Two Hypertensive Parents (EH-offspring)

Through the hospital registry in Aarhus County we traced 5,743 adults aged 35–75 years who had been discharged from hospital over the previous five years with the diagnosis code 'essential hypertension'. Only persons with Caucasian names were included. By letter these persons were asked if their spouse had hypertension as well and if they had common children of age 18–35 years. Those who responded (664 couples) were sent further information and a questionnaire regarding their BP status, and of these 341 couples were prepared to participate. Participation involved acceptance that we could (a) contact their general practitioners/hospitals where their BP was being treated and (b) contact their children, whose contact details they had provided. This enabled us to obtain confirmation from their general practitioners or hospitals that both parents did indeed have EH, and that it had been present for more than one year, together with information on the last measured BP (measured a maximum of six months before) and their antihypertensive treatment. From these, 104 couples were selected as fulfilling all criteria, and their 172 children of age 18–35 years were invited to participate. This procedure resulted in the inclusion of 101 healthy children, all Caucasian, without daily medication except for oral contraceptives.

Subjects with Two Normotensive Parents (controls)

Through posters at the University of Aarhus, teacher training colleges, high schools, work places (hospitals, police stations, fire stations) and the blood bank in Aarhus City, healthy subjects of age 18–35 years were invited to participate. Before inclusion, their parents had to fill in a questionnaire. Subjects were included if neither parent had a history of high BP or was receiving antihypertensive medication, and provided that the parents' BP as measured at their general practitioner or at the hospital a maximum of six months previously was below 140 mmHg systolic and 90 mmHg diastolic.

Informed, written consent was obtained from all participants, and the Ethical Committee, Aarhus County, approved the study protocol in accordance with the Helsinki Declaration.

Protocol

All subjects collected urine samples during the 24 hours before the study, with failure of urine collection for one of the EH-offspring. Their usual diet was not altered, but they were asked to stop eating, drinking and smoking from 8.00 pm the evening before to allow a 12-hour fasting period before examination. At 10.00 pm on the day before the examination, 300 mg lithium carbonate was taken orally. The subjects arrived at the laboratory at 8.00 am. Clinical examination was performed, preceded by weight and height measurements, with the subject wearing indoor clothes but no shoes. ECG was obtained. For female participants, a urine test for pregnancy was performed. After 30 minutes of rest in the supine position the BP in the left arm was measured twice with a semiautomatic oscillometric BP apparatus (Digital Blood Pressure Meter UA-751, Takeda Medican Inc., Japan) by a trained technician. Thereafter two readings were made every 30–45 minutes up to a total of 10 measurements. During the study, subjects remained in the supine position except when voiding; no bladder catheterisation was performed, but the subjects were carefully instructed to empty the bladder. To ensure adequate urinary flow, an oral load of 200 ml tap water was given every 30 minutes from 7.00 am until the end of the study. Before beginning the renal function test, two intravenous cannulae, one in each cubital fossa, were inserted. Venous blood samples were collected from the left arm: the subject then remained supine in a quiet room for 30 minutes, after which, venous blood samples were collected: 6 ml in a chilled tube containing disodium ethylenediamine tetra-acetic acid (EDTA) (0.125 M) and O-phenanthroline (0.025 M) for measurement of immunoreactive angiotensin II and two times 3 ml in tubes containing disodium EDTA (0.125 M) for measurement of active renin, aldosterone and angiotensinogen concentrations. Two venous blood samples were collected into disodium EDTA tubes and DNA was extracted by standard procedures.[18] Glomerular filtration rate (GFR) and the effective renal plasma flow were calculated on the basis of measurements of the clearance of ^{51}Cr-EDTA and ^{125}I-hippuran measured with use of constant-infusion technique and timed collections of urine.[19,20] A priming dose was given at 9.00 am ensuring a plasma activity of 800–1600 cpm/ml for ^{51}Cr-EDTA and 200-600 cpm/ml for ^{125}I-hippuran. Plasma activities were kept stable by constant infusion with an infusion pump (Terufusion Syringe Pump STC-521, Terumo Corporation, Tokyo, Japan). Infusion rate of tracer substances and vehicle was 8 ml/hour totally. From 10.00 am urine was collected in three consecutive clearance periods, each lasting 30 minutes. Venous blood samples, which were drawn at the beginning and end of each clearance period, and urine samples from the whole clearance period were analysed for concentration of sodium, lithium, ^{51}Cr-EDTA and ^{125}I-hippuran.

Measurements

^{51}Cr-EDTA and ^{125}I-hippuran were measured in plasma and urine samples at the beginning and end of each clearance period. To ensure sufficient bladder emptying subjects were included only if all three clearances of ^{51}Cr-EDTA were within 15% of the mean value of the periods. This resulted in

the inclusion for the renal function test of 136 subjects: 92 EH-offspring, 44 controls. Renal blood flow was estimated by dividing the effective renal plasma flow by 1 minus the haematocrit. The filtration fraction was calculated by dividing the GFR by the effective renal plasma flow. Mean BP was calculated as diastolic BP plus one third pulse pressure, measured during the renal function test. RVR was estimated by dividing the calculated mean arterial BP by the renal blood flow. Based on the assumption that the lithium ion is solely reabsorbed in the proximal tubules in approximately the same proportions as sodium and water, the clearance of lithium (C_{Li}) was taken as an estimate of the delivery of isotonic fluid from the proximal tubules into the thin segment of the loop of Henle.[21] Plasma and urinary concentrations of lithium were measured by atomic absorption spectrophotometer (Perkin Elmer Corporation, Norwalk, Connecticut, USA). The renal CLi and clearance of sodium (C_{Na}) were calculated as the ratio between urinary excretion rate and the mean plasma concentrations. Plasma angiotensinogen concentration was determined using the principle of antibody trapping[22] as modified by Millar *et al*.[23] Plasma renin activity was determined by a double-sided immunoradiometric method, using two monoclonal antibodies against human-active renin linked to biotin and ^{125}I (Nichols Institute, Geneva, Switzerland). Angiotensin II (Ang II rabbit-antibody kindly provided by Professor Jan Danser, Rotterdam, Holland)[24] and aldosterone (DSL-8600 active aldosterone™ Coated-Tube Ria Kit, Diagnostics Systems Laboratories Inc., Webster, Texas, USA) were measured in plasma by radioimmunoassay. For plasma angiotensinogen, women taking anticontraceptive medication (22 subjects, 18 controls) and two outliers deviating from the mean by three (a control) and five (an EH-offspring) standard deviations were excluded from calculation. For plasma renin activity one measurement failed, for aldosterone two measurements failed, for plasma angiotensinogen two measurements failed, all in EH-offspring. One 24-hour urine sodium measurement failed in a control subject.

Genotyping

Angiotensinogen M235T gene polymorphism was detected manually by DNA amplification followed by enzymatic digestion.[8] ACE insertion/deletion (I/D) polymorphism was detected as reported by Morgan *et al*.[25] Alpha-adducin G460W genotyping was carried out on ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Connecticut, USA) using the 5' nuclease detection assay, with specifically designed conditions.[10] Successful analyses were made in 89 EH-offspring and 44 controls.

Statistics

All results are presented as mean±SD. Characteristics of subjects and their parents were evaluated with Student's *t*-test. Polymorphism distributions were tested by chi^2-test and Hardy-Weinberg equilibrium analysis. Differences between EH-offspring and controls regarding gene polymorphisms and measured parameters were tested among groups by 2-factor and 1-factor analysis of variance (ANOVA). Probability levels less than 5% were considered significant.

Results

General characteristics

Table 1 shows the general characteristics of the two groups of parents and subjects. The systolic and diastolic BP were 5% higher in the EH-offspring, as was mean BP (Figure 1). Heart rate was 7% higher in the EH-offspring. The 24-hour urinary excretion of sodium was 20% higher in the EH-offspring, and also higher after adjustment for differences in body weight (Figure 1). The fasting serum levels of potassium, sodium, creatinine, urea, thyroid stimulating hormone, alanine aminotransferase, bilirubin, alkaline phosphatases, leucocytes, albumin and blood glucose and haematocrit were similar in the two groups (data not shown).

Renal Haemodynamics

RVR was 13% higher in EH-offspring compared to controls (Figure 1). RVR was positively correlated with mean BP in the EH-offspring ($p<0.001$) and controls ($p=0.02$), but there was no difference in GFR, renal blood flow or filtration fraction between the two groups (Table 2). There was no difference in C_{Li} or C_{Na} between the two groups or in any of the calculated parameters regarding renal tubular sodium handling (Table 3).

Hormones

In the EH-offspring, there was a positive correlation between plasma angiotensinogen and BP ($p<0.001$), with a similar tendency in the controls ($p=0.08$), see Figure 2. Plasma angiotensinogen was not different in EH-offspring and controls, nor were there differences in plasma renin activity, angiotensin II or aldosterone (Table 2).

Genetic analysis

Figure 3 shows the relation between the angiotensinogen polymorphism and systolic BP in EH-offspring and controls. In EH-offspring, the TT-genotype was associated with lower systolic BP, while in controls this polymorphism was associated with higher systolic BP. The difference in effect of TT-genotype on systolic BP was significant ($p_{interaction}=0.005$). Similarly, the TT-genotype was associated with lower diastolic BP and mean BP in EH-offspring, but higher values in controls (analysis not shown). However, the distribution of polymorphisms for angiotensinogen (M235T) was similar in EH-offspring and controls, as was the case for ACE (I/D), and alpha-adducin (G460W), see Table 4. The tendency for the TT-genotype to be higher in the EH-offspring was not significant ($p=0.1$).

Table 1
Blood pressure and related characteristics of subjects and their parents.

Characteristics	EH-offspring	Controls	p
Subjects			
Sex (M/F)	51/50	27/23	
Age (yr)	28.2±5.0	27.6±4.6	0.47
Height (cm)	176.2±10.1	176.5±7.7	0.84
Weight (kg)	77.8±17.7	73.5±12.6	0.13
Blood pressure (mmHg)			
Systolic	123.5±11.6	115.3±8.8	<0.0001
Diastolic	75.7±7.9	68.9±8.1	<0.0001
24-hour urinary output (ml)	1787±685	2071±804	0.02
U-Na/24 h (mmol)	102.2±44.3	84.7±33.5	0.02
Parents			
No. of couples	70	50	-
Age (yr)	58.0±6.3	54.9±5.1	0.01
Blood pressure (mmHg)			
Systolic	142.5±18.6	128.0±13.3	<0.0001
Diastolic	86.0±10.3	77.9±7.6	<0.0001
Duration of EH (yr)	8.8±7.1		-
Pharmacological treatment (%)	95	-	-

Values are means±SD

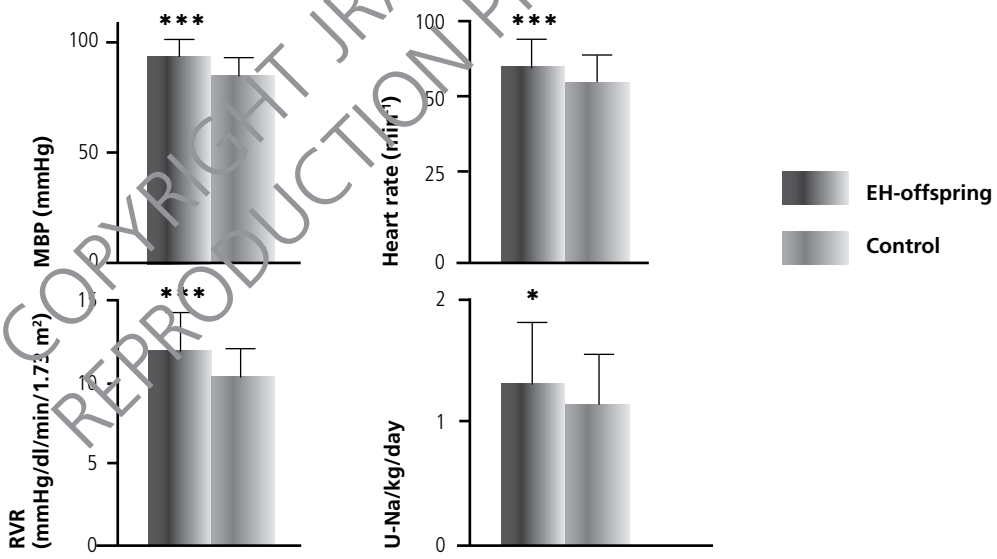

Figure 1
Main differences found between EH-offspring and controls. SBP = systolic blood pressure, RVR = renal vascular resistance. Values show mean±SD. *p<0.05. ***p<0.0001.

Plasma angiotensinogen was higher in controls with TT-genotypes (MM: 1031±238, MT: 905±112, TT: 1226±216 nmol/l, p<0.05, 1-way ANOVA). By contrast, no relation between plasma angiotensinogen and TT-genotype was seen in EH offspring (MM: 931±174, MT: 1096±172, TT: 924±183 nmol/L).

No relation was seen between angiotensinogen polymorphism and GFR, effective renal plasma flow, renal blood flow, renal vascular resistance, plasma renin activity PRA angiotensin II, aldosterone and urinary sodium excretion. No clear relation between ACE or alpha-adducin polymorphisms and any of the above parameters was seen.

Discussion

This study shows that in EH-offspring, BP, heart rate and RVR were 5%, 7% and 15% higher,

Table 2
Renal haemodynamics characteristics and renin-angiotensin-aldosterone system parameters in subjects.

Characteristic	EH-offspring	Controls	p
Effective renal plasma flow (ml/min/1.73 m^2)	471±74	468±78	0.84
Renal blood flow (ml/min/1.73 m^2)	78 ±133	822±102	0.14
Glomerular filtration rate (ml/min/1.73 m^2)	100±10	101±12	0.65
Filtration fraction (%)	21.5±2.2	21.7±2.2	0.76
Plasma renin activity (mU/L)	15.9±8.9	17.8±11.3	0.25
Plasma aldosterone (pmol/l)	189.6±97.3	214.9±126.8	0.19
Plasma angiotensin II (pmol/l)	7.6±4.4	7.8±6.3	0.69
Plasma angiotensinogen (nmol/l)	1012±247	993±202	0.70

Values are means±SD

Table 3
Renal clearance of sodium and lithium, and calculated parameters regarding tubular sodium handling.

Characteristics	EH-offspring	Controls	p
C_{Li} (ml/min/1.73 m^2)	24.8±5.5	26.5±5.6	0.08
C_{Na} (ml/min/1.73 m^2)	1.73±0.56	1.82±0.57	0.36
$PAR_{Na,water}$ (mmol/min)	10.5±1.3	10.2±1.5	0.21
$PFR_{Na/water}$ (%)	75.2±4.8	73.6±5.0	0.06
DAR_{Na} (mmol/min)	3.28±0.74	3.40±0.77	0.36
DFR_{Na} (%)	92.9±2.1	93.0±2.2	0.79

Values are mean±SD. There was no difference in renal clearance of lithium or sodium or in any of the calculated parameters regarding renal tubular sodium handling between the two groups. C_{Li} = clearance of lithium, C_{Na} = clearance of sodium. Renal handling of sodium in the proximal and distal segments was estimated on the basis of the following equations.[21] Proximal absolute reabsorption of sodium ($[PAR_{Na}]$ = [GFR - C_{Li}) x P_{Na} ; where GFR is glomerular filtration rate and P_{Na} is plasma sodium). Proximal fractional reabsorption of sodium and water ($PFR_{Na/water}$) = (1 - C_{Li}/GFR) x 100%. Distal absolute reabsorption of sodium (DAR_{Na}) = (C_{Li} - C_{Na}) x P_{Na}. Distal fractional reabsorption of sodium (DFR_{Na}) = (1 - C_{Na}/C_{Li}) x 100. All clearance calculations were standardised for body-surface area (1.73 m^2).

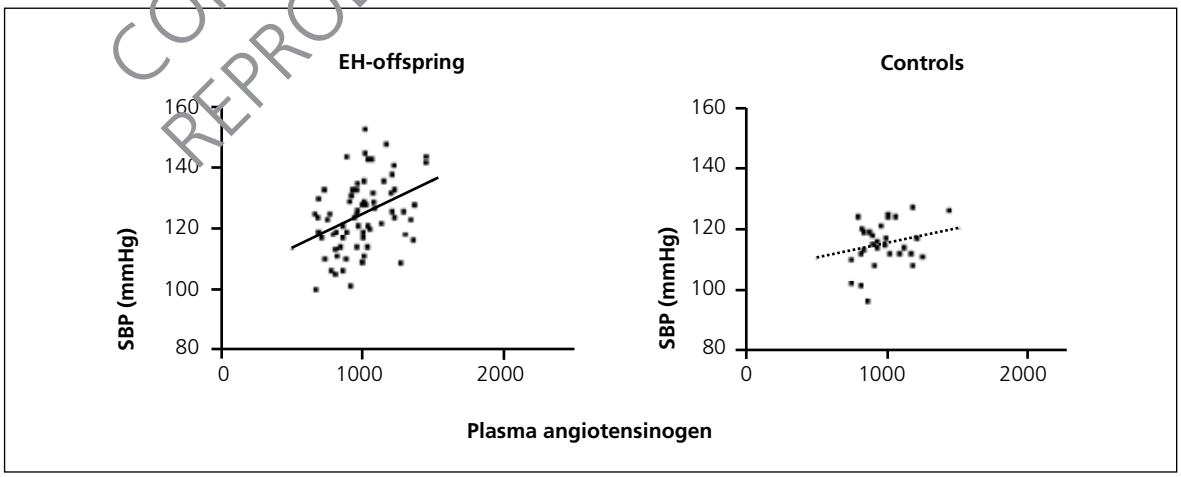

Figure 2
Correlations between plasma angiotensinogen and blood pressure in EH-offspring (p<0.001) and controls (p=0.08).

respectively, compared to controls. Twenty-four-hour urine sodium content was 20% increased in EH-offspring, indicating a greater sodium intake, even when body weight was taken into account. The distribution of three polymorphisms in EH-offspring and controls were similar. However, while the TT-genotype was associated with high BP in the control group (as found in other studies), the genotype was associated with low BP in the EH-offspring.

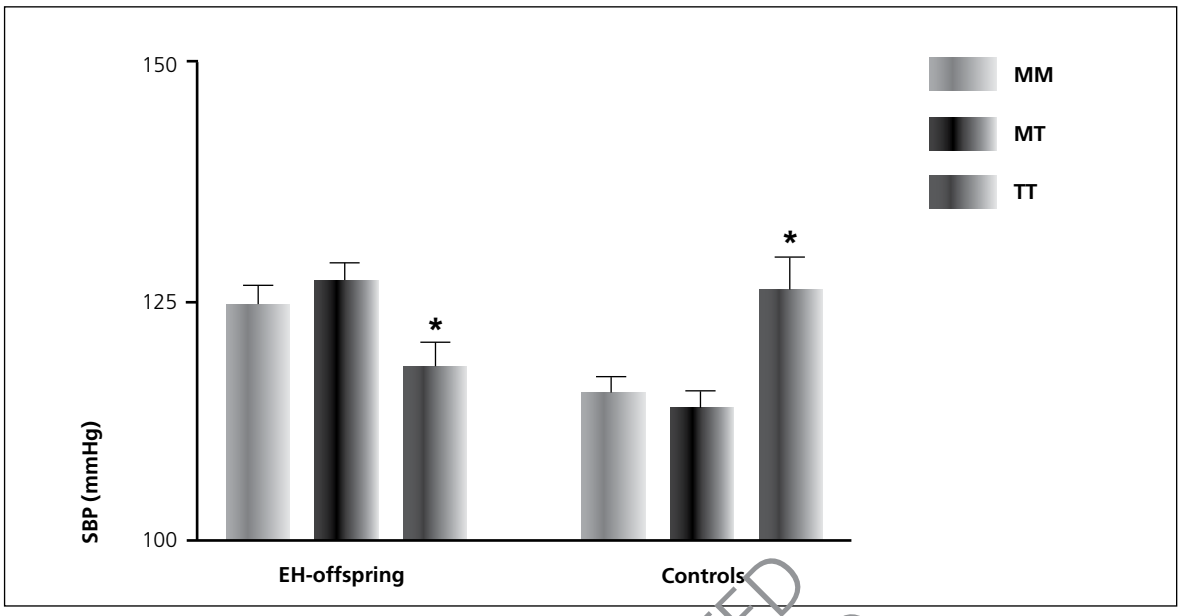

Figure 3
Relation of blood pressures to M235T angiotensinogen polymorphism in EH-offspring and controls. In EH-offspring, the TT-genotype was associated with decreased systolic blood pressure (1-way ANOVA; *p=0.03), while in controls this polymorphism was associated with increased systolic blood pressure (1-way ANOVA, *p=0.02); the difference in distribution was significant (2-way ANOVA: $p_{interaction}$=0.005). Values show mean±SD.

Blood Pressure and Renal Haemodynamics

Previous studies have not been conclusive with respect to renal functional alterations in subjects with a familial predisposition to hypertension. RVR, for example, has been found to be higher,[6,26] normal[27] or lower[28,29] in subjects with a positive family history of essential hypertension. van Hooft and colleagues,[6] whose study in this respect most closely corresponds to ours, found, like ourselves a higher RVR and normal GFR in offspring of hypertensives, but in contrast to our findings renal blood flow was lower, whereas we found it was similar. In the van Hooft study, however, the subjects were slightly younger (9 to 34 years, mean age ca. 22 years) than in ours (mean age 28 years), which may explain the discrepancy, since experimental studies[30] have shown lower renal blood flow only in young animals. Support for a causal relation between RVR and BP as suggested by animal experiments[30,31] is provided by our finding that RVR is positively correlated with BP in the EH-offspring, since those with the highest BPs are those most likely to develop clinical hypertension.[32]

Sodium

Epidemiological data have shown a direct relation between dietary sodium intake and BP at the population level.[33] However, although it remains controversial whether reduced salt intake will lower BP in individuals,[34-36] the Dietary Approaches to Stop Hypertension (DASH) study has demonstrated rather conclusively that modest BP reductions can be achieved using low salt diets.[37] The present study showed that 24-hour sodium excretion on a free diet was significantly higher in the EH-offspring than in controls even when corrected for body weight. On the other hand, our investigation carried out under standardised conditions after a 12-hour fasting period revealed no difference in kidney function, sodium handling and excretion between EH-offspring and controls. Renal function and sodium excretion data on normotensive offspring of hypertensives on a free diet are diverging. While some authors have found higher GFR and lower fractional excretion of sodium,[38] others, like ourselves have found similar GFR.[6] Why 24-hour sodium excretion was higher in EH-offspring is not clear. This could not readily be explained by higher compliance in 24-hour urine collection in this group since urine volume was lower in the EH-offspring. A possible explanation is a higher sodium intake in EH-offspring due to social conditioning or a genetically-determined appetite for salt. A confirmation of such assumptions requires further studies on dietary intake and excretion in the two groups.

Genetic analysis

Jeunemaitre and colleagues[8] were the first to demonstrate that the M235T polymorphism in the angiotensinogen gene in the homozygous TT state was associated with an odds ratio for hypertension of 1.95 compared with the MM wild type. This finding was subsequently confirmed in several studies,[39,40] but not in all (e.g.[41]), as reviewed recently.[42] One explanation for the discrepancies could be population dependent differences in the distribution of M235T genotypes;[39] for example in several European studies, the frequency of the TT-genotype is typically between 0.1 and 0.2,[40] as in our study, while in Japanese studies reported values are around 0.7.[43] Our findings, however,

Table 4
Distribution of angiotensin II I/D, adducin G460W and angiotensinogen M235T polymorphisms in EH-offspring and controls.

	EH-offspring		Controls	
	No.	%	No.	%
MM	32	36	24	55
MT	38	43	15	34
TT	19	21	5	11
DD	29	32	13	29
ID	38	43	21	48
II	22	25	10	23
GG	55	62	32	73
GW	31	35	11	25
WW	3	3	1	2
Totals	**89**	**100**	**44**	**100**

Data show numbers and percentage with each genotype. No significant difference in any of the polymorphism distributions was noted (chi^2-test). None of the distributions was significantly different from Hardy-Weinberg equilibrium (chi^2-test).

point to another possible explanation for the conflicting results. The, respectively, positive and negative associations between TT-genotype and BP in the controls and EH-offspring suggest that strong genetic predisposition to hypertension may negate relationships which are otherwise seen in a general population. Consistent with this, no positive relation between TT-genotype and BP has been seen in either of other offspring studies of which we are aware.[13,14] Thus, one may speculate that genetically predisposed individuals may have other genetic combinations, which protect against the prohypertensive mechanisms associated with the TT genotype. Without knowing the link between the TT genotype and BP[44] it is difficult to suggest a mechanism by which the TT genotype could have a hypotensive effect in genetically disposed individuals. In any event, the results show that genetically homogenous subgroups are needed in order to obtain consistent results.[3]

Many studies have failed to demonstrate a relationship between the ACE I/D polymorphism and BP,[45,46] whereas some have demonstrated a linkage or association in male but not female subjects.[9,47] Two studies of offspring of hypertensive parents have also given conflicting results: a Dutch study[15] showed no association in subjects with high or low BP and their offspring, while a Finnish study[13] demonstrated that DD-genotype males with hypertensive parents had higher BP. In the present study there was no significant association between BP and the ACE gene DD-genotype and no significant interaction between familiarity for hypertension and the ACE gene polymorphism in relation to BP or indeed any of the other parameters measured. The present study did not investigate possible gender specific differences due to the relatively small number of subjects. Regarding the alpha-adducin WW-genotype, an association to hypertension seen earlier was confirmed in a population of older persons,[48] but not in a Scottish population.[49] Our data are consistent with these generally negative findings, in that neither the DD nor the WW-genotype is increased in the EH-offspring.

The genetic results thus show no clear relationship between the polymorphisms studied and hypertension. Nor were the polymorphisms related to any of the renal parameters measured. It may be argued that the study is too small to detect such relationships, and the study is indeed smaller than many of the genetic studies in the literature. However, the groups were extremely homogeneous, and the EH-offspring group (n=101) would be expected to show differences from controls (n=50), if these were of pathophysiological importance. Furthermore, the groups were large and well-controlled enough to demonstrate the anomalous association between angiotensinogen TT-genotype and BP between the groups with high significance ($p<0.005$). Although our finding of interaction between the TT-genotype and BP in EH-offspring and controls is consistent with the possibility of epistatic relations between the polymorphisms studied, the weakness of the relations suggests that these polymorphisms are of limited importance in the pathogenesis of the disease. The conclusion is therefore, we believe, realistic and provides strong and new support for much of the more recent literature on this topic.[50]

Plasma Angiotensinogen

Previous investigations have shown that plasma angiotensinogen and BP are positively correlated,[8] and our data support this in both EH-offspring and controls. There is also evidence in the literature that the TT-genotype of the M235T angiotensinogen polymorphism is associated with increased plasma angiotensinogen,[42] which it is suggested results in increased activity of the RAAS, and thus higher BP. This attractive hypothesis was supported for the controls. To some extent the hypothesis was also supported for the EH-offspring, but in converse manner: here the lack of increased plasma angiotensinogen in those with the TT-genotype was also associated with lower BP. Thus, for some reason, the EH-offspring have a genetic or environmental background which prevents the TT-genotype expressing an increased plasma angiotensinogen as seen in controls. Therefore, the relation between genotype and plasma angiotensinogen is not clear-cut, as also discussed previously.[44]

Perspectives

The present study supports much available experimental and clinical evidence indicating that increased RVR is a crucial part of the

pathogenesis of essential hypertension, in that we show that genetic predisposition to hypertension is associated with increased RVR. The results also support previous findings that increased levels of plasma angiotensinogen are associated with increased BP, and show furthermore that the EH-offspring have increased salt intake. Thus, the results support the logic of inhibiting the renin-angiotensin system for antihypertensive therapy in genetically predisposed individuals. The genetic basis for this remains unresolved, underlining the growing awareness of the complexity of epistatic interactions,[50] even in a homogeneous population like ours of which at least half may be expected to develop hypertension. The results suggest that other approaches are needed to elucidate the undoubted genetic component of the pathogenesis of essential hypertension.

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